Indian Journal of Chemistry
Vol. 45B, February 2006, pp. 461-465

A convenient stereoselective synthesis of β-D-glucopyranosides

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Received 20 October 2004; accepted (revised) 27 July 2005

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 $LiCO_3$ is used for glycosidation of several fatty alcohols including an aromatic alcohol. $LiCO_3$ can be easily separated from the reaction mass and gives good yield.

Keywords: Koenigs-Knorr method, β-D-glucopyranosides, alkyl glucosides, $LiCO_3$

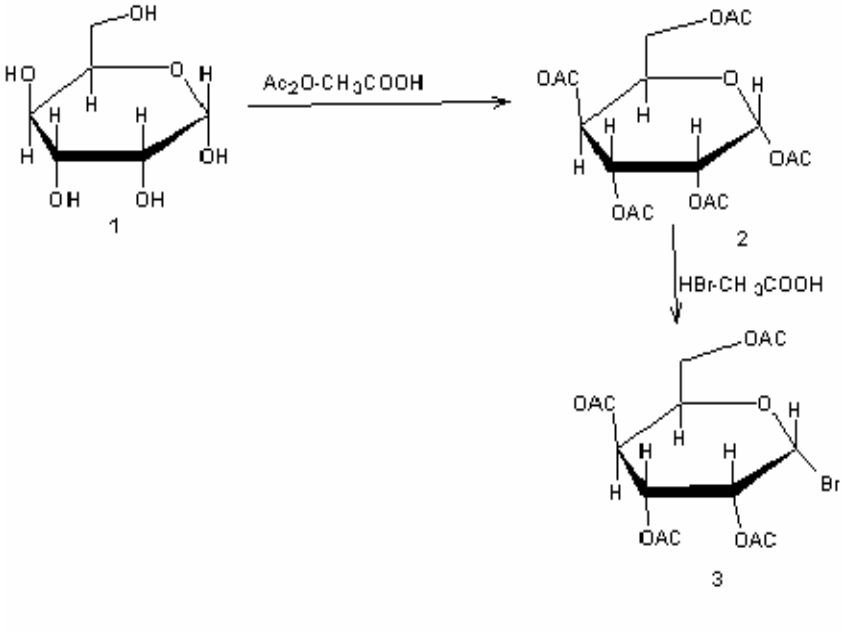
IPC: **Int.Cl.**[7] **C 07 H 3/00**

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[1-2]. 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[3]. Such glycosylation is normally carried out using expensive heavy metal catalysts, having separation problems, and gives only moderate yield (40-50%)[4]. 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[5] 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[6]. 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[7]. With this in mind critical glucosylation of tetra-O-acetylbromo-β-D-glucopyranosides with alcohols in the presence of $LiCO_3$ as a promoter was carried out.

Results and Discussion

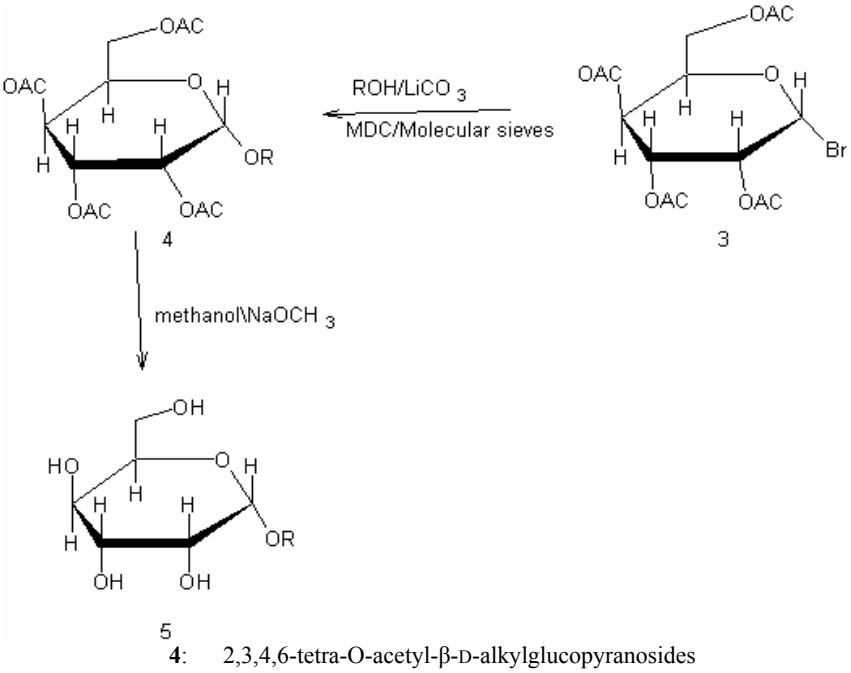
The peracetate of glucose **2** is readily prepared as the β-anomer by standard procedure[8]. When 1,2-*trans* sugar per-O-acetate **2** (step-1, **Scheme I**) is dissolved as per standard[9] procedure in acetic acid containing hydrobromic acid, 2,3,4,6-tetra-O-acetyl-α-glycosyl bromide **3** is formed. Compound **3** shows inversion of configuration[10], so instead of β-D-glycosyl halide, α-glycosyl halide is formed with high degree of purity. This unstable reactive intermediate product **3** can be isolated in dichloromethane and converted to the corresponding peracetylated alkyl glucosides **4**. 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 $LiCO_3$ 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*=7.8Hz) as shown in **Table II**. The physical data of β-D-glucopyranosides were identical with those of the reported β-D-glucopyranosides[11-14]. 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 $LiCO_3$ promoted reaction involving glycosidic bond formation is thought to be mechanistically similar to the Koenigs-Knorr method for formation of glycosides[5]. Lithium as the active site of $LiCO_3$ 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

$LiCO_3$ 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 pollution[15]. This made the present method using $LiCO_3$ 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% sulfuricacid 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 (R_f value – 0.78) moved farthest followed by the alkyl mono glucosides

Table I − Synthesis of β-D-glucopyranosides using alcohols

Compd	ROH (1 eq.)	glu-OR G (%)	Yield* Time (hr)	Reaction
1	$CH_3(CH_2)_6$-OH	glu-O-$(CH_2)_6$-CH_3	6(65)	16
2	$CH_3(CH_2)_7$-OH	glu-O-$(CH_2)_7$-CH_3	7(67)	18
3	$CH_3(CH_2)_8$-OH	glu-O-$(CH_2)_8$-CH_3	8(65)	20
4	$CH_3(CH_2)_9$-OH	glu-O-$(CH_2)_9$-CH_3	9(64)	21
5	$CH_3(CH_2)_{11}$-OH	glu-O-$(CH_2)_{11}$-CH_3	10(66)	22
6	$CH_3(CH_2)_{13}$-OH	glu-O-$(CH_2)_{13}$-CH_3	11(67)	24
7	$Ph(CH_2)_2$-OH	glu-O-$(CH_2)_2$-Ph	12(45)	20

*Isolated yield after purification.

Table II – ^{1}H NMR** data for acetylated and glucopyranosides **1-7**.

Compd	Acylated compd	Glucopyranosides
glu-O-$(CH_2)_6$-CH_3	4.50(d,*J*=7.9Hz)	4.09(d,*J*=7.8Hz)
glu-O-$(CH_2)_7$-CH_3	4.50(d,*J*=7.9Hz)	4.09(d,*J*=7.8Hz)
glu-O-$(CH_2)_8$-CH_3	4.50(d,*J*=7.9Hz)	4.09(d,*J*=7.8Hz)
glu-O-$(CH_2)_9$-CH_3	4.50(d,*J*=7.9Hz)	4.09(d,*J*=7.8Hz)
glu-O-$(CH_2)_{11}$-CH_3	4.50(d,*J*=7.9Hz)	4.09(d,*J*=7.8Hz)
glu-O-$(CH_2)_{13}$-CH_3	4.50(d,*J*=7.9Hz)	4.09(d,*J*=7.8Hz)
glu-O-$(CH_2)_2$-Ph	4.62(d,*J*=8Hz)	4.32(d,*J*=8.3Hz)

**All the compounds were satisfactorily characterized by ^{1}H NMR spectroscopy. Chemical shifts (δ, ppm) relative to TMS as internal standard; coupling constants *J* (in Hz) are given in the parentheses; d=doublet

(R_f value – 0.71), di-(R_f value – 0.66) and oligo glycosides (R_f 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; $[\alpha]^{25}_D$ +4° (c=1, $CHCl_3$); IR(KBr): 1735 cm^{-1}. Anal. Found C, 63.45; H, 7.2. Calcd for C, 63.55; H, 7.15%.

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 $CaCl_2$ and then concentrated to afford **3** (6.72 mmoles, 90%). Observed m.p. 87-8°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 $LiCO_3$ (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. 73-5°C; $[\alpha]^{26}_D$ –32° (c=0.51, CH_3OH); 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 $LiCO_3$ (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; $[\alpha]^{25}_D$–33.8° (c=0.58, H_2O); 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 $LiCO_3$ (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 mmoles), *n*-decanol (6.72 mmoles) and $LiCO_3$ (8.30 mmoles) in dichlorome-

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-*n*-decyl-β-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 β-D-glucopyranosides **9** (0.951g, 64%). m.p.135.6°C; $[\alpha]^{25}_{D}$–27.8° (H_2O); IR(KBr): 3386, 2925, 2829, 1080, 1036 cm^{-1}. Anal. Found C, 60.78; H, 10.15. Calcd. for C, 60.75; H,10.12%.

n-Dodecyl-β-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-β-D-glucopyranosides (2.22 g, 5.5 mmoles) as a colourless solid. Deacetylation (step-2, **Scheme I**) of per acetylated 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 β-D-glucopyranosides **10** (1.08 g, 66%). m.p.144-45°C; $[\alpha]^{25}_{D}$ –22.7° (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-β-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-β-D-glucopyranosides (2.222 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 β-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-β-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-tetra-acetyl-2-phenylethyl-β-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 β-D-glucopyranosides **12** (0.44 g, 45%). m.p. 38.5°C; $[\alpha]^{27}_{D}$ 35.3° (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

1 Wong H & Whitesides G in *Enzymes in Synthetic Organic Chemistry*, Vol.12, (Pergamon Press, Oxford) **1994,** 252.

2 Faber K in *Biotransformations in Organic Chemistry*: *A Text Book*, 6th edition, (Springer-Verlag, Berlin) **2000**, 307.

3 Petrovic Z, Konstantinovic S & Spasojevic A, *Indian J Chem*, 43 B, **2004**, 132.

4 Lieunt R & Shylak N, *Can J Chem*, 31, **1953**, 528.

5 Koenigs W & Knorr E, C*hem Ber*, 34, **1901**, 957.

6 Grener J, Millius A, Hale K J & Vaccaro H A, *J Am Chem Soc*, 113, **1991**, 2092.

7 Thiem J & Bocker T, *Industrial Applications of Surfactants-III*, *Surfactant Science Series*, edited by Karsa, (Marcel Dekker Inc. New York) **1987**.

8 Vogel A I, *Textbook of Practical Organic Chemistry Including Qualitative Organic Analysis*, 4th edition, (Longman Scientific and Technical, London) **1978**, 454.

9 Vogel A I, *Textbook of Practical Organic Chemistry Including Qualitative Organic Analysis*, 4th edition, (Longman Scientific and Technical, London) **1978**, 455.

10 Kennedy J & White C, *Bioactive Carbohydrates in Chemistry, Biochemistry and Biology*, (Ellis Horwoop Publishers, Berlin) **1983**, 63.

11 Pigman W & Richtmyer N, *J Am Chem Soc*, 64, **1942**, 369.

12 Fan W, Tezuka Y & Ni K, *Chem Pharm Bull*, 49, **2001**, 396.

13 Kitajima J, Ishikawa T, Tanaka Y, Ono M, Ito Y & Nohara T, *Chem Pharm Bull*, 46, **1998**, 1587.

14 Kitajima J, Ishikawa T, Tanaka Y & Nohara T, *Chem Pharm Bull*, 46, **1998**, 1643.

15 Garett R L, *American Chemical Society Symposium Series-640*, Washington DC, **1996**, Chapter 1.

16 Ballini R, Bosica G, Carloni S, Maggi R & Satori G, *Tetrahedron Lett*, 39, **1998**, 6049.