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Synthesis of arbutin by two-step reaction from glucose*

HUANG Shen-lin (黄申林), ZHU Yu-lin (朱育林), PAN Yuan-jiang (潘远江)†, WU Shi-hua (吴世华)

(*Department of Chemistry, Zhejiang University, Hangzhou 310027, China*)

†E-mail: panyuanjiang@zju.edu.cn

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Abstract: Arbutin was synthesized from glucose by two-step reaction below: (a) 2,3,4,6-tetra-O-acetyl-α-D-glucosyl chloride or bromide was prepared by glucose and acetyl halide (chloride or bromide). (b) 2,3,4,6-tetra-O-acetyl-α-D-glucosyl halide (Cl, Br) reacted with hydroquinone, methanol as solvent at pH=9.5~10.0.

Key words: Arbutin, Synthesis, 2,3,4,6-tetra-O-acetyl-α-D-glucosyl halide (chloride or bromide), Acetyl halide (Cl, Br)
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INTRODUCTION

2,3,4,6-tetra-O-acetyl-*α*-D-glucosyl chloride or bromide (Fig.2, 3a-b) is important and versatile synthetic intermediates used as electrophiles in glycosidic bond formation in carbohydrate chemistry (Kovac *et al*., 1985; Mukherjee *et al*., 2001).

The procedure for the preparation 2,3,4,6-tetra-O-acetyl-*α*-D-glucosyl chloride (3a) was reported by Pacsu (1928) and involved reaction of *β*-D-glucopyranose pentaacetate (Fig.1). Chlorinating agents such as: $AlCl_3$, PCl_5, $SOCl_2$-HAc, PPh_3-CCl_4, haloenamimes, BCl_3, TsCl and $(Cl_3CO)_2CO$ were described in literature (Chittenden, 1993; Ohrui and Fox, 1973; Ernst and Winkler, 1989; Peromo and Krepinsky, 1987; Kovac and Edgar, 1992; Kartha and Jennings, 1990; Hwang *et al.*, 1984; Cicchillo and Norris, 2000). 2,3,4,6-tetra-O-acetyl-*α*-D-glucosyl bromide was prepared by the methods of Karjala and Link (1940) and Bárczai-Martos and Kórösy (1950) from pentaacetylglucose using naphthalene/Br_2 or phosphorus/bromine/water or haloenamimes as bromine resource. Those preparations generally involved the use of hydrogen bromide dissolved in glacial acid which was very troublesome to handle and prepare.

In our experiment, acetyl halide was used as either acetyl agent or halogenating agent (Fig.2). The reaction of *β*-D-glucose with acetyl chloride was calm and the gas hydrogen chloride appeared. The product was isolated and identified as 2,3,4,6-tetra-O-acetyl-*α*-D-glucosyl chloride in yield of 71.8% (in glucose). The small coupling constant (3.65 Hz in the ^{1}H NMR spectrum) of the anomeric H-1 at 6.36 indicated that this form was *α*-D-model.

In another experiment, *β*-D-glucose reacted with acetyl bromide below −15 °C by using $CHCl_3$ as solvent; this reaction was very vigorous and hydrogen bromide appeared. Needle crystalloid 2,3,4,6-tetra-O-acetyl-*α*-D-glucosyl bromide was obtained in yield of 79.3% (in glucose). In the ^{1}H NMR spectrum, the small coupling constant (3.98 Hz) of the anomeric H-1 at 6.63 is characteristically in the formed of *α*-D-model.

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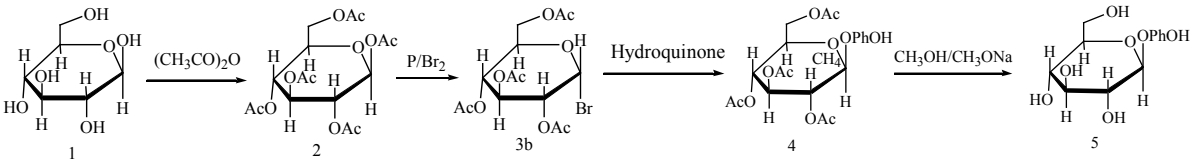

Fig.1 The chemical synthesis of arbutin in literatures

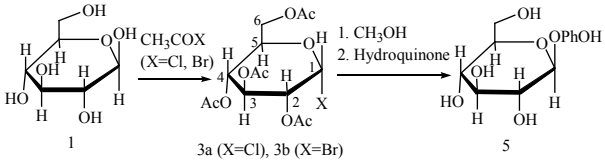

Fig.2 A convenient route of arbutin synthesis

Arbutin, the *β*-D-glucoside of hydroquinone, was discovered in the last century and is widely distributed among plants especially of the families Ericaceae and Saxifragaceae. Arbutin inhibits the melanin biosynthetic pathway and is used as a skin lightener in cosmetics. The chemical synthesis of arbutin is shown in Fig.1 (Pong *et al.*, 1989).

Compared to the classical methods, using *β*-D-glucose as beginning substance, arbutin is synthesized by reaction of 2,3,4,6-tetra-O-acetyl-*α*-D-glucosyl chloride or bromide with hydroquinone (Fig.2), which is a method using a more convenient route.

To increase the yield, different reaction parameters including solvent and pH value were varied. This reaction is strongly affected by the solvent. When the reaction usefully involved methanol and many other solvents such as acetone, benzene, toluene, ethyl acetate, chloroform, no product was obtained. In order to cover the desired range in pH, the experiments were carried out over a wide range of pH values: 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, and 12.0. There was no reaction in the pH range of 6.5–8.0. The product yield increased from 8.0 to 9.5. When pH>10, the hydrolyzed velocity of 3a-b in Fig.2 was much higher than the reaction of 3a-b in Fig.2 with hydroquinone. For this series of experiments, the optimal reaction condition occurred at pH of 9.5–10.0.

The large coupling constant (12.7 Hz in the ^{1}H NMR spectrum) of the anomeric H-1 at 4.86 was characteristic for the *β*-glucosidic linkages which identified the product formed as *β*-D-Arbutin of yields (3a, 38%; 3b, 27%).

EXPERIMENTAL DETAILS

^{1}H and ^{13}C-NMR data were recorded on Bruker Avance DMX-500 spectrometer; chemical shifts are given in δ; TMS as internal standard and coupling constants (J) are given in Hz. Mass spectra were recorded on Bruker Daltonics Esquire 3000plus. All materials were commercially available.

Preparation of tetra-O-acetyl-*α*-D-glocopyranosyl chloride

Acetyl chloride (0.65 mol) and *β*-D-glucose (0.10 mol) were added into a three-neck round-bottom flask and stirred at room temperature, taking care that the temperature should not rise above 25 °C. After 16 h, it became a yellowish liquid. Then 300 ml chloroform was added and the mixture was poured into about 500 ml ice-water. The organic layer was filtered and immediately washed with water three times, dried with calcium chloride, and half an hour later, was evaporated under reduced pressure to a yellow syrupy residue. A white powder (26.3 g) was obtained after processing as described in literature (Lemeux, 1963).

Preparation of tetra-O-acetyl-*α*-D-glocopyranosyl bromide

This reaction was carried out in a three-neck round-bottom flask equipped with a dropping funnel. Fifty mmol *β*-D-glucose was dissolved in 50 ml of pure, dry chloroform, vigorously stirred while it was maintained at approximately −15 °C with ice-salt bath. Acetyl bromide (260 mmol) was then added very slowly from a burette to the solution which was then stirred 3 h at −10 °C. The above procedure yielded a needle-shaped colorless crystalloid.

Preparation of *β*-D-Arbutin

Under an argon atmosphere in a three-neck round-bottom flask equipped with a dropping funnel, 5 mmol of 2,3,4,6-tetra-O-acetyl-*α*-D-glucosyl chloride or bromide and 6 mmol hydroquinone were dissolved in 20 ml of pure, dry methanol. After 5% CH_3ONa/CH_3OH was added to the solution so that its pH=9.5~10, it was stirred at room temperature. After the reaction ended in 2 h, the solvent methanol was evaporated and separated by counter current chromatography (in yield: 3a, 38%; 3b, 27%).

(1) 2,3,4,6-tetra-O-acetyl-*α*-D-glocopyranosyl chloride:

^{1}H-NMR (500 M, $CDCl_3$): 6.36 (d, 1H, H-1, J=3.65 Hz), 5.50–5.11 (m, 3H, H-2, H-3, H-4), 4.31–4.11 (m, 3H, H-5, H-6, H-6′), 2.21, 2.13, 2.07, 2.05 (4s, 12H, $4COCH_3$). ESI-MS (m/z): 265.

(2) 2,3,4,6-tetra-O-acetyl-*α*-D-glocopyranosyl bromide:

^{1}H-NMR (500 M, $CDCl_3$): 6.63 (d, 1H, H-1, J=3.98 Hz), 5.57–4.87 (m, 3H, H-2, H-3, H-4), 4.33–4.15 (m, 3H, H-5, H-6, H-6′), 2.12, 2.11, 2.07, 2.05 (4s, 12H, $4COCH_3$). ESI-MS (m/z): 409.

(3) *β*-D-Arbutin:

^{1}H-NMR (D_2O): 6.94 (d, 2H, J=8.7 Hz, H-2, H-6), 6.76 (2H, J=8.7 Hz, H-3, H-5), 4.86 (d, 1H, J=12.7 Hz, H-1), 3.81 (d, 1H, J=12.4, H-6A), 3.65 (dd, 1H, J=5.4, J=5.5, H-6B), 3.54–3.38 (m, 4H, H-2′, H-5′). ^{13}C-NMR (D_2O): 151.4 (C-1′), 150.6 (C-4′), 118.6 (C-2′, C-6′), 116.4 (C-3′, C-5′), 101.5 (C-1), 76.2 (C-3), 75.7 (C-5), 73.1 (C-2), 69.6 (C-4), 60.7 (C-6). ESI-MS (m/z): 295 $[M+Na]^+$.

References

Bárczai-Martos, M., Kórösy, F., 1950. Preparation of Acetobrome-Sugars. *Nature*, **165**:369.

Chittenden, G.J.F., 1993. Reaction of some 1,2-trans-aldose peracetates with thionyl chloride-acetic acid–a convenient synthesis of some 1,2-trans-per-O-acetyl-D-glycosyl chlorides. *Carbonhydr. Res.*, **242**:297-301.

Cicchillo, R.M., Norris, P., 2000. A convenient synthesis of glycosyl chlorides from sugar hemiacetals using triphosgene as the chlorine source. *Carbonhydr. Res.*, **328**(3):431-434.

Ernst, B., Winkler, T., 1989. Preparation of glycosyl halides under neutral conditions. *Tetrahedron Lett.*, **30**(23):3081-3084.

Hwang, C.K., Li, W.S., Nicolaou, K.C., 1984. Reactions of hydroxyl groups with tosylchloride-dimethylaminopyridine system. Direct synthesis of chlorides from hydroxycompounds. *Tetrahedron Lett.*, **25**(22):2295-2296.

Karjala, S., Link, K.P., 1940. Synthesis of glycol glucosides. *J. Am. Chem. Soc.*, **62**(4):917-920.

Kartha, K.P.R., Jennings, H., 1990. A facile, one-step procedure for the conversion of 2-(trimethylsilyl) ethyl glycosides to their glycosyl chlorides. *Tetrahedron Lett.*, **31**(18):2537-2540.

Kovac, P., Edgar, K.J., 1992. Synthesis of ligands related to the O-specific antigen of type 1 Shigella dysenteriae. 3. Glycosylation of 4,6-O-substituted derivatives of methyl 2-acetamido-2-deoxy-.alpha.-D-glucopyranoside with glycosyl donors derived from mono- and oligosaccharides. *J. Org. Chem.*, **57**(8):2455-2467.

Kovac, P., Taylor, R.B., Glaudemans, C.P.J., 1985. General synthesis of (1. fwdarw. 3)-.beta.-D-galacto oligosaccharides and their methyl .beta.-glycosides by a stepwise or a blockwise approach. *J. Org. Chem.*, **50**(25):5323-5333.

Lemeux, R.U., 1963. Methods in Carbohydrate Chemistry. Academic Press, New York, U.S.A., p.221.

Mukherjee, D., Ray, P.K., Chowdhury, U.S., 2001. Synthesis of glycosides via indium(III) chloride mediated activation of glycosyl halide in neutral condition. *Tetrahedron*, **57**(36):7701-7704.

Ohrui, H., Fox, J.J., 1973. Nucleosides LXXXI. An approach to the synthesis of C-C linked *β*-D-ribofuranosyl nucleosides from 2,3-O-isopropylidene-5-O-trityl-*β*-D-ribofuranosyl chloride. *Tetrahedron Lett.*, **14**(22):1951-1954.

Pacsu, E., 1928. Über die Einwirkung von Titan (IV)-chlorid auf Zucker-Derivate, I.: Neue Methode zur Darstellung der Aceto-chlor-zucker und Umlagerung des *β*-Methyl-glucosidsinseine *α*-Form. *Ber.*, **61**:1508-1513.

Peromo, G.R., Krepinsky, J.J., 1987. A glycosylation reaction: Conversion of methyl glicosides to glycosyl chlorides by boron trichloride. *Tetrahedron Lett.*, **28**(46):5595-5598.

Pong, S.Q., Li, L.P., Wu, J.W., An, Y., Cheng, T.M., Cai, M.S., 1989. Synthesis of Arbutin Analogs. *Acta Chimica Sinica*, **47**:512-515.