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Study on the synthesis of 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide

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2, 3, 4, 6-*O*-Tetraacetyl-α-D-glucopyranosyl bromide **3** is widely used as an intermediate for the synthesis of sugar esters. Red phosphorus and bromine were reacted in glacial acetic acid to generate phosphorus tribromide. Then glucose pentaacetate and phosphorus tribromide were reacted to provide compound **3**. The yield of product obtained was 83.5%. ^{1}H NMR and ^{13}C NMR were used to confirm the structure of 2, 3, 4, 6-*O*-tetraacetyl-α-D-glucopyranosyl bromide **3**.

Keywords: 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide, synthesis, optimization.

INTRODUCTION

Studies on the modification of sugars and their derivatives to leading drugs have become an active field in the research and development of new drugs. The brominated derivatives of sugars are important intermediates, which can be used to synthesize sugar-containing drugs and biochemical reagents of sugars. Based on the intermediates of sugar-brominated derivatives, other carbohydrate derivatives with biological and pharmacological functions can be further synthesized [1,2]. Herein, the synthesis of 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide **3** was investigated.

RESULTS AND DISCUSSION

In order to prepare α-D-glucose pentaacetate, the catalysts mainly used are proton acids, Lewis acids, solid acids, and enzymes. The traditional homogeneous catalysts have low phase diffusion resistance, are easy to control and conveniently operated in the catalytic process, but the selectivity of the reactions and the yields of the products need to be further improved. Moreover, the homogeneous catalysts are not easy to reuse. In heterogeneous catalysis, solid acid catalysts have high selectivity and yields, but the preparation process of catalysts is complex. So, it is of very high importance to develop simple and effective catalysts with high catalytic activity and selectivity, to improve the yield of a single configuration, and to reduce the production costs [3]. Herein, glucose pentaacetate **2** was synthesized by esterification of glucose **1** and acetic anhydride, using pyridine as a catalyst (Fig. 1). The molar ratio of glucose and acetic anhydride was 1:26, the dosage of catalyst was 13 times the glucose mass, the reaction time was 20 h at room temperature, the esterification yield of glucose and acetic anhydride was up to 98%. The molar ratio of α-glucose pentaacetate and β-glucose pentaacetate was 3:1.

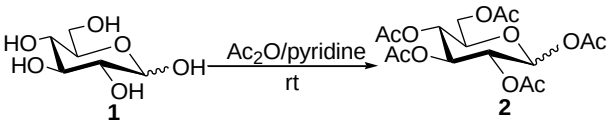

Fig. 1. Synthesis of glucose pentaacetate **2**.

The system temperature is too high to be easily reached by the decomposition of 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide **3**, which affects the final yield and purity of product. The bromination reaction is carried out at room temperature.

The reaction time has a great influence on the product yield. Short reaction time greatly reduced the yield of product. But long reaction time also caused the yield to decrease. This is due to the fact that the stability of 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide **3** is not high: the bromide **3** is easily decomposed by light or heat. It was proven that the optimum reaction time is 3 h.

1,2,3,4,6-Penta-*O*-acetyl-(α,β)-D-glucopyranose **2** was reacted with phosphorus tribromide. After stirring for 3 h at room temperature, 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide **3** was obtained in a yield of 83.5% (Fig. 2).

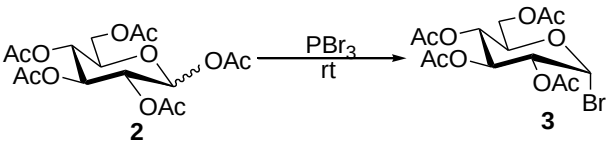

Fig. 2. Synthesis of 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide **3**.

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EXPERIMENTAL

General

^{13}C and ^{1}H NMR spectra were recorded using a Bruker DPX-300 spectrometer at 75 and 300 MHz, respectively. Mass spectra were recorded with a VG PLATFORM mass spectrometer using the ESI mode. TLC was performed on silica gel plates (GF_{254}) with detection by UV light or by charring with 10% H_2SO_4 in EtOH.

*Synthesis of D-glucose pentaacetate **2***

70 mL of acetic anhydride was added to a flask and was carefully mixed with 5 g of D-glucose **1**. While stirring with a magnetic stirrer, anhydrous pyridine (70 mL) was added. This mixture was kept at room temperature under stirring for 20 h. When the reaction was completed, the solution was mixed with ice and was stirred until all ice melted. The filtered product was recrystallized in a solution of water/methanol (v/v=1/2). Yield: 98%; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 170.5, 170.2, 169.3, 167.3 (5× C=O), 92.0 (C-1β), 89.8 (C-1α), 68.8 (C-5), 67.6 (C-3 and C-4), 66.7 (C-2), 61.5 (C-6), 21.2, 21.0, 20.9, 20.8, 20.7 (5× C(O)$\underline{C}H_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.33 (d, $1H_\alpha$, $J_{1,2}$ 1.5 Hz, H-1α), 5.64 (d, $1H_\beta$, $J_{1,2}$ 1.5 Hz, H-1β), 5.45 (dd, 1H, $J_{3,4}$ < 1.0 Hz, $J_{4,5}$ 1.3 Hz, H-4), 5.34-5.28 (m, 2H, H-2, H-3), 4.30 (dt, 1H, $J_{5,6}$ 6.5 Hz, H-5), 4.16-4.01 (m, 2H, H-6a, H-6b), 2.13, 2.09, 2.00, 1.99, 1.97, 1.96 (all s, 15H, 10× C(O)CH_3); ESI-MS: *m*/*z*=413.3 $[M+Na]^+$.

Preparation of phosphorus tribromide

1.5 g of red phosphorus was suspended in 15 mL of glacial acetic acid, mixed and cooled in ice water bath to 4 °C. 3 mL of bromine was dropwise added to the above solution. After dropping, the temperature was maintained at 20 °C and the reaction mixture was stirred for 1 h, then the insoluble solid was filtered out. The filtrate was phosphorus tribromide, which was sealed for storage at low temperature.

*Synthesis of 2,3,4,6-O-tetraacetyl-α-D-glucopyranosyl bromide **3***

1.75 g (4.5mmol) of D-glucose pentaacetate **2** and 5 mL of phosphorus tribromide were added into a 25 mL flask, and the reaction mixture was stirred at room temperature for 3 h. Then 25 mL of chloroform was added, and washed with ice water (100 mL×2), saturated sodium hydrogen carbonate solution, and water. The liquid was separated, and the chloroform layer was dried with anhydrous magnesium sulfate. After filtering, the filtrate was decompressed and concentrated, giving a light yellow syrup. The syrup was dissolved in diethyl ether under heating, then iced for 24 h. After filtering, 1.5 g of white solid was obtained. The yield was 83.5%. ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (4×C=O), 88.1 (C-1), 70.9 (C-5), 67.8, 67.1 (C-3/C-4), 66.8 (C-2), 60.9 (C-6), 21.0, 20.7 (4× C(O)$\underline{C}H_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 5.49 (dd, 1H, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 1.1 Hz, H-4), 5.38 (dd, 1H, $J_{2,3}$ 10.2 Hz, H-3), 5.02 (dd, 1H, H-2), 4.46 (m, 1H, H-5), 4.17 (dd, 1H, $J_{6a,6b}$ 11.3 Hz, $J_{5,6}$ 5.8 Hz, H-6a), 4.01 (dd, 1H, $J_{5,6b}$ 6.6 Hz, H-6b), 2.14, 2.11, 2.05, 2.01 (all s, 12H, 4× C(O)CH_3).

CONCLUSIONS

2,3,4,6-O-Tetraacetyl-α-D-glucopyranosyl bromide **3** is easily removed the hydroxyl protection. It is often used for structure modification of drugs to increase the polarity of drug, reduce the toxic effects, and improve drug activity [1]. So, compound **3** has been widely used as an intermediate to modify drugs. However, due to the instability of 2,3,4,6-O-tetraacetyl-α-D-glucopyranosyl bromide **3**, its application has been limited. Therefore, the development of a more rapid, more concise, and more effective synthesis method for improving the application of compound **3** is of great importance. Herein, using phosphorus tribromide as bromide reagent, 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide **3** was obtained by reaction at room temperature for 3 h with high yield (83.5%).

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ИЗСЛЕДВАНЕ НА СИНТЕЗАТА НА 2,3,4,6-*O*-ТЕТРААЦЕТИЛ-α-D-ГЛЮКОПИРАНОЗИЛ БРОМИД

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(Резюме)

Съединението 2, 3, 4, 6-*O*-тетраацетил-α-D-глюкопиранозил бромид **3** се използва широко като междинно съединение при синтезата на захарни естери. Червен фосфор и бром реагират в ледена оцетна киселина за получаването на фосфорен трибромид. След това глюкозо-пентаацетат реагира с фосфорния бромид за получаването на съединението **3**. Добивът на получения продукт бе 83.5%. Използвани са ЯМР-методите ^{1}H NMR и ^{13}C NMR за да се потвърди структурата 2, 3, 4, 6-*O*-тетраацетил-α-D-глюкопиранозил бромид **3**.