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One-pot synthesis of 1,2-*O*-isopropylidene-*α*-D-xylofuranose

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Abstract

The title compound **1** was prepared by sulfuric acid-catalyzed acetalation of D-xylose followed by partial hydrolysis with aqueous sodium carbonate added directly to a crude acetalation mixture. The yield of crystalline **1** (mp 42–43°C) was 80%.

Keywords: 1,2-*O*-Isopropylidene-*α*-D-xylofuranose; 1,2 : 3,5-di-*O*-Isopropylidene-*α*-D-xylofuranose; Acetalation; D-Xylose; Partial hydrolysis

1. Introduction

1,2-*O*-Isopropylidene-*α*-D-xylofuranose (**1**), a key intermediate in syntheses of antibiotics [1,2], nucleosides [3,4], herbicides [5,6], anti-HIV agents [7,8], and other biologically active compounds [9–11], is generally synthesized by a two-step procedure from D-xylose (**2**) via 1,2 : 3,5-di-*O*-isopropylidene-*α*-D-xylofuranose (**3**), using the high selectivity of partial hydrolysis of the latter compound [12–14]. Mineral acids [12,15,16], anhydrous copper sulfate with sulfuric acid [17,18], or Lewis acids [19–22] are the catalysts of choice of the first step [23,24], namely for the condensation of **2** with acetone. Long reaction times of acetalation (20 or more hours), two tedious and cumbersome neutralization and isolation procedures, and some reproducibility problems in obtaining a ca. 80% yield of **3** and 65% yield of **1** in standard quality are serious drawbacks of this sequence of large-scale applications.

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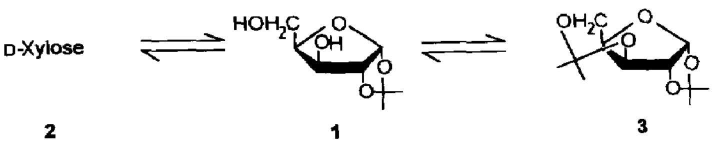

Scheme 1.

In 1985, the results by Poopeiko et al. [16] implied the feasibility of partial isopropylidenation of D-xylose (**2**). By stopping the reaction of **2** with acetone and sulfuric acid (0.37 M) after only 30 min by neutralization with aqueous potassium hydroxide, 65% of **1** and 22% of **3** were isolated by simple hexane–water extraction. Since, in our hands, the yield of **1** in this attractive version was substantially lower and not easily reproducible, we decided to reinvestigate this almost classical reaction sequence.

2. Results and discussion

Monitoring the heterogeneous reaction of D-xylose (**2**) with acetone and sulfuric acid under Poopeiko's conditions [16] (Table 1), by GLC of the corresponding acetates, we were surprised to observe only minor changes in the ratios of **1**, **2**, and **3** present in the sulfuric acid–acetone solution. As the starting material **2** dissolved, the ratio of **3** to intermediate **1** decreased after 60 min from 20:1 to 10:1 (no more solid D-xylose could be recovered), but **1** was never the dominant component of the mixture. For the next 20 h, the changes of this ratio were almost insignificant, the only changes being the formation of mesityl oxide and darkening of the reaction mixture. Evidently, the equilibrium composition of **1**, **2**, and **3** in solution is permanently retained under these reaction conditions, and the overall rate is determined only by the rate of dissolution of **2**. As expected, the rate depends on the sulfuric acid concentration; with 0.28 M sulfuric acid in acetone [25], almost 70% of **2** remained undissolved after stirring for 30 min. Complete

Table 1
Acetalation of D-xylose (**2**) with acetone and 0.37 M sulfuric acid at 20°C

Time (h)	Composition (% by weight)			
	2 solid	**2** dissolved	**1**	**3**
0.08	79.0	0.8	1.1	19.1
0.5	14.0	0.9	5.3	79.8
1.0	0	1.2	8.1	90.7
2.0	0	1.4	10.1	88.5
3.0	0	1.0	9.1	89.9
4.0	0	0.6	8.9	90.5
21.5	0	0.9	10.1	89.0

Table 2
Effect of water on the composition of the **3** hydrolysis mixture [a] after reaction at 20°C for 60 min

Water (vol%)	Sulfuric acid (M)	Composition (% by weight)		
		2	**1**	**3**
9.1	0.60	3.7	70.8	25.6
16.7	0.55	3.1	83.6	13.2
23.1	0.51	3.0	89.2	7.8
28.6	0.47	1.1	92.9	6.0
33.3	0.44	1.1	93.0	5.9
37.5	0.41	1.0	93.0	6.0

[a] Starting mixture: **3**, 91.8; **1**, 7.1; **2**, 1.1%.

dissolution in 30 min was achieved with 0.66 M sulfuric acid, and this concentration was used in all subsequent experiments. All attempts to neutralize sulfuric acid prior to acetylation for GLC analysis resulted in a decreased concentration of **3**. Neutralization with dry, solid sodium carbonate gave only 82.7% of **3** compared with the 91% originally present in the mixture; the results with aqueous ammonia [18] or barium carbonate [12,15] were even less satisfactory. Any presence of water in the neutralization mixture decreases the yield of **3**. Even a slow addition of the acetalation mixture to the stirred solution of excess of potassium carbonate or hydroxide resulted in serious hydrolysis of **3** to give 51% of **1** and 47.5% of **3**. This could be the reason for the poor reproducibility of Poopeiko's experiment, where the process of neutralization is not specified [16]. Evidently, **1** is isolated as a product of partial hydrolysis of **3**, and not as a product of partial acetalation of **2**.

This experience prompted us to combine the acetonation of **2** and the subsequent hydrolysis of **3** in a one-pot procedure for the synthesis of **1**, simply by adding water to the crude sulfuric acid (0.66 M)–acetone solution containing 91% of **3**, 8% of **1**, and 1% of starting **2**. With a low content of water, hydrolysis [1] of **3** to **1** is slow and complicated by the relatively rapid consecutive conversion of **1** into **2** (Table 2). On the other hand, the final neutralization of sulfuric acid with solid sodium carbonate gave an easily separable crystalline sodium sulfate at only a lower content of water; with a higher than 1 : 2 water–acetone ratio, two layers were formed with subsequent losses of the water-soluble product **1**. The compromise [29 vol% of water (ratio 1 : 2.5)] was used for further optimization of the hydrolysis. It was soon realized that the hydrolysis is too rapid at the high concentration of sulfuric acid necessary for effective acetalation (Fig. 1a). To avoid problems with reproducibility on a large scale, a partial neutralization with sodium carbonate was used to reduce the rate and to increase the stability of **1** produced; the optimum concentration was established as 0.15 M sulfuric acid (Fig. 1b,c).

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[1] Standard hydrolysis of **3** to **1** is complicated by the poor solubility of **3** in water and by tedious removal of salts from the water-soluble product **1**; simple catalysis with a strong cation-exchanger was used in our laboratory, and addition of acetone helped with solubility problems.

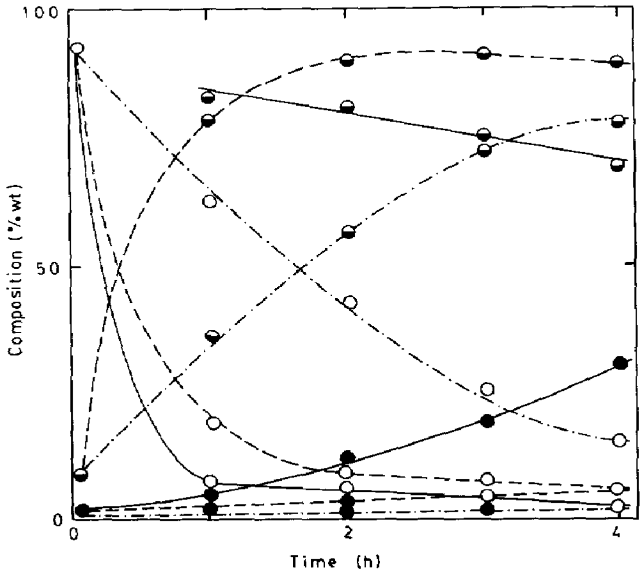

Fig. 1. Hydrolysis of crude **3** with partially neutralized sulfuric acid [a, 0.47 M (———); b, 0.15 M (- - - - - -); c, 0.03 M (·—·—·); **1** (◒), **2** (●), **3** (○)].

Under these optimized conditions, crude 1,2-*O*-isopropylidene-α-D-xylofuranose (**1**) can be easily synthesized on a large scale, and used directly for further transformations (tosylation, benzoylation, etc.). Silica gel filtration gives pure **1** in 80% yield, requiring only 5 h from D-xylose for a decagram experiment. Furthermore, this procedure results in crystalline **1**, mp 42–43°C, which has not been reported previously [17].

3. Experimental

General methods. —Optical rotations were measured on an Opton Photoelectric Precision Polarimeter 0.005 at 25°C. Melting points were determined with a Kofler apparatus and are uncorrected. Column chromatography was performed on silica gel Lachema (Brno), 100–160 μm, and TLC on Silica Gel G according to Stahl, 10–40 μm (Merck, Darmstadt). Components on TLC were visualized by spraying with 1% cerium(IV) sulfate and subsequent mineralization. Solutions were concentrated under reduced pressure with a bath temperature below 40°C.

GLC.—GLC was performed with a Hewlett–Packard 5890 A instrument equipped with a flame-ionization detector. A fused-silica capillary column (50 m × 0.31 mm i.d.) coated with crosslinked phenyl methyl silicone (5%, film thickness 0.52 μm) was used with N_2 as carrier gas at a flow rate of 103 mL/min (split 1:50). Temperature: 150°C (5 min), 4°C/min up to 180°C (10 min); detector, 230°C; injector, 200°C. The following retention times were obtained: **3**, 7.2 min; 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-xylofuranose, 12.3 min; and per-*O*-acetyl-

D-xylose, 29.4, 30.1, 31.7, and 32.3 min in the area ratios of 50:6.3:1.5:1, respectively. Acetic anhydride and pyridine (1:2) were used to derivatize **1** and **2**.

Acetalation of D-*xylose* (**2**).—D-Xylose (2.4 g, 0.016 mol) was stirred in acetone (80 mL) containing 0.37 M H_2SO_4 (1.6 mL, 96%) [16] at 20°C. The aliquots (10 mL) were filtered, undissolved D-xylose was dried and weighed, and 0.15 mL of the filtrate was added to pyridine (0.6 mL) containing Ac_2O (0.3 mL). After 6 h at 20°C, the mixture was analyzed by GLC. The results are given in Table 1.

The effect of water on the composition of the 1,2:3,5-di-O-isopropylidene-α-D-xylofuranose hydrolysis mixture.—D-Xylose (3.4 g, 0.023 mol) was acetalated with acetone (90 mL) and 0.66 M H_2SO_4 (3.4 mL, 96%) for 30 min at 20°C. The clear solution was diluted with water (9.1–37.5 vol%) and the composition of the mixture at 30-min intervals was estimated by direct acetylation and GLC as described above. Results are given in Table 2.

The effect of sulfuric acid concentration on the composition of the 1,2:3,5-di-O-isopropylidene-α-D-xylofuranose hydrolysis mixture.—D-Xylose (3.4 g, 0.023 mol) was acetalated for 30 min as described above, and the clear solution (10 mL) was diluted with 0–1.6 M Na_2CO_3 in water (4 mL) to give samples with 0.47–0.01 M H_2SO_4 in 10:4 acetone–water. The composition of the mixture was estimated as described above; the results are given in Fig. 1.

One-pot synthesis of 1,2-O-isopropylidene-α-D-xylofuranose (**1**).—Finely powdered D-xylose (10.0 g, 0.067 mol) was dissolved in acetone (260 mL) containing 0.66 M H_2SO_4 (10.0 mL, 96%) by stirring for 30 min. A solution of Na_2CO_3 (13.0 g, 0.123 mol) in water (112 ml) was carefully added under external cooling so as to keep the temperature of the mixture at 20°C, and the mixture was stirred for a further 2.5 h. Then, solid Na_2CO_3 (7.0 g, 0.066 mol) was added, Na_2SO_4 (22.3 g) was filtered off and washed with acetone, and the combined filtrates were evaporated to yield 13.8 g of crude **1** contaminated with 5% of **3**, 5% of **2**, and 8% of inorganic salts. The crude **1** was purified by silica gel filtration using 30:1 $CHCl_3$–CH_3OH, and pure **1** was obtained as a syrup (10.1 g, 80%); $[\alpha]_D^{25}$ – 21.1° (*c* 2.0, H_2O); lit. [18] $[\alpha]_D^{22}$ – 20.6° (H_2O); which crystallized on standing, and had mp 42–43°C after recrystallization from ethyl acetate–light petroleum (bp 40–60°C) at –20°C.

References

[1] S. DeBernardo, J.P. Tengi, G.J. Sasso, and M. Weigele, *J. Org. Chem.*, 50 (1985) 3457–3462.
[2] F. Matsuda and S. Terashima, *Tetrahedron*, 44 (1988) 4721–4736.
[3] A. Holý, *Collect. Czech. Chem. Commun.*, 44 (1979) 593–612.
[4] G. Gosselin, M.Ch. Bergogne, and J.L. Imbach, *Nucleic Acid Chem.*, 4 (1991) 41–45.
[5] W. Loh, U.S. Pat. 4, 429, 119 (1984).
[6] W. Loh, U.S. Pat. 4, 515, 618 (1985).
[7] J.D. Wilson, M.R. Almond, and J.L. Rideout, Eur. Pat. 295, 090 (1988).
[8] M.R. Almond, J.D. Wilson, and J.L. Rideout, U.S. Pat. 4, 916, 218 (1990).
[9] V. Nair and D.J. Emanuel, *J. Am. Chem. Soc.*, 99 (1977) 1571–1576.
[10] A.U. Rahman, J.R. Daniel, and R.L. Whistler, *J. Chem. Soc. Pak.*, 8 (1986) 397–407.

[11] S. Achab and B.C. Das, *J. Chem. Soc., Perkin Trans. 1*, (1990) 2863–2873.
[12] O. Svanberg and K. Sjöberg, *Ber.*, 56 (1923) 863–869.
[13] A.H. Haines, *Adv. Carbohydr. Chem. Biochem.*, 39 (1981) 13–70.
[14] P.A. Levene and R.S. Tipson, *J. Biol. Chem.*, 115 (1936) 731–747.
[15] K. Freudenberg and O. Svanberg, *Ber.*, 55 (1922) 3239–3242.
[16] N.E. Poopeiko, E.I. Kvasyuk, I.A. Mikhailopulo, and M.J. Lidaks, *Synthesis*, (1985) 605–609.
[17] P.A. Levene and A.L. Raymond, *J. Biol. Chem.*, 102 (1933) 317–330.
[18] B.R. Baker and R.E. Schaub, *J. Am. Chem. Soc.*, 77 (1955) 5900–5905.
[19] P.P. Singh, M.M. Gharia, F. Dasgupta, and H.C. Srivastava, *Tetrahedron Lett.*, (1977) 439–440.
[20] K. Matsumura and T. Aono, Eur. Pat. 76, 118 (1983).
[21] K. Matsumura, Eur. Pat. 139, 486 (1985).
[22] K.P. Pfaff, J. Paust, and H. Hartmann, Ger. Offen. 3, 505, 150 (1986).
[23] A.N. deBelder, *Adv. Carbohydr. Chem.*, 20 (1965) 219–302.
[24] A.N. deBelder, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 179–241.
[25] O.T. Schmidt, *Methods Carbohydr. Chem.*, 2 (1963) 318–325.