Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 340 (2005) 373–377
Carbohydrate RESEARCH

Isomerisation of aldoses in pyridine in the presence of aluminium oxide

Dag Ekeberg, Svein Morgenlie* and Yngve Stenstrøm

Department of Chemistry, Biotechnology and Food Science, Section Chemistry, Agricultural University of Norway, PO Box 5003, N-1432 Ås, Norway

Received 17 September 2004; accepted 3 December 2004
Available online 13 January 2005

Abstract—Addition of aluminium oxide to boiling pyridine solutions of D-xylose, L-arabinose, D-mannose and D-glucose strongly increased the reaction rate of the aldose–ketose transformation. The maximum content of 2-ketose was reached after less than 2 h for the aldopentoses and 3 h for the aldohexoses. D-*threo*-2-Pentulose (xylulose) was prepared from D-xylose, and isolated as its *O*-isopropylidene derivative, the yield was nearly twice that compared to that usually obtained in the classical Lobry de Bruyn–Alberda van Ekenstein transformation in pyridine.

Keywords: Aldoses; 2-Ketoses; D-*threo*-2-Pentulose; Isomerisation; Pyridine; Aluminium oxide

1. Introduction

The introduction in 1927 of pyridine both as a solvent and a base represented an important improvement of the Lobry de Bruyn–Alberda van Ekenstein aldose–ketose transformations.[1] When these reactions are carried out in alkali hydroxide solution, extensive isomerisation and retro aldol reactions occur,[2] and in addition, acids are formed. After prolonged reaction time, more than 50 compounds have been observed in the product mixture from D-glucose and aqueous calcium hydroxide.[3] Review articles of the Lobry de Bruyn–Alberda van Ekenstein reaction have been published by Speck[4] and Angyal.[5] In pyridine, the reactions occurring are limited to aldose–ketose transformations and epimerisations, and some rare or otherwise unavailable ketoses have been prepared from aldoses by isomerisation in boiling pyridine. The yields in these reactions are generally low, but much of the unreacted starting material may in several cases be recovered by crystallisation,[6–8] and yields are therefore often calculated from the amount of aldose consumed. One reason for the low yields is that the equilibrium seldom is reached due to sluggish reaction, typical reaction times reported, ranging from about 4–20 h, are often far from enough, but prolonged reaction is avoided in order to prevent extensive formation of side products. For the pentoses, an additional reason for the low yields is that the ketose:aldose ratios at equilibrium are well below one. This is due to the lower stability of the pentuloses compared to the aldopentoses, since the former cannot exist in pyranose form.[5]

In continuation of a previously reported work on aldol reactions,[9] we required D-*threo*-2-pentulose (xylulose) as a starting material. The pentulose may be prepared by several microbial and enzymatic methods, and it is, for example, formed by isomerisation of D-xylose.[4,10,11] The yields are low also in these enzyme catalysed isomerisation reactions, but despite the fact that they may be improved through stabilisation of the product through complex formation,[12] a more simple, chemical method was preferable in our case. We have some experiences with aluminium oxide in wanted, as well as in unwanted isomerisation reactions, and it has found use as a catalyst, especially in hydrocarbon isomerisations.[13,14] We therefore hoped to improve the aldose–ketose transformation in boiling pyridine of D-xylose

* Corresponding author. Tel.: +47 64 94 77 14; fax: +47 64 94 77 20; e-mail: svein.morgenlie@nlh.no

0008-6215/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2004.12.006

by the addition of aluminium oxide. Since we were encouraged by the observed results, three other common aldoses, L-arabinose, D-mannose and D-glucose, were included in the investigation.

2. Results and discussion

The presence of aluminium oxide gave a remarkable increase in the reaction rate of the aldose–ketose transformation of D-xylose in boiling pyridine. After conversion of the sugars to *O*-isopropylidene derivatives, GC–MS analysis of the reaction mixture showed the presence of *threo*-2-pentulose and small amounts of *erythro*-2-pentulose (ribulose) and lyxose, in addition to xylose. After prolonged reaction time, arabinose was also observed. The change in content of *threo*-2-pentulose with time in boiling pyridine with and without aluminium oxide is shown in Figure 1.

For preparative purposes, it was necessary to choose a way for the isolation of D-*threo*-2-pentulose. Several different methods have been reported for product isolation after aldose–ketose transformations. Oxidation of excess aldose with bromine and removal of the aldonic acid formed as a salt[15] or with anion exchange resin[6,16] is one possibility. For some aldoses, fermentation may be used for their removal from the product mixture.[17] When the ketose produced is noncrystalline, chromatography has in some cases been the preferred isolation method.[18,19] The ketoses have also been obtained via derivatives such as hydrazones[8] or isopropylidene acetals.[7] The last mentioned method seemed most attractive in the case of D-*threo*-2-pentulose. Fractional vacuum distillation has been described[7] as a method for the separation of the 2,3-*O*-isopropylidene-β-D-*threo*-2-pentulofuranose (**1**) from 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**2**), obtained on acetonation of the reaction mixture after isomerisation of D-xylose in boiling pyridine (see Scheme 1 for structures **1**–**3**). An 11.4% yield of the pentulose was reported, calculated from the amount of unrecovered xylose. Our choice for the isolation was partitioning of the isopropylidene derivatives between dichloromethane and water. The dichloromethane phase then contained compound **2** and 1,2:3,4-di-*O*-isopropylidene-β-D-*erythro*-2-pentulofuranose (**3**), whereas **1** was obtained on evaporation of the water phase in addition to some 2,3-*O*-isopropylidene-D-lyxose, which could be removed as aldonic acid after oxidation with bromine. After boiling of D-xylose in pyridine in the presence of aluminium oxide for 90 min and acetonation of the product mixture, D-*threo*-2-pentulose was obtained from compound **1** by hydrolysis in 23% yield, calculated from the starting amount of xylose. As observed for xylose, L-arabinose reacted rapidly under the same conditions, and after 60 min, the reaction mixture contained 27% *erythro*-2-pentulose, 61%

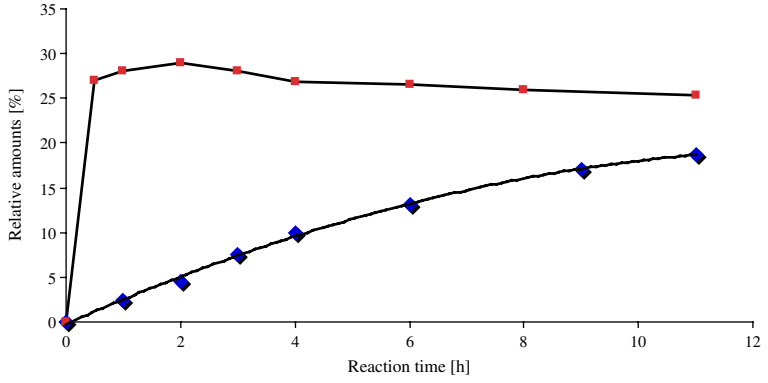
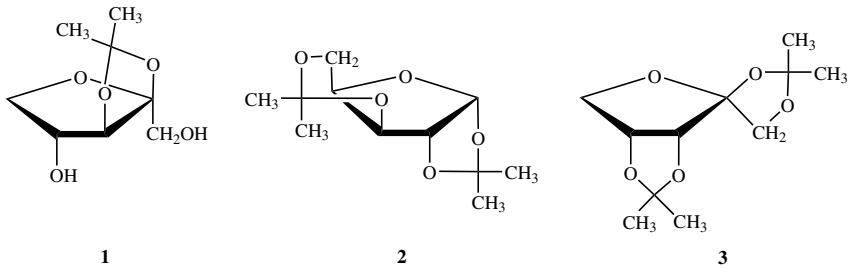


Figure 1. Change in content of *threo*-2-pentulose (xylulose) with time in a solution of xylose in boiling pyridine with –■–■–■– and without –♦–♦–♦– aluminium oxide.



1 **2** **3**

Scheme 1.

Table 1. Composition in percent in the reaction mixtures of unreacted aldopentose (A); ketose (K); 2-epimeric aldose (EA); 3-epimeric ketose (EK); and tertiary aldopentose (TA) after different reaction times in the presence of Al_2O_3

	30 min					60 min					120 min				
	A	K	EA	EK	TA	A	K	EA	EK	TA	A	K	EA	EK	TA
D-Xylose	56	27	9	7	1	52	28	10	8	2	48	29	10	10	3
L-Arabinose	67	23	6	2	2	61	27	7	3	2	57	26	9	5	3

arabinose and small amounts of ribose, *threo*-2-pentulose and xylose. In Table 1 is shown the content of the isomeric pentoses in the reaction mixtures from the two aldopentoses after 30, 60 and 120 min. The presence of aluminium oxide also had a pronounced effect on the reaction rate of the two aldohexoses, it is shown for D-mannose in Figure 2. The reaction mixture contained 50% *arabino*-2-hexulose (fructose) after 120 min. Glucose reacts at a similar speed, but the ketose content here is somewhat lower than that observed for mannose. The 2-epimeric aldose is formed from both aldohexoses, and *ribo*-2-hexulose (psicose), the 3-epimer of *arabino*-2-hexulose, is observed in small, but slowly increasing amounts The composition of the reaction mixtures from mannose and glucose after 60, 120 and 180 min is shown in Table 2.

That the product mixtures after boiling of glucose or mannose in pyridine in the presence of aluminium oxide contain almost exclusively the 2-epimeric aldoses, *arabino*-2-hexulose and small amounts of its 3-epimeric ketose is due to the stability of *arabino*-2-hexulose. From the aldopentoses, on the other hand, the less stable primarily formed 2-pentuloses undergo 3-epimerisation more easily, and both 2-pentuloses isomerise to the more stable aldopentoses. Thus, arabinose is formed in amounts of 2–3% as a tertiary product from xylose and vice versa. The same compounds are present in the reaction mixtures also when the reactions are carried out without aluminium oxide, and the shortened reaction time with aluminium oxide present results in lower amounts of secondary and tertiary products relative to the primarily formed 2-pentulose.

Anhydrous γ-Al_2O_3 and activated, neutral aluminium oxide were found to be effective in the isomerisation reactions. In some cases, however, the former caused some degradation of the sugars, and the activated form was chosen for these reactions.

It is generally agreed that the Lobry de Bruyn–Alberda van Ekenstein transformation proceeds via an enediol intermediate.[5] A possible explanation of the catalytic effect of aluminium oxide on the aldose–ketose transformation may be stabilisation of this enediol intermediate through adsorption on the aluminium oxide surface, and thereby probably lowering the energy of the rate determining transition state in the transformation.

Despite the continuously growing number of reported bacterial and enzymatic methods for the preparation of

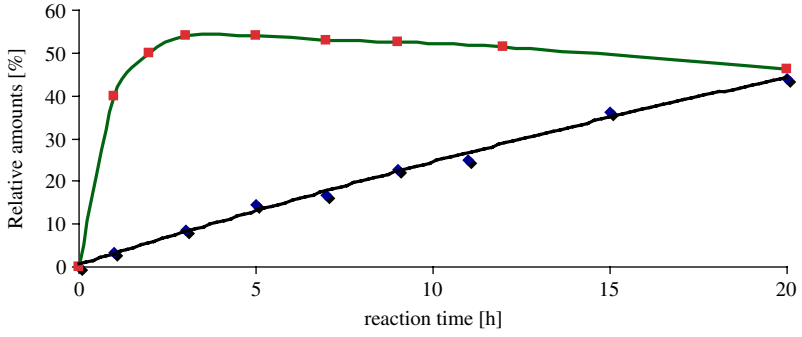


Figure 2. Change in content of *arabino*-2-hexulose (fructose) with time in a solution of mannose in boiling pyridine with –■–■–■– and without –♦–♦–♦– aluminium oxide.

Table 2. Composition in percent in the reaction mixtures of unreacted aldohexose (A); ketose (K); 2-epimeric aldose (EA) and 3-epimeric ketose (EK) after different reaction times in the presence of Al_2O_3[a]

	60 min				120 min				180 min			
	A	K	EA	EK	A	K	EA	EK	A	K	EA	EK
D-Mannose	52	40	6	2	36	50	10	4	29	54	12	5
D-Glucose	54	36	6	4	46	42	7	5	41	43	9	7

[a] Tertiary products were not observed in these reaction mixtures.

ketoses, some of these sugars are still very expensive. Thus, the need continues to exist for simple, chemical methods for their preparation. The observed improvement of the Lobry de Bruyn–Alberda van Ekenstein transformation in pyridine, obtained by the application of aluminium oxide as an additional catalyst, and resulting in increased reaction rate and a potential to achieve higher yields, should contribute to keep this simple, classical reaction still attractive as an alternative for the preparation of several ketoses.

3. Experimental

3.1. General methods

Optical rotations were measured with a Carl Zeiss Kreispolarimeter 0.01°. For TLC were used pre-coated Silica Gel G plates with 7:2:1 acetone–1-butanol–water as eluent. Spots were detected by spraying with diphenylamine-aniline-phosphoric acid[20] followed by H_2SO_4 in EtOAc and heating at 110 °C for 10 min. GC was performed with a Shimadzu GC-14B gas chromatograph, equipped with an open tubular fused silica column, 25 m × 0.32 mm ID, wall coated with CP-SIL 43 CB, programmed at 6°/min from 90 to 225 °C. For GC–MS was used a HP 6890 gas chromatograph in combination with an AutoSpec Ultima 2000 (Micromass Ltd, Manchester England) mass spectrometer with EBE geometry, operated in EI mode at 70 eV and an ion source temperature at 200 °C. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury instrument at 300 and 75 MHz, respectively. The spectra were recorded in $CDCl_3$ and in D_2O with $CHCl_3$ and Me_2SO (^{13}C NMR δ_{ref} 40.40 ppm) as internal standards, respectively.

3.2. Materials

D-*threo*-2-Pentulose[7] and L-*erythro*-2-pentulose[16] were prepared according to reported methods. The other sugars were obtained commercially. The aluminium oxide samples used were activated, neutral, Brockmann grade 1 (Merck) and anhydrous γ-Al_2O_3 (Merck). Pyridine was distilled from BaO or anhydrous Al_2O_3 and kept over KOH pellets.

3.3. Isomerisation of aldoses, analysis of product mixtures

Aldose (0.3 g) in pyridine (30 mL) was stirred at reflux temperature with neutral, activated aluminium oxide (0.2 g). Aliquots (1.5 mL) were withdrawn at intervals, and after filtration, the solvent was evaporated under reduced pressure. The residues were stirred with 2% H_2SO_4 in acetone (3 mL) for 90 min (pentoses) or with 3% H_2SO_4 in acetone (3 mL) for 2 h (hexoses). The solutions were neutralised by stirring with solid $NaHCO_3$ and subjected to GC or GC–MS for identification and quantification of aldoses[21] and ketoses.[22] The experiments were repeated without aluminium oxide.

3.4. Preparation of D-*threo*-2-pentulose

D-Xylose (4 g) in pyridine (300 mL) was boiled under vigorous stirring with neutral, activated aluminium oxide (2 g) for 90 min. After filtration, the solvent was removed under reduced pressure and the residue stirred with 2% H_2SO_4 in acetone (30 mL) for 90 min. The solution was neutralised with solid $NaHCO_3$, filtered and concentrated to a syrupy residue, which was partitioned between water (30 mL) and CH_2Cl_2 (25 mL). The water phase was extracted with CH_2Cl_2 (3 × 15 mL), and to the water solution were added $BaCO_3$ (1 g) and Br_2 (0.3 mL) to oxidise the small amounts of 2,3-*O*-isopropylidene-D-lyxose, which were present. After stirring for 90 min in the dark and removal of excess Br_2 in a stream of nitrogen, the solution was filtered and treated with Amberlite IRA 400 (HCO_3^-) ion exchange resin, then with Dowex 50 W (H^+) and finally once more with Amberlite IRA 400 (HCO_3^-) resin. Filtration and evaporation of the solvent gave syrupy, chromatographically homogeneous (GC: t_R 13.1 min, TLC: R_f 0.76) 2,3-*O*-isopropylidene-β-D-*threo*-2-pentulofuranose (**1**, 1.27 g, 25% from xylose), $[\alpha]_D^{20}$ +2 (*c* 5, acetone); lit.[7] + 2°. EIMS *m*/*z* (% rel int.): 175 (32), 159 (25), 157 (18), 130 (4), 115 (17), 101 (5), 97 (22), 71 (37), 69 (5), 59 (100), 43 (72). The spectrum was identical with that of an authentic sample. The ^1H NMR spectrum is in accordance with that reported for the racemic compound.[23] ^{13}C NMR δ : 26.1, 27.0 ($CH_3 \times 2$), 63.2 (C-1), 74.1 (C-5), 74.4 (C-4), 85.3 (C-3), 112.0, 114.0 (O–C–O × 2). Compound **1** (1.1 g) was hydrolysed in 0.1 M oxalic acid (40 mL) at 65 °C, the reaction was stopped after 5 h to prevent isomerisation of the unstable pentulose. The solution was then neutralised with Amberlite IRA 400 (HCO_3^-) resin, filtered and concentrated under reduced pressure. Extraction of the residue with CH_2Cl_2 (2 × 5 mL) to remove small amounts of remaining **1**, gave D-*threo*-2-pentulose as a syrup (0.80 g, representing 23% yield from the starting amount of xylose), $[\alpha]_D^{20}$ −30 (*c* 3, water); lit.[7] −33°. The product is indistinguishable by TLC, R_f 0.58, from an authentic sample. The ^{13}C NMR data are in accordance with those reported for the D-[24] as well as for the L-enantiomer.[25] GC after re-acetonation of a small amount of the pentulose as described above, showed the presence of **1** as single product.

References

1. Fischer, H. O. L.; Taube, G.; Baer, E. *Ber.* **1927**, *60*, 479–485.
2. El Khadem, H. S.; Ennifar, S.; Isbell, H. S. *Carbohydr. Res.* **1987**, *169*, 13–21.

3. Yang, B. Y.; Montgomery, R. *Carbohydr. Res.* **1996**, *280*, 27–45.
4. Speck, J. C., Jr. *Adv. Carbohydr. Chem.* **1958**, *13*, 63–103.
5. Angyal, S. J. *Top. Curr. Chem.* **2001**, *215*, 1–14.
6. Ennifar, S.; El Khadem, H. S. *Carbohydr. Res.* **1989**, *193*, 303–306.
7. Hough, L.; Theobald, R. S. *Methods Carbohydr. Chem.* **1962**, *1*, 94–98.
8. Barnett, J.; Reichstein, T. *Helv. Chim. Acta* **1937**, *20*, 1529–1536.
9. Ekeberg, D.; Morgenlie, S. *Carbohydr. Res.* **2004**, *339*, 2171–2176.
10. Bock, K.; Meldal, M.; Meyer, B.; Wiebe, L. *Acta Chem. Scand. B* **1983**, *37*, 101–108.
11. Häusler, H.; Stütz, A. E. *Top. Curr. Chem.* **2001**, *215*, 77–114.
12. Shao, Y. Y.; Seib, P. A.; Kramer, K. J.; Vangalen, D. A. *J. Agric. Food Chem.* **1993**, *41*, 1391–1396.
13. Panchenkov, G. M.; Korpusov, O. V.; Volokhova, G. S. *Kinet. Catal.* **1974**, *15*, 1189–1192.
14. Kozlov, N. S.; Polikarpov, V. A.; Tarasevich, V. A.; Moiseenok, L. I.; Kozlyak, M. I. *Kinet. Catal.* **1975**, *16*, 1040–1042.
15. Montgomery, E. M. *Methods Carbohydr. Chem.* **1962**, *1*, 175–176.
16. Ekeberg, D.; Morgenlie, S.; Stenstrøm, Y. *Carbohydr. Res.* **2002**, *337*, 779–786.
17. Totton, E. L.; Lardy, H. A. *Methods Carbohydr. Chem.* **1962**, *1*, 155–157.
18. Touster, O. *Methods Carbohydr. Chem.* **1962**, *1*, 98–101.
19. Linek, K.; Fedoronko, M. *Carbohydr. Res.* **1972**, *21*, 326–330.
20. Schwimmer, S.; Bevenue, A. *Science* **1956**, *123*, 543–544.
21. Morgenlie, S. *Carbohydr. Res.* **1975**, *41*, 285–289.
22. Morgenlie, S. *Carbohydr. Res.* **1980**, *80*, 215–222.
23. Morgenlie, S. *Acta Chem. Scand. B* **1987**, *41*, 745–748.
24. Angyal, S. J.; Bethell, G. S.; Cowley, D. E.; Pickles, V. A. *Aust. J. Chem.* **1976**, *29*, 1239–1247.
25. Gorshkova, R. P.; Isakov, V. V.; Kalmykova, E. N.; Ovodov, Y. S. *Carbohydr. Res.* **1995**, *268*, 249–255.