Synthetic Communications®, 43: 2452–2456, 2013
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.711882

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CONDENSATION AND DEHYDRATION REACTIONS OF L-SORBOSE IN ECOFRIENDLY MELT SYSTEMS

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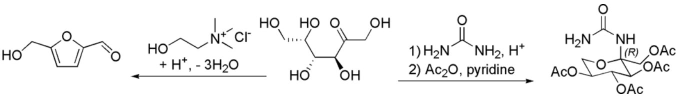
GRAPHICAL ABSTRACT



Abstract *L-Sorbose **1** was converted to 5-hydroxymethylfurfural **8** in choline chloride melts in moderate yields. A simplified synthesis of sorbosylurea tetraacetate **4** in two steps using urea melts was performed, achieving good yields.*

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Keywords 5-Hydroxymethylfurfural; low melting mixtures; L-sorbose; sorbosylurea

INTRODUCTION

In 2011, a review by Zebiri et al. criticized the fact that the use of L-sorbose in organic chemistry is exceedingly poor, and they encouraged the development of new synthetic methods.[1] For this reason, reactions of L-sorbose in the unconventional carbohydrate melts developed in our working group were examined.[2–4] Low-melting mixtures allow the conversion of biomass at high concentration into valuable intermediates.

L-Sorbose is one of the rare natural L-sugars and is mainly used as a starting material in the synthesis of vitamin C. Therefore, it is the most readily available L-sugar on a large scale.[1,5] As 5-epimer of D-fructose, its structural similarity would suggest a comparable reactivity. Both fructose and sorbose form a mixture of two pyranoid **1** and two furanoid stereoisomers **3** (plus negligible amounts of acyclic form **2**) (Scheme 1). The composition is not only strongly dependent on the solvent employed but also on the temperature.[6,7] Simple derivatization reactions with fructose often yield product mixtures.[5] In contrast to fructose, sorbose highly favors the

Received June 7, 2012.

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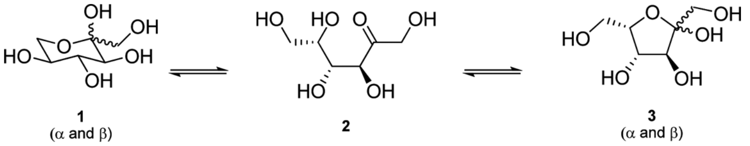


Scheme 1. Pyranose **1** and furanose **3** form and acyclic form of L-sorbose **2**.

α-pyranoid form in solution: In water, the α-pyranoid form amounts to 87–98% in a temperature range of 25–85 °C.[6] The benefit of sorbose is that reactions to pyranosid derivatives proceed in a more uniform manner and allow better yields than in the case of fructose.

We therefore investigated the reaction behavior of L-sorbose in four carbohydrate melts: urea, dimethylurea, ethylene urea, and choline chloride melts. Significant conversions were only observed in urea and choline chloride melts.

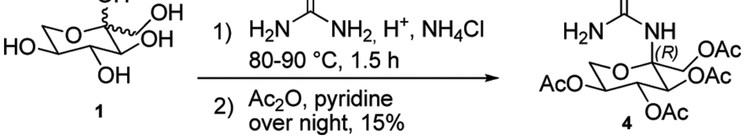
RESULTS AND DISCUSSION

From our former investigations we know that glycosyl ureas are formed in carbohydrate–urea melts.[8] L-Sorbose also forms stable melts with urea, giving a melting point of 79–80 °C.

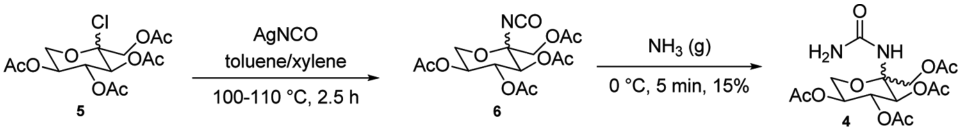
Under acidic conditions, approximately 30% of the L-sorbose were mainly converted to sorbosyl urea **4** after 1.5 h reaction time at 80 °C (estimated by ^{13}C NMR) (Scheme 2). Most of the starting material was recovered, but degradation to 5-hydroxymethyl furfural (5-HMF) and to brown humins was also observed, especially for longer reaction times and at higher temperatures. The isolated *N*-(1,3,4,5-tetra-*O*-acetyl-L-sorbopyranosyl)urea **4** has (2*R*)-configuration (α-anomer), which was ascertained by nuclear Over hauser spectrascopy (NOESY) experiments. A second fraction (approx. 67 wt% of the total yield) was an inseparable mixture presumably composed of sorbosyl acetate, the β-anomer of sorbosyl urea **4**, and the sorbosylbiuret, inferred from ^{13}C NMR spectra and electrospray ionization–mass spectrometry (ESI-MS) measurements.

The synthesis of the peracetylated derivative **4** was reported by Tokuyama and Katsuhara in 1966 (Scheme 3).[9] They obtained the peracetylated sorbosyl urea **4** (α -anomer and β-anomer in 15% yield each) by immediate ammonolysis of the isocyanate **6** starting from 1,3,4,5-tetra-*O*-acetyl-L-sorbopyranosyl chloride **5**.

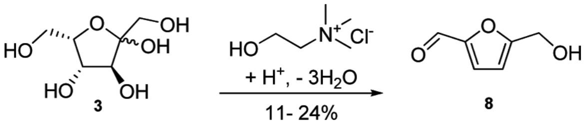
Comparing the overall yields of both methods starting from unmodified L-sorbose, the synthesis in the melt yielded 15% of product **4** over two steps while



Scheme 2. Synthesis of *N*-(1,3,4,5-tetra-*O*-acetyl-L-sorbopyranosyl)urea **4** in sorbose–urea melts under acidic conditions.



Scheme 3. Synthesis of *N*-(1,3,4,5-tetra-*O*-acetyl-L-sorbopyranosyl)urea **4** according to Tokuyama and Katsuhara.[9]



Scheme 4. Synthesis of HMF **8** from L-sorbose **3** in a choline chloride melt.

the four-step procedure of Tokuyama *et al.* provided an overall yield of 6%. According to that publication, the transformation to the chloride **5** was performed in 32% yield and the direct reaction via the isocyanate **6** afforded both anomers in 30% yield. As no yield was given for the acetylation of L-sorbose, it was assumed that the reaction proceeded with a maximum yield of 65%.[10]

Our previous investigations showed that choline chloride melts promote the production of 5-HMF **8** from carbohydrates.[11] The production of 5-HMF **8** from L-sorbose has already been patented in 1948 by Haworth (yield: 27%)[12] and was later investigated in organic solvents catalyzed by lanthanide(III) ions (61.4%),[13] in DMA-LiCl and dimethylsulfoxide (DMSO) by Binder et al. (37–60%),[14] and subcritical water by Asghari et al. (50%).[15] Other reaction conditions to make 5-HMF **8** from different sugars were recently reviewed.[16,17]

As expected, the only product from a choline chloride–sorbose melts was 5-HMF **8** (Scheme 4). After 1.5 h at 80 °C under acidic conditions using Amberlyst 15 as catalyst, the starting material was completely consumed and 24% of 5-HMF was obtained.

Under the same reaction conditions used by Ilgen et al. (100 °C, 0.5 h, 10% *p*-TsOH),[11] L-sorbose yielded only 11% of 5-HMF while 67% were obtained starting from D-fructose. The lower 5-HMF yields starting from L-sorbose were previously observed by Seri et al.[13] and Asghari et al.[15] They suggested that the different configurations of the hydroxyl groups at the C-3 and the C-4 atom in L-sorbose impair the dehydration reaction, leading to lower yields.

CONCLUSION

In summary, new reactions of L-sorbose were investigated using low melting carbohydrate mixtures as an ecofriendly reaction medium. We showed that the important intermediate 5-HMF can be produced from L-sorbose in choline chloride melts under acidic conditions.

Furthermore, a new, time-saving synthesis of sorbosylurea tetraacetate **4** is reported here. Using urea melts, we successfully simplified the literature four-step synthetic route to a two-step procedure starting from unprotected L-sorbose, without the need for expensive reagents and inconvenient reaction conditions. For the first time, the structure of the selectively formed α-pyranose form was proven by two-dimensional NMR techniques. We introduced two new solvent-free systems here based on nontoxic and renewable resources for the conversion of L-sorbose.

EXPERIMENTAL

L-Sorbose (0.6 g, 3.3 mmol), urea (1.4 g, 26.7 mmol), and NH_4Cl (0.2 g, 3.7 mmol) were heated in a 10-mL reaction flask at 80 °C until a clear melt was formed. Amberlyst 15 (150 mg) was added, and the reaction was stirred for 1.5 h at that temperature. Methanol was added, solids were filtered off, and the solvent evaporated. Then, 6 mL (5.8 g, 74.3 mmol) of pyridine and 3.5 mL of Ac_2O (3.8 g, 37.0 mmol) were added to the mixture, and the mixture was first stirred for 1 h in the ultrasounic bath and then overnight at room temperature without sonication. The reaction was stopped by pouring the solution into saturated $NaHCO_3$ solution. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed twice with 2N HCl and twice with water, dried over $MgSO_4$, and evaporated. The pure product was crystallized from ethyl acetate, affording a colorless powder (0.215 g, 0.55 mmol, 16%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.02, 2.04, 2.08, 2.10 (s, 12 H, OAc), 3.75 (dd, 1 H, H-6), 4.01 (dd, 1H, ^3J(H-5, H-6′) = 5.91 Hz, H-6′), 4.03 (dd, 1H, ^2J(H-1, H-1′) = 12.36 Hz, 166.24 Hz, H-1), 4.58 (dd, J_1 = 12.33 Hz, J_2 = 166.24 Hz, 1H, H-1′), 5.00–5.09 (m, 1H, H-5), 5.24–5.40 (m, 5H, H-3, H-4, urea); ^{13}C NMR (75 Hz, $CDCl_3$): δ (ppm) = 20.5, 20.6, 20.5, 20.7 (CH_3-Ac), 59.9 (C-5), 62.0 (C-1), 68.3 (C-4), 69.0 (C-5), 70.4 (C-3), 85.3 (C-2), 156.6 (urea), 168.6, 169.8, 170.1, 170.2 (C=O, Ac).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.01, 2.04, 2.07, 2.10 (4 × s, 4 × 3H, OAc), 3.74 [“dd”, ^2J(H-6^{ax}, H-6^{eq}) = 10.98 Hz, ^3J(H-6^{ax}, H-5) = 10.98 Hz, 1 H, H-6^{ax}], 4.00 [dd, ^3J(H-5, H-6′) = 5.91 Hz, ^2J(H-6^{ax}, H-6^{eq}) = 11.07 Hz, 1H, H-6^{eq}], 4.04 [d, 1H, ^{2}J(H-1, H-1′) = 12.37 Hz, H-1], 4.58 [d, ^2J(H-1, H-1′) = 12.37 Hz, 1H, H-1′], 5.02–5.06 (m, 1H, H-5), 5.26 [d, ^3J(H-3, H-4) = 9.87 Hz, 1H, H-3], 5.35–5.38 (m, 2H, H-4, urea); ^{13}CNMR (75 Hz, $CDCl_3$): δ (ppm) = 20.5, 20.6, 20.6, 20.7 (CH_3-Ac), 59.8 (C-5), 62.0 (C-1), 68.3 (C-4), 69.0 (C-5), 70.4 (C-3), 85.3 (C-2), 156.7 (urea), 168.6, 169.8, 170.1, 170.2 (C=O, Ac); FT-IR (ATR): ν (cm^{-1}) = 3487, 3458, 3341, 1753, 1744, 1697, 1665, 1620, 1614, 1591, 1564, 1547, 1535, 1441, 1433, 1377, 1371, 1275, 1229, 1211, 1138, 1103, 1061, 1032, 908; mp: 192 °C. ESI-MS: m/z (%) = 407.9 (MNH_4^+, 100), 431.9 (MH^+ + MeCN, 37), 390.9 (MH^+, 15).$[\alpha]_D^{20} = -37.395$ (c 1.000, chloroform) (α-anomer) (literature[9]: $[\alpha]_D^{23.5} = -34.4$ (c 0.973, chloroform).

SUPPORTING INFORMATION

General experimental information, NOE spectrum of compound **7**, and synthesis of HMF from sorbose can be found via the Supplementary Content section of this article’s web page.

ACKNOWLEDGMENTS

We thank the Suedzucker AG and the Fachagentur fuer Nachwachsende Rohstoffe for financially supporting this project.

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