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Isomerization as a route to rare ketoses: the beneficial effect of microwave irradiation on Mo(VI)-catalyzed stereospecific rearrangement

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Abstract—Mo(VI)-catalyzed isomerization of easily accessible 2-*C*-(hydroxymethyl)-branched aldoses to rare ketoses was achieved in 3 min using microwave flash heating. This contribution highlights the remarkable advantages of Mo(VI) catalysis and the beneficial effects of microwave irradiation in carbohydrate synthesis. The transformation yielded the respective ketoses in good yields (46–86%). Furthermore, the potential of the Mo(VI)-catalyzed transformation was studied using a new branched 6-deoxy-aldose to prepare 7-deoxy-L-*gluco*-heptulose. The method is fast and useful for the preparation of rare ketoses under microwave conditions.

1. Introduction

Saccharides are a highly abundant class of compounds that play a broad range of roles in biochemistry. They often serve as essential biosynthetic precursors or structural elements. They have also found application as chemical intermediates,[1] biological probes,[2] pharmaceuticals, etc. Especially higher carbon saccharides have been attracting increasing attention due to the fact that they can be used as non-metabolized analogues of oligosaccharides or components of antibiotics.[3,4] The importance of these compounds is evident and is reflected in numerous papers in the area of carbohydrate synthesis. Stereocontrolled carbon–carbon bond formations are useful methods in synthesizing complex compounds, including carbohydrates. One of the most important methods of carbohydrate transformation is the conversion of sugars into their valuable epimers or isomers. Several enzymatic methods towards the preparation of higher carbon sugars have been developed.[5,6] Such enzymatic syntheses are stereospecific, but they are often very laborious. Thus, there is a need for simple, general and convenient methodologies for the stereocontrolled construction of C–C bonds in carbohydrate molecules. The rearrangement reactions have become very useful for this purpose. Their mechanism usually involves a highly organized transition state that directs the stereochemical course of the reaction and enables the simultaneous formation of new compounds in a single step. Microwave irradiation as a non-conventional energy source has a strong influence on the course of the reaction as well. Spectacular accelerations, higher yields under milder reaction conditions and higher product purities have been reported.[7]

In continuation of our research on the Mo(VI)-catalyzed rearrangement of reducing saccharides, we expanded our study to microwave-assisted isomerization reactions. Recently, we have reported the preliminary results of a beneficial effect of a microwave field on the epimerization of aldoses catalyzed by molybdate ions.[8] Herein, we report the potential of microwave irradiation on the isomerization of several branched chain aldoses to less common carbohydrates. We describe the improved method of microwave-accelerated synthesis of some rare ketoses and test the possibility of the preparation of deoxy-ketoses using this approach. The benefits associated with the effect of microwave irradiation in this type of stereospecific rearrangement are also discussed.

2. Results and discussion

2-*C*-(Hydroxymethyl)-branched aldoses with the C-2, C-3 *erythro* configuration are easily accessible via the base

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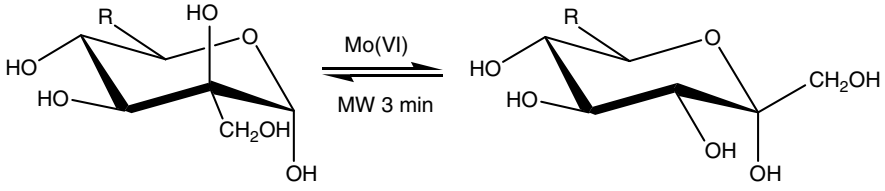
catalyzed aldolization of their 2,3-*O*-isopropylidene derivatives with formaldehyde. Treatment of an aqueous solution of 2-*C*-(hydroxymethyl)-branched aldose, with a catalytic amount of molybdic acid in a microwave field, afforded the thermodynamic equilibrium mixture of the starting aldose and corresponding 2-ketose in very short reaction time (Scheme 1). It was observed that the reaction proceeded efficiently with very good yields and the reaction rates were dramatically enhanced. The same reaction under conventional conditions (80–85 °C) took 5–8 h to afford comparable yields.

The rate enhancement under microwave irradiation may be attributed to the absorption of more energy by the polar media, which generates sufficient heat energy to promote the reaction. Microwave thermal effects originate from dielectric heating as the consequence of intermolecular friction and collisions. These phenomena result from the polarization in molecules due to dipole–dipole interactions between polar molecules and the electromagnetic field. As water and alcohols are polar molecules, having high dielectric losses, carbohydrates as polyhydroxy compounds dissolved in water are suitable chemical systems for microwave irradiation. Consequently, the high demands in activation energy of the isomerization process can be completed in a very short reaction time in the carbohydrates studied. Furthermore, the rate of the transformation increased in line with the microwave power and optimal conditions were found at 700 W. The scope and generality of this transformation is illustrated on various 2-*C*-(hydroxymethyl)-branched aldoses (Table 1). The results presented in Table 1 show the Mo(VI)-catalyzed isomerization of branched aldoses to 2-ketoses in both cases, conventional heating and heating in microwave field.[9] The yields of products obtained by oil-bath heating in previous studies (except of compound II)[10–13] are presented in column 6, the microwave data (this work) are shown in column 4. The comparison of these results clearly shows that microwave irradiation markedly accelerates the isomerization process and that the microwave field also caused the differences in the equilibration of reaction mixtures. As indicated from the data in Table 1, the effect of microwave irradiation increases the yields of 2-ketoses up to 15%, but the beneficial effect of microwaves is significant, mainly from the reaction kinetics point of view. The reaction time decreased from hours to minutes, which is up to 160-fold shorter than in the case of conventional oil-bath heating, and, at the same time, obtaining better yield.

The transformation studies involves the formation of molybdate complexes of corresponding reducing saccharides. The molybdate ions can form highly reactive, catalytically active complexes that promote an unique stereospecific rearrangement of the saccharide carbon skeleton.[14,15] Effective, stereospecific transformations occur in the case of 2-*C*-(hydroxymethyl)-branched aldoses with C-2–C-3 bond cleavage and transposition.[16,17] The transformation proceeds via acyclic dimolybdate–saccharide complexes (Scheme 2). The formation of the dimolybdate complex with the carbonyl-oxygen atom C-1 and the adjacent three hydroxylic oxygen atoms at C-2, C-3 and C-4 of the 2-*C*-(hydroxymethyl)-branched aldose (Scheme 2A), leads to the transition state, (Scheme 2B) in which a branched saccharide functions as a bidentate ligand bound to the metal centre. The design of the ligand is a key issue for the catalytic process. The critical C-2–C-3 and new C-1–C-3 bond is formed stereospecifically. Dissociation of the complex produces either the starting 2-*C*-(hydroxymethyl)-branched aldose or the isomeric 2-ketose (Scheme 2C) generated by the stereospecific rearrangement. The thermodynamic equilibrium favours, in this case, the 2-ketoses. This deduction was confirmed by the NMR experiments in the detailed study of the mechanism of this transformation with ^{13}C-enriched saccharides.[16,17]

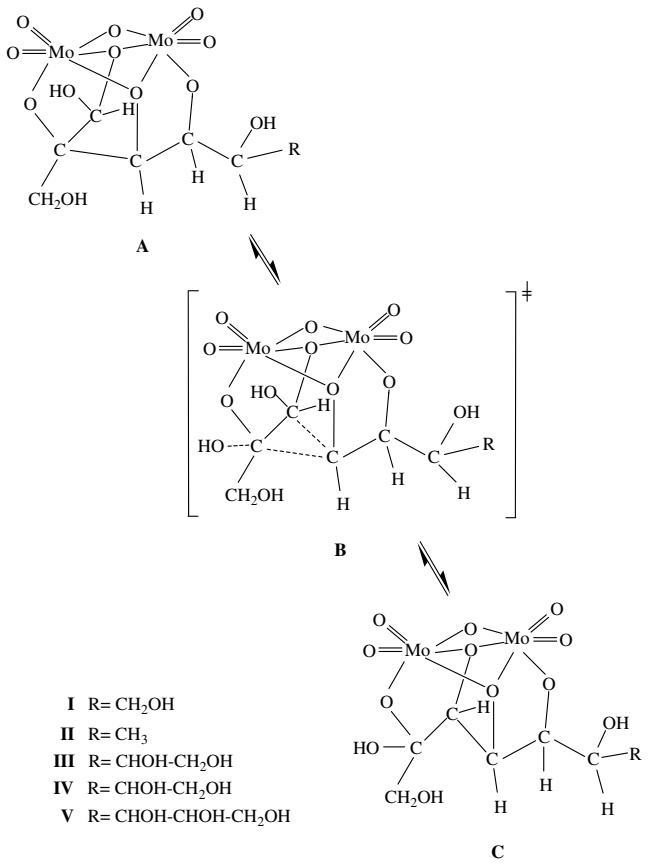
The results presented suggest that the ability of molybdate ions to form catalytically active complexes with 2-*C*-(hydroxymethyl)-branched sugars to promote the isomerization process during microwave irradiation is maintained, and even improved upon. Fast complex formation, subsequent intramolecular rearrangement and the release of the product 2-ketoses from the dimolybdate complex



Scheme 1.

Table 1. Mo(VI)-catalyzed isomerizations of reducing saccharides under conventional heating and microwave irradiation

	2-*C*-(Hydroxymethyl)-branched aldose	Product 2-ketose	MW field		Conventional heating	
			Time (min)	Yield (%)	Time (min)	Yield (%)
I	2-*C*-Gulose	IdoHeptulose	3	86	420	83
II	2-*C*-Rhamnose	7-Deoxy-GlucoHeptulose	3	85	360	77
III	2-*C*-Guloheptose	IdoOctulose	3	46	480	40
IV	2-*C*-Taloheptose	GalactoOctulose	3	65	360	59
V	2-*C*-Mannooctose	GlucoNonulose	3	76	300	61



Scheme 2.

resulted in good yields (46–86%). Moreover, the problems with partial decomposition of less stable compounds[11,12] have been conveniently overcome by the use of microwave irradiation. Microwave chemistry, thus, opens up new possibilities for modifying the reactions with relatively demanding transition states.

Previous studies indicated that aldoses, as well as some deoxy aldoses, namely 5-deoxy-L-arabinose, 6-deoxy-L-talose and 7-deoxy-L-*galacto*-heptose, epimerized in a mild acidic solution of molybdic acid.[15] Similarly, branched chain aldoses also isomerized to their counterparts, 2-ketoses. To verify whether this transformation could be also used in the preparation of deoxy-ketoses, we tested the synthesis of 7-deoxy-L-*gluco*-heptulose. To the best of our knowledge, this compound has not yet been prepared synthetically. A new model compound, 2-*C*-(hydroxymethyl)-L-rhamnose, was prepared to study the details of the isomerization mechanism. L-Rhamnose was acetonated with 2,2-dimethoxypropane to give 2,3-*O*-isopropylidene-L-rhamnopyranose **1**. The introduction of a hydroxymethyl group at C-2 was provided by alkali-based addition of 2,3-*O*-isopropylidene-L-rhamnose to formaldehyde, yielding new 2-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-β-L-rhamnopyranose **2**. Subsequent removal of the isopropylidene groups by acid hydrolysis gave a new compound 2-*C*-(hydroxymethyl)-L-rhamnose **3**. The structures of these branched sugars were fully characterized by NMR and MS spectroscopy. Complexation of **3** proceeds through the catalytically active dimolybdate complex which requires four hydroxyl groups (C-1, C-2, C-3 and C-4) of the acyclic hydrated form. We also observed that this transformation proceeds very efficiently yielding (85%) the desired 7-deoxy-L-*gluco*-heptulose **4**. The structure of **4** in aqueous solution was analyzed by 1D and 2D NMR spectroscopy and MS spectrometry.

A comparative study of the progressive isomerization under classical and microwave-assisted conditions showed the potential advantage of this approach. We have shown that microwave irradiation plays an important role in Mo(VI)-catalyzed isomerizations. The isomerization reaction is suitable for preparative purposes, because the isomers can be very effectively separated by chromatography.[9] This approach should provide access to useful alternatives in chemical synthesis of rare carbohydrates. Further applications of this developed route are currently under investigation.

3. Conclusions

We have demonstrated a facile procedure for the direct conversion of 2-*C*-(hydroxymethyl)-branched aldoses to higher ketoses using the effect of catalyst and microwave field. The method was tested on the preparation of D-*ido*-heptulose, 7-deoxy-L-*gluco*-heptulose, D-*glycero*-D-*ido*-octulose, D-*glycero*-L-*galacto*-octulose and D-*erythro*-L-*gluco*-nonulose. Examples of chemical reactions producing higher yields in dramatically shorter reaction times using the beneficial effect of microwave energy compared to traditional methods are presented. The method is universal and leads to rare sugars in a single step. Application of this methodology greatly reduces the required effort in the synthesis of rare carbohydrates.

4. Experimental

4.1. General experimental methods

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (300 MHz) and Varian Unity 600 (600 MHz) spectrometer. The experiments were carried out in aqueous solution at 40 °C and in acetone at 25 °C. The chemical shifts were referenced to internal TSP (D_2O) and TMS (acetone). Presaturation of the residual HDO resonance was achieved by low-power irradiation and typically 8–16 scans were collected to achieve a good signal/noise ratio in the one-dimensional spectra. A 5 mm QNP probe was used for the measurements of the 1D ^{13}C NMR spectra. Two-dimensional techniques (2D), COSY, HMBC and HSQC were used to determine the ^{1}H and ^{13}C chemical shifts; the 2D HSQC experiment was performed in a phase-sensitive pure-absorption mode.

Optical rotations were determined with an automatic polarimeter Perkin–Elmer Model 141 using a 10 cm, 1-mL cell. Experiments were conducted using domestic microwave oven producing continuous irradiation at 2450 MHz. HRMS (high-resolution mass spectra) were ta-

ken with a MALDI-TOF-MS; R_f values were obtained using thin layer chromatography (TLC) on silica gel glass plates (Merck $60F_{254}$) with the indicated solvent mixture. Detection was effected by spraying the chromatograms with 10% ethanolic sulfuric acid and heating them to 100 °C. Flash column chromatography was performed with silica gel (40–100 μm, Merck). Separations of the free sugars were accomplished by column chromatography on a Dowex 50W X8 resin (Sigma–Aldrich) in the Ba^{2+} form (200–400 mesh). Paper chromatography (PC) was performed by the descending method on the Whatman No. 1 paper using ethyl acetate–pyridine–water (8:2:1) as the mobile phase. The chromatograms were made visible by means of alkaline silver nitrate. All concentrations were carried out under reduced pressure at a bath temperature not exceeding 50 °C. *Caution*! Suitable precautions should always be taken with reactions carried out in closed vessels due to the risk of explosion.

4.2. 2,3-*O*-Isopropylidene-L-rhamnnopyranose 1

The reaction mixture of L-rhamnose monohydrate (1 g; 5.5 mmol), 1,2-dimethoxyethane (50 mL), toluene-4-sulphonic acid monohydrate (100 mg) and 2,2-dimethoxypropane (6.8 mL; 55 mmol) was stirred for 6 h. Then Drierite (1 g) was added and stirring continued at room temperature overnight until the disappearance of the starting material on TLC solvent A (3:1 ethyl acetate–hexane). The reaction mixture was neutralized by the addition of sodium carbonate. The neutral mixture was filtered, washed with methanol and evaporated. A syrupy isopropylidene derivative was purified by flash-chromatography on silica gel (solvent A). TLC indicated one major product **1** isolated as syrup. Yield 0.73 g (65%); $R_f = 0.55$ (solvent A); $[\alpha]_D^{20} = -11.0$ (*c* 1, acetone); δ_C (acetone-d_6, 75.45 MHz): 113.55 (2,3-*C*Me$_2$β), 113.03 (2,3-*C*Me$_2$α), 103.03 (C-1β), 94.87 (C-1α), 87.95 (C-2β), 86.15 (C-4β), 82.24 (C-3β), 80.31 (C-3α), 79.09 (C-2α), 76.53 (C-4α), 69.07 (C-5α), 67.76 (C-5β), 22.75 (C-6β), 19.72 (C-6α); HRMS *m*/*z* calcd for $C_9H_{16}O_5$ 204.2203. Found 227.2187 $[M+Na]^+$.

4.3. 2-*C*-(Hydroxymethyl)-2,3-*O*-isopropylidene-β-L-rhamnopyranose 2

A reaction mixture of **1** (1 g; 4.9 mmol), potassium carbonate (0.8 g) methanol (15 mL) and 37% aqueous solution of formaldehyde (15 mL; 147 mmol) was refluxed under an argon atmosphere at 85 °C for 48 h until the disappearance of **1** on TLC solvent B (6:1 ethyl acetate–hexane). The reaction mixture was neutralized with 10% aqueous sulfuric acid and evaporated. Extraction with chloroform (4 × 30 mL) gave a combined fraction that was dried over anhydrous $MgSO_4$ overnight. Evaporated syrupy **2** was purified by column chromatography on silica gel (solvent B). TLC indicated one major product **2** isolated as a syrup. Yield 0.81 g (70.4%); $R_f = 0.44$ (solvent B); $[\alpha]_D^{20} = -18.0$ (*c* 1, Ac); δ_C (acetone-d_6, 75.45 MHz): 114.78 (2,3-*C*Me$_2$) 105.42 (C-1), 99.51 (C-2), 86.47 (C-3), 84.94 (C-4), 69.52 (*C*H$_2$(C-2)). 66.64 (C-5), 15.54 (C-6); HRMS *m*/*z* calcd for $C_{10}H_{18}O_6$ 234.2463. Found 257.2443 $[M+Na]^+$.

4.4. 2-*C*-(Hydroxymethyl)-L-rhamnopyranose 3

A mixture of **2** (0.35 g; 1.5 mmol), water (10 mL) and Dowex 50W X4 resin in the H^+ form (5 mL) was stirred at 75 °C for 5 h. The resin was filtered off, and the combined filtrate was purified with charcoal and evaporated to afford syrupy **3**. Yield 0.28 g (96.5%); $[\alpha]_D^{20} = -12.0$ (*c* 1, H_2O) (24 h); δ_C (D_2O, 75.45 MHz): 96.76 (C-1β), 96.52 (C-1α), 78.28 (C-2β), 77.89 (C-2α), 75.62 (C-4α,β), 74.42 (C-3α), 74.32 (C-5α), 73.72 (C-3β), 70.41 (C-5β), 66.23 (*C*H$_2$(C-2)β), 62.97 (*C*H$_2$(C-2)α), 20.07 (C-6αβ); HRMS *m*/*z* calcd for $C_7H_{14}O_6$ 194.1825. Found 217.1805 $[M+Na]^+$; 233.2805 $[M+K]^+$.

4.5. 7-Deoxy-α-L-*gluco*-Hept-2-ulose 4

(A) A mixture of branched-chain aldose **3** (150 mg; 0.77 mmol) was dissolved in D_2O (10 mL) and molybdic acid (20 mg; 0.12 mmol) was added. The reaction mixture was exposed to microwave irradiation for 3 min. The reaction mixture was worked up as in the typical procedure.[9] The syrupy residue containing an equilibrium mixture of two sugars was applied on a column (1.5 cm × 95 cm) of Dowex 50W X8 in the Ba^{2+} form and eluted with water at a flow rate of 5 mL/h. Fraction **1** contained chromatographically pure title compound 7-deoxy-L-*gluco*-heptulose. Yield 127 mg (84, 7%); $[\alpha]_D^{20} = -40.0 \rightarrow -38.0$ (*c* 1, H_2O) (24 h); δ_C (D_2O, 75.45 MHz): 98.22 (C-2) 76.05 (C-5), 74.37 (C-4), 71.56 (C-3), 69.15 (C-6), 64.55 (C-1), 17.65 (C-7); HRMS *m*/*z* calcd for $C_7H_{14}O_6$ 194.1825. Found 217.1807 $[M+Na]^+$; 233.2808 $[M+K]^+$. Fraction **2** contained 7-deoxy-L-*gluco*-heptulose with admixture of 2-*C*-(hydroxymethyl)-L-rhamnose (15 mg, 10%). Fraction **3** contained chromatographically pure starting compound, 2-*C*-(hydroxymethyl)-L-rhamnose (5 mg, 3%); $[\alpha]_D^{20} = -11.0$ (*c* 1, H_2O) (24 h).

(B) A mixture of **3** (0.15 g) and 0.2% aqueous solution of molybdic acid (10 mL) was heated at 85 °C for 6 h. The composition of the reaction mixture was examined by ^1H NMR spectroscopy until the equilibrium mixture was reached. The reaction mixture was worked up as mentioned in the typical procedure.[9] Fractionization of the syrupy residue afforded 7-deoxy-L-*gluco*-heptulose (115 mg, 76.6%) as a mixture of both sugars (17 mg, 11%) and 2-*C*-(hydroxymethyl)-L-rhamnose (10 mg, 6.6%).

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9. *Typical procedure:* An aqueous solution of 2-*C*-(hydroxymethyl) branched aldose (1 equiv) and molybdic acid (0.1 equiv) was exposed to microwave irradiation using a microwave oven operated at 700 W for an appropriate time (Table 1). Samples (0.5 mL) were taken at selected intervals (0.5, 1, 2, 3, 4, 5 min), treated with Amberlite IRA-400 in the HCO_3^- form (3 mL) to remove the catalyst. The composition of the reaction mixture was determined by ^1H NMR spectroscopy to determine the ratio of sugars present in equilibrium mixture. Upon the completion of the isomerization, the rest of the reaction mixture was cooled to room temperature and treated batch-wise with an excess of the ion-exchange resin, filtered off, washed with water and combined filtrates were evaporated. The syrupy residue was fractionated by column chromatography on Dowex 50W X8 in Ba^{2+} form with water as eluent. Fractionization of the syrupy residue afforded the desired 2-ketose and starting 2-*C*-(hydroxymethyl)branched aldose.
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