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Note

The effect of microwave irradiation on Mo(VI) catalyzed transformations of reducing saccharides

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Abstract—Efficient microwave-assisted Mo(VI)-catalyzed transformations of the 10 most common aldoses are described. Both pentoses and hexoses were converted to the corresponding epimers in considerably shorter reaction times. The yields were comparable, or better compared to conventional synthetic methods.

Keywords: Microwave; Isomerization; Saccharide; Mo(VI)-catalysis; Aldose/epialdose; Ketose/2-*C*-branched aldose

Microwave activations have been employed to accelerate various organic reactions, including alkylations, nucleophilic substitutions, condensations, cycloadditions, protection and deprotection reactions with the advantages of optimal use of material and energy, short reaction times, high stereoselectivity and increased yields compared to conventional methods.[1,2] In particular this approach has opened-up the possibility of optimizing chemical reactions where equilibria were reached in a very short time.

We have previously reported convenient synthetic methods for the preparation of some rare carbohydrates.[3–6] The approach was based on molybdic acid-catalyzed reactions[7] and showed that the application of a catalytic amount of molybdate ions significantly simplified the synthesis of these compounds.[4,5] The typical feature of Mo(VI)-catalyzed interconversions of reducing sugars is both high stereoselectivity and yield. We now further examine methodologies to optimize the reaction conditions. The knowledge of structure of Mo(VI) complexes[8–11] and mechanism of isomerization of aldose/epialdose[12] and 2-ketose/2-*C*-(hydroxymethyl)branched aldose[3,4] lead us to the idea that microwave irradiation might have a considerable effect on Mo(VI)-catalyzed saccharide transformations. The present investigation is thus devoted to examining the effect of microwave irradiation on the Bílik reaction in which Mo(VI) complexes play a crucial role in isomerization of reducing sugars.

A series of monosaccharides were isomerized in aqueous media with catalytic amounts of molybdic acid under the influence of microwave irradiation. These substrates were chosen to allow the comparison of microwave-assisted reactions with conventionally heated reactions, with respect to stereo/chemoselectivity as well as isomerization processes. The reactions were performed under standardized reaction conditions to permit the rigorous comparison of results and are summarized in Table 1.

Table 1 shows the results of Mo(VI)-catalyzed isomerization of aldoses under both conventional and microwave heating. The comparison of equilibrium mixtures obtained by conventional and microwave heating shows that microwave irradiation markedly accelerated the isomerization process and resulted in different equilibria of the products.

Applying microwave irradiation of moderate power and using a catalytic amount of molybdic acid resulted in the reaction time decreasing from hours to minutes, that is 60- to 200-fold shorter than with conventional oil-bath heating. At the same time, improved yields were

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Table 1. Compositions of reaction mixtures of aldoses/epialdoses obtained by Mo(VI)-catalyzed isomerizations under conventional heating and microwave irradiation[g]

Aldose	Conventional heating[a]			MW filed[b]		
	Epialdose	Time (min)	Aldose/epialdose	Time (min)	Aldose/epialdose	Yield[h] (%) aldose/epialdose
Ara	Rib	360	2:1[c]	3	2:1	65/30
Rib	Ara	360	1:2[c]	3	1:1	47/45
Xyl	Lyx	360	1.4:1[c]	3	1.9:1	62/31
Lyx	Xyl	360	1:1.4[c]	3	1:1.9	30/63
Glc	Man	180	3:1[d]	3	2.5:1	69/27
Man	Glc	180	1:3[d]	3	1:2.5	27/65
Gal	Tal	600	4:1[e]	3	3.2:1	73/22
Tal	Gal	600	1:4[e]	3	1.4:1	53/40
Allo	Altro	180	1.5:1[f]	3	1.2:1	50/42
Altro	Allo	180	1:1.5[f]	3	2.8:1	70/24

[a] Heating was carried out by conventional method.

[b] Heating was carried out by microwave irradiation.

[c] Ref. 13.

[d] Ref. 7.

[e] Ref. 14.

[f] Ref. 15.

[g] Reactions were performed in Pyrex tubes essentially following the literature procedures.

[h] Semi-preparative scale.

obtained for instance in the D-Gal/D-Tal conversion. The microwave-enhanced Mo(VI)-catalyzed transformation of aldoses occurred with full stereospecificity resulting in the formation of the corresponding epialdose. The catalytic system survived microwave irradiation and conversion was achieved in a few minutes in higher yields.

Microwave thermal effects originate from dielectric heating as the consequence of intermolecular friction and collisions. The latter phenomena result from 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 dissolved in water are suitable systems for microwave irradiation and, consequently, the reaction rate increased considerably. On the other hand, two heating techniques yielded different ratios of stereoisomers. So, there must be some difference in the susceptibility of the transition state of the two stereoisomers to microwave heating. This would be caused by differences in dipole moment or polarizability of the complex in the transition states. However, details of the latter mechanism are not clear and would require thorough theoretical study.

The comparative study of the progress of aldose/epialdose isomerization under classical and microwave-assisted conditions has shown the potential advantage of this approach. There are also differences in the composition of the reaction products. The equilibria were shifted to the aldose with the lower value of conformational instability (e.g., during D-Glc/D-Man interconversion, a larger amount of D-glucose was present). Under classical conditions, the equilibrium mixture of two isomeric saccharides was obtained in 3–10 h. The ratio of aldose and epialdose at equilibrium was the same regardless of the starting sugar. The microwave-assisted isomerization reached thermodynamic equilibrium after 2–3 min. However, the true thermodynamic equilibrium was not reached in several cases, because the prolonged microwave irradiation (more than 10 min) led to the decomposition of saccharides.

In both cases the reaction equilibrium was shifted to the saccharide with the lower value of conformational instability, but the yield of the corresponding epialdose was different. The results suggest that the ability of molybdate ions to form complexes with reducing sugars and promote the isomerization processes during microwave irradiation are maintained and improved. Fast complex formation, subsequent intramolecular rearrangements and release of the epialdoses from the molybdate complexes resulted in good yields (Table 1). The most studied example, D-Glc/D-Man and D-Man/D-Glc epimerizations, was 60 times faster than the conventional approach[7] and the yield slightly improved in favour of D-mannose (1:2.5 compared to 1:3). The same is valid for the D-Gal/D-Tal system. However, the reverse epimerization, D-Tal/D-Gal, was found to be less efficient (1.4:1, compared to 1:4), thus D-galactose was formed in considerably smaller amounts (though this type of interconversion is less synthetically interesting). Different final concentrations of epimers, obtained under microwave-assisted interconversions, were also observed for other aldose/epialdose conversions, namely, D-Ara/D-Rib–D-Rib/D-Ara, D-Allo/D-Altro–D-Altro/D-Allo and D-Gal/D-Tal–D-Tal/D-Gal. Interestingly, a characteristic feature of these aldoses is that they have cis configuration of hydroxyl groups at C-3 and C-4. In contrast, those that reached the same final concentration after interconversion (epimers D-Xyl/D-Lyx–D-Lyx/D-Xyl and D-Glc/D-Man–D-Man/D-Glc), have trans configuration of hydroxyl groups. It thus appears, that configuration at C-3 and C-4 carbons is an important factor that influences the final equilibria of the products obtained under microwave conditions. The reason for this effect is not fully understood at present, but might originate in lower stability of cis-configured aldoses due to steric effects at C-3 and C-4 carbons leading to easier decomposition under microwave irradiation. In fact, when attempting to reach the expected equilibria in cis-configured saccharides using longer irradiation times (15 min), partial decomposition was observed.

The efficiency of the method was also demonstrated in the semi-preparative scale, where 1 g of compounds and molybdic acid were dissolved in 50 mL of water. The transformation occurred in 5 min reaching comparable final concentrations. The yields and recovery of starting material are listed in Table 1. The advantages of performing these reactions under microwave heating are evident in all cases in terms of shorter reaction times, (reaction rate enhancements of up to 200 times as compared to conventional methods), better yields, stereoselectivity and purity of obtained products. This approach opens the way for the preparation of many interesting sugar derivatives. Preliminary experiments with mutual interconversions of 2-ketoses and 2-*C*-hydroxymethyl aldoses under microwave irradiation showed that these transformations were markedly faster as well. For example, about 15% conversion to the branched chain saccharide, D-hamamelose, was observed after 3 min in the case of D-Fru/D-Ham interconversion. This is a considerably higher yield than that obtained under classical conditions (about 7% after 4 h).[3] It appears therefore that even branched chain saccharides can be prepared successfully under microwave heating and further experiments with 2-ketoses are in progress.

In summary, microwave heating has been shown to be a very useful method for preparation of epimeric aldoses. Dramatically shorter reaction times (about two orders) were observed compared to conventional methods and yields were comparable (or higher), where short reaction time also prevented decomposition. Such reaction times in combination with the easy performance and work-up also make the method attractive and applicable on a semi-preparative scale.

1. Experimental

1.1. General methods

Experiments were conducted using domestic microwave oven producing continuous irradiation operated at 0–800 W. The influence of power output upon the reaction time and the selectivity of isomerization were studied. Reactions were performed in Pyrex glass vessels. The reaction volume filled not more than 1/5th of the total volume of the vessel, allowing head space for pressure build-up during the microwave treatment. Reaction mixtures were irradiated in microwave field for different lengths of time. The ratio of saccharides in the products at equilibrium was determined from high-resolution NMR spectra. The purity of isolated saccharides was checked by NMR spectroscopy and by measuring of optical rotation. NMR spectra were recorded on a Bruker DPX 300 spectrometer equipped with a 5 mm inverse broadband probe with a shielded *z*-gradient. The experiments were carried out at 40 °C in D_2O. The proton and carbon chemical shifts were referenced to external TSP. One-dimensional ^1H and ^{13}C NMR spectra and two-dimensional COSY and HSQC were used to determine ^1H and ^{13}C chemical shifts. All chemicals were of reagent grade and used without further purification.

1.2. Reaction of the saccharide with Mo(VI) ions under microwave irradiation

Aldose (10 mg, 0.056 mmol) was dissolved in D_2O (0.5 mL), and molybdic acid (1 mg, 0.006 mmol) was added. The tube was exposed to microwave irradiation for 3 min. The reaction mixture was analyzed by NMR spectroscopy measurements and the ratio of aldose/epialdose was determined by integration of selected resonances in ^1H NMR spectra.

1.3. Reaction of the saccharide with Mo(VI) ions with oil-bath heating

Aldose (10 mg, 0.056 mmol) was dissolved in D_2O (0.5 mL), and molybdic acid (1 mg, 0.006 mmol) was added. The tube was sealed and heated in an oil-bath at 90–95 °C according to the literature data.[7,13–15] The reaction mixture was analyzed by NMR spectroscopy measurements and the ratio of aldose/epialdose was determined by integration of selected resonances in ^1H NMR spectra.

1.4. Reaction of the saccharide with Mo(VI) ions under microwave irradiation on a semi-preparative scale

A solution of saccharide (D-glucose) (1 g, 5.6 mmol), molybdic acid (100 mg, 0.6 mmol) in water (50 mL) was exposed to microwave irradiation. Samples (0.5 mL) were taken at selected intervals (0.5, 1, 2, 3, 4 and 5 min) and 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. The rest of the reaction mixture was also treated batchwise with an excess of the ion-exchange resin, filtered, washed with water and the combined filtrates evaporated. The syrupy residue was fractionated by column chromatography on Dowex 50 W X8 (200–400 mesh) in Ba^{2+} form with water as eluent. Fractionization of the syrupy residue afforded D-glucose (0.69 g, 69%) and D-mannose (0.27 g, 27%).

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