Tetrahedron Letters 50 (2009) 2154–2157

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Direct synthesis of 1,6-anhydro sugars from unprotected glycopyranoses by using 2-chloro-1,3-dimethylimidazolinium chloride

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ARTICLE INFO

Article history:
Received 29 January 2009
Accepted 23 February 2009
Available online 26 February 2009

ABSTRACT

Various 1,6-anhydro sugars have been synthesized directly from the corresponding unprotected glycopyranoses in excellent yields by using 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as a dehydrative condensing agent. The reactions took place smoothly under mild reaction conditions in aqueous media. The present method would be a practical tool for synthesis of 1,6-anhydro derivatives of monosaccharides, linear-oligosaccharides, and branched-oligosaccharides.

1,6-Anhydro sugars and their derivatives are known to be useful synthetic intermediates for preparation of various glycosyl compounds such as *S*-glycosides,[1–7] *N*-glycosides,[8] glycosyl halides,[9–12] *C*-glycosides,[13–17] and proteoglycans.[18] In addition, 1,6-anydro sugars are important monomers for the cationic ring-opening polymerizations, which afford stereoregular linear polysaccharide derivatives[19] or hyperbranched polysaccharide derivatives.[20] However, there have been no practical method especially that of 1,6-anhydro oligosaccharides with higher molecular weight in spite of their utility as precursors for functionalized polymers in the field of materials science.

The formation of 1,6-anhydro structures has so far been achieved via chemical processes which involve protection of the hydroxy groups, activation of the anomeric center, and the removal of the protecting groups.[21] Since each step requires various kinds of chemical agents as well as organic solvents, the total process becomes extremely laborious and time-consuming. It is, therefore, almost impossible to convert an unprotected oligosaccharide of higher molecular weight to the corresponding 1,6-anhydro sugar derivative without damaging the inner glycosidic bonds.

Another classical method for preparation of 1,6-anhydro sugar is to utilize pyrolysis of polysaccharides.[22,23] Thermal degradations under high pressure or high temperature,[24,25] thermal degradations in supercritical acetone,[26] aprotic polar solvents,[27] and ionic liquid,[28] and pyrolysis by microwave[29,30] have been reported. These methods, however, can only be applied to synthesis of 1,6-anhydro monosaccharides, and it is difficult to control the pyrolysis conditions in order that a 1,6-anhydro oligosaccharide may be produced selectively. Furthermore, the purification of the product from a reaction mixture is extremely difficult.

Recently, we have developed a one-step method for synthesis of sugar oxazolines in aqueous media starting from unprotected 2-acetamido-2-deoxy sugars through an intramolecular dehydration reaction by using 2-chloro-1,3-dimethyl imidazolinium chloride (DMC)[31] as dehydrative condensing agent.[32] These findings prompted us to investigate the possibility of an intramolecular cyclization between two kinds of hydroxy groups in a saccharide unit by DMC. The present Letter describes a DMC-mediated intramolecular dehydration reaction between the 1-OH and the 6-OH of various glycopyranoses to afford the corresponding 1,6-anhydro sugars. The reactions proceed under mild reaction conditions in aqueous media without using any protecting groups.

It was estimated that DMC would partly be decomposed during the reaction by the attack of water in aqueous solution, suggesting that an excess amount of DMC would be needed. We optimized the amount of DMC using D-glucose as a model substrate and found that when the reaction was carried out in the presence of 10 equiv of DMC for D-glucose, the yield of 1,6-anhydro sugars was almost quantitative (Table 1, entry 4). When the amount of DMC decreased, the yields decreased significantly (entries 1–3).

It was also predicted that two molecules of hydrogen chloride would be liberated from one molecule of DMC if the reagent was completely consumed. We screened the types of bases in order to optimize the yield of 1,6-anhydro glucose, and found that triethylamine (Et_3N) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the best results (entries 4 and 5). Other bases, diisopropylethylamine ($(i\text{-}Pr)_2NEt$), 2,6-lutidine, pyridine, *N*-methylmorpholine (NMM), and sodium hydrogen carbonate ($NaHCO_3$) afforded no 1,6-anhydro glucose (entries 6–10). Next, we carefully investigated the amount of acid scavenger, and found that at least 3 equiv of triethylamine against DMC is necessary for the reaction to occur.

Table 2 summarizes the synthesis of various 1,6-anhydro sugars starting from the corresponding monosaccharides or oligosaccharides. Among the monosaccharides, D-glucose and D-galactose were successfully converted to the corresponding 1,6-anhydro derivatives almost quantitatively (Table 2, entries 1 and 2). Various oligosaccharides like lactose, malto-oligosaccharides (DP = 2–7),

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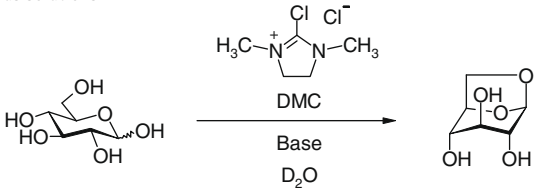
doi:10.1016/j.tetlet.2009.02.171

Table 1
Effect of the equivalence (D-Glucose/DMC/base) on the yields of 1,6-anhydro glucose in aqueous solutions[a]



Entry	Concn of D-glucose (mM)	Equiv of DMC	Base (equiv)	Yield[b] (%)
1	250	2	Et_3N (6)	29
2	250	3	Et_3N (9)	40
3	250	4	Et_3N (12)	36
4	50	10	Et_3N (30)	Quant.
5	50	10	DBU (30)	Quant.
6	50	10	$(i\text{-Pr})_2$NEt (30)	0
7	50	10	2,6-Lutidine (30)	0
8	50	10	Pyridine (30)	0
9	50	10	NMM (30)	0
10	50	10	$NaHCO_3$ (30)	0

[a] The reactions were carried out at 0 °C for 15 min.
[b] Determined by ^{1}H NMR by comparing the integrals of the anomeric proton of D-glucose and that of 1,6-anhydro glucose.

cello-oligosaccharides (DP = 2–6), and oligoxyloglucan having α1,6-branched linkages, were able to be converted to the corresponding 1,6-anhydro derivatives in good yields (entries 6–20). It should also be noted that this method is applicable to polysaccharides such as amylose (average MW = 2900) and xyloglucan from *Tamarindus indica* (MW > 300,000) (data not shown).

The following is a typical procedure for synthesis of 1,6-anhydro maltotetraose (entry 9). A mixture of maltotetraose (16.7 mg, 0.025 mmol), DMC (25.4 mg, 0.15 mmol), and Et_3N (0.063 mL, 0.45 mmol) in water (0.5 mL) was stirred for 15 min at 0 °C. The resulting product was purified by using HPLC (column; Amide80 (21.5 × 300 mm), eluent; water/acetonitrile = 3/2, flow rate; 8 mL/min, column oven; 60 °C, detection; RI) and concentrated in vacuo to give 1,6-anhydro maltotetraose (14.1 mg, 0.022 mmol, 87%). The ^{1}H NMR spectrum of 1,6-anhydro maltotetraose shows the anomeric proton at 5.4 ppm characteristic to 1,6-anhydro sugars. The ^{13}C NMR spectrum indicated that the C-6 carbon peak of the product appears at 65 ppm lower than that of C-6′, 6″, 6‴ (60 ppm), clearly indicating the formation of a 1,6-anhydro moiety as a result of intramolecular cyclization (Fig. 1). It is noteworthy that each carbon atom can be clearly identified as a separated peak because the anomeric hydroxy group is fixed in the 1,6-anhydro moiety.

On the other hand, D-mannose, 2-deoxy-D-glucose, and 2-fluoro-2-deoxy-D-glucose gave no dehydrative products (entries 3–5), indicating that the existence of 2-hydroxy group and its configuration are important factors that determine the course of the formation of 1,6-anhydro structures. The yield of 1,6-anhdyro sugars derived from nigerose (Glcα1→3Glc) and laminaribiose (Glcβ1→3Glc) was low, showing that a substituent on the 3 position strongly hinders the intramolecular cyclization due to steric repulsion between the 1-*O*-substituent and 3-*O*-substituent (entries 21 and 22). These results were in consistent with the fact that 3-*O*-methyl-D-glucose cannot be converted to the corresponding 1,6-anhydro derivative (entry 23).

Based on these results, the following reaction mechanism for DMC-mediated formation of 1,6-anhydro glucose was proposed. The first step is a nucleophilic attack of β-glucose (**1β**) to the 2 position of DMC, giving rise to the intermediate **2β**. The 2-hydroxy group of **2β** then attacks the anomeric carbon atom to afford a 1,2-anhydro intermediate **3**, which is converted to the 1,6-anhydro sugar **4** via intramolecular attack of the 6-hydroxy group. α-Glucose (**1α**) that is in equilibrium with β-glucose also reacts with DMC to give the corresponding α-intermediate **2α**, from which glucose is regenerated by the attack of water via S_N2 or S_N1 process. The results that the reaction with D-mannose, 2-deoxy-D-glucose, and 2-fluoro-2-deoxy-D-glucose did not proceed (Table 2, entries 3–5) strongly supported the participation of the intermediate **3**. The formation of anhydro moieties of other glycopyranoses can be explained in a similar manner (see Scheme 1).

In conclusion, we achieved a one-step synthesis of 1,6-anydro sugars by using DMC as dehydrative agent under mild reaction conditions. The reaction requires no protection of the hydroxyl groups and proceeds smoothly in aqueous media. The present method would be a general and practical tool for synthesis of 1,6-anhydro sugars starting from various glycopyranoses including oligosaccharides with higher molecular weights.

Table 2
Synthesis of various 1,6-anhydro sugars

Entry	Substrate	(mM)	DMC (equiv)	Et_3N (equiv)	Yield[a] (%)
1	D-Glucose	50	10	30	99
2	D-Galactose	50	10	30	99
3	D-Mannose	50	10	30	0
4	2-Deoxy-D-glucose	50	10	30	0
5	2-Fluoro-2-deoxy-D-glucose	50	10	30	0
6	Lactose	250	3	9	Quant.
7	Maltose	250	3	9	89
8	Maltotriose	50	6	18	91
9	Maltotetraose	50	6	18	87
10	Maltopentaose	50	6	18	70
11	Maltohexaose	50	10	30	64
12	Maltoheptaose	50	10	30	92
13	Cellobiose	250	3	9	Quant.
14	Cellotriose	50	6	18	Quant.
15	Cellotetraose	50	6	18	94
16	Cellopentaose	40	8	24	81
17	Cellohexaose	20	10	30	91
18	Panose	50	6	18	Quant.
19	Xyloglucan-heptasaccharide	20	10	30	74
20	Xyloglucan-nonasaccharide	50	10	30	97
21	Nigerose	250	3	9	Trace[b]
22	Laminaribiose	250	3	9	Trace[b]
23	3-*O*-Methyl-D-glucose	50	10	30	Trace[b]

[a] Isolated yield.
[b] The reaction was carried out in deuterium oxide solution at 0 °C for 15 min and a trace amount of the product was detected by ^{1}H NMR.

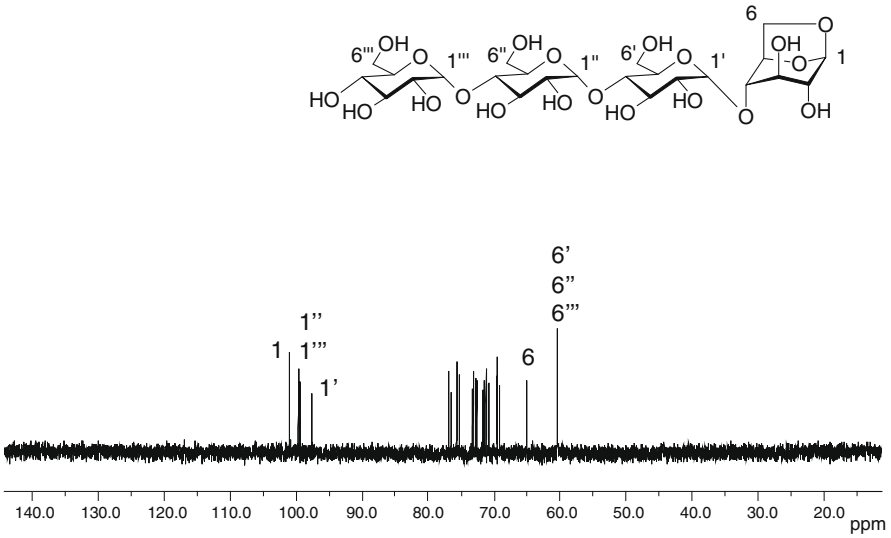
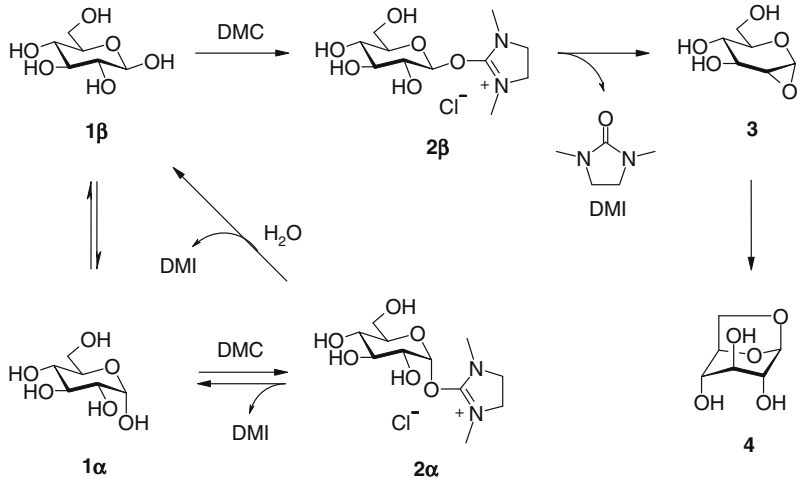


Figure 1. ^{13}C NMR spectrum of isolated 1,6-anhydro maltotetraose in D_2O (Table 2, entry 9).



Scheme 1. Plausible reaction mechanism of 1,6-anhydro sugar formation.

Acknowledgments

This work was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Sports, Science and Technology, Industrial Technology Research Grant Program in 2006 from NEDO of Japan, and an International Center of Research & Education for Molecular Complex Chemistry in 2007 from TOHOKU UNIVERSITY Global COE Program.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.171.

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