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Degradation of Unprotected Aldohexonic Acids to Aldopentoses Promoted by Light and Oxygen

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Degradation of Unprotected Aldohexonic Acids to Aldopentoses Promoted by Light and Oxygen

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Herein reported is a photoredox-catalyzed oxidative degradation reaction of unprotected aldohexonic acids, which are shortened by one-carbon to the corresponding aldopentoses. Oxygen including atmospheric one is used as a terminal oxidant. The mild reaction conditions permit even disaccharides to successfully undergo the degradation reaction with the glycosidic bond remaining intact. Quinic acid is also converted to a useful chiral synthetic intermediate.

Keywords: sugar, degradation, oxygen, photocatalyst

Pentoses, i.e., monosaccharides comprised by five carbon atoms play a number of important roles not only in biology but also in food and pharmaceutical industries (Figure 1). For example, D-deoxyribose and D-ribose are the repeating units of the backbones of vital DNA and RNA, respectively. D-Ribose is contained also in riboflavin (vitamin B_2). Xylitol produced by hydrogenation of xylose has come into wide use as a sugar substitute.[1] There are a series of anti-cancer drugs such as cytarabine, fludarabine, and nelarabine, which all contain D-arabinose.[2] Some of these pentoses are difficult to obtain in nature, and therefore, it has been desired to derivatize readily available naturally occurring compounds, hexoses for example, into pentoses.[3] There are a diverse range of hexose derivatives abundantly available from natural sources, and a convenient and practical way to access pentoses is given by degradation of hexoses. For example, the Ruff degradation reaction, which uses hydrogen peroxide as an oxidant along with a copper or iron catalyst, degrades calcium D-gluconate to D-arabinose through decarboxylation.[4] Alternatively, a decarboxylation reaction of a gluconate salt into D-arabinose is carried out by an electrochemical method,[5] which is implemented even on an industrial scale.[6] However, it would provide a more sustainable method of degradation of hexose derivatives if gaseous oxygen, hopefully atmospheric one, can be used as an oxidant, dispensing with the need of a metal catalyst, hydrogen peroxide, electrolyte, and electricity.

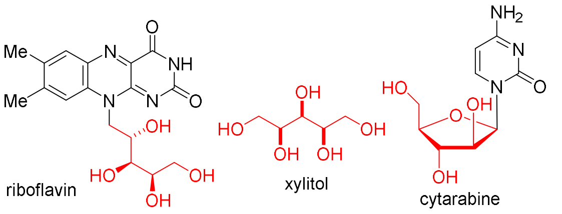


Figure 1. Products containing pentoses

Herein reported is a photoredox-catalyzed degradation reaction of aldohexonic acids using oxygen as a terminal oxidant (Figure 2). The starting carboxylic acid derivatives are shortened to aldopentoses through decarboxylation. Not only monosaccharides but also disaccharides and other α-hydroxycarboxylic acids in general participate in the degradation reaction. The present method avoids strong oxidants or metal catalysts, instead utilizes visible light and oxygen, which are readily available, non-hazardous, and environmentally innoxious.[7]

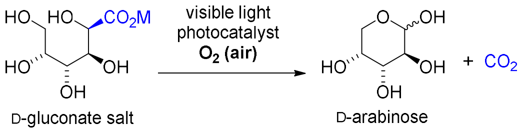
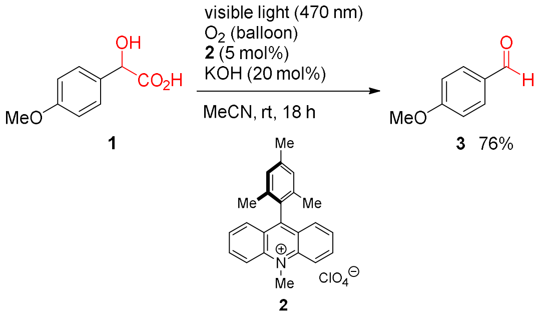


Figure 2. Degradation of gluconate salts

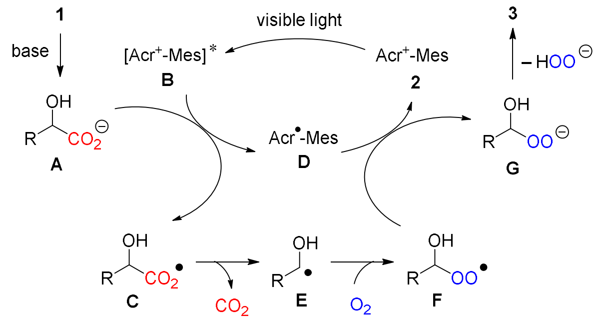
We initially found that a combination of an acridinium photocatalyst, visible light, and gaseous oxygen effectuated a decarboxylation reaction of α-hydroxycarboxylic acids (Scheme 1).[8] For example, 4-methoxymandelic acid (**1**) in acetonitrile was irradiated with blue light (470 nm) in the presence of 9-mesityl-10-methylacridinium perchlorate[9] (**2**, 5 mol%) and KOH (20 mol%) under an atmospheric pressure of oxygen for 18 h. After purification by silica gel chromatography, *p*-anisaldehyde (**3**) was isolated in 76% yield.[10] Other photoredox catalysts such as eosin Y and iridium-based complexes failed to give **3**.



Scheme 1. Photo-degradation of mandelic acid **1**

A mechanism which would reasonably explain the formation of the aldehyde **3** from the carboxylic acid **1** is shown in Scheme 2. It has been reported that the acridinium salt **2** catalyzes an oxidative decarboxylation reaction of pivalic acid to form *t*-butyl hydroperoxide upon photoirradiation, albeit limited to this single example.[11] We assume that a similar mechanism would operate up to the formation of peroxy anion **G**. Initially, carboxylic acid **1** is deprotonated by a base. The resulting carboxylate anion **A**

($E_{1/2}^{red}$ = +1.39 V vs SCE for sodium gluconate)[12] transfers single electron to the photoexcited catalyst **B** ($E_{1/2}^{red}$ = +2.06 V vs SCE)[13] to generate the carboxy radical **C** and the reduced photocatalyst **D**. Decarboxylation of **C** gives rise to the hydroxycarbon radical **E**, which captures oxygen to furnish peroxy radical species **F**. The reduced photocatalyst **D** transfers a single electron to the generated peroxy radical **F**, forming peroxy anion **G** and the photocatalyst **2**. Finally, hydrogen peroxide anion eliminates to afford the carbonyl product **3**.[14]

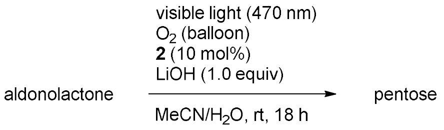


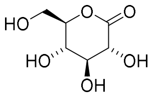
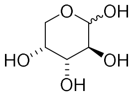
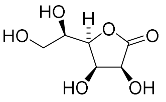
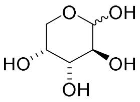
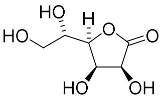
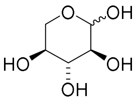
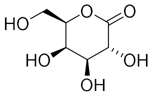
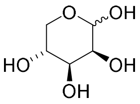
Scheme 2. Proposed reaction pathway.

We have been applying the photocatalysis chemistry to unprotected sugars dissolved in hydrous solvents to develop their straightforward transformations.[15] With the preliminary result mentioned above in hand, we next examined an analogous degradation reaction using an unprotected sugar lactone, D-glucono-1,5-lactone (**4**) (Table 3, entry 1). D-Glucono-1,5-lactone (**4**), photocatalyst **2** (10 mol%), and LiOH (1 equiv) were dissolved in acetonitrile/water (1/1) and irradiated with blue light (470 nm) under an atmospheric pressure of oxygen for 18 h. After the solvent was removed under reduced pressure, the residue was subjected to silica gel chromatography and D-arabinose (**5**) was isolated in 64% yield. Of note was that D-glucono-1,5-lactone (**4**) with its multiple hydroxy groups unprotected was successfully transformed to D-arabinose (**5**) in a straightforward way. Furthermore, the reaction conditions tolerated the use of water as the co-solvent, which is necessary for direct derivatizations of unprotected sugars.

Other aldonolactones were subjected to the photo-degradation reaction. D-Arabinose (**5**) was obtained also from D-mannono-1,4-lactone (**6**) in 41% yield. D-Gulono-1,4-lactone (**7**) afforded L-xylose (**8**) in 62% yield. The reaction of D-galactono-1,5-lactone (**9**) produced D-lyxose (**10**), which is hardly obtained from nature.

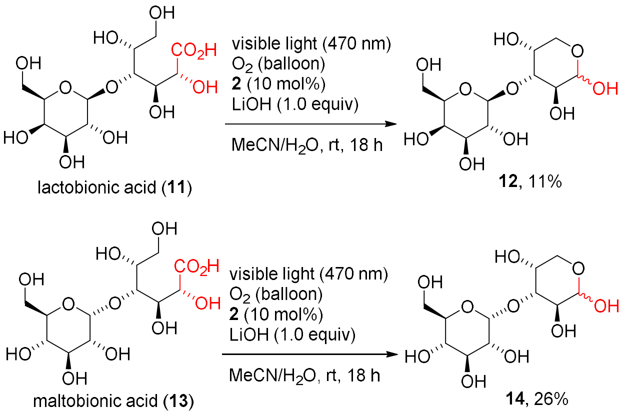
Table 3. Substrate scope with respect to monosaccharides.[a]



entry	aldonolactone	pentose	yield[b]
1	 D-glucono-1,5-lactone (**4**)	 D-arabinose (**5**)	64%
2	 D-mannono-1,4-lactone (**6**)	 D-arabinose (**5**)	41%
3	 L-gulono-1,4-lactone (**7**)	 L-xylose (**8**)	62%
4	 D-galactono-1,5-lactone (**9**)	 D-lyxose (**10**)	40%

[a] Reaction conditions: aldonolactone (0.20 mmol), **2** (8.2 mg, 0.02 mmol, 10 mol%), LiOH (4.8 mg, 0.20 mmol, 1.0 equiv), O_2 (balloon), MeCN (1 mL), H_2O (1 mL), LED lamp (470 nm), rt, 18 h. [b] Isolated yield.

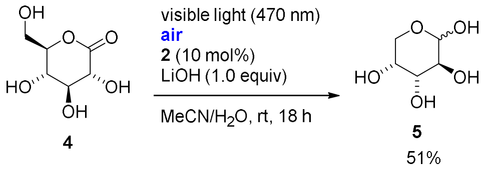
Thus, unprotected monosaccharides were successfully degraded under the present reaction conditions. It is even more challenging to subject unprotected disaccharides possessing a glycosidic bond to chemical transformation. Next, we examined disaccharrides **11** and **13** (Scheme 3). Lactobionic acid (**11**) was converted to 3-*O*-β-galactopyranosyl-D-arabinose (**12**) with the glycosidic bond unaffected, albeit in low yield. Maltobionic acid (**13**) was also shortened to 3-*O*-α-glucopyranosyl-D-arabinose (**14**) in 26% yield.



Scheme 3. Degradation of disaccharides.

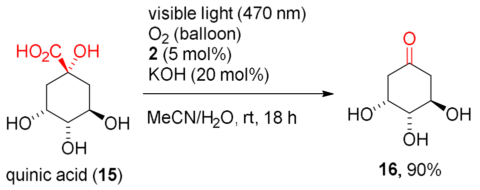
It was also possible to carry out the present degradation reaction under atomospheric oxygen (Scheme 4). A solution of the lactone **4**, the photocatalyst **2**, and

LiOH was placed simply in an open flask and irradiated with blue LEDs for 18 h. D-Arabinose (**5**) was produced in 51% yield.



Scheme 4. Degradation of D-glucono-1,5-lactone (**4**) in the air

The polyhydroxy ketone **16** is a versatile chiral compound often employed in asymmetric syntheses of various natural products and bioactive compounds.[16] It is conventionally prepared from readily available quinic acid (**15**) by an oxidation reaction which uses a stoichiometric amount of sodium periodate[17] or a hypochlorite solution.[18] We next tried to apply the present degradation reaction to the synthesis of the ketone **16** from quinic acid (**15**) (Scheme 5). When **15** in acetonitrile/water was irradiated with blue light under an oxygen atmosphere in the presence of the acridinium catalyst **2** and KOH, the corresponding ketone **16** was produced in 90% yield. Thus, the present degradation reaction presents a facile access to the valued carbonyl compound from the naturally occurring compound dispensing with the use of strong oxidants or protective groups.



Scheme 5. Degradation of quinic acid (**15**)

In summary, we have developed the degradation reaction of aldohexonic acids which are shortened by one-carbon to aldopentoses. It makes use of readily available naturally occurring hexose derivatives as the feedstocks, and light and molecular oxygen as the driving forces for their direct transformation.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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