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Effect of temperature modulations on TEMPO-mediated regioselective oxidation of unprotected carbohydrates and nucleosides

Mahipal Yadav [a,c], Charles L. Liotta [b,c,*], Ramanarayanan Krishnamurthy [a,c,*]

[a] Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, United States
[b] School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, United States
[c] NSF-NASA Center for Chemical Evolution, Atlanta, GA 30332, United States

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ABSTRACT

Regioselective oxidation of unprotected and partially protected oligosaccharides is a much sought-after goal. Herein, we report a notable improvement in the efficiency of TEMPO-catalyzed oxidation by modulating the temperature of the reaction. Mono-, di-, and tri-saccharides are oxidized regioselectively in yields of 75 to 92%. The present method is simple to implement and is also applicable for selective oxidations of other mono- and poly-hydroxy compounds including unprotected and partially protected nucleosides.

Introduction

Uronic acids are important class of biological compounds. Oligo-saccharides and poly-saccharides containing uronic acid units such as glucosaminoglycans, heparin, heparan sulphate, chondroitin sulphate, dermatan sulphate and hyaluronic acid (HA) have important physiological functions.[1] The glycosaminoglycan hyaluronan (HA), a major component of extracellular matrices, and cell surface receptors of HA have been proposed to have pivotal roles in cell proliferation, migration, and invasion, which are necessary for inflammation and cancer progression.[2–4] Some of the proteins interact with these negatively charged polysaccharides; these include antithrombin III (which is activated by heparin)[5] and fibroblast growth factor (which is activated by heparan sulphate).[6] Understanding of the more detailed molecular mechanism of these negatively charged oligo- and poly-saccharides will require the synthesis of modified oligosaccharide analogues.

For the synthesis of uronic acid analogues, selective oxidation of primary alcohols to carboxylic acids in carbohydrates is one of the long-standing challenges. Although there are many protocols for the oxidation are known,[7] it is difficult to find a procedure which is selective, cheap, efficient, and easy to work up. Many of the well-established procedures require the use of a toxic stoichiometric oxidant, transition metal catalyst and/or halogenated solvents.[8–12] In this respect, the TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) based reagents have emerged as highly selective catalytic systems for the oxidation of primary alcohols to the corresponding aldehydes or acids.[7] TEMPO-mediated method for the selective oxidation of primary alcohols in the presence of secondary alcohols originates from the work of Semmelhack et al.[13] Anelli et al., reported the oxidation of alcohols and diols with sodium hypochlorite, potassium bromide and TEMPO or 4- methoxy-TEMPO in a two-phase solvent system (dichloromethane and water) at pH 9.5.[14,15] The same protocol was used for the oxidation of monosaccharide[16] wherein the acetal hydroxyl groups are protected and for polysaccharides as well.[17] Most of the above methods use sodium bromide as co-catalyst which could cause serious environment problems. Later, much effort was spent on developing bromide free[18,19] and environmentally friendly methods for oxidation of alcohols using either air/oxygen as the terminal oxidant or using transition metal salts as co-catalysts.[20–23] But these methods also suffer either from low reaction yields or the need for transition metal catalyst. Also, most of the methods using sodium hypochlorite as an oxidant need continuous adjustment of pH throughout the reaction.[18,19] As a consequence there is still a need

* Corresponding authors at: Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, United States (R. Krishnamurthy). School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, United States (C.L. Liotta).

E-mail addresses: charles.liotta@carnegie.gatech.edu (C.L. Liotta), rkrishna@scripps.edu (R. Krishnamurthy).

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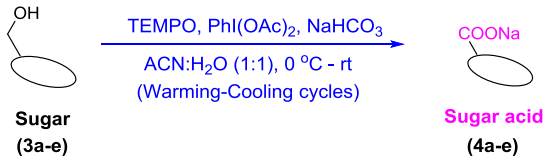
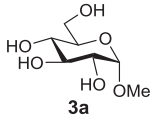
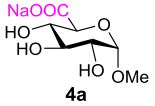
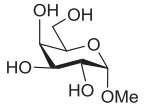
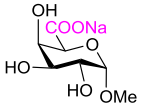
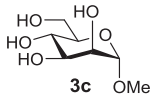
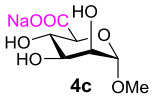
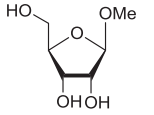
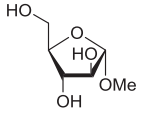
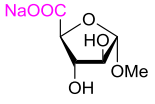
to develop new methods or improve the existing methods for the regioselective oxidation of carbohydrates.

Polysaccharides form an important class of biopolymers (apart from nucleic acids and proteins). Inspired by the search of the origins of proto-polysaccharides in the context of origins of life,[24] we have been investigating the polymerization of some of the most abundant sugar acids under potentially pre-biotic conditions.[24b] The complex mixtures of the oligomeric sugar-acids that are likely be generated by prebiotic means will require standards of oligosaccharide acids to aid in characterization. For this purpose, we decided to systematically synthesize different sugar-diacids by employing TEMPO-mediated oxidation strategies.[7] After several attempts, we developed an oxidative protocol, which by modulating the reaction temperature leads to a simple, selective and efficient oxidation process. In this report we describe our rationale behind this approach and document the general validity of this approach by extending this protocol to a wide variety of substrates.

We initially chose the commercially available and synthetically accessible disaccharides as model substrates to generate a library of corresponding sugar acids with different glycosidic linkages. Regioselective oxidation of the primary hydroxyl group of 1-*O*-benzyl cellobioside **1** by using the standard TEMPO oxidative conditions in CH_2Cl_2: H_2O (1:1) as solvent was tested but there was no reaction; the starting material was unchanged (Table 1, entry 1). Changing the solvent to only H_2O, or use of different secondary oxidants instead of $PhI(OAc)_2$ and use of 2 N NaOH as base also resulted in no reaction (Table 1, entries 2 and 3). To our delight, use of ACN: H_2O (1:1) as solvent system in presence of base and TEMPO/$PhI(OAc)_2$ produced the desired product **2** in moderate yield (Table 1, entry 4). We looked into the mechanism of the TEMPO-mediated oxidation and reasoned that lowering of temperature may stabilize the active oxidant species and, therefore, could increase the yields. However, when the same reaction (Table 1, entry 4) was carried out at 0 °C, there was no improvement in yield of the di-acid product **2** (Table 1, entry 5). We reasoned that the low yield may be due to the lower solubility of reagents at lower temperature. We hypothesized that if we can alternate between higher temperatures (such as room temperature, to make the reagents soluble) and lower temperatures (for example, 0 °C to stabilize the TEMPO oxoammonium ion) and subject the reaction to the cycle between the two temperatures, we may be able to increase the yield of the reaction, as well as shorten the time of reaction. To test this hypothesis, an oxidation reaction of **1** was performed at room temperature in ACN: H_2O (1:1). After 5 min, temperature of the reaction mixture was lowered to 0 °C for 5 min. After that, warming (room temperature for 15 min) and cooling (0 °C for 5 min) cycles were repeated till the reaction was complete (6h, monitored by TLC and MS). After purification the

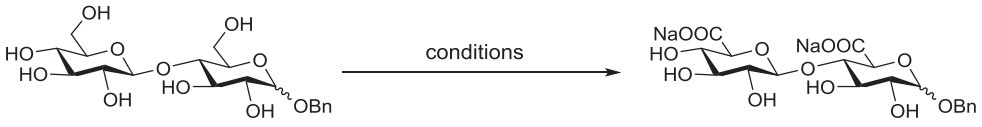
Table 2
Oxidation of monosaccharide sugars.[a,b]



Entry	Substrate	Product	Yield
1	 **3a**	 **4a**	90%
2	 **3b**	 **4b**	88%
3	 **3c**	 **4c**	92%
4	 **3d**	Unindentified mixture of products	
5	 **3e**	 **4e**	60%

[a] Reagents and conditions: sugar (0.5 mmol), TEMPO (0.1 mmol), $PhI(OAc)_2$ (1.5 mmol), and $NaHCO_3$ (1.0 mmol) in ACN:H_2O (2.0 mL) at 0 °C – rt (Warming – Cooling cycles) for 2 h.
[b] Isolated yield.

Table 1
Optimization table for regioselective oxidation of primary hydroxyl groups.[a,b]



Entry	Conditions	Yield (%)
1	TEMPO, $PhI(OAc)_2$, CH_2Cl_2: H_2O (1:1), rt	NR
2	TEMPO, $PhI(OAc)_2$, H_2O, rt	NR
3[c]	TEMPO, NaOCl, H_2O, EtOAc, NaOH, 0 °C-rt	NR
4	TEMPO, $PhI(OAc)_2$, $NaHCO_3$, ACN: H_2O (1:1), rt	60
5	TEMPO, $PhI(OAc)_2$, $NaHCO_3$, ACN: H_2O (1:1), 0 °C	40
6[d]	TEMPO, $PhI(OAc)_2$, $NaHCO_3$, ACN: H_2O (1:1), 0 °C-rt	75
7[d]	TEMPO, NaOCl, $NaHCO_3$, ACN: H_2O (1:1), 0 °C-rt	74
8	TEMPO, $PhI(OAc)_2$, $NaHCO_3$, ACN: H_2O (1:1), 12 °C	74

[a] Reagents and conditions: 1 (0.23 mmol), TEMPO (0.09 mmol), oxidant (1.38 mmol), and $NaHCO_3$ (0.92 mmol) in solvent (2.0 mL) for 6 h.
[b] Isolated yield. NR = no reaction.
[c] 2N NaOH (aqueous solution) was used until pH of the reaction mixture reached up to 8.5.
[d] Warming–Cooling cycles applied.