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A highly efficient TEMPO mediated oxidation of sugar primary alcohols into uronic acids using 1-chloro-1,2-benziodoxol-3(1H)-one at room temperature

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ABSTRACT

Oxidation of various sugar primary alcohols into corresponding uronic acids was demonstrated using 1-chloro-1,2-benziodoxol-3(1H)-one and TEMPO. The reaction proceeds at room temperature in good to excellent yields. Primary alcohols get oxidized selectively over the secondary alcohols under mild reaction conditions.

Introduction

Uronic acid containing polysaccharides are widespread in nature and involved in many biological processes (Fig. 1).[1] For instance, glycosaminoglycans (GAGs) such as heparin sulphate, dermatan sulphate, chondroitin sulphate and hyaluronan are made up of uronic acids (Fig. 1).[2] In addition, capsular polysaccharides of various bacteria, marine polysaccharides, homoglycuronans, saponinsas, etc. possess uronic acid units.[1a–c,3] A typical route for the preparation of uronic acid involves the direct oxidation of primary alcohols in a pyranose sugar.[1a,1b] Nevertheless, *de novo* synthesis also developed for the preparation of some rare uronic acids (e.g. L-iduronic acid, L-altruronic acid, etc.).[4] Although numerous oxidants have been developed for the oxidation of simple aryl and aliphatic alcohols, only few of them have proved to be an efficient for the oxidation of sugar primary alcohols into corresponding uronic acids.[5] In general, TEMPO mediated oxidations in the presence of different co-oxidants such as NaOCl, $Ca(OCl)_2$, PhI$(OAc)_2$, *t*-BuOCl, TCC, etc. have shown high efficiency and selectivity for oxidation of sugar primary alcohols.[5a,6] Nevertheless, each method of alcohol oxidation has its own advantages and limitations. It is also often noticed that direct oxidation of alcohol to carboxylic acid is accompanied by few other disadvantages like use of unstable and toxic oxidants, inconvenient reaction conditions, formation of undesired products, low yield, etc. For example, use of NaOCl as a co-oxidant requires pH maintenance to obtain a good conversion in alcohol oxidation.[5a,6a] On the other hand, a different side reactions have been observed during the oxidation of allyl, thioacetal and methoxybenzyl groups functionalized alcohols.[7] Therefore, the development of simple and efficient method for the direct oxidation of alcohols to corresponding uronic acids is of great interest.

Recently, the hypervalent iodine compound, 1-chloro-1,2-benziodoxol-3-one (CBI) has proved as an important reagent in organic synthesis.[8] In this context, CBI is also reported for the oxidation of aryl and alkyl alcohols to corresponding aldehydes in the presence of TEMPO.[8d] However, to our surprise, it has not been evaluated for the oxidation of primary alcohols to carboxylic acids. This bench stable compound is commercially available and also easy to prepare which can be stored for a long time. As part of our continuing investigation on carbohydrate synthesis and oxidation reactions,[9] here we report an efficient and practical method for the conversion of sugar primary alcohols into uronic acids using CBI/TEMPO at room temperature.

At the outset, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**1a**) was chosen as a model substrate and oxidized using CBI with catalytic amount of TEMPO (10 mol%) in different solvents at room temperature (Table 1). In most of the solvents, including acetoni-

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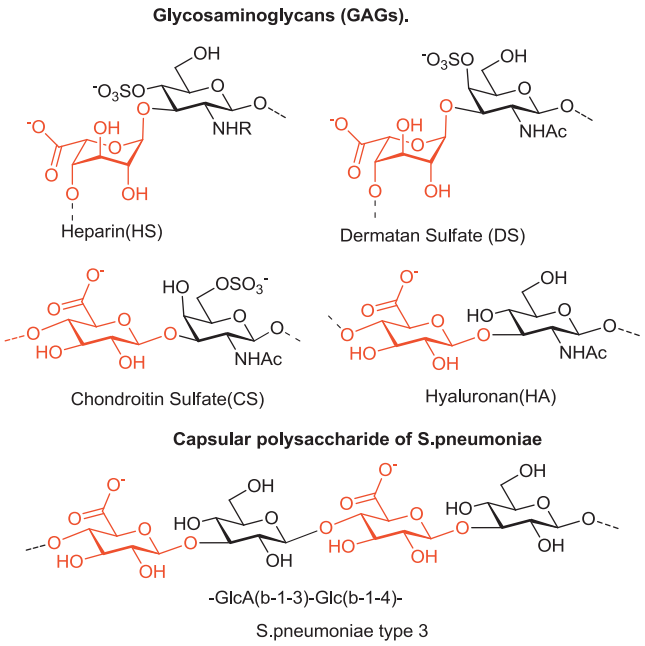


Fig. 1. Structures of uronic acid containing polysaccharides.

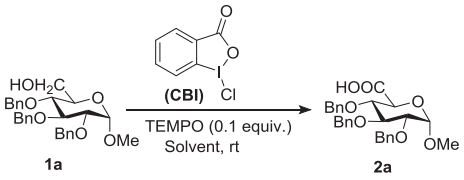
trile, tetrahydrofuran, diethyl ether and dichloromethane the corresponding uronic acid **2a** was obtained only in insignificant amount (Table 1, entries 1–4). In fact, the reagent CBI found to be insoluble in diethyl ether while sparingly soluble in DCM, THF and acetonitrile. In all these reactions, starting material **1a** was recovered in >80% (Table 1, entries 1–4). However, in the presence of water, the reaction proceeds better while the uronic acid **2a** was obtained in 13–43% yields (Table 1, entries 5–7). Among the different water mixed solvents, DCM-water (2:1 ratio) provides the maximum yield of **2a** (*i.e.* 43%) after 12 h at room temperature (Table 1, entry 7). Further, the oxidation reaction was investigated with increased amount of CBI in DCM-water (Table 1, entries 8–9). To our delight, the desired uronic acid was obtained in 93% yield in the presence of two equiv. of CBI at room temperature within 2.0 h (Table 1, entry 9). It is also important to note that in the absence of TEMPO, no reaction takes place (Table 1, entry 10).

Further, to realize the efficiency of CBI, other halogen mediated oxidants such as molecular iodine (I_2), *t*-butyl hypochlorite (*t*-BuOCl), Dess-Martin periodinane (DMP), cyanuric chloride and $PhI(OAc)_2$ were evaluated for the oxidation under same condition (Table 1, entries 11–15). Among them, *t*-BuOCl and $PhI(OAc)_2$ showed a comparable reactivity to that of CBI and gave 75–79% yield of desired uronic acid (Table 1, entries 12 and 15). However, *t*-butyl hypochlorite is very unstable and light sensitive which requires extra care for the preparation and usage.

After establishing the optimized condition (Table 1, entry 9), the direct oxidation of various sugar primary alcohols was investigated (Table 2). For this study, a series of monosaccharides possessing primary alcohols (**1b–1r)** were prepared with structurally diverse moieties in different positions. Acetyl, benzoyl and benzyl protected glucopyranoside primary alcohols were efficiently oxidized to corresponding uronic acids **2b–2g** in excellent yields (*i.e.* >83%) within 3 h at room temperature. Similar to glucopyranoside, oxidation of primary alcohols in various mannopyranosides was successfully accomplished with good to excellent yields (Table 2 , **2h, i**). Moreover, this method also found to be suitable for the oxidation of acid-labile group protected monosaccharide such as 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside. It provides the corresponding uronic acid **2j** in 92% yield under optimized condition.

Thioglycopyranoside uronic acids are important building blocks in the synthesis of uronic acid containing oligosaccharides.[1a,1b]

Table 1
Oxidation of benzyl protected glucopyranoside primary alcohol under various reaction conditions.[a]



S. No.	Reagents (equiv.)	Solvents	Time (h)	Yield (%)[b]
1.	CBI (1.0)	CH_3CN	12	<5
2.	CBI (1.0)	THF	12	<5
3.	CBI (1.0)	Diethyl ether	12	NR
4.	CBI (1.0)	DCM	12	<5
5.	CBI (1.0)	CH_3CN:H_2O	12	22
6.	CBI (1.0)	THF:H_2O	12	13
7.	CBI (1.0)	DCM:H_2O	12	43
8.	CBI (1.5)	DCM:H_2O	4.0	71
9.	CBI (2.0)	DCM:H_2O	2.0	93
10.	CBI (2.0)	DCM:H_2O	2.0	<5[c]
11.	I_2 (2.0)	DCM:H_2O	2.0	20
12.	*t*-BuOCl (2.0)	DCM:H_2O	2.0	79
13.	CyanuricChloride (2.0)	DCM:H_2O	2.0	52
14.	DMP (2.0)	DCM:H_2O	2.0	<10
15	$PhI(OAc)_2$ (2.0)	DCM:H_2O	2.5	75

[c]Reaction was carried out in the absence of TEMPO.
[a] Reaction conditions: Alcohol (0.3 mmol), oxidant and TEMPO (0.1 equiv.) were stirred together in different solvents (3.0 mL) for appropriate time at room temperature.
[b] Isolated yield.