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Selective Oxidation of Unprotected Carbohydrates to Aldehyde Analogues by Using TEMPO Salts

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The primary alcohol function of essentially unprotected carbohydrates (methyl-α-D-mannopyranoside, methyl-α-D-glucopyranoside and methyl-α-D-galactopyranoside) was selectively converted into the corresponding aldehyde in the form of acetals by using TEMPO$^+$ BF_4^- (2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) in organic medium with 2,6-lutidine as the base. Indeed, organic anhydrous conditions prevent over oxidation of the alcohol group to the carboxylate form. The resulting compounds, methyl-α-D-*gluco*hexodialdo-1,5-pyranoside and methyl-α-D-*mano*-hexodialdo-1,5-pyranoside were characterized by NMR and mass spectrometry. Additionally, the results obtained in a TEMPO electrochemically mediated system were compared with those of the pure TEMPO$^+$ BF_4^- system, but lower yields were attained under the electrochemical conditions as a result of a very slow reaction rate.
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The chiral pool of carbohydrates is often used as a basis for the synthesis of novel compounds. The selective transformation of the primary 6-hydroxy function to the corresponding aldehyde affords a compound that can serve as a useful intermediate in numerous applications.[1] However, as is common with the chemistry of carbohydrates, elegant approaches for the selective protection/deprotection of the hydroxy functionalities are devised and employed in order to judiciously introduce modifications at specific positions.[2] This procedure can include several steps before the required function can actually be used. We describe herein the selective oxidation of only the primary hydroxy function of anomerically methylated carbohydrates to their corresponding aldehydes in which only the 6-hydroxy function reacts. Methyl-α-D-mannopyranoside (**3**), methyl-α-D-glucopyranoside (**4**) and methyl-α-D-galactopyranoside (**5**) were employed as representative examples in this study (Figure 1).

It is now well established that amongst the oxidation reagents used for the transformation of various types of primary and secondary alcohols, 2,2,6,6-tetramethylpiperidine-1-oxoammonium salts (TEMPO$^+$ X^-; e.g. **1**),[3] the oxidized form of the nitroxyl radical TEMPO (**2**), is the mildest. Depending on the reaction conditions, either an aldehyde or a carboxylate functionality can be obtained according to the starting substrate.[4,5] The selective oxidation of the primary alcohol functions with TEMPO$^+$ salts is generally carried out by one of two methods. The first makes use of previously prepared oxoammonium salts,[6,7] whereas the other method involves nitroxide catalysts in the presence of a primary oxidant, which oxidizes the nitroxide to its oxoammonium form.[8–10] The use of electrochemical systems, in the presence of perchlorate ions as the electrolyte, was also found to be an interesting alternative[11] with the use of TEMPO-modified electrodes.[12]

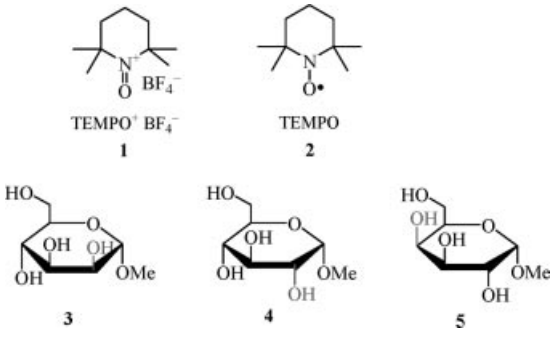

Figure 1. TEMPO$^+$ BF_4^- (**1**), TEMPO (**2**), methyl-α-D-mannopyranoside (**3**), methyl-α-D-glucopyranoside (**4**) and methyl-α-D-galactopyranoside (**5**).

Specifically in carbohydrate chemistry, the good selectivity of TEMPO$^+$ salts towards primary alcohols to obtain the corresponding carboxylic acids has been previously demonstrated.[13,14] Under such conditions, TEMPO$^+$ salts, in mild alkaline aqueous medium, lead only to the corresponding uronate carboxylic acid. Attempts to stop the oxidation at the aldehyde stage, which has been identified as the intermediate form, have not succeeded.[15] A large pH scale was investigated, but the transformation of the aldehyde functionality into a carboxylate group is substantially

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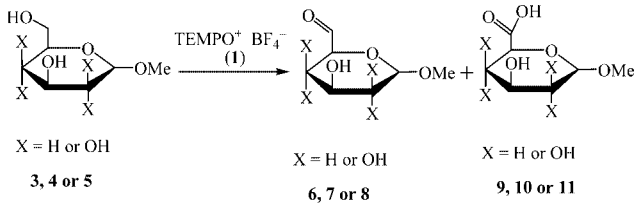
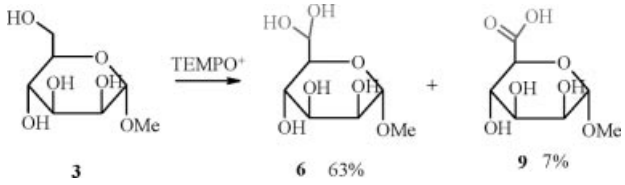
more rapid than the oxidation of the starting alcohol into the aldehyde. The focus of our work has been the discovery and application of the conditions required to stop the oxidation at the proper stage to obtain the corresponding aldehydes selectively (Scheme 1).



Scheme 1. Oxidation of monosaccharides.

In general, oxidations of sugars are carried out in an aqueous medium for evident solubility reasons, and it was demonstrated that alkaline conditions (pH between 9 and 10) provide the best results.[12] We reasoned that anhydrous conditions would avoid the hydration of the intermediate aldehyde, which would stop further oxidation, and so we decided to use dimethylformamide (DMF) as the reaction medium. Thus, TEMPO$^+$ BF_4^- (**1**) was prepared in 83% yield by electrochemical oxidation of TEMPO (**2**)[16] and used to explore the selective oxidation of anomerically methylated monosaccharides **3**, **4** and **5** (Scheme 1). Three equivalents of **1** were used to compensate for the mediamutation (oxidoreduction) between **1** and hydroxylamine **15**, which is produced during the reaction (**1** + **15** → **2**). The addition of 2,6-lutidine (3 equiv.) was necessary to neutralize the protons in the complex that formed between the alcohol and TEMPO$^+$. The concentration of organic base was found to not affect the rate of the reaction even when more than 3 equiv. were used (Scheme 2).

The reactions were carried out by stirring a mixture of carbohydrate (1 mmol), TEMPO$^+$ BF_4^- (3 mmol) and lutidine (3 mmol), maintained at 25 °C, under a nitrogen atmosphere in DMF until the alcohol concentration reached a minimum value. After the reaction was complete, DMF was removed under vacuum at 45 °C, and then water (20 mL) was added. TEMPO (**2**) was recovered quantitatively by extraction of the reaction mixture with dichloromethane. The reaction mixture was then treated with a cation exchange resin (Amberlite IR 200) to remove protonated lutidine and TEMPO$^+$ BF_4^- (**1**) and then with an anion exchange resin (Amberlite IR 900) to obtain an aqueous solution free from tetrafluoroborate ions. Finally, water was removed by lyophilization, and the obtained white solid residue was purified by column chromatography on silica gel (methanol/ethyl acetate, 1:3). Methyl-α-D-mannohexodialdo-1,5-pyranoside (**6**) was obtained in 63% yield after purification.[17] A minor amount of carboxylate **9** (7%), was also obtained (Scheme 3). The acetal form of **6** was formed during the aqueous workup.

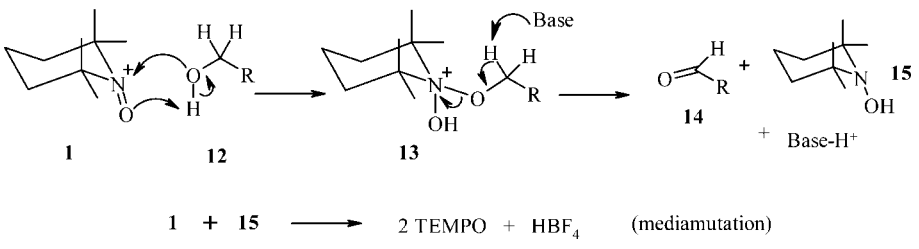


Scheme 3. Selective oxidation of methyl-α-D-mannopyranoside.

As we had expected under these conditions, the oxidation proceeded only to the required aldehyde stage. It was observed that the reaction rate was rather slow (maximum concentration reached after 110 h). The slow reactivity could be explained by several factors. One of them could be the poorer solvation of the saccharides in DMF than in water. It has also been proposed that the oxidation with **1** involves a cyclic concerted mechanism[13] where the solvent plays a key role in the formation and stability of the intermediate. The second assumption concerns the organic base used. 2,6-Lutidine might be too weak of a base, or perhaps too sterically hindered, to approach intermediate complex **13** and effect deprotonation and elimination of hydroxylamine **15** (Scheme 2). However, the choice is very limited because of the oxidizing ability of **1** towards most bases that are soluble in DMF (particularly amines).

The reactions were followed by HPLC,[18] and the substrate/products balance curve (Figure 2) was plotted. The plots of the oxidation of **3** in anhydrous and aqueous media clearly illustrate the great difference in the selectivity of the reaction.

In aqueous carbonate-buffered solution, the maximum aldehyde concentration reached about 10% at the outset of the reaction, but it was totally consumed (as previously shown by de Nooy et al.[15]) and total conversion of the starting alcohol into the corresponding uronate was achieved. Conversely, in DMF containing 2,6-lutidine, although the reaction rate was slow, the balance curves exhibit a high selectivity towards aldehyde formation. This tendency confirms that in the absence of water, oxidation of the aldehyde cannot occur. The conversion of **3** into corre-



Scheme 2. Proposed mechanism for the oxidation of the primary alcohol position of saccharides by TEMPO$^+$ BF_4^- (**1**) and the side reaction.

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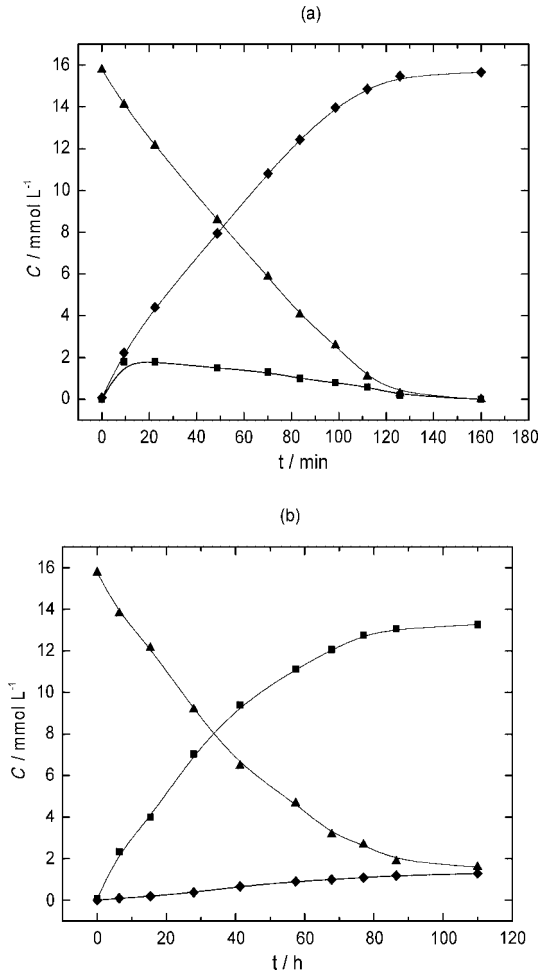
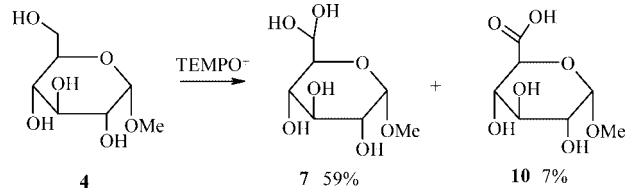


Figure 2. Material balance curve of methyl-α-D-mannopyranoside (-▲-), methyl-α-D-manno-hexodialdo-1,5-pyranoside (-■-) and methyl-α-D-mannuronate (-♦-) during the oxidation of methyl-α-D-mannopyranoside in DMF containing 2,6-lutidine (a). In comparison, a reaction performed in aqueous carbonate-buffered solution (b).

sponding aldehyde **6** reached 86%, and a longer reaction time did not allow the transformation of the remaining alcohol (8–10%). After purification, the yield of methyl-α-D-mannohexodialdo-1,5-pyranoside (**6**) was 63% and that of carboxylate **9** was 7%. The formation of **9** was certainly due to the presence of water traces in DMF, which causes partial hydration of the formed aldehyde. By performing the reaction in dry DMF, the formation of carboxylate was indeed avoided, but a decrease in the conversion of the alcohol (74% over 110 h) was observed, which resulted in a decrease in the yield of the aldehyde.

By the same procedure, the primary alcohol of glucose analogue **4** was oxidized to the corresponding aldehyde with similar kinetics and methyl-α-D-gluco-hexodialdo-1,5-pyranoside (**7**) was isolated in 59% yield (Scheme 4).[19] Carboxylate analogue **10** was obtained in 8% yield. The observed product distribution is thus essentially identical to that of the previous example and the rates of conversion, studied by HPLC, were also comparable to those reported in Table 1. Obviously, the configuration at C-2 seems to have no effect on the oxidation process by TEMPO$^+$ BF_4^- (**1**).



Scheme 4. Selective oxidation of methyl-α-D-glucopyranoside.

Table 1. Comparison of the conversions observed in the oxidation of saccharides using TEMPO$^+$ BF_4^- (**1**) or electrochemically mediated conditions, as determined by HPLC.

Entry	Saccharide	Products alc./**ald.**/carboxyl.	TEMPO$^+$ BF_4^- ratio	Electro mediated ratio
1	**3**	3:**6**:9	14:**79**:7	67:**27**:6
2	**4**	4:**7**:10	11:**81**:8	73:**21**:6
3	**5**	5:**8**:11	41:**49**:10	81:**15**:4

In contrast, the conversion of galactose analogue **5** was substantially slower and only 59% conversion after 110 h was observed, and the reaction was less selective. This is in contrast with the work reported by de Nooy et al for carboxylates.[13] However, this result tends to indicate that the configuration at the adjacent C-4 position can affect the kinetics of oxidation; the β-configuration probably induces steric hindrance either for the formation of charged complex **13** or for the approach of the base to effect elimination. Furthermore, the isolation of the resulting methyl-α-D-galactodialdo-1,5-pyranoside (**8**) proved to be particularly delicate and its total purification could not be achieved.

Following the above encouraging results, we saw an opportunity to apply the TEMPO electrochemically mediated system previously described by us[20,21] in order to reduce the amount of TEMPO used and to facilitate the purification of the products [remaining TEMPO$^+$ BF_4^- (**1**) can be electroreduced after reaction and easily extracted with dichloromethane]. The electrolyses were carried out in DMF containing 0.3 equiv. of nitroxyl radical **2**; 5 equiv. instead of 3 equiv. of lutidine were required to compensate for the consumption of the base during the hydroxylamine regeneration. Unfortunately, the conversion remained very low (<35%, see Table 1) and the electrochemically mediated oxidation did not exhibit improved selectivity. This result is probably a consequence of the insufficient concentration of TEMPO (**2**) in the cell (tenfold less than that used with the tetrafluoroborate salt).

It was also reported that reactions using TEMPO$^+$ BF_4^- for the oxidation are less rapid and less selective toward primary alcohols in acidic medium, but they still remain possible.[15] Nevertheless, under our anhydrous conditions, no conversion was observed when the reaction was carried out in neutral or acidic media. The base was indispensable and probably is involved as depicted in Scheme 2; however, its role shall be studied further.

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In conclusion, we describe herein a new procedure by which carbohydrates, protected only at the anomeric position, undergo selective oxidation to an aldehyde function only at the primary 6-position. All other nonprotected hydroxy functionalities remain untouched under our oxidation conditions. The advantage of this method is the fast preparation of the versatile aldehyde function, which can then be employed in a number of further functionalizations without the need to proceed with lengthy selective protections of the remaining hydroxy groups.

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[16] Preparation of 1-tetrafluoroborate: J. M. Bobbit, M. C. Flores, M. Zhenkum, T. Huitong, *Heterocycles* **1990**, *30*, 1131.
[17] **6**: ^{1}H NMR (300 MHz, D_2O): δ = 5.28 (d, $^3J_{5,6}$ = 1.2 Hz, 1 H, 6-H), 3.67 (td, $^3J_{2,3}$ = 8.85 Hz, $^3J_{1,2}$ = 1.0 Hz, 1 H, 2-H), 3.53–3.61 (m, 2 H, 3,4-H), 3.49 (dm, $^3J_{5,6}$ = 9.0 Hz, 1 H, 5-H), 3.43 (s, 3 H, OMe) ppm. ^{13}CNMR (300 MHz, D_2O): δ = 99.6 (C-1), 88.2 [$C(OH)_2$], 73.2 (C-3), 72.7 (C-5), 71.4 (C-2), 70.6 (C-4), 55.4 (OMe) ppm. ESI-MS: *m*/*z* = 228.9 [$M(H_2O)$ + H]$^+$, 210.9 [M + H]$^+$.
[18] HPLC equipment (DIONEX) comprised a double on-line detection system with UV (λ = 210 nm) and refractive index detectors. An Aminex HPX-87H column from Bio-Rad was used and the eluent was a sulfuric solution at a 0.6 cm^3 min^{-1} flow rate. This eluent was prepared by adding 185 µL of H_2SO_4 (density = 1.48 gmL^{-1} with 95–98% of purity) to Millipore water to obtain 1 L of solution (i.e. 3.3 mM).
[19] **7**: ^{1}H NMR (300 MHz, D_2O): δ = 5.27 (d, $^3J_{5,6}$ = 1.0 Hz, 1 H, 6-H), 4.71 (d, $^3J_{1,2}$ = 2.9 Hz, 1 H, 1-H), 3.83–3.91 (m, 2 H, 2,5-H), 3.54–3.67 (m, 2 H, 3,4-H), 3.44 (s, 3 H, -OMe) ppm. ^{13}CNMR (300 MHz, D_2O): δ = 102.4 (C-1), 89.1 [$C(OH)_2$], 72.3 (C-3), 71.5 (C-5), 70.6 (C-2), 68.8 (C-4), 55.2 (OMe) ppm. ESI-MS: *m*/*z* = 228.9 [$M(H_2O)$ + H]$^+$, 210.9 [M + H]$^+$.
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