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Metal-free oxidative lactonization of carbohydrates using molecular iodine

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ABSTRACT

We describe herein the oxidative lactonization of fully or partially protected carbohydrates using molecular iodine. Oxidation of aldose hemiacetals is generally carried out by classical procedures, which are rarely chemo or regioselective. We recently reported an optimized methodology for the oxidative amidation of aldose with functionalized amines and we found molecular iodine as a good selective oxidant. This property has been already observed by other research groups but the scope of this reactivity has never been studied for carbohydrates. The main advantage of this approach relies on the operational simplicity, elimination of use of complicated reagents and procedures.

1. Introduction

Diversely protected carbohydrate lactones are useful precursors for the synthesis of natural products, in particular for an easy access to compounds involving a *C*-glycosidic junction.[1–6] The preparation of these lactones can be obtained by classical oxidation reaction and numerous procedures have already been employed.[1–5,7–18] However, as carbohydrates contain a large number of hydroxyl groups, control of both chemo- and regio-selectivity is difficult, therefore specific protecting groups are required. Concerning the oxidation of a hemiacetalic function to produce lactones, only few methodologies are well described, and they are rarely chemoselective. Oxidative lactonization of reducing sugars can then be obtained using bromine water and a $BaCO_3$ buffer to form in situ the hypobromite/bromate oxidative agents.[19] Under these conditions, oxidation is selective for the anomeric position but restricted to water soluble derivatives. Moreover, this methodology generally provides a mixture of δ- and γ-lactones. A similar procedure with molecular iodine has been developed and has the same disadvantages.[20–23]

Another procedure has been used by Cordova and co-workers on deoxycarbohydrates but implies large amounts of MnO_2 (15 equiv).[24] Under these conditions, the hemiacetalic functional group was selectively oxidized and secondary hydroxyls were not affected. Those molecules being often key reaction intermediates, this emphasizes the need to find softer and selective methodologies.

We recently reported an optimized procedure for the direct oxidative amidation of benzylated carbohydrates using molecular iodine.[25] This process allows a large variety of functional groups and implies the lactonization, which results in the oxidation of the hemiacetal group. The reaction of this lactone with primary amines led to glyconamides in high yields. The free primary or secondary hydroxyls of these compounds being not affected during the reaction, we decided to investigate the potential of molecular iodine on the direct oxidative lactonization of carbohydrates.

This oxidation process has already been observed by other research teams but, to our knowledge, the scope of this methodology has never been studied for carbohydrates.[26–28]

2. Results

Lactol **1**[29] (easily available at multi-gram scale) was chosen as starting material for optimization of the reaction conditions defined during our previous investigations on the oxidative amidation.[25]

Thus, compound **1** was treated with iodine (2 equiv) and K_2CO_3 (2 equiv) in methanol (0.1 M) at room temperature. The reaction was monitored by TLC on silica gel, which showed complete conversion after 24 h (Scheme 1). Under these conditions, NMR analyses and mass spectroscopy indicated the presence of the desired

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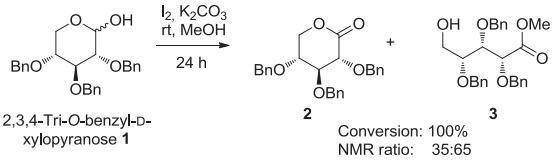
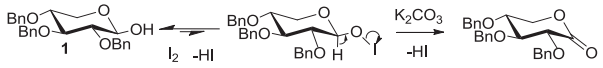


Scheme 1. Oxidative lactonization by molecular iodine in methanol.

lactone as well as the corresponding methyl ester (singlet at 3.62 ppm), which was identified as the major product (35:65, respectively).

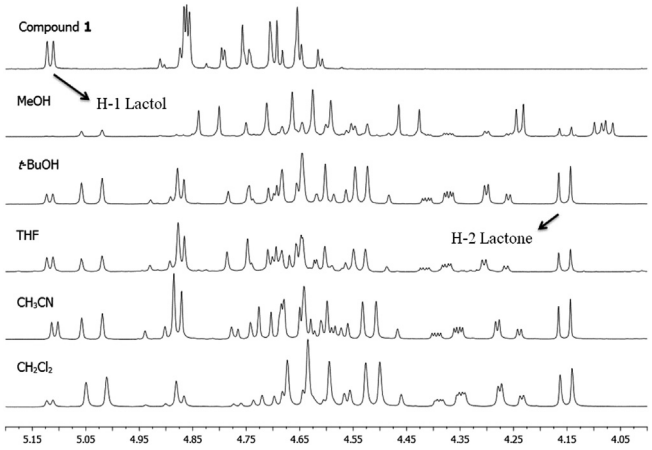
The mechanism of the reaction is believed to go through *O*-iodinated species, which allow an elimination of an HI molecule. The need of a base has been previously demonstrated.[25] When the reaction is carried out without potassium carbonate, the oxidation could not be obtained (Scheme 2).



Scheme 2. Mechanism of the oxidation process.

As reactions implying molecular iodine are affected by solvent effects,[30] we studied the influence of different solvents on the oxidative lactonization. After 24 h, reactions were directly neutralized by a saturated solution of sodium thiosulfate and the aqueous phase extracted with dichloromethane, dried and evaporated. Evaluation of crude reaction mixtures was carried out by NMR spectroscopy. As shown in Table 1, in contrast with the reaction carried out in methanol, other solvents led to a slow formation of the desired lactone **2** (doublet at 4.15 ppm).

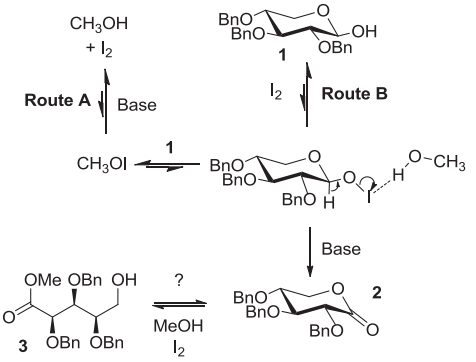
Table 1
Solvent effect using 2 equiv of iodine



Entry	Solvent	**1** (%)	**2** (%)	**3** (%)
1	CH_2Cl_2	19	81	—
2	CH_3CN	41	59	—
3	THF	47	53	—
4	*t*-BuOH	28	72	—
5	MeOH	—	35	65

Reaction conditions: I_2 (2 equiv), K_2CO_3 (2 equiv), 24 h at room temperature. When dichloromethane was replaced by *t*-BuOH, the temperature was raised to 30 °C.

As shown in Scheme 3, we assume that methanol could participate either in the formation of the *O*-iodinated species (Route A) and/or in the elimination of HI (Route B) through an acidic interaction. Moreover, the presence of iodine probably facilitates the opening of the lactone to form the non desired ester **3**.

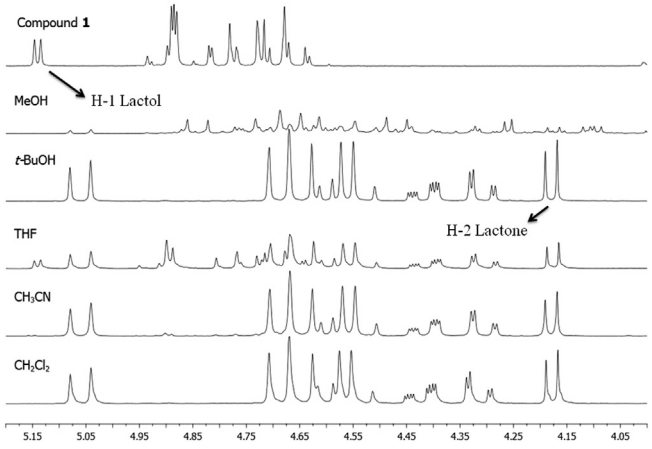


Scheme 3. Role of methanol on the oxidation process.

It is important to note that, using methanol as solvent, we were not able to avoid the formation of ester **3**, which is rapidly formed, even after 30 min of stirring (data not shown). Best yields were obtained with dichloromethane and *t*-butanol (81 and 72%, respectively).

The use of a more important excess of iodine was necessary to reduce the reaction time. Thus, we performed the reaction in different solvents using 5 equiv of molecular iodine and potassium carbonate. As before, reactions were monitored by TLC on silica gel and by NMR spectroscopy. Results are summarized in Table 2.

Table 2
Solvent effect using 5 equiv of iodine



Entry	Solvent	**1** (%)	**2** (%)	**3** (%)
1	CH_2Cl_2	—	100	—
2	CH_3CN	Traces	>98	—
3	THF	30	70	—
4	*t*-BuOH	—	100	—
5	MeOH	Complex mixture		

Reaction conditions: I_2 (5 equiv), K_2CO_3 (5 equiv), 5 h at room temperature. When dichloromethane was replaced by *t*-BuOH, the temperature was raised to 30 °C.

In dichloromethane and *t*-butanol the reaction is quantitative and the crude reaction mixture was very clean. Using anhydrous or analytical grade THF, 30% of compound **1** were recovered. Acetonitrile seems to be a better solvent than THF, but after 5 h, traces of starting material were detected by ^{1}H NMR (<5%). These reaction conditions are thus well adapted for the oxidative lactonization if dichloromethane or *t*-butanol is used as solvent. We demonstrated that THF can be used but will induce longer reaction times. In the case of methanol (entry 5), a complex mixture has been obtained. Compound **3** was detected by mass spectrometry and NMR spectroscopic analysis. We were also able to detect by ^{13}C NMR the presence of a mixture of α- and β-methyl-D-xylopyranosides. We assume that using a large excess of iodine, its Lewis acid property

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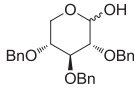
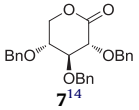
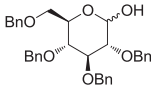
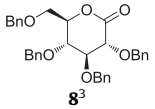
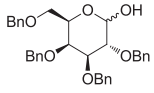
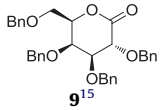
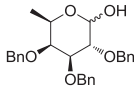
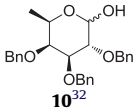
allows the formation of acetals. In comparison with methanol, the same reactivity was observed using 2,2,2-trifluoroethanol despite its weakest nucleophilicity.

The structure of the 2,3,4-tri-*O*-benzyl-D-xylono-1,5-lactone **2** is in accordance with the literature.[14] The presence of a $^4J_{H,H}$ coupling constant indicates clearly a predominantly $^2S_4$ conformation ($^4J_{3,5eq}$=1.5 Hz).

Finally, to extend the scope of this methodology and to avoid the use of too large excess of iodine, which could interact with protecting groups like acetonides,[30] we attempted the oxidative lactonization using 3 equiv of iodine and potassium carbonate.

The reaction was carried out in dichloromethane, which has been selected regarding to the results previously obtained (Tables 1 and 2). Different benzylated carbohydrates were tested and results are summarized in Table 3.

Table 3
Oxidation of benzylated aldose hemiacetals to δ-lactones[a]

Entry	Substrate	Product	Time	Yield
1	 **1**	 **7**[14]	16 h	100%
2	 **4**	 **8**[3]	24 h	100%
3	 **5**	 **9**[15]	16 h	100%
4	 **6**	 **10**[32]	16 h	100%

[a] Reaction conditions: Carbohydrate (0.238 mmol), K_2CO_3 (0.713 mmol), I_2 (0.713 mmol), CH_2Cl_2 (2.4 mL) at room temperature for 16–24 h.

Using 3 equiv of iodine and potassium carbonate, benzylated derivatives **1**, **5** and **6** were quantitatively oxidized after 16 h.[31]

In the case of compound **4**, 24 h were required, which is in agreement with the difference of reactivity of the anomeric position described during our previous researches with glucose derivatives.[25] Similar observations have been reported upon palladium-catalysed oxidation of benzylated aldose hemiacetals.[33]

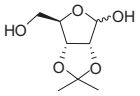
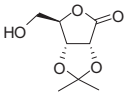
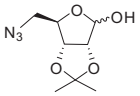
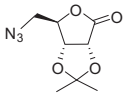
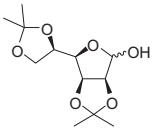
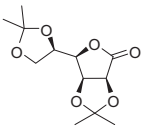
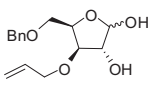
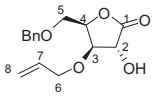
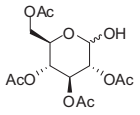
We then examined the scope of this process using various carbohydrates bearing different functional groups (Table 4).

Under these conditions, reaction times were shorter than those observed with benzylated derivatives (2–5 h). 2,3-*O*-Isopropylidene-D-ribofuranose **11** was chemoselectively oxidized with 80% yield (entry 1). Primary and secondary hydroxyl groups were not affected by iodine (entry 1 and 4).

It is also important to note that acetonides **11**, **12** and **13** were not deprotected (entry 1, 2 and 3), which highlights the mild reaction conditions despite the Lewis acid nature of molecular iodine.

Allyl ether protecting groups are known to be reactive with electrophiles like bromine or iodine. Deprotection of unsaturated ethers can be observed depending on the solvent used. In the case of dichloromethane, the addition of iodine to the double bond of the allyl group can be observed as well as the deprotection. However, acetonitrile or *t*-BuOH do not seem to affect these unsaturated groups.[30] As shown in Table 4, compound **14** behaves differently

Table 4
Oxidative lactonization of aldose hemiacetals[a]

Entry	Substrate	Product	Time	Yield[c]
1	 **11**[34]	 **16**[35]	3 h	80%
2	 **12**[36]	 **17**[36]	3 h	100%
3	 **13**[37]	 **18**[37]	5 h	100%
4	 **14**[37]	 **19**	5 h[b]	70%
5	 **15**[39]	—	2 h	—

[a] Reaction conditions: Carbohydrate (0.238 mmol), K_2CO_3 (0.713 mmol), I_2 (0.713 mmol), CH_2Cl_2 (2.4 mL) at room temperature for 16–24 h.
[b] Dichloromethane was replaced by *t*-BuOH and temperature raised to 30 °C.
[c] Yields after purification by column chromatography on silica gel.

towards lactonization depending on the solvent used. When the reaction was performed in dichloromethane, the different products formed during the oxidation process were not soluble in organic solvents. This is probably due to the deprotection of the allyl group. Nevertheless, the use of *t*-BuOH to replace dichloromethane did not induce this deprotection and lactone **19** was obtained in 70% yield after 5 h. One limitation of this procedure was reached when using 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose **15**. Whatever the applied conditions, the deprotection of acetates could not be avoided.

3. Conclusion

To conclude, this methodology allows quick access in one-step to lactones starting from variously substituted lactols. Dichloromethane and *t*-BuOH seem to be the most indicated solvents. Dichloromethane allows the oxidation at room temperature but the use of *t*-BuOH involves heating the reaction mixture to 30 °C. However, this alcohol is surely more eco-friendly and should be favoured for environmental reasons. The advantages of this method are the operational simplicity, elimination of use of complicated reagents and procedures, and chemoselectivity of the reaction.

4. Experimental section

4.1. General

All reagent-grade chemicals were obtained from commercial suppliers and were used as received. Characterizations of known

compounds were in accordance with literature. Optical rotations were recorded in CH_2Cl_2 solution. FTIR spectra were obtained using ATR and are reported in cm^{-1}. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The proton and carbon signal assignments were determined from decoupling experiments, COSY spectra and HSQC spectra. TLC were performed on Silica F_{254} and detection by UV light at 254 nm or by charring with cerium molybdate reagent. Column chromatography was performed on Silica Gel 60 (230 mesh). High-resolution electrospray mass spectra in the positive ion mode were obtained on a Q-TOF Ultima Global hybrid quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (*Z*-spray) ion source and an additional sprayer (Lock Spray) for the reference compound. The source and desolvation temperatures were kept at 80 and 150 °C, respectively. Nitrogen was used as the drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 3.5 kV, the cone voltage 100 V and the RF lens1 energy was optimised for each sample (40 V). For collision-induced dissociation (CID) experiments, argon was used as collision gas at an indicated analyser pressure of 5×10^{-5} Torr and the collision energy was optimised for each parent ion (50–110 V). Lock mass correction, using appropriate cluster ions of sodium iodide $(NaI)_nNa^+$, was applied for accurate mass measurements. The mass range was typically 50–2050 Da and spectra were recorded at 2 s/scan in the profile mode at a resolution of 10,000 (FWMH).

4.2. General procedure A for oxidative lactonization reactions

Aldose (0.476 mmol) was dissolved in dichloromethane (analytical grade; 0.1 M) and K_2CO_3 (3 equiv) and iodine (3 equiv) were added. The solution was stirred at room temperature and monitored by TLC on silica gel. Then a saturated aqueous solution of $Na_2S_2O_3$ (1 mL) was added with vigorous stirring until complete disappearance of the dark brown colour. The organic phase was isolated and the aqueous phase extracted with ethyl acetate (3×20 mL). All the organic phases were combined, dried over $MgSO_4$ and evaporated under reduced pressure. When needed, the residue was purified by chromatography on silica gel (cyclohexane/EtOAc) to give the desired lactone.

4.3. 3-*O*-Allyl-6-*O*-benzyl-D-xylono-1,4-lactone (19)

Lactol **14**[38] (200 mg, 0.714 mmol) was treated as described in the general procedure using K_2CO_3 (296 mg, 2.14 mmol) and I_2 (543 mg, 2.14 mmol). The resulting crude product was purified by silica gel chromatography (cyclohexane/EtOAc gradient) to provide **19** (139 mg, 70%) as a colourless oil: $[\alpha]_D^{20}$ +65.0 (*c* 0.2, CH_2Cl_2); IR (ATR) 1786 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.12 (m, 5H, Ph), 6.00–5.80 (m, 1H, H-7), 5.40–5.14 (m, 2H, H-8), 4.75 (d, *J*=8.0 Hz, 1H, H-2), 4.64 (dt, *J*=7.8, 2.7 Hz, 1H, H-4), 4.58 (d, *J*=12.2 Hz, 1H, C*H*$_2$-Ph), 4.53 (d, *J*=12.1 Hz, 1H, C*H*$_2$-Ph), 4.31 (t, *J*=7.9 Hz, 1H, H-3), 4.30–4.23 (m, 1H, H-6), 4.18–4.07 (m, 1H, H-6), 3.77 (dd, *J*=11.1, 2.8 Hz, 1H, H-5), 3.73 (dd, *J*=11.0, 2.9 Hz, 1H, H-5), 3.28 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (C-1), 137.7 (Ph), 133.9 (C-7), 128.5 (Ph), 127.8 (Ph), 127.6 (Ph), 117.8 (C-8), 80.4 (C-3), 77.3 (C-4), 73.7 (C*H*$_2$-Ph), 72.3 (C-2), 71.7 (C-6), 67.1 (C-5); HRMS calcd for $C_{15}H_{18}O_5Na$ 301.1052, found *m*/*z* 301.1047 $[M+Na]^+$.

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