Tetrahedron 69 (2013) 5880–5883

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Metal-free oxidative lactonization of carbohydrates using molecular iodine

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ARTICLE INFO

Article history:
Received 25 March 2013
Received in revised form 7 May 2013
Accepted 9 May 2013
Available online 15 May 2013

Keywords:
Oxidative lactonization
Iodine chemistry
Metal-free oxidation
Carbohydrates chemistry
Lactone

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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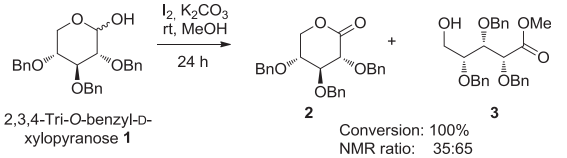
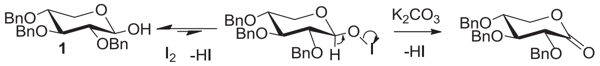
0040-4020/$ – see front matter
http://dx.doi.org/10.1016/j.tet.2013.05.021



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).

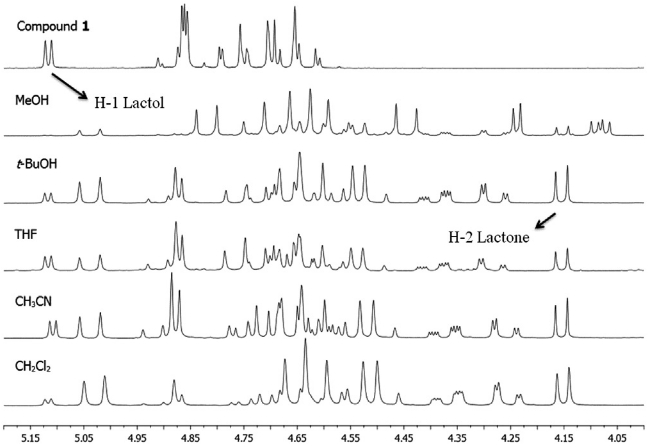
The mechanism of the reaction is believed to go through *O*-iodinated species, which allow an elimination of an HI molecule. The need of a base has been previously demonstrated.[25] When the reaction is carried out without potassium carbonate, the oxidation could not be obtained (Scheme 2).



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).

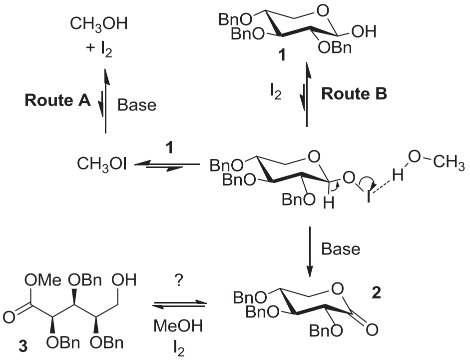
Table 1
Solvent effect using 2 equiv of iodine



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**.

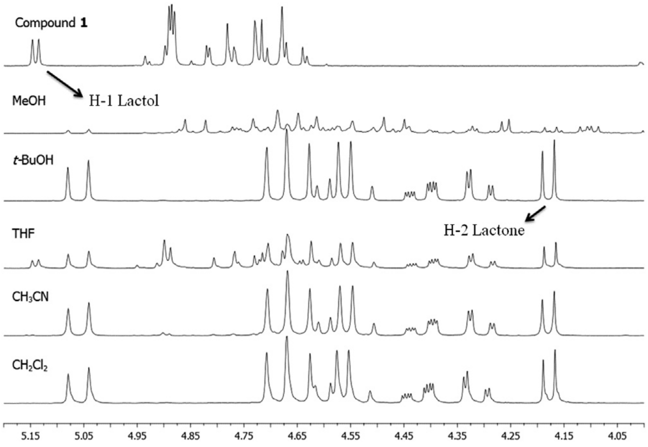


Scheme 3. Role of methanol on the oxidation process.

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 ^1H 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