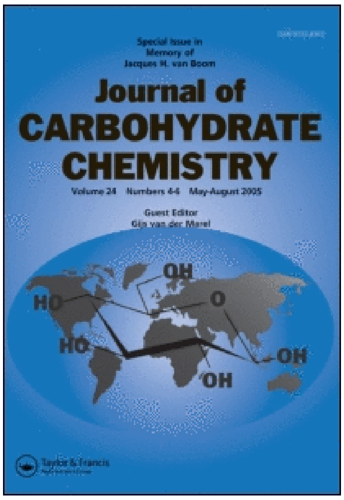

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A Novel Deoxygenation of Hydroxy Groups Activated by a Vicinal Carbonyl Group *via* Reaction with Ph_3P/I_2/Imidazole

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A NOVEL DEOXYGENATION OF HYDROXY GROUPS ACTIVATED BY A VICINAL CARBONYL GROUP *VIA* REACTION WITH Ph_3P/I_2/IMIDAZOLE[1,2]

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ABSTRACT

A new procedure for a direct conversion of an α-hydroxy sugar ester, lactone or amide into the corresponding α-deoxyester, lactone or nitrile using the system Ph_3/I_2 /imidazole is reported. Its efficiency is illustrated by deoxygenation in good yields at position 2 of methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate (**1**), and at positions 5 of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranuronamide (**3**) and 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**5**). Reaction with 5,6-*O*-isopropylidene-L- and -D-*gulo*-1,4-lactones (**7**) and (**9**), respectively, afforded the corresponding α,β-unsaturated lactones in good yields.

INTRODUCTION

Deoxy sugars are widespread in nature and constituents of antibiotics and other biologically active molecules. The deoxygenation methods described in the literature usually involve two or more steps; nucleophilic displacement of an activated hydroxyl group by a halide followed by reduction, or radical deoxygenation, such as reduction with

Bu_3SnH of the appropriate thiocarbonates.[3,4] Samarium diiodide is an efficient reagent for deoxygenation of α-oxygenated esters[5] and also of aldonolactones.[6,7,8] Aldonolactones have also been deoxygenated by reaction of their 2-*O*-trifluoromethanesulfonate esters with lithium iodide trihydrate.[9] Synthesis of 2-deoxylactones was also accomplished from glycerol derivatives *via* highly enantioselective carbon-hydrogen insertion reactions.[10]

RESULTS AND DISCUSSION

We wish to report a one step deoxygenation of hydroxy groups activated by the presence of a vicinal carbonyl group, using the reagent Ph_3P/I_2 /imidazole. This system is known to replace a hydroxy group with an iodo function in carbohydrates with inversion of configuration.[11-14] This system was tried for the deoxygenation of the α-hydroxyester methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate (**1**),[15-17] synthesized by reaction of D-glucono-1,5-lactone with dimethoxypropane/*p*-TsOH in acetone

Synthesis of the deoxyester methyl 2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-*arabino* -hexonate (**2**) was accomplished in 55% yield using the above mentioned reaction system. The presence of a C-2 methylene group was confirmed from the ^1H NMR and ^{13}C NMR spectra. H-2a and H-2b each appeared as a double doublet at δ 2.51 and δ 2.78 ($J_{2a,2b}$ = 15.80 Hz, $J_{2a,3}$ = 8.67 Hz, $J_{2b,3}$ = 3.27 Hz) and C-2 at δ 38.3 (Tables 3, 4 and 5). This ester has been previously synthesized by hydrogenation of the corresponding 2-chloro-2-deoxy precursor.[18]

Deoxygenation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranuronamide (**3**)[19] afforded the deoxynitrile 3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranurononitrile (**4**) in 74% yield. Comparison of its ^1H NMR spectrum with that of the substrate showed that it contained a new multiplet at δ 2.78 - 2.72 corresponding to H-5a and H-5b. The unexpected dehydration of the amide leading to the formation of the nitrile was detected by the presence of its characteristic IR band at 2260 cm^{-1} . The ^{13}C NMR spectrum was in agreement with the proposed structure containing signals at 17.39 and δ 116.96 corresponding to the methylene group and nitrile carbons, respectively. The high resolution mass spectrum of **4** also supported the assigned structure.

Table 1. α-Deoxygenation of Carbonyl Compounds and Synthesis of α,β-Unsaturated-γ-Lactones Using Ph_3P/I_2/Imidazole in Toluene.

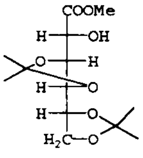
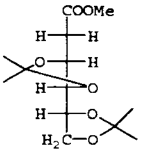
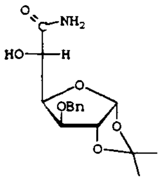
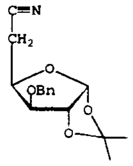
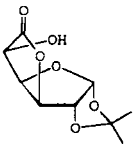
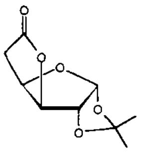
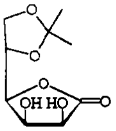
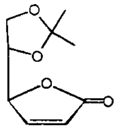
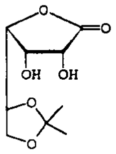
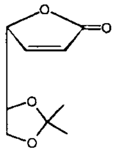
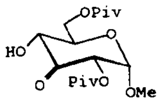
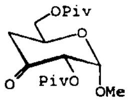
Starting Material	Derivative Obtained	Reaction Temp (°C)	Reaction Time	Yield (%)
 1	 2	90	3 days	55
 3	 4	60	3.5 h	74
 5	 6	60	3.5 h	67
 7	 8	60	3.5 h	51
 9	 10	60	3.5 h	59
 11	 12	60	3.5 h	61

Table 2. Physical Properties, IR and HRMS Data.

Compd. No.	R_f	[α]	mp. (°C)	IR (cm^{-1})	HRMS Calcd	HRMS Found
2	0.50[a]	+15.2 (*c* 1, CH_2Cl_2)	33-34	1738 (C=O)[d] 1378 (isop)	274.141	274.144
4	0.60[b]	-48.2 (*c* 1, $CHCl_3$)	115-117	2260 (C≡N)[f] 1383 (isop)	289.329	289.331
6	0.49[b]	+ 108.0 (*c* 1, CH_2Cl_2)	91-93	1785 (C=O)[d] 1386 (isop)	-	-
8	0.63[c]	-107.3 (*c* 1, CH_2Cl_2)	syrup	1758 (C=O)[e] 1606 (C=C) 1380 (isop)	184.073	184.069
10	0.63[c]	+107.3 (*c* 1, CH_2Cl_2)	syrup	1758 (C=O)[e] 1606 (C=C) 1380 (isop)	-	-

a. 1:8 EtOAc/toluene. b. 1:5 EtOAc/toluene. c. 1:2 EtOAc/toluene.
d. in $CHCl_3$. e. neat. f. in Kbr.

Treatment of 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**5**) with the title reagent led to the formation of the corresponding deoxylactone 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranurono-6,3-lactone (**6**) in 67% isolated yield, higher than that previously reported (57%) when the system Ph_3PBr_2/Ph_3P was used.[20]

The enantiomeric lactones 2,3-dideoxy-5,6-isopropylidene-L- and -D-*threo*-hex-2-enono-1,4-lactones (**8**) and (**10**) were isolated in 51% and 59% yield, respectively, when 5,6-*O*-isopropylidene-L- and -D-*gulo*-1,4-lactones (**7**) and (**9**), respectively, were used as substrates, although some physical data are not in complete agreement with those previously reported for **8**.[21] The ^{1}H NMR spectra of the enantiomers **8** and **10** confirmed

Table 3. ^{1}H NMR Spectroscopic Data - Chemical Shifts (δ in ppm) of Compounds **2**, **4**, **6**, **8** and **10** in $CDCl_3$.

Compd No.	H-1	H-2a	H-2b	H-3	H-4	H-5a	H-5b	H-6a	H-6b	Others
2	–	2.51 dd	2.78 dd	4.27 ddd	3.52 t	3.98 ddd	–	3.88 dd	4.07 dd	3.65[a] 1.33[b] 1.31[c] 1.21[b]
4	5.91 d	4.64 d	–	4.00 d	4.51-4.45 m	2.78-2.72 m	2.78-2.72 m	–	–	7.37-7.30[d] 4.74[e] 4.70[e] 4.58[f] 4.54[f] 1.50[b] 1.32[b]
6	5.97 d	4.85-4.81 m	–	4.85-4.81 m	5.01-4.98 m	2.73-2.71 m	2.73-2.71 m	–	–	1.52[b] 1.35[b]
8	–	6.16 dd	–	7.39 dd	5.03-5.00 m	4.38-4.33 m	–	3.75 dd	4.01 dd	1.36[b] 1.28[b]
10	–	6.16 dd	–	7.39 dd	5.03-5.00 m	4.38-4.33 m	–	3.75 dd	4.01 dd	1.36[b] 1.28[b]

a. 3H, OMe. b. 3H, Me (isop). c. 6H, Me (isop). d. 5H-arom (Bn). e. 1H, part A of AB system (Bn). f. 1H, part B of AB system (Bn).

Table 4. ^1H NMR Spectroscopic Data - Coupling Constants J (in Hz) - for Compounds **2**, **4**, **6**, **8** and **10** in $CDCl_3$.

J	2	4	6	8	10
$J_{1,2}$	–	3.69	3.75	–	–
$J_{2a,2b}$	15.8	–	–	–	–
$J_{2a,3}$	8.67	–	–	5.88	5.88
$J_{2b,3}$	3.27	–	–	–	–
$J_{2,4}$	–	–	–	2.01	2.01
$J_{3,4}$	8.0	3.39	–	1.32	1.32
$J_{4,5}$	8.0	–	–	–	–
$J_{5,6a}$	4.57	–	–	5.31	5.31
$J_{5,6b}$	5.86	–	–	6.69	6.69
$J_{6a,6b}$	7.79	–	–	8.82	8.82
$J_{A,B}$	–	11.58	–	–	–

the proposed structures, each presenting a double doublet at δ 7.39 corresponding to H-3 ($J_{2,3}$ = 5.88 Hz, $J_{3,4}$ = 1.32 Hz), and another double doublet at δ 6.16 due to H-2 with a long range coupling with H-4 ($J_{2,4}$ = 2.01 Hz). The ^{13}C NMR signals for C-2 and C-3 at δ 122.3 and δ 151.6, respectively, were also in agreement with the formation of the double bond.

The one-step conversion of these *cis*-vicinal diols into olefins was unexpected since Garegg and Samuelsson[22] reported this reagent system as appropriate for the one-step conversion of *trans*-1,2-diols in nonactivated pyranosidic systems into the corresponding olefins and ineffective for converting *cis*-1,2-diols into the corresponding olefins, unless tetrabutyl ammonium iodide and potassium iodide were added. Preparation of 4-substituted

Table 5. ^{13}C NMR Spectroscopic Data (δ in ppm) for Compounds **2**, **6**, **8** and **10** in CDCl$_3$.

Compd No.	C-1	C-2	C-3	C-4	C-5	C-6	Others
2	171.0	38.3	76.6	80.3	76.8	67.7	109.6[a] 109.5[a] 51.7[b] 27.0 26.9[c] 26.6[c] 25.1[c]
4	105.31	81.96[d]	81.51[d]	75.89	17.39	116.96	128.68[e] 128.34[e] 128.00[e] 136.81[f] 112.24[a] 72.51[g] 26.85[c] 26.26[c]
6	106.2	85.4[d]	82.4[d]	78.0	35.8	174.2	112.7[a] 26.9[c] 26.4[c]
8	177.7	122.3	151.6	80.9[d]	73.2[d]	63.6	24.9[c] 23.9[c]
10	177.7	122.3	151.6	80.9[d]	73.2[d]	63.6	24.9[c] 23.9[c]

a. Cq (isop) b. OMe. c. Me (isop) d. These signals may be interchanged. e. CH (Ph)
f. Cq (Ph). g. CH$_2$ (OBn)

2,3-unsaturated lactones was previously described in the literature using a three step synthesis consisting of regioselective bromination of position 2, followed by acetylation of OH-3 and treatment with NaHSO$_3$ in aqueous alcohol.[23]

The Ph$_3$/I$_2$/imidazole system was previously reported by us to accomplish deoxygenation at position 4 of the 3-ketosugar **11** in 61% yield.[24]

CONCLUSION

Ph_3/I_2/imidazole seems to be a promising reagent system for converting α-hydroxyketones, esters, and lactones into the corresponding α-deoxy compounds. The system promoted α-deoxygenation and dehydration of an alduronamide, providing a simple synthetic procedure for obtaining the deoxygenated nitrile. The reagent was also used to transform activated *cis*-1,2-diols in good yields into α,β-unsaturated lactones.

EXPERIMENTAL

General methods. Melting points were determined with a melting point apparatus (Tottoli) and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter and IR spectra were recorded with an IR-Hitachi 270-50 spectrophotometer. ^{1}H NMR spectra experiments were run with a Brucker CXP 300. Chemical shifts are expressed in parts per million downfield from TMS. ^{13}C NMR spectra were recorded with a Brucker AC-250 P spectrometer at 62.90 MHz. Mass spectra were obtained with a FTICR spectrometer either by laser desorption (1064 nm) or by electron impact. The progress of all reactions was monitored by thin layer chromatography (TLC) using aluminum sheets precoated with silica gel $60F_{254}$ to a thickness of 0.2 mm. Compounds were detected with UV light (254 nm) and/or by spraying the sheets with a 3% vanillin-sulfuric acid solution. Column chromatography was conducted under pressure (2 bar) with silica gel (0.043-0.063 mm).

General procedure for the deoxygenation reaction: Iodine (3 equiv), triphenylphosphine (4 equiv) and imidazole (4 equiv) were stirred in anhydrous toluene at room temperature for 10 min and a solution of the substrate (1 mmol) in toluene (5 mL) was then added. The reaction mixture was stirred at 60 °C during 3.5 h. The work up consisted of filtration and solvent evaporation, followed by column chromatography of the residue.

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