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Note

Palladium-catalyzed oxidation of benzylated aldose hemiacetals to lactones

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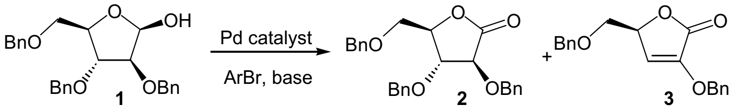
Abstract—Benzyl protected sugar hemiacetals are oxidized to the corresponding lactones in excellent yields using bromobenzene, K_2CO_3 and the $Pd(OAc)_2/PPh_3$ catalytic system.

Keywords: Oxidation; Catalysis; Palladium; Sugar hemiacetals; Sugar lactones; Bromobenzene

Metal-catalyzed oxidation appears to be advantageous from economical and environmental points of view. Nevertheless, oxidation of the anomeric hydroxyl group of carbohydrates is still mainly carried out using classical stoichiometric oxidants although various catalytic processes have been proposed.[1–7] Pursuing our studies of palladium-catalyzed oxidations of alcohols,[6] we now report the highly efficient oxidation of benzyl protected sugar hemiacetals using the Yoshida's methodology,[6,8,9] which has also been developed by Choudary and co-workers.[10,11] This process, which involves Pd^{II} as catalyst and an aryl halide as hydrogen acceptor, has allowed the oxidation of various alcohols but to our knowledge has never been used for the oxidation of sugar compounds.

The oxidation of 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**1**) was chosen for the optimization of the reaction conditions (Eq 1, Table 1).

When **1** was treated with 4-bromobiphenyl[†] (2 equiv), *t*-BuONa (2 equiv), $Pd(OAc)_2$ (0.1 equiv) and PPh_3 (0.2 equiv) in refluxing dioxane for 1 h, lactones **2**[12–14] and **3**[14,15] were isolated in 44% and 17% yield, respectively; only 21% of the substrate was recovered indicating some decomposition reaction (run 1). The formation of **3** was ascribed to a base-mediated elimination reaction from **2**.[14,15] The conversion yield was greatly diminished in modifying the $Pd(OAc)_2/PPh_3$ ratio (runs 2 and 3). To overcome undesirable decomposition and elimination reactions, the oxidation was carried out using other bases and at reflux of THF



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[†] This aromatic halide was chosen for initial studies because we expected that the presence of the *p*-phenyl substituent could facilitate the insertion of the reduced Pd species into the C–Br bond.

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Table 1. Optimization of reaction conditions in the oxidation of 2,3,4-tri-*O*-benzyl-β-D-arabinofuranose (**1**)[a]

Run	Pd catalyst (mol %)	Ligand (equiv/Pd)	Aryl halide 1 equiv/**1**	Base 2 equiv/**1**	Solvent	Time, h	Conv., %[b]	**2**, %[b]	**3**, %[b]
1	$Pd(OAc)_2$ (10)	PPh_3 (2)	Ph–PhBr	*t*-BuONa	Dioxane	1	79	44[c]	17[c]
2	$Pd(OAc)_2$ (10)	PPh_3 (4)	Ph–PhBr	*t*-BuONa	Dioxane	4	10	Trace	Trace
3	$Pd(OAc)_2$ (10)	PPh_3 (1)	Ph–PhBr	*t*-BuONa	Dioxane	4	10	Trace	Trace
4	$Pd(OAc)_2$ (10)	PPh_3 (2)	Ph–PhBr	NaOAc	THF	4	0		
5	$Pd(OAc)_2$ (10)	PPh_3 (2)	Ph–PhBr	NEt_2(*i*-Pr)	THF	4	0		
6	$Pd(OAc)_2$ (10)	PPh_3 (2)	Ph–PhBr	DBU	THF	4	0		
7	$Pd(OAc)_2$ (10)	PPh_3 (2)	Ph–PhBr	Cs_2CO_3	THF	2	100	100	0
8	$Pd(OAc)_2$ (5)	PPh_3 (2)	Ph–PhBr	Cs_2CO_3	THF	4.5	100	85	15
9	$Pd(OAc)_2$ (5)	PPh_3 (2)	Ph–PhBr	Cs_2CO_3	THF	48	100	10	90
10	$Pd(PPh_3)_4$ (5)	—	Ph–PhBr	Cs_2CO_3	THF	4	65	15	50
11	$Pd_2(dba)_3{\cdot}CHCl_3$ (5)	PPh_3 (2)	Ph–PhBr	Cs_2CO_3	THF	4	0		
12	$Pd(acac)_2$ (5)	PPh_3 (2)	Ph–PhBr	Cs_2CO_3	THF	4	0		
13	$Pd(OAc)_2$ (5)	PPh_3 (2)	Ph–PhBr	K_2CO_3	THF	4	100	100	0
14	$Pd(OAc)_2$ (5)	PPh_3 (2)	Ph–PhBr	K_2CO_3	THF	20	100	100	0
15	$Pd(OAc)_2$ (5)	P(*o*-tol)$_3$ (2)	Ph–PhBr	K_2CO_3	THF	4	100	100	0
16	$Pd(OAc)_2$ (5)	(*R*)-BINAP (2)	Ph–PhBr	K_2CO_3	THF	2	100	100	0
17	$Pd(OAc)_2$ (5)	PPh_3 (2)	PhBr	K_2CO_3	THF	2	100	100	0
18	$Pd(OAc)_2$ (2)	PPh_3 (2)	PhBr	K_2CO_3	THF	6	100	95[c]	
19	$Pd(OAc)_2$ (1)	PPh_3 (2)	PhBr	K_2CO_3	THF	6	100	100	0
20	$Pd(OAc)_2$ (0.5)	PPh_3 (2)	PhBr	K_2CO_3	THF	40	50	25	25

[a] All reactions were carried out at reflux under Ar with 0.5 mmol of **1** and 4 mL of solvent. The course of the reaction was monitored by TLC.

[b] Estimated by ^1H NMR analysis.

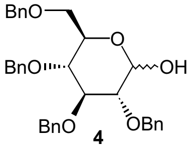
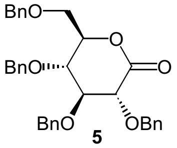
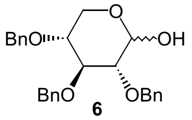
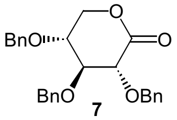
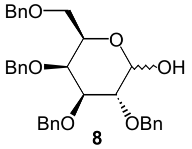
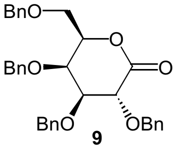
[c] Isolated yield.

instead of dioxane. Screening of the base indicated that the nature of the base play a key role, sodium acetate, diethyl(*i*-propyl)amine and DBU being ineffective (runs 4–6) while the use of 2 equiv of Cs_2CO_3 with 0.1 equiv of $Pd(OAc)_2$ and 0.2 equiv of PPh_3 led to a complete and selective consumption of **1** to **2** in 2 h (run 7). However, decreasing the amount of catalyst increased the reaction time to reach a complete reaction; this resulted in a lower selectivity and the butenolide could become the main compound (runs 8 and 9). The use of $Pd(PPh_3)_4$, $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$ or $Pd(acac)_2/PPh_3$ as catalytic system was either less or not effective (runs 10–12). Switching from Cs_2CO_3 to K_2CO_3 was of great interest because **2** was selectively obtained even after a prolonged reaction time (runs 13 and 14). Associated to $Pd(OAc)_2$, the sterically hindered tris(*o*-tolyl)phosphine and the bidentate phosphine, (*R*)-BINAP, were also excellent ligands for this reaction (runs 15 and 16). Interestingly, replacing 4-bromobiphenyl by bromobenzene provided **2** quantitatively through a fast reaction (run 17). Bromobenzene is more convenient than 4-bromobiphenyl as hydrogen acceptor; indeed, it is much cheaper and allows an easier product separation since it produces benzene instead of biphenyl. Thus, an aqueous work-up followed by evaporation of volatiles at 70 °C under diminished pressure led to a crude white-solid product, which could be used without additional purification in a multistep synthesis since only minute amounts of phosphorus compounds were detected as impurities by NMR analysis. Furthermore, 2 and even 1 mol % of the catalyst also provided **2** quantitatively, a longer reaction time being however necessary (runs 18 and 19). A further decrease of the amount of catalyst to 0.5 mol % reduced both conversion and selectivity (run 20).

We then examined the scope of this process using the D-glucopyranose **4**, D-xylopyranose **6** and D-galactopyranose **8** analogues and the $Pd(OAc)_2/PPh_3/PhBr/K_2CO_3$ system in refluxing THF (Table 2). With 1 mol % of $Pd(OAc)_2$, the oxidation of the D-glucose derivative **4** (entry 1) was neither efficient nor selective, the ^1H NMR analysis of the crude reaction mixture after heating for 8 h showing the presence of lactol **4**, lactone **5**[14,16–18] and 2,4,6-tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone[17] (the elimination reaction product) in the ratio 2:5:1. Fortunately, increasing the amount of $Pd(OAc)_2$ to 2 mol % resulted in the complete conversion of **4** in 4 h leading to **5** in 98% isolated yield. Under such experimental conditions, D-xylose derivative **6**[19] and D-galactose derivative **8** afforded the corresponding lactones **7**[20] and **9**,[16] respectively, with excellent yields (entries 2 and 3). In contrast, an acetyl protected sugar hemiacetal such as 2,3,4-tri-*O*-acetyl-D-xylopyranose was almost quantitatively recovered under the above oxidation conditions. A possible explanation for this reluctance to oxidation could be the ability of the alcohol substrate or the lactone product to chelate too strongly the palladium thus inhibiting the oxidation as already proposed for other unreactive alcohols.[6,21,22]

In conclusion, we have developed a mild process for the oxidation of benzyl protected sugar hemiacetals into lactones with high yields. Owing to the great importance of the benzyl-protecting group in carbohydrate chemistry,[23] this efficient catalytic oxidation method, which

Table 2. Palladium-catalyzed oxidation of benzyl protected sugar hemiacetals to δ-lactones[a]

Entry	Substrate	Product	Time, h	Isolated yield, %
1	 **4**	 **5**	8[b] 4[d]	56[c] 98
2	 **6**	 **7**	7[d]	94
3	 **8**	 **9**	6[d]	94

[a] Reaction conditions: carbohydrate (0.5 mmol), PhBr (1.0 mmol), K_2CO_3 (1.0 mmol), $Pd(OAc)_2/2PPh_3$ (cat.), THF (5 mL), heating to reflux under Ar. After conventional work-up, the products were purified by flash chromatography (9:1 petroleum ether/EtOAc).

[b] $Pd(OAc)_2$: 1 mol%, PPh_3: 2 mol%.

[c] ^1H NMR yield.

[d] $Pd(OAc)_2$: 2 mol%, PPh_3: 4 mol%.

requires only commercial reagents, can be of practical use for glyconolactone synthesis.

1. Experimental

1.1. General

NMR spectra were determined in $CDCl_3$ with a Bruker AC 250 spectrometer (^1H: 250 MHz, ^{13}C: 62 MHz). E. Merck Silica Gel 60 F_{254} (0.25 mm plates) was employed for analytical TLC. THF was distilled over sodium/benzophenone prior to use. Substrates **1**, **4** and **8** were commercial compounds from SIGMA, FLUKA and ACROS, respectively, and used as received; **6**[19] was prepared from D-xylose by allylation of the anomeric hydroxyl[24] followed by benzylation of the other hydroxyls[24] and then selective Pd-mediated deallylation.[25] All reactions were carried out under Ar atmosphere.

Typical oxidation procedure as applied to **1**. To a mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and PPh_3 (13.1 mg, 0.05 mmol) in dry THF (20 mL) stirred under Ar for 2 min was added 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose **1** (1.050 g, 2.5 mmol), K_2CO_3 (690 mg, 5 mmol) and PhBr (0.56 mL, 5.00 mmol). The mixture was stirred vigorously under reflux for 6 h, cooled to room temperature, diluted with water and extracted with EtOAc. The organic layer was washed with water and then dried over anhyd $MgSO_4$. Filtration was followed by removal of the solvents and the excess of PhBr at 70 °C under diminished pressure. According to NMR data,[13] the residual solid contained essentially 2,3,5-tri-*O*-benzyl-D-arabinono-1,4-lactone. Further purification by crystallization from petroleum ether/EtOAc gave **2** as a white solid (856 mg, 82%); mp 70–70.5 °C, $[\alpha]_D$ +6.3° (*c* 1.56, $CHCl_3$); lit.[13] mp 67.5–68.5 °C, $[\alpha]_D$ +6.6° (*c* 1.65, $CHCl_3$).

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