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Hydrogen Transfer of D-Glycals by Palladium Complexes under Ethylene Atmosphere

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Abstract

D-Glucal was oxidized to 1,5-anhydrohex-1-en-3-ulose in high yield by treatment with a catalytic amount of a palladium complex under ethylene atmosphere.

Keywords: carbohydrates, glycals, oxidation, palladium catalyst

Transition metals have been used for the transformation of alcohols into carbonyl compounds in organic synthesis [1]. Among the transition metal complexes, a Pd(II) complex such as $PdCl_2$ and $Pd(OAc)_2$ has been widely used in homogeneous oxidation. The oxidation of simple alcohols with palladium (II) salts was first reported by Lloyd in 1967 [2]. He revealed that primary and secondary alcohols were oxidized to the corresponding acetals and ketones by $PdCl_2$ under an oxygen atmosphere in the presence of a reoxidant such as $CuCl_2$ and $Cu(NO_3)_2$. After this report, Schwartz *et al.* reported homogeneous oxidation of secondary alcohols to ketones by a catalytic amount of $PdCl_2$–NaOAc in the presence of molecular oxygen as the sole reoxidant [3]. Very recently, Uemura and his co-workers reported $Pd(OAc)_2$-catalyzed oxidation of alcohols by molecular oxygen in the presence of pyridine and molecular sieves (MS) 3A [4]. A similar type of palladium-catalyzed oxidation of alcohols was also reported by Peterson and Larock [5]. These oxidation methods require molecular oxygen in order to achieve the catalytic effect of palladium in the process.

On the other hand, hexenuloses have played an important role in carbohydrate synthesis [6]. Among these, 1,5-anhydrohex-1-en-3-ulose derivatives are of particular interest, because the 1,4-addition allows the carbon-carbon bond formation at the anomeric center which leads to the formation of 2-deoxy-*C*-glycosides [7,8]. In 1993, Czernecki and co-workers reported the oxidation of allylic alcohol of D-glucal (**1**) with a stoichiometric amount of $Pd(OAc)_2$ in aqueous DMF (1% H_2O) [9]. However, they disclosed that several attempts at oxidation with a catalytic amount of palladium acetate in the presence of copper acetate as reoxidant were unsuccessful.

Here we would like to report a novel type of oxidation of D-glycals by a catalytic amount of $Pd(OAc)_2$ *in the absence of* molecular oxygen. During the course of our study on the synthesis of unprotected branched-chain sugars using a palladium catalyst [10], we found D-glucal was converted into a mixture of approximately equimolar amounts of an oxidation product of allylic alcohol (1,5-anhydrohex-1-en-3-ulose) **2** and hydrogenated product **3** by treatment with a catalytic amount of $Pd(OAc)_2$ in CH_3CN (eq. 1). The obtained results are summarized in Table 1. The yields in Table 1 represent the combined yield of **2** and **3**, and

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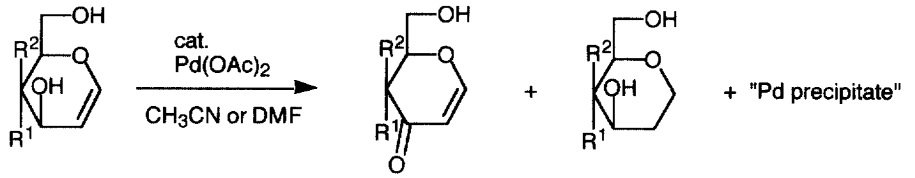
the ratio of **2**/**3** was determined by ^{1}H NMR analysis after acetylation. The ratio of **2**/**3** thus calculated was fully consistent with the isolated yields of **2** and **3**. For example, the reaction of **1** with 5 mol% of $Pd(OAc)_2$ afforded the combined yield of **2** and **3** in 88% in a ratio of 54.5:45.5 (determined by ^{1}H NMR), whereas the independent reaction gave **2** and **3** in 44% and 37% isolated yield, respectively. Under neutral and mild conditions, the use of 1–2 mol% of



(1)

1; R^1 = OH, R^2 = H
4; R^1 = H, R^2 = OH

2; R^1 = OH, R^2 = H
5; R^1 = H, R^2 = OH

3; R^1 = OH, R^2 = H
6; R^1 = H, R^2 = OH

Table 1. Catalytic oxidation of D-glycal (**1**,**4**) by palladium complexes[a]

			Conditions			Product
Entry	Glycal	Palladium (mol%)	Solvent	temp/°C	time/h	% yield[b] (**2**/**3**)
1	1	$Pd(OAc)_2$ (1)	CH_3CN	25	96	72 (50.2/49.8)
2	1	$Pd(OAc)_2$ (2)	CH_3CN	25	95	90 (50.5/49.5)
3	1	$Pd(OAc)_2$ (5)	CH_3CN	25	23	88 (54.5/45.5)
4	1	$Pd(OAc)_2$ (5)	CH_3CN	25	25	44 (**2**), 37 (**3**)
5	1	$Pd(OAc)_2$ (5)	DMF	20	3	88 (57/43)
6	1	$PdCl_2$ (5)–NaOAc (10)	CH_3CN	25	60	92 (52.6/47.4)
7	1	Pd precipitate (7)	CH_3CN	25	17	50 (**2**), 43 (**3**)
8	4	$Pd(OAc)_2$ (5)	DMF	25	5	49 (**5**), 36 (**6**)

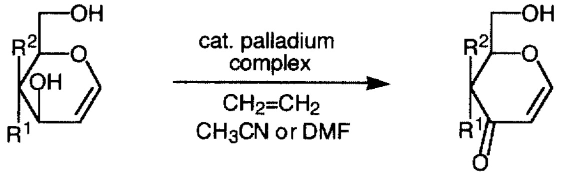
[a] All reactions were carried out under argon atmosphere. [b] Isolated yield after silica-gel column chromatography.

$Pd(OAc)_2$ afforded satisfactory yield (72–90%), though prolonged reaction time (96 h) was required. Among the solvents we examined, CH_3CN and DMF gave the best results. Considering the operation for recovery of the palladium precipitate by centrifugation, we selected CH_3CN as a solvent. In the case of D-galactal (**4**), the reaction in DMF proceeded more effectively than in CH_3CN because of the solubility of **4**. The combined $PdCl_2$–NaOAc catalyst system afforded similar results as in the case of $Pd(OAc)_2$; however, the use of $PdCl_2$ alone proved to be ineffective for the present reaction.

It should be mentioned that precipitation of the palladium complex was observed immediately after mixing D-glucal and $Pd(OAc)_2$ and the solution became heterogeneous. The fact that the only a catalytic amount of $Pd(OAc)_2$ was required to complete the reaction suggested that the palladium precipitate thus formed would be reusable. So, we next examined the reuse of this palladium complex, and found the recovered palladium precipitate was also effective in the next reaction. The yield of the second run was comparable to that of the first run, namely, the first use of the palladium precipitate (5 mol%) gave **2** (50%) and **3** (49%) (total 99%) and the second use afforded **2** (39%) and **3** (39%) (total 78%); thus, successive use of the palladium catalyst was realized. In these cases, the ratio of **2** and **3** was fairly equal compared with the reactions in which $Pd(OAc)_2$ was added. These results indicate that, after oxidation of D-glucal forming enone by $Pd(OAc)_2$ in the initial step, the formed palladium compound caused some type of hydrogen transfer reaction [11], that is, one molecule of D-glucal was dehydrogenated (oxidized) and another hydrogenated (reduced).

The palladium-catalyzed oxidation is initiated by the complexation of the alcohol to the Pd(II) catalyst involving formation of a palladium alkoxide which then undergoes β-hydride transfer from C to Pd to yield the carbonyl product and Pd(II)-hydride complex (H-Pd(II)-OAc). If this Pd-hydride species then undergoes reductive elimination to form Pd(0), a reoxidant such as molecular oxygen should be necessary to regenerate the active Pd(II) species. In the present case, however, the forming Pd(II)-hydride complex is supposedly capable of oxidizing another mol of alcohol to the carbonyl compound, and palladium dihydride will be formed. This palladium dihydride complex then converts **1** to hydrogenated product **3**, and active Pd(II) would be regenerated, which oxidizes **1** to **2** again. Another plausible mechanism to regenerate the Pd(II) species would include the process in which H-Pd(II)-OAc coordinates to olefin, followed by insertion, and the resulting compound possessing a Pd-σ bond will react with HOAc to generate the reduced product and regenerate $Pd(OAc)_2$. Thus, a catalytic amount of $Pd(OAc)_2$ was adequate to produce **2** and **3** in high yield in approximately equal amounts.

The above-mentioned redox reaction of D-glucal is interesting; however, the yield of the desired oxidation product was up to 50%, which was unsatisfactory from the synthetic viewpoint. Therefore, we then aimed at suppression of the generation of reduced glucal **3**. We expected that ethylene might work as a simple and sacrificial olefin and we employed the reaction under ethylene atmosphere. As expected, when D-glucal was treated with the above palladium precipitate catalyst obtained from the reaction shown in eq. 1 under ethylene atmosphere, the formation of hydrogenated product **3** was suppressed, and enone product **2** was obtained in high yield (eq. 2). To our knowledge, this is the first example of palladium-catalyzed catalytic oxidation of alcohols to ketones in the absence of a reoxidant such as molecular oxygen. The obtained results are summarized in Table 2. $Pd(OAc)_2$ also worked as an oxidizing reagent though it was less reactive than the above palladium precipitate.



(2)

1; $R^1 = OH$, $R^2 = H$
4; $R^1 = H$, $R^2 = OH$

2; $R^1 = OH$, $R^2 = H$
5; $R^1 = H$, $R^2 = OH$

The treatment of D-galactal **4** with the above palladium catalyst in DMF under ethylene atmosphere at room temperature for 45 h gave the oxidation product in 81% yield. In this reaction also the formation of a hydrogenated product was not observed. Furthermore, epimerization at the C-4 position was not observed, which was quite in contrast to the result of a stoichiometric reaction [9].

Table 2. Oxidation of D-glycal (**1**,**4**) to enones (**2**,**5**).[a]

Entry	Glycal	Palladium[b]	Solvent	Conditions temp/°C	Conditions time/h	Product (% yield)[c]
1	**1**	A	CH_3CN	50	30	**2** (98)
2	**1**	B	CH_3CN	60	30	**2** (62)[d]
3	**4**	A	DMF	50	96	**5** (81)
4	**4**	B	DMF	25	45	**5** (66)[e]

[a] All reactions were carried out under ethylene atmosphere. In all cases, the formation of a hydrogenation product (**3**, **6**) was not observed. [b] A: palladium precipitate (7–8 weight%), B: $Pd(OAc)_2$ (10 mol%). [c] Isolated yield after acetylation unless otherwise noted. [d] Isolated yield as unprotected enone **2**. [e] Starting material was recovered in 17% yield.

A typical experimental procedure is as follows (entry 1 in Table 2): A mixture of palladium precipitate (17.0 mg), D-glucal (204.3 mg, 1.37 mmol), and CH_3CN (1.5 mL) was stirred at 50 °C for 30 h under ethylene atmosphere. After confirmation of the completion of the reaction, pyridine (0.8 mL) and acetic anhydride (0.6 mL) were added, and the whole was stirred for 12 h at room temperature. The black palladium solid was separated by centrifugation, and the solution was concentrated. Purification by silica-gel column chromatography afforded the oxidized product (307.6 mg, 98%). The absence of a hydrogenated product was confirmed by ^1H NMR analysis.

In conclusion, we have succeeded in palladium-catalyzed oxidation of allylic alcohol of D-glycal under ethylene atmosphere using a catalytic amount of palladium. This new method represents a new process in which the palladium (II) species, required for the oxidation of the alcohol, is regenerated and shows unique characteristic features compared with the conventional aerobic method. The mechanistic study and synthetic application of the present oxidations are now in progress in our laboratory.

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