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Efficient Syntheses of Penta-hydroxylated Cyclohexanones via $PdCl_2$-Mediated Ferrier-II Reaction of 6-*O*-Acetyl-5-enopyranosides

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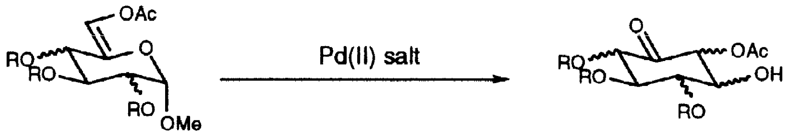
Abstract

The conversion of 6-*O*-acetyl-5-enopyranosides into fully oxygenated cyclohexanones was found to proceed efficiently with a catalytic amount of palladium chloride under neutral conditions. This method was proved to be superior in efficacy to the conventional Hg method.

Keywords: cyclohexanones; palladium and compounds; ring transformation; enols and derivatives

Since 1979, Ferrier's carbocyclization reaction (Ferrier-II reaction) [1], [2] has become one of the most efficient methods for the preparation of chiral substituted cyclohexanones, which should be useful synthetic intermediates for biologically active compounds. [3-11] There are numerous reports concerning the improvement of the reaction conditions of this rearrangement. Lukacs[3] and Ogawa[4] have independently developed the use of a catalytic amount of Hg(II) salts as effective promoters. Recently, we have revealed the effective use of a catalytic amount (5 mol%) of palladium chloride[12],[13] in the conversion of a variety of 6-deoxyhex-5-enopyranosides to cyclohexanones and found that the reaction proceeded stereoselectively in good yields.[14] These observations prompted us to examine the reaction of terminally substituted 6-deoxyhex-5-enopyranosides.[7] In this paper, we report the applicability of this transformation to 6-*O*-acetyl-5-enopyranosides in comparison with use of a Hg(II) promoter.



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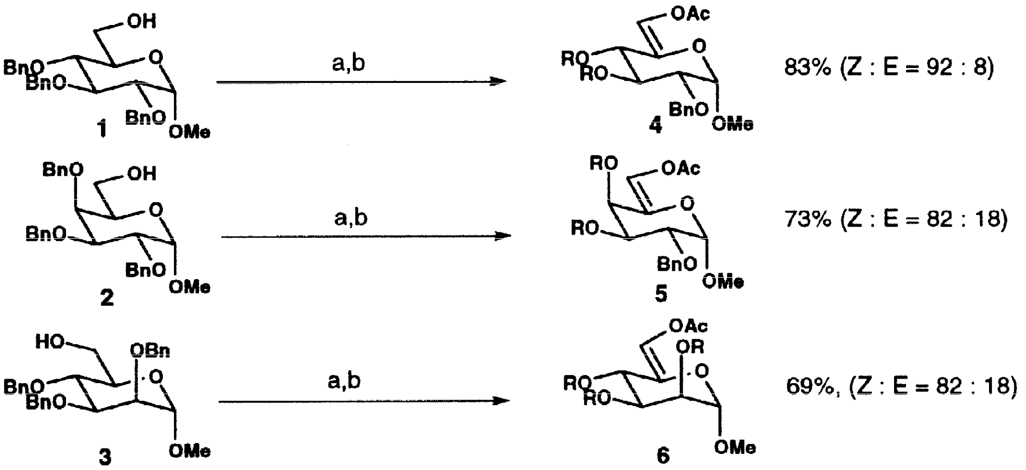
The substrates, enol acetates, were prepared from known pyranosides[15] as shown in Scheme 1. Oxidation of the hydroxyl groups of **1**, **2** and **3** by the method reported by Moffat [16] (DMSO, DCC, TFA, pyridine, benzene) provided the corresponding unstable aldehydes, which were immediately treated with acetic anhydride in the presence of appropriate bases (Et_3N and DMAP) to afford the desired enol acetates (**4**, **5** and **6**). In all cases, the Z-isomers were the predominant products. With the substrates thus prepared in hand, we examined the palladium chloride-promoted Ferrier-II reaction according to the protocol we reported previously.

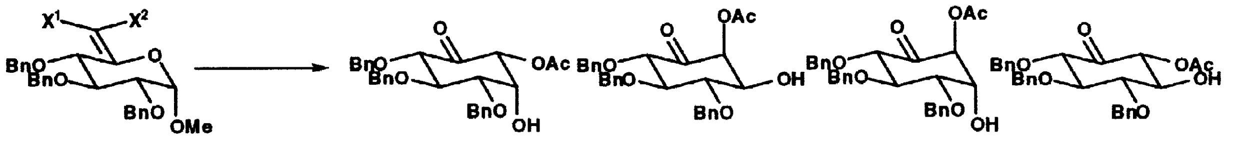
Scheme 1



Reagents and conditions: (a) DCC, DMSO, pyridine, TFA, benzene, r.t., 12 h.
(b) Ac_2O, Et_3N, DMAP, $ClCH_2CH_2Cl$, 100 °C, 2 h.

The Z- and E-isomers of **4** (**4a** and **4b** respectively) were treated with a catalytic amount of $PdCl_2$ in aqueous dioxane at 60 °C. The results are shown in Table 1.

Table 1



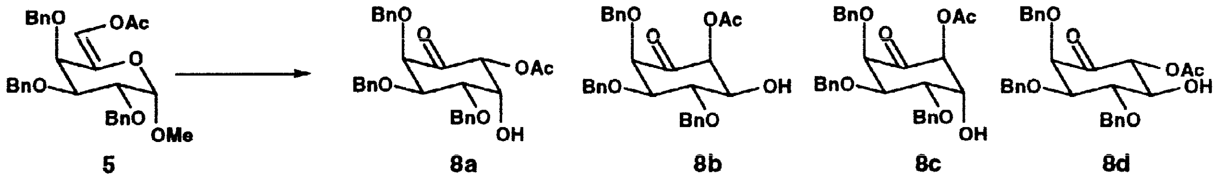
4 7a 7b 7c 7d

Run	Substrate	Condition	Yield (%)	**7a** : **7b** : **7c** : **7d**
1	**4a** $X^1 = H, X^2 = OAc$	$PdCl_2$ (0.05 eq), dioxane - H_2O (4 : 1), 60 °C, 3 h	77	49 : 24 : 17 : 10
2	**4b** $X^1 = OAc, X^2 = H$	$PdCl_2$ (0.2 eq), dioxane - H_2O (4 : 1), 60 °C, 4 h	81	46 : 22 : 22 : 10
3	**4a** $X^1 = H, X^2 = OAc$	$Hg(OCOCF_3)_2$ (0.1 eq), acetone - H_2O (4 : 1), r.t., 16 h	20	80 : 20

Penta-oxygenated cyclohexanones were obtained as a diastereomeric mixture in high combined yields (run 1 and 2). It is noteworthy that palladium salt was a superior catalyst compared with conventional mercury salt (run 1 and 3). Interestingly, the geometry of the enol acetates did not affect the stereochemical outcome of the reaction. This observation suggests that the stereochemical integrity at the C-6 position of the substrates must be lost during or prior to the subsequent cyclization. Similar stereochemical scrambling at the C-6 of enopyranosides with a Hg(II) salt promoter has been reported by Bender[7] and Kakinuma[18], and this fact would support our speculation. Encouraged by these results, the generality of the palladium-catalyzed reaction was investigated (Table 2, Table 3).

In the case of galactose (Table 2), both $PdCl_2$ and $Hg(OCOCF_3)_2$ gave comparable results in yield (88% and 75% respectively). Although the Hg(II)-catalyzed process provided only the two diastereomers, the four isomers could be obtained by the present method (**8a**~**8d**).

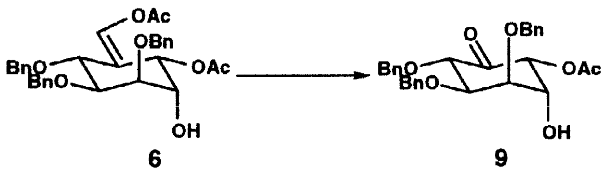
Table 2



Run	Condition	Yield (%)	**8a** : **8b** : **8c** : **8d**
1	$PdCl_2$ (0.05 eq), dioxane - H_2O (2 : 1), 60 °C, 3 h	88	11 : 40 : 42 : 7
2	$Hg(OCOCF_3)_2$ (0.05 eq), dioxane - H_2O (2 : 1), 60 °C, 3 h	75	52 : 48

A more remarkable result was observed with the excellent stereoselectivity and efficacy in the mannoside case (Table 3). The Ferrier product was obtained as a single isomer **9** and other isomers were not detected spectroscopically. Moreover, the use of a palladium catalyst was essential to carry out this transformation at a practical reaction rate (compare runs 1 and 2). The higher efficacy of $PdCl_2$ compared with $Hg(OCOCF_3)_2$ as a catalyst might be attributed to the coordination effect of the palladium salt to a C-C double bond in the initial oxypalladation step of the reaction.

Table 3



Run	Condition	Yeld (%)
1	$PdCl_2$ (0.05 eq), dioxane - H_2O (2 : 1), 60 °C, 3 h	76
2	$Hg(OCOCF_3)_2$ (0.05 eq), dioxane - H_2O (2 : 1), 60 °C, 3 h	19

Mention must be made of the difference in the diastereomeric ratio of the two methods. In our previous study on the Ferrier-II reaction of terminally unsubstituted enopyranosides by palladium chloride and mercury salt, no remarkable difference in diastereomeric ratio was observed. However, dependent on the choice of promoter, the enol acetates of glucose and galactose were converted into the corresponding carbocycles in a distinct diastereomer distribution, which would be easily separable over silica-gel chromatography. Judging from these results, the Pd(II) salt- and Hg(II) salt-catalyzed Ferrier-II reaction of enol acetates may proceed *via* different reaction courses. Further experiments are required to clarify the exact mechanism of the reaction.

In summary, palladium chloride was found to be an effective catalyst for the Ferrier-II reaction of 6-O-acetyl-5-enopyranosides. It is noteworthy that the catalytic activity of $PdCl_2$ is superior to that of a Hg(II) salt. The mildness and efficiency of our conditions encouraged us to apply this reaction to the syntheses of inositols. The synthetic study is described in the succeeding paper in this issue.

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