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PALLADIUM(II) PROMOTED CARBOCYCLISATION OF AMINODEOXYHEX-5-ENOPYRANOSIDES

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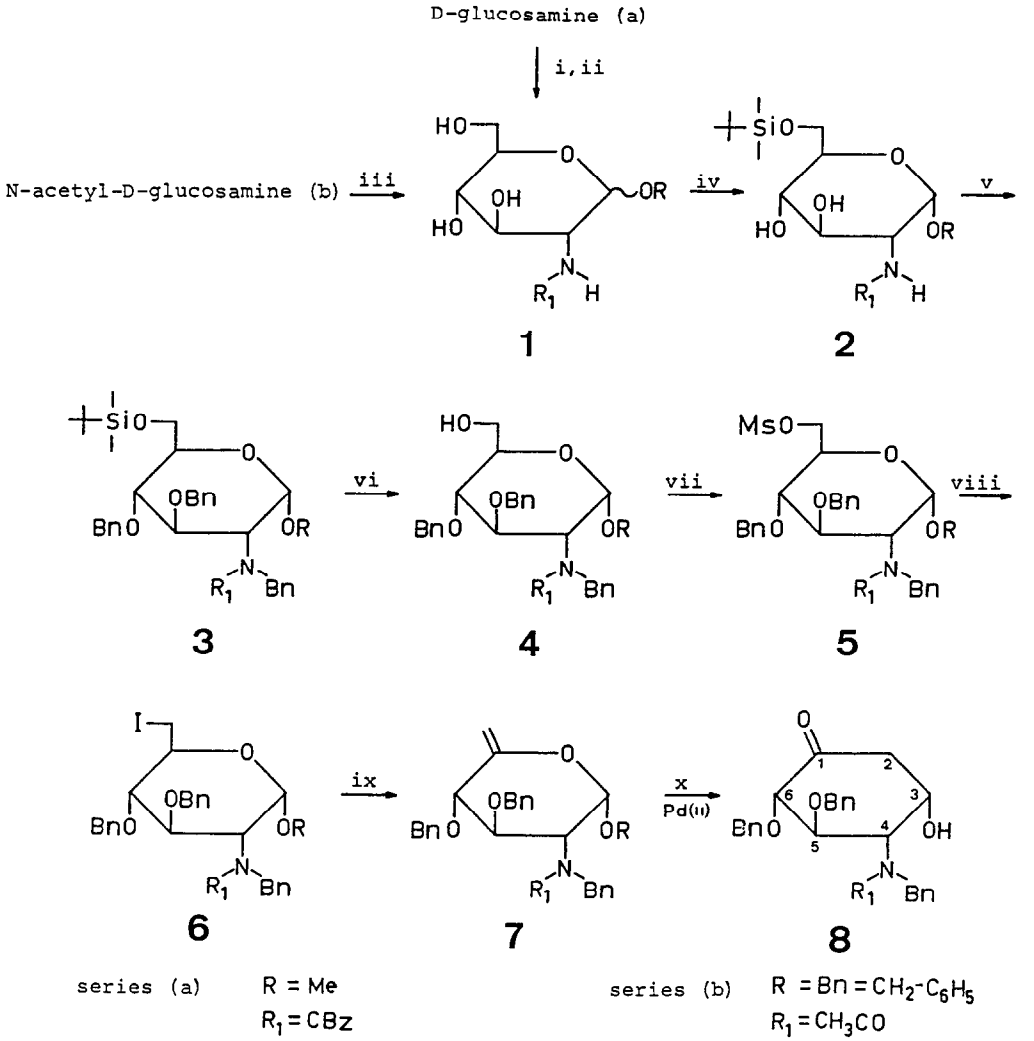
Summary: Under catalytic conditions, Pd(II) salts effect the clean conversion of aminodeoxyhex-5-enopyranosides 7 into the corresponding 3-hydroxy cyclohexanones 8.

The discovery of new pseudosaccharide amino cyclitol antibiotics[1] and the accumulating experimental evidence that simple monopseudosugars, like bromoconduritol or valienamine may provide potent antivirals[2] and active-site directed covalent inhibitors of glucosidases[3], has reinforced interest in the conversion of carbohydrates into carbocyclic compounds[4]. Particularly noteworthy in this context is the Ferrier mercury-salt mediated ring transformation of 6-deoxyhex-5-enopyranosides into 3-hydroxy cyclohexanones[5]. This method is however limited in scope when contemplating its potential industrial utilization.

We have now found that this conversion may be brought about catalytically with Pd(II) salts, though initial studies were carried out under stoichiometric conditions. This novel palladium-catalysed carbon-carbon bond coupling reaction is characterized by its rapidness under mild conditions and is unique among the reported palladium-catalysed reactions.



Reagents and conditions: (i) MeOH, H^+, reflux; (ii) CBzCl, Na_2CO_3, 0°C; (iii) ϕCH_2OH, H^+, 60°C; (iv) $+\dot{S}iCl$, imidazole, DMF, 20°C; (v) NaH, BnBr, DMF; (vi) $(n\text{-}Bu)_4NF$, THF; (vii) MsCl, NEt_3, DMAP(cat.), 0°C, 10 min.; (viii) NaI, DMF, 80°C, 2-4 hours; (ix) DBU, DMF, 80°C, 4 hours; (x) $Pd(OAc)_2$ or $PdCl_2$ (10-20 mol % equiv.), dioxane or acetone, water, H^+, 60°C, 40-60 min.

While the overall transformation seemingly implies the Ferrier rearrangement, the exact mechanism by which this conversion occurs is not known actually.

The C-5 exomethylene sugars 7a and 7b were prepared according to standard procedures starting from D-glucosamine (series a) and N-acetyl-D-glucosamine (series b) as shown in the scheme. Almost all the intermediates in series b are crystalline thus facilitating their isolation and purification.

All experimental operations were carried out under argon and in dried equipment, if necessary.

A typical procedure for the conversion of 7 into 8 with catalytic amounts of $PdCl_2$ or $Pd(OAc)_2$ is as follows:

To a solution of 7 (1 mmol) in 15 ml dioxane-aqueous H_2SO_4 (5 mM) (2:1) was added $PdCl_2$ (10-20 mol%). The mixture was heated at 60°C for 40-60 min. (tlc monitoring). The resulting mixture was cooled and concentrated under reduced pressure. The residue was taken up in ethyl acetate and water. The extract was washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (n-hexane-CH_3CO_2Et, silica gel) yield of purified compounds: 60-80%.

Actually, we are exploring the scope of this new methodology by extending it to other substrates and to other experimental conditions. We are particularly investigating the potential of this palladium-catalysed reaction in the conversion of a furanose derivative into its carbocyclic counterpart, were the Ferrier conditions have been reported to be inoperative[6]. Further reports from this lab will deal with additional aspects or applications of this new palladium-induced carbocyclisation.

8a: ^{1}H NMR ($CDCl_3$, 250 MHz): δ ~ 7.1-7.45 (m, aromatics); 5.16 (AB-spectrum, nearly a s, $J_{AB} \simeq 11$ Hz, $-COO-CH_2Ø$); 5.05 (broad, ~ d, and 4.11, d, $J_{gem} \simeq 15$ H_z, $N-CH_2Ø$); 4.99 and 4.56 (2 x d, $J_{gem} = 11.5$ H_z, $O-CH_2Ø$); 4.88 and 4.56 (2 x d, $J_{gem} = 11$ H_z, $O-CH_2Ø$); ~ 4.72 (dd, J ≈ 9 H_z, J ~ 9 H_z, H_5); 4.08 (m, H_3); 4.03 (d, J = 9 H_z, H_6); ~ 3.5 (very broad s, H_4); ~ 2.5 (dd, $J_{gem} = 16$ H_z, $J_{H_3H_{ax}} = 4$ H_z); ~ 2.25 (broad ~ d, J_{gem} = 16 H_z, H_{eq}) ppm.
$[\alpha]_D^{20} = -20.1°$ (c = 1, $CHCl_3$), litt.[7] $[\alpha]_D^{20} = -23°$ (c = 1.52, $CHCl_3$).
8b: ^{1}H NMR ($CDCl_3$, 250 MHz): δ ~ 7.2-7.5 (m, aromatics); ~ 6.5 (very broad s, OH); ~ 5 and ~ 4.59 (2 x d, $J_{gem} = 11.5$ H_z, $O-CH_2Ø$); 5.00 and 4.99 (2 x d, 4.58 and 4.56, 2 x d, $J_{gem} = 11.5$ H_z, $O-CH_2Ø$); ~ 4.82 (dd, J ≈ 9 Hz, J ~ 9 H_z, H_5); ~ 4.7 and ~ 4.3, (2 x d, J = 16.5 H_z, $N-CH_2Ø$; ~ 4.12 (broad s, H_3); ~ 4 (d, J = 9 H_z, H_5); ~ 3.5 very broad s, H_4); 2.51 (dd, $J_{gem} = 14$ H_z, $J_{H_{ax}H_3} = 4$ H_z, H_a); ~ 2.25 (broad, ~ d, $J_{gem} = 14$ H_z, H_{eq}; 2.04 (s, $-COCH_3$) ppm.

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