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Regiospecific Reaction of Enol Ethers with an Organopalladium Salt. Stereochemical and Conformational Effects on Product Formation
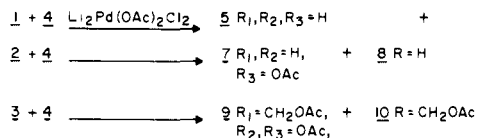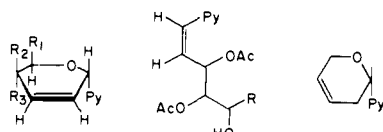
Sir:

In connection with our interest in synthetic routes to C-nucleosides,[1-4] we have studied reactions of three cyclic enol ethers, 3,4-dihydro-2H-pyran (**1**), 3,4-di-*O*-acetyl-D-arabinal[5] (**2**), and 3,4,6-tri-*O*-acetyl-D-glucal[6] (**3**) with an organopalladium reagent generated in situ by treatment of 1,3-dimethyl-2,4-pyrimidinedion-5-ylmercuric acetate[7,8] (**4**) with palladium salts.[9,10] Each of the reactions exhibited complete
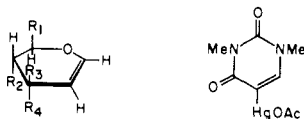

regiospecificity with carbon–carbon bond formation solely between C-5 of the pyrimidine and C-1 of the cyclic enol ether.[9] Otherwise, the three reactions exhibited significant differences. Three distinct modes of decomposition of the intermediate enol ether–organopalladium salt adducts were observed. The various reaction pathways giving rise to the products isolated are a consequence of the respective stereochemical requirements of the addition and elimination reactions involved.

The preparation[7] of 1,3-dimethyl-2,4-pyrimidinedion-5-ylmercuric acetate (**4**) was accomplished by addition of a stoicheometric amount of mercuric acetate to 1,3-dimethyl-2,4-pyrimidinedione[11] in methanol containing perchloric acid. When **4** (1 equiv), palladium acetate (1 equiv), lithium chloride (2 equiv), and 3,4-dihydro-2H-pyran (**1**, 1.5 equiv) in acetonitrile were stirred at 25 °C for 12 h, a precipitate of finely divided palladium was formed. Treatment of the reaction mixture with hydrogen sulfide to remove mercuric and residual palladium(II) ions followed by chromatography of the residue (after removal of solvent) on silica gel using dichloromethane yielded 1,3-dimethyl-5-(2′,3′-dihydro-6′H-pyran-2′-yl)-

Scheme I. Stereochemistries of Organopalladium Salt Addition and Elimination Reactions

Py = 1,3-dimethyl-2,4-pyrimidinedion-5-yl
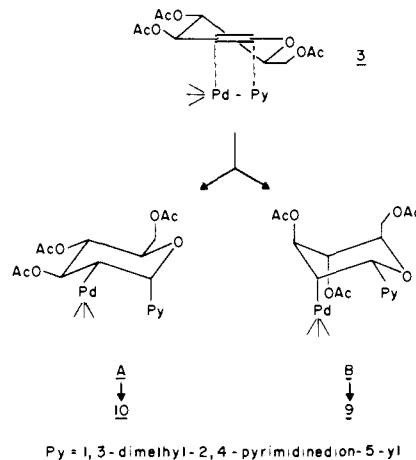
2,4-pyrimidinedione (**6**): 24%; mp 134–135 °C; λ_{max}^{MeOH} 270 nm; ¹H NMR δ (CDCl₃) 1.8–2.8 (m, 3′-CH₂), 3.38, 3.43 (NMes), 4.35 (m, 6′-CH₂), 4.59 (d of d, J = 10, 3.5 Hz, 2′-CH), 5.6–6.1 (m, 4′-, 5′-CHs), 7.29 (s, 6-CH); mass spectrum, m/e 222 (M⁺·). Further elution produced 1,3-dimethyl-5-(5′,6′-dihydro-2′H-pyran-2′-yl)-2,4-pyrimidinedione (**5**): 66%; mp 123–124 °C; λ_{max}^{MeOH} 270 nm; ¹H NMR δ (CDCl₃) 1.8–2.5 (m, 5′-CH₂), 3.37, 3.41 (NMes), 3.6–4.2 (6′-CH₂), 5.25 (br, 2′-CH), 5.65–6.10 (m, 3′-, 4′-Hs), 7.27 (6-CH); mass spectrum m/e 222 (M⁺·).

In similar experiments,[12] reactions of the unsaturated pyrano sugar derivatives **2** and **3** with **4** in the presence of palladium salts yielded products in which C-5 of the pyrimidine ring is bonded to a cyclic dihydropyranyl moiety (**7**[13] and **9**,[13] respectively) or to an open-chain carbohydrate derivative (**8** and **10**, respectively). Thus, from reaction of **2** and **4** in the presence of Li₂Pd(OAc)₂Cl₂ was obtained 1,3-dimethyl-5-(5′-acetoxy-5′,6′-dihydro-2′H-pyran-2′-yl)-2,4-pyrimidinedione (**7**:[13] λ_{max}^{MeOH} 282, 235 nm; ¹H NMR δ (CDCl₃), 2.11 (OAc), 3.37, 3.43 (NMes), 3.66 (d of d, J = 12, 8 Hz, 6′-CH), 4.17 (d of d, J = 12, 6 Hz, 6′-CH), 5.30 (br, 2′-, 5′-CHs), 6.02 (m, 3′-, 4′-CHs), 7.25 (6-CH); mass spectrum m/e 210 (M − HOAc)) in 20% yield and 2,3-diacetoxy-5-(1′,3′-dimethyl-2′,4′-pyrimidinedion-5′-yl)pent-4-en-1-ol (**8**: mp 146–147 °C; λ_{max}^{MeOH} 270 nm; ¹H NMR λ (CDCl₃), 2.08, 2.11 (OAcs), 3.36, 3.50 (NMes), 3.81 (d, J = 5 Hz, 1-CH), 5.01 (d of t, J = 5, 4 Hz, 2-CH), 5.61 (d of d, J = 12,[14] 10 Hz, 4-CH), 5.95 (d of d, J = 10, 4 Hz, 3-CH), 6.50 (d, J = 12[14] Hz, 5-CH), 7.84 (s, 6′-CH); mass spectrum m/e 340 (M⁺·)) in 32% yield. From 3,4,6-tri-*O*-acetyl-D-glucal (**3**) and **4** were obtained the corresponding dihydropyranyl product **9**[13] in ~20% yield[15] and the acyclic carbohydrate product 6-(1′,3′-dimethyl-2′,4′-pyrimidinedion-5′-yl)-1,3,4-triacetoxyhex-5-en-2-ol (**10**: λ_{max}^{MeOH} 282, 236 nm; ¹H NMR δ (CDCl₃) 2.05, 2.08, 2.10 (OAcs), 3.35, 3.44 (NMes), 3.96 (m, 2-CH), 4.11 (d, J = 5 Hz, 1-CH₂), 5.14 (d of d, J = 6, 5 Hz, 3-CH), 5.59 (d of d, J = 12.12,[14] 10 Hz, 5-CH), 5.94 (d of d, J = 10, 5 Hz, 4-CH), 6.38 (d, J = 12 Hz,[14] 6-CH), 7.66 (6′-CH); mass spectrum m/e 412 (M⁺·)) in 73% yield.

The general reaction of aryl (alkyl) palladium species with olefins is syn addition of the palladium derivative to the double bond followed by syn elimination of a hydridopalladium salt.[10,16-18] The major product (**5**) resulting from reaction of 3,4-dihydro-2H-pyran (**1**) with the organopalladium reagent derived from **4** is that expected for this process. The minor product (**6**) arises by isomerization of **5**.[10] It is noteworthy that the addition reaction is regiospecific owing to the strong polarization of the enol ether double bond; this electronic effect is largely lacking in reactions of aryl palladium salts with

Py = 1,3-dimethyl-2,4-pyrimidinedion-5-yl

simple olefins where steric effects appear to determine the mode of addition.[10]

The reactions involving the sugar derivatives **2** and **3** are significantly more complex. Consideration of the results obtained and examination of molecular models indicate that approach of the organopalladium salt for complexation[10] occurs primarily from the face of the cyclic enol ether ring opposite the allylic acetate substituent.[19] Decomposition of the resulting cis adduct with olefin formation depends on the conformation(s) that this adduct assumes. In Scheme I it is seen that addition of the organopalladium species to **3** produces an adduct which, in its most stable conformation (A), possesses an equatorial palladium function, i.e., a geometry improper for anti elimination of palladium acetate.[10,20,21] The less favorable conformation B, obtained by chair–chair interconversion, possesses the proper geometry for this elimination and presumably gives rise to the minor reaction product **9**. The palladium substituent in conformation A is, however, positioned with respect to the ring oxygen so as to permit anti elimination with alkoxide expulsion,[9,22-25] ring cleavage, and formation of a Z-olefinic[14] bond, i.e., the major product (**10**) of the reaction. For the reaction involving **2**, the energy difference between the two conformational isomers corresponding to A and B is less; as a result less selectivity is observed in the adduct decomposition.

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Direct Two-Step Conversion of Penicillins to 3-Acetoxymethylcephems

Sir:

Recently, we reported the transformation of penicillins to 3'-substituted cephems through the intermediate 3-*exo*-methylenecepham **2**.[1,2] Thus, the conversion of **2** to **3** and the subsequent displacement of halogen with the acetate ion afforded **4a**.[2] Such a transformation required initial activation of **2** with base to give the allylic anion which was then trapped with halogen to give **3**.[2] Subsequent transformation converted **4a** to the important intermediate 7-aminocephalosporanic acid (7-ACA, **5**).[2] We have since theorized that, if one could transform the 3-*exo*-methylenecepham **2** to an intermediate which could be intercepted directly by acetate, then the need for the initial conversion to **3** would be obviated.
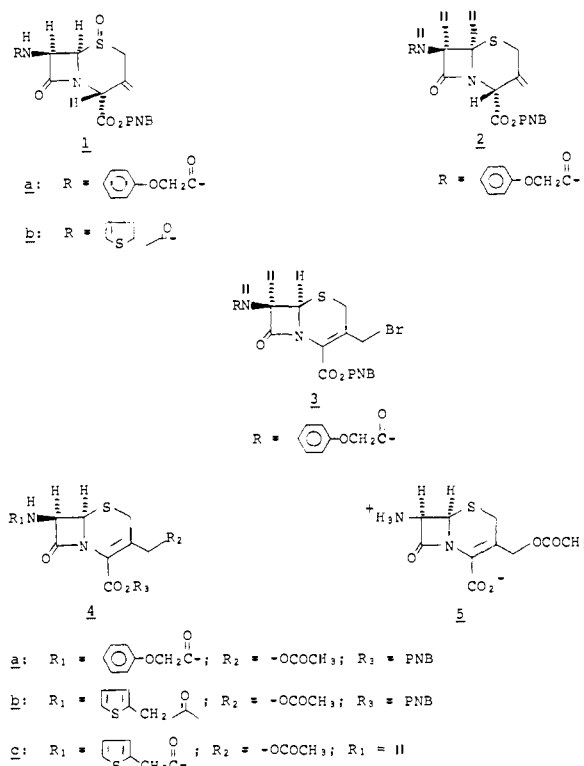
One possibility which we considered was that 3-*exo*-methylenecepham sulfoxide **1** might be a precursor to the desired activated intermediate **6** which could be trapped at the 3' carbon by acetate (**1 → 6 → 7**).

When we treated compound **1a** with mixtures of acetic anhydride and acetic acid at reflux (126 °C), we obtained a mixture of Δ^2,Δ^3-3'-OAc cephems **7a** and **4a**, respectively (R = phenoxyacetyl): IR (CHCl₃) 1785 cm⁻¹; NMR (3:1 mixture of Δ^2 and Δ^3) (CDCl₃) δ 6.5 (br s, 0.75, Δ^2-C₂ H), 5.8 (dd, 1, C₇ H), 4.6 (s, 2, C₇ side-chain methylene), 3.6 (br s, 0.5, Δ^3 C₂), 2.1–2.2 (ss, 3, Δ^2- and Δ^3-3'-acetoxy).

This reaction presumably proceeds through a Pummerer-type intermediate **6** which is then trapped in a 1,4 manner by