Notes

One-Step Synthesis of 1,4-Benzodioxanes by Reaction of 1,2-Cyclohexanedione with Vicinal Diols Promoted by Dichlorobis(benzonitrile)palladium(II)

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During investigations of the reactivity of dichlorobis(benzonitrile)palladium(II) with alcohols and vicinal diols,[1] we observed that this reactant promotes the reaction of 1,2-cyclohexanedione (I) with vicinal diols to give the corresponding 1,4-benzodioxane structures in one step and in satisfactory yields (50–65%) (Scheme I).

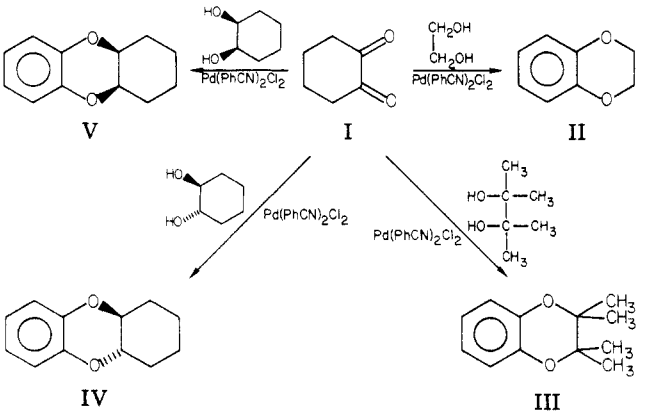
Mild conditions are required: refluxing of reagents in benzene with a molar excess of the coordination compound. The reaction of I with *cis*- and *trans*-1,2-cyclohexanediols permits the stereoselective synthesis of both tetrahydrodibenzo-1,4-dioxanes V and IV, respectively.

The reported dioxanes II and III were identified by comparison with authentic samples. As regards the structures of IV and V, not previously described, these are in accordance with the following data. In the mass spectrum the molecular ion for both lies at m/e 190; the appearance of three peaks at m/e 52, 80, and 110 is characteristic of ion A (Scheme II). Moreover, the peak at m/e 121 corresponding to ion B is typical of the 1,4-benzodioxane fragmentation.[2] In the NMR spectrum both IV and V have the same signal (singlet) at 6.82 ppm, corresponding to four aromatic protons, identical with the aromatic proton signal of catechol. By hydrogenolysis on Pd-charcoal of both IV and V, catechol is obtained as the main product. As to the cis and trans stereochemistry assigned to the ether hydrogens of V and IV, respectively, this is consistent with the NMR signals: two different multiplets (2 H) centered at 3.7 and 4.20 ppm are observed for V, attributable, respectively, to axially and equatorially oriented hydrogens; only one multiplet (2 H) centered at 3.7 ppm is observed for IV according to the same axial orientation of both hydrogens (Scheme II).

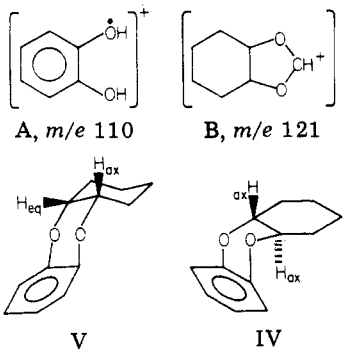
We suggest that a reasonable mechanism for this synthetic path is a nucleophilic reaction of enolizable I with the complexed diols and the final aromatization by Pd^{2+} salts of intermediate diene. In this way, for instance, V is obtained (Scheme III).

The effectiveness of the preliminary complexation of the alcoholic function by the Pd(II) complex is confirmed by the shift, in benzene solution, of the absorbance maximum from 370 nm, ascribed to $Pd(PhCN)_2Cl_2$, to 440 nm by addition of the 1,2-cyclohexanediols or primary and secondary alcohols, in agreement with the replacement of a nitrogen-bonded ligand, in higher position in the spectrochemical series[3] by oxygen-bonded donors. The suggested enolization step is supported by the fact that enol ether VIII is obtained, in addition to aromatic ether VII,

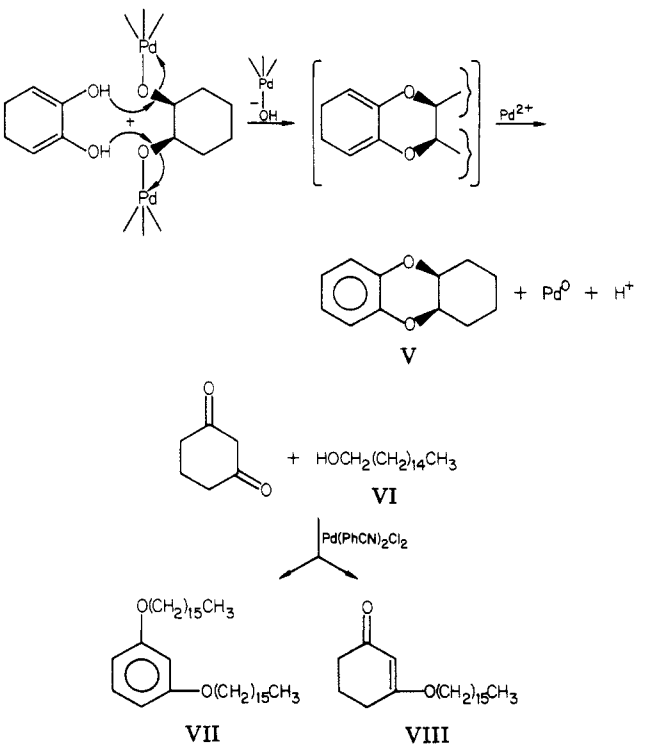
Scheme I



Scheme II



Scheme III



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upon reacting alcohol VI (Scheme III) with 1,3-cyclohexanedione in the presence of $Pd(PhCN)_2Cl_2$. An alternative step, involving the initial aromatization of I to catechol followed by etherification to dioxane, may be excluded since no reaction of catechol with both 1,2-cyclohexandiols is promoted by $Pd(PhCN)_2Cl_2$ in the reported conditions. Furthermore, we observed that the benzodioxanes IV and V are obtained in the same way in the absence of dione I by the reaction of *trans*- and *cis*-1,2-cyclohexanediols, respectively, with $Pd(PhCN)_2Cl_2$. This reaction proceeds via an initial oxidation, to dione I, of a certain amount of diol by the Pd^{2+} salt as reported for the oxidation of simple alcohols.[4]

1,4-Benzodioxanes are a class of heterocyclic compounds with hypnotic and sedative activity.[5] The novel synthetic route reported appears of some interest when compared with alternative syntheses requiring more severe reaction conditions or generally giving low yields.[6] From these results, and others reproted previously,[1] dichlorobis(benzonitrile)palladium(II) appears to be a versatile activating agent, under unusually mild conditions, for the alcoholic and epoxidic functions.

Experimental Section

General. $Pd(PhCN)_2Cl_2$ was prepared by the method of Kharasch.[7] Benzene was distilled over sodium metal. Melting points were determined with a Kofler apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 257 Infracord and NMR spectra with a Perkin-Elmer apparatus (90 MHz) in $CDCl_3$; for TLC, Kieselgel G from Merck was used. GLC analyses were carried out with a "Carlo Erba" Fractovap G-1 using a 60-m capillary column with 5% Carbowax as the stationary phase.

Synthesis of Dioxanes II-V. The following procedure for the preparation of V is representative. Dione I (1 mmol), 1 mmol of *cis*-1,2-cyclohexanediol, and 2 mmol of $Pd(PhCN)_2Cl_2$ were made to react by refluxing in 3 mL of benzene overnight in a dry nitrogen atmosphere. The reaction mixture was then hydrolyzed with water and extracted with ethyl ether. The aqueous phase was evaporated to dryness to recover the palladium salt. The ether extracts were dried (anhydrous Na_2SO_4) and evaporated. The reaction mixture was chromatographed on a silica gel column. By elution with 90:10 hexane–ethyl ether, V was obtained (65% yield) as microcrystals, mp 43–44 °C, from methanol: IR 1260 and 1050 cm^{-1} (aromatic ether), 1590 and 1490 cm^{-1} (phenyl group), 2860 cm^{-1} (aliphatic carbons); NMR 3.7 (1 H, m), 4.20 (1 H, m), 6.82 (4 H, s) ppm.

In the same way, from I and *trans*-1,2-cyclohexanediol, IV is obtained (50% yield) as an uncrystallizable compound; in the IR spectrum the same typical bands as for V were found; in the NMR spectrum V is different from IV in a single multiplet (2 H) centered at 3.7 ppm in the ethereal region. By further elution of the reaction mixture, a minor compound (15% yield) that is under examination was obtained.

The benzodioxanes II and III were identified by GLC comparison with authentic samples. The respective yields were 50% and 52%. In these reported reactions the residual yields are attributable to starting compounds as well as to a variable amount of catechol derived from the aromatization of I by Pd^{2+} salts.

Preparation of VII and VIII by Reaction of 1,3-Cyclohexanedione with Alcohol VI and $Pd(PhCN)_2Cl_2$. We utilized the same ratio of reagents and conditions reported above. The crude reaction mixture was chromatographed on a silica gel column by eluting with 50:40:20 benzene–hexane–ethyl ether. We obtained VII (22% yield) as a liquid; in the IR spectrum there was no absorbance in the carbonyl region. In the NMR spectrum a complex signal in the aromatic region (4 H) centered at 6.40 ppm, a single triplet (4 H) centered at 3.90 ppm (attributable to four ethereal protons), and a strong singlet centered at 1.3 ppm (attributable to the alcoholic aliphatic chain) were found. By further elution, we obtained a small amount of starting compound and then VIII (60% yield) as an uncrystallizable compound. In the IR spectrum two strong bands at 1660 and 1615 cm^{-1} typical of an O=C–C=C–OR system were found. In the NMR spectrum characteristic signals at 5.25 (1 H, s, olefinic proton) and 3.75 ppm (2 H, t, ethereal protons) were found.

Registry No. I, 765-87-7; II, 493-09-4; III, 75768-16-0; IV, 75768-17-1; V, 75459-45-9; VI, 36653-82-4; VII, 75768-18-2; VIII, 75768-19-3; *cis*-1,2-cyclohexanediol, 1792-81-0; *trans*-1,2-cyclohexanediol, 1460-57-7; dichlorobis(benzonitrile)palladium(II), 14220-64-5; 1,3-cyclohexanedione, 504-02-9; 1,2-ethanediol, 107-21-1; 2,3-dimethyl-2,3-butanediol, 76-09-5.

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Synthesis of Aryl Ortho Esters from Benzanilide Acetals

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The recent report[1] of a new method for the preparation of aryl ortho esters[2] prompts us to describe a procedure which we have recently found successful. Our approach involves the intermediate preparation of a benzanilide acetal (1, Scheme I), this being produced easily from the corresponding benzanilide by using standard amide acetal synthetic procedures.[3] The benzanilide acetal is not purified but simply treated for 5–10 min with excess acetic acid in methanol. After neutralization of the acid, standard workup produces a 1:1 mixture of the desired ortho ester and *N*-methylaniline. These can be easily separated by fractional distillation or, in the case of the 4-nitrobenzoate, by recrystallization of the ortho ester. The approach produces good yields of pure ortho ester. We have used it now in three cases: Ar = 4-MeOC_6H_4 (58% yield after separation from *N*-methylaniline, based on initial benzanilide), Ar = 4-MeC_6H_4 (67% yield), and Ar = $4\text{-NO}_2C_6H_4$ (40% yield). The procedure appears capable of extension to aliphatic ortho esters and, by using a different alcohol in the final step, should also be able to produce a mixed ortho ester.

The method owes its success to the very labile nature of the C–N bond of the anilide acetal in an acid solution.[4] Mechanistically, the final step in the synthesis must be proceeding with protonation on nitrogen and loss of *N*-methylaniline, followed by reaction of the so-formed dialkoxycarbonium ion with solvent. This same ion is also formed as an intermediate in the Pinner ortho ester synthesis.[2] The advantage of the anilide acetal procedure comes from the very mild acid conditions and short re-

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(2) (a) The standard procedure starting from a nitrile, the Pinner synthesis,[2b] usually results in a mixture which is difficult to separate[1] when applied to the preparation of an aryl ortho ester. (b) DeWolfe, R. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970; pp 2–11.
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