Palladium-Catalyzed Phenylation of Enol Ethers and Acetates

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Reaction of iodobenzene with 3,4-dihydro-2*H*-pyran in the presence of diacetatobis(triphenylphosphine)palladium(II) and triethylamine at 100 °C occurred with high regioselectivity yielding 2-phenyl-3,4-dihydro-2*H*-pyran (63%) as the sole, isolated product. Similar reaction of iodobenzene with ethyl vinyl ether exhibited little regioselectivity, producing low yields of 1-ethoxyethylbenzene and (*E*)- and (*Z*)-2-ethoxyethenylbenzenes. The difference in regioselectivities observed for phenylation of these cyclic and acyclic enol ethers is attributed to the relatively greater electronic effect and the lesser steric difference between the olefinic carbons of the cyclic 3,4-dihydro-2*H*-pyran as compared with the acyclic ethyl vinyl ether. Similar palladium-catalyzed phenylation of vinyl acetate yielded, for a variety of reaction times and temperatures, mixtures of six products: styrene, (*E*)- and (*Z*)-phenylvinyl acetates, *trans*- and *cis*-stilbenes, and biphenyl.

Motivated by our recent success with palladium-catalyzed reactions of pyrimidin-5-yl derivatives with cyclic enol ethers[1,2] and with vinyl acetate[3] leading to syntheses of pyrimidine-5-yl carbohydrates[1] (C-nucleosides[4]), 5-dihydropyranylpyrimidines,[1,2] and 5-vinylpyrimidines,[3] we have investigated reactions of iodobenzene (1) with 3,4-dihydro-2*H*-pyran (2), ethyl vinyl ether (3), and vinyl acetate (4) in the presence of diacetatobis(triphenylphosphine)palladium(II).

In an early investigation of palladium-catalyzed arylation reactions, Heck[5] allowed a number of arylmercuric chlorides and acetates to react with various enol esters and with one enol ether (butyl vinyl ether) in the presence of palladium salts. At about the same time Danno et al.[6] reported the palladium-catalyzed reactions of benzene with vinyl acetate and ethyl vinyl ether. These reactions resulted in complex product mixtures and rather low yields. Heck[7] succeeded in obtaining high yields of arylated enol esters by utilizing stoichiometric quantities of arylmercuric acetate and palladium acetate and excess enol ester. Reaction of iodobenzene with vinyl acetate in the presence of a catalytic amount of palladium acetate produced mainly stilbene.[8]

In the present study, when iodobenzene (1) was allowed to react with excess[9] 3,4-dihydro-2*H*-pyran (2) in the presence of triethylamine and a catalytic amount of diacetatobis(triphenylphosphine)palladium(II),[10] 2-phenyl-3,4-dihydro-2*H*-pyran[11] (5) was formed in 63% yield; only traces of other products were formed. The migration of the double bond presumably occurred as a result of the high (100 °C) reaction temperature.[2,12] Quite a different result was obtained upon similar reaction of iodobenzene (1) with the acyclic enol ether, ethyl vinyl ether (3). In this reaction three products, 1-ethoxyethenylbenzene[13] (6), (*E*)-2-ethoxyethenylbenzene[13] (7), and (*Z*)-2-ethoxyethenylbenzene[13] (8), were formed in comparable, low yields.

The palladium-catalyzed reaction of iodobenzene (1) with the cyclic enol ether, 3,4-dihydro-2*H*-pyran (2), was highly regioselective in accord with previous results involving more complex pyrimidinylpalladium reagents.[1-3] The acyclic ethyl vinyl ether (3) reacted with little regioselectivity and, in contrast to the cyclic system, favored aryl substitution at the nonoxygenated carbon of the double bond.[14] Also, it is noteworthy that reaction of the cyclic enol ether (2) resulted in a yield nearly double that obtained in the corresponding reaction of the acyclic analogue 3.

Two differences in the structures of the two enol ethers studied may account for the observed differences in reaction regioselectivities. The disubstituted carbon–carbon double bond of 2 possesses minimal steric differences at the two olefinic carbons whereas the steric differences at the olefinic carbons of 3 are appreciable. Also, the restricted conformational flexibility of the cyclic compound 2 will tend to increase the bonding character of the olefin-oxygen π system and provide a greater electronic preference for the observed regioselectivity. Both these factors are consistent with the observation of increased regioselectivity in reactions of the cyclic system. However, the reason for the lower yields observed for the acyclic ethyl vinyl ether (3) is not obvious since both steric effects and electron-donating substituents can adversely affect palladium-catalyzed olefin arylations.[14,15]

A somewhat more extensive study of the palladium-catalyzed arylation of vinyl acetate (4) was made. In particular, variations were made in both reaction time and temperature in an attempt to increase product yields and to decrease the complexity of the product mixture. The results (Table I) reveal the very limited success which was achieved. The principal problem appears to be the high reactivity of the initially formed olefinic products to further arylation. It is well established[14,15] that styrene (9) readily undergoes arylation producing mixtures of *trans*- and *cis*-stilbene (12 and 13, respectively). The data in Table I which show that the combined yield of *trans*- and *cis*-2-phenylvinyl acetates (10 and 11) increase with increased reaction time and temperature suggest, but do not establish, that these compounds are not precursors to stilbenes under the reaction conditions. If the bulk of the stilbene formed arises from styrene (9), the regioselectivity of the initial vinyl acetate–phenylpalladium adduct formation is higher than that observed for the enol ether analogue 3 (Table I).

Comparison of results obtained in the present study with

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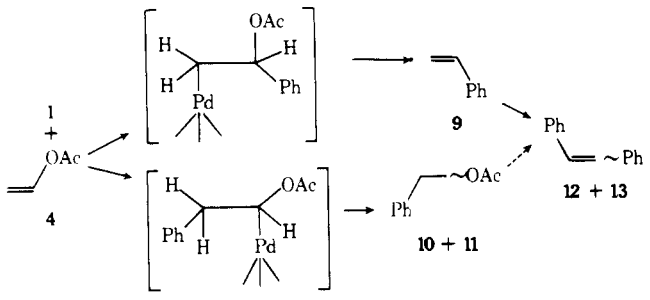
Table I. Palladium-Catalyzed Reaction of Iodobenzene[a] with Vinyl Acetate:[b] Effects of Reaction Time and Temperature on Product Distribution

Reaction time, h	temp, °C	recovered PhI, %	total products, %	% yield of products: Ph[c]	Ph~OAc	Ph, Ph[d]	Ph~Ph[e]	Ph—Ph[f]
3	70	40.5	18.2	5.5		10.9	1.8	trace
1	100	33.7	25.2	13.4	3.0	7.5	1.3	<1
2	100	18.5	45.8	18.0	5.6	18.1	2.6	1.5
1	130	14.8	44.3	17.4	8.3	16.8	1.8	<1
3	130	11.5	46.7	13.6	12.2	17.8	3.1	<1

[a] Registry no. 591-50-4. [b] Registry no. 108-05-4. [c] Registry no. 100-42-5. [d] Registry no. 103-30-0. [e] Registry no. 645-49-8. [f] Registry no. 92-52-4.



those of previous investigations emphasizes the strong influences of reaction conditions on these olefin arylations. Kasahara and co-workers,[8] who used palladium acetate without triphenylphosphine ligands and conditions otherwise similar to those used here, obtained principally stilbenes and did not report styrene formation. Heck[5,7] generated his arylpalladium reagent by transmetallation of phenylmercuric salts with palladium(II) salts and carried out arylation reactions at room temperature. In the sole reaction involving an enol ether which he reports,[5] no products corresponding to those observed in the present study (**6**–**8**) were obtained; instead the two products derived from both reactants were *trans*-stilbene, **12**, and phenylacetaldehyde. Differences in products formed (and their relative yields) were also observed for reactions involving vinyl acetate (**4**).[5,7] Danno et al.[6] carried out the phenylation of ethyl vinyl ether (**3**) and of vinyl acetate (**4**) with benzene and palladium acetate in acetic acid with results which differ with both those of Heck[5,7] and those reported here. Perhaps most surprising is the fact that under the conditions of Danno et al.,[6] no styrene or stilbenes were isolated. The stereoselective arylation of the cyclic enol ether 3,4-dihydro-2*H*-pyran (**2**) reported here and in previous studies utilizing pyrimidinyl palladium reagents,[1,2] and the equally regioselective formation of 5-vinylpyrimidines by palladium-catalyzed arylation,[3] are particularly encouraging and indicate that with proper selection of reaction conditions synthetically useful arylation of enol ethers and enol acetates is possible.

Experimental Section

General Comments. ^{1}H nuclear magnetic resonance spectra were obtained on deuteriochloroform solutions using a Varian Associates HA-100 spectrometer. Mass spectra were obtained using a DuPont 21-491 gas chromatograph–mass spectrometer. Quantitative gas chromatographic analyses utilized a Perkin-Elmer 900 instrument equipped with a 3 m × 3 mm stainless steel column of 3% Dexsil 300 on 80–100 Chromosorb W (AW/DMCS) and a flame ionization detector. For analyses the column oven was temperature programmed from 50–250 °C (10 °C/min) with a helium carrier gas flow rate of 20 mL/min. Relative elution band areas were determined manually; the elution band area for iodobenzene was multiplied by 1.4 (a relative detector response factor determined experimentally). Product yields for reactions of ethyl vinyl ether (**3**) and vinyl acetate (**4**) were determined by gas chromatographic analysis.

Procedure for Palladium-Catalyzed Phenylation Reactions. A mixture consisting of 2 g (10 mmol) of iodobenzene, 10 mL of enol ethers **2** or **3** or enol acetate **4**, 1.5 g (15 mmol) of triethylamine, and 0.07 g (0.01 mmol) of diacetatobis(triphenylphosphine)palladium(II)[10] in a sealed tube was heated at 100 °C for 3 h (or other reaction times and temperatures as noted, Table I). The cooled reaction mixture was then partitioned between water and chloroform. The chloroform solution was evaporated, hexane was added, the insoluble residue was removed, and the hexane solution was analyzed by gas chromatography and gas chromatography–mass spectrometry as described.

2-Phenyl-3,4-dihydro-2*H*-pyran (5).[11] The residue obtained from the hexane extract following reaction of iodobenzene (**1**) with 3,4-dihydro-2*H*-pyran (**2**) was chromatographed on silica gel by elution with hexane to remove unreacted **1**. The product, 2-phenyl-3,4-dihydro-2*H*-pyran[11] (**5**), 0.96 g (63.5%), was obtained as a viscous oil: ^{1}H NMR δ 1.8–2.8 (4 H, m, C-3,C-4-Hs), 4.65–4.95 (2 H, m, C-2-H, C-5-H), 6.53 (1 H, d, J = 7 Hz, C-6 H), 7.33 (5 H, aryl).

(*E*)-2-Ethoxyethenylbenzene[13](7) and (*Z*)-2-Ethoxyethenylbenzene[13](8). Gas chromatographic analysis of the product mixture obtained from reaction of iodobenzene (**1**) with ethyl vinyl ether (**3**) showed unreacted **1**, 1-ethoxyethenylbenzene[13] (**6**), and (*E*)- and (*Z*)-2-ethoxyethenylbenzenes[13] (**7** and **8**) to be present. Column chromatography on silica gel using hexane for elution produced two fractions. One fraction (0.4 g), consisting of **1** and **6**[13] (0.22 g, 13%, 0.18 g, 11%, respectively by gas chromatographic analysis), was not further separated. The second fraction, 0.32 g, consisted of a mixture of (*E*)- and (*Z*)-2-ethoxyethenylbenzenes (**7** and **8**). A second fractionation permitted the isomers to be separated. (*E*)-2-Ethoxyethenylbenzene[13] (**7**) exhibited ^{1}H NMR resonances: δ 1.35 (3 H, t), 3.89 (2 H, q), 5.85 (1 H, d, J = 13 Hz), 6.99 (1 H, J = 13 Hz), 7.21 (aryl). (*Z*)-2-Ethoxyethenylbenzene[13] (**8**) exhibited resonances: δ 1.35 (3 H, t), 3.95 (2 H, q), 5.22 (1 H, d, J = 7 Hz), 617 (1 H, d, J = 7 Hz), 7.0–7.7 (aryl).

Reactions of Iodobenzene (1) with Vinyl Acetate (4). Reaction mixtures obtained using the reaction conditions noted in Table I were analyzed by gas chromatography–mass spectrometry to assure product identities and by quantitative gas chromatography to determine yields. A mixture of phenylvinyl acetates **10** and **11**[16] was isolated by column chromatography (silica gel/hexane) and examined by ^{1}H NMR to insure identity. The *E* isomer **10**[16] exhibited an olefinic AB system, δ 6.42, 7.87 (J = 12 Hz); the *Z* isomer **11**[16] exhibited a doublet, J = 7 Hz, at δ 5.74 (the second olefinic doublet was obscured by olefinic resonances at δ 7.2–7.5).

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Registry No.—**2**, 110-87-2; **3**, 109-92-2; **5**, 16015-12-6; **6**, 6230-62-2; **7**, 20565-86-0; **8**, 13294-31-0; **10**, 1566-65-0; **11**, 1566-67-2; diacetatobis(triphenylphosphine)palladium(II), 14588-08-0.

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Reduction of Antimony Pentafluoride by Alkanes: Implications for Mechanisms in Superacid Chemistry

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Reductions of SbF_5 in HF proceed only very slowly in the presence of H_2 as the lone reducing agent, but the addition of certain alkanes causes a large increase in the rate of reduction. For example, a 1:10 mixture of SbF_5/HF gives only about 2% Sb(V) reduction by reaction with H_2 at 5.8 atm partial pressure after 4 h at 50 °C. About ten times as much reduction occurs when a mixture of hexane and cyclohexane (9:1) is added to the reaction. Other hydrocarbons gave the following reductions (wt %) in a 0.5-h reaction time: propane, 2.1; *n*-butane, 1.9; isobutane, 9.0; isobutane (no applied H_2), 9.0. These results are discussed in terms of either a direct hydride abstraction from alkane by SbF_5 or a series of single electron transfer steps.

The ionization of alkanes in superacids, such as SbF_5/HF and SbF_5/FSO_3H, has been formulated as occurring by the loss of hydrogen (H_2) from a protonated alkane.[1] Although the protonation mechanism is considered to be quite well-established, skeptics have continued to raise doubts about its exclusivity. Other processes, oxidations by SbF_5, SO_3, or FSO_3H and the like, have been suggested.[2-5] The results of the present work give support to the arguments of the skeptics and raise additional doubts about the exclusivity of the protonation mechanism for the ionization of alkanes.

$$HF + SbF_5 \rightleftharpoons H^+ SbF_6^-$$

$$R^1R^2CH_2 + H^+ \rightleftharpoons R^1R^2CH_3^+ \rightleftharpoons R^1R^2CH^+ + H_2$$

Perhaps the opening of the controversy can be dated with the suggestion of the direct hydride mechanism by Holmes and Pettit[2] in a study of cycloheptatriene. Other workers later extended the idea to explain reactions of lower alkanes in "neat" SbF_5.[3,4] In contrast, Olah has interpreted his oligocondensation of methane[6] and many other reactions of paraffins in superacids in terms of the protonation mechanism for ionization.[1] He argued that SbF_5 cannot be made sufficiently free of HF to preclude operation of the protonation mechanism; i.e., even if hydride abstraction were to occur in a very pure sample of SbF_5, the reaction would produce HF from collapse of the intermediate SbF_5H^- and cause a change to the protonation mechanism for further ionization.

$$CH_4 + SbF_5 \rightleftharpoons CH_3^+ + SbF_5H^-$$

$$SbF_5H^- \rightarrow SbF_3 + HF + F^-$$

$$\text{or } H^+ + SbF_5H^- \rightleftharpoons SbF_5 + H_2$$

Bobilliart, Thiébault, and Herlem[7] have found that FSO_3H alone is reduced by butane and by pentane with production of SO_2. Larsen, Pagni, and co-workers have shown that cycloheptatriene is oxidized by FSO_3H to produce tropylium ion and SO_2.[8] This result led them to examine the reaction of isobutane in SbF_5/FSO_3H mixtures. Neither hydrogen nor SO_2 were observed, but cycloheptatriene did cause production of SO_2 this system.

Herlem has presented an argument[5] that, in superacid solutions, SbF_5 is a stronger oxidizing agent than the hydrogen ion.

One might expect that an important test for the protonation mechanism would be the measurement of hydrogen produced by the second step in the ionization. In fact, the lower alkanes produce only traces of hydrogen in contact with superacids. This apparent stoichiometric deficiency in hydrogen production has been attributed by Olah[1] to uptake of "nascent" hydrogen by the acid, causing reduction of SbF_5 in an SbF_5/HF system.

There is an appearance of disagreement as to whether SbF_5 is reduced by H_2. Olah reported that "neat" SbF_5 can be reduced quantitatively by 50 atm of H_2 at room temperature in 24 h,[1] but other workers have reported that H_2 does not reduce systems such as HSO_3F, FSO_3H/SbF_5, and HF/SbF_5.[9] A possible reason for this difference is that SbF_5 is stabilized toward reduction by interaction with strongly coordinating solvents such as HF or FSO_3H, expecially in dilute solutions.

Key questions then are the following: is SbF_5 reduced in a superacid such as the SbF_5/HF system; and if so, is the reduction caused by direct reaction between an alkane and the SbF_5 or by a reaction of SbF_5 with H_2 produced from a protonated alkane? A demonstration of SbF_5 reduction by alkanes instead of H_2 would have important mechanistic implications for the ionization process itself.

How can one distinguish reductions caused by an alkane from reductions caused by H_2 produced from a protonated alkane? A helpful approach to separating these effects has developed from a fortuitous use of hydrogen in industrial isomerization processes. In a prospective industrial isomerization process one would normally use moderate hydrogen pressure (2–10 atm) over the acid mixture to prevent the buildup of acid-soluble oily byproducts that cause loss of acid strength and activity. Fortuitously the addition of this H_2 allows one to "swamp" the system with much more H_2 than would be produced by alkane ionization alone. This has proved to be helpful in separating the reductive effect of alkanes from that of H_2.

Results and Discussion

In the following experiments the superacid (1:10 mole ratio of SbF_5/HF) was allowed to contact 1.4 times its weight of a hydrocarbon feed. The feed, unless otherwise specified, is a mixture of 9:1 *n*-hexane/cyclohexane. The acid–feed mixture

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