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The Palladium-catalyzed Arylation of 4-Chromanone Enol Esters. A New Synthesis of Isoflavanones

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Heck's reaction of 4-chromanone enol esters with arylpalladium compounds in acetic acid afforded isoflavanones in a high yield. The structural elucidation of these products was accomplished by spectral inspections.

Isoflavanones (I) have been synthesized by the hydrogenation of the corresponding isoflavones,[1-4] by the oxidation of isoflavanes,[5] by the reduction of 3-hydroxyisoflavanones with zinc in aqueous acetic acid,[6] and by the action of methylene diiodide on *o*-hydroxydeoxybenzoin.[7] Recently, Heck[8] has reported that arylpalladium compounds, generated *in situ* from arylmercury compounds (II) and palladium salts, reacted with ketone enol esters to form α-arylketones as the major products. In this report we wish to report

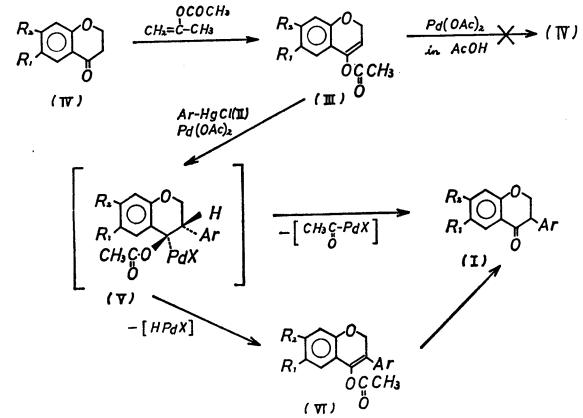

Fig. 1

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Table 1. Arylation reaction of 4-chromanone enol acetates (III)

4-Chromanone enol acetate	Arylating agent	Product	Yield %
IIIa	IIa	Isoflavanone (Ia)	75
IIIa	IIb	4'-Methylisoflavanone (Ib)	70
IIIa	IIc	4'-Methoxyisoflavanone (Ic)	75
IIIa	IId	3'-Nitroisoflavanone (Id)	65
IIIa	IIe	4'-Phenylisoflavanone (Ie)	60
IIIa	IIf	4'-Chloroisoflavanone (If)	60
IIIb	IIa	6-Methoxyisoflavanone (Ig)	68
IIIb	IIb	6-Methoxy-4'-methylisoflavanone (Ih)	72
IIIb	IIc	6,4'-Dimethoxyisoflavanone (Ii)	70
IIIb	IId	6-Methoxy-3'-nitroisoflavanone (Ij)	70
IIIb	IIe	6-Methoxy-4'-phenylisoflavanone (Ik)	65
IIIb	IIf	6-Methoxy-4'-chloroisoflavanone (Il)	68
IIIc	IIa	7-Methoxyisoflavanone (Im)	60
IIIc	IIb	7-Methoxy-4'-methylisoflavanone (In)	65
IIIc	IIc	7,4'-Dimethoxyisoflavanone (Io)	70
IIIc	IId	7-Methoxy-3'-nitroisoflavanone (Ip)	70
IIIc	IIe	7-Methoxy-4'-phenylisoflavanone (Iq)	65
IIIc	IIf	7-Methoxy-4'-chloroisoflavanone (Ir)	70

the application of this new reaction to 4-chromanone enol esters (III); this method gave I in a high yield.

III was obtained in 80—90% yields by the reaction of 4-chromanones (IV) with isopropenyl acetate at reflux. In the presence of palladium acetate, III was treated with II in acetic acid at room temperature to produce I. For example, the reaction of 4-chromanone enol acetate (IIIa) with phenylmercuric acetate (IIa) resulted in the formation of isoflavanone (Ia) (yield=75%), which was identified by a comparison of its NMR and IR spectra with those of an authentic sample.[4] Similarly, 6-methoxy- and 7-methoxy-isoflavanone (Ig and Im) were synthesized from 6-methoxy- and 7-methoxy-4-chromanone enol acetate (IIIb and IIIc) respectively. The reactions carried out are summarized in Table 1.

Recent studies of the Heck reaction have shown that the reaction usually gives products consistent with a *cis* addition of the arylpalladium compounds to olefin, followed by a *cis* palladium hydride elimination and readdition.[9] In the reaction of III with arylpalladium compounds, the sterically-preferred direction of addition appears to be to add the aryl group to the least-substituted carbon atom (C_3) of the double bond. In the initially-formed adduct (V), the *trans* elimination of palladium with a neighboring hydride produces an arylated enol ester (VI), while the elimination of palladium with an acyl group produces a carbonyl compound (I). Previously it was suggested that, in the phenylation of enol esters, the elimination of palladium with an acyl group in the adduct appears to be produce the carbonyl compounds,[8] but Heck[10] has recently shown that the cupric chloride used as a co-catalyst is responsible for the formation of phenylacetaldehyde in the phenylation of vinyl acetate and that presumably the elimination of palladium with an acyl group does not occur. However, in the arylation reaction of III without using cupric chloride as a co-catalyst, the reaction mixtures produced little, if any, VI, affording only I. Moreover, since the enol ester, IIIa, can not be changed to the IVa ketone in an acetic acid solution of palladium acetate, it is clear that the I does not all come from the hydrolysis of VI and that the elimination of palladium with an acyl group produces I.

Experimental

All the melting points and boiling points are uncorrected. The IR spectra were taken with a Hitachi model 215 grating spectrometer. The NMR spectra were recorded on a Hitachi model H-60 spectrometer, operating at 60 MHz in a $CDCl_3$ solution; the chemical shifts were given in ppm from the TMS internal standard. The NMR signals in a singlet are designated as s; in a doublet, as d; in a triplet, as t, and in a multiplet, as m.

Materials. The palladium acetate was prepared according to the procedure of Wilkinson.[11] The following compounds were synthesized by the methods described in the literature: 4-chromanone (IVa), bp 120—122 °C/9 mmHg (lit,[12] bp 127—128 °C/13 mmHg); 6-methoxy-4-chromanone (IVb), mp 48—49 °C (lit,[13] mp 49 °C); 7-methoxy-4-chromanone (IVc), mp 52—53 °C (lit,[14] mp 52—54 °C); *p*-tolylmercuric chloride (IIb), mp 232—233 °C (lit,[15] mp 233 °C); *p*-anisylmercuric chloride (IIc), mp 173—174 °C (lit,[16] mp 173—174 °C); *m*-nitrophenylmercuric chloride

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TABLE 2. ANALYSES AND PROPERTIES OF ISOFLAVANONES (I)

Compound	Mp °C (lit)	Found (%) C	Found (%) H	Calcd (%) C	Calcd (%) H	IR and NMR spectra
Ia	76—77 (77[a])					
Ib	83—84	80.52	5.81	80.64	5.92	IR 1683, 800, and 760 cm^{-1}. NMR δ 2.36 (s 3H, CH_3–), 3.94 (t 1H, J=6.0 Hz, proton on C_3), 4.65 (d 2H, J=6.0 Hz, protons on C_2), and 6.89—7.98 ppm (m 8H, aromatic ring protons).
Ic	98—99	75.43	5.38	75.57	5.55	IR 1685, 810, and 740 cm^{-1}. NMR δ 3.80 (s 3H, CH_3O–), 3.94 (t 1H, J=6.6 Hz, proton on C_3), 4.65 (d 2H, J=6.6 Hz, protons on C_2), and 6.77—7.97 ppm (m 8H, aromatic protons).
Id	139—140	66.85 (N=5.06)	4.01	66.91 (N=5.20)	4.12	IR 16.85, 1532, 1350, 810, and 730 cm^{-1}. NMR δ 4.11 (t 1H, J=7.2 Hz, proton on C_3), 4.72 (d 2H, J=7.2 Hz, protons on C_2), and 6.93—8.13 ppm (m 8H, aromatic ring protons).
Ie	170—171	83.83	5.19	83.98	5.37	IR 1685, 810, 740, and 690 cm^{-1}. NMR δ 4.01 (t 1H, J=6.6 Hz, proton on C_3), 4.70 (d 2H, J=6.6 Hz, protons on C_2), and 6.90—7.98 ppm (m 13H, aromatic ring protons).
If	111—112 (111[b])					
Ig	107—108 (108[a])					
Ih	84—85	75.95	5.89	76.10	6.01	IR 1680, 820, 800, and 720 cm^{-1}. NMR δ 2.35 (s 3H, CH_3–), 3.81 (s 3H, CH_3O–), 3.92 (t 1H, J=6.6 Hz, proton on C_3), 4.62 (d 2H, J=6.6 Hz, protons on C_2), and 6.97—7.37 ppm (m 7H, aromatic ring protons).
Ii	51—53	71.69	5.62	71.82	5.67	IR 1680, 820, 755, and 725 cm^{-1}. NMR δ 3.79 (s 6H, CH_3O–), 3.88 (t 1H, J=6.6 Hz, proton on C_3), 4.59 (d 2H, J=6.6 Hz, protons on C_2), and 6.77—7.38 ppm (m 7H, aromatic ring protons).
Ij	119—120	64.07 (N=4.52)	4.30	64.21 (N=4.68)	4.38	IR 1680, 1527, 1345, 860, and 808 cm^{-1}. NMR δ 3.80 (s 3H, CH_3O–), 3.89 (t 1H, J=6.0 Hz, proton on C_3), 4.68 (d 2H, J=6.0 Hz, protons on C_2), and 6.79—7.38 ppm (m 7H, aromatic ring protons).
Ik	122—123	79.85	5.37	79.98	5.49	IR 1680, 820, 750, 720, and 690 cm^{-1}. NMR δ 3.78 (s 3H, CH_3O–), 3.89 (t 1H, J=6.6 Hz, proton on C_3), 4.68 (d 2H, J=6.0 Hz, protons on C_2), and 6.79—7.45 ppm (m 12H, aromatic ring protons).
Il	100—101	65.36	4.41	66.55	4.53	IR 1680, 820, and 740 cm^{-1}. NMR δ 3.78 (s 3H, CH_3O–), 3.89 (t 1H, J=6.6 Hz, proton on C_3), 4.68 (d 2H, J=6.6 Hz, protons on C_2), and 6.79—7.38 ppm (m 7H aromatic ring protons).
Im	92—93 (93[a])					
In	122—123	76.03	5.90	76.10	6.01	IR 1683, 820, 805, and 720 cm^{-1}. NMR δ 2.34 (s 3H, CH_3–), 3.82 (s 3H, CH_3O–), 3.87 (t 1H, J=6.6 Hz, proton on C_3), 4.64 (d 2H, J=6.6 Hz, protons on C_2), and 6.64—7.92 ppm (m 7H, aromatic ring protons).
Io	128—129 (126,[c,d] 128—129[e])					
Ip	130—131	64.12 (N=4.60)	4.26	64.21 (N=4.68)	4.38	IR 16.80, 1529, 1345, 860, and 800 cm^{-1}. NMR δ 3.79 (s 3H, CH_3O–), 3.89 (t 1H, J=6.6 Hz, proton on C_3), 4.66 (d 2H, J=6.6 Hz, protons on C_2), and 6.48—7.87 ppm (m 7H, aromatic ring protons).

Table 2. (continued)

Compound	Mp °C (lit)	Found (%) C	Found (%) H	Calcd (%) C	Calcd (%) H	IR and NMR spectra
Iq	187—188	79.94	5.37	79.98	5.49	IR 1680, 817, 750, 720, and 690 cm^{-1}. NMR δ 3.82 (s 3H, CH_3O–), 3.93 (t 1H, J=6.0 Hz, proton on C_3), 4.66 (d 2H, J=6.0 Hz, protons on C_2), and 6.44—7.91 ppm (m 12H, aromatic ring protons).
Ir	141—142	66.48	4.47	66.55	4.53	IR 1680, 820, and 738 cm^{-1}. NMR δ 3.83 (s 3H, CH_3O–), 3.88 (t 1H, J=6.6 Hz, proton on C_3), 4.68 (d 2H, J=6.6 Hz, protons on C_2), and 6.41—7.92 ppm (m 7H, aromatic ring protons).

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(IId), mp 218—220 °C (lit,[17] mp 218—221 °C); *p*-phenylphenylmercuric chloride (IIe), mp>360 °C (lit,[18] mp> 360 °C); and *p*-chlorophenylmercuric chloride (IIf); mp 223—225 °C (lit,[19] mp 225 °C). The phenylmercuric acetate (IIa) and isopropenyl acetate were of a commercial grade. The acetic acid was dried over phosphorus pentoxide and distilled before use.

Preparation of 4-Chromanone Enol Acetates (III). A mixture of 4.0 g of IV, 16 ml of isopropenyl acetate, and 0.4 g of *p*-toluene sulfonic acid was refluxed for 36 hr under nitrogen. After 200 ml of benzene was added to the reaction mixture, the benzene solution was washed successively with water, dilute aqueous sodium bicarbonate, and water. The benzene extracts were dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo*. The residue was distilled under reduced pressure to give enol acetates (III) (yield, 80—90%). The following compounds were prepared in this manner.

4-Chromanone Enol Acetate (IIIa, R_1=R_2=H). Bp 150—152 °C/13 mmHg. IR spectrum: 1760, 1210, and 743 cm^{-1}. NMR spectrum: δ 2.33 (s, 3H, CH_3COO–), 4.87 (d, 2H, J=4.2 Hz, protons on C_2), 5.46 (t, 1H, J=4.2 Hz, olefinic proton on C_3), and 6.81—7.83 *ppm* (m, 4H, aromatic ring protons).

Found: C, 69.61; H, 5.38%. Calcd for $C_{11}H_{10}O_3$: C. 69.46; H, 5.30%.

6-Methoxy-4-chromanone Enol Acetate (IIIb, R_1=–OCH_3, R_2=H). Bp 162—164 °C/7 mmHg. IR spectrum: 1765, 1210, 900, and 802 cm^{-1}. NMR spectrum: δ 2.15 (s, 3H, CH_3COO–), 3.69 (s, 3H, CH_3O–), 4.82 (d 2H, J= 4.8 Hz, protons on C_2), 5.29 (t, 1H, J=4.8 Hz, olefinic proton on C_3), and 6.96—7.38 ppm (m, 3H, aromatic ring protons).

Found: C, 65.57; H, 5.60%. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49%.

7-Methoxy-4-chromanone Enol Acetate (IIIc, R_1=H, R_2=CH_3O–). Bp 159—161 °C/6 mmHg. IR spectrum: 1760, 1208, 900, and 800 cm^{-1}. NMR spectrum: δ 2.18 (s, 3H, CH_3COO–), 3.67 (s, 3H, CH_3O–), 4.84 (d, 2H, J= 4.6 Hz, protons on C_2), 5.36 (t, 1H, J=4.6 Hz, olefinic proton on C_3), and 6.88—7.64 ppm (m, 3H, aromatic ring protons).

Found: C, 65.48; H, 5.58%. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49%.

General Procedures for the Arylation of III. A mixture of 10 mmol of III, 10 mmol of II, and 10 mmol of palladium acetate was stirred overnight in 80 ml of acetic acid at room temperature. After the resulting mixture has been filtered to remove the precipitated palladium metal, the filtrate was evaporated to dryness *in vacuo* to remove the acetic acid. The residue was poured into water and was extracted with chloroform. The chloroform solution was treated with dilute aqueous sodium bicarbonate, washed with water to free it from acetic acid, and then dried over anhydrous magnesium sulfate. After the evaporation of the solvent, the products were isolated by column chromatography on alumina with benzene and by crystallization from alcohol. The identities of the products formed were proved by mixed-melting-point determinations or by comparisons of the IR or NMR spectra with those of authentic samples. The analytical results and properties of the products are listed in Table 2.

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