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A New Method of Preparing Flavones

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The reaction of the sodium salt of 2′-hydroxychalcones with palladium(II) salt led to the formation of flavones, accompanied by a small amount of flavanones. The reaction proceeds *via* a phenoxypalladation, followed by the elimination of a hydridopalladium(II).

In the presence of palladium(II) salt, the reaction of the oxygen nucleophile with the carbon-carbon double bond has received wide attention.[1] Hosokawa *et al.*[2] have recently reported that the reaction of the sodium salt of 2-allylphenol with dichlorobis(benzonitrile) palladium in refluxing benzene proceeds *via* an intramolecular phenoxypalladation and gives 2-methylbenzofuran in a 31% yield. Independently of their work, we wish now to report that flavones (**1**) can be prepared in a high yield by the reaction of the sodium salt of 2′-hydroxychalcones (**2**) with lithium chloropalladite in a polar solvent, such as acetonitrile or ethanol. On the other hand, numerous reports of the synthesis of **1** have appeared in literature.[3] No direct cyclization of **2** into **1** is, however, known with the exception of the reaction of **2** with selenium dioxide in amyl alcohol or in xylene (the yields are not very good).[4]

Results and Discussion

At room temperature, the sodium salt of **2** was treated with lithium chloropalladite or with palladium(II) acetate in a polar solvent, such as acetonitrile or ethanol, to produce **1**, accompanied by a small amount of flavanone (**3**). For example, the reaction of 2′-hydroxychalcone (**2a**) with lithium chloropalladite in acetonitrile resulted in the formation of flavone (**1a**) (yield=75%) and flavanone (**3a**) (yield=6%). Similarly, 6-methoxy- and 7-methoxyflavone (**1d** and **1e**) were synthesized from the corresponding 2′-hydroxychalcones (**2d** and **2e** respectively). The reactions carried out are summarized in Table 1, and the usual conversions of **2** in the range of 40—90% were obtained. On the other hand, the reaction of **2a** with a combination of the palladium(II) catalyst and the copper(II) chloride co-catalyst gave **1a** (yield=62%) and **3a** (yield=16%). In the conversion of **2** to **1** with palladium(II) salt, no formation of the five-membered-ring product [benzylidenebenzofuran-3(2H)-one] was observed.

Usually, the addition of oxygen nucleophile to the carbon-carbon double bond of the olefin-palladium complex proceeds by the attack at the double bond on the side opposite from that facing the metal.[5] In addition, Henry *et al.*[6] have recently reported that the oxidation of deuterated cyclohexene by a mixture of palladium(II) chloride and copper(II) chloride in acetic acid gave products which were consistent with a *trans* acetoxypalladation, followed by a *cis* palladium(II)-hydride elimination. The reaction of **2** with palladium(II) salt, therefore, involves an intramolecular *trans* phenoxypalladation, followed by a *cis* palladium(II)-hydride elimination. On the other hand, the formation of **3** proceeds *via* a base-catalyzed cyclization of **2**.

Experimental

Materials. All the melting points are uncorrected. The following compounds were synthesized by the methods described in the literature: 2′-hydroxychalcone (**2a**),[7] 2′-hydroxy-4-methoxychalcone (**2b**),[8] 2′-hydroxy-3,4-methylenedioxychalcone (**2c**),[9] 2′-hydroxy-5′-methoxychalcone (**2d**),[10] 2′-hydroxy-4′-methoxychalcone (**2e**),[11] 2′-hydroxy-4,4′-dimethoxychalcone (**2f**),[12] and 2′-hydroxy-4,5′-dimethoxychalcone (**2g**).[13]

*General Procedure for the Preparation of **1**.* A solution of 10 mmol of **2** in benzene (20 ml) was stirred with 10 mmol of sodium methoxide for 5 min at room temperature. To the mixture, lithium chloropalladite or palladium(II) acetate (10 mmol in 70 ml of solvent) was then added, after which the mixture was stirred at reaction temperature. After the resulting mixture had been filtered to remove the precipitated palladium metal, the filtrate was evaporated to dryness *in vacuo* to remove the solvent. The residue was poured into water and extracted with chloroform. The chloroform solution was washed with water, and then dried over anhydrous magnesium sulfate. After the evaporation of the solvent, the products were isolated by column chromatograph on silica gel. The first elution with benzene afforded the unreacted starting material (**2**), while the second elution and recrystallization from ethanol afforded the respective flavanones (**3**). Further elution with benzene-chloroform and recrystallization from benzene or ethanol afforded the respective flavones (**1**). The structures of the products were confirmed by mixed-melting-point determination with an authentic sample and by the observation of the IR and NMR spectra. The results are summarized in Table 1.

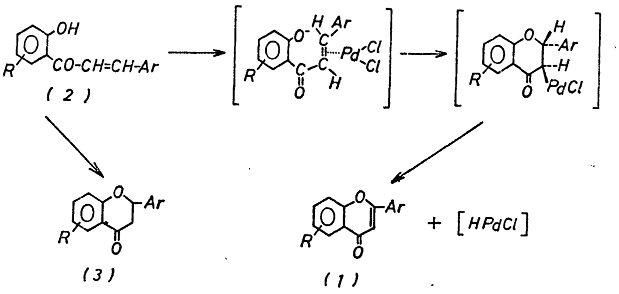

Fig. 1.

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Table 1. The Reaction of 2′-hydroxychalcone (**2**) with palladium(II) salt

Substrate	Pd(II) salt	Solvent	Reaction temp.	Reaction time(hr)	Convn (%)[a]	Product	Mp °C (lit.)	Yield (%)
2a	Li_2PdCl_4	C_2H_5OH	room temp.	24	80	Flavone (**1a**)	96—97 (97[b])	65
						Flavanone (**3a**)	75—76 (76[c])	15
2a	Li_2PdCl_4	CH_3CN	room temp.	24	81	**1a**		75
						3a		6
2a	Li_2PdCl_4	CH_3CN	reflux	2	70	**1a**		55
						3a		15
2a	Li_2PdCl_4[d] + $CuCl_2$	CH_3CN	reflux	8	78	**1a**		62
						3a		25
2a	$Pd(OAc)_2$	CH_3CN	room temp.	48	40	**1a**		25
						3a		15
2a	$Pd(OAc)_2$	CH_3CN	reflux	2	65	**1a**		52
						3a		13
2b	Li_2PdCl_4	CH_3CN	room temp.	24	90	4′-Methoxyflavone (**1b**)	156—158 (157—158[e])	83
						4′-Methoxyflavanone (**3b**)	96—97 (97[f])	7
2c	Li_2PdCl_4	CH_3CN	room temp.	24	87	3′,4′-Methylenedioxyflavone (**1c**)	199—200 (200—201[e])	78
						3′,4′-Methylenedioxyflavanone (**3c**)	127—128 (127[g])	9
2d	Li_2PdCl_4	CH_3CN	room temp.	24	90	6-Methoxyflavone (**1d**)	152—154 (154[h])	83
						6-Methoxyflavanone (**3d**)	140—142 (142[i])	7
2e	Li_2PdCl_4	CH_3CN	room temp.	24	85	7-Methoxyflavone (**1e**)	110—112 (110—111[j])	78
						7-Methoxyflavanone (**3e**)	90—91 (91[k])	7
2f	Li_2PdCl_4	CH_3CN	room temp.	24	80	4′,7-Dimethoxyflavone (**1f**)	142—143 (143—144[l])	72
						4′,7-Dimethoxyflavanone (**3f**)	94—95 (94—95[m])	8
2g	Li_2PdCl_4	CH_3CN	room temp.	24	88	4′,6-Dimethoxyflavone (**1g**)	192—194 (194—195[n])	82
						4′,6-Dimethoxyflavanone (**3g**)	159—160 (160[o])	6

a) Conversion is defined as convn $\% = \frac{\text{mol } (\mathbf{1}+\mathbf{3})}{\text{mol } (\mathbf{2}) \text{ charged}} \times 100$. b) T. S. Wheeler, "Organic Syntheses," Vol. 32, p. 72 (1952). c) A. Lowenbein, *Ber.*, **57**, 1515 (1924). d) In the reaction, 10 mmol of **2a**, 10 mmol of sodium methoxide, 2 mmol of Li_2PdCl_4, and 20 mmol of $CuCl_2 \cdot 2H_2O$ were used. e) K. v. Auwers and L. Auschutz, *Ber.*, **54**, 1543 (1921). f) A. Edelstein and S. v. Kostanecki, *ibid.*, **38**, 1507 (1905). g) S. Fujise and S. Sasaki, *Nippon Kagaku Zasshi*, **72**, 462 (1951). h) H. Simonis and D. Danischewski, *Ber.*, **59**, 2914 (1926). i) H. Simonis and C. Lear, *ibid.*, **59**, 2908 (1926). j) T. Emilewicz and S. v. Kostaneck, *ibid.*, **32**, 309 (1899). k) S. v. Kostanecki and M. L. Stoppani, *ibid.*, **37**, 1180 (1904). l) J. Tambor, *ibid.*, **49**, 1704 (1916). m) K. Juppen and S. v. Kostanecki, *ibid.*, **37**, 4161 (1904). n) A. T. M. Dunne, J. E. Gowan, J. Keane, B. M. O'Kelly, D. O'Sullivan, M. M. Rocke, P. M. Ryan, and T. S. Wheeler, *J. Chem. Soc.*, **1950**, 1252. o) S. v. Kostanecki and M. L. Stoppani, *Ber.*, **37**, 781 (1904).

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