FACILE SYNTHESIS OF ISOFLAVONES BY THE CROSS-COUPLING REACTION OF 3-iodochromone WITH ARYLBORONIC ACIDS

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We describe a convenient preparation of isoflavones by the cross-coupling reactions of 3-iodochromone (1) with arylboronic acids (2) catalyzed by tetrakis(triphenylphosphine)palladium(0).

KEYWORDS isoflavone; 3-iodochromone; phenylboronic acid; cross-coupling reaction; tetrakis(triphenylphosphine)palladium

Isoflavonoids are widely distributed in plants, especially in Leguminosae, Moraceae, Iridaceae and Rosaceae. Some of these isoflavonoids have physiological activities such as estrogenic, antispastic, antibacterial, antiprotozoal, and insecticidal.¹⁾

Synthesis of isoflavones is needed to confirm the structures of natural products, and for this the long-established methods of ring closure of a C₁ unit onto a deoxybenzoin are still widely used. While the addition of one-carbon unit to a deoxybenzoin can be accomplished efficiently, synthesis of the deoxybenzoin itself may proceed in rather poor yields, and starting materials are not readily available.

Recently the cross-coupling reactions of arylhalides with alkenes, alkynes, and arylboronic acids catalyzed by Pd-complex have been studied extensively.²⁾ We have applied the reaction to the novel and efficient synthesis of isoflavones (3) by using tetrakis(triphenylphosphine)palladium as a catalyst.

A typical experiment can be described as follows. Isoflavone (3a): To a solution of 3-iodochromone (1) (0.5 mmol), Pd(PPh₃)₄ (0.05 mmol), and 1 ml of 2M-Na₂CO₃ in benzene (20 ml) was added phenylboronic acid (2a) (2 mmol) in 2 ml of ethanol under argon with stirring at room temperature. The reaction mixture was refluxed for 15 h followed by the addition of 1 ml of 30% H₂O₂ to oxidize excess phenylboronic acid. After being stirred for 1 h at room temperature the mixture was poured into ice and extracted with CH₂Cl₂ (3 x 15 ml). The organic layer was washed with water and dried over anhydrous Na₂SO₄. Removal of the solvent gave a pale yellow product which was purified by silica gel chromatography with benzene as an eluent to give isoflavone (3a), mp 135 °C, in 97.8% yield. Palladium(0) catalyzed the cross-coupling reactions of other arylboronic acids (2b-2e), prepared by the reported method³⁾ through the corresponding Grignard reagents, with 3-iodochromone (1) using the above general procedure, are summarized in Table I. The results show that the cross-coupling reaction of substituted arylboronic acids (2) with 1 is a quite general and simple method for the synthesis of isoflavones (3).

When palladium acetate was used as the catalyst instead of Pd(PPh₃)₄, the yield of isoflavone was decreased to ca. 30%.

Thiophen-2-boronic acid (4) was also coupled with 1 under the same condition to afford 5, mp 138-139 °C, in 70.2% yield. This implies that we could introduce aromatic and heterocyclic ring systems into the 3-position of chromone under the mild condition in the presence of "Pd" catalyst.

Table I. Reactions of 3-Iodochromone (**1**) with Arylboronic Acids (**2**) Catalyzed by $\text{Pd(PPh}_3)_4$

	Arylboronic acid (2)		Yield of 3 (%) ^a	mp of 3 (°C)
	R ₁	R ₂		
a	H	H	97.8	135
b	CH ₃	H	93.2	154–156
c	OCH ₃	H	94.1	144
d	OCH ₃	OCH ₃	95.8	144–145
e	–O–CH ₂ –O–		92.8	158

a) Satisfactory spectroscopic data were obtained for all **3** and yields were after the isolation by the silica gel column chromatography.

REFERENCES AND NOTES

- 1) E. Wong, "The Flavonoids," ed. by J. B. Harborne, T. J. Mabry and H. Mabry, Chapman and Hall, London, 1975, p. 743.
- 2) N. Miyaara, T. Yanagi, and A. Suzuki, *Synth. Commun.*, **11**, 513 (1981) and references cited therein; T. Jeffery, *J. Chem. Soc., Chem. Commun.*, **1984**, 1287; R. F. Heck, "Palladium Reagents in Organic Syntheses", Academic Press, Inc., London, 1985; V. Nair, D. W. Powell, and S. C. Sri, *Synth. Commun.*, **17**, 1897 (1987); T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, and H. Yamanaka, *Chem. Pharm. Bull.*, **36**, 1305 (1988); T. Sakamoto, M. An-naka, Y. Kondo, T. Araki, and H. Yamanaka, *ibid.*, **36**, 1890 (1988); T. Sakamoto, T. Nagano, Y. Kondo, and H. Yamanaka, *ibid.*, **36**, 2255 (1988); N. Miyaara, and A. Suzuki, *Yuki Gosei Kagaku Kyokai Shi*, **46**, 848 (1988).
- 3) W. J. Thompson, and J. Gaudino, *J. Org. Chem.*, **49**, 5237 (1984):

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