Novel Synthesis of Isoflavones by the Palladium-Catalyzed Cross-Coupling Reaction of 3-Bromochromones with Arylboronic Acids or Its Esters

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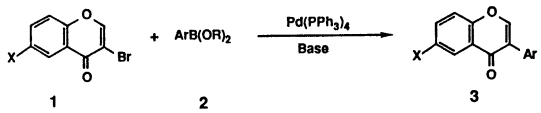
(Received February 26, 1988)

Synopsis. The synthesis of isoflavone derivatives by means of palladium-catalyzed cross-coupling reaction between 3-bromochromones and arylboronic acids or its butyl esters is described.

Isoflavones (3-phenyl-4*H*-1-benzopyran-4-ones) belong to the main categories of flavonoids, such as flavones (2-phenyl-4*H*-1-benzopyran-4-ones) and chalcones, which exist in plants, fruit, and flowers. Although many synthetic methods of isoflavones have been reported, including: (1) the oxidative rearrangement of chalcones with thallium(III) nitrate;[1] (2) the aryl migration of 2′-hydroxychalcone epoxides using $BF_3 \cdot OEt_2$;[2] and (3) the oxidation of products obtained by boiling *N*-styrylmorpholine and salicylaldehyde with CrO_3–pyridine in benzene;[3] no synthetic procedures of isoflavones have been presented hitherto using a direct arylation on a chromone framework. Recently, we have reported that the palladium-catalyzed cross-coupling reaction[4] of phenylboronic acids with haloarenes proceeds smoothly in the presence of bases to give corresponding biaryls. Thereafter, several articles[5] with respect to the application of this reaction have appeared. We report here the preparation of isoflavones (**3**) from 3-bromochromones (**1**) and arylboronic acids or its esters (**2**) by applying the above-mentioned cross-coupling reaction (Eq. 1).

Results and Discussion

The optimum conditions for carrying out the reaction of Eq. 1 were studied by using 3-bromochromone and phenylboronic acid or its butyl ester in the presence of 3 mol% of $Pd(PPh_3)_4$ and 2 equivs of various bases. The results are summarized in Table 1. From



1 2 3 (1)

the table, it is shown that the best yield of isoflavone can be obtained by using aqueous Na_2CO_3 as a base. The reaction is also effected with aqueous Tl_2CO_3[6] and found to be complete in the shorter reaction time compared with other bases (Entry 4). A more interesting use of Tl_2CO_3 may be the reaction of dibutyl phenylboronate with **1** under nonaqueous conditions (Entry 5). The desired isoflavone was obtained in 91% yield, whereas the reaction time had to be increased to 6 h. When the coupling reaction was carried out in the presence of NaOH or NaOAc, the formation of *o*-hydroxyacetophenone was observed in the GLC analysis. It has been known that chromones are subject to ring fission[7] by a strong base such as NaOH to give the corresponding *o*-hydroxyacetophenones. Furthermore, it has also been reported that arylboronic acids are protonized[5a,b] with water in the presence of a base. The low yields of isoflavone in those cases may be due to such side reactions.

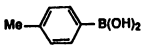
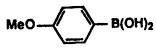
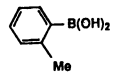
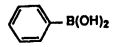
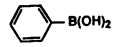
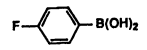
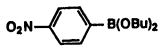
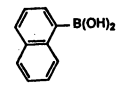
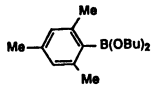
Table 1. Effects of Bases on the Cross-Coupling Reaction of 3-Bromochromone with Phenylboronic Acid or Its Butyl Ester[a]

Entry	$PhB(OR)_2$	Base	Reaction time/h	Yield/%[b]
1	OH	3 M $NaOH/H_2O$	3	49
2	OH	3 M $NaOAc/H_2O$	8[c]	25
3	OH	2 M Na_2CO_3/H_2O	6	94
4	OH	1 M Tl_2CO_3/H_2O	1.5	85
5	OBu	Tl_2CO_3[d]	6	91

a) All the reactions were conducted under reflux temperature of benzene, using 3-bromochromone (1 mmol), phenylboron compound (1.1 mmol), $Pd(PPh_3)_4$ (0.03 mmol), and base (2 mmol). b) Isolated yield beased on 3-bromochromone. c) Reaction was not complete. d) Powdered Tl_2CO_3 was suspended in benzene.

To establish a generality of this method as a synthetic procedure of **3**, eleven isoflavone derivatives were prepared from the corresponding 3-bromochromones and arylboronic acids. Representative results are summarized in Table 2. The conditions using aqueous Na_2CO_3 as a base (Entry 3 in Table 1) were found to work for the most of phenylboronic acids with ortho and para substituents, and for the 3-bromochromones substituted with 6-Cl and 6-MeO groups. The yields of **3** seem to largely depend upon the functional groups on **2** rather than those of **1**. Namely, the reaction of *p*-nitrophenylboronic acid with **1** gave only 23% of 4′-nitroisoflavone after refluxing for 4 h. Mesitylboronic acid reacted only slowly (completed after 26 h) and gave less than 5% of 2′,4′,6′-trimethylisoflavone together with a substantial amount of mesitylene. The results indicated that the protonolysis of phenylboronic acids is competitive with the coupling even under the conditions using aqueous Na_2CO_3. Thus, such aqueous conditions are not suitable for the phenylboronic acids with electron-withdrawing substituents which accelerate the rate of protonolysis or two ortho substituents which retard the transmetallation step in the mechanism[8] of cross-coupling reaction. For these boronic acids, an alternative procedure (Entry 5 in Table 1) using the esters of boronic acids and Tl_2CO_3 was developed. Under these

Table 2. Synthesis of Isoflavones (Eq. 1)

Entry	1, X=	$ArB(OR)_2$	Base	Reaction time/h	Yield %[a]
1	H		2 M Na_2CO_3/H_2O	10	84
2	H		2 M Na_2CO_3/H_2O	3	94
3	H		2 M Na_2CO_3/H_2O	6	94
4	Cl		2 M Na_2CO_3/H_2O	23	71
5	MeO		2 M Na_2CO_3/H_2O	7	87
6	H		2 M Na_2CO_3/H_2O	6	80
7	H		Tl_2CO_3	9	88[b]
8	H		2 M Na_2CO_3/H_2O	7	90
9	H		Tl_2CO_3	48	47[b]

a) Isolated yields based on 3-bromochromones. b) Reaction was carried out under the nonaqueous conditions (Entry 5 in Table 1).

nonaqueous conditions, the protonolysis of arylboronic acids can be prevented. Indeed, the reactions of dibutyl mesitylboronate and *p*-nitrophenylboronate with **1** gave the corresponding coupling products in yields of 47 and 88% (Entries 7 and 9 in Table 2). Although it is necessary to further define the scope and limitations of this nonaqueous procedure, the conditions should be more useful for the coupling reactions[5] of the arylboron compounds which are sensitive to protonolysis or sterically hindered.

Since, the 3-bromochromones are readily prepared from commercially available *o*-hydroxyacetophenone and the arylboronic acids are also conventionally prepared by the reaction of aryl-Grignard reagents with trialkylborates followed by hydrolysis, it can be concluded that the present procedure is a general and straightforward method for isoflavone synthesis.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO-IRA-1 spectrometer by means of KBr pellet. ^1H NMR spectra were obtained with a Hitachi-R-90H Fourier Transform NMR spectrometer (90 MHz) and are reported in δ units using tetramethylsilane as an internal standard. Mass spectra were taken on a JEOL JMS-D300. GLC analyses were performed on a Hitachi 163 instrument using silicon OV-17 (2 m) on Uniport B.

Materials and Reagents. Benzene was the commercially available grade, and was distilled and dried over sodium before use. Tetrakis(triphenylphosphine)palladium(0) was prepared by the literature procedure.[9] Phenylboronic acid,[10] *p*-tolylboronic acid,[10] *p*-methoxyphenylboronic acid,[10] *p*-fluorophenylboronic acid,[11] 1-naphthylboronic acid,[12] *p*-nitrophenylboronic acid,[10] and mesitylboronic acid[13] were prepared by the known procedures.[14] 3-Bromochromones were also synthesized by the method reported by Gammill.[15] All isoflavones isolated and 3-bromo-6-methoxychromone were identified by IR, ^1H NMR, and mass spectra, and these physical data are as follows.

3-Bromo-6-methoxychromone: Mp 122.0—122.5 °C; IR (KBr) 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=3.90 (s, 3H, OCH_3), 7.20—7.48 (m, 2H, aromatic), 7.59 (d, 1H, J=2.6 Hz, C_5-H), and 8.20 (s, 1H, C_2-H); MS, Found: m/z 255.9566, Calcd for $C_{10}H_7BrO_3$: M, 255.9558.

Isoflavone: Mp 131.5—132.0 °C; IR (KBr) 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=7.32—7.78 (m, 8H, aromatic), 8.01 (s, 1H, C_2-H), and 8.31 (dd, 1H, C_5-H, J=7.5 and 1.8 Hz); MS, Found: m/z 222.0682, Calcd for $C_{15}H_{10}O_2$: M, 222.0681.

4′-Methylisoflavone: Mp 153.5—154.5 °C; IR (KBr) 1635 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=2.38 (s, 3H, CH_3), 7.18—7.77 (m, 7H, aromatic), 7.99 (s, 1H, C_2-H), and 8.31 (dd, 1H, C_5-H, δ=8.4 and 1.8 Hz); MS, Found: m/z 236.0838, Calcd for $C_{16}H_{12}O_2$: M, 236.0838.

4′-Methoxyisoflavone: Mp 141—142 °C; IR (KBr) 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=3.84 (s, 3H, OCH_3), 6.92—7.77 (m, 7H, aromatic), 7.99 (s, 1H, C_2-H), and 8.31 (dd, 1H, C_5-H, J=7.5 and 1.9 Hz); MS, Found: m/z 252.0782, Calcd for $C_{16}H_{12}O_3$: M, 252.0787.

2′-Methylisoflavone: Mp 113.5—114.0 °C; IR (KBr) 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=2.26 (s, 3H, CH_3), 7.08—7.80 (m, 7H, aromatic), 7.87 (s, 1H, C_2-H), and 8.30 (dd, 1H, C_5-H, J=7.6 and 1.4 Hz); MS, Found: m/z 236.0821, Calcd for $C_{16}H_{12}O_2$: M, 236.0837.

6-Chloroisoflavone: Mp 186.0—186.5 °C; IR (KBr) 1635 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=7.37—7.69 (m, 7H, aromatic), 8.01 (s, 1H, C_2-H), and 8.26 (d, 1H, C_5-H, J=2.4 Hz); MS, Found m/z 256.0276. Calcd for $C_{15}H_9ClO_2$: M, 256.0292.

6-Methoxyisoflavone: Mp 172—173 °C; IR (KBr) 1625 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=3.91 (s, 3H, OCH_3), 7.19—7.64 (m, 7H, aromatic), 7.68 (d, 1H, C_5-H, δ=2.4 Hz), and 8.00 (s, 1H, C_2-H); MS, Found: m/z 252.0797, Calcd for $C_{16}H_{12}O_3$: M, 252.0787.

4′-Fluoroisoflavone: Mp 192.0—192.5 °C; IR (KBr) 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=7.02—7.79 (m, 7H, aromatic), 7.99 (s, 1H, C_2-H), and 8.30 (dd, 1H, C_5-H, J=7.4 and 1.8 Hz); MS, Found: m/z 240.0583, Calcd for $C_{15}H_9FO_2$: M, 240.0587.

4′-Nitroisoflavone: Mp 202—204 °C; IR (KBr) 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=7.38—8.46 (m, 8H, aromatic), and 8.13 (s, 1H, C_2-H); MS, Found: m/z 267.0533, Calcd for $C_{15}H_9NO_4$: M, 267.0532.

2′,3′-Benzoisoflavone: Mp 107.5—108.0 °C; IR (KBr) 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=7.35—7.96 (m, 10H, aromatic), 8.00 (s, 1H, C_2-H), and 8.34 (dd, 1H, C_5-H, J=7.9 and 1.5 Hz); MS, Found: m/z 272.0818, Calcd for $C_{19}H_{12}O_2$: M, 272.0837.

2′,4′,6′-Trimethylisoflavone: Mp 105.5—106.0 °C; IR (KBr) 1635 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=2.13 (s, 6H, 2′-CH_3 and 6′-CH_3), 2.31 (s, 3H, 4′-CH_3), 6.94 (s, 2H, C_3-H, C_5-H), 7.24—7.80 (m, 3H, aromatic), 7.75 (s, 1H, C_2-H), and 8.28 (dd, 1H, C_5-H, J=7.8 and 1.8 Hz); MS, Found: m/z 264.1131, Calcd for $C_{18}H_{16}O_2$: M, 264.1151.

General Procedure. A 25 mL two-necked round-bottomed flask equipped with a reflux condenser, a septum inlet, and a magnetic stirring bar, was charged with 3-bromochromone (2.0 mmol), phenylboronic acid (2.2 mmol), and $Pd(PPh_3)_4$ (0.072 g, 0.06 mmol). The flask was flushed with nitrogen and filled with 4 ml of dry benzene and 2 ml of aqueous 2 M-Na_2CO_3 solution through the septum inlet with a syringe. For the reaction under nonaqueous conditions, dibutyl arylboronate (2.2 mmol) and powdered Tl_2CO_3 (2 mmol) were

used in place of phenylboronic acid and aqueous Na_2CO_3 solution. The mixture was refluxed in an oil bath with stirring. At suitable time intervals, a part of the reaction solution was sampled with a microsyringe and was subjected to GLC analysis. After the reaction was complete, the flask was cooled to room temperature. The product was extracted with benzene, washed with brine, and dried over anhydrous magnesium sulfate. Finally the product was isolated by silica gel column chromatography using a mixture of benzene, dichloromethane, and ether (2:2:1) as an eluent, followed by recrystallization from a mixture of hexane and a small amount of benzene.

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