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Palladium-catalyzed one-pot Suzuki–Miyaura cross coupling followed by oxidative lactonization: a novel and efficient route for the one-pot synthesis of benzo[*c*]chromene-6-ones

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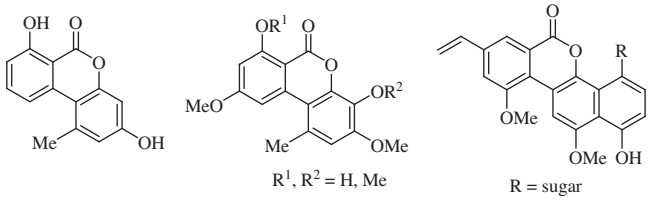
Oxidative lactonization

ABSTRACTS

A number of 6*H*-benzo[*c*]chromene-6-ones, 5*H*-naphtho[1,2-*c*]chrome-5-ones, and 6*H*-naphtho[2,1-*c*]chromene-6-one have been synthesized starting with 2-hydroxyphenylboronic acid and *o*-bromobenzaldehyde or *o*-bromonaphthalene carboxaldehyde derivatives via a one-pot Suzuki–Miyaura cross coupling followed by oxidative lactonization reactions. The overall transformation consists of three reactions: Suzuki–Miyaura cross coupling, hemi-acetal formation, and oxidation.

Benzo[*c*]chromen-6-ones and the relevant lactones serve as the core structure of many natural products,[1] such as autumnariol (Fig. 1, **1**), alternariol, altenuisol, autumnariniol, and graphislactones (Fig. 1, **2**) and in biologically important compounds.[2] They are also present in a number of natural antitumor and antibiotic agents, such as chrysomycins (Fig. 1, **3**), gilvocarcins, and ravidomycins.[3] In addition, such lactones are also important as intermediates for the synthesis of several pharmaceutically important compounds, such as progesterone, androgen, glucocorticoid receptor agonists,[4] and endothelial cell proliferation inhibitors.[5] Benzo[*c*]chromen-6-ones also occur naturally in a number of food resources including citrus fruits, herbs, and vegetables.[6]

There are several methods available for the synthesis of benzo[*c*]chromen-6-ones which usually are multi-step processes. Some of these recent methods are the Diels–Alder cycloaddition of 4-cyanocumarins,[7] *tert*-butyllithium-mediated cyclization of bromobenzylfluorophenyl ethers,[8] and ruthenium-catalyzed cyclotrimerization of aryl diynes.[9] The most used method involves Suzuki–Miyaura cross coupling of methyl 2-bromobenzoate and 2-methoxyphenylboronic acids followed by Lewis acid[10] or metal[11] mediated lactonization. There are also some other synthetic routes for the lactonization step, such as, the direct lactonization of carboxylic acid to an aromatic ring,[12] the displacement of a nitro group with carboxylic acid,[13] and the displacement of a benzyl group.[14] However, these methods are the multi-step sequences and need purification of intermediates. Thus, a new route for the synthesis of benzo[*c*]chromen-6-ones from readily available starting materials in a single step is still of critical importance.



1 2 3

Figure 1. Structure of some natural products and bioactive compounds.

Herein, we have reported a novel and efficient methodology for the one pot synthesis of benzo[*c*]chromen-6-ones and its higher analogues by reacting 2-bromobenzaldehyde or *o*-bromonaphthalene carboxaldehyde derivatives with 2-hydroxyphenylboronic acid via Suzuki–Miyaura cross coupling followed by oxidative lactonization[15] of aldehyde and hydroxy groups.

Our investigation began with an effort to optimize reaction conditions for the one-pot synthesis of benzo[*c*]chromen-6-ones and its higher analogues and for that 2-bromobenzaldehyde and 2-hydroxyphenylboronic acid were chosen as the coupling partners for Suzuki–Miyaura cross coupling reaction. Then various

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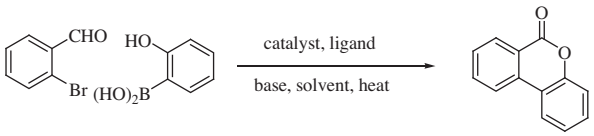
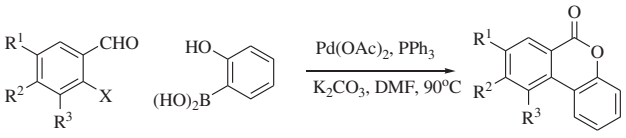
Table 1
Screening of the reaction conditions*



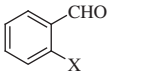
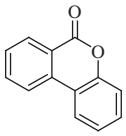
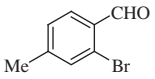
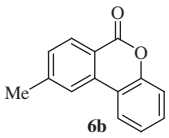
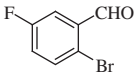
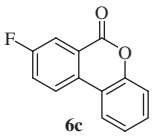
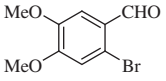
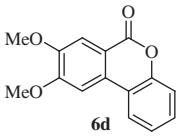
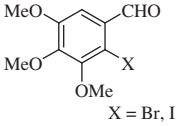
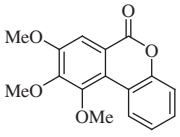
Entry	Catalyst	Ligand	Base	Solvent	Temperature (°C)	Time (h)	Yield**
1	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	80	6	63
2	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF	80	6	86
3	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	80	6	89
4	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	80	6	87
5	$Pd(OAc)_2$	PPh_3	Et_3N	DMF	80	6	47
6	$PdCl_2$	PPh_3	K_2CO_3	DMF	80	6	81
7	$PdCl_2(PPh_3)_2$	–	K_2CO_3	DMF	80	6	80
8	$Pd(PPh_3)_4$	–	K_2CO_3	DMF	80	6	75
9	$PdCl_2(CH_3CN)_2$	PPh_3	K_2CO_3	DMF	80	6	78
10	$Pd_2(dba)_3$	PPh_3	K_2CO_3	DMF	80	6	67
11	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	90	4	90
12	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	95	4	89
13	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMA	90	4	82
14	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMSO	90	4	76
15	$Pd(OAc)_2$	PPh_3	K_2CO_3	CH_3CN	90	4	62

* Reactions were carried out with 0.2 mmol of 2-bromobenzaldehyde, 2-hydroxyphenylboronic acid (1 equiv), catalyst (5 mol %), ligand (0.25 equiv), base (1 equiv), and solvent (1 mL).
** Isolated yield by column chromatography.

Table 2
One-pot synthesis of benzo[*c*]chromen-6-ones*



4 **5** **6**

Entry	*o*-Bromobenzaldehyde	Product	Time (h)	Yield** (%)
1	 X = Cl, Br, I **4a**	 **6a**	X = Cl, 8 X = Br, 4 X = I ,3	X = Cl, 87 X = Br, 90 X = I ,91
2	 **4b**	 **6b**	4	89
3	 **4c**	 **6c**	4	92
4	 **4d**	 **6d**	4	93
5	 X = Br, I **4e**	 **6e**	6	X = Br, trace X = I, 68

* Reactions were carried out with 1 mmol of 2-bromobenzaldehyde derivatives, 2-hydroxyphenylboronic acid (1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (0.25 equiv), K_2CO_3 (1 equiv), DMF (3 mL), and heated at 90 °C.
** Isolated yield by column chromatography.