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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

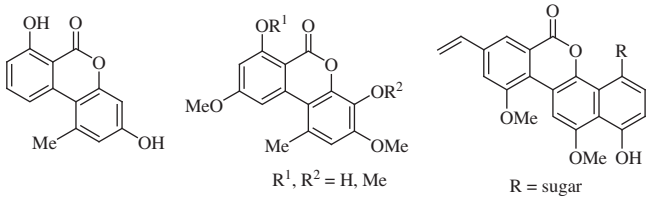
ABSTRACTS

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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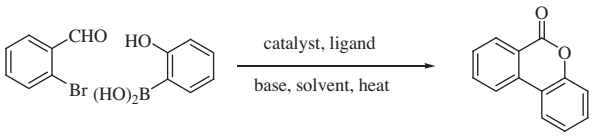
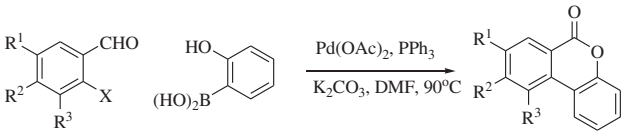
**Table 1**
Screening of the reaction conditions*



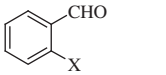
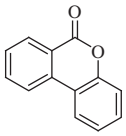
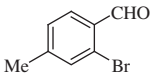
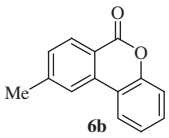
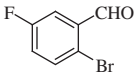
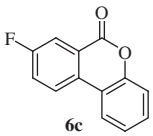
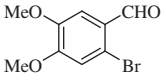
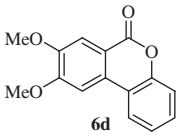
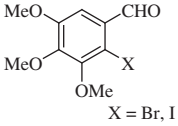
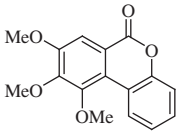

| Entry | Catalyst | Ligand | Base | Solvent | Temperature (°C) | Time (h) | Yield** |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $PPh_3$ | NaOAc | DMF | 80 | 6 | 63 |
| 2 | $Pd(OAc)_2$ | $PPh_3$ | $Na_2CO_3$ | DMF | 80 | 6 | 86 |
| 3 | $Pd(OAc)_2$ | $PPh_3$ | $K_2CO_3$ | DMF | 80 | 6 | 89 |
| 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<br>X = Br, 4<br>X = I ,3 | X = Cl, 87<br>X = Br, 90<br>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<br>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.

catalysts, ligands, bases, and solvents were used for screening the Suzuki–Miyaura cross coupling followed by oxidative lactonization reactions. Progress of the reaction was monitored by TLC and the results are shown in Table 1.

A set of initial conditions were selected consisting 0.2 mmol of 2-bromobenzaldehyde, 2-hydroxyphenylboronic acid (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $PPh_3$ (0.25 equiv), base (1 equiv), DMF (1 mL) under nitrogen atmosphere with stirring at 80 °C for 6 h. The first reaction was carried out with NaOAc base and it gave the desired product benzo[*c*]chromen-6-one in 63% yield. Then different bases were used (Table 1, entries 1–5) and the best result was obtained with $K_2CO_3$. The next task was to find the best catalyst for the reaction and for that a series of six catalysts was used (Table 1, entries 5–10). The catalyst $Pd(OAc)_2$ was found to be the prominent catalyst and gave the highest yield for the transformation whereas $Pd_2(dba)_3$ gave the poorest result. On increasing the temperature to 90 °C, the time for completion of the reaction decreased to 4 h (Table 1, entry 11). On further increasing the temperature to 95 °C, the reaction time remained the same (Table 1, entry 12). Then different solvents were employed (Table 1, entries 13–15) and the best yields were obtained from DMF. Thus, the optimized reaction condition for the one-pot synthesis of benzo[*c*]chromen-6-ones was 5 mol % of $Pd(OAc)_2$, $K_2CO_3$ (1 equiv) in DMF solvent heated at 90 °C for 4 h.[16]

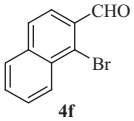
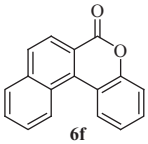
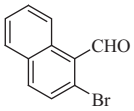
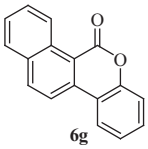
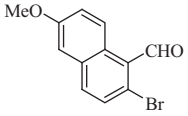
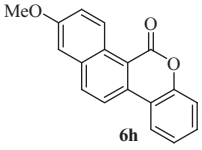
After developing the optimized reaction condition, the scope of this methodology was explored. Thus several substituted 2-bromobenzaldehyde derivatives were employed to prepare the corresponding benzo[*c*]chromen-6-ones. The results are shown in Table 2.

The coupling of *o*-hydroxyphenylboronic acid **5** and *o*-haloarylcarboxaldehydes **4** bearing both electron donating and withdrawing groups gave the corresponding benzo[*c*]chromen-6-ones in good to excellent yields. For 2-halobenzaldehyde (Table 2, entry 1) when X = Cl, it took 8 h for completion of the reaction and when X = I, the reaction completed within 3 h. For 2-bromo-3,4,5-trimethoxybenzaldehyde (Table 2, entry 5), the yield of the reaction was trace and for 2-iodo-analogue the yield was 68% after 6 h (Table 2, entry 5). This poor reactivity is probably due to the sterically hindered position of halogens. After this, the methodology was applied on fused *o*-bromoarylcarboxaldehydes (Table 3). 2-bromonaphthalene-1-carboxaldehydes gave good yields (Table 3, entries 2,3) while 1-bromonaphthalene-2-carboxaldehyde gave comparatively lower yield probably due to the sterically hindered location of bromine at 1-position of naphthalene. The results are shown in Table 3.

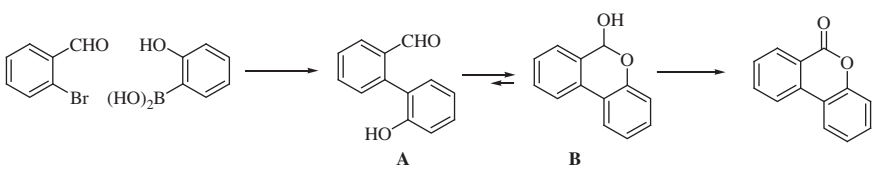
A plausible mechanism for the formation of the products is shown in Scheme 1. At first, the Suzuki–Miyaura cross coupling of *o*-bromoarylcarboxaldehyde and o-hydroxyphenylboronic acid affords the intermediate **A**. The intermediate **A** equilibrates to form hemi-acetal **B** which afforded the desired product benzo[*c*]chromen-6-one by palladium-catalyzed aerial oxidation,[17] that is, oxidative lactonization. Thus, the oxidative lactonization is the key step of this transformation. The development of exact reaction mechanism and application of this methodology in the synthesis of some bioactive natural products are in progress.

In summary, we have developed an advanced methodology for the one-pot synthesis of benzo[*c*]chromen-6-ones and its higher analogues via tandem Suzuki–Miyaura cross coupling followed by oxidative lactonization in good to excellent yields. In addition, such oxidative lactonization will be helpful for the synthesis of a number of natural products and bioactive molecules having pharmaceutical importance. The bio-activity test of some compounds is in progress.

**Table 3**
One-pot synthesis of naphthochromens

| Entry | *o*-Bromobenzaldehyde | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  **4f** |  **6f** | 6 | 71* |
| 2 |  **4g** |  **6g** | 4 | 86** |
| 3 |  **4h** |  **6h** | 4 | 83** |

* Entry 1, the reactions were carried out at 110 °C.
** Other reactions were carried with the optimized reaction conditions.




**Scheme 1.** Plausible rational for the formation of the product.

## Acknowledgment

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## Supplementary data

Supplementary data (detailed experimental procedure and spectral data for the compounds (**6a**–**h**)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.144.

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16. *General procedure for the one-pot synthesis of benzo[c]chromen-6-ones:* 2-bromoarylcarboxaldehyde (1 mmol), 2-hydroxyphenylboronic acid (1 mmol), $K_2CO_3$ (1 mmol), $PPh_3$ (0.25 mmol) were taken in a two-necked round bottomed flask and flushed with nitrogen gas. Then 3 mL of DMF was added and degassed with $N_2$. The catalyst $Pd(OAc)_2$ (5 mol %) was added to the reaction mixture and heated at 90 °C for 4 h. After completion of the reaction, the reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh) and hexane/EtOAc as eluent.
*Spectral data for the representative compound 6H-benzo[c]chromen-6-one (**6a**):*[10a] white solid; yield 90%; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.30–7.39 (2H, m), 7.45–7.63 (2H, m), 7.79–7.87 (1H, m), 8.04–8.14 (2H, m), 8.40 (1H, d, $J$ = 8 Hz); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 117.9, 118.2, 121.4, 121.9, 122.9, 124.7, 129.1, 130.6, 130.8, 134.9, 135.0, 151.5, 161.4. HRMS (ESI) for $C_{13}H_8O_2$: Calcd 197.0603 ($M^+$+H); Found: 197.0609.
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