CONVENIENT ONE-POT SYNTHESIS OF 3-ARYL-2H-CHROMENE-4-CARBONITRILES VIA A TANDEM O-ALKYLATION-KNOEVENAGEL CONDENSATION

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Abstract – 3-Aryl-2H-chromene-4-carbonitriles were synthesized through one-pot tandem reaction of easily available 2-(2-hydroxyphenyl)acetonitrile (1) and 2-bromo-1-arylethanones (2) under the condition of K₂CO₃/dioxane. These functionalized chromenes could be useful building-blocks for estrogen receptor ligands and other related heterocycles.

INTRODUCTION

2H-Chromenes exist widely in plants. They have attracted widespread interest in view of their various biological activities, especially as potentially useful pesticides,¹ endothelin-A selective receptor antagonists,² and potassium channel-opening vasodilators.³ Some 2H-chromenes are effective photoaffinity reagents for the cytochrome P450 superfamily of enzymes and probably other proteins as well.⁴ 3-Phenyl substituted 2H-chromenes belong to trans-1,2-diphenylethenes, which are an important scaffold for estrogen receptor modulators.⁵ So far, considerable literatures have reported the synthesis of 2H-chromenes, but very few methods are known to synthesize 4-substituted 3-aryl-2H-chromenes. Besides the classic synthesis by the reaction of Grignard reagent with 3-arylchroman-4-ones,⁵b,⁶ Tech-Peng Loh’s group has reported the synthesis of 4-amide substituted 3-aryl-2H-chromenes by palladium-catalyzed direct arylation of cyclic enamides with aryl silanes.⁷ José Barluenga’s group synthesized this type of compounds by cyclization of aryl propargyl ethers followed by Suzuki reaction.⁸ Both reported methods needed expensive palladium catalyst.
Herein, we synthesized 4-cyano substituted 3-aryl-2H-chromenes through metal-free one-step reaction of easily available 2-(2-hydroxyphenyl)acetonitrile (1) and 2-bromo-1-arylethanones (2) under the condition of K$_2$CO$_3$/dioxane. These chromenes are important building-blocks for other 4-substituted 3-aryl-2H-chromenes because of the presence of functional cyano and vinyl groups.

**RESULTS AND DISCUSSION**

A few of methods have been reported to synthesize 2-(2-hydroxyphenyl)acetonitrile (1). Most of them used highly toxic cyanide.$^9$ Nakamura reported hydrolysis, decarboxylation and rearrangement of methyl 4H-benzo[e][1,2]oxazine-3-carboxylate through two steps.$^10$ Ryozo Maeda employed reduction, diazotization and hydrolysis of 2-nitrophenylacetonitrile.$^11$ However, 1H-indazole-3-carbonitrile was gained under the same condition as the latter by our lab. Finally, compound (1) was synthesized by demethylation of 2-(2-methoxyphenyl)acetonitrile by BBr$_3$ for the first time.

Then 2-(2-hydroxyphenyl)acetonitrile (1) was reacted with 2-bromo-1-phenylethanone (2a) to optimize the reaction conditions (Table 1). Initially, the effect of base was examined. We found that strong or moderate base such as MeONa and Ca(OH)$_2$ gave little product (entries 1 and 2). DMAP reacted with the compound (2a) to give quaternary ammonium, which was demonstrated by LC-MS (entry 3). DBU gave a trace amount of the product (entry 4). K$_2$CO$_3$ was much better than Cs$_2$CO$_3$, giving the desired product with moderate yield (entries 5 and 6). However, the intermediate 2-(2-(2-oxo-2-phenylethoxy)-phenyl)acetonitrile (3a) was not completely converted to the product even after 24 h.

The solubility of K$_2$CO$_3$ in organic solvent was also taken into consideration. One of the strategies was to add 0.5 mL of water into the reaction. But the yield was not improved as expected (entry 7). The other strategy was to try different solvents. When the reaction was carried out in acetone or dioxane instead of toluene, the reaction could be finished within 4 h and the yield was dramatically increased (entries 8 and 9). Interestingly the polar solvent DMF hardly gave any product (entry 10).

The microwave-assisted reaction could not shorten the reaction time and its main product was the intermediate (entry 11). The amount of base could be decreased into 1.2 equivalent without influencing the reaction (entry 12).

Finally, we investigated the effect of the reaction temperature. When lowering the temperature to 80 °C, the starting material was converted to the intermediate within 4 h (entry 13). Prolonging the reaction time, the intermediate could be converted to the product slowly.

Under the optimized reaction condition (1.2 eq K$_2$CO$_3$, dioxane, 120 °C), we investigated the scope and the limitations of the reaction employing a variety of 2-bromo-1-arylethanones with the compound (1). The results were summarized in Table 2.
Table 1. The annulation reaction of 2-(2-hydroxyphenyl)acetonitrile with 2-bromo-1-phenylethanone

![Reaction diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Yield (%)&lt;sup&gt;d&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>MeONa</td>
<td>toluene</td>
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<td>120</td>
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<tr>
<td>2</td>
<td>Ca(OH)₂</td>
<td>toluene</td>
<td>24</td>
<td>120</td>
<td>0</td>
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<tr>
<td>3</td>
<td>DMAP</td>
<td>toluene</td>
<td>2</td>
<td>120</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>toluene</td>
<td>1</td>
<td>120</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃</td>
<td>toluene</td>
<td>1</td>
<td>120</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>K₂CO₃</td>
<td>toluene</td>
<td>24</td>
<td>120</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃</td>
<td>toluene/water</td>
<td>24</td>
<td>120</td>
<td>37</td>
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<tr>
<td>8</td>
<td>K₂CO₃</td>
<td>acetone</td>
<td>4</td>
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<td>82</td>
</tr>
<tr>
<td>9</td>
<td>K₂CO₃</td>
<td>dioxane</td>
<td>4</td>
<td>120</td>
<td>90</td>
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<tr>
<td>10</td>
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<td>DMF</td>
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<td>120</td>
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<td>12</td>
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<td>dioxane</td>
<td>4</td>
<td>80</td>
<td>0</td>
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</tbody>
</table>

<sup>a</sup>Reaction conditions: 1 (0.5 mmol), 2a (0.5 mmol), base (1.5 mmol), solvent (5 mL).

<sup>b</sup>The reaction was assisted by microwave.

<sup>c</sup>Base (0.6 mmol).

<sup>d</sup>The isolated yield.

When R₂ was hydrogen, substitution with electron-donating groups on phenyl group gave very excellent yield (88-99%), such as methyl and methoxy (entries 1 and 2); substitution with electron-withdrawing groups such as chlorine, fluorine or trifluoromethyl gave moderate yield (58-71%, entries 3, 4, 6, 7, and 9). However, when phenyl group was substituted with nitro at the para or ortho position, there was almost no desired product but only complex side products (entries 5 and 8). To our delight, the bulky substrates such as 2-bromo-1-(naphthalen-2-yl)ethanone and 2-bromo-1,2-diphenylethanone reacted smoothly and gave good yield (entries 10 and 11). Heterocycles such as 2-bromo-1-(thiophen-2-yl)ethanone could be also reacted with compound (1) with an acceptable yield (entry 12).
Table 2. The annulation reaction of 2-(2-hydroxyphenyl)acetonitrile with 2-bromo-1-arylethanones$^a$

$$\text{NC} \quad \text{OH} \quad + \quad \text{O} \quad \text{CN}$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Yield (%)$^b$</th>
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<tr>
<td>1</td>
<td>4-MeOPh</td>
<td>H</td>
<td>99</td>
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<tr>
<td>2</td>
<td>4-MePh</td>
<td>H</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>4-ClPh</td>
<td>H</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>4-FPh</td>
<td>H</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>4- $\text{O}_2\text{N}$Ph</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>4-CF$_3$Ph</td>
<td>H</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>3-ClPh</td>
<td>H</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>2- $\text{O}_2\text{N}$Ph</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
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<td>2,4-difluorophenyl</td>
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<td>68</td>
</tr>
<tr>
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<td>naphthalen-2-yl</td>
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<tr>
<td>11</td>
<td>Ph</td>
<td>Ph</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>thiopheny-2-yl</td>
<td>H</td>
<td>29</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1 (0.5 mmol), 2 (0.5 mmol), base (0.6 mmol), solvent (5 mL).

$^b$The isolated yield.

In summary, a convenient method was discovered to synthesize 3-aryl-2H-chromene-4-carbonitriles through one-pot tandem reaction of easily available 2-(2-hydroxyphenyl)acetonitrile (1) and 2-bromo-1-arylethanones (2) under the condition of K$_2$CO$_3$/dioxane, which was general to aryl ring with electron-donating and electron-withdrawing groups. These functionalized chromenes could be useful building-blocks for estrogen receptor ligands and other related heterocycles.

EXPERIMENTAL

Except the starting material (1), the other chemical reagents were commercial products and used without purification in all cases. Solvents were dried by standard methods. $^1$H and $^{13}$C NMR spectra were recorded on Varian Mercury-300 and Varian Mercury-400 spectrometers. MS and HRMS spectra were recorded on a MAT-95 spectrometer. Melting points were measured by Büchi 510 melting point apparatus and were uncorrected.

2-(2-Hydroxyphenyl)acetonitrile (1)

To a solution of 2-(2-methoxyphenyl)acetonitrile (9.4 g, 64 mmol) in 200 mL of absolute CH$_2$Cl$_2$ was added 80 mL of 4 N BBr$_3$ in CH$_2$Cl$_2$ at 0 °C slowly. Then the reaction mixture was stirred at room temperature overnight and added into ice-water under stirring. The resulting white precipitate was filtered,
washed with water and dried. The crude solid was purified by column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to gain 4.4 g white solid. Yield: (52%); mp 122-123 °C (lit., mp 118.5-119 °C).

The general procedure of 3-aryl-2H-chromene-4-carbonitrile (4)
A mixture of 2-(2-hydroxyphenyl)acetonitrile (0.5 mmol), 2-bromo-1-arylethanone (0.5 mmol) and K2CO3 (0.6 mmol) in 5 mL of dioxane was heated under reflux for 4 h. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, with petroleum ether/EtOAc (30:1) as eluent to give the desired product.

3-Phenyl-2H-chromene-4-carbonitrile (4a)
White solid, mp 47-49 °C. 1H NMR (300 MHz, CDCl3): δ 7.60 (m, 2H), 7.50 (m, 4H), 7.28 (t, J = 7.9 Hz, 1H), 7.07 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 5.11 (s, 2H). 13C NMR (100 MHz, CDCl3): δ 152.4, 146.2, 134.3, 130.9, 130.3, 129.0, 127.4, 125.6, 122.5, 119.1, 116.1, 115.3, 106.4, 68.3. MS (EI) m/z (%): 233 (M+, 100). HRMS (EI) calcd. for C16H11NO, 233.0841; found 233.0837.

3-(4-Methoxyphenyl)-2H-chromene-4-carbonitrile (4b)
White solid, mp 126-128 °C. 1H NMR (300 MHz, CDCl3): δ 7.58 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 7.6 Hz, 1H), 5.07 (s, 2H), 3.87 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 161.1, 152.3, 145.8, 130.4, 129.0, 126.5, 125.4, 122.4, 119.4, 116.1, 115.8, 114.4, 104.6, 68.2, 55.4. MS (EI) m/z (%): 263 (M+, 100). HRMS (EI) calcd. for C17H13NO2, 263.0946; found 263.0953.

3-(4-Tolyl)-2H-chromene-4-carbonitrile (4c)
White solid, mp 98-100 °C. 1H NMR (300 MHz, CDCl3): δ 7.51 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 5.08 (s, 2H), 2.41 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 152.4, 146.2, 140.8, 131.4, 130.6, 129.7, 127.3, 125.5, 122.4, 119.2, 116.1, 115.5, 105.6, 68.3, 21.4. MS (EI) m/z (%): 247 (M+, 100). HRMS (EI) calcd. for C17H13NO, 247.0997; found 247.0998.

3-(4-Chlorophenyl)-2H-chromene-4-carbonitrile (4d)
Yellow solid, mp 129-131 °C. 1H NMR (300 MHz, CDCl3): δ 7.54 (d, J = 8.5 Hz, 2H), 7.52 – 7.44 (m, 3H), 7.28 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 5.07 (s, 2H). 13C NMR (100 MHz, CDCl3): δ 152.4, 144.6, 136.4, 132.7, 131.1, 129.3, 128.7, 125.7, 122.6, 118.9, 116.2, 115.1, 106.9, 68.1. MS (EI) m/z (%): 267 (M+, 100), 269 (M+2, 33). HRMS (EI) calcd. for C16H10NOCl, 267.0451; found 267.0450.

3-(4-Fluorophenyl)-2H-chromene-4-carbonitrile (4e)
Yellow solid, mp 106-107 °C. 1H NMR (300 MHz, CDCl3): δ 7.64 – 7.56 (m, 2H), 7.49 (d, J = 7.6 Hz,
1H), 7.32 – 7.24 (m, 1H), 7.19 (t, J = 8.6 Hz, 2H), 7.07 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 5.07 (s, 2H). 13C NMR (100 MHz, CDCl3): δ 163.6 (d, J = 251 Hz), 152.4, 144.9, 131.0, 130.4, 129.6, 129.5, 125.6, 122.6, 118.9, 116.4, 116.2, 116.1, 115.2, 106.5, 68.2. MS (EI) m/z (%): 251 (M+, 100). HRMS (EI) calcd. for C16H10NOF, 251.0746; found 251.0740.

3-(4-(Trifluoromethyl)phenyl)-2H-chromene-4-carbonitrile (4f)
Yellow solid, mp 132-134 °C. 1H NMR (300 MHz, CDCl3): δ 7.76 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.51 (t, J = 7.9 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 7.9 Hz, 1H), 5.11 (s, 2H). 13C NMR (100 MHz, CDCl3): δ 152.5, 144.1, 137.9, 131.9 (d, J = 32 Hz), 131.5, 127.8, 126.1, 126.0, 125.9, 123.5 (d, J = 271 Hz), 122.7, 118.7, 116.3, 114.7, 108.2, 68.0. MS (EI) m/z (%): 301 (M+, 100). HRMS (EI) calcd. for C17H10NOF3, 301.0715; found 301.0720.

3-(3-Chlorophenyl)-2H-chromene-4-carbonitrile (4g)
Yellow solid, mp 100-101 °C. 1H NMR (300 MHz, CDCl3): δ 7.56 – 7.46 (m, 3H), 7.47 – 7.40 (m, 2H), 7.29 (td, J = 8.1, 1.0 Hz, 1H), 7.07 (td, J = 7.5, 1.0 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 5.07 (s, 2H). 13C NMR (100 MHz, CDCl3): δ 152.5, 144.3, 136.1, 135.0, 131.3, 130.4, 130.3, 127.3, 125.8, 125.7, 122.6, 118.8, 116.3, 114.8, 107.6. MS (EI) m/z (%): 267 (M+, 100), 269 (M+2, 33). HR MS (EI) calcd. for C16H10NOCl, 267.0451; found 267.0452.

3-(2, 4-Difluorophenyl)-2H-chromene-4-carbonitrile (4h)
Yellow solid, mp 133-135 °C. 1H NMR (300 MHz, CDCl3): δ 7.61 (dd, J = 14.7, 8.4 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.12 – 6.97 (m, 2H), 6.94 (d, J = 7.8 Hz, 2H), 5.01 (s, 2H). 13C NMR (100 MHz, CDCl3): δ 164.0 (dd, J = 253, 12 Hz), 160.3 (dd, J = 251, 12 Hz), 152.7, 140.6, 131.5, 131.1 (dd, J = 10, 4.9 Hz), 125.7, 122.6, 118.8 (dd, J = 15, 3.3 Hz), 118.7, 116.3, 114.5, 112.3 (dd, J = 21, 3.2 Hz), 109.6, 105.0 (t, J = 25 Hz), 67.7 (d, J = 6.8 Hz). MS (EI) m/z (%): 269 (M+, 100). HRMS (EI) calcd. for C16H9NOF2, 269.0652; found 269.0645.

3-(Naphthalen-2-yl)-2H-chromene-4-carbonitrile (4i)
Yellow solid, mp 118-119 °C. 1H NMR (300 MHz, CDCl3): δ 8.09 (s, 1H), 8.00 – 7.84 (m, 3H), 7.69 (d, J = 8.6 Hz, 1H), 7.62 – 7.52 (m, 3H), 7.28 (t, J = 8.6 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 5.21 (s, 2H). 13C NMR (100 MHz, CDCl3): δ 152.5, 146.0, 136.4, 135.0, 131.1, 130.0, 129.2, 128.8, 128.7, 127.7, 127.6, 126.9, 125.7, 124.1, 122.5, 119.2, 116.2, 115.4, 106.6, 68.4. MS (EI) m/z (%): 283 (M+, 100). HRMS (EI) calcd. for C20H13NO, 283.0997; found 283.1000.

2, 3-Diphenyl-2H-chromene-4-carbonitrile (4j)
Yellow solid, mp 109-111 °C. 1H NMR (300 MHz, CDCl3): δ 7.56 – 7.52 (m, 3H), 7.43 – 7.36 (m, 3H), 7.37 – 7.18 (m, 6H), 7.03 (t, J = 8.1 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.22 (s, 1H). 13C NMR (100 MHz, CDCl3): δ 150.6, 147.0, 136.4, 135.0, 131.1, 130.0, 129.2, 128.8, 128.7, 127.7, 127.6, 125.4, 122.1, 118.8,
116.9, 115.4, 107.2, 78.8. MS (EI) m/z (%): 309 (M⁺, 45), 232 (M-C₆H₅, 100). HRMS (EI) calcd. for C₂₂H₁₅NO, 309.1154; found 309.1159.

3-(Thiophen-2-yl)-2H-chromene-4-carbonitrile (4k)

Yellow solid, mp 119-120 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.77 (d, J = 3.4 Hz, 1H), 7.56 (d, J = 5.2 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 5.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 5.13 (S, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 152.4, 137.5, 136.2, 130.5, 129.3, 129.1, 128.3, 125.6, 122.6, 119.3, 116.1, 101.9, 67.6. MS (EI) m/z (%): 239 (M⁺, 100). HRMS (EI) calcd. for C₁₄H₉NOS, 239.0405; found 239.0405.

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REFERENCES