Facile Three-Component Synthesis of 7-Arylbenzof[f]chromeno[4,3-b]chromen-6(7H)-ones Catalyzed by Potassium Phthalimide in Aqueous Media

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Abstract

A series of 7-arylbenzof[f]chromeno[4,3-b]chromen-6(7H)-one derivatives were obtained by one-pot three-component strategy involving 2-naphthol, substituted benzaldehyde and 4-hydroxycoumarin in aqueous media, using potassium phthalimide (PPI) as a catalyst.

Keywords: Arylbenzof[f]chromeno[4,3-b]chromen-6(7H)-one; Potassium phthalimide; 2-Naphthol; Aryl aldehydes; Three-component reaction.

Introduction

The benzochromenone based molecules are one of the oxygen-containing heterocyclic compounds that have been most attractive to biological and synthetic chemists because of their unique chemical and diverse pharmaceutical properties. Moreover, the chromene ring is a scaffold for fascinating therapeutic compounds and it plays important role in biological activities.[1-5] It was found that compounds containing a chromene framework show significant biological activities, such as anticoagulant,[6] anticancer,[7, 8] antiplasmodial,[9] antimicrobial,[8] cytotoxic,[10] antituberculosis[11] and anti-proliferative.[12] In addition, benzochromenones represent specific inhibitors of endothelial cell[13] and oestrogen receptor growth,[14] as well as being recently recognized as potential receptor ligands for progesterone,[15] glucocorticoid[16] and androgen.[17]

Water is one of the most attractive solvents in synthetic chemistry. This is due to several features including environmental friendliness, safety, cleanliness, low-cost, non-toxicity, non-flammability and availability. The use of water as a solvent not only decreases the risk of organic solvents, but can also increase the rate of chemical reactions.[18-21] Development of solid basic catalytic systems utilizing inexpensive, clean, environmentally benign and commercially available catalysts has been a challenge in organic synthesis.[22]

Potassium phthalimide (PPI) is a mild, green, inexpensive, commercially available, efficient solid basic recyclable catalyst and is also a stable reagent. This

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reagent has been employed in the synthesis of primary amines by Gabriel method,\cite{23} in the synthesis of phthalimide derivatives\cite{24} and as a catalyst for the preparation of cyanohydrin trimethylsilyl ethers.\cite{25} Literature review revealed the lack of reports on the synthesis of 7- arylenbenzo[f]chromeno[4,3-b]chromen-6(7H)-ones using PPI as a catalyst. Only one report on the synthesis of these compounds from 2-naphthol, aryl aldehydes and 4-hydroxycoumarin catalyzed by Zr(HSO₄)₄ was published in 2011.\cite{26} Knowing that, we decided to synthesize these compounds through a one-pot three-component process using PPI as a catalyst (Scheme 1).

Scheme 1: Preparation of 7-arylenbenzo[f]chromeno[4,3-b]chromen-6(7H)-one (4a-g) via one-pot three-component reaction of 4-hydroxycoumarin (1), substituted benzaldehyde (2) and 2-naphthol (3) catalyzed by PPI (5) in water.

**Experimental**

Melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded using a BRUKER AVANCE DRX-400 MHz in CDCl₃ as solvent. FT-IR spectra were obtained with a Perkin Elmer
RXI spectrometer. Chemicals were obtained from Merck, Fluka and Alfa-Aesar. The progress of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F_{254} aluminum sheets and visualized by UV light. All the synthesized 7-arylbenzo[f]chromeno[4,3-b]chromen-6(7H)-ones are previously reported in literature and are characterized by comparison of their spectral and physical data with those reported in the literature.

General procedure for the synthesis of 7-arylbenzo[f]chromeno[4,3-b]chromen-6(7H)-ones (4a-g)

Equimolar quantities of 4-hydroxycoumarin 1 (1 mmol), aromatic aldehyde 2 (1 mmol), 2-naphthol 3 (1 mmol) and PPI (15 mol%) were refluxed for the indicated time presented in Scheme 1. After completion of the reaction, the reaction mixture was cooled down to room temperature and precipitated solid was filtered, washed with cold distilled water (10 mL) and air-dried to obtain the title compounds. If necessary, solid products can be recrystallized from hot ethanol. After removing water from filtrate, the catalyst is recovered and used for the subsequent reaction.

Results and Discussion

In order to establish the optimal reaction conditions, the reaction of equimolar quantities of 4-hydroxycoumarin, p-methylbenzaldehyde and 2-naphthol (the model reaction) was conducted under catalyst free conditions as well as with different catalyst ratios (3, 5, 10, 15 and 20 mol%). In addition, it was carried out in different solvents such as water, ethanol, 1,4-dioxane, acetonitrile, acetone and water-ethanol mixture (1:1) at room temperature and under reflux (Table 1).

Table 1: Optimization of the reaction conditions for the one-pot three-component synthesis of 7-(p-tolyl)benzo[f]chromeno[4,3-b]chromen-6(7H)-one (4f)\(^a\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst loading (mol%)</th>
<th>Time (min)</th>
<th>Temp. (°C)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H(_2)O</td>
<td>-</td>
<td>120</td>
<td>r.t.</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>H(_2)O</td>
<td>-</td>
<td>120</td>
<td>Reflux</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>H(_2)O</td>
<td>15</td>
<td>60</td>
<td>Reflux</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>15</td>
<td>80</td>
<td>Reflux</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>1,4-dioxane</td>
<td>15</td>
<td>80</td>
<td>Reflux</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>15</td>
<td>80</td>
<td>Reflux</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)COCH(_3)</td>
<td>15</td>
<td>80</td>
<td>Reflux</td>
<td>Trace</td>
</tr>
<tr>
<td>8</td>
<td>H(_2)O/EtOH (1:1)</td>
<td>15</td>
<td>70</td>
<td>Reflux</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>H(_2)O</td>
<td>3</td>
<td>60</td>
<td>Reflux</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>H(_2)O</td>
<td>5</td>
<td>60</td>
<td>Reflux</td>
<td>55</td>
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<tr>
<td>12</td>
<td>H(_2)O</td>
<td>20</td>
<td>60</td>
<td>Reflux</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 4-hydroxycoumarin (1 mmol), 4-methylbenzaldehyde (1 mmol), 2-naphthol (1 mmol), solvent (5 mL).
\(^b\) Isolated yields.

As can be seen in Table 1, the reaction in water provided the highest yield and required shorter reaction time than in ethanol, 1,4-dioxane, acetonitrile, acetone or water-ethanol mixture (Table 1, entries 3-8). Consequently, water was implemented as
the solvent for the other reactions. In absence of catalyst, it was found that only partial transformation to the product occurred even after 120 min at room temperature or under reflux (Table 1, entries 1-2). With increasing the catalyst amount to 15 mol% under reflux in water, the yield of product 4f was improved and the reaction time was shortened. The effect of the catalyst amount was then examined in the model reaction in refluxing water (Table 1, entries 9-11). The results revealed that 15 mol % of catalyst was the best selection for carrying out the reaction and the use of excess amount of catalyst had no effect on the rate or yield of the reaction (Table 1, entry 12). Optimization studies indicated that the best conditions for this reaction were obtained by conducting the reaction in the presence of 15 mol% of PPI in water for 1 h under reflux.

Several functional groups on the phenyl component of the aldehyde were tolerated, including —NO₂, —Cl, —CH₃, and —OCH₃. Aldehydes with electron-withdrawing groups reacted at faster rate than aldehydes bearing electron-releasing groups. Various functional groups had no obvious effect on the yield under optimal conditions. Low yield in the case of 2,4-dichlorobenzaldehyde is most likely due to steric hindrance. The results are summarized in scheme 1.

A reasonable mechanism for the synthesis of the chromenes 4a-g is showed in Scheme 2. The potassium naphthalen-2-olate (naphtholate anion) (6) was generated by abstraction of hydrogen from active 2-naphthol (3). Then, nucleophilic addition of naphtholate anion (6) to the aldehyde gives 1-arylidenenaphthalen-2(1H)-one (ortho-quinone methide) intermediate (7). The latter intermediate is formed due to the higher electron density at the C-1 position compared to the C-3 position. The Michael-type addition of the 4-hydroxycoumarin (1) to the 1-arylidenenaphthalen-2(1H)-one (7) lead to 3-(aryl-(2-hydroxynaphthalen-1-yl)methyl)chroman-2,4-dione (8). The subsequent intramolecular nucleophilic cyclization of Michael adducts (8) to the five ring intermediate 9, followed by a proton transfer, gave compound 10 which underwent dehydration under the reaction conditions, to give the desired compounds (4a-g).
Scheme 2: A reasonable mechanism for the formation of compounds 4(a-g).

The catalyst in the aqueous filtrate can be easily recovered by evaporation of solvent after each run. The recovered catalyst was applied as such for the consecutive runs in five series of the reaction of 1-hydroxycoumarin, 4-methylbenzaldehyde and 2-naphthol in aqueous media; the results are shown in Table 2.

Table 2. Results obtained using recycled PPI.\(^a\)

<table>
<thead>
<tr>
<th>No. of cycles</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td>Time (min)</td>
<td>60</td>
<td>60</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Isolated yields</td>
<td>90</td>
<td>90</td>
<td>87</td>
<td>85</td>
<td>82</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 1-hydroxycoumarin (1 mmol), 4-methylbenzaldehyde (1 mmol), 2-naphthol (1 mmol), catalyst (15 mol\%), water (5 mL), reflux.

Conclusions

PPI was found to be an efficient catalyst for the cyclocondensation of 2-naphthol, aryl aldehydes and 1-hydroxycoumarin in water leading to 7-aryl-benzo[\(f\)]chromeno[4,3-b]chromen-6(7\(H\))-ones in high yields. This approach is very simple from the experimental point of view and would permit easy access to benzo-chromenones. Avoiding the use of hazardous organic solvents, minimizing the amount of waste for organic transformations, reasonable reaction times, efficiency, and reusability of the organocatalyst are the other noticeable features of this method.

Acknowledgement

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References