Modified Algar–Flynn–Oyamada Reaction for the Synthesis of 3-Hydroxy-2-styryl-chromen-4-ones under Solvent-Free Conditions †

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Abstract: The simple and efficient conditions for a Algar–Flynn–Oyamada reaction for the synthesis of 3-hydroxy-2-styryl-chromen-4-ones involving the grinding of different 1-(2′-hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones with UHP (urea–hydrogen peroxide), pulverized potassium hydroxide and a few drops of ethanol at room temperature under solvent-free conditions are described. A presented protocol offers a faster reaction and a higher yield compared to conventional methods. The structure of the synthesized compounds was identified from their spectral data (IR, 1H-NMR).

Keywords: Algar–Flynn–Oyamada reaction; 3-hydroxy-2-styryl-chromen-4-ones; 1-(2-hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones; UHP; solvent-free conditions

1. Introduction

Styryl chromones are an important class of the flavonoid family possessing various biological activities, including antioxidant, anti-inflammatory, antimicrobial, antitumor, and neuroprotective activities [1–7]. Currently, only nine derivatives of styryl chromones have been isolated from natural sources, which include cryptophycean alga, Chrysophaeum taylori, Imperata cylindrica, Chinese eaglewood, Platanus × acerifolia, Juniperus chinensis, and Dioscorea bulbifera [8].

In styryl chromones, 4H-1-benzopyran-4-ones with a styryl (phenylethenyl) substituent at position 2 has a distinct place in the realm of flavonoid chemistry. Hormothamnione, the first naturally occurring example of 2-styrylchromone, was isolated from blue-green algae Hormothamnion enteromorphoides which showed potent in vitro cytotoxicity against human leukemia cells [9]. Synthetic derivatives of 2-styrylchromones have also been reported to show promising antitumor and anti-allergic activities [10,11]. It has been demonstrated that certain synthetic derivatives are inhibitors of the replication of both 1B and 14 serotypes of the human anti-rhinovirus [12], 3′-allyl-5,7,4′-trimethoxy-2-styrylchromone uncouples oxidative phosphorylation [13], others act as potent xanthine oxidase inhibitors [14], antiproliferative agents targeting carcinoma cells [15], β-amyloid imaging agents [16] and potential anti-inflammatory agents [17].

2-Styrylchromones, because of their conjugated diene structure, in which one of the double bonds is part of the heterocyclic ring, undergo a Diels–Alder reaction with different dienophiles to afford the condensed heterocyclic system, which otherwise are difficult to prepare [18,19].

Although, 2-styrylchromones ((E)-2-styryl-4H-chromen-4-ones) are seldom in nature, they have been synthesized by various strategies, including Allan–Robinson condensation [20], Baker–Venkataraman rearrangement [21], cyclization of an acetylenic ketone [22], intramolecular Wittig reactions [23], condensation of 2-methylchromones with benzaldehydes [24], and aldol condensation followed by oxidative cyclization [25].
Further, the introduction of a hydroxyl group at position C-3 to 2-styrylchromones (giving 3-hydroxy-2-styrylchromones) improves the anti-rhinovirus activity against both A and B serotypes of the human rhinovirus [26]. Currently, no reports of naturally occurring 3-hydroxy-2-styrylchromones have been published in the literature so far. Keeping in view the significant biological properties and scarcity of 2-styrylchromones [4], the artificial synthesis of 3-hydroxy-2-styrylchromones has been considered. Few reports have been published for the synthesis of 3-hydroxy-2-styrylchromones via the Algar–Flynn–Oyamada reaction using hydrogen peroxide in an alkaline medium using H2O2-NaOH/EtOH, H2O2-KOH/MeOH, H2O2-NaOH/THF-MeOH, H2O2-NEt2/DMSO:1,4-dioxane as oxidizing agents [27–34].

However, the above-mentioned conditions suffer from one or the other limitations, as hydrogen peroxide is only available as aqueous solution (30–40 %) and its use increases the amount of water in the reaction mixture, the result makes 1-(2′-hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones insoluble. Further addition of a sufficient amount of pyridine is required to homogenize the reaction mixture and as a result increases the bulk of the reaction mixture [35]. Additionally, as the reaction is carried out under heating conditions, the formation of 2-cinnamylidene-3(2H)-benzofuranones may also accompany the reaction, making the purification of the required 3-hydroxy-2-styrylchromones difficult and lowering the yield.

These shortcomings led us to develop a rapid, safe, and environmentally friendly method for the synthesis of 3-hydroxy-2-styrylchromones using UHP (urea–hydrogen peroxide), avoiding the use of pyridine, a highly toxic substance when using the grinding technique.

In the last few years, the grinding technique has increasingly been used in organic synthesis. It has received much attention due to its operational simplicity. However, it is recognized as an important tool to carry out the reactions under solvent-free conditions with minimal cost and maximum yield compared to conventional methods [36,37]. Moreover, this technique has been used on an industrial scale, using an electric food mixer with stainless-steel rotors, or by using a ball mill [38]. Therefore, in continuation of our work on the synthesis of organic compounds using the grinding technique [39], here we developed an efficient method for the synthesis of 3-hydroxy-2-styrylchromones using UHP (urea–hydrogen peroxide) under solvent-free conditions using the grinding technique (Scheme 1).


2. Results and Discussion

Herein, we wish to report a facile and efficient protocol for the synthesis of 3-hydroxy-2-styrylchromones (Scheme 1) making use of UHP [40] as a source of hydrogen peroxide, which avoids increasing the bulk of the reaction mixture and using pyridine, a toxic reagent under grinding conditions. A mixture of 1-(2′-hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones, UHP, and moist potassium hydroxide with a few drops of ethanol was ground with a mortar and pestle at room temperature, affording 3-hydroxy-2-styrylchromones with excellent yield in one step (Scheme 1). The compound was extracted after acidification of the reaction mixture in cold concentrated HCl. As the reaction was carried out at room temperature, the formation of 2-cinnamylidene-3(2H)-benzofuranones as side products, generally formed at elevated temperatures, was suppressed; confirmed by thin-layer chromatography, thus resulting in higher yields of 3-hydroxy-2-styrylchromones. An IR
spectrum of the formed product showed an absorption peak at 3250 cm$^{-1}$ due to O-H stretching and absorption at 1610 cm$^{-1}$ due to C=O stretching. An $^1$H-NMR spectrum showed a singlet at δ 9.60, a doublet at δ 8.05, and a multiplet at δ 7.85–7.55, due to the presence of OH, -CH=CH-, and aromatic protons, respectively. Further, the formation of 3-hydroxy-2-styrylchromones was confirmed by comparing the melting point with literature values [33,35] (Table 1).

**Table 1.** Physical data of 3-hydroxy-2-styrylchromones synthesized via modified AFO reaction.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
<th>Time (min) (a + b)</th>
<th>Yield c (%)</th>
<th>Mp d (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>5 + 5</td>
<td>92</td>
<td>188–190</td>
</tr>
<tr>
<td>2b</td>
<td>H</td>
<td>4'-OCH$_3$</td>
<td>5 + 5</td>
<td>92</td>
<td>217–220</td>
</tr>
<tr>
<td>2c</td>
<td>H</td>
<td>4'-Cl</td>
<td>5 + 5</td>
<td>90</td>
<td>220–222</td>
</tr>
<tr>
<td>2d</td>
<td>H</td>
<td>4'-NO$_2$</td>
<td>5 + 10</td>
<td>88</td>
<td>222–225</td>
</tr>
<tr>
<td>2e</td>
<td>6-Cl</td>
<td>H</td>
<td>5 + 10</td>
<td>90</td>
<td>220–222</td>
</tr>
<tr>
<td>2f</td>
<td>6-Cl</td>
<td>4'-OCH$_3$</td>
<td>5 + 10</td>
<td>85</td>
<td>218–222</td>
</tr>
<tr>
<td>2g</td>
<td>6-Cl</td>
<td>4'-Cl</td>
<td>5 + 10</td>
<td>88</td>
<td>220–222</td>
</tr>
<tr>
<td>2h</td>
<td>6-Cl</td>
<td>4'-NO$_2$</td>
<td>5 + 5</td>
<td>90</td>
<td>222–225</td>
</tr>
<tr>
<td>2i</td>
<td>6-F</td>
<td>H</td>
<td>5 + 10</td>
<td>90</td>
<td>225–228</td>
</tr>
<tr>
<td>2j</td>
<td>6-CH$_3$</td>
<td>H</td>
<td>5 + 10</td>
<td>88</td>
<td>229–230</td>
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<tr>
<td>2k</td>
<td>5,7-CH$_3$</td>
<td>H</td>
<td>5 + 10</td>
<td>85</td>
<td>194–196</td>
</tr>
</tbody>
</table>

a: grinding time; b: time for digestion; c: isolated yields. d: melting points are uncorrected and compared with literature values [26,33].

The present method is simple, as UHP is used as a source of hydrogen peroxide, which avoids increasing the bulk volume of the reaction and makes handling easy. Moreover, the present method avoids the use of hazardous and toxic solvents, making the reaction eco-friendly.

3. Experimental Section

Melting points were determined in open capillaries. The IR spectra were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer with KBr pellets. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on Bruker Avance (400 MHz & 100 MHz) instruments, respectively, using TMS as the internal standard. All the chemicals were obtained commercially and used without further purification. 1-(2'$'$-Hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones required for the present study were prepared using the method available in the literature [26].

**General Procedure for the Synthesis of 3-Hydroxy-2-styrylchromones 2a–2k**

A mixture of 1-(2'$'$-Hydroxy-phenyl)-5-aryl-penta-2,4-dien-1-ones (1 mmol), urea–hydrogen peroxide complex (UHP) (2 mmol), and pulverized potassium hydroxide was homogenized with 5–10 drops of ethanol (approx. 0.1–0.2 mL) and ground with a mortar and pestle at room temperature for 5 min. The completion of the reaction was monitored by thin-layer chromatography, confirming the presence of a single product. The reaction mixture was left at room temperature for 10 min to allow digestion. The mixture was subsequently diluted with ice-cold water, and then acidified with concentrated HCl. The solid obtained was filtered, washed with water, and recrystallized from ethanol to give 3-hydroxy-2-styrylchromones.
4. Conclusions

The present approach for the synthesis of 3-hydroxy-2-styrylchromones using UHP via the Algar–Flynn–Oyamada reaction is highly efficient and eco-friendly as it avoids the use of organic solvents at any stage of the reaction. This is a clean, mild, high-yield and expeditious method, avoiding the formation of any 2-cinnamylidene-3(2H)-benzofuranones byproducts.

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**Conflicts of Interest:** The author declares no conflict of interest.

**References**


