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Cross-aldol reaction of 3-acetyl-2H-chromen-2-one by using Amberlyst 26A as catalyst

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ABSTRACT
Synthesis of a series of 3-acetylcoumarin-derived chalcones (1a–16a) was catalyzed with Amberlyst 26A in ethanol. Using reusable Amberlyst 26A and biobased solvent ethanol make this method highly ecofriendly and simple. Amberlyst 26A was found to be a highly effective catalyst for cross aldol reaction. The results shown that the method is operationally simple to implement with a wide scope of substrates.

GRAPHICAL ABSTRACT

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KEYWORDS
3-Acetylcoumarin; Amberlyst 26A; coumarin–chalcone hybrid; flavonones; ultrasonic vibration

Introduction
The development of hybrid compounds which are combinations of two different biologically active compounds in the same structure has been previously reported in the literature and is likely to lead with significant activity.[1] In the literature, several research groups have recently reported hybrid molecules by coupling coumarins with different bioactive molecules like resveratrol, maleimide, and alpha-lipoic acid.[2] On the basis of these observations, we wanted to design and synthesize molecules which include both coumarin and chalcone pharmacophore in one frame.

Coumarin (1,2-benzopyrone) derivatives constitute one of the most common families of green plant secondary metabolites, with several of them being reported to display multiple biological properties such as antitumor, antioxidant, and anti-inflammatory activities[3–5] and in particular they are important as photochemotherapeutic agents that are used to treat a variety of skin diseases.[6] Compounds that include coumarin subunits exhibit biological activities such as molluscidal, anthelmintic, hypnotic, and insecticidal activity.[7]

Also, the medicinal properties of coumarins include inhibition of platelet aggregation, cytochrome P450, and steroid 5α-reductase.[8,9]
Because of their interesting and potential pharmacological activities, the members of the chalcone, (1,3-diaryl-2-propen-1-ones), and flavonid family have attracted a great deal of interest.\textsuperscript{[10–13]} They also are important intermediates in the synthesis of many pharmaceuticals. Traditionally they are synthesized via the Claisen–Schmidt condensation between acetophenone and benzaldehyde in acidic or basic medium under homogeneous conditions. On the other side, some reagents such as NaOH, KOH, Ba(OH)\textsubscript{2}, and 2,2-bipyridine complex of Co(OAc)\textsubscript{2} were used as basic catalysts.\textsuperscript{[14]} However, when KOH or NaOH are used, the reaction time is sometimes very long (2–4 days), with a strong possibility of side reactions.\textsuperscript{[15]} On the other hand, AlCl\textsubscript{3}, anhydrous HCl, TiCl\textsubscript{4}, RuCl\textsubscript{3}, BF\textsubscript{3}, B\textsubscript{2}O\textsubscript{3}, and p-toluenesulfonic acid were mostly used as acid catalyst.\textsuperscript{[15,16]} Recently, in the synthesis of trans-chalcone derivatives, different heterogeneous acid or basic catalysts such as commercial acid clays, potassium hydroxide–impregnated silica gel, bamboo char sulfonic acid, amino-grafted zeolites, Amberlyst 15, and Amberlite 200C appeared in the literature.\textsuperscript{[17–23]} All these reactions have various disadvantages, such as problem of catalyst recovery, the use of hazardous solvents, need special efforts to prepare catalysts and generation of side products\textsuperscript{[17]} Thus, the development of environmentally friendly catalytic systems for chalcone synthesis remains challenging. For organic synthesis using heterogeneous catalyst has advantage such as to be an eco-friendly alternative due to simplification of work–up technique and catalyst recovery. Hence, the development of environmentally friendly solid catalysts has experienced with growing interest and they are a good promising candidates to be an alternative green catalyst.\textsuperscript{[24]}

In this study we report chalcone synthesis with Amberlyst 26A as a reusable, easily separable, ecofriendly, and highly effective solid base catalyst. In continuation of our efforts to develop green methods for organic synthesis, the synthesis of novel chalcone scaffolds which contain coumarin pharmacophores into some novel scaffolds was attempted by using Amberlyst 26A as catalyst. The reaction was carried out simply by reflux of aryl aldehydes and 3-acetyl-2H-chromen-2-one \textit{3} with Amberlyst 26A in ethanol. When a green methodology was concerned, the use of organic solvents or liquid catalysts would be avoided. In this sense, the present work optimizes the use of Amberlyst 26A as a reusuable catalysts in ethanol, which is biobased solvent. On the other hand, purification of products was very simple and the products were easily obtained without needing neutralization via crystallization in chloroform. The route followed for the preparation of several 3-acetyl-2H-chromen-2-one–chalcone hybrids is illustrated in Scheme 1. At first, compound \textit{3} was prepared in ethanol with Amberlyst 26A from salicylaldehyde \textit{1} and ethylacetooacetate \textit{2}. The crossed aldol-type reaction of compound \textit{3} and benzaldehydes \textit{2} and \textit{4–16} resulted in the formation of chalcones \textit{4a–16a} in ethanol with a catalytic amount of Amberlyst 26A. This method allows high yield in a relatively short time and at moderate temperatures.

**Results and discussion**

Initially, we began our study with the synthesis of 3-acetyl-2H-chromen-2-one \textit{3}. A mixture of salicylaldehyde, ethylacetooacetate, and Amberlyst 26A were reacted in an ultrasonic bath for 30 min. This method is also the first example of synthesis of 3-acetyl-2H-chromen-2-one \textit{3} using Amberlyst 26A with ultrasonic irradiation. After preparing the main substrate (3-acetyl-2H-chromen-2-one), the preliminary crossed-aldol
condensation reaction of benzaldehyde (10 mmol) and 3-acetyl-2H-chromen-2-one 3 (10 mmol) was achieved with over 10% w/w Amberlyst 26A when the reaction mixture was refluxed in 25 ml ethanol at 80 °C for 5 h. As is shown in Table 1, the synthesis of 3-cinnamoyl-2H-chromen-2-one 4a was obtained in a good yield (81%).

**Scheme 1.** Cross-aldol reaction of 3-acetyl-2H-chromen-2-one with benzaldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Yield (%) of hybrid compounds</th>
<th>1a</th>
<th>4a</th>
<th>6a</th>
<th>7a</th>
<th>8a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 h</td>
<td>72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>61</td>
<td>75</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24 h</td>
<td>80</td>
<td>55</td>
<td>72</td>
<td>85</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Pyridine (7 h)</td>
<td>82&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>70</td>
<td>80</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Pyridine (24 h)</td>
<td>88</td>
<td>55</td>
<td>78</td>
<td>92</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Amberlyst 26A (7 h)</td>
<td>72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>61</td>
<td>75</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Amberlyst 26A (24 h)</td>
<td>80</td>
<td>55</td>
<td>72</td>
<td>85</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>NaOH (7 h)</td>
<td>70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
<td>63</td>
<td>74</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NaOH (24 h)</td>
<td>78</td>
<td>55</td>
<td>63</td>
<td>74</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5%</td>
<td>74</td>
<td>50</td>
<td>78</td>
<td>80</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10%</td>
<td>80</td>
<td>55</td>
<td>85</td>
<td>85</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>15%</td>
<td>80</td>
<td>55</td>
<td>84</td>
<td>85</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>20%</td>
<td>78</td>
<td>55</td>
<td>82</td>
<td>83</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>25%</td>
<td>75</td>
<td>55</td>
<td>80</td>
<td>80</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction completed in 5 h.

Table 1. Optimization of reaction conditions.
After this promising result, to optimize the reaction conditions we changed reaction
time (7 and 24 h) and amount of Amberlyst 26A (5–25% of total weight of substrates)
(Table 1, entries 3–8) and also used NaOH and pyperidine (10% of total weight of
substrates) for 3-cinnamoyl-2H-chromen-2-one 4a synthesis. Then a series of experiments
were performed by using the same model reaction. The results of optimization study are
summarized in Table 1. At first changing the amount of Amberlyst 26A to more than
10% w/w did not show any considerable effect on the yield of 4a. To be sure of the efficient
amount of catalyst, some different chalcone derivatives of compound 3 were also
performed with several benzaldehydes: salicylaldehyde 1, benzaldehyde 4, 4-chlorobenzal-
dehyde 6, 4-methoxybenzaldehyde 7, and 4-methylbenzaldehyde 8, under same conditions
(Table 1, entries 9–13). As seen from Table 1, 10% w/w of Amberlyst 26A is sufficient for
the reaction.

To prove the benefit of the method for synthesis of 3-acetyl-2H-chromen-2-one/
chalcone hybrids, we compared the efficiency of Amberlyst 26A with widely used bases
NaOH and piperidine (10%, w/w). 3-Acetyl-2H-chromen-2-one 3 reacted with some
aldehydes; salicylaldehyde 1, benzaldehyde 4, 4-chlorobenzaldehyde 6, 4-methoxyben-
zaldehyde 7, and 4-methylbenzaldehyde 8 were performed in ethanol (Table 1, entries
3–8). It is clearly observed that when Amberlyst 26A (10% w/w) was replaced by solid
NaOH (10% w/w), the yield of hybrid compounds (1a, 4a, 6a, 7a, and 8a) was
increased while almost similar results were obtained with piperidine (10% w/w). In
spite of piperidine being a better catalyst than Amberlyst 26A (Table 1, entries 4
and 6) in the terms of product yields, we preferred to use of Amberlyst 26A because
Amberlyst 26A is a reuseable solid catalyst. Also, its removal from reaction media is
very simple. These properties of Amberlyst 26A make it a more desirable catalyst for
a cleaner method for the synthesis of 3-acetyl-coumarin hybrid molecules. It is well
known that time is another effective parameter for organic synthesis. For this reason,
some reactions were carried out at two different reaction times (7 and 24 h) and exten-
sion of reaction time was effective on the yield of compounds 1a, 4a, 6a, 7a, and 8a
(Table 1).

The reusability of Amberlyst 26A was also studied with four consecutive cycles of use.
The results of these test (summarized in Fig. 1) demonstrated that Amberlyst 26A has
good catalytic activity even after four cycles of use for the synthesis of (E)-3-(3-(p-tolyl)acryloyl)-2H-chromen-2-one 7a. From first to fourth cycle of use, the yield of

![Figure 1. Reusability of Amberlyst 26A in the synthesis of (E)-3-(3-(p-tolyl)acryloyl)-2H-chromen-2-one (7a).](image-url)
hybrid compound 7a decreased from 85% to 74%. This can be explained by a partial deactivation of some basic sites on macropores due to the catalyst washing by organic solvents.

After these promising results we decided to use Amberlyst 26 A for other chalcone derivatives of 3-acetyl-2H-chromen-2-one. Under the optimal reaction conditions, various aryl aldehydes were employed. As can be seen from Table 2, yield of products was from moderate to excellent (56–91%).

In order to investigate the effect of some electron-donating and electron-withdrawing substituents on benzaldehyde, the crossed-aldol reactions of 3-acetyl-2H-chromen-2-one 3 were carried out at optimum condition. It is clearly shown that aryl aldehydes bearing electron-donating groups such as OMe and Me gave slightly higher yield than the corresponding reaction of benzaldehyde (compare compounds 4a, 6a, 7a, 10a, and 15a in Table 2). In the case of the presence of electron-withdrawing groups (Cl, F, Br, and CF3) the reaction was slower and then gave slightly lower yields (compare 4a, 5a, 8a, 11a, 13a, and 16a). For the benefit of the method, the yield of compounds 2a and 4a–10a were compared with counterparts previously reported in Table 2. It is clearly seen that the method we adopted is more effective than the others. For example, the condensation product of benzaldehyde with 3-acetyl-2H-chromen-2-one 4a afforded in 80% yield in the presence of Amberlyst 26A while condensation of benzaldehyde gave 81% yield with cellulose sulfonic acid and 60% yield with piperidine. The condensation of 4-methoxybenzaldehyde 6 and 2-methoxybenzaldehyde 10 afforded 86% and 81% yields respectively, in our method. However, condensation of 4-methoxybenzaldehyde 6 afforded 68% yield with cellulose sulfonic acid in ethanol at room temperature after 2 h and 2-methoxybenzaldehyde 10 gave 68% yield at room temperature, after 2–4 h using silica sulfuric acid as catalyst. The condensation of 2-chlorobenzaldehyde 8 with 3-acetyl-2H-chromen-2-one afforded product 8a with 70% yield reflux in ethanol with piperidine after 8–10 h. The present synthesis afforded 78% yield after 24 h.

Our present method is better or comparable with others in terms of yields, easy workup procedure, and reusability of Amberlyst 26A. In this study some novel 3-acetyl-2H-chromen-2-one-substituted chalcone derivatives 12a–16a were also synthesized. The newly synthesized compounds were characterized by elemental, FT-IR, 1H NMR, and mass spectral analysis. The structure of the synthesized compounds was elucidated using infrared (IR), 1H NMR, and 13C NMR spectroscopic methods. The IR spectra of newly synthesized compounds 12a–15a showed coumarinyl chalcone compounds H-C=CH bands in 3100–3050 cm⁻¹ (weak signal) and H-C=CH (trans) bands in 1700–1650 cm⁻¹ (weak) and 990–960 cm⁻¹ (strong signal). The 1H NMR spectrum of 4a (J = 16.0) confirms that under our experimental conditions, trans-chalcone is obtained selectively. The present method was found to be highly useful as condensation between aryl aldehydes 1 and 4–16 and compound 3, and no cyclization was found to take place under these conditions to give side products. 1H NMR spectra of 12a and 15a showed two signals in the δ 6.80, 8.39 ppm (d, J = 15.6 Hz, 1H) and δ 7.97, 7.76 ppm (d, J = 15.6 Hz, 1H), which were attributed to the H-C=CH trans coumarinyl chalcone protons, respectively. 13C NMR spectrum of selected compounds 12a and 15a showed H-C=CH carbon in the coumarinyl chalcone structures were observed at δ 154.36, 125.66 and δ 154.57, 124.42 ppm.
<table>
<thead>
<tr>
<th>No.</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>Other methods and yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td><img src="image1.png" alt="Image" /></td>
<td>80</td>
<td>201–202</td>
<td>Celulose sulfonic acid, EtOH, rt, 2 h, 81% Piperidine, EtOH, 2–12 h, 60%</td>
<td>1</td>
</tr>
<tr>
<td>2a</td>
<td><img src="image2.png" alt="Image" /></td>
<td>56</td>
<td>280–281</td>
<td>Piperidine, EtOH, glacial acetic acid, reflux, 48%</td>
<td>3</td>
</tr>
<tr>
<td>5a</td>
<td><img src="image3.png" alt="Image" /></td>
<td>72</td>
<td>188–190</td>
<td>Abs. ethanol, piperidine, reflux, 8–10 h, 70%</td>
<td>26</td>
</tr>
<tr>
<td>6a</td>
<td><img src="image4.png" alt="Image" /></td>
<td>86</td>
<td>205–206</td>
<td>30% NaOH (aq), EtOH, 24 h, 85% Piperidine, EtOH, 2–12 h, 61% 30% NaOH (aq), EtOH, 24 h, 85%</td>
<td>1</td>
</tr>
<tr>
<td>7a</td>
<td><img src="image5.png" alt="Image" /></td>
<td>85</td>
<td>221–222</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td><img src="image6.png" alt="Image" /></td>
<td>78</td>
<td>158–160</td>
<td>Piperidine, EtOH, reflux, 8–10 h, 70%</td>
<td>2</td>
</tr>
<tr>
<td>9a</td>
<td><img src="image7.png" alt="Image" /></td>
<td>76</td>
<td>248–249</td>
<td>Piperidine, EtOH, glacial acetic acid, reflux, 6 h, 44%</td>
<td>3</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>No.</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a</td>
<td><img src="image1.png" alt="Diagram" /></td>
</tr>
<tr>
<td>11a</td>
<td><img src="image2.png" alt="Diagram" /></td>
</tr>
<tr>
<td>12a</td>
<td><img src="image3.png" alt="Diagram" /></td>
</tr>
<tr>
<td>13a</td>
<td><img src="image4.png" alt="Diagram" /></td>
</tr>
<tr>
<td>14a</td>
<td><img src="image5.png" alt="Diagram" /></td>
</tr>
<tr>
<td>15a</td>
<td><img src="image6.png" alt="Diagram" /></td>
</tr>
<tr>
<td>16a</td>
<td><img src="image7.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>
**Experimental**

All required chemicals were purchased from Merck and Sigma Aldrich chemical companies. The melting points were determined on a Electro thermal 9100 melting-point instrument and are uncorrected. IR spectra were recorded on a Perkin-Elmer 55148 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 300-MHz Ultrashield spectrometer or a Bruker Avance III 400-MHz spectrometer and a Bruker Avance III 600-MHz spectrometer. NMR analysis were used and shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Elemental analyses were measured on a Thermo Flash 2000 Organic Elemental Analyzer.

**General experimental procedure (3)**

A mixture of salicylaldehyde (10 mmol), ethylacetoacetate (10 mmol), and Amberlyst 26A (10% w/w) was mixed in an ultrasonic bath for 30 min. After the solid formation, ethanol was added to dissolve the product. The catalyst was removed simply by ordinary filtration and synthesized 3-acetyl coumarin was crystallized from ethanol (88% yield). The product was identified using FT-IR and NMR spectroscopy.

**General experimental procedure (2a, 4a–16a)**

A round-bottomed flask equipped with a magnetic stirrer was charged with 3-acetylcoumarin (10 mmol), aryl aldehyde (10 mmol), and ethanol (30 mL), and Amberlyst 26A was added to the mixture (10% w/w of whole substrates). The flask content was refluxed at 80 °C for 5–7 h. The reaction was monitored by thin-layer chromatography (TLC) (n-hexane/ethylacetate). The solid product was filtered off at the end of the reaction. After three washes with ethanol, the residual solid crystallized from chloroform. The product was filtered and identified using FT-IR and NMR spectroscopy. Compounds 3, 2a, 4a, 5a, 6a, 7a, 8a, 9a, and 10a were reported in literature and fully characterized by spectral analysis.[1–4,21,25,26]

3-Acetyl-2H-chromen-2-one (3)$^{[21]}$

Yellow solid, mp 119–120 °C. IR $\nu_{\text{max}}$(KBr)/cm$^{-1}$: 3029.59 (k, C-H), 1738.64 (k, C=O), 1674.0 (k, C=O), 1555.79, 1452.87 (k,C=C), 1264.24 (k,C-O); $\delta_{\text{H}}$ (300 MHz, DMSO$_4$-d$_6$) 8.65 (s, 1H), 7.96–7.93 (m, 1H), 7.77–7.71 (m, 1H), 7.47–7.39 (m, 2H), 2.58 (s, 3H); $\delta_{\text{C}}$(75 MHz, DMSO$_4$-d$_6$) 195.06, 158.39, 154.56, 147.01, 134.45, 130.74, 124.90, 118.12, 116.07, 30.01. Anal. calcd. for C$_{11}$H$_8$O$_3$: C, 70.21; H, 4.28; O, 25.51. Found: C, 70.43; H, 4.25; O, 25.32.

(E)-3-(3-(2,4-Difluorophenyl)acryloyl)-2H-chromen-2-one (12a)

Red solid; mp 189–190 °C; yield 2.51 g (80.5%); $\nu_{\text{max}}$(KBr) 3103, 3047, 2991, 1723, 1607, 1585, 1558, 1520, 1452, 1271, 1245, 1171, 1091, 981, 751 cm$^{-1}$; $\delta_{\text{H}}$(400 MHz, DMSO$_4$-d$_6$) 8.72 (s, 1H), 8.39 (d, $J$ = 15.6 Hz 1H), 7.99–7.93 (m, 3H), 7.51–7.40 (m, 4H), 6.80 (d, $J$ = 15.6 Hz, 1H); $\delta_{\text{C}}$(100 MHz, DMSO$_4$-d$_6$) 186.78, 160.80, 158.49, 158.43, 154.53, 154.36,
Anal. calcd. for C_{18}H_{10}F_{2}O_{3}: C, 69.23; H, 3.23; F, 12.17; O, 15.37. Found: C, 69.48; H, 3.20; F, 12.10; O, 15.22.

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**References**


