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Chapter

One-Pot Synthesis of Coumarin Derivatives

Inul Ansary and Abu Taher

Abstract

Coumarin derivatives have a myriad of applications in medical science, biomedical research, and many industrial branches. For this reason, many efforts are being dedicated to the development of novel and more practical methods for synthesizing these compounds. This chapter describes several methods of one-pot synthesis of coumarin derivatives, including von Pechmann condensation, Knoevenagel condensation, Baylis-Hillman reaction, Michael addition, Kostanecki reaction, vinyl phosphonium salt-mediated electrophilic reaction, and Heck-lactonization reaction. The methods are compared with each other, and the advantages and disadvantages of each of them are addressed.

Keywords: coumarin derivatives, one-pot synthesis, methods and procedures, advantages and disadvantages

1. Introduction

Coumarin (2H-chromen-2-one) derivatives have spawn great interest over the years because of their significant biological importance [1]. They are associated with various biological activities viz. antiviral [2, 3], antibacterial [4, 5], antimicrobial [6], anticoagulant [7], anti-inflammatory [8, 9], anticancer [10, 11], anticonvulsant [12], antioxidant [13], antifungal [14, 15], and anti-HIV [16]. They also possess the properties like inhibition of platelet aggregation [17] and inhibition of steroid 5α-reductase [18]. Besides, they are attracting considerable attention of chemists due to their wide range of applications such as optical brighteners [19], photosensitizers [20], fluorescent and laser dyes [21], and additives [22] in food, perfumes, cosmetics, and pharmaceuticals. The novel compounds are also utilized in drug and pesticidal preparations [23]. Considering these multifarious activities of coumarins, synthetic chemists are actively engaged in developing new and superior methods for the isolation of coumarin derivatives. The most widely used method for their synthesis is Pechmann reaction [24–27], which involves the condensation between phenols and β-keto esters, in the presence of an acid catalyst. This method employs both homogeneous catalysts such as concentrated H$_2$SO$_4$ [24, 25], trifluoroacetic acid (TFA) [28], and Lewis acids (LA) such as AlCl$_3$ [29], ZnCl$_2$ [30], ZrCl$_4$ [31], TiCl$_4$ [32], etc. and heterogeneous catalysts such as cation-exchange resins [33], Nafion resin/silica composites [34], zeolite H-BEA (H-beta, SiO$_2$/Al$_2$O$_3$ = 14) [35], and other solid acids.
2. Methods to synthesize coumarin derivatives

2.1 Pechmann condensation reaction

The general reaction sequence of Pechmann reaction and its mechanism, shown in Figure 1, involves an esterification/transesterification between the phenol 1 and β-keto ester 2 in the presence of protonic acid or Lewis acid (LA) catalyst to produce species 4 followed by an attack to the activated carbonyl carbon by the aromatic ring at ortho-position to yield the new ring in species 5. Finally, dehydration of species 5 affords coumarin derivative 2.

A series of substituted coumarins 8 have been synthesized in 25–77% yields by the reactions of substituted phenols 6 with ethyl acetoacetate 7 in the presence of zinc-iodine mixture in refluxing toluene (Figure 2) [36]. It is observed that phenols containing electron-donating substituent like –CH₃ group result in higher yields compared to unsubstituted phenols and phenols having electron-withdrawing group such as NO₂ group.

When 3-([N,N-Dimethylamino)phenol 9 is subjected to react with ethyl 2-acetamide-3-oxobutyrate 10 in the presence of anhydrous ZnCl₂ in absolute ethanol under reflux condition, the acetamido coumarin 11 is obtained only in 12.4% yield (Figure 3) [30].

Substituted coumarins 14 have been achieved in moderate to good yields from substituted phenols 12 and methyl acetoacetate 13 under conventional and microwave heating, respectively, catalyzed by concentrated H₂SO₄ (Figure 4) [37]. It is found that the reactions using the latter method are faster coupled with product in better yields compared to former one.

Synthesis of substituted coumarins 16 in 62–98% yields has also been described by Maheswara et al. [38] via reactions of substituted phenols 1 with β-keto esters 15 in the presence of a heterogeneous catalyst, HClO₄·SiO₂ under solvent-free conditions (Figure 5, Condition A). The aforementioned method involves recoverable cheap catalyst and shorter reaction time with high product yields. However, relatively lower yields (35–55%) of substituted coumarins 16 have been isolated from the similar starting precursors catalyzed by Amberlyst-15 acidic catalyst [39] in toluene under refluxing condition (Figure 5, Condition B).

Pechmann condensation reactions for the synthesis of substituted coumarins using various homogeneous and heterogeneous catalysts have been reported in literature and some important ones are summarized in Table 1.
From Table 1, it is quite evident that the reactions under microwave as well as ultrasound irradiation occur at a faster rate than those of the conventional methods (entries 10, 14, 15, 16, 25, 31, 32, and 39). Unsubstituted phenol produces lower yields of corresponding coumarin derivatives and/or requires longer reaction time (entries 2–4, 7, 10, 12, 13, 24, 28, 30, and 38), higher temperature (entries 2, 3, 7, and 12), and excess amount of catalysts (entries 7 and 12) than di- and trihydric phenols. This may presumably be due to the less reactivity of unsubstituted phenol toward Pechmann condensation reaction compared to di- and trihydric phenols. In
addition, the substitution of an electron-donating group such as \( m/p \)-Me or \( p \)-OMe in the phenols leads to decrease of catalytic activity and, hence, requires longer reaction time and/or gives rise to lower yields of products (entry 13). The reactivity of monohydric phenols having electron-withdrawing groups such as \( m \)-NH\(_2\) and \( m \)-OMe is also lowered compared with simple di- and trihydric phenols (entries 19, 28, and 37). 1-Naphthol and 2-naphthol need longer reaction time (entries 13, 33, and 39) and/or furnish products with lower yields (entries 13, 37, and 40) compared to other phenols, due to the presence of another phenyl ring. However, better yield of benzocoumarin is obtained from the reaction between 1-naphthol and more reactive \( \beta \)-keto ester, ethyl 4-chloro-3-oxobutanoate (entry 37). It is interesting to note that \( \beta \)-keto ester having phenyl group at the \( \beta \)-position such as ethyl 3-oxo-3-phenylpropanoate is found to be less reactive in Pechmann condensation with resorcinol and 1,3-dihydroxy-5-methyl benzene due to the presence of conjugated keto center, which lengthens the reaction time than in the reactions of EAA and/or ethyl 4-chloro-3-oxobutanoate with resorcinol and 1,3-dihydroxy-5-methyl benzene (entries 21, 28, and 37). Besides, the reactivity of different types of phenols and \( \beta \)-keto esters, catalyst efficiency, and solvent effect of Pechmann condensation has also been studied. It is observed that TiCl\(_4\) (entry 5) is the most effective catalyst as far as reaction time is considered, whereas montmorillonite K-10 (entry 1) and sulfated zirconia (SZr) (entry 9) are found to be less effective. Ionic liquids (ILs) such as 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF\(_6\) and 1,3-disulfonic acid imidazolium hydrogen sulfate (DSIMHS) have been used as effective and reusable catalysts and reaction media as well (entries 6 and 18).

Lewis acid–surfactant-combined catalyst (LASC) such as nano-TiO\(_2\) on dodecyl-sulfated silica support (NTDSS) is used as a reusable and highly effective catalyst for Pechmann condensation of phenols containing different types of substituents in water led to excellent product yields (entry 20). Other recyclable solid acid catalysts have also been employed in Pechmann condensation reactions leading to coumarin derivatives in good to excellent yields under solvent-free (entries 22–24, 26–27, 29–30, and 42), microwave irradiation (entry 25) and/or ultrasound irradiation (entry 39) conditions.

More importantly, sulfonic acid-supported silica-coated magnetic nanoparticles (Fe\(_3\)O\(_4\)@SiO\(_2\)@PrSO\(_3\)H), CuFe\(_2\)O\(_4\) nanoparticles, and zirconium(IV) complex grafted silica coated magnetic nanoparticles are found to be the most efficient catalysts toward Pechmann condensation, in which case the catalyst can be effortlessly separated by external magnet after completion of the reaction and reused for 22, 6, and 5 consecutive runs, without any significant loss in catalytic efficiency (entries 33–35).

Pechmann condensation of pyrogallol and resorcinol with ethyl acetoacetate over nanosponge MFI zeolite in comparison with conventional zeolites (MFI, BEA, and USY) and other layered MFI (lamellar, pillared, and self-pillared) have been investigated. It is important to note that the nanosponge catalysts exhibit the best catalytic performance with respect to the products’ selectivity in the liquid-phase condensation reactions among all the investigated zeolites (entry 36).

On the other hand, the catalytic behavior of metal–organic frameworks such as Cu-benzene-1,3,5-tricarboxylate (CuBTC) and Fe-benzene-1,3,5-tricarboxylate (FeBTC) is investigated and compared with large-pore zeolites, beta (BEA), and ultrastable Y (USY) (entry 41). It is clear that zeolites BEA and USY are found to be more active catalysts in transformations of the most active substrates like resorcinol and pyrogallol but a low conversion of naphthol is observed. However, almost total transformation of naphthol (93–98% conversion) to the target product occurs within 23 h of the reaction time over metal–organic frameworks, CuBTC and FeBTC.
One-Pot Synthesis of Coumarin Derivatives

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<table>
<thead>
<tr>
<th>Entry</th>
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<th>Reaction conditions</th>
<th>Time</th>
<th>Yields (%)</th>
<th>Reference</th>
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<tr>
<td>1</td>
<td>Montmorillonite K-10</td>
<td>K-10 (30 wt% of 12), toluene, reflux</td>
<td>8–10 h</td>
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<td>[40]</td>
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<tr>
<td>2</td>
<td>1-Butyl-3-methylimidazolium chloroaluminate [bmim]Cl₂AlCl₃</td>
<td>[bmim]Cl₂AlCl₃ (1.1 equiv of 12), 30–120°C</td>
<td>10–120 min</td>
<td>40–95</td>
<td>[41]</td>
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<tr>
<td>3</td>
<td>InCl₃</td>
<td>InCl₃ (10 mol%), 65–130°C</td>
<td>30–240 min</td>
<td>65–98</td>
<td>[42]</td>
</tr>
<tr>
<td>4</td>
<td>ZrCl₄</td>
<td>ZrCl₄ (2 mol%), 70°C</td>
<td>5–30 min</td>
<td>56–95</td>
<td>[31]</td>
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<tr>
<td>5</td>
<td>TiCl₄</td>
<td>TiCl₄ (0.5 equiv of 12), rt</td>
<td>50–70 s</td>
<td>56–95</td>
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<td>6</td>
<td>1-Butyl-3-methylimidazolium hexafluorophosphate [bmim]PF₆</td>
<td>[bmim]PF₆ (4 ml), solvent-free, 100°C</td>
<td>45 min</td>
<td>90–95</td>
<td>[43]</td>
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<td>7</td>
<td>Bi(NO₃)₃·5H₂O</td>
<td>Bi(NO₃)₃·5H₂O (5–10 mol%), 80–130°C</td>
<td>15–300 min</td>
<td>47–94</td>
<td>[44]</td>
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<td>8</td>
<td>SO₄²⁻/CeO₂-ZrO₂</td>
<td>SO₄²⁻/CeO₂-ZrO₂ (10 wt% of 12), 120°C</td>
<td>4–143 min</td>
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<td>9</td>
<td>SZr (sulfated zirconia)</td>
<td>SZr (1 wt% of 12), 80°C</td>
<td>24 h</td>
<td>52–92</td>
<td>[46]</td>
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<td>10</td>
<td>Ceric ammonium nitrate (CAN)</td>
<td>Condition A: CAN (10 mol%), solvent-free, 110°C</td>
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<td>92–96</td>
<td>[47]</td>
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<td>Condition B: CAN (10 mol%), solvent-free, MW (300 W)</td>
<td>2–3 min</td>
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<td>11</td>
<td>CISO₂H</td>
<td>CISO₂H (0.2 ml), solvent-free, 100°C</td>
<td>10 min</td>
<td>91–98</td>
<td>[48]</td>
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<td>12</td>
<td>LiBr</td>
<td>LiBr (10–20 mol%), 75–125°C</td>
<td>15–90 min</td>
<td>54–92</td>
<td>[1]</td>
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<td>13</td>
<td>Nanocrystalline-cellulose-supported sulfonic acid ionic liquid</td>
<td>NCC-supported sulfonic acid IL (10 wt% of 12), solvent-free, 80°C</td>
<td>18 min–24 h</td>
<td>20–98</td>
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<td>14</td>
<td>Cu(ClO₄)₂</td>
<td>Cu(ClO₄)₂ (20 mol%), solvent-free, US (35 kHz), 45–50°C</td>
<td>30–50 min</td>
<td>70–96</td>
<td>[50]</td>
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<td>15</td>
<td>Selectfluor</td>
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<td>85–90 min</td>
<td>70–79</td>
<td>[51]</td>
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<td>Condition B: Selectfluor (10 mol%), solvent-free, US (30 kHz, 780 W)</td>
<td>15–40 min</td>
<td>82–94</td>
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<td>Entry</td>
<td>Catalyst</td>
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<td>Time</td>
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<tr>
<td>16</td>
<td>I\textsubscript{2}</td>
<td>Condition A: I\textsubscript{2} (25 mol%), toluene, 90°C &lt;br&gt; Condition B: I\textsubscript{2} (1 mol%), MW</td>
<td>18 h</td>
<td>42–89</td>
<td>80–96</td>
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<td></td>
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<td></td>
<td>1.5–5 min</td>
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<td>17</td>
<td>AgOTf</td>
<td>AgOTf (10 mol%), solvent-free, 60°C</td>
<td>3–12 h</td>
<td>60–95</td>
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<td>18</td>
<td>1,3-Disulfonic acid imidazolium hydrogen sulfate (DSIMHS)</td>
<td>DSIMHS (7 mol%), solvent-free, 70°C</td>
<td>2–27 min</td>
<td>80–96</td>
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<td>19</td>
<td>[\text{N,N'}-dimethylaminoethanol hydrosulfate ([N\textsubscript{112}OH][HSO\textsubscript{4}])]</td>
<td>[N\textsubscript{112}OH][HSO\textsubscript{4}] (5 mol%), solvent-free, 90°C</td>
<td>3–24 h</td>
<td>20–99</td>
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<td>20</td>
<td>Nano-TiO\textsubscript{2} on dodecyl-sulfated silica support (NTDSS)</td>
<td>NTDSS (5 mol% TiO\textsubscript{2}, H\textsubscript{2}O, reflux</td>
<td>3–8 h</td>
<td>89–98</td>
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<td>21</td>
<td>ZrOCl\textsubscript{2}·8H\textsubscript{2}O/SiO\textsubscript{2}</td>
<td>ZrOCl\textsubscript{2}·8H\textsubscript{2}O/SiO\textsubscript{2} (10 mol%), solvent-free, 90°C</td>
<td>5–80 min</td>
<td>75–99</td>
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<td>22</td>
<td>Polydivinylbene-bound perfluoroalkysulfonyl imide polymers (H-PDVB-x-SSFAI)</td>
<td>H-PDVB-x-SSFAI (10 mol%), solvent-free, 140°C</td>
<td>2 h</td>
<td>78–94</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Polyaniline–fluoroboric acid–dodecyl hydrogen sulfate (PANI–HBF\textsubscript{4}–DHS)</td>
<td>PANI–HBF\textsubscript{4}–DHS (20 wt.% of I2), solvent-free, 150°C</td>
<td>6 h</td>
<td>94–98</td>
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<td>24</td>
<td>Silica sulfuric acid (SSA)</td>
<td>SSA (15 mol%), solvent-free, 80°C</td>
<td>0.5–2 h</td>
<td>70–97</td>
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<td>25</td>
<td>ZrPW (Zirconium IV Phosphotungstate) 12-TPA/ZrO\textsubscript{2} (12-Tungstophosphoric acid supported onto ZrO\textsubscript{2})</td>
<td>Condition A: ZrPW (0.2 g), solvent-free, 130°C &lt;br&gt; Condition B: ZrPW (0.2 g), solvent-free, MW (250 W), 130°C &lt;br&gt; Condition C: 12-TPA/ZrO\textsubscript{2} (0.2 g), solvent-free, 130°C &lt;br&gt; Condition D: 12-TPA/ZrO\textsubscript{2} (0.2 g), solvent-free, MW (250 W), 130°C</td>
<td>8 h</td>
<td>42–65</td>
<td>47–66</td>
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<td></td>
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<td></td>
<td>30 min</td>
<td>41–65</td>
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<td>26</td>
<td>12-Tungstophosphoric acid supported on SnO\textsubscript{2} nanoparticles (12-TPA-SnO\textsubscript{2})</td>
<td>12-TPA-SnO\textsubscript{2} (30 wt% of TPA), solvent-free, 120°C</td>
<td>2 h</td>
<td>78</td>
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<td>27</td>
<td>Poly(4-vinylpyridine)-supported copper iodide</td>
<td>P\textsubscript{4}VPy-Cu (0.3 g), solvent-free, 80°C</td>
<td>10–90 min</td>
<td>84–92</td>
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<td>28</td>
<td>Polystyrene-supported GaCl\textsubscript{3} (PS–GaCl\textsubscript{3})</td>
<td>PS–GaCl\textsubscript{3} (10 mol%), ethanol, reflux</td>
<td>45–300 min</td>
<td>45–96</td>
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<tr>
<td>29</td>
<td>Silica tungstic acid (STA)</td>
<td>STA (5 mol%), solvent-free, 80°C</td>
<td>20–90 min</td>
<td>75–97</td>
<td></td>
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<td>30</td>
<td>CMK-5 supported sulfonic acid (CMK-5-SO\textsubscript{3}H)</td>
<td>CMK-5-SO\textsubscript{3}H (3 mol%), solvent-free, 130°C</td>
<td>15–120 min</td>
<td>60–97</td>
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<tr>
<td>31</td>
<td>FeF\textsubscript{3}</td>
<td>FeF\textsubscript{3} (0.05 g), solvent-free, MW (450 W), 110°C</td>
<td>6–9 min</td>
<td>61–98</td>
<td></td>
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</table>
Catalytic activity of many other catalysts under different reaction conditions is delineated in the recently published review [80].

### 2.2 Knoevenagel condensation reaction

An efficient green one-pot synthetic method for the synthesis of 3-substituted coumarin derivatives 21/22 has been observed by Knoevenagel condensation of various o-hydroxybenzaldehydes 18/19 with 1,3-dicarbonyl compounds 20 using...
nano-ZnO catalyst under microwave or thermal conditions, which affords moderate to good yield of the products (Figure 6) [81]. Reactions under microwave-irradiation conditions are found to be more convenient than thermal conditions.

Various coumarin-3-carboxylic acid derivatives 25/26 have been synthesized in good yields using catalytic amounts of SnCl₂·2H₂O under solvent-free condition (Figure 7) [82].

Ultrasound irradiation technique is also useful to synthesize 3-arylcoumarin derivatives. Treatment of o-hydroxybenzaldehydes 18 with aryl substituted acetyl chloride 27 in the presence of K₂CO₃ as a catalyst in tetrahydrofuran (THF) using ultrasound irradiation leads to the formation of 3-arylcoumarin derivatives 28 in moderate to high yields (Figure 8) [83]. This green method appears to be a convenient and simple pathway than that of conventional heating.

Coumarin-substituted benzimidazole or benzoxazole derivatives 32 that are known as coumarin dyes have been synthesized in good yields from 4-diethylamino-2-hydroxybenzaldehyde 29, ethyl cyanoacetate 30, and ortho-phenylenediamine/phenylenehydroxylamine derivatives 31 in the presence of reusable green solid acid like HZSM-5 zeolite, heteropoly acids, e.g., tungstophosphoric acid (H₃PW₁₂O₄₀), and/or tungstosilicic acid (H₄O₄₀SiW₁₂) in n-pentanol or water and even solvent-free conditions (Figure 9) [84].

Cellulose sulfonic acid (CSA) is an efficient catalyst for the synthesis of 3-substituted coumarin via Knoevenagel condensation reaction. Thus, 3-acetyl coumarin 34 is obtained in 88% yield in the reaction between salicylaldehyde 33 and ethyl acetoacetate 7 in the presence of CSA under solvent-free conditions (Figure 10) [85].

Figure 6.
Synthesis of 3-substituted coumarins.

Figure 7.
Synthesis of coumarin 3-carboxylic acid derivatives.
Shaabani et al. [86] have described the synthesis of 3-substituted coumarins 21 in good yields via Knoevenagel condensation of 2-hydroxybenzaldehydes 18 with β-dicarbonyl compounds 35 in the presence of a recyclable ionic liquid 1,1,3,3-N,N,N′,N′-tetramethylguanidinium trifluoroacetate (TMGT) under thermal heating (Figure 11, Condition A) and/or microwave irradiation conditions (Figure 11, Condition B). 3-Substituted coumarins 21 are also synthesized from similar starting precursors using the 1,3-dimethylimidazolium methyl sulfate [MMIm][MSO$_4$] ionic liquid in the presence of L-proline as an additional promoter under heating condition (Figure 11, Condition C) [87].

Imidazolium based phosphinite ionic liquid (IL-OPPh$_2$) catalyzed synthesis of 3-substituted coumarin derivatives has been reported in literature; when o-hydroxy benzaldehydes 18 are treated with active methylene containing compounds 35 in the presence of IL-OPPh$_2$ catalyst at 60°C, 3-substituted coumarin derivatives are obtained in moderate to good yields (Figure 12) [88]. TSIL plays both the reaction media and catalyst as well.

Reactions of o-hydroxybenzaldehydes 18 with activated methylene compounds 35 catalyzed by Bronsted acid ionic liquid (BAIL) and 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate [(CH$_2$)$_4$SOHMIM][HSO$_4$] in water lead to 3-substituted coumarin derivatives in good yields (Figure 13) [89].

Synthesis of substituted coumarins via Knoevenagel condensation using various organic catalysts such as piperidine, ammonia, L-lysine, L-proline, benzoic acid, etc. has been reported in literature and some are summarized in Table 2.
It is quite evident that in Table 2 several methodologies for the synthesis of substituted coumarins using different organic catalysts are established. Among these, L-proline-catalyzed reactions offer high yields (entry 3), which explains synthesis of 3-substituted coumarins by the condensation of \( \alpha \)-hydroxybenzaldehydes with a variety of active methylene compounds catalyzed by 1,3-dimethyl imidazolium methyl sulfate \([\text{MMIm}]\text{[MSO}_4\text{]}\) and L-proline. Another L-proline-catalyzed synthesis of coumarins is known, but in that case, the yield is very poor (entry 4). Similar result is also observed under L-lysine-catalyzed synthesis of coumarins (entry 5).

A series of 3-phenyl substituted coumarin analogues have been achieved via a two-step process involving esterification using 1,1-carbonyldiimidazole (CDI) followed by condensation reaction in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under mild conditions (entry 1).

Microwave-assisted synthesis of coumarins is also known, which not only reduces the reaction time but also increases the yields of the products (entries 2, 6, and 7).

Benzocoumarin derivatives have been synthesized from 1-hydroxy-4-methyl-naphthalene-2-carbaldehyde and compounds containing active methylene group via piperidine-catalyzed Knoevenagel condensation reaction (entry 8). Moreover, benzothiazolyl coumarins with isothiocyanate functionality have been synthesized from commercially available 2-hydroxy-4-nitro benzoic acid in the presence of piperidine in ethanol (entry 9).

Application of sonochemistry for the synthesis of different coumarin derivatives is also useful due to better yield and shorter reaction time compared with the classical procedures (entry 10).

![Figure 11. Synthesis of 3-substituted coumarins.](image_url)

![Figure 12. Synthesis of 3-substituted coumarins.](image_url)
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DOI: http://dx.doi.org/10.5772/intechopen.89013

Figure 13. Synthesis of 3-substituted coumarins.

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<th>Time</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>CDI-DBU</td>
<td>(i) CDI (1.2 equiv.), DCM, rt. (ii) DBU (1.0 equiv.), DCM, rt</td>
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<td>42–59</td>
<td>[90]</td>
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<td>2</td>
<td>PhCOOH</td>
<td>Condition A: Polyphosphoric acid, MW (900 W), 100°C</td>
<td>4–6 min</td>
<td>60–75</td>
<td>[91]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition B: H₂SO₄, Benzoic acid, MW (900 W), 90°C</td>
<td>3–4 min</td>
<td>58–75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition C: benzoic acid, n-pentanol, MW (900°C), 110°C</td>
<td>3 min</td>
<td>85–95</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>L-proline</td>
<td>1,3-dimethyl imidazolium methyl sulfate, [MMIm][MSO₄], L-proline (1 equiv.), 90°C</td>
<td>15–1440 min</td>
<td>87–99</td>
<td>[87]</td>
</tr>
<tr>
<td>4</td>
<td>L-proline</td>
<td>L-proline (20 mol%), EtOH, rt</td>
<td>15–20 h</td>
<td>54–76</td>
<td>[92]</td>
</tr>
<tr>
<td>5</td>
<td>L-lysine</td>
<td>L-lysine (20 mol%), H₂O, rt, –80°C</td>
<td>6–24 h</td>
<td>50–90</td>
<td>[93]</td>
</tr>
<tr>
<td>6</td>
<td>Piperidine</td>
<td>Piperidine (catalytic), rt.</td>
<td>20 min</td>
<td>84</td>
<td>[94]</td>
</tr>
<tr>
<td>7</td>
<td>Piperidine</td>
<td>Piperidine (2.0 mol%), solvent-free, MW (400 W)</td>
<td>1 min</td>
<td>50–97</td>
<td>[95]</td>
</tr>
<tr>
<td>8</td>
<td>Piperidine</td>
<td>Piperidine (1.48 equiv.), EtOH, reflux</td>
<td>30 min</td>
<td>85–92</td>
<td>[96]</td>
</tr>
<tr>
<td>9</td>
<td>Piperidine</td>
<td>Piperidine (catalytic), EtOH, reflux</td>
<td>2 h</td>
<td>82</td>
<td>[97]</td>
</tr>
<tr>
<td>10</td>
<td>Piperidine</td>
<td>Piperidine (1.0 equiv.), AcOH (2.5 mol%), EtOH, US, rt</td>
<td>5–30 min</td>
<td>49–90</td>
<td>[98]</td>
</tr>
<tr>
<td>11</td>
<td>Piperidine</td>
<td>Piperidine, EtOH, rt-reflux</td>
<td>1–2 h</td>
<td>82–92</td>
<td>[99]</td>
</tr>
<tr>
<td>12</td>
<td>Piperidine</td>
<td>Piperidine (74 equiv.), EtOH, reflux</td>
<td>2 h</td>
<td>92</td>
<td>[100]</td>
</tr>
</tbody>
</table>

Table 2. Synthesis of substituted coumarins via Knoevenagel condensation reactions.
6,8-Diiodocoumarin derivatives have also been synthesized in good yields by Knoevenagel condensation using piperidine as catalyst (entry 11). The reaction of 3-ethoxysalicyaldehyde with ethyl acetoacetate in the presence of piperidine leads to 3-acetyl-8-ethoxycoumarin (entry 12).

2.3 Baylis-Hillman reaction

Baylis-Hillman strategy has been employed to the synthesis of substituted coumarins as shown in Figure 14. When 2-hydroxybenzaldehydes 18 are subjected to react with methyl acrylate 39a (R² = Me) in the presence of DABCO (1,4-Diazabicyclo[2.2.2]octane), a mixture of chromenes 40 and coumarins 41 are formed [101, 102]. However, similar reactions of 2-hydroxybenzaldehydes 18 with tert-butyl acrylate 39b (R² = tBu) under classical method [103] and/or microwave irradiation [104] afford corresponding Baylis-Hillman adducts 42, which undergo cyclization under reflux in AcOH yielding a mixture of 3-substituted chromene 43 and coumarin 44. Treatment of the Baylis-Hillman adducts 42 with concentrated HCl in refluxing AcOH produces 3-(chloromethyl) coumarins 45 in excellent yields. Moreover, the reaction of 42 with HI under reflux in a mixture of Ac₂O and AcOH furnishes 3-methyl coumarins 46, which upon further reaction with SeO₂ affords the corresponding 3-formyl coumarins 47.

The suggested mechanism for the formation of the coumarin derivatives 44/45/46 is shown in Figure 15.

Kaye et al. have also demonstrated the synthesis of substituted coumarins employing Baylis-Hillman strategy in different ways as shown in Figure 16 [105, 106].

2.4 Kostanecki reaction

4-Arylcoumarins 59 have been synthesized in good yields employing Kostanecki reaction between 2-hydroxybenzophenones 57 and acetic anhydride 58 in the presence of DBU under mild condition (Figure 17) [107].

The mechanism of the Kostanecki reaction is outlined in Figure 18. Similarly, 3,4-disubstituted coumarins 65 are isolated from readily available 2-acyloxybenzophenones 64 under Kostanecki reaction conditions (Figure 19) [107].

2.5 Michael addition reaction

Michael addition could be applied [108] to the synthesis of 3-arylcoumarins 68 in good yields from easily available 2-hydroxybenzaldehydes 66 and α-arylketene dithioacetals (AKDTAs) 67 in the presence of a catalytic amount of piperidine in refluxing THF (Figure 20).

The reaction proceeds via initial Michael addition followed by intramolecular aldol condensation reaction as depicted in Figure 21.

2.6 Wittig reaction

Kumar and coworkers [109] have reported the synthesis of substituted coumarins 3 from phenolic compounds 23 containing ortho-carbonyl group and triphenyl (α-carboxymethylene)phosphorane imidazole ylide 73 via intramolecular Wittig cyclization in good yields (Figure 22). All the reactions proceed via formation of the phosphorane intermediates 74 as established by spectroscopic results.

2.7 Vinyl phosphonium salt-mediated electrophilic substitution reaction

A series of 4-carboxy(ethyl/methyl) coumarins 76 have been synthesized in good yields from substituted phenols 1 and di(ethyl/methyl)
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Acetylene-dicarboxylate 75 in the presence of phosphinite ionic liquid (IL-OPPh3) under solvent-free microwave irradiation conditions (Figure 23) [110]. It is noticed that the diphenylphosphine group in ionic liquid accelerates the reaction.

The proposed mechanism for the formation of coumarins 76 via vinyl phosphonium salt-mediated electrophilic substitution is shown in Figure 24.

4-Carboxymethyl coumarins 82 have been synthesized by Yavari et al. [111] in moderate to excellent yields from the reactions of substituted phenols 1 and dimethyl acetylenedicarboxylate (DMAD) 81 in the presence of triphenylphosphine (Figure 25) via vinyl triphenylphosphonium salt-mediated aromatic electrophilic
substitution reaction as mentioned in Figure 24. Similar results are found from the given starting materials under microwave irradiation in shorter reaction time [112]. However, reactions of di- and trihydric phenols with dimethyl acetylenedicarboxylate (DMAD) in the presence of triphenylphosphine in toluene under reflux afford polyfunctionalized coumarin analogues along with unwanted by-products in appreciable amount (Figure 26) [113].
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Similar reactions of 2-hydroxybenzaldehydes with di(ethyl/methyl)acetyl-enedicarboxylates leads to the corresponding 4-carboxy(ethyl/methyl)-8-formyl coumarins in moderate to good yields (Figure 27) [114].

The methodology has also been employed to the synthesis of angular pyridocoumarins and benzo-fused 6-azacoumarin as shown in Figure 28 [115].
Palladium-catalyzed reactions

Palladium-catalyzed reactions between substituted phenols 101 and ethyl propiolates 102 lead to substituted coumarins 103/104 (Figure 29) \([116, 117]\).

Unsymmetrical monohydric phenols having \(m\)-OMe or \(m\)-Me substituent as respectively in 3-methoxyphenol and \(m\)-cresol show regioselectivity toward the
formation of a new bond in coumarins, which occurs at the para position to the methoxy group, and therefore, the regioisomers 103 are found to be formed predominantly over 104. However, symmetrical dihydric phenol with OMe substituent like that in 5-methoxybenzene-1,3-diol affords the regioisomer 104 predominantly over 103 under the reaction condition applied. This may be due to the steric effects.
of the R group of ethyl propiolate 102, which dominates over the electronic effect of the methoxy group of the phenol.

A proposed mechanism for the formation of coumarins 103/104 is shown in **Figure 30**.

Substituted coumarins 3 have been synthesized in moderate yields (42–69%) via Pd(OAc)$_2$-catalyzed reaction of substituted phenols 1 with substituted propiolic acid 110 (R$^3$ = CO$_2$H) in TFA under mild conditions (Figure 31, Condition A) [118]. However, a mixture of catalysts FeCl$_3$ and AgOTf showed better catalytic efficiency toward yields (60–93%) of coumarin derivatives 3 (Figure 31, Condition B). Propiolic acid ester 110 (R$^3$ = CO$_2$Et) also furnishes the desired products 3 upon
reactions with substituted phenols 1 under specified conditions as provided in Figure 31 (Conditions C and D) [119–121].

4,6-Disubstituted coumarins 113 have been achieved employing palladium-catalyzed tandem Heck-lactonization of the Z- or E-enoates 112 with o-iodophenols 111 (Figure 32, Conditions A, B, and C) [122, 123].

For Heck-lactonization, the enoate Z-112a is found to be more reactive than its E-isomer, leading to the corresponding coumarin 113 in good yields (68–84%) under all reaction conditions studied. The enoate Z-112b leads to coumarin derivative 113 in relatively lower yields (42–56%), which may be due to the presence of the bulky \( \text{tBu} \) ester group that hampers the lactonization step. Moreover, the reactivity of \( E \)-enoates depends on the \( \beta \)-substituent. \( E \)-enoates 112c (\( R^2 = \text{CH}_2\text{CHMe}_2 \),
Figure 32. Synthesis of 4,6-disubstituted coumarins.

Figure 33. Synthesis of 3, and 4-substituted and 3,4-disubstituted coumarins.

Figure 34. Possible mechanism for the synthesis of coumarins via carbonylative annulation.
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R\textsuperscript{3} = CH\textsubscript{3} and 112d (R\textsuperscript{2} = CH\textsubscript{3}) having CH\textsubscript{2}CHMe\textsubscript{2} and CH\textsubscript{3} group, respectively, at the β-carbon, and their double bonds are therefore less sterically hindered than that in E-enoate 112a. This reduced hindering is a major factor for the higher reactivity of E-enoates 112c and 112d than E-enoate 112a.

Palladium-catalyzed carbonylative annulation of terminal alkynes 110 (R\textsuperscript{2} = H; R\textsuperscript{3} = 3Pr, Ph, SiMe\textsubscript{3}, SiEt\textsubscript{3}, CO\textsubscript{2}Et, etc.) with o-iodophenols 111 affords 3-substituted coumarins 114 (R\textsuperscript{2} = H) in poor yields (18–36%) (Figure 33) [124]. On the other hand, both 3- and 4-substituted coumarins 114 (R\textsuperscript{2} = H) and 115 (R\textsuperscript{2} = H) have been synthesized from o-iodophenols 111 and terminal alkynes 110 (R\textsuperscript{2} = H; R\textsuperscript{3} = 9C\textsubscript{9}H\textsubscript{5}, 9C\textsubscript{8}H\textsubscript{17}) bearing long alkyl chain. In addition, a wide variety of 3,4-disubstituted coumarins 114/115 (R\textsuperscript{2}, R\textsuperscript{3} ≠ H) have also been achieved in moderate to good yields (43–78%) via carbonylative annulation between o-iodophenols 111 and internal alkynes 110 (R\textsuperscript{2}, R\textsuperscript{3} ≠ H) [125].

The suggested mechanism of the carbonylative annulation is presented in Figure 34. The carbonylative annulation process is believed to proceed via (a) oxidative addition of o-iodophenol 111 to Pd(0), (b) insertion of alkyne 110 into the aryl-palladium complex 116, (c) CO insertion into the resulting vinylic palladium species 118, and (d) nucleophilic attack of the phenolic oxygen on the carbonyl carbon of the acylpalladium complex 119 with simultaneous regeneration of the Pd(0) catalyst.

3,4-Disubstituted coumarins 121 are also isolated in good to excellent yields from readily available 2-(1-hydroxyprop-2-ynyl)phenols 120 via palladium-catalyzed

![Figure 35. Synthesis of 3,4-disubstituted coumarins.](image)

![Figure 36. Synthesis of 4-arylcoumarins.](image)

![Figure 37. Synthesis of 4-arylcoumarins.](image)
dicarbonylation process in the presence of KI in MeOH at room temperature (Figure 35) [126].

Furthermore, electrophilic palladium-catalyzed cycloisomerization of brominated arylpropiolates 122 followed by Suzuki coupling with arylboronic acids furnishes 4-arylcoumarins 123 in moderate to good yields (Figure 36) [127]. This strongly suggests that a single loading of catalyst Pd(OAc)$_2$ could be used to conduct sequential reactions for the synthesis of substituted coumarins.

2.9 Other methods

CuOAc-catalyzed hydroarylation of methyl phenylpropiolates 124 having a methoxy methyl (MOM)-protected hydroxyl group at the ortho-position with various arylboronic acids followed by acidic workup leads to 4-arylcoumarins 59 in good to excellent yields (Figure 37) [128].

Substituted coumarins 126 are obtained in moderate to excellent yields by Yb(OTf)$_3$-catalyzed reactions of substituted phenols 1 with alkylidene Meldrum’s acid 125 in CH$_3$NO$_2$ at 100°C (Figure 38) [129].

A series of 3-alkylcoumarins 128 are obtained in moderate yields from 2-hydroxybenzaldehydes 18 and $\alpha,\beta$-unsaturated aldehydes 127 via generation of N-heterocyclic carbenes (NHC) in ionic liquid under conventional heating (Figure 39, Condition A) and/or microwave irradiation conditions (Figure 39, Condition B) [130].

3-Benzylocoumarins 130/131 and coumarin-3-carbaldehydes 47 have also been isolated in moderate to dear yields from the reactions of 2-hydroxybenzaldehydes 18/19 with phenylpropionyl chloride 129a and/or propionyl chloride 129b under esterification conditions (Figure 40) [131].

An electrochemical method has been developed for the synthesis of 6$\text{H}$-benzo[c]chromen-6-ones 133 in good to excellent yields from biphenyl-2-carboxylic acids 132 via radical arene carbon–oxygen bond formation reaction (Figure 41) [132].
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The method involves DDQ as a redox mediator, inexpensive glassy carbon electrodes to facilitate an intramolecular lactonization of biphenyl-2-carboxylic acid derivatives, and 2,6-lutidine as an additive, in 0.1 M $\text{nBu}_4\text{NClO}_4$ electrolyte mixture of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP).

3. Concluding remarks
In this chapter, we have discussed a plethora of methods for the one-pot synthesis of coumarin derivatives and their advantages and/or demerits compared to other methods. Both the Pechmann as well as Knoevenagel condensation reactions under microwave and/or ultrasound irradiation conditions, and catalyzed by ionic liquids and/or solid acids have several advantages including high products yields, diminutive reaction times, ease of isolation of products, recycle of catalysts, and green aspects by avoiding toxic catalysts and solvents. Chemo- and regioselective syntheses of 3-substituted coumarins have been reported via Baylis-Hillman reactions under mild conditions. On the other hand, vinyl phosphonium salt-mediated electrophilic substitution reactions of phenols afford 4-carboxyalkyl coumarin derivatives in good yields under neutral conditions. This method offers significant advantages for the synthesis of coumarins having acid sensitive functional groups. In contrast, the most widely used method von Pechmann condensation requires acidic conditions. Moreover, palladium-catalyzed Heck lactonization protocol has been employed for the regioselective synthesis of coumarin derivatives from o-iodophenols and enoates. It is revealed that this reaction is sensitive to steric hindrance around the double bound in the enoates. Regioselective synthesis of 3,4-disubstituted coumarins
achieved from substituted 2-iodophenols and alkynes containing different substituents via palladium-catalyzed carbonylative annulative process is sensitive to the steric bulk of the alkynes, and alkynes bearing tertiary alkyl substituents generally fail to undergo annulation. Unsymmetrical alkynes produce mixtures of regioisomers with generally only modest selectivity. Kostanecki reaction protocol furnishes a notable improvement in reaction conditions for coumarin synthesis and gives rise to the advantage of its synthetic capability, especially for highly functionalized 4-arylcoumarins with structural diversity.

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Conflict of interest

The authors declare no conflict of interest.

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