

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# 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 spawned 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 5 $\alpha$ -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  $\beta$ -keto esters, in the presence of an acid catalyst. This method employs both homogeneous catalysts such as concentrated H<sub>2</sub>SO<sub>4</sub> [24, 25], trifluoroacetic acid (TFA) [28], and Lewis acids (LA) such as AlCl<sub>3</sub> [29], ZnCl<sub>2</sub> [30], ZrCl<sub>4</sub> [31], TiCl<sub>4</sub> [32], etc. and heterogeneous catalysts such as cation-exchange resins [33], Nafion resin/silica composites [34], zeolite H-BEA (H-beta, SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> = 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  $\beta$ -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 **3**.

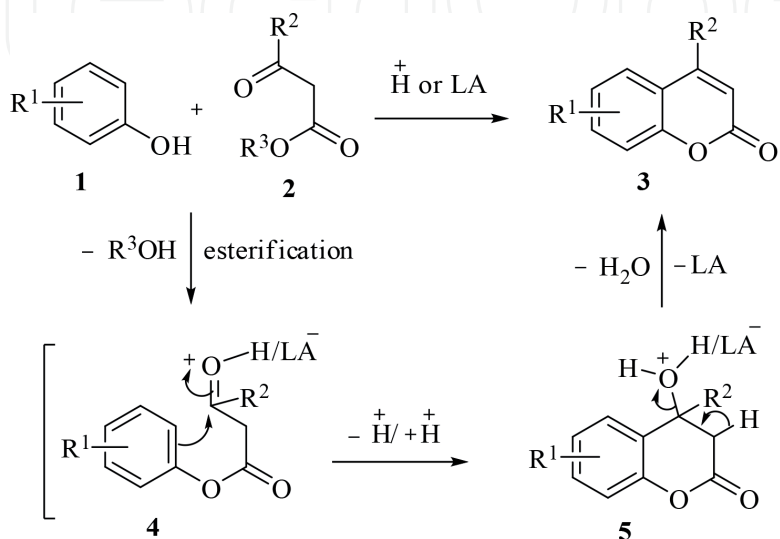
A series of substituted coumarins **8** have been synthesized in 25–77% yields by the reactions of substituted phenols **6** with ethyl acetoacetate **7** in the presence of zinc-iodine mixture in refluxing toluene (**Figure 2**) [36]. It is observed that phenols containing electron-donating substituent like  $-\text{CH}_3$  group result in higher yields compared to unsubstituted phenols and phenols having electron-withdrawing group such as  $\text{NO}_2$  group.

When 3-(*N,N*-dimethylamino)phenol **9** is subjected to react with ethyl 2-acetamido-3-oxobutyrates **10** in the presence of anhydrous  $\text{ZnCl}_2$  in absolute ethanol under reflux condition, the acetamido coumarin **11** is obtained only in 12.4% yield (**Figure 3**) [30].

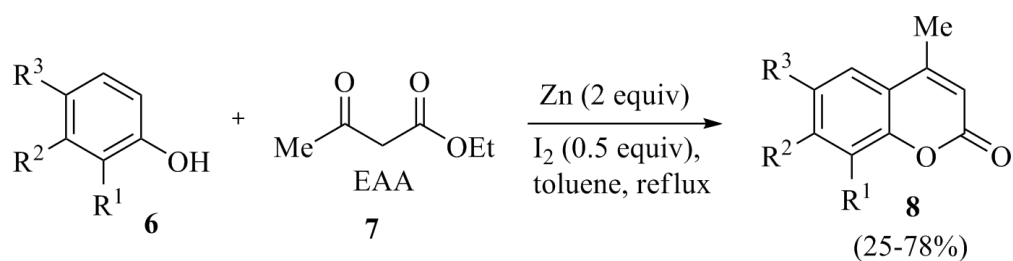
Substituted coumarins **14** have been achieved in moderate to good yields from substituted phenols **12** and methyl acetoacetate **13** under conventional and microwave heating, respectively, catalyzed by concentrated  $\text{H}_2\text{SO}_4$  (**Figure 4**) [37]. It is found that the reactions using 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  $\beta$ -keto esters **15** in the presence of a heterogeneous catalyst,  $\text{HClO}_4 \cdot \text{SiO}_2$  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).

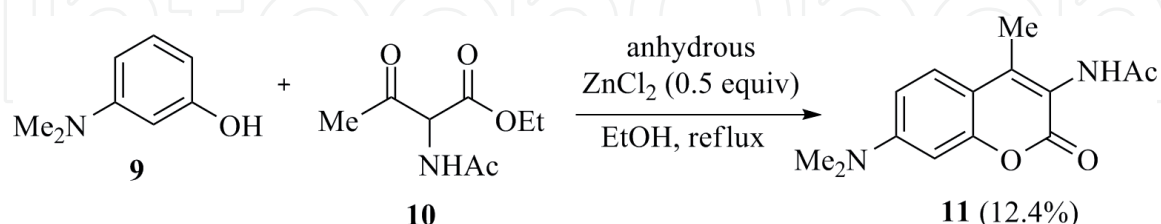
Pechmann condensation reactions for the synthesis of substituted coumarins using various homogeneous and heterogeneous catalysts have been reported in literature and some important ones are summarized in **Table 1**.



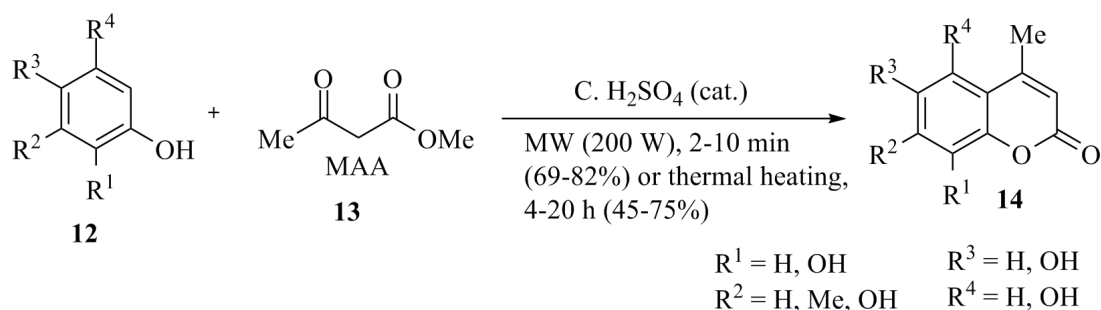
**Figure 1.**  
Mechanism for the acid-catalyzed Pechmann condensation.



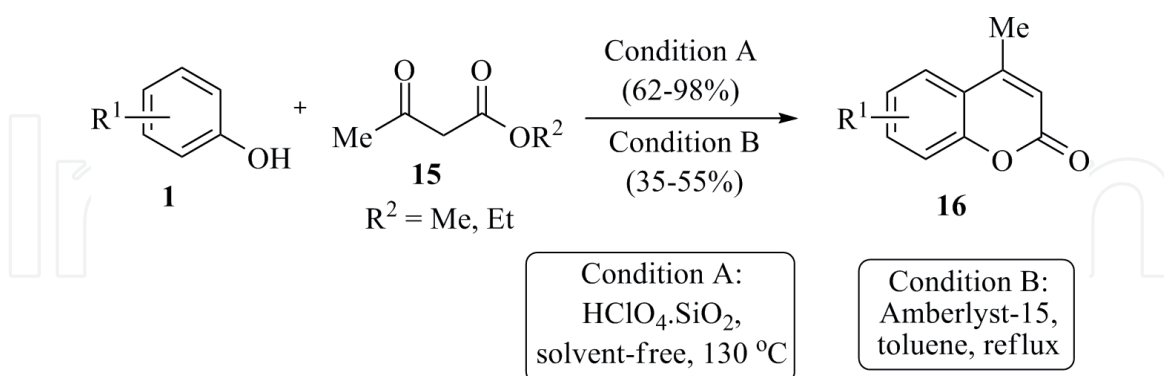
**Figure 2.**  
*Synthesis of substituted coumarins.*



**Figure 3.**  
*Synthesis of acetamido coumarin.*



**Figure 4.**  
*Synthesis of substituted coumarins.*



**Figure 5.**  
*Synthesis of substituted coumarins.*

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<sub>2</sub> 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<sub>4</sub> (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<sub>6</sub> 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<sub>2</sub> 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<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>@PrSO<sub>3</sub>H), CuFe<sub>2</sub>O<sub>4</sub> 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.





Entry	Catalyst	Reaction conditions	Time	Yields (%)	Reference
16	I <sub>2</sub>	Condition A: I <sub>2</sub> (25 mol%), toluene, 90°C Condition B: I <sub>2</sub> (1 mol%), MW	18 h 1.5–5 min	42–89 80–96	[52] [53]
17	AgOTf	AgOTf (10 mol%), solvent-free, 60°C	3–12 h	60–95	[54]
18	1,3-Disulfonic acid imidazolium hydrogen sulfate (DSIMHS)	DSIMHS (7 mol%), solvent-free, 70°C	2–27 min	80–96	[55]
19	<i>N,N'</i> -dimethylaminoethanol hydrosulfate ([N <sub>112</sub> OH][HSO <sub>4</sub> ])	[N <sub>112</sub> OH][HSO <sub>4</sub> ] (5 mol%), solvent-free, 90°C	3–24 h	20–99	[56]
20	Nano-TiO <sub>2</sub> on dodecyl-sulfated silica support (NTDSS)	NTDSS (5 mol% TiO <sub>2</sub> ), H <sub>2</sub> O, reflux	3–8 h	89–98	[57]
21	ZrOCl <sub>2</sub> ·8H <sub>2</sub> O/SiO <sub>2</sub>	ZrOCl <sub>2</sub> ·8H <sub>2</sub> O/SiO <sub>2</sub> (10 mol%), solvent-free, 90°C	5–80 min	75–99	[58]
22	Polydivinylbene-bound perfluoroalkylsulfonyl imide polymers (H-PDVB- <i>x</i> -SSFAI)	H-PDVB- <i>x</i> -SSFAI (10 mol%), solvent-free, 140°C	2 h	78–94	[59]
23	Polyaniline–fluoroboric acid–dodecyl hydrogen sulfate (PANI–HBF <sub>4</sub> –DHS)	PANI–HBF <sub>4</sub> –DHS (20 wt.% of 12), solvent-free, 150°C	6 h	94–98	[60]
24	Silica sulfuric acid (SSA)	SSA (15 mol%), solvent-free, 80°C	0.5–2 h	70–97	[61]
25	ZrPW (Zirconium IV Phosphotungstate) 12-TPA/ZrO <sub>2</sub> (12-Tungstophosphoric acid supported onto ZrO <sub>2</sub> )	Condition A: ZrPW (0.2 g), solvent-free, 130°C Condition B: ZrPW (0.2 g), solvent-free, MW (250 W), 130°C Condition C: 12-TPA/ZrO <sub>2</sub> (0.2 g), solvent-free, 130°C Condition D: 12-TPA/ZrO <sub>2</sub> (0.2 g), solvent-free, MW (250 W), 130°C	8 h 30 min 8 h 30 min	42–65 47–66 38–63 41–65	[62]
26	12-Tungstophosphoric acid supported on SnO <sub>2</sub> nanoparticles (12-TPA-SnO <sub>2</sub> )	12-TPA-SnO <sub>2</sub> (30 wt% of TPA), solvent-free, 120°C	2 h	78	[63]
27	Poly(4-vinylpyridine)-supported copper iodide	P <sub>4</sub> VPy-CuI (0.1 g), solvent-free, 80°C	10–90 min	84–92	[64]
28	Polystyrene-supported GaCl <sub>3</sub> (PS–GaCl <sub>3</sub> )	PS–GaCl <sub>3</sub> (10 mol%), ethanol, reflux	45–300 min	45–96	[65]
29	Silica tungstic acid (STA)	STA (5 mol%), solvent-free, 80°C	20–90 min	75–97	[66]
30	CMK-5 supported sulfonic acid (CMK-5-SO <sub>3</sub> H)	CMK-5-SO <sub>3</sub> H (3 mol%), solvent-free, 130°C	15–120 min	60–97	[67]
31	FeF <sub>3</sub>	FeF <sub>3</sub> (0.05 g), solvent-free, MW (450 W), 110°C	6–9 min	61–98	[68]

Entry	Catalyst	Reaction conditions	Time	Yields (%)	Reference
32	FeCl <sub>3</sub>	FeCl <sub>3</sub> (10 mol%), solvent-free, US (20 kHz, 130 W)	1–20 min	55–99	[69]
33	Sulfonic acid supported silica coated magnetic nanoparticles (Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> @PrSO <sub>3</sub> H)	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> @PrSO <sub>3</sub> H (1.6 mol%), solvent-free, 130°C	3–50 min	87–98	[70]
34	CuFe <sub>2</sub> O <sub>4</sub> nanoparticles	CuFe <sub>2</sub> O <sub>4</sub> (5 mol%), H <sub>2</sub> O, rt	15–34 min	82–98	[71]
35	Zr(IV)-HMNQ@ASMPs [Zirconium(IV)-3-hydroxy-2-methyl-1,4-naphthoquinone (HMNQ)@3-aminopropylated silica coated magnetic nanoparticles (ASMPs)]	Zr(IV)-HMNQ@ASMPs (20 mg), solvent-free, 110°C	10 min	95–100 (selectivity)	[72]
36	MFI nanosponge zeolite (MFI-NSZ)	MFI-NSZ (0.1 g), dodecane (0.5 g, internal standard), nitrobenzene, 120–150°C	70 h	80–90 (selectivity)	[73]
37	In(OTf) <sub>3</sub>	In(OTf) <sub>3</sub> (1 mol%), solvent-free, 80°C	10–87 min	68–98	[74]
38	Mg(NTf <sub>2</sub> ) <sub>2</sub>	Mg(NTf <sub>2</sub> ) <sub>2</sub> (1 mol%), solvent-free, 80°C	25–60 min	85–98	[75]
39	Poly(4-vinylpyridinium) hydrogen sulfate (PVPHS)	PVPHS (2 mol%), solvent-free, US (35 kHz, 200 W)	3–18 min	62–96	[76]
40	Polyvinylpolypyrrolidone-bound boron trifluoride (PVPP-BF <sub>3</sub> )	PVPP-BF <sub>3</sub> (33 mol%), ethanol, reflux	2–3 h	76–96	[77]
41	Zeolites e.g., beta (BEA) and ultrastable Y (USY) Metal–organic frameworks (MOFs) such as Cu-benzene-1,3,5-tricarboxylate (CuBTC) and Fe-benzene-1,3,5-tricarboxylate (FeBTC)	Condition A: Zeolite (0.2 g), nitrobenzene, 130°C Condition B: MOF (0.2 g), nitrobenzene, 130°C	23 h 23 h	23–91 (conversion) 2–98 (conversion)	[78]
42	Zn <sub>0.925</sub> Ti <sub>0.075</sub> O NPs	Zn <sub>0.925</sub> Ti <sub>0.075</sub> O (10 mol%), solvent-free, 110°C	3–5 h	51–89	[79]

**Table 1.**  
*Synthesis of substituted coumarins via Pechmann condensation reactions.*

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



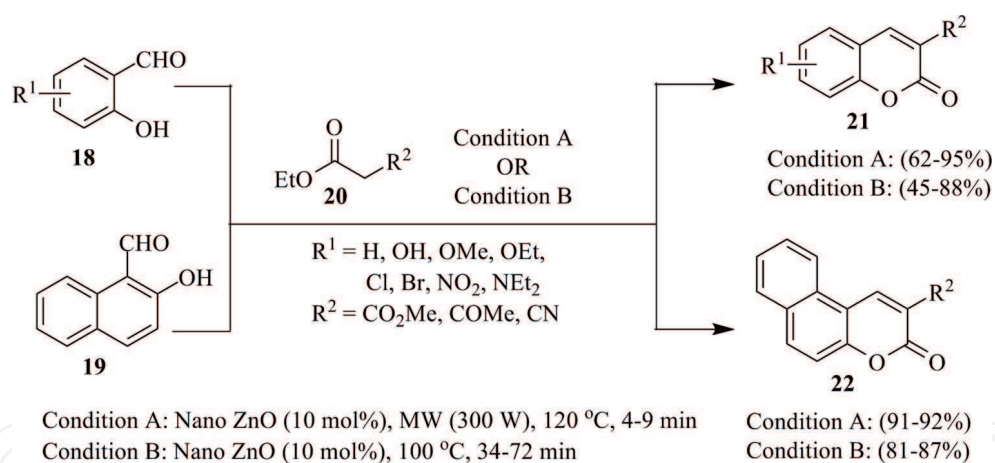
nano-ZnO catalyst under microwave or thermal conditions, which affords moderate to good yield of the products (**Figure 6**) [81]. Reactions under microwave-irradiation conditions are found to be more convenient than thermal conditions.

Various coumarin-3-carboxylic acid derivatives **25/26** have been synthesized in good yields using catalytic amounts of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  under solvent-free condition (**Figure 7**) [82].

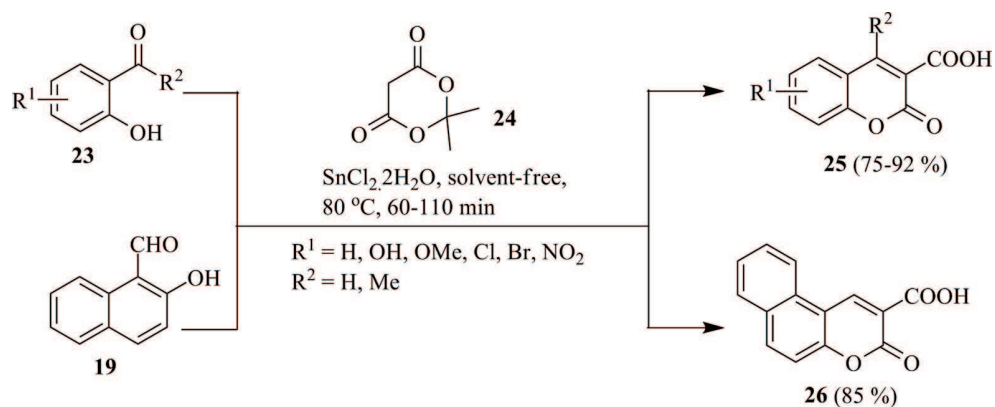
Ultrasound irradiation technique is also useful to synthesize 3-aryl coumarin derivatives. Treatment of *o*-hydroxybenzaldehydes **18** with aryl substituted acetyl chloride **27** in the presence of  $\text{K}_2\text{CO}_3$  as a catalyst in tetrahydrofuran (THF) using ultrasound irradiation leads to the formation of 3-aryl coumarin 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-diethyl-amino-2-hydroxybenzaldehyde **29**, ethyl cyanoacetate **30**, and ortho-phenylene-diamine/phenylenediamine derivatives **31** in the presence of reusable green solid acid like HZSM-5 zeolite, heteropoly acids, e.g., tungstophosphoric acid ( $\text{H}_3\text{PW}_{12}\text{O}_{40}$ ), and/or tungstosilicic acid ( $\text{H}_4\text{O}_{40}\text{SiW}_{12}$ ) 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.



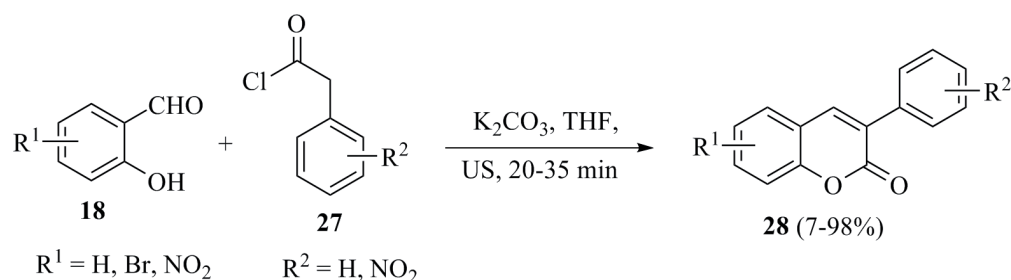
**Figure 7.**  
Synthesis of coumarin 3-carboxylic acid derivatives.

Shaabani et al. [86] have described the synthesis of 3-substituted coumarins **21** in good yields via Knoevenagel condensation of 2-hydroxybenzaldehydes **18** with  $\beta$ -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<sub>4</sub>] ionic liquid in the presence of L-proline as an additional promoter under heating condition (**Figure 11**, Condition C) [87].

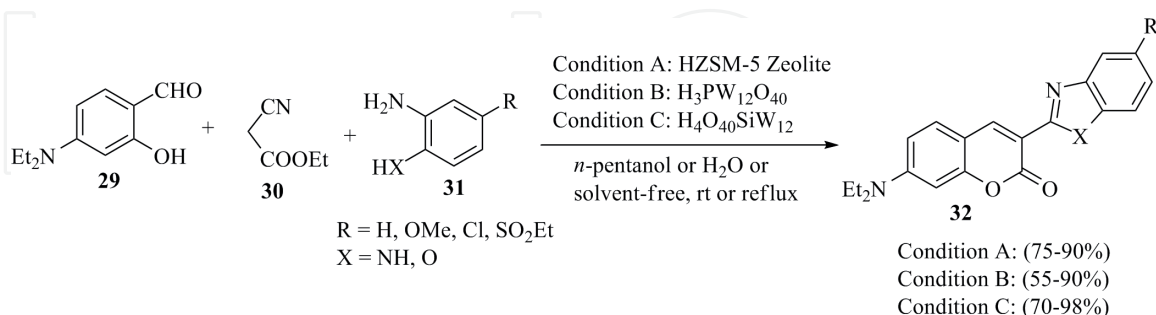
Imidazolium based phosphinite ionic liquid (IL-OPPh<sub>2</sub>) catalyzed synthesis of 3-substituted coumarin derivatives has been reported in literature; when *o*-hydroxy benzaldehydes **18** are treated with active methylene containing compounds **35** in the presence of IL-OPPh<sub>2</sub> catalyst 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<sub>2</sub>)<sub>4</sub>SO<sub>3</sub>HMIM][HSO<sub>4</sub>] in water lead to 3-substituted coumarin derivatives in good yields (**Figure 13**) [89].

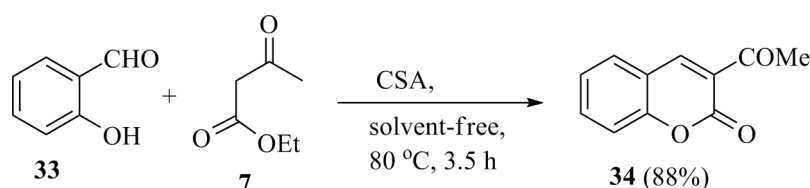
Synthesis of substituted coumarins via Knoevenagel condensation using various organic catalysts such as piperidine, ammonia, L-lysine, L-proline, benzoic acid, etc. has been reported in literature and some are summarized in **Table 2**.



**Figure 8.**  
Synthesis of 3-aryl coumarin derivatives.



**Figure 9.**  
Synthesis of coumarin-substituted benzimidazoles/benzoxazoles.



**Figure 10.**  
Synthesis of 3-acetyl coumarin.

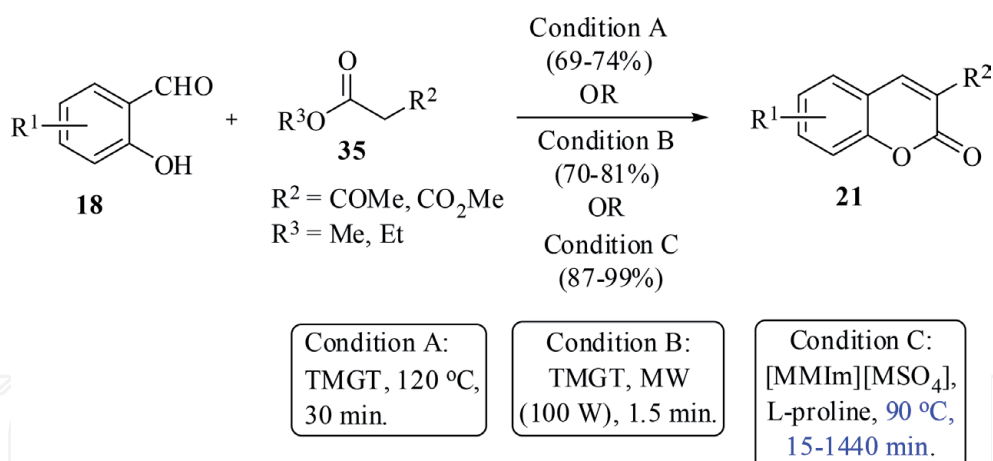
It is quite evident that in **Table 2** several methodologies for the synthesis of substituted coumarins using different organic catalysts are established. Among these, L-proline-catalyzed reactions offer high yields (entry 3), which explains synthesis of 3-substituted coumarins by the condensation of *o*-hydroxybenzaldehydes with a variety of active methylene compounds catalyzed by 1,3-dimethylimidazolium methyl sulfate [MMIm][MSO<sub>4</sub>] 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).

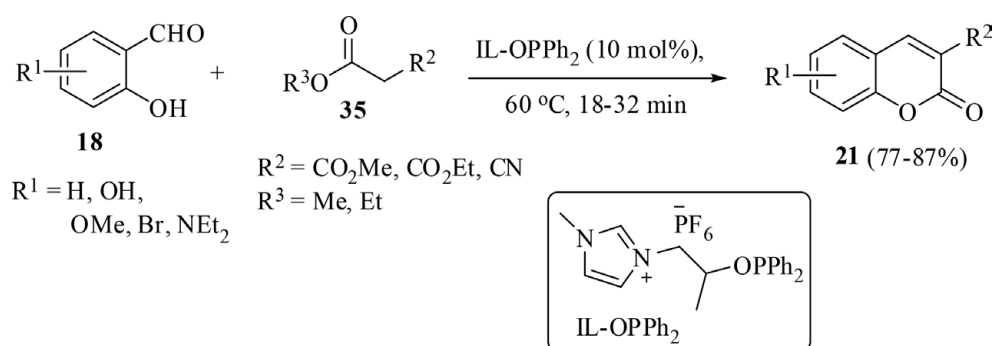
Microwave-assisted synthesis of coumarins is also known, which not only reduces the reaction time but also increases the yields of the products (entries 2, 6, and 7).

Benzocoumarin derivatives have been synthesized from 1-hydroxy-4-methylnaphthalene-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).

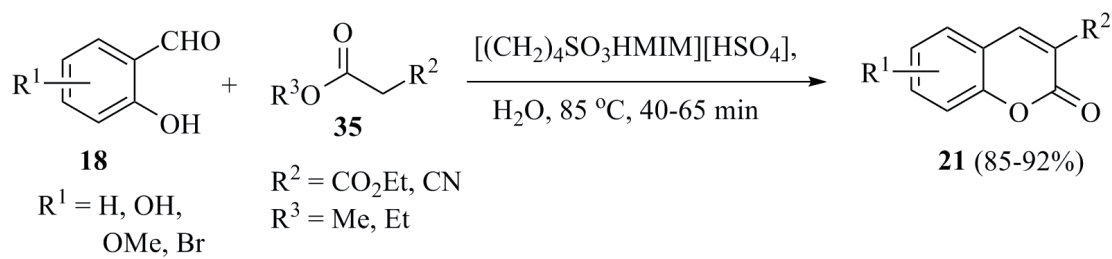
Application of sonochemistry for the synthesis of different coumarin derivatives is also useful due to better yield and shorter reaction time compared with the classical procedures (entry 10).



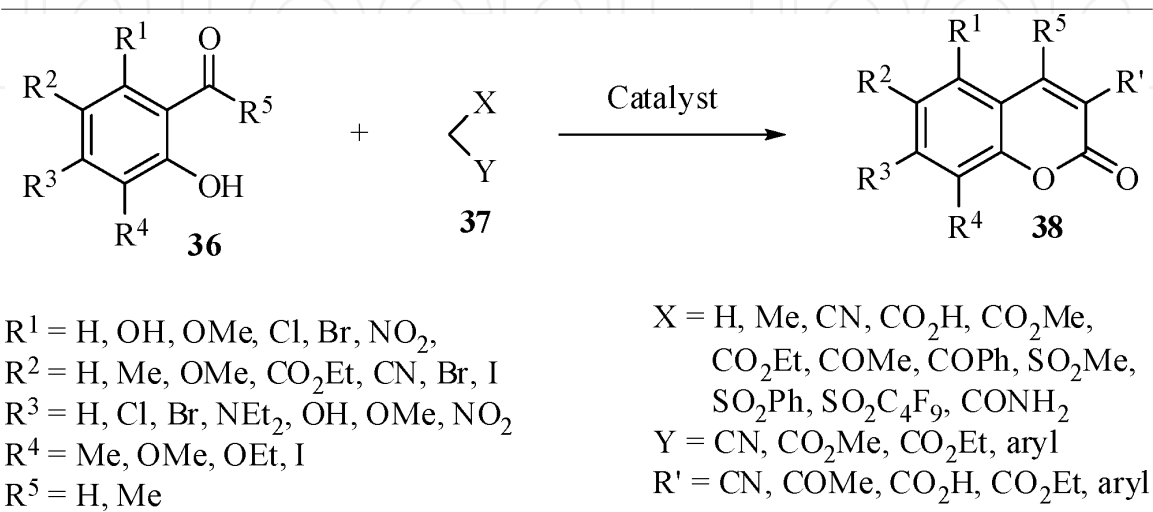
**Figure 11.**  
Synthesis of 3-substituted coumarins.



**Figure 12.**  
Synthesis of 3-substituted coumarins.



**Figure 13.**  
Synthesis of 3-substituted coumarins.



Entry	Catalyst	Reaction conditions	Time	Yield (%)	Reference
1	CDI-DBU	(i) CDI (1.2 equiv.), DCM, rt. (ii) DBU (1.0 equiv.), DCM, rt	30 min 1-2 h	42-59	[90]
2	PhCOOH	Condition A: Polyphosphoric acid, MW (900 W), 100°C Condition B: H <sub>2</sub> SO <sub>4</sub> , Benzoic acid, MW (900 W), 90°C Condition C: benzoic acid, n-pentanol, MW (900°C), 110°C	4-6 min 3-4 min 3 min	60-75 58-75 85-95	[91]
3	L-proline	1,3-dimethyl imidazolium methyl sulfate, [MMIm][MSO <sub>4</sub> ], L-proline (1 equiv.), 90°C	15-1440 min	87-99	[87]
4	L-proline	L-proline (20 mmol%), EtOH, rt	15-20 h	54-76	[92]
5	L-lysine	L-lysine (20 mol%), H <sub>2</sub> O, rt. -80°C	6-24 h	50-90	[93]
6	Piperidine	Piperidine (catalytic), rt.	20 min	84	[94]
7	Piperidine	Piperidine (2.0 mol%), solvent-free, MW (400 W)	1 min	50-97	[95]
8	Piperidine	Piperidine (1.48 equiv.), EtOH, reflux	30 min	85-92	[96]
9	Piperidine	Piperidine (catalytic), EtOH, reflux	2 h	82	[97]
10	Piperidine	Piperidine (1.0 equiv.), AcOH (2.5 mol%), EtOH, US, rt	5-30 min	49-90	[98]
11	Piperidine	Piperidine, EtOH, rt-reflux	1-2 h	82-92	[99]
12	Piperidine	Piperidine (7.4 equiv.), EtOH, reflux	2 h	92	[100]

**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-ethoxysalicylaldehyde 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** ( $R^2 = \text{Me}$ ) 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** ( $R^2 = \text{tBu}$ ) 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  $\text{Ac}_2\text{O}$  and AcOH furnishes 3-methyl coumarins **46**, which upon further reaction with  $\text{SeO}_2$  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  $\alpha$ -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**.

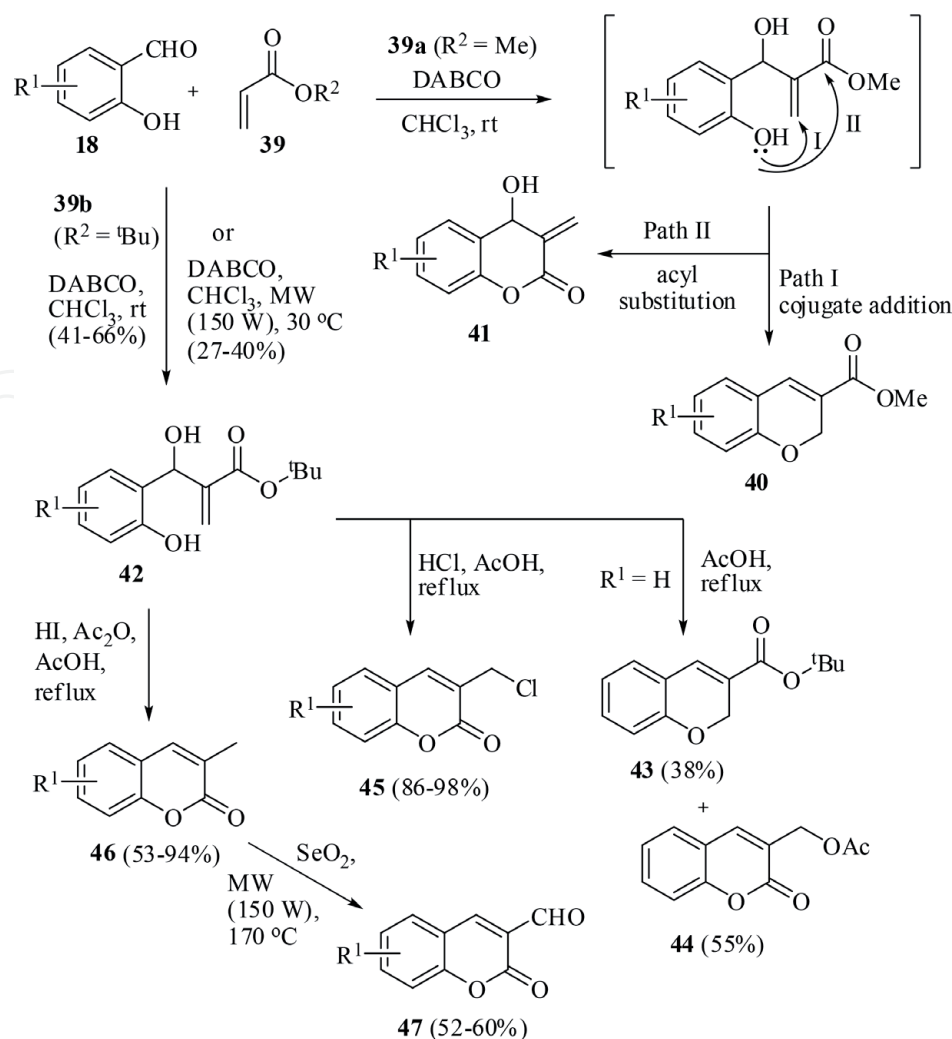
### 2.6 Wittig reaction

Kumar and coworkers [109] have reported the synthesis of substituted coumarins **3** from phenolic compounds **23** containing ortho-carbonyl group and triphenyl ( $\alpha$ -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.

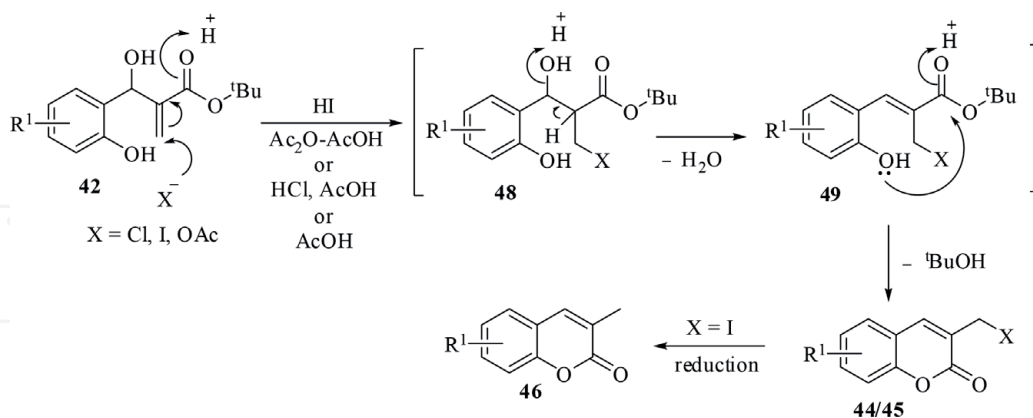
### 2.7 Vinyl phosphonium salt-mediated electrophilic substitution reaction

A series of 4-carboxy(ethyl/methyl) coumarins **76** have been synthesized in good yields from substituted phenols **1** and di(ethyl/methyl)





**Figure 14.**  
Synthesis of 3-substituted coumarins.



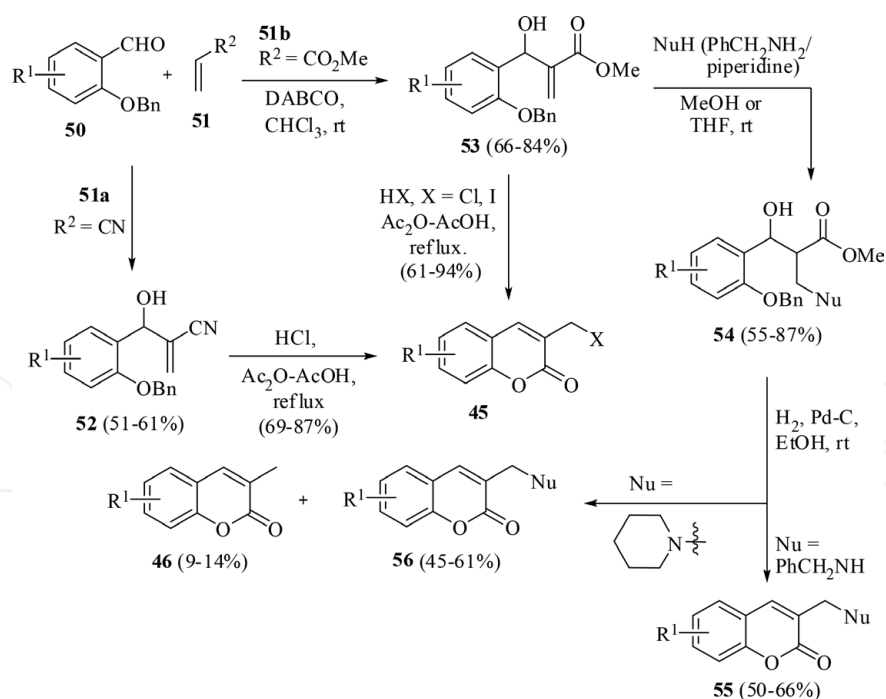
**Figure 15.**  
Possible mechanism for the formation of 3-substituted coumarins.

acetylene-dicarboxylate **75** in the presence of phosphinite ionic liquid (IL-OPPh<sub>2</sub>) under solvent-free microwave irradiation conditions (**Figure 23**) [110]. It is noticed that the diphenylphosphine group in ionic liquid accelerates the reaction.

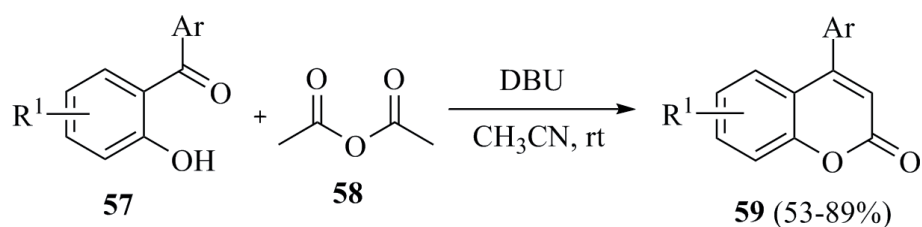
The proposed mechanism for the formation of coumarins **76** via vinyl phosphonium salt-mediated electrophilic substitution is shown in **Figure 24**.

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

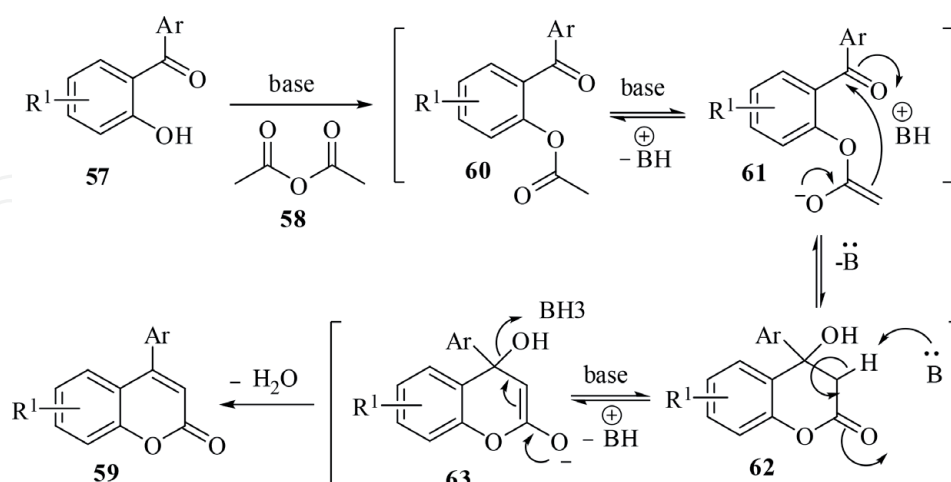




**Figure 16.**  
Synthesis of 3-substituted coumarins.



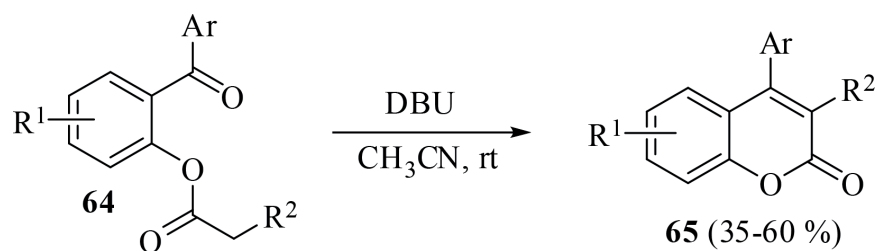
**Figure 17.**  
Synthesis of 4-arylcoumarins.



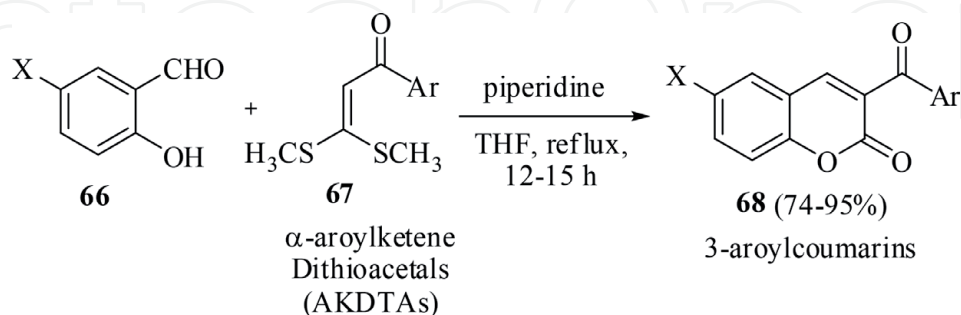
**Figure 18.**  
Mechanism for Kostanecki reaction.

substitution reaction as mentioned in **Figure 24**. Similar results are found from the given starting materials under microwave irradiation in shorter reaction time [112].

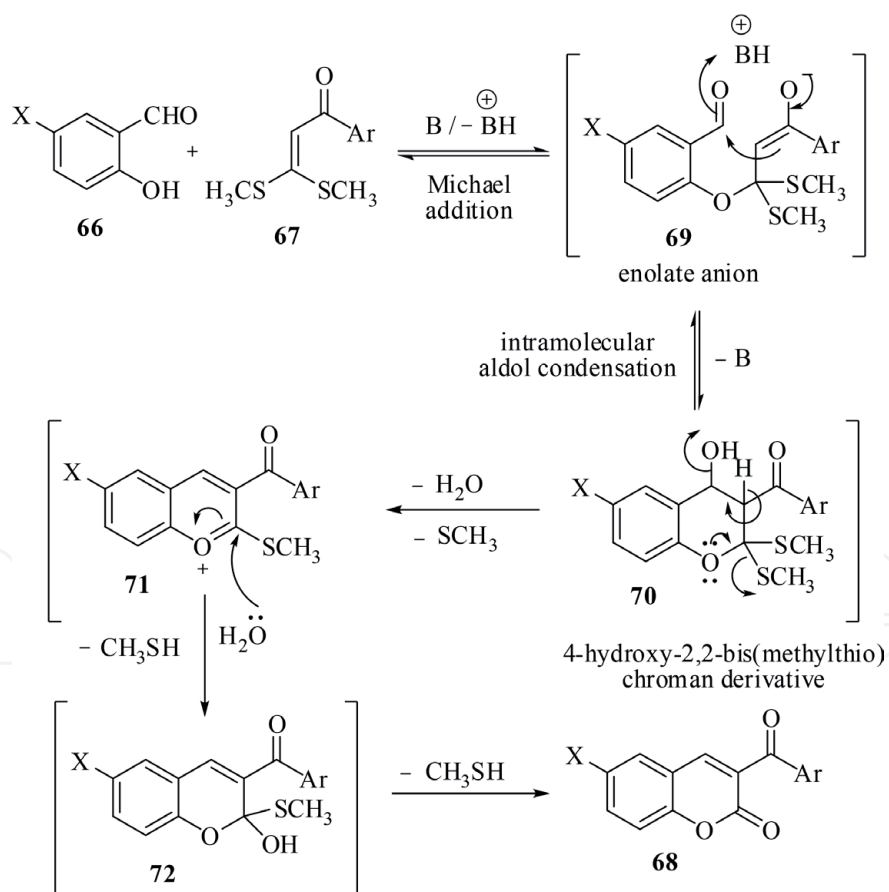
However, reactions of di- and trihydric phenols with dimethyl acetylenedicarboxylate (DMAD) in the presence of triphenylphosphine in toluene under reflux afford polyfunctionalized coumarin analogues along with unwanted by-products in appreciable amount (**Figure 26**) [113].



**Figure 19.**  
Synthesis of 3,4-disubstituted coumarins.



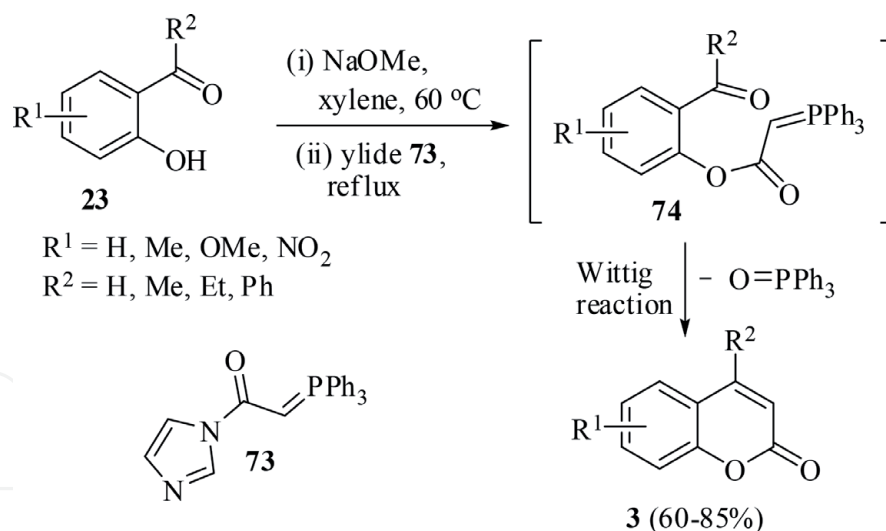
**Figure 20.**  
Synthesis of 3-aryl coumarins.



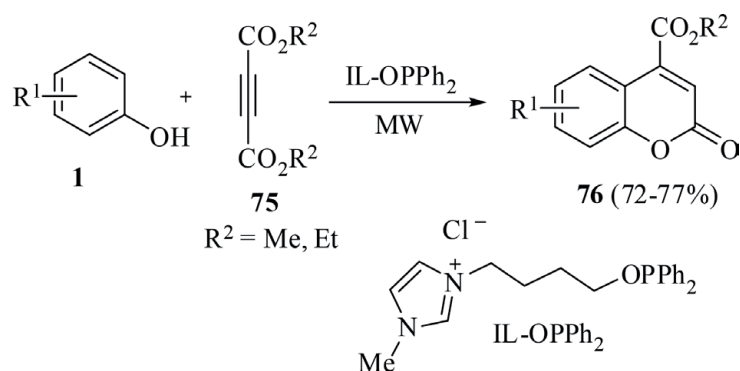
**Figure 21.**  
Probable mechanism for the formation of 3-aryl coumarins.

Similar reactions of 2-hydroxybenzaldehydes **18** with di(ethyl/methyl)acetylenedicarboxylates **75** leads to the corresponding 4-carboxy(ethyl/methyl)-8-formyl coumarins **93** in moderate to good yields (**Figure 27**) [114].

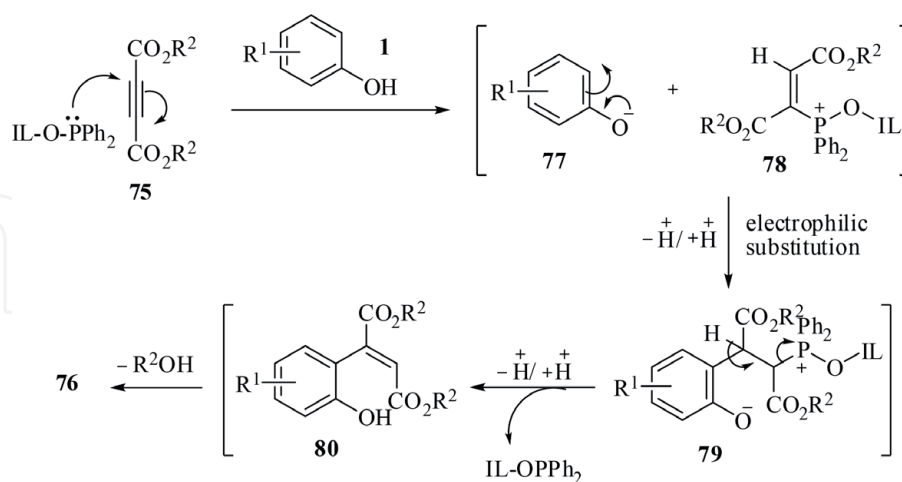
The methodology has also been employed to the synthesis of angular pyridocoumarins **97/98** and benzo-fused 6-azacoumarin **100** as shown in **Figure 28** [115].



**Figure 22.**  
Synthesis of substituted coumarins.



**Figure 23.**  
Synthesis of 4-carboxy(ethyl/methyl) coumarins.

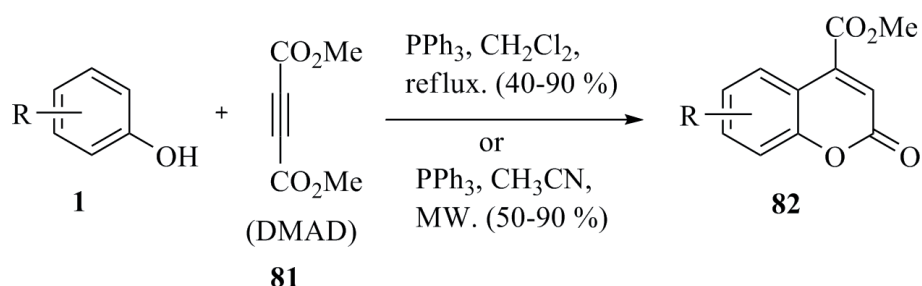


**Figure 24.**  
Proposed mechanism for the synthesis of substituted coumarins via vinyl phosphonium salt-mediated electrophilic substitution.

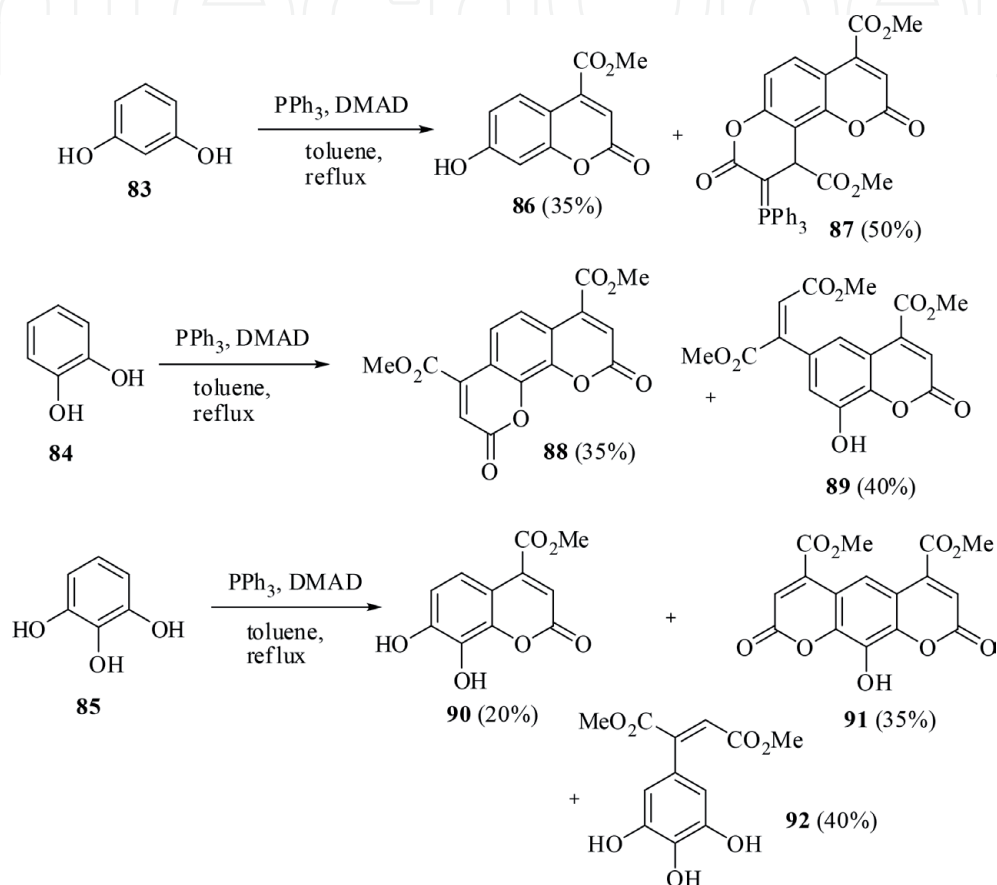
## 2.8 Palladium-catalyzed reactions

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

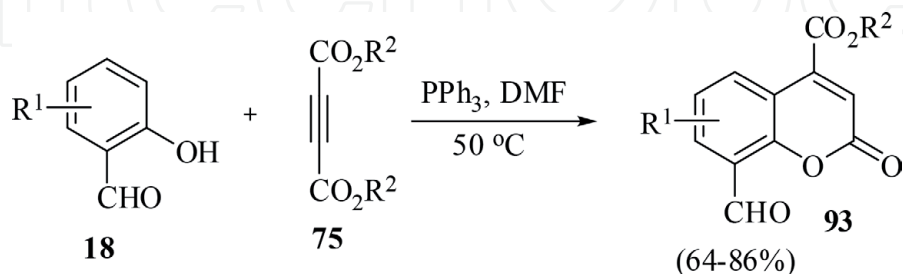
Unsymmetrical monohydric phenols having *m*-OMe or *m*-Me substituent as respectively in 3-methoxyphenol and *m*-cresol show regioselectivity toward the



**Figure 25.**  
Synthesis of 4-carboxymethyl coumarins.

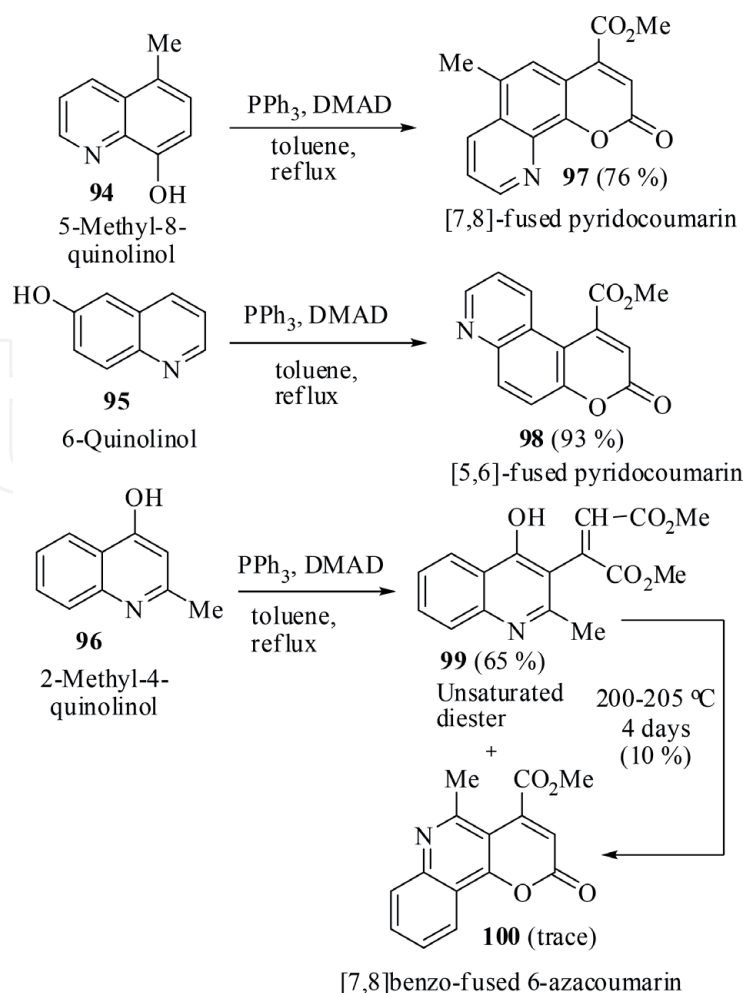


**Figure 26.**  
Synthesis of polyfunctionalized coumarin analogues.

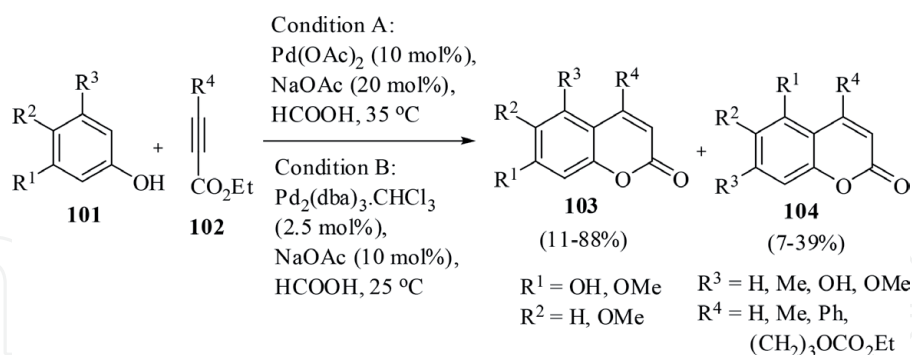


**Figure 27.**  
Synthesis of 4-carboxy(ethyl/methyl)-8-formyl coumarins.

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



**Figure 28.**  
Synthesis of pyridocoumarins and benzo-fused azacoumarin.

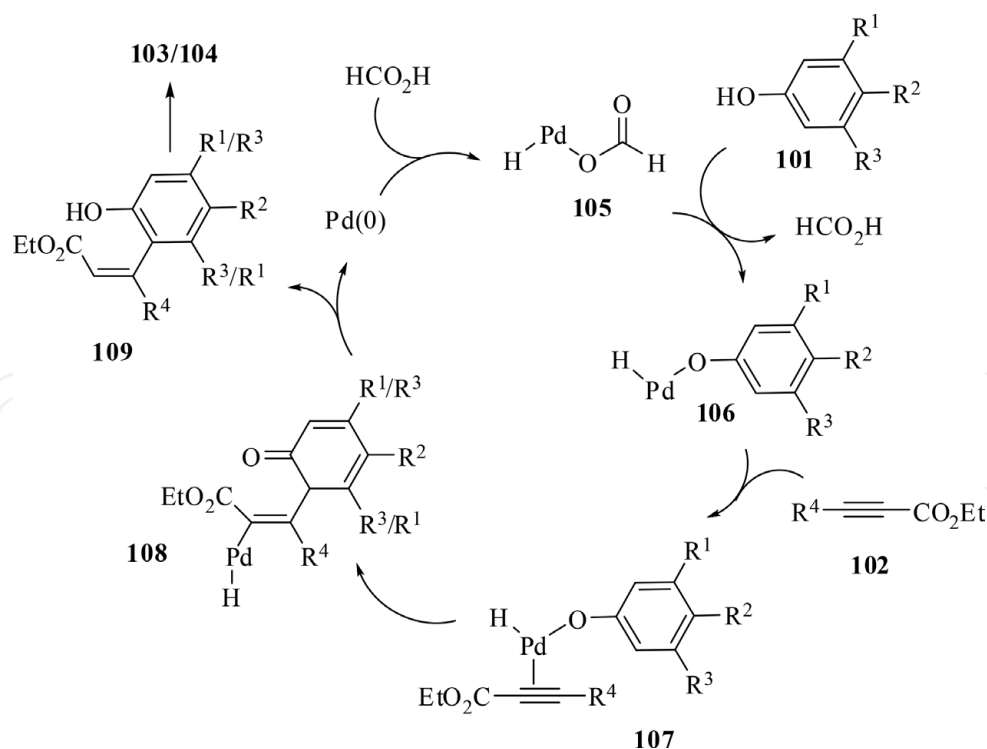


**Figure 29.**  
Synthesis of substituted coumarins.

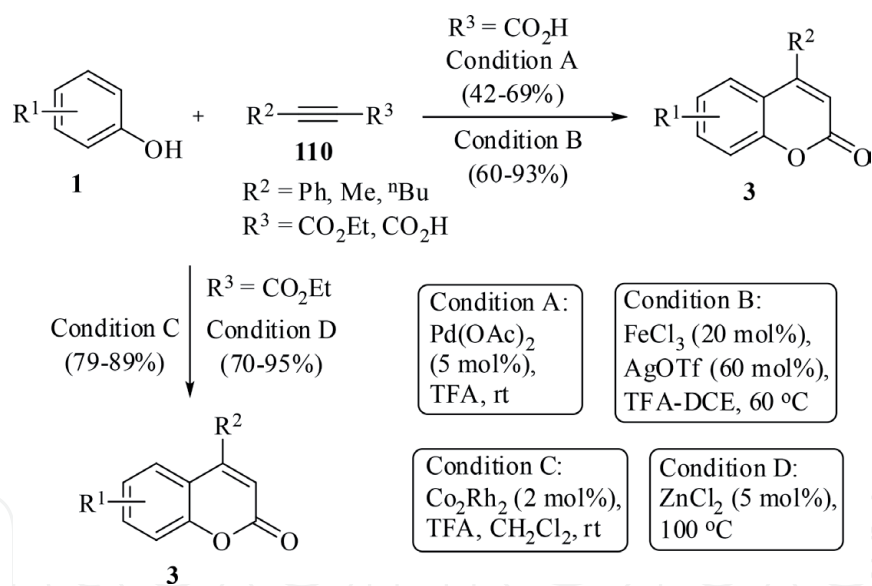
of the  $\text{R}^4$  group of ethyl propiolate **102**, which dominates over the electronic effect of the methoxy group of the phenol.

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  $\text{Pd}(\text{OAc})_2$ -catalyzed reaction of substituted phenols **1** with substituted propiolic acid **110** ( $\text{R}^3 = \text{CO}_2\text{H}$ ) in TFA under mild conditions (**Figure 31**, Condition A) [118]. However, a mixture of catalysts  $\text{FeCl}_3$  and  $\text{AgOTf}$  showed better catalytic efficiency toward yields (60–93%) of coumarin derivatives **3** (**Figure 31**, Condition B). Propiolic acid ester **110** ( $\text{R}^3 = \text{CO}_2\text{Et}$ ) also furnishes the desired products **3** upon



**Figure 30.**  
Possible mechanism for Pd-catalyzed synthesis of coumarins.



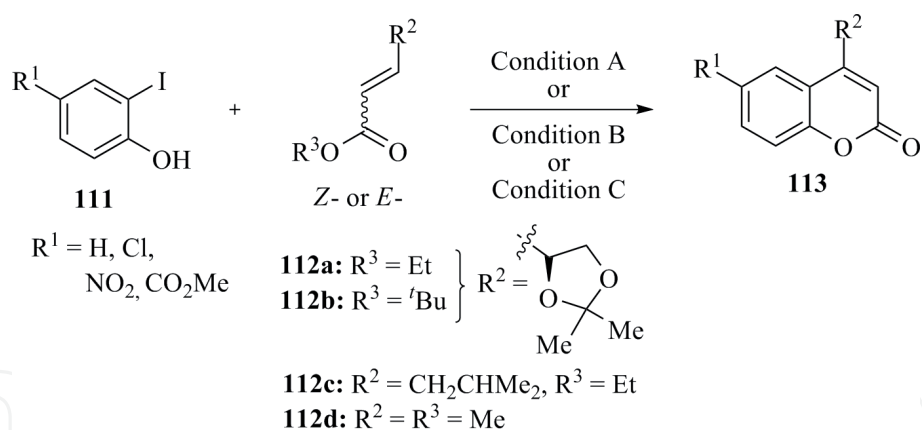
**Figure 31.**  
Synthesis of substituted coumarins.

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 <sup>t</sup>Bu ester group that hampers the lactonization step. Moreover, the reactivity of *E*-enoates depends on the β-substituent. *E*-enoates **112c** ( $R^2 = \text{CH}_2\text{CHMe}_2$ ,





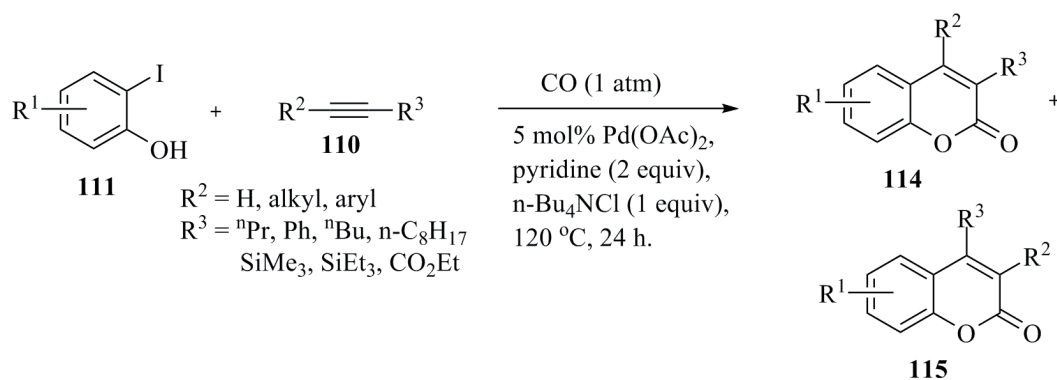
Condition A: 10 mol% of  $\text{Pd}(\text{OAc})_2$ , 3 equiv  $\text{Et}_3\text{N}$ ,  $\text{H}_2\text{O}$ , 80 °C, 40 h.

Condition B: 10 mol% of  $\text{PdCl}_2$ , 3 equiv  $\text{Et}_3\text{N}$ ,  $\text{H}_2\text{O}$ , 80 °C, 40 h.

Condition C: 10 mol% of  $\text{Pd}(\text{OAc})_2$ , in the presence or absence of 20 mol% of  $\text{PPh}_3$ , 3 equiv  $\text{AgCO}_3$ , acetone, reflux, 40 h.

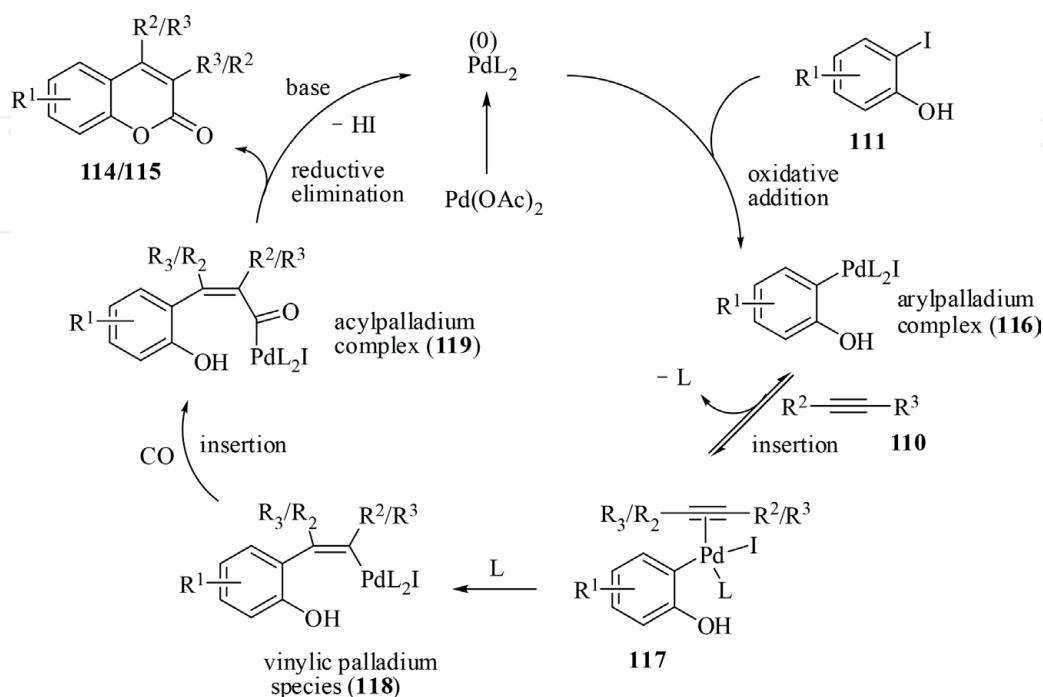
**Figure 32.**

Synthesis of 4,6-disubstituted coumarins.



**Figure 33.**

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



**Figure 34.**

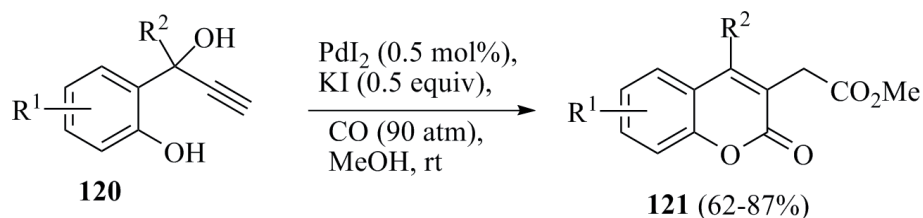
Possible mechanism for the synthesis of coumarins via carbonylative annulation.

$R^3 = \text{CH}_3$ ) and **112d** ( $R^2 = R^3 = \text{CH}_3$ ) having  $\text{CH}_2\text{CHMe}_2$  and  $\text{CH}_3$  group, respectively, at the  $\beta$ -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**.

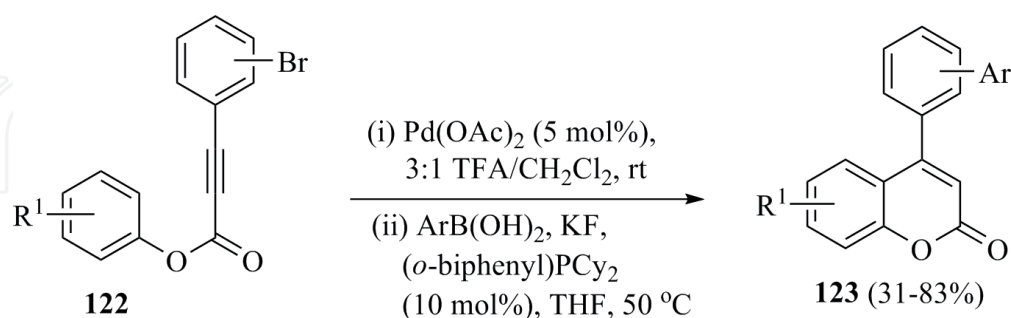
Palladium-catalyzed carbonylative annulation of terminal alkynes **110** ( $R^2 = \text{H}$ ;  $R^3 = \text{}^n\text{Pr}$ ,  $\text{Ph}$ ,  $\text{SiMe}_3$ ,  $\text{SiEt}_3$ ,  $\text{CO}_2\text{Et}$ , etc.) with *o*-iodophenols **111** affords 3-substituted coumarins **114** ( $R^2 = \text{H}$ ) in poor yields (18–36%) (**Figure 33**) [124]. On the other hand, both 3- and 4-substituted coumarins **114** ( $R^2 = \text{H}$ ) and **115** ( $R^2 = \text{H}$ ) have been synthesized from *o*-iodophenols **111** and terminal alkynes **110** ( $R^2 = \text{H}$ ;  $R^3 = \text{}^n\text{C}_4\text{H}_9$ ,  $\text{}^n\text{C}_8\text{H}_{17}$ ) bearing long alkyl chain. In addition, a wide variety of 3,4-disubstituted coumarins **114/115** ( $R^2, R^3 \neq \text{H}$ ) have also been achieved in moderate to good yields (43–78%) via carbonylative annulation between *o*-iodophenols **111** and internal alkynes **110** ( $R^2, R^3 \neq \text{H}$ ) [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  $\text{Pd}(0)$ , (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  $\text{Pd}(0)$  catalyst.

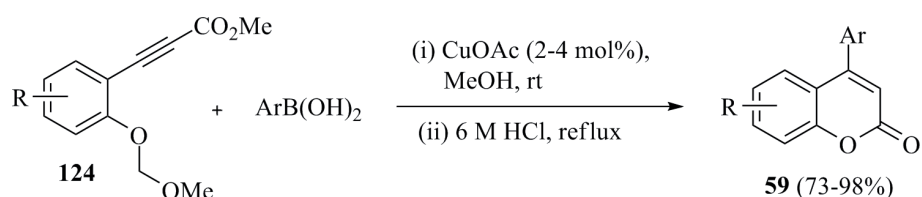
3,4-Disubstituted coumarins **121** are also isolated in good to excellent yields from readily available 2-(1-hydroxyprop-2-ynyl)phenols **120** via palladium-catalyzed



**Figure 35.**  
Synthesis of 3,4-disubstituted coumarins.



**Figure 36.**  
Synthesis of 4-arylcoumarins.



**Figure 37.**  
Synthesis of 4-arylcoumarins.

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)<sub>2</sub> could be used to conduct sequential reactions for the synthesis of substituted coumarins.

## 2.9 Other methods

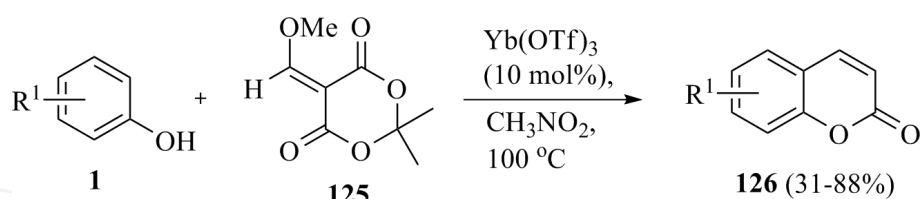
CuOAc-catalyzed hydroarylation of methyl phenylpropiolates **124** having a methoxy methyl (MOM)-protected hydroxyl group at the ortho-position with various arylboronic acids followed by acidic workup leads to 4-arylcoumarins **59** in good to excellent yields (**Figure 37**) [128].

Substituted coumarins **126** are obtained in moderate to excellent yields by Yb(OTf)<sub>3</sub>-catalyzed reactions of substituted phenols **1** with alkylidene Meldrum's acid **125** in CH<sub>3</sub>NO<sub>2</sub> at 100°C (**Figure 38**) [129].

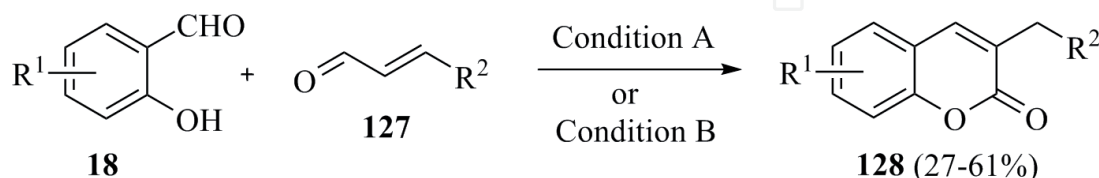
A series of 3-alkylcoumarins **128** are obtained in moderate yields from 2-hydroxybenzaldehydes **18** and  $\alpha,\beta$ -unsaturated aldehydes **127** via generation of *N*-heterocyclic carbenes (NHC) in ionic liquid under conventional heating (**Figure 39**, Condition A) and/or microwave irradiation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

3-Benzoylcoumarins **130/131** and coumarin-3-carbaldehydes **47** have also been isolated in moderate to good 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*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].



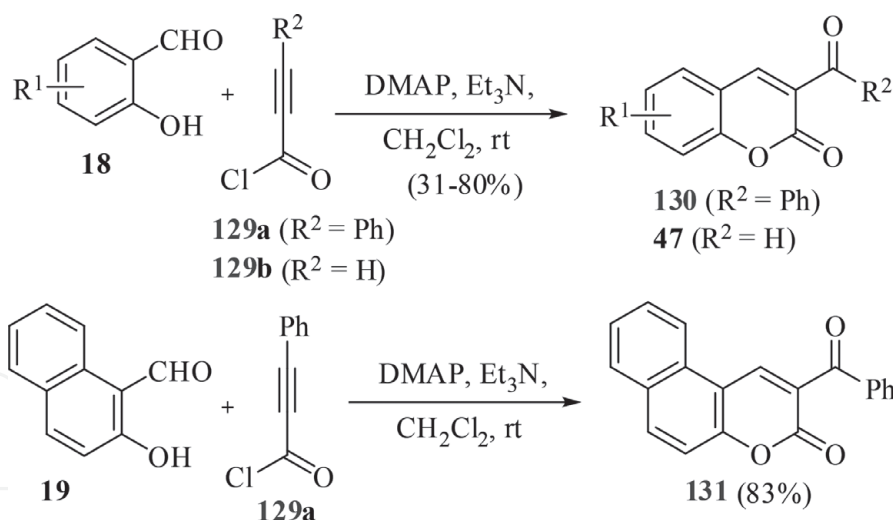
**Figure 38.**  
Synthesis of substituted coumarins.



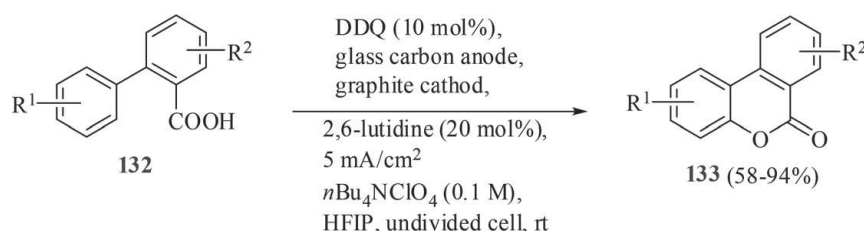
Condition A:  
Dimethyl 1,3-  
dimethylimidazolium  
phosphate, K<sub>2</sub>CO<sub>3</sub>,  
toluene, 100 °C

Condition B:  
Dimethyl 1,3-  
dimethylimidazolium  
phosphate, K<sub>2</sub>CO<sub>3</sub>,  
toluene, MW (200W)

**Figure 39.**  
Synthesis of 3-alkylcoumarins.



**Figure 40.**  
Synthesis of 3-benzoyl coumarins and coumarin-3-carbaldehyde.



**Figure 41.**  
Synthesis of 6H-benzo[c]chromen-6-ones.

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 bond 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.

## Acknowledgements

Dr. I. Ansary and Dr. A. Taher highly acknowledge the Department of Chemistry (Burdwan University) and Burdwan Raj College, respectively, for infrastructural facilities.

## Conflict of interest

The authors declare no conflict of interest.

## Author details

Inul Ansary<sup>1\*</sup> and Abu Taher<sup>2,3</sup>

1 Department of Chemistry, The University of Burdwan, Burdwan, West Bengal, India

2 Burdwan Raj College, Burdwan, West Bengal, India

3 Department of Chemistry, Bankura University, Bankura, West Bengal, India

\*Address all correspondence to: [iansary@chem.buruniv.ac.in](mailto:iansary@chem.buruniv.ac.in)

## IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 



## References

- [1] Kumar S, Saini A, Sandhu JS. LiBr-mediated, solvent free von Pechmann reaction: Facile and efficient method for the synthesis of 2H-chromen-2-ones. ARKIVOC. 2007;2007:18-23. DOI: 10.3998/ark.5550190.0008.f03
- [2] Zembower DE, Liao S, Flavin MT, Xu ZQ, Stup TL, Buckheit RW, et al. Structural analogues of the calanolide anti-HIV agents. Modification of the trans-10,11-dimethyldihydropyran-12-ol ring (ring C). Journal of Medicinal Chemistry. 1997;40:1005-1017. DOI: 10.1021/jm960355m
- [3] Završnik D, Muratović S, Makuc D, Plavec J, Cetina M, Nagl A, et al. Benzylidene-bis-(4-hydroxycoumarin) and benzopyranocoumarin derivatives: Synthesis,  $^1\text{H}/^{13}\text{C}$ -NMR conformational and X-ray crystal structure studies and in vitro antiviral activity evaluations. Molecules. 2011;16:6023-6040. DOI: 10.3390/molecules16076023
- [4] Nawrot-Modranka J, Nawrot E, Graczy K. In vivo antitumor, in vitro antibacterial activity and alkylating properties of phosphorohydrazine derivatives of coumarin and chromone. European Journal of Medicinal Chemistry. 2006;41:1301-1309. DOI: 10.1016/j.ejmech.2006.06.004
- [5] El-Saghier AMM, Naili MB, Rammash BK, Saleh NA, Kredan KM. Synthesis and antibacterial activity of some new fused chromenes. ARKIVOC. 2007;2007:83-91. DOI: 10.3998/ark.5550190.0008.g09
- [6] Creaven BS, Egan DA, Kavanagh K, McCann M, Mahon M, Noble A, et al. Synthesis and antimicrobial activity of copper(II) and silver(I) complexes of hydroxynitrocoumarins: X-ray crystal structures of  $[\text{Cu}(\text{hnc})_2(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O}$  and  $[\text{Ag}(\text{hnc})]$  ( $\text{hncH}$  = 4-hydroxy-3-nitro-2H-chromen-2-one). Polyhedron. 2005;24:949-957. DOI: 10.1016/j.poly.2005.03.006
- [7] Golfakhrabadi F, Abdollahi M, Ardakani MRS, Saeidnia S, Akbarzadeh T, Ahmadabadi AN, et al. Anticoagulant activity of isolated coumarins (suberosin and suberenol) and toxicity evaluation of *Ferulago carduchorum* in rats. Pharmaceutical Biology. 2014;52:1335-1340. DOI: 10.3109/13880209.2014.892140
- [8] Ronad P, Dharbamalla S, Hunshal R, Maddi V. Synthesis of novel substituted 7-(benzylideneamino)-4-methyl-2H-chromen-2-one derivatives as anti-inflammatory and analgesic agents. Archiv der Pharmazie: Chemistry in Life Sciences. 2008;341:696-700. DOI: 10.1002/ardp.200800057
- [9] Lin CM, Huang ST, Lee FW, Sawkuo H, Lin MH. 6-Acyl-4-aryl/alkyl-5,7-dihydroxycoumarins as anti-inflammatory agents. Bioorganic & Medicinal Chemistry. 2006;14:4402-4409. DOI: 10.1016/j.bmc.2006.02.042
- [10] Wang CJ, Hsieh YJ, Chu CY, Lin YL, Tseng TH. Inhibition of cell cycle progression in human leukemia HL-60 cells by esculetin. Cancer Letters. 2002;183:163-168. DOI: 10.1016/S0304-3835(02)00031-9
- [11] Dexeus FH, Logothetis CJ, Sella A, Fitz K, Amato R, Reuben JM, et al. Phase II study of coumarin and cimetidine in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 1990;8:325-329. DOI: 10.1200/JCO.1990.8.2.325
- [12] Bhat MA, Siddiqui N, Khan SA. Synthesis of novel thioureido derivatives of sulfonamides and thiosemicarbazido derivatives of coumarin as potential anticonvulsant and analgesic agents. Indian Journal of Pharmaceutical



- Sciences. 2006;**68**:120-124. DOI: 10.4103/0250-474X.22984
- [13] Tyagi YK, Kumar A, Raj HG, Vohra P, Gupta G, Kumari R, et al. Synthesis of novel amino and acetyl amino-4-methylcoumarins and evaluation of their antioxidant activity. *European Journal of Medicinal Chemistry*. 2005;**40**:413-420. DOI: 10.1016/j.ejmech.2004.09.002
- [14] Sardari S, Mori Y, Horita K, Micetich RG, Nishibe S, Daneshmandi M. Synthesis and antifungal activity of coumarins and angular furanocoumarins. *Bioorganic & Medicinal Chemistry*. 1999;**7**:1933-1940. DOI: 10.1016/S0968-0896(99)00138-8
- [15] Stein AC, Alvarez S, Avancini C, Zacchino S, von Poser G. Antifungal activity of some coumarins obtained from species of *Pterocaulon* (Asteraceae). *Journal of Ethnopharmacology*. 2006;**107**:95-98. DOI: 10.1016/j.jep.2006.02.009
- [16] Chen Y, Zhang Q, Zhang B, Xia P, Xia Y, Yang Z-Y, et al. Anti-AIDS agents. Part 56: Synthesis and anti-HIV activity of 7-thia-di-O-(–)-camphanoyl-(+)-*cis*-khellactone (7-thia-DCK) analogs. *Bioorganic & Medicinal Chemistry*. 2004;**12**:6383-6387. DOI: 10.1016/j.bmc.2004.09.038
- [17] Cravotto G, Nano GM, Palmisano G, Tagliapietra S. An asymmetric approach to coumarin anticoagulants via hetero-Diels–Alder cycloaddition. *Tetrahedron: Asymmetry*. 2001;**12**:707-709. DOI: 10.1016/S0957-4166(01)00124-0
- [18] Fan GJ, Mar W, Park MK, Choi EW, Kim K, Kim S. A novel class of inhibitors for steroid 5 $\alpha$ -reductase: Synthesis and evaluation of umbelliferone derivatives. *Bioorganic & Medicinal Chemistry Letters*. 2001;**11**:2361-2363. DOI: 10.1016/S0960-894X(01)00429-2
- [19] Zahradnik M. The Production and Application of Fluorescent Brightening Agents. Chichester: John Wiley & Sons; 1992
- [20] Hepworth JD, Gabbutt CD, Heron BM. In: Katritzky AR, Rees CW, Scriven EFV, editors. *Comprehensive Heterocyclic Chemistry II*. Vol. 5. Oxford: Pergamon Press; 1996. pp. 301-350
- [21] Green GR, Evans JM, Vong AK. In: Katritzky AR, Rees CW, Scriven EFV, editors. *Comprehensive Heterocyclic Chemistry II*. Vol. 5. Oxford: Pergamon Press; 1996. pp. 469-500
- [22] O’Kennedy R, Coumarins TRD. *Biology, Applications and Mode of Action*. Chichester: John Wiley & Sons; 1997
- [23] Meuly WC, Kirk-Othmer. *Encyclopedia of Chemical Technology*. 3rd ed. Vol. 7. New York: John Wiley & Sons; 1979. p. 196
- [24] von Pechmann H, Duisberg C. Ueber die Verbindungen der Phenole mit Acetessigäther. *Berichte der Deutschen Chemischen Gesellschaft*. 1883;**16**:2119-2128. DOI: 10.1002/cber.188301602117
- [25] von Pechmann H, Duisberg C. Neue Bildungsweise der Cumarine. *Synthese des Daphnetins*. I. *Berichte der Deutschen Chemischen Gesellschaft*. 1884;**17**:929-979. DOI: 10.1002/cber.188401701248
- [26] Panetta A, Rapoport H. New syntheses of coumarins. *The Journal of Organic Chemistry*. 1982;**47**:946-950. DOI: 10.1021/jo00345a009
- [27] Miyano M, Dorn CR. Mirestrol. I. Preparation of the tricyclic intermediate. *The Journal of Organic Chemistry*. 1972;**37**:259-268. DOI: 10.1021/jo00967a017

- [28] Woods LL, Sapp J. A new one-step synthesis of substituted coumarins. *The Journal of Organic Chemistry*. 1962;**27**:3703-3705. DOI: 10.1021/jo01057a519
- [29] Sethna SM, Shah NM, Shah RC. Aluminium chloride, a new reagent for the condensation of  $\beta$ -ketonic esters with phenols. Part I. The condensations of methyl  $\beta$ -resorcyate,  $\beta$ -resorcylic acid, and resacetophenone with ethyl acetoacetate. *Journal of the Chemical Society*. 1938:228-232. DOI: 10.1039/JR9380000228
- [30] Corrie JET. A convenient synthesis of N-(7-dimethylamino-4-methylcoumarin-3-yl)-maleimide incorporating a novel variant of the Pechmann reaction. *Journal of the Chemical Society. Perkin Transactions*. 1990;(7):2151-2152. DOI: 10.1039/P19900002151
- [31] Smitha G, Reddy SC. ZrCl<sub>4</sub>-catalyzed Pechmann reaction: Synthesis of coumarins under solvent-free conditions. *Synthetic Communications*. 2004;**34**:3997-4003. DOI: 10.1081/SCC-200034821
- [32] Valizadeh H, Shockravi A. An efficient procedure for the synthesis of coumarin derivatives using TiCl<sub>4</sub> as catalyst under solvent-free conditions. *Tetrahedron Letters*. 2005;**46**:3501-3503. DOI: 10.1016/j.tetlet.2005.03.124
- [33] John EVO, Israelstam SS. Notes. Use of cation exchange resins in organic reactions. I. The Von Pechmann reaction. *The Journal of Organic Chemistry*. 1961;**26**:240-242. DOI: 10.1021/jo01060a602
- [34] Laufer MC, Hausmann H, Hölderich WF. Synthesis of 7-hydroxycoumarins by Pechmann reaction using Nafion resin/silica nanocomposites as catalysts. *Journal of Catalysis*. 2003;**218**:315-320. DOI: 10.1016/S0021-9517(03)00073-3
- [35] Hoefnagel AJ, Gunnewegh EA, Downing RS, van Bekkum H. Synthesis of 7-hydroxycoumarins catalysed by solid acid catalysts. *Journal of the Chemical Society, Chemical Communications*. 1995:225-226. DOI: 10.1039/C39950000225
- [36] Chavan SP, Shivasankar K, Sivappa R, Kale R. Zinc mediated transesterification of  $\beta$ -ketoesters and coumarin synthesis. *Tetrahedron Letters*. 2002;**43**:8583-8586. DOI: 10.1016/S0040-4039(02)02006-3
- [37] Singh V, Singh J, Kaur KP, Kad GL. Acceleration of the Pechmann reaction by microwave irradiation: Application to the preparation of coumarins. *Journal of Chemical Research, Synopses*. 1997:58-59. DOI: 10.1039/A605672E
- [38] Maheswara M, Siddaiah V, Damu GLV, Rao YK, Rao CV. A solvent-free synthesis of coumarins via Pechmann condensation using heterogeneous catalyst. *Journal of Molecular Catalysis A: Chemical*. 2006;**255**:49-52. DOI: 10.1016/j.molcata.2006.03.051
- [39] Holden MS, Crouch RD. The Pechmann reaction. *Journal of Chemical Education*. 1998;**75**:1631. DOI: 10.1021/ed075p1631
- [40] Li T-S, Zhang Z-H, Yang F, Fu C-G. Montmorillonite clay catalysis. Part 7. An environmentally friendly procedure for the synthesis of coumarins via Pechmann condensation of phenols with ethyl acetoacetate. *Journal of Chemical Research, Synopses*. 1998:38-39. DOI: 10.1039/a703694i
- [41] Potdar MK, Mohile SS, Salunkhe MM. Coumarin syntheses via Pechmann condensation in Lewis acidic chloroaluminate ionic liquid. *Tetrahedron Letters*. 2001;**42**:9285-9287. DOI: 10.1016/S0040-4039(01)02041-X

- [42] Bose DS, Rudradas AP, Babu MH. The indium(III) chloride-catalyzed von Pechmann reaction: A simple and effective procedure for the synthesis of 4-substituted coumarins. *Tetrahedron Letters*. 2002;**43**:9195-9197. DOI: 10.1016/S0040-4039(02)02266-9
- [43] Potdar MK, Rasalkar MS, Mohile SS, Salunkhe MM. Convenient and efficient protocols for coumarin synthesis via Pechmann condensation in neutral ionic liquids. *Journal of Molecular Catalysis A: Chemical*. 2005;**235**:249-252. DOI: 10.1016/j.molcata.2005.04.007
- [44] Alexander VM, Bhat RP, Samant SD. Bismuth(III) nitrate pentahydrate—A mild and inexpensive reagent for synthesis of coumarins under mild conditions. *Tetrahedron Letters*. 2005;**46**:6957-6959. DOI: 10.1016/j.tetlet.2005.07.117
- [45] Reddy BM, Patil MK, Lakshmanan P. Sulfated  $\text{Ce}_x\text{Zr}_{1-x}\text{O}_2$  solid acid catalyst for solvent free synthesis of coumarins. *Journal of Molecular Catalysis A: Chemical*. 2006;**256**:290-294. DOI: 10.1016/j.molcata.2006.05.001
- [46] Rodríguez-Domínguez JC, Kirsch G. Sulfated zirconia, a mild alternative to mineral acids in the synthesis of hydroxycoumarins. *Tetrahedron Letters*. 2006;**47**:3279-3281. DOI: 10.1016/j.tetlet.2006.03.030
- [47] Reddy YT, Sonar VN, Crooks PA, Dasari PK, Reddy PN, Rajitha B. Ceric ammonium nitrate (CAN): An efficient catalyst for the coumarin synthesis via Pechmann condensation using conventional heating and microwave irradiation. *Synthetic Communications*. 2008;**38**:2082-2088. DOI: 10.1080/00397910802029091
- [48] Kotharkar SA, Bahekar SS, Shinde DB. Chlorosulfonic acid-catalysed one-pot synthesis of coumarin. *Mendeleev Communications*. 2006;**16**:241-242. DOI: 10.1070/MC2006v016n04ABEH002256
- [49] Lakouraj MM, Bagheri N, Hasantabar V. Synthesis and application of nanocrystalline-cellulose-supported acid ionic liquid catalyst in Pechmann reaction. *International Journal of Carbohydrate Chemistry*. 2013;**2013**:1-8. DOI: 10.1155/2013/452580
- [50] Puri S, Kaur B, Parmar A, Kumar H. Ultrasound-promoted greener synthesis of 2H-chromen-2-ones catalyzed by copper perchlorate in solventless media. *Ultrasonics Sonochemistry*. 2009;**16**:705-707. DOI: 10.1016/j.ultsonch.2009.04.002
- [51] Ranjbar-Karimi R, Hashemi-Uderji S, Mousavi M. Selectfluor promoted environmental-friendly synthesis of 2H-chromen-2-ones derivatives under various reaction conditions. *Journal of the Iranian Chemical Society*. 2011;**8**:193-197. DOI: 10.1007/BF03246215
- [52] DeGrote J, Tyndall S, Wong KF, VanAlstine-Parris M. Synthesis of 7-alkoxy-4-trifluoromethylcoumarins via the von Pechmann reaction catalyzed by molecular iodine. *Tetrahedron Letters*. 2014;**55**:6715-6717. DOI: 10.1016/j.tetlet.2014.10.025
- [53] Prajapati D, Gohain M. Iodine a simple, effective and inexpensive catalyst for the synthesis of substituted coumarins. *Catalysis Letters*. 2007;**119**:59-63. DOI: 10.1007/s10562-007-9186-6
- [54] Wu J, Diao T, Sun W, Li Y. Expedition approach to coumarins via Pechmann reaction catalyzed by molecular iodine or AgOTf. *Synthetic Communications*. 2006;**36**:2949-2956. DOI: 10.1080/00397910600773692
- [55] Shirini F, Yahyazadeh A, Mohammadi K. A solvent-free synthesis of coumarins using 1,3-disulfonic



acid imidazolium hydrogen sulfate as a reusable and effective ionic liquid catalyst. *Research on Chemical Intermediates*. 2015;**41**:6207-6218. DOI: 10.1007/s11164-014-1733-3

[56] Zhang Y, Zhu A, Li Q, Li L, Zhao Y, Wang J. Cholinium ionic liquids as cheap and reusable catalysts for the synthesis of coumarins via Pechmann reaction under solvent-free conditions. *RSC Advances*. 2014;**4**:22946-22950. DOI: 10.1039/c4ra02227k

[57] Khalafi-Nezhad A, Haghighi SM, Panahi F. Nano-TiO<sub>2</sub> on dodecyl-sulfated silica: As an efficient heterogeneous Lewis acid-surfactant-combined catalyst (HLASC) for reaction in aqueous media. *ACS Sustainable Chemistry & Engineering*. 2013;**1**:1015-1023. DOI: 10.1021/sc4000913

[58] Karami B, Kiani M. ZrOCl<sub>2</sub>.8H<sub>2</sub>O/SiO<sub>2</sub>: An efficient and recyclable catalyst for the preparation of coumarin derivatives by Pechmann condensation reaction. *Catalysis Communications*. 2011;**14**:62-67. DOI: 10.1016/j.catcom.2011.07.002

[59] Ma Z, He M, Zhang H, Ma J, Yuan H. Hydrophobic perfluoroalkylsulfonylester solid acid as catalyst of esterification and Pechmann condensation. *Chinese Journal of Organic Chemistry*. 2014;**34**:2255-2261. DOI: 10.6023/cjoc201406027

[60] Palaniappa S, John A. A novel polyaniline-fluoroboric acid-dodecylhydrogensulfate salt: Versatile reusable polymer based solid acid catalyst for organic transformations. *Journal of Molecular Catalysis A: Chemical*. 2005;**233**:9-15. DOI: 10.1016/j.molcata.2005.02.002

[61] Dabiri M, Salehi P, Zolfigol MA, Baghbanzadeh M. Silica sulfuric acid as an efficient and reusable catalyst for the Pechmann synthesis of coumarins under solvent-free conditions. *Heterocycles*.

2007;**71**:677-682. DOI: 10.3987/COM-06-10956

[62] Ghodke S, Chudasama U. Solvent free synthesis of coumarins using environment friendly solid acid catalysts. *Applied Catalysis A: General*. 2013;**453**:219-226. DOI: 10.1016/j.apcata.2012.12.024

[63] Ahmed AI, El-Hakam SA, Elghany MAA, El-Yazeed WSA. Synthesis and characterization of new solid acid catalysts, H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> supported on nanoparticle tin oxide: An efficient catalyst for the preparation of 7-hydroxy-4-methylcoumarin. *Applied Catalysis A: General*. 2011;**407**:40-48. DOI: 10.1016/j.apcata.2011.08.020

[64] Albadi J, Shirini F, Abasi J, Armand N, Motaharizadeh T. A green, efficient and recyclable poly(4-vinylpyridine)-supported copper iodide catalyst for the synthesis of coumarin derivatives under solvent-free conditions. *C. R. Chimie*. 2013;**16**:407-411. DOI: 10.1016/j.crci.2012.10.002

[65] Rahmatpour A, Mohammadian S. An environmentally friendly, chemoselective, and efficient protocol for the preparation of coumarin derivatives by Pechman condensation reaction using new and reusable heterogeneous Lewis acid catalyst polystyrene-supported GaCl<sub>3</sub>. *C. R. Chimie*. 2013;**16**:271-278. DOI: 10.1016/j.crci.2013.01.006

[66] Karami B, Khodabakhshi S, Eskandari K. Alternative two-step route to khellactone analogues using silica tungstic acid and sodium hydrogen phosphate. *Chemical Papers*. 2013;**67**:474-478. DOI: 10.2478/s11696-013-0411-z

[67] Zareyee D, Serehneh M. Recyclable CMK-5 supported sulfonic acid as an environmentally benign catalyst for solvent-free one-pot construction of coumarin through Pechmann

condensation. *Journal of Molecular Catalysis A: Chemical*. 2014;**391**:88-91. DOI: 10.1016/j.molcata.2014.04.013

[68] Vahabi V, Hatamjafari F. Microwave assisted convenient one-pot synthesis of coumarin derivatives via Pechmann condensation catalyzed by  $\text{FeF}_3$  under solvent-free conditions and antimicrobial activities of the products. *Molecules*. 2014;**19**:13093-13103. DOI: 10.3390/molecules190913093

[69] Prousis KC, Avlonitis N, Heropoulos GA, Calogeropoulou T.  $\text{FeCl}_3$ -catalysed ultrasonic-assisted, solvent-free synthesis of 4-substituted coumarins. A useful complement to the Pechmann reaction. *Ultrasonics Sonochemistry*. 2014;**21**:937-942. DOI: 10.1016/j.ultsonch.2013.10.018

[70] Esfahani FK, Zareyee D, Yousefi R. Sulfonated core-shell magnetic nanoparticle ( $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{PrSO}_3\text{H}$ ) as a highly active and durable protonic acid catalyst; synthesis of coumarin derivatives through Pechmann reaction. *ChemCatChem*. 2014;**6**:3333-3337. DOI: 10.1002/cctc.201402547

[71] Baghbanian SM, Farhang M.  $\text{CuFe}_2\text{O}_4$  nanoparticles: A magnetically recoverable and reusable catalyst for the synthesis of coumarins via Pechmann reaction in water. *Synthetic Communications*. 2014;**44**:697-706. DOI: 10.1080/00397911.2013.835423

[72] Sharma RK, Monga Y, Puri A. Zirconium(IV)-modified silica@magnetic nanocomposites: Fabrication, characterization and application as efficient, selective and reusable nanocatalysts for Friedel-Crafts, Knoevenagel and Pechmann condensation reactions. *Catalysis Communications*. 2013;**35**:110-114. DOI: 10.1016/j.catcom.2013.02.016

[73] Kim J-C, Ryoo R, Opanasenko M, Shamzhy M, Čejka J. Mesoporous

MFI zeolite nanosponge as a high performance catalyst in the Pechmann condensation reaction. *ACS Catalysis*. 2015;**5**:2596-2604. DOI: 10.1021/cs502021a

[74] Karami B, Kiani M, Hoseini MA.  $\text{In}(\text{OTf})_3$  as a powerful and recyclable catalyst for Pechmann condensation without solvent. *Chinese Journal of Catalysis*. 2014;**35**:1206-1211. DOI: 10.1016/S1872-2067(14)60090-5

[75] Wang H. Magnesium bis(trifluoromethane)sulfonimide: An efficient catalyst for the synthesis of coumarins under solvent-free conditions. *Monatshefte fuer Chemie*. 2013;**144**:411-414. DOI: 10.1007/s00706-012-0823-4

[76] Khaligh NG. Ultrasound-assisted one-pot synthesis of substituted coumarins catalyzed by poly(4-vinylpyridinium) hydrogen sulfate as an efficient and reusable solid acid catalyst. *Ultrasonics Sonochemistry*. 2013;**20**:1062-1068. DOI: 10.1016/j.ultsonch.2013.01.001

[77] Mokhtary M, Najafizadeh F. Polyvinylpolypyrrolidone-bound boron trifluoride ( $\text{PVPP-BF}_3$ ); a mild and efficient catalyst for synthesis of 4-methyl coumarins via the Pechmann reaction. *C. R. Chimie*. 2012;**15**:530-532. DOI: 10.1016/j.crci.2012.03.004

[78] Opanasenko M, Shamzhy M, Čejka J. Solid acid catalysts for coumarin synthesis by the Pechmann reaction: MOFs versus zeolites. *ChemCatChem*. 2013;**5**:1024-1031. DOI: 10.1002/cctc.201200232

[79] Jadhav NH, Sakate SS, Rasal NK, Shinde DR, Pawar RA. Heterogeneously catalyzed Pechmann condensation employing the tailored  $\text{Zn}_{0.925}\text{Ti}_{0.075}\text{O}$  NPs: Synthesis of coumarin. *ACS Omega*. 2019;**4**:8522-8527. DOI: 10.1021/acsomega.9b00257

- [80] Zambare AS, Khan FAK, Zambare SP, Shinde SD, Sangshetti JN. Recent advances in the synthesis of coumarin derivatives via Pechmann condensation. *Current Organic Chemistry*. 2016;**20**:798-828. DOI: 10.2174/1385272820666151026224227
- [81] Kumar BV, Naik HSB, Girija D, Kumar BV. ZnO nanoparticle as catalyst for efficient green one-pot synthesis of coumarins through Knoevenagel condensation. *Journal of Chemical Sciences*. 2011;**123**:615-621. DOI: 10.1007/s12039-011-0133-0
- [82] Karami B, Farahi M, Khodabakhshi S. Rapid synthesis of novel and known coumarin-3-carboxylic acids using stannous chloride dihydrate under solvent-free conditions. *Helvetica Chimica Acta*. 2012;**95**:455-460. DOI: 10.1002/hlca.201100342
- [83] Sripathi SK, Logeeswari K. Synthesis of 3-aryl coumarin derivatives using ultrasound. *International Journal of Organic Chemistry*. 2013;**3**:42-47. DOI: 10.4236/ijoc.2013.31004
- [84] Nourmohammadian F, Norozy S. Application of non-corrosive acids in three-component, one-pot synthesis of commercial coumarin dye. *Progress in Color, Colorants and Coatings*. 2010;**03**:102-109. DOI: not available
- [85] Gholap SS, Deshmukh UP, Tambe MS. Synthesis and in-vitro antimicrobial screening of 3-cinnamoyl coumarin and 3-[3-(1H-indol-2-yl)-3-aryl-propanoyl]-2H-chromen-2-ones. *Iranian Journal of Catalysis*. 2013;**3**:171-176. DOI: not available
- [86] Shaabani A, Ghadari R, Rahmati A, Rezayan AH. Coumarin synthesis via Knoevenagel condensation reaction in 1,1,3,3-N,N,N',N'-tetramethylguanidinium trifluoroacetate ionic liquid. *Journal of the Iranian Chemical Society*. 2009;**6**:710-714. DOI: 10.1007/BF03246160
- [87] Verdía P, Santamarta F, Tojo E. Knoevenagel reaction in [MMIm][MSO<sub>4</sub>]: Synthesis of coumarins. *Molecules*. 2011;**16**:4379-4388. DOI: 10.3390/molecules16064379
- [88] Valizadeh H, Gholipour H. Imidazolium-based phosphinite ionic liquid (IL-OPPh<sub>2</sub>) as reusable catalyst and solvent for the Knoevenagel condensation reaction. *Synthetic Communications*. 2010;**40**:1477-1485. DOI: 10.1080/00397910903097310
- [89] Heravi MM, Ansari P, Saeedi M, Tavakoli-Hosseini N, Karimi N. Green and practical synthesis of benzopyran and 3-substituted coumarine derivatives by Bronsted acid ionic liquid [(CH<sub>2</sub>)<sub>4</sub>SO<sub>3</sub>HMIM][HSO<sub>4</sub>]. *Bulletin of the Chemical Society of Ethiopia*. 2011;**25**:315-320. DOI: 10.4314/bcse.v25i2.65915
- [90] Roussaki M, Kontogiorgis CA, Hadjipavlou-Litina D, Hamilakis S, Detsi A. A novel synthesis of 3-aryl coumarins and evaluation of their antioxidant and lipoxygenase inhibitory activity. *Bioorganic & Medicinal Chemistry Letters*. 2010;**20**:3889-3892. DOI: 10.1016/j.bmcl.2010.05.022
- [91] Nourmohammadian F, Gholami MD. Microwave-promoted one-pot syntheses of coumarin dyes. *Synthetic Communications*. 2010;**40**:901-909. DOI: 10.1080/00397910903026699
- [92] Han J, Xin Y, Zhao J, Zhu S. L-Proline catalyzed condensation-cyclization tandem process: Facile and effective synthesis of 3-polyfluoroalkanesulfonyl coumarin. *Journal of Fluorine Chemistry*. 2011;**132**:409-413. DOI: 10.1016/j.jfluchem.2011.04.001
- [93] You X, Yu H, Wang M, Wu J, Shang Z. A Green method for the



synthesis of 3-substituted coumarins catalyzed by L-lysine in water via Knoevenagel condensation. *Letters in Organic Chemistry*. 2012;**9**:19-23. DOI: 10.2174/157017812799303953

[94] Lunkad AS, Sawant RL. Conventional and microwave assisted synthesis of some new derivatives of coumarin containing pyrazoline and investigation of their antibacterial and antifungal activities. *International Journal of Pharmaceutical Sciences and Research*. 2018;**9**:2852-2858. DOI: 10.13040/IJPSR.0975-8232.9(7).2852-58

[95] Ajani OO, Nwinyi OC. Microwave-assisted synthesis and evaluation of antimicrobial activity of 3-{3-(s-aryl and s-heteroaromatic)acryloyl}-2H-chromen-2-one derivatives. *Journal of Heterocyclic Chemistry*. 2010;**47**:179-187. DOI: 10.1002/jhet.298

[96] Sashidhara KV, Kumar A, Kumar M, Sonkar R, Bhatia G, Khanna A. Novel coumarin derivatives as potential antidyslipidemic agents. *Bioorganic & Medicinal Chemistry Letters*. 2010;**20**:4248-4251. DOI: 10.1016/j.bmcl.2010.05.023

[97] Bhusal RP, Cho PY, Kim SA, Park H, Kim HS. Synthesis of green emitting coumarin bioconjugate for the selective determination of flu antigen. *Bulletin of the Korean Chemical Society*. 2011;**32**:1461-1462. DOI: 10.5012/bkcs.2011.32.5.1461

[98] De Souza M, da Silveira Pinto L. Sonochemistry as a general procedure for the synthesis of coumarins, including multigram synthesis. *Synthesis*. 2017;**49**:2677-2682. DOI: 10.1055/s-0036-1590201

[99] El-Wahab AHFA, Mohamed HM, El-Agrody AM, Bedair AH, Eid FA, Khafagy MM, et al. Synthesis and reactions of some new diiodocoumarin derivatives bearing side chains and some

of their biological activities. *American Journal of Chemistry*. 2011;**1**:1-8. DOI: 10.5923/j.chemistry.20110101.01

[100] Mohamed HM, Abd El-Wahab AHF, Ahmed KA, El-Agrody AM, Bedair AH, Eid FA, et al. Synthesis, reactions and antimicrobial activities of 8-ethoxycoumarin derivatives. *Molecules*. 2012;**17**:971-988. DOI: 10.3390/molecules17010971

[101] Kaye PT, Robinson RS. Dabco-catalysed reactions of salicylaldehydes with acrylate derivatives. *Synthetic Communications*. 1996;**26**:2085-2097. DOI: 10.1080/00397919608003567

[102] Bacsa J, Kaye PT, Robinson RS. Novel products from Baylis-Hillman reactions of salicylaldehydes. *South African Journal of Chemistry*. 1998;**51**:47-54. Available at: [https://hdl.handle.net/10520/AJA03794350\\_1721](https://hdl.handle.net/10520/AJA03794350_1721)

[103] Kaye PT, Musa MA, Nocanda XW. Efficient and chemoselective access to 3-(chloromethyl)coumarins via direct cyclisation of unprotected Baylis-Hillman adducts. *Synthesis*. 2003;**2003**:531-534. DOI: 10.1055/s-2003-37655

[104] Olomola TO, Klein R, Kaye PT. Convenient synthesis of 3-methylcoumarins and coumarin-3-carbaldehydes. *Synthetic Communications*. 2012;**42**:251-257. DOI: 10.1080/00397911.2010.523491

[105] Kaye PT, Musa MA. A convenient and improved Baylis-Hillman synthesis of 3-substituted 2H-1-benzopyran-2-ones. *Synthesis*. 2002;**2002**:2701-2706. DOI: 10.1055/s-2002-35984

[106] Kaye PT, Musa MA. Application of Baylis-Hillman methodology in the synthesis of coumarin derivatives. *Synthetic Communications*. 2003;**33**:1755-1770. DOI: 10.1081/SCC-120018937

- [107] Hwang I-T, Lee S-A, Hwang J-S, Lee K-I. A facile synthesis of highly functionalized 4-arylcoumarins via Kostanecki reactions mediated by DBU. *Molecules*. 2011;**16**:6313-6321. DOI: 10.3390/molecules16086313
- [108] Rao HSP, Sivakumar S. Condensation of  $\alpha$ -aroylketene dithioacetals and 2-hydroxyarylaldehydes results in facile synthesis of a combinatorial library of 3-aroylcoumarins. *The Journal of Organic Chemistry*. 2006;**71**:8715-8723. DOI: 10.1021/jo061372e
- [109] Upadhyay PK, Kumar P. A novel synthesis of coumarins employing triphenyl( $\alpha$ -carboxymethylene)-phosphorane imidazolide as a C-2 synthon. *Tetrahedron Letters*. 2009;**50**:236-238. DOI: 10.1016/j.tetlet.2008.10.133
- [110] Valizadeh H, Gholipour H, Mahmoudian M. Phosphinite ionic liquid (IL-OPPh<sub>2</sub>) as a recyclable reagent for the efficient synthesis of coumarins under microwave irradiation conditions. *Journal of the Iranian Chemical Society*. 2011;**8**:862-871. DOI: 10.1007/BF03245917
- [111] Yavari I, Hekmatshoar R, Zonouzi A. A new and efficient route to 4-carboxymethylcoumarins mediated by vinyltriphenylphosphonium salt. *Tetrahedron Letters*. 1998;**39**:2391-2392. DOI: 10.1016/S0040-4039(98)00206-8
- [112] Hekmatshoar R, Souri S, Rahimifard M, Faridbod F. Novel synthesis of oxygenated coumarins from substituted phenols mediated by vinyl triphenylphosphonium salt under microwave irradiation. *Phosphorus, Sulfur and Silicon*. 2002;**177**:2827-2833. DOI: 10.1080/10426500214882
- [113] Yavari I, Adib M, Hojabri L. Vinyltriphenylphosphonium salt mediated synthesis of functionalized coumarins. *Tetrahedron*. 2001;**57**:7537-7540. DOI: 10.1016/S0040-4020(01)00703-7
- [114] Majumdar KC, Ansary I, Samanta S, Roy B. Aromatic electrophilic substitution vs. intramolecular Wittig reaction: Vinyltriphenylphosphonium salt mediated synthesis of 4-carboxyalkyl-8-formyl coumarins. *Synlett*. 2011;**2011**:0694-0698. DOI: 10.1055/s-0030-1259534
- [115] Galariniotou E, Fragos V, Makri A, Litinas KE, Nicolaides DN. Synthesis of novel pyridocoumarins and benzo-fused 6-azacoumarins. *Tetrahedron*. 2007;**63**:8298-8304. DOI: 10.1016/j.tet.2007.05.102
- [116] Trost BM, Toste FD. A new palladium-catalyzed addition: A mild method for the synthesis of coumarins. *Journal of the American Chemical Society*. 1996;**118**:6305-6306. DOI: 10.1021/ja961107i
- [117] Trost BM, Toste FD, Greenman K. Atom economy. Palladium-catalyzed formation of coumarins by addition of phenols and alkynoates via a net C-H insertion. *Journal of the American Chemical Society*. 2003;**125**:4518-4526. DOI: 10.1021/ja0286573
- [118] Kotani M, Yamamoto K, Oyamada J, Fujiwara Y, Kitamura T. A convenient synthesis of coumarins by palladium(II)-catalyzed reaction of phenols with propiolic acids. *Synthesis*. 2004;**2004**:1466-1470. DOI: 10.1055/s-2004-822360
- [119] Kutubi Md S, Hashimoto T, Kitamura T. Improved synthesis of coumarins by iron(III)-catalyzed cascade reaction of propiolic acids and phenols. *Synthesis*. 2011;**2011**:1283-1289. DOI: 10.1055/s-0030-1258473
- [120] Park KH, Jung IG, Chung YK. Synthesis of coumarins catalyzed by

heterobimetallic Co/Rh nanoparticles. *Synlett.* 2004;**2004**:2541-2544. DOI: 10.1055/s-2004-834826

[121] Leão RAC, De Moraes PF, Pedro MCBC, Costa PRR. Synthesis of coumarins and neoflavones through zinc chloride catalyzed hydroarylation of acetylenic esters with phenols. *Synthesis.* 2011;**2011**:3692-3696. DOI: 10.1055/s-0031-1289576

[122] Fernandes TA, Carvalho RCC, Goncalves TMD, da Silva AJM, Costa PRR. A tandem palladium-catalyzed heck-lactonization through the reaction of ortho-iodophenols with b-substituted acrylates: Synthesis of 4,6-substituted coumarins. *Tetrahedron Letters.* 2008;**49**:3322-3325. DOI: 10.1016/j.tetlet.2008.03.037

[123] Fernandes TA, Vaz BG, Eberlin MN, da Silva AJM, Costa PRR. Palladium-catalyzed tandem Heck-lactonization from o-iodophenols and enoates: Synthesis of coumarins and the study of the mechanism by electrospray ionization mass spectrometry. *The Journal of Organic Chemistry.* 2010;**75**:7085-7091. DOI: 10.1021/jo1010922

[124] Kadnikov DV, Larock RC. Palladium-catalyzed carbonylative annulation of terminal alkynes: Synthesis of coumarins and 2-quinolones. *Journal of Organometallic Chemistry.* 2003;**687**:425-435. DOI: 10.1016/S0022-328X(03)00786-1

[125] Kadnikov DV, Larock RC. Palladium-catalyzed carbonylative annulation of internal alkynes: Synthesis of 3,4-disubstituted coumarins. *The Journal of Organic Chemistry.* 2003;**68**:9423-9432. DOI: 10.1021/jo0350763

[126] Gabriele B, Mancuso R, Salerno G, Plastina P. A novel palladium-catalyzed dicarbonylation process leading to coumarins. *The Journal of Organic*

*Chemistry.* 2008;**73**:756-759. DOI: 10.1021/jo702243m

[127] Li K, Zeng Y, Neuenswander B, Tunge JA. Sequential Pd(II)-Pd(0) catalysis for the rapid synthesis of coumarins. *The Journal of Organic Chemistry.* 2005;**70**:6515-6518. DOI: 10.1021/jo050671l

[128] Yamamoto Y, Kirai N. Synthesis of 4-aryl coumarins via Cu-catalyzed hydroarylation with arylboronic acids. *Organic Letters.* 2008;**10**:5513-5516. DOI: 10.1021/ol802239n

[129] Fillion E, Dumas AM, Kuropatwa BA, Malhotra NR, Sitler TC. Yb(OTf)<sub>3</sub>-catalyzed reactions of 5-alkylidene Meldrum's acids with phenols: One-pot assembly of 3,4-dihydrocoumarins, 4-chromanones, coumarins, and chromones. *The Journal of Organic Chemistry.* 2006;**71**:409-412. DOI: 10.1021/jo052000t

[130] Toräng J, Vanderheiden S, Nieger M, Bräse S. Synthesis of 3-alkyl coumarins from salicylaldehydes and  $\alpha,\beta$ -unsaturated aldehydes utilizing nucleophilic carbenes: A new umpoled domino reaction. *European Journal of Organic Chemistry.* 2007;**2007**:943-952. DOI: 10.1002/ejoc.200600718

[131] Majumdar KC, Samanta S, Ansary I, Roy B. An unusual one-pot synthesis of 3-benzoyl coumarins and coumarin-3-carbaldehydes from 2-hydroxybenzaldehydes under esterification conditions. *RSC Advances.* 2012;**2**:2137-2143. DOI: 10.1039/C2RA00820C

[132] Li L, Yang Q, Jia Z, Luo S. Organocatalytic electrochemical C-H lactonization of aromatic carboxylic acids. *Synthesis.* 2018;**50**:2924-2929. DOI: 10.1055/s-0036-1591558