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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 α -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 H₂SO₄ [24, 25], trifluoroacetic acid (TFA) [28], and Lewis acids (LA) such as AlCl₃ [29], ZnCl₂ [30], ZrCl₄ [31], TiCl₄ [32], etc. and heterogeneous catalysts such as cation-exchange resins [33], Nafion resin/silica composites [34], zeolite H-BEA (H-beta, SiO₂/Al₂O₃ = 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 **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 NO_2 group.

When 3-(*N,N*-dimethylamino)phenol **9** is subjected to react with ethyl 2-acetamide-3-oxobutyrate **10** in the presence of anhydrous 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 H_2SO_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 β -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**.

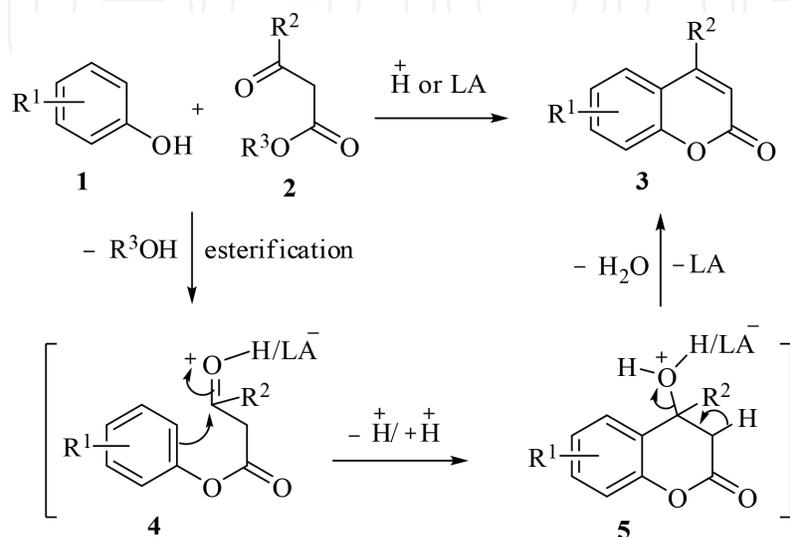


Figure 1.
Mechanism for the acid-catalyzed Pechmann condensation.

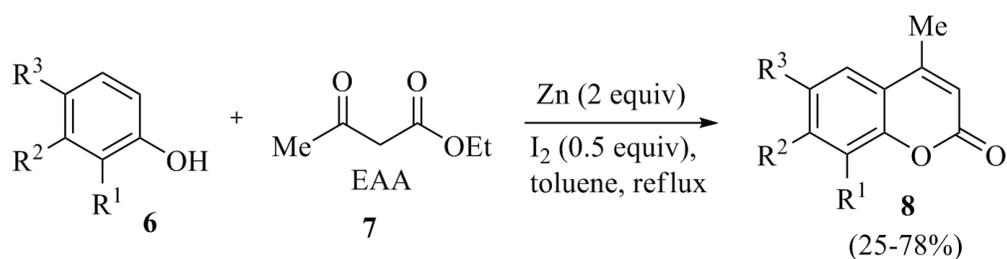


Figure 2.
 Synthesis of substituted coumarins.

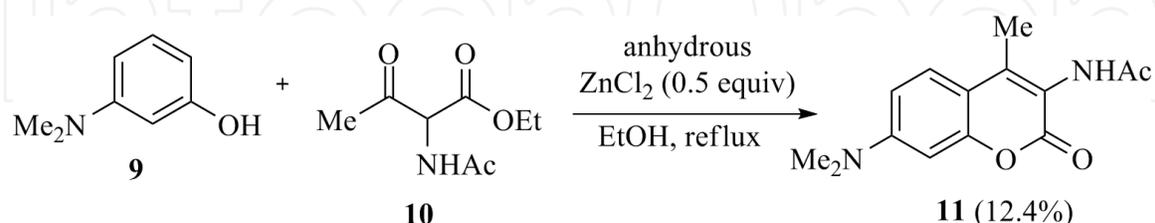


Figure 3.
 Synthesis of acetamido coumarin.

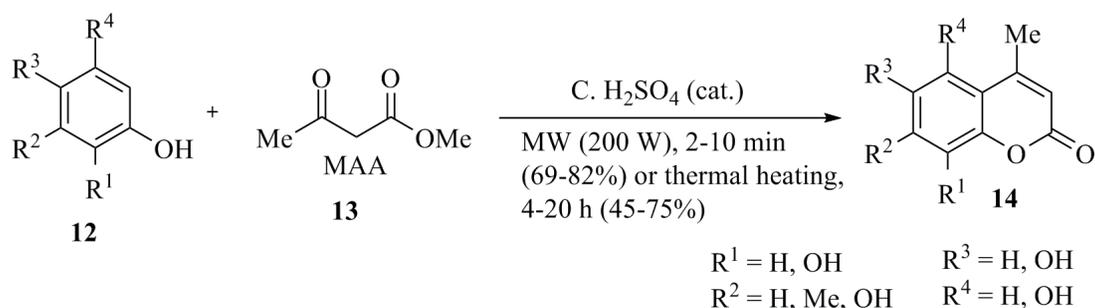


Figure 4.
 Synthesis of substituted coumarins.

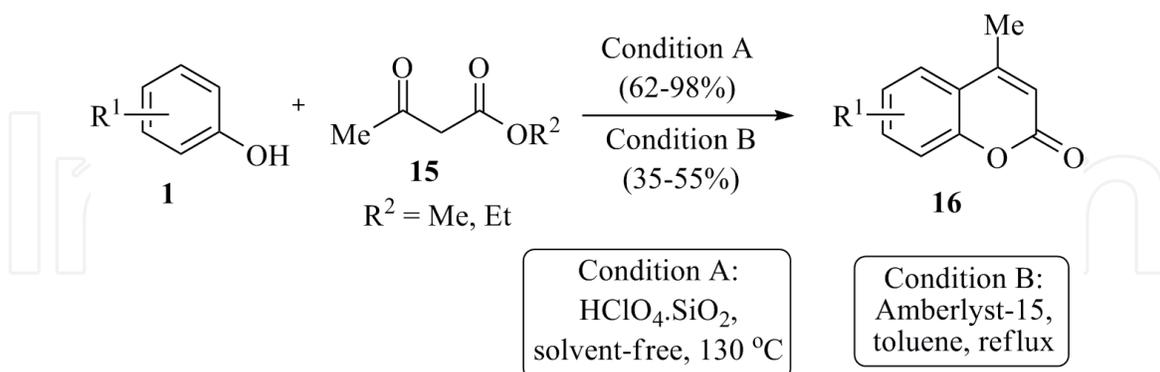


Figure 5.
 Synthesis of substituted coumarins.

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

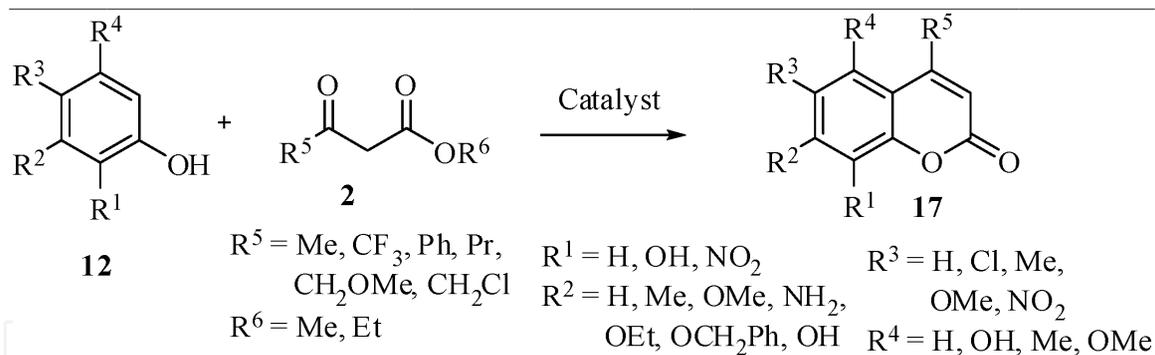
addition, the substitution of an electron-donating group such as *m/p*-Me or *p*-OMe in the phenols leads to decrease of catalytic activity and, hence, requires longer reaction time and/or gives rise to lower yields of products (entry 13). The reactivity of monohydric phenols having electron-withdrawing groups such as *m*-NH₂ 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 β -keto ester, ethyl 4-chloro-3-oxobutanoate (entry 37). It is interesting to note that β -keto ester having phenyl group at the β -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 β -keto esters, catalyst efficiency, and solvent effect of Pechmann condensation has also been studied. It is observed that TiCl₄ (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]PF₆ 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-TiO₂ 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 (Fe₃O₄@SiO₂@PrSO₃H), CuFe₂O₄ 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
1	Montmorillonite K-10	K-10 (30 wt% of 12), toluene, reflux	8–10 h	66–94	[40]
2	1-Butyl-3-methylimidazolium chloroaluminate [bmim] Cl. 2AlCl ₃	[bmim]Cl.2AlCl ₃ (1.1 equiv. of 12), 30–120°C	10–120 min	40–95	[41]
3	InCl ₃	InCl ₃ (10 mol%), 65–130°C	30–240 min	65–98	[42]
4	ZrCl ₄	ZrCl ₄ (2 mol%), 70°C	5–30 min	56–95	[31]
5	TiCl ₄	TiCl ₄ (0.5 equiv. of 12), rt	50–70 s	56–95	[32]
6	1-Butyl-3-methylimidazolium hexafluorophosphate [bmim]PF ₆	[bmim]PF ₆ (4 ml), solvent-free, 100°C	45 min	90–95	[43]
7	Bi(NO ₃) ₃ ·5H ₂ O	Bi(NO ₃) ₃ ·5H ₂ O (5–10 mol%), 80–130°C	15–300 min	47–94	[44]
8	SO ₄ ²⁻ /CeO ₂ -ZrO ₂	SO ₄ ²⁻ /CeO ₂ -ZrO ₂ (10 wt% of 12), 120°C	4–143 min	80–94	[45]
9	SZr (sulfated zirconia)	SZr (1 wt% of 12), 80°C	24 h	52–92	[46]
10	Ceric ammonium nitrate (CAN)	Condition A: CAN (10 mol%), solvent-free, 110°C Condition B: CAN (10 mol%), solvent-free, MW (300 W)	10–15 min 2–3 min	92–96 94–97	[47]
11	ClSO ₃ H	ClSO ₃ H (0.2 ml), solvent-free, 10°C	10 min	91–98	[48]
12	LiBr	LiBr (10–20 mol%), 75–125°C	15–90 min	54–92	[1]
13	Nanocrystalline-cellulose-supported sulfonic acid ionic liquid	NCC-supported sulfonic acid IL (10 wt% of 12), solvent-free, 80°C	18 min–24 h	20–98	[49]
14	Cu(ClO ₄) ₂	Cu(ClO ₄) ₂ (20 mol%), solvent-free, US (35 kHz), 45–50°C	30–50 min	70–96	[50]
15	Selectfluor	Condition A: Selectfluor (10 mol%), solvent-free, rt. Condition B: Selectfluor (10 mol%), solvent-free, US (30 kHz, 780 W)	85–90 min 15–40 min	70–79 82–94	[51]

Entry	Catalyst	Reaction conditions	Time	Yields (%)	Reference
16	I ₂	Condition A: I ₂ (25 mol%), toluene, 90°C	18 h	42–89	[52]
		Condition B: I ₂ (1 mol%), MW	1.5–5 min	80–96	[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 ₁₁₂ OH] [HSO ₄])	[N ₁₁₂ OH][HSO ₄] (5 mol%), solvent-free, 90°C	3–24 h	20–99	[56]
20	Nano-TiO ₂ on dodecyl- sulfated silica support (NTDSS)	NTDSS (5 mol% TiO ₂), H ₂ O, reflux	3–8 h	89–98	[57]
21	ZrOCl ₂ .8H ₂ O/SiO ₂	ZrOCl ₂ .8H ₂ O/SiO ₂ (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 ₄ –DHS)	PANI–HBF ₄ –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 ₂ (12-Tungstophosphoric acid supported onto ZrO ₂)	Condition A: ZrPW (0.2 g), solvent-free, 130°C	8 h	42–65	[62]
		Condition B: ZrPW (0.2 g), solvent-free, MW (250 W), 130°C	30 min	47–66	
		Condition C: 12-TPA/ ZrO ₂ (0.2 g), solvent- free, 130°C	8 h	38–63	
		Condition D: 12-TPA/ ZrO ₂ (0.2 g), solvent- free, MW (250 W), 130°C	30 min	41–65	
26	12-Tungstophosphoric acid supported on SnO ₂ nanoparticles (12-TPA-SnO ₂)	12-TPA-SnO ₂ (30 wt% of TPA), solvent-free, 120°C	2 h	78	[63]
27	Poly(4-vinylpyridine)- supported copper iodide	P ₄ VPy-CuI (0.1 g), solvent-free, 80°C	10–90 min	84–92	[64]
28	Polystyrene-supported GaCl ₃ (PS–GaCl ₃)	PS–GaCl ₃ (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 ₃ H)	CMK-5-SO ₃ H (3 mol%), solvent-free, 130°C	15–120 min	60–97	[67]
31	FeF ₃	FeF ₃ (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 ₃	FeCl ₃ (10 mol%), solvent-free, US (20 kHz, 130 W)	1–20 min	55–99	[69]
33	Sulfonic acid supported silica coated magnetic nanoparticles (Fe ₃ O ₄ @SiO ₂ @PrSO ₃ H)	Fe ₃ O ₄ @SiO ₂ @PrSO ₃ H (1.6 mol%), solvent-free, 130°C	3–50 min	87–98	[70]
34	CuFe ₂ O ₄ nanoparticles	CuFe ₂ O ₄ (5 mol%), H ₂ 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) ₃	In(OTf) ₃ (1 mol%), solvent-free, 80°C	10–87 min	68–98	[74]
38	Mg(NTf ₂) ₂	Mg(NTf ₂) ₂ (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	Polyvinylpyrrolidone-bound boron trifluoride (PVPP-BF ₃)	PVPP-BF ₃ (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 _{0.925} Ti _{0.075} O NPs	Zn _{0.925} Ti _{0.075} 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 K_2CO_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-phenylenediamine/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].

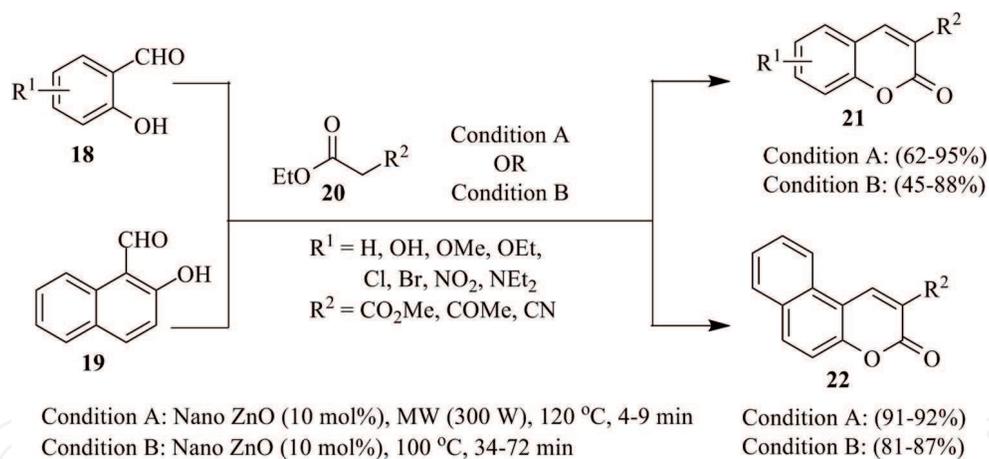


Figure 6.
Synthesis of 3-substituted coumarins.

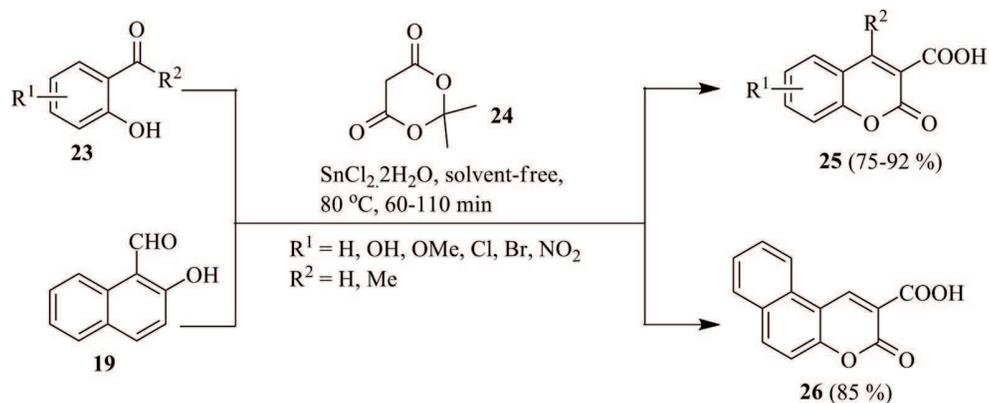


Figure 7.
Synthesis of coumarin 3-carboxylic acid derivatives.

Shaabani et al. [86] have described the synthesis of 3-substituted coumarins **21** in good yields via Knoevenagel condensation of 2-hydroxybenzaldehydes **18** with 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][MSO₄] 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-OPPh₂) 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-OPPh₂ 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 [(CH₂)₄SO₃HMIM][HSO₄] 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**.

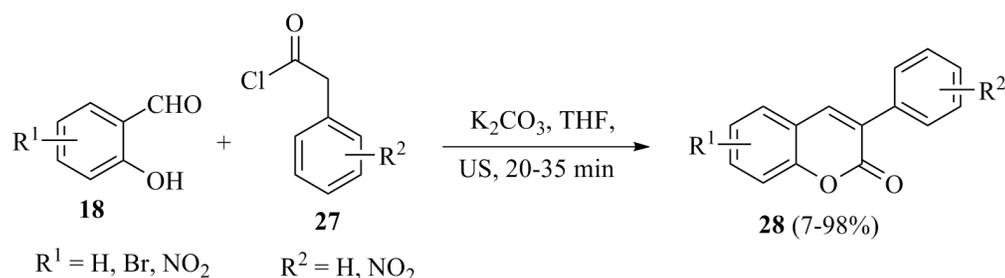


Figure 8.
 Synthesis of 3-aryl coumarin derivatives.

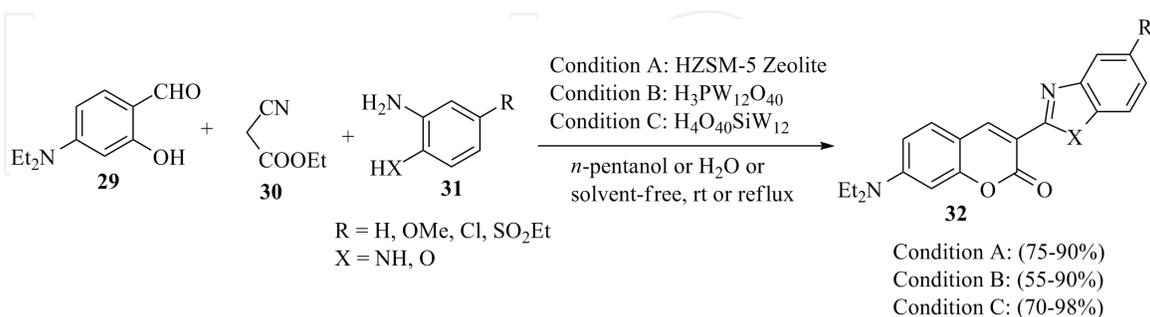


Figure 9.
 Synthesis of coumarin-substituted benzimidazoles/benzoxazoles.

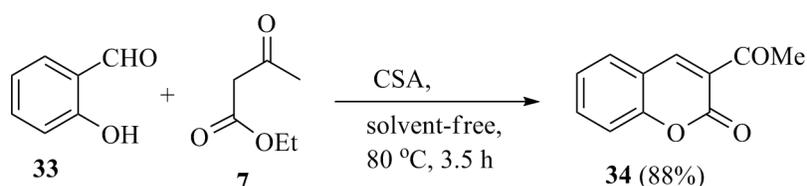


Figure 10.
 Synthesis of 3-acetyl coumarin.

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-dimethyl imidazolium methyl sulfate [MMIm][MSO₄] 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).

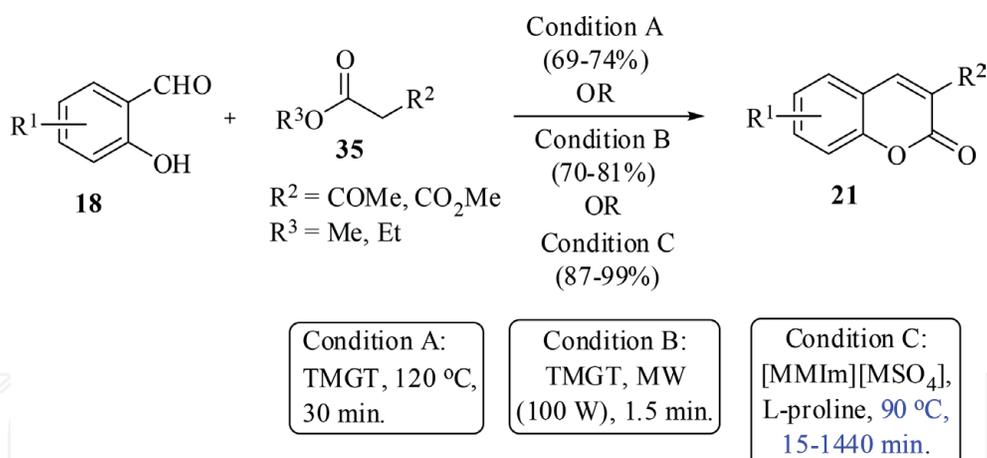


Figure 11.
Synthesis of 3-substituted coumarins.

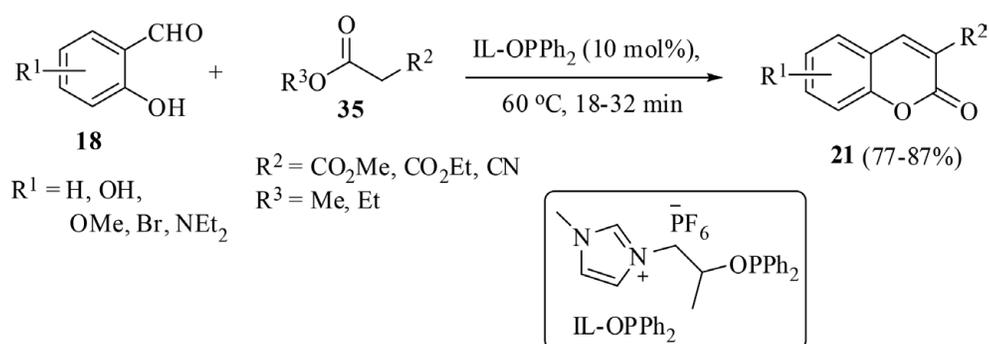


Figure 12.
Synthesis of 3-substituted coumarins.

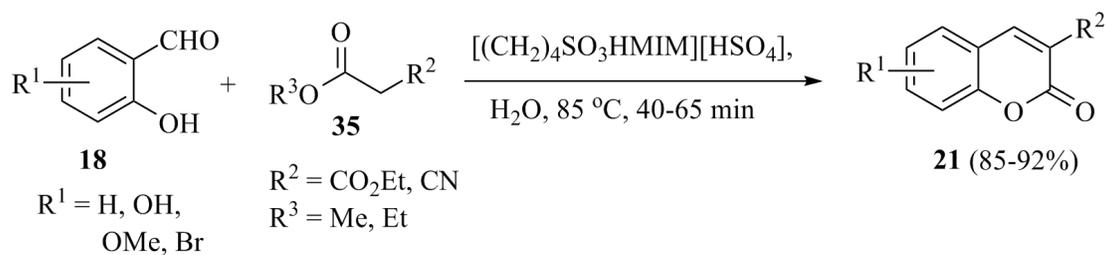
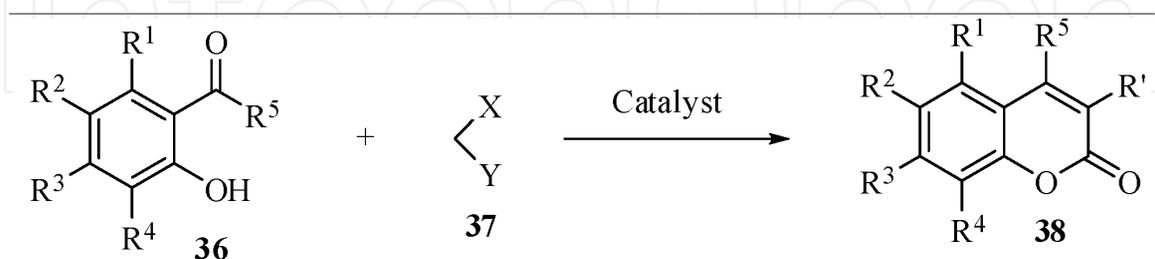


Figure 13.
 Synthesis of 3-substituted coumarins.



$\text{R}^1 = \text{H, OH, OMe, Cl, Br, NO}_2,$
 $\text{R}^2 = \text{H, Me, OMe, CO}_2\text{Et, CN, Br, I}$
 $\text{R}^3 = \text{H, Cl, Br, NEt}_2, \text{OH, OMe, NO}_2$
 $\text{R}^4 = \text{Me, OMe, OEt, I}$
 $\text{R}^5 = \text{H, Me}$

$\text{X} = \text{H, Me, CN, CO}_2\text{H, CO}_2\text{Me, CO}_2\text{Et, COMe, COPh, SO}_2\text{Me, SO}_2\text{Ph, SO}_2\text{C}_4\text{F}_9, \text{CONH}_2$
 $\text{Y} = \text{CN, CO}_2\text{Me, CO}_2\text{Et, aryl}$
 $\text{R}' = \text{CN, COMe, CO}_2\text{H, CO}_2\text{Et, aryl}$

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 ₂ SO ₄ , 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 ₄], 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 ₂ 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 Ac_2O and AcOH furnishes 3-methyl coumarins **46**, which upon further reaction with 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 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)

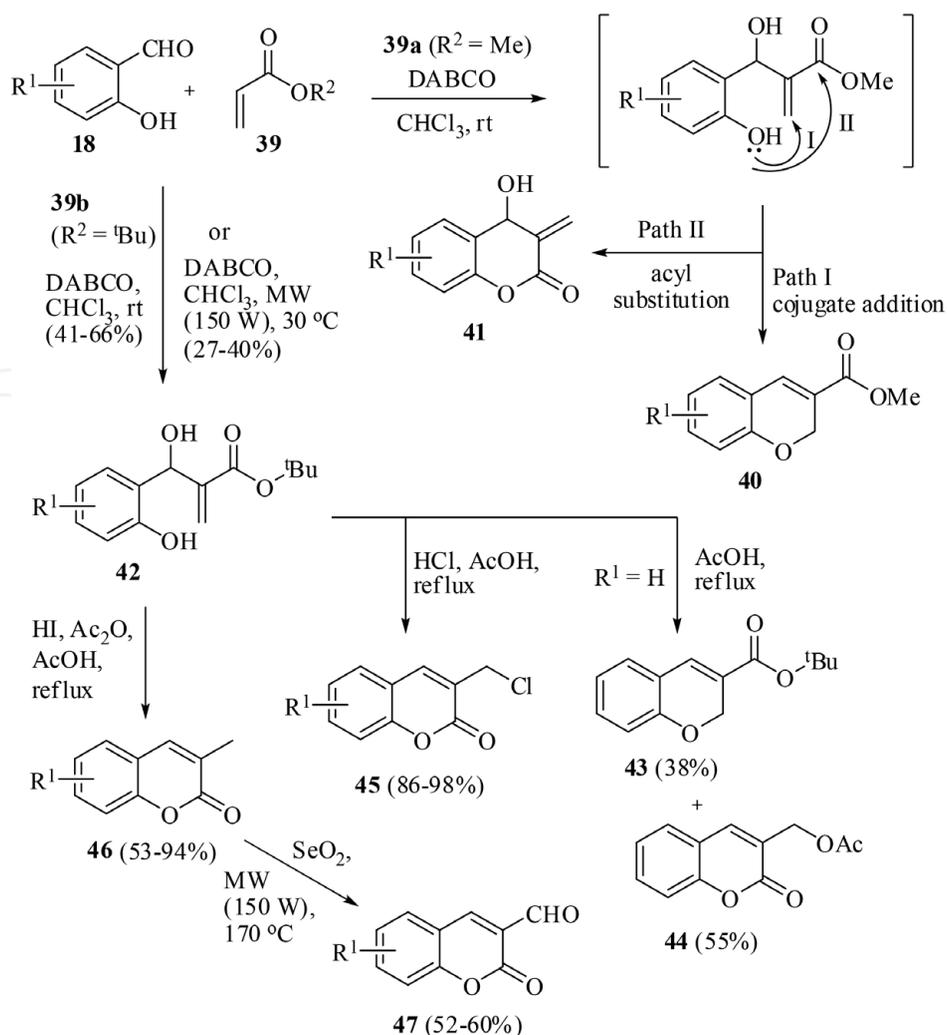


Figure 14.
 Synthesis of 3-substituted coumarins.

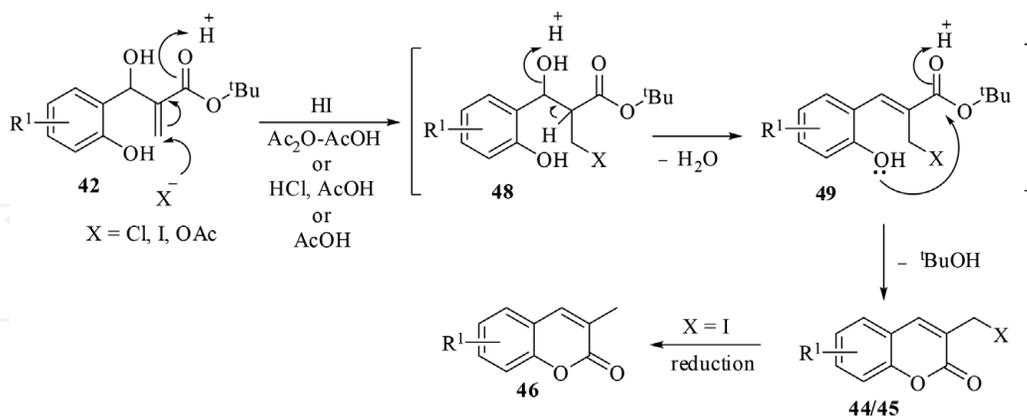


Figure 15.
 Possible mechanism for the formation of 3-substituted coumarins.

acetylene-dicarboxylate **75** in the presence of phosphinite ionic liquid (IL-OPPh_2) 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

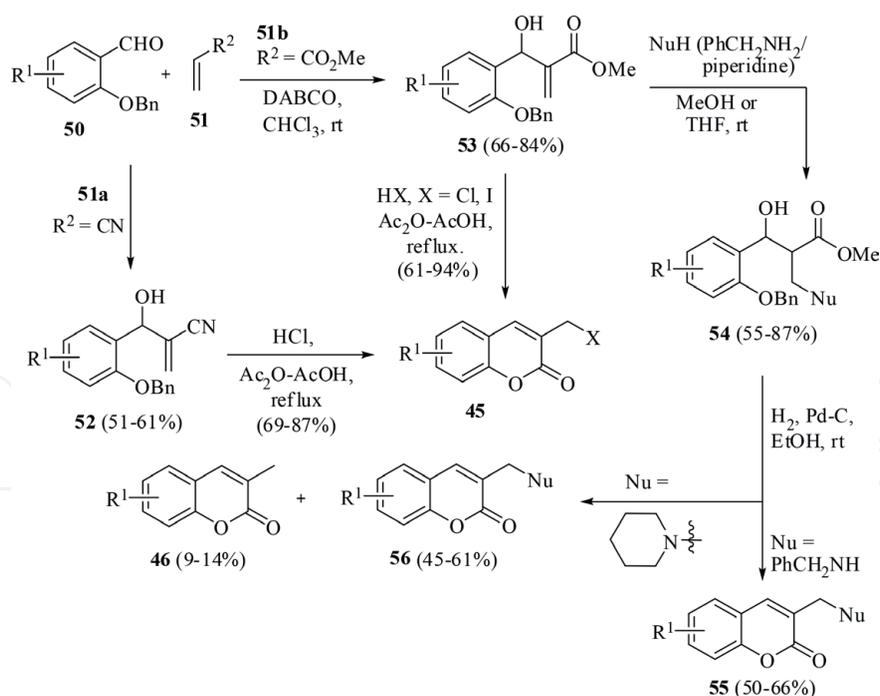


Figure 16.
Synthesis of 3-substituted coumarins.

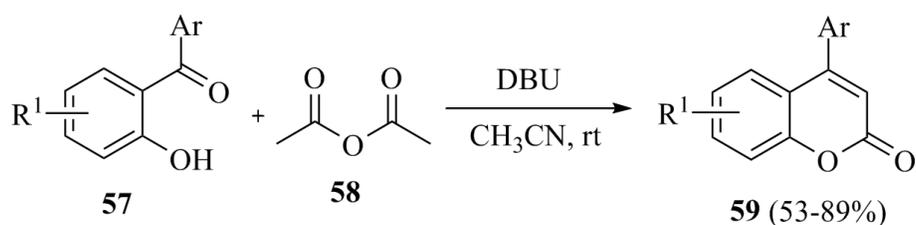


Figure 17.
Synthesis of 4-arylcoumarins.

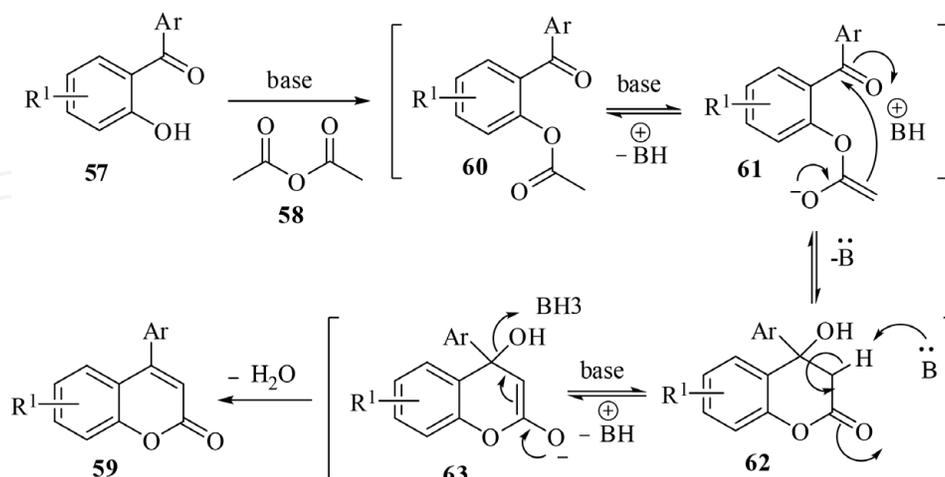


Figure 18.
Mechanism for Kostanecki reaction.

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].

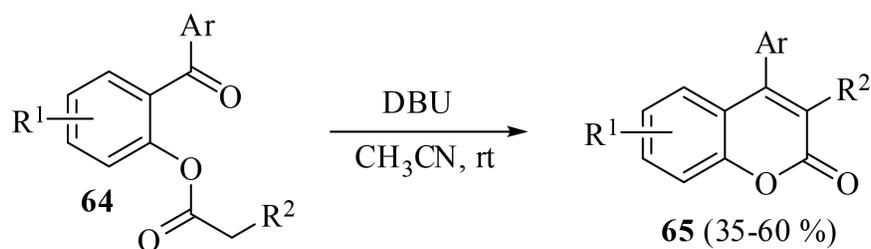


Figure 19.
 Synthesis of 3,4-disubstituted coumarins.

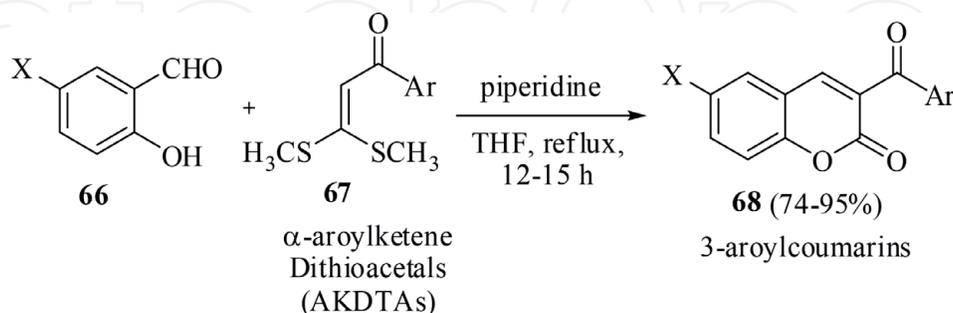


Figure 20.
 Synthesis of 3-aryl coumarins.

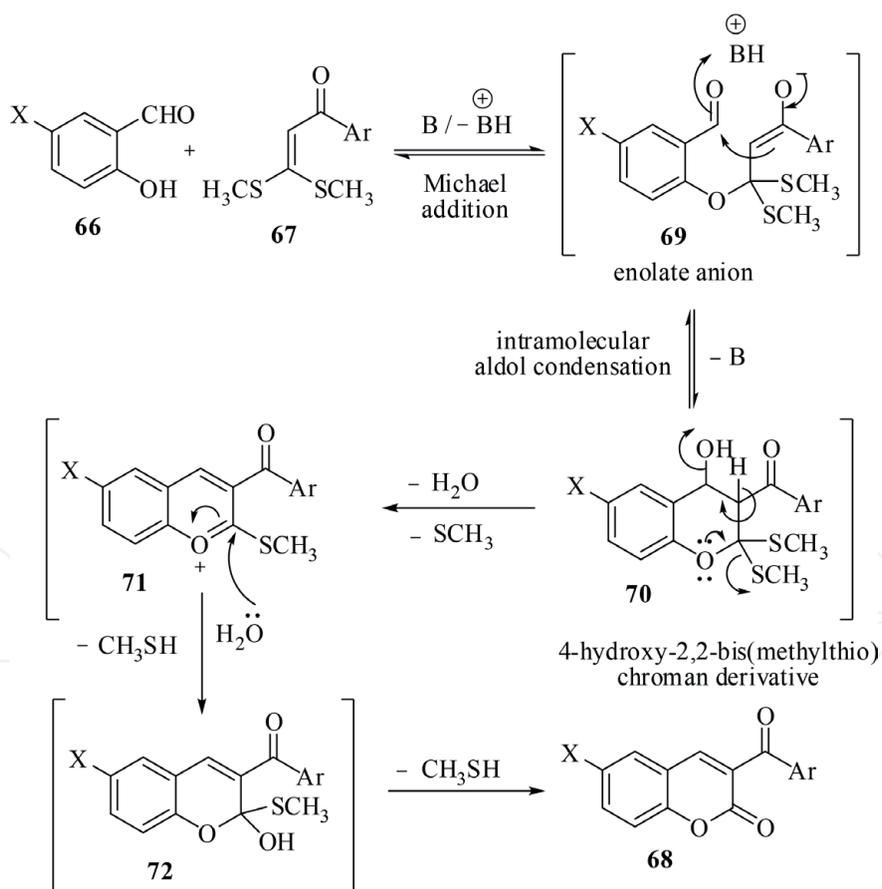


Figure 21.
 Probable mechanism for the formation of 3-aryl coumarins.

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].

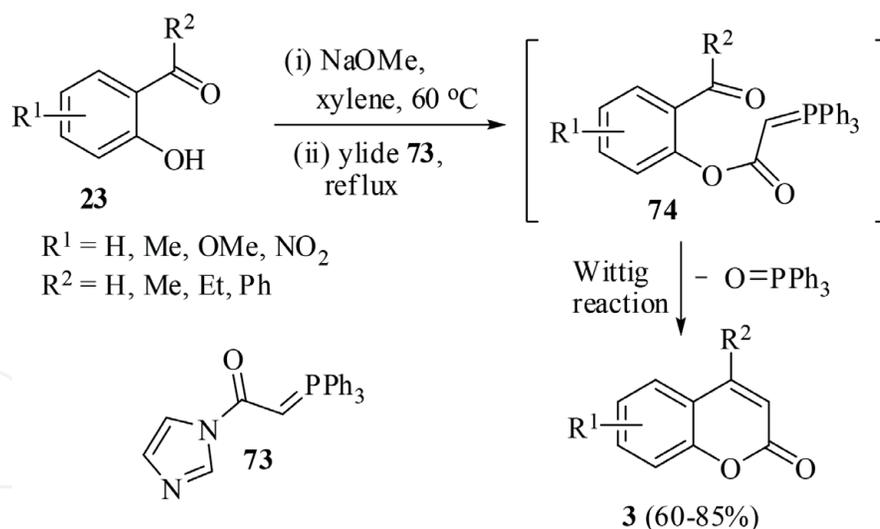


Figure 22.
Synthesis of substituted coumarins.

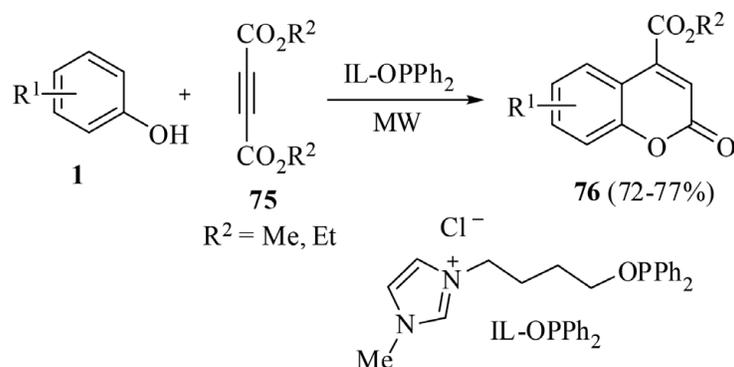


Figure 23.
Synthesis of 4-carboxy(ethyl/methyl) coumarins.

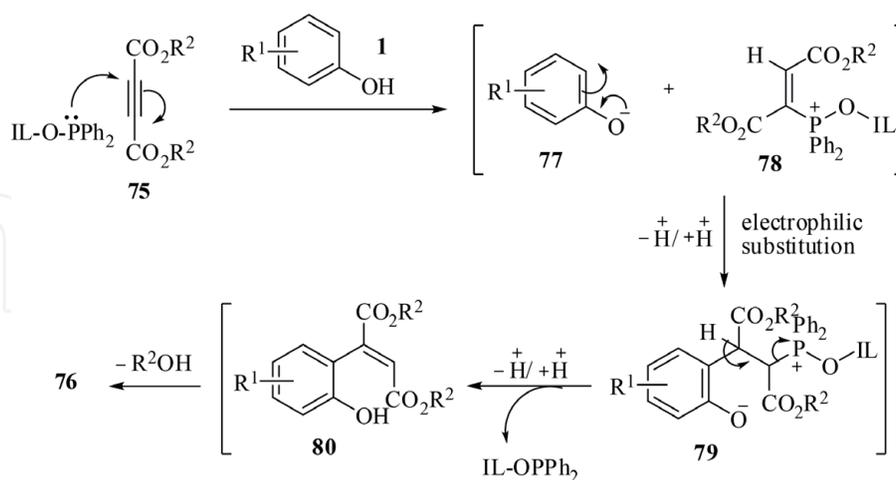


Figure 24.
Proposed mechanism for the synthesis of substituted coumarins via vinyl phosphonium salt-mediated electrophilic substitution.

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

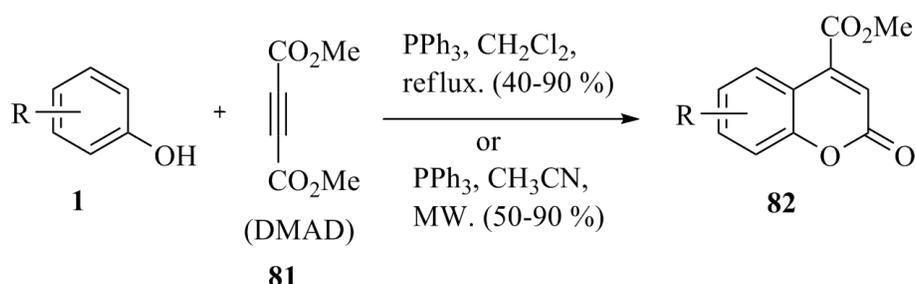


Figure 25.
 Synthesis of 4-carboxymethyl coumarins.

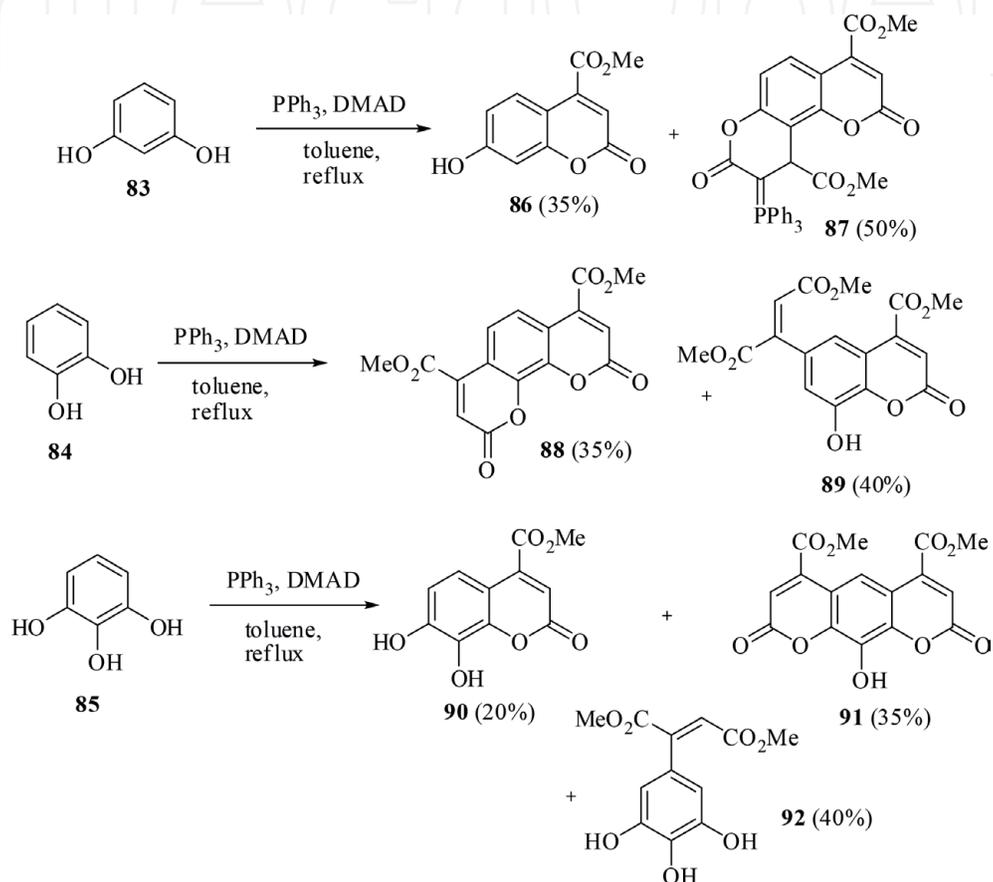


Figure 26.
 Synthesis of polyfunctionalized coumarin analogues.

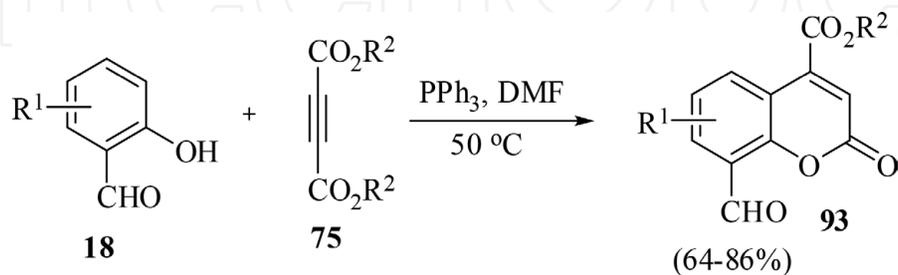


Figure 27.
 Synthesis of 4-carboxy(ethyl/methyl)-8-formyl coumarins.

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

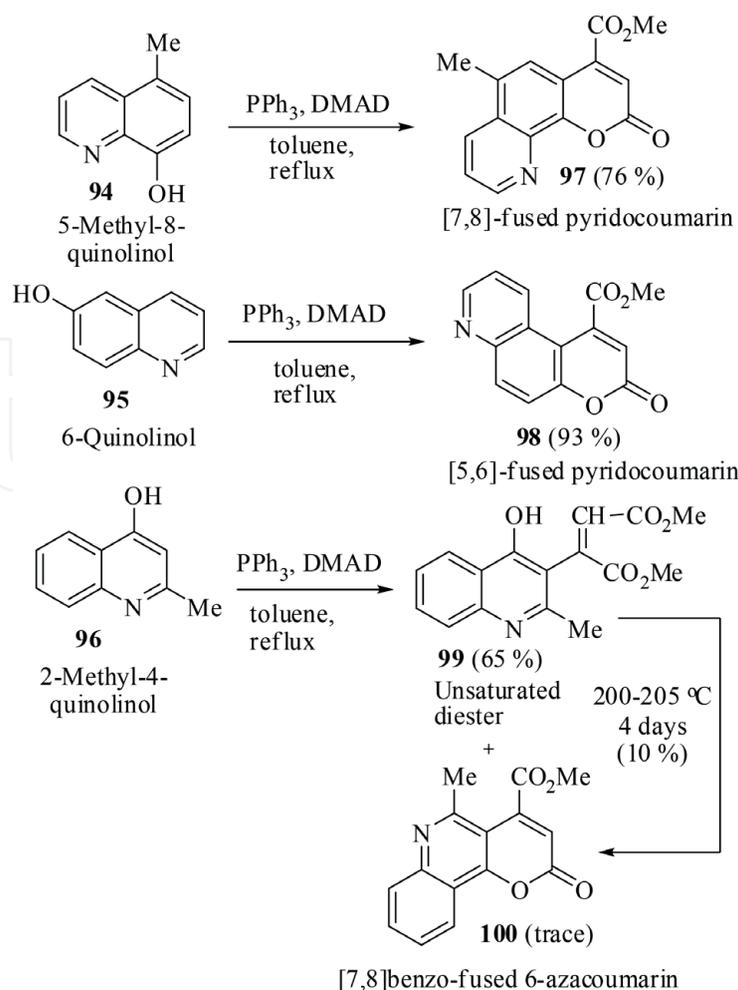


Figure 28. Synthesis of pyridocoumarins and benzo-fused azacoumarin.

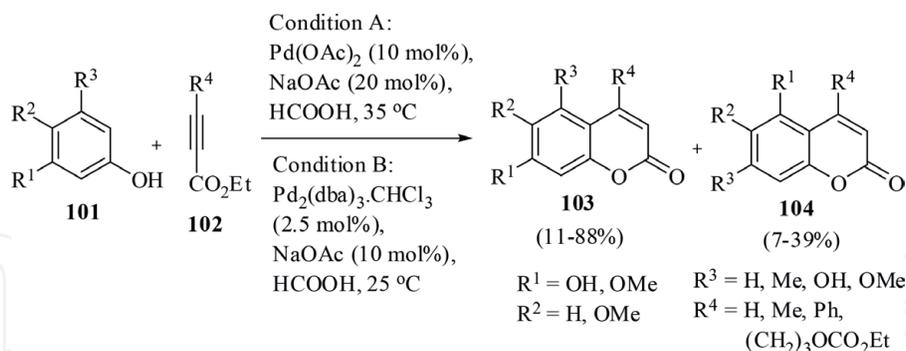


Figure 29. Synthesis of substituted coumarins.

of the R⁴ 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** (R³ = CO₂H) in TFA under mild conditions (**Figure 31**, Condition A) [118]. However, a mixture of catalysts FeCl₃ and AgOTf showed better catalytic efficiency toward yields (60–93%) of coumarin derivatives **3** (**Figure 31**, Condition B). Propiolic acid ester **110** (R³ = CO₂Et) also furnishes the desired products **3** upon

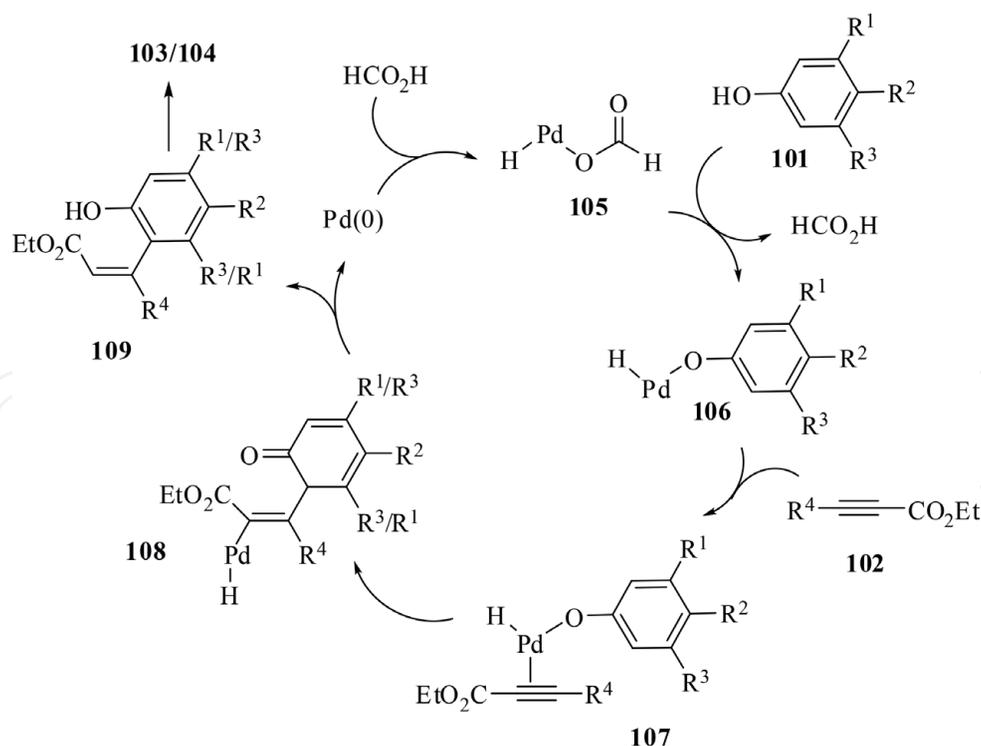


Figure 30.
 Possible mechanism for Pd-catalyzed synthesis of coumarins.

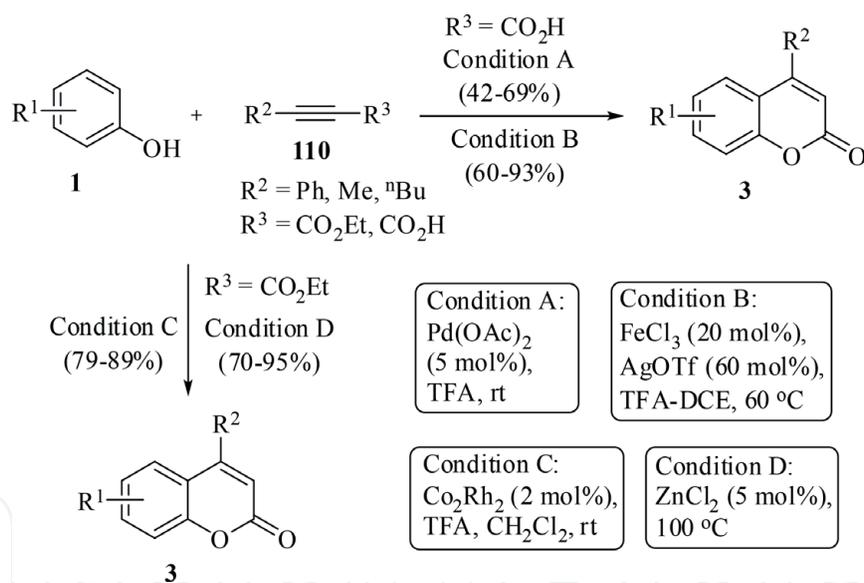
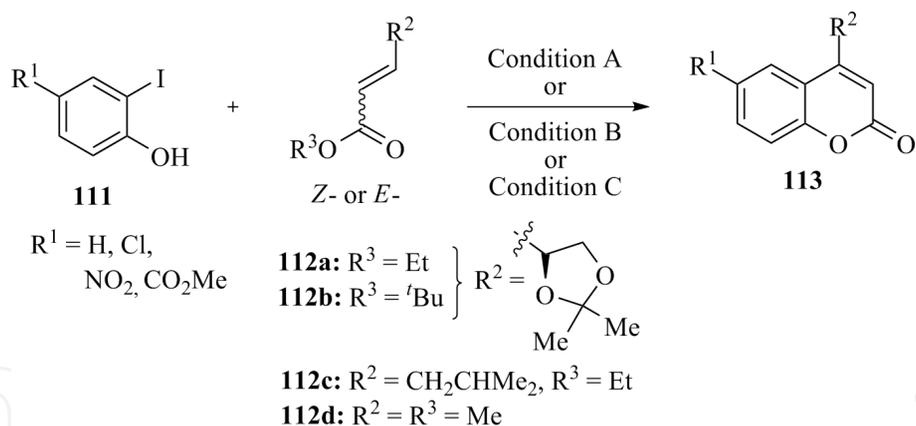


Figure 31.
 Synthesis of substituted coumarins.

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 ^tBu ester group that hampers the lactonization step. Moreover, the reactivity of *E*-enoates depends on the β-substituent. *E*-enoates **112c** (R² = CH₂CHMe₂,



Condition A: 10 mol% of Pd(OAc)₂, 3 equiv Et₃N, H₂O, 80 °C, 40 h.

Condition B: 10 mol% of PdCl₂, 3 equiv Et₃N, H₂O, 80 °C, 40 h.

Condition C: 10 mol% of Pd(OAc)₂, in the presence or absence of 20 mol% of PPh₃, 3 equiv AgCO₃, acetone, reflux, 40 h.

Figure 32.

Synthesis of 4,6-disubstituted coumarins.

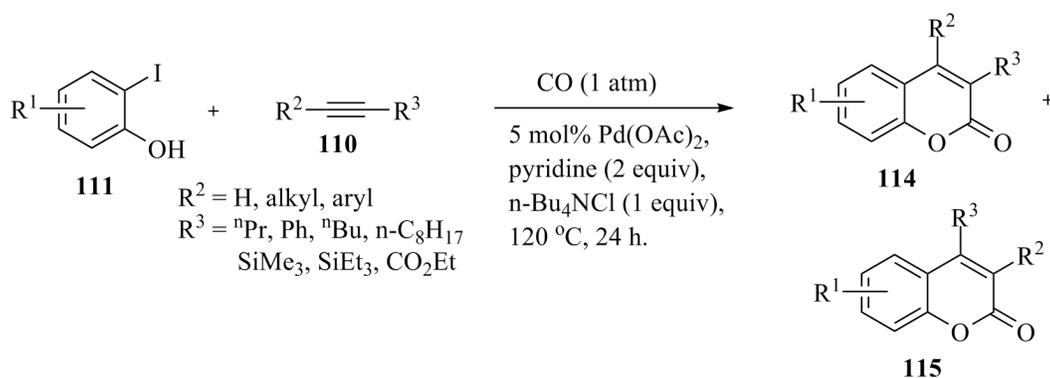


Figure 33.

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

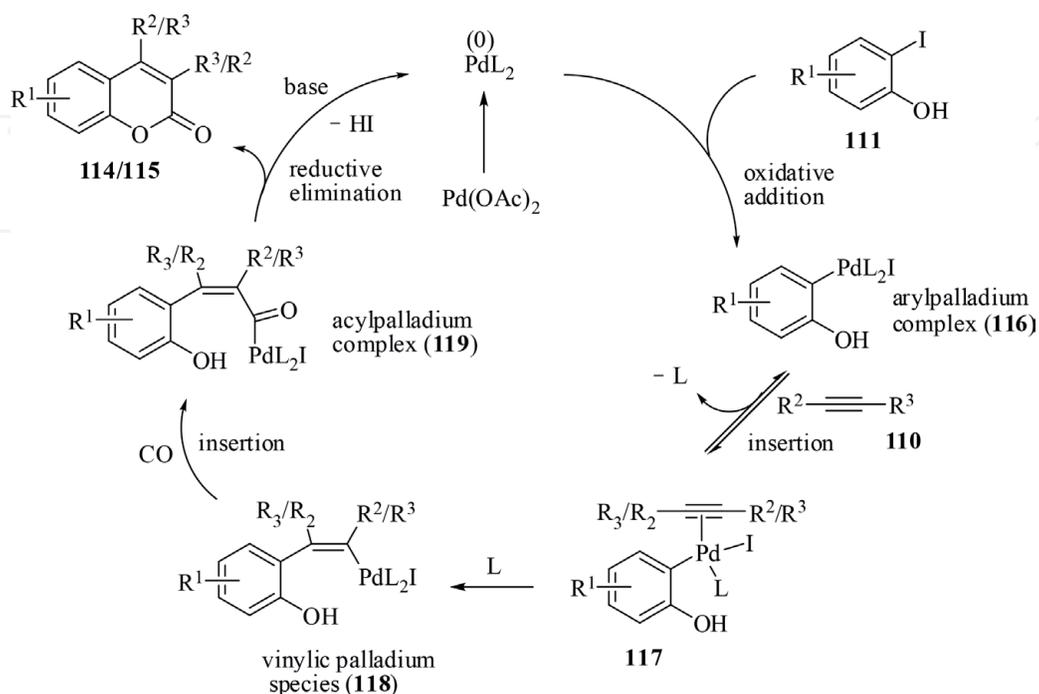


Figure 34.

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 CH_2CHMe_2 and CH_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** ($R^2 = \text{H}$; $R^3 = \text{}^n\text{Pr}$, Ph , SiMe_3 , SiEt_3 , CO_2Et , 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

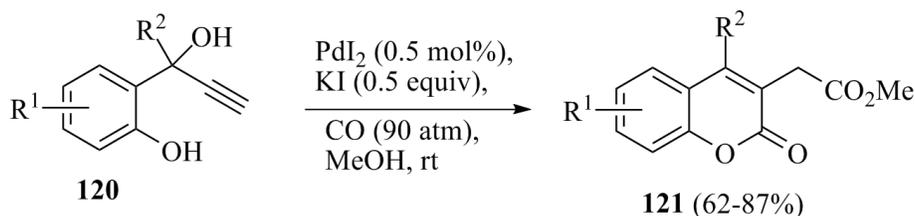


Figure 35.
Synthesis of 3,4-disubstituted coumarins.

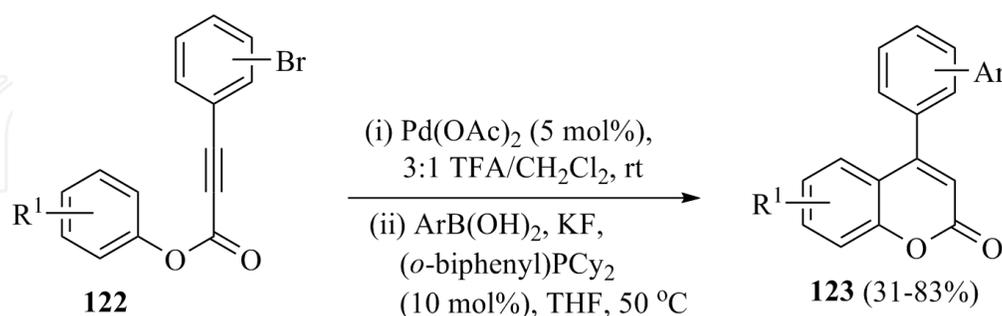


Figure 36.
Synthesis of 4-arylcoumarins.

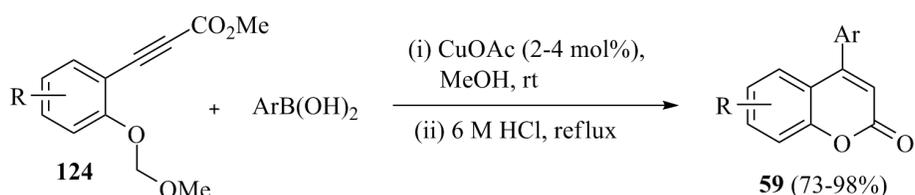


Figure 37.
Synthesis of 4-arylcoumarins.

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)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 CH₃NO₂ at 100°C (**Figure 38**) [129].

A series of 3-alkylcoumarins **128** are obtained in moderate yields from 2-hydroxybenzaldehydes **18** and α,β-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].

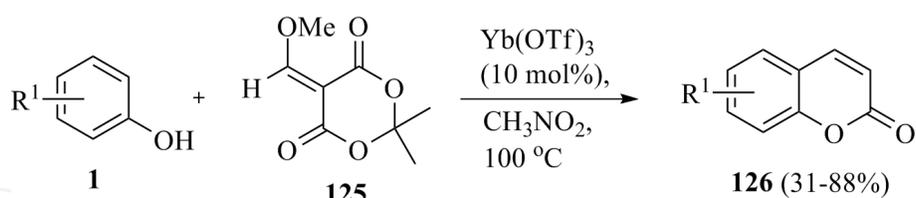
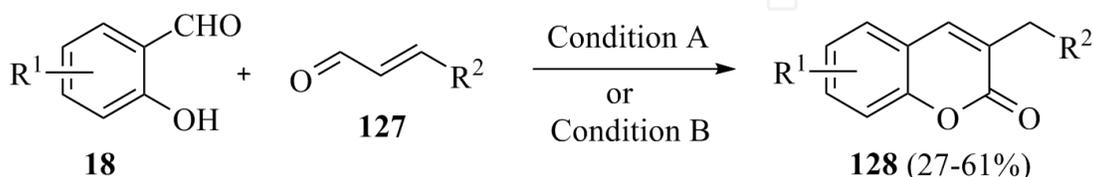


Figure 38.
Synthesis of substituted coumarins.



Condition A:
Dimethyl 1,3-
dimethylimidazolium
phosphate, K₂CO₃,
toluene, 100 °C

Condition B:
Dimethyl 1,3-
dimethylimidazolium
phosphate, K₂CO₃,
toluene, MW (200W)

Figure 39.
Synthesis of 3-alkylcoumarins.

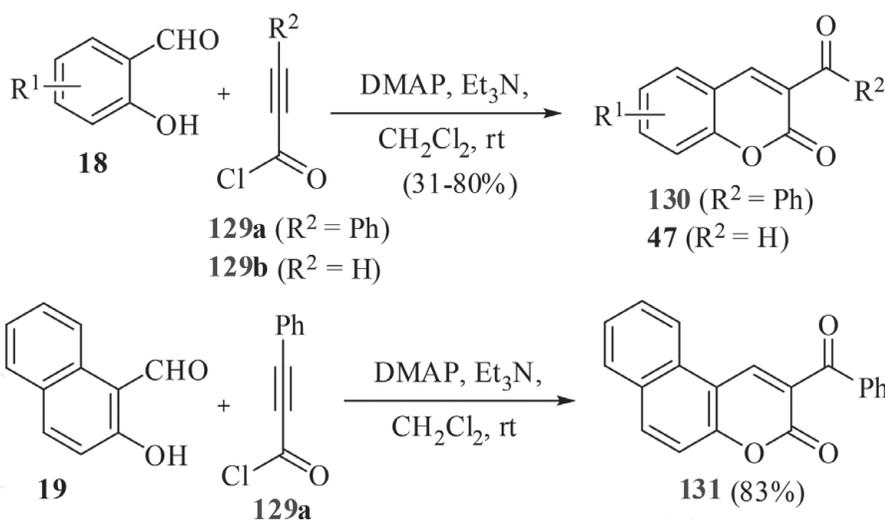


Figure 40.
Synthesis of 3-benzoyl coumarins and coumarin-3-carbaldehyde.

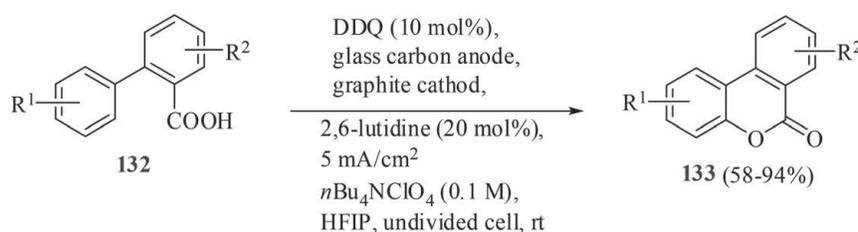


Figure 41.
Synthesis of 6H-benzo[c]chromen-6-ones.

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 ⁿBu₄NClO₄ 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.

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Conflict of interest

The authors declare no conflict of interest.

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