Chapter

Recent Methods for Synthesis of Coumarin Derivatives and Their New Applications

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Abstract

Coumarin (2*H*-1-benzopyran-2-one) and its heterocyclic derivatives are widely used as lactone scaffolds used by innovative methods for the preparation of heterocyclic molecules. Nowadays, significant biological activities, as well as properties of unique nature coumarin derivatives, have played an important role in the development of novel drugs. This chapter entitles numerous methods of one-pot construction of coumarin derivatives, together with well-known name reactions and other type reactions as well, in the presence of various metal-based homogenous and heterogeneous catalyst system. Coumarin is one of the very important heterocycles and its analogs like natural product and pharmaceutically active drug molecules are extracted/isolated from a plants, animals, and microbes. Coumarin precursors have a wide range of biological activities Hence, the synthesis of coumarins and their heterocyclic analogs have become among the most interesting compound over the last many years in the growth of improved synthetic methodologies to form different types of functional groups that are present in coumarins derivatives. The synthesis of coumarins enabled by current approaches and their most recent bio-applications are discussed in this book chapter. Corresponding complex heterocycles-based coumarin analogs are produced from substituted alkyne substrates and other starting materials as well.

Keywords: coumarin, drugs, catalysis, name reactions, arylation, heterocycles, radical reaction

1. Introduction

Coumarin heterocycle is an award gifted from nature, coumarins get the name from "Coumarou" which is the vulgarity term of the plant that belongs to the Fabaceae family named tonka bean. The natural product of coumarin and its scaffolds were isolated and purified by Vogel in 1820 [1], and it was prepared by Perkin in 1868 [2]. The lactones-based ubiquitous heterocyclic coumarins have been known as fragrance products in perfumes, because of their nature of sweet smell. Naturally appearing coumarins and their analogs are known in about 700 chemical

structures in more than 100 plant families [3] and remarkably, the number of core structures of coumarin derivatives still increases. Coumarins (2*H*-1-benzopyran-2-one) are one the most important heterocyclic compounds and their scaffolds are an essential class of lactone family with a fused α-pyrone ring attached to a benzene moiety. The centre core of coumarins has shown great interest over the years because of their significant biological importance and applications [4–14]. This type of fused oxygen heterocycles is associated with a wide range of biological properties like antitubercular, anti-inflammatory, anticancer, anticonvulsant, and neuroprotective, such as antiviral, antifungal, antibacterial, antihyperglycemic, anticoagulant, antihypertensive, antiadipogenic, anti-HIV, antibacterial, antimicrobial and antioxidant, etc. effects.

Moreover, coumarins analogs are attracting the vital attention of chemists due to their broad range of materials applications like photosensitizers, fluorescent, optical brighteners [15, 16], and laser dyes [17, 18], and additives [19] in food, cosmetics, and pharmaceuticals, etc.

In this particular lactone based coumarin family of drug molecules such as warfarin [20], acenocoumarol [21], and phenprocoumon [22] are the most prominent ones, which are currently used in a many different nations (**Figure 1**). Due to their unique nature and greater half-life, notably, warfarin is used more often compare to acenocoumarol. These results highlight a significant new development in the biological evaluation of coumarins and their derivatives, as well as medicinal chemistry [23–30]. As a current result, the

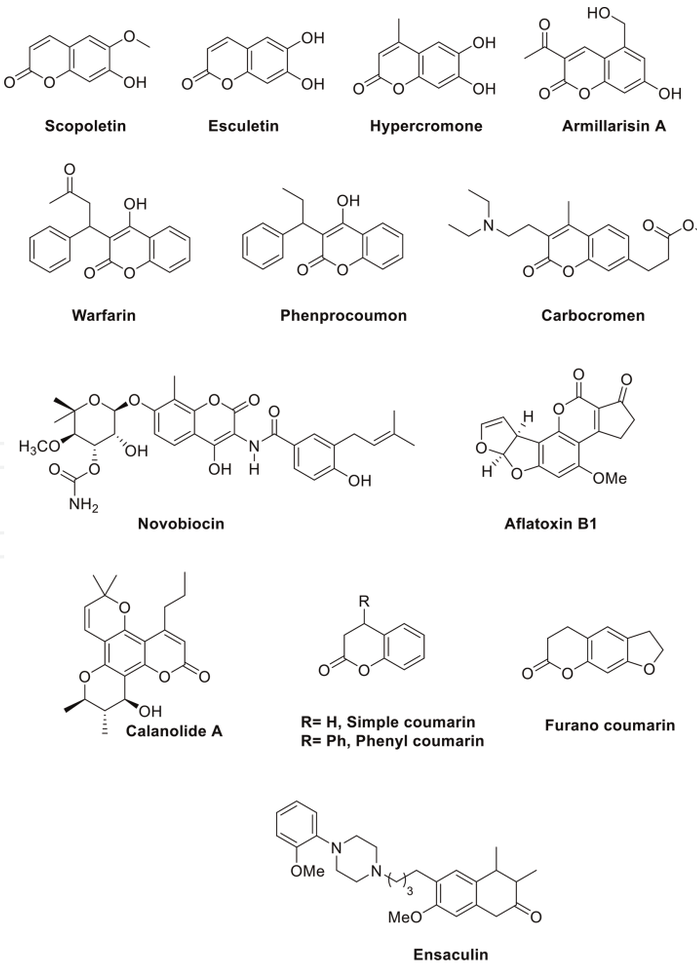


Figure 1.
Representative examples of lactone-based bioactive coumarin-based derivatives.

coumarin heterocyclic ring system is widely used mostly in pharmaceutical industry to build a various functional groups present in the drug molecules. Significant research has been shown to isolate and purify naturally present biological active coumarins from a range of plants, animals, and microbes, and to artificially design and synthesize functionalized coumarin molecules from academic and industry as well with unique heterocyclic structures and characteristics [31–36]. Given the importance of coumarin parent compounds and their derivatives in medicinal chemistry, we have gathered diverse methods for the preparation of coumarin and its scaffolds from alkyne type aryl propiolate as suitable starting materials *via* transition metal and, non-metal mediated catalysis and photo-chemical and radical based transformations. In this chapter, we mostly tried to cover the traditional name reactions mediated coumarin synthesis and described new synthetic methods to access coumarin heterocycles and also showed recent exciting applications which are reported in recent years. As a result, we think that this book chapter will be useful for not just the students but for researchers and scientists as well, who are trying to figure out new ways to build complicated coumarins, therapeutic compounds based on coumarins, and polycyclic coumarin derivatives.

2. Name reaction enabled coumarin synthesis

In the present literature, several name reaction mediated methods are reported for the synthesis of coumarin derivatives used by following well-established reaction protocols such as Perkin reaction, Pechmann reaction, Claisen rearrangement, Knoevenagel reaction, Kostanecki-Robinson coupling reaction, Reformatsky Reaction, Wittig reaction, Michael addition, Heck-lactonization reaction, and Baylis–Hillman reaction in the presence of various metal-free or metal-based homogenous and heterogeneous catalyst systems. We have demonstrated suitable reaction and mechanisms for following name reactions mediated preparation of coumarin motifs (**Figure 2**).

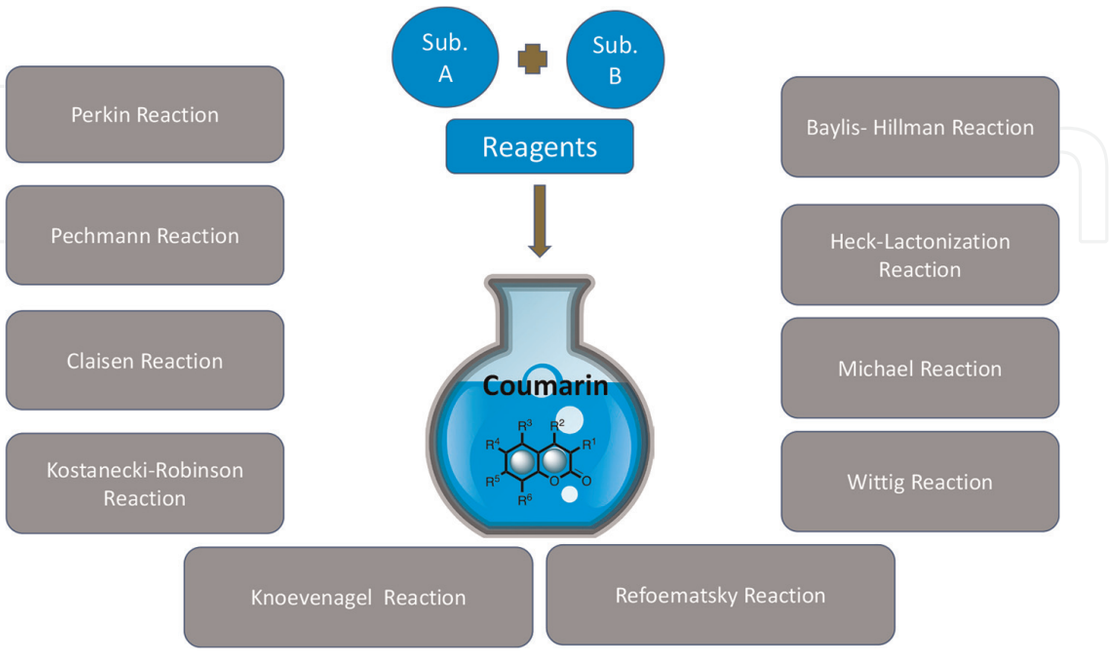


Figure 2.
Name reactions mediated synthesis of coumarin.

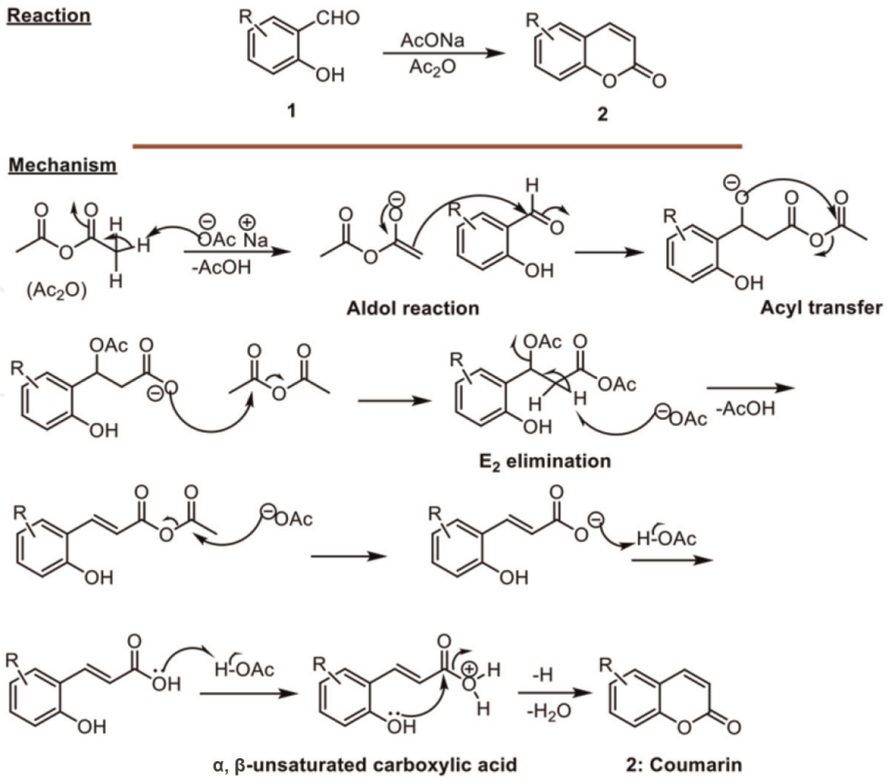


Figure 3.
Synthesis of coumarin via Perkin reaction.

2.1 Perkin reaction

In 1968, the first time Pekin demonstrated the method for the construction of coumarin by the condensation reaction of simple salicylaldehyde in the presence of acetic anhydride [37].

The Perkin reaction of salicylaldehyde **1** and an acetic anhydride are mixed together in the basic reaction condition, a chemical process that furnished, α, β-unsaturated aromatic acid in the presence of sodium acetate followed by intramolecular cyclization produced the expected substituted coumarin **2**. The proposed mechanism of this reaction is described in **Figure 3** [2, 37, 38].

2.2 Pechmann reaction

The Pechmann achieved the initial discovery of the Pechmann condensation in 1883 [39]. Typically, carbolic acid **3** reacts with a carboxylic ester having α-carbonyl group **4** in an acidic environment to produce the desire coumarins **5** [40]. The most widely reported process for producing coumarins through Pechmann condensation, which scheme starts with two basic building blocks, phenol and β-ketoester, and produces good coumarin yields most of the cases. Several catalysts were tested for this reaction, including sulfuric acid, trifluoroacetic acid, phosphorous pentoxide, $ZrCl_4$, $TiCl_4$, and ionic liquids, etc. enabled by Pechmann condensation [41]. Various groups have reported for the preparation of coumarin scaffolds *via* Pechmann methods. In the mechanism of the reaction involved following paths initial step is esterification followed by the attack of activated carbonyl group, allows to forms the ring system. The last step of the reaction involves dehydration. The proposed plausible mechanism of this

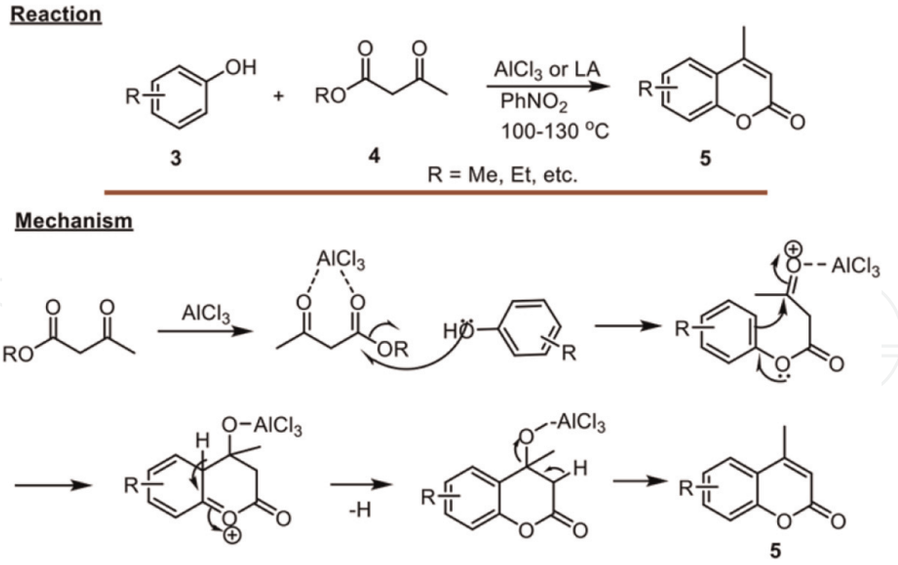


Figure 4.
Coumarin synthesis via Pechmann reaction.

reaction shown in **Figure 4**. By reacting substituted phenols and ethyl acetoacetate in the presence of a zinc-iodine mixture in refluxing toluene, a number of substituted coumarins have been produced in yields ranging from 25 to 77%. The proposed plausible mechanism of this reaction is shown in **Figure 4** [42].

2.3 Claisen rearrangement

The preparation of 3,4-substituted coumarin utilizing trifluoroacetic acid (TFA) as homogeneous promoter *via* Claisen rearrangement reaction. The reaction of phenol 3 reacts with protected allyl alcohol 6 in the presence of basic condition offers desired target compound followed by underwent 3,3 sigmatropic Claisen rearrangement in the presence TFA in moderate temperature followed by tautomerism or basic condition produced 3,4-substituted coumarin 7 in good yields. Several groups reported Claisen rearrangement mediated synthesis of coumarin analogs. The proposed plausible mechanism of this reaction is shown in **Figure 5** [43].

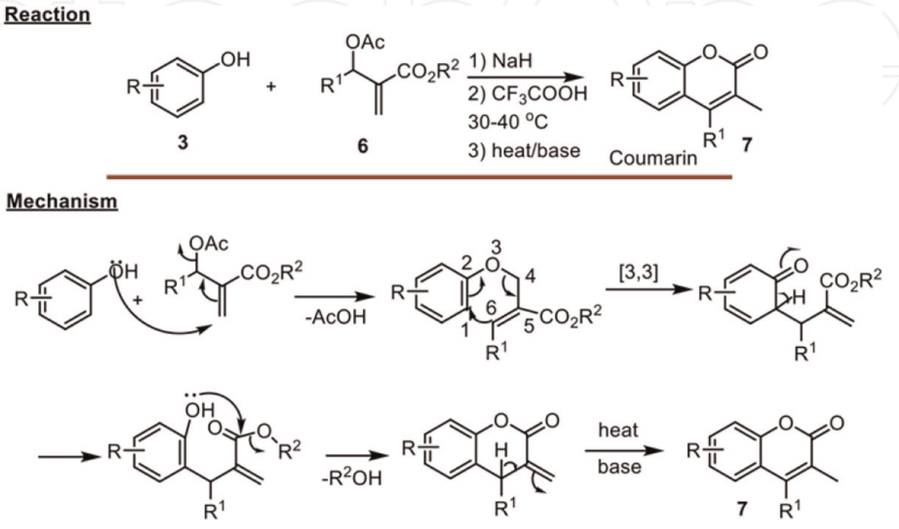


Figure 5.
Synthesis of 3,4-disubstituted coumarin via Claisen rearrangement.

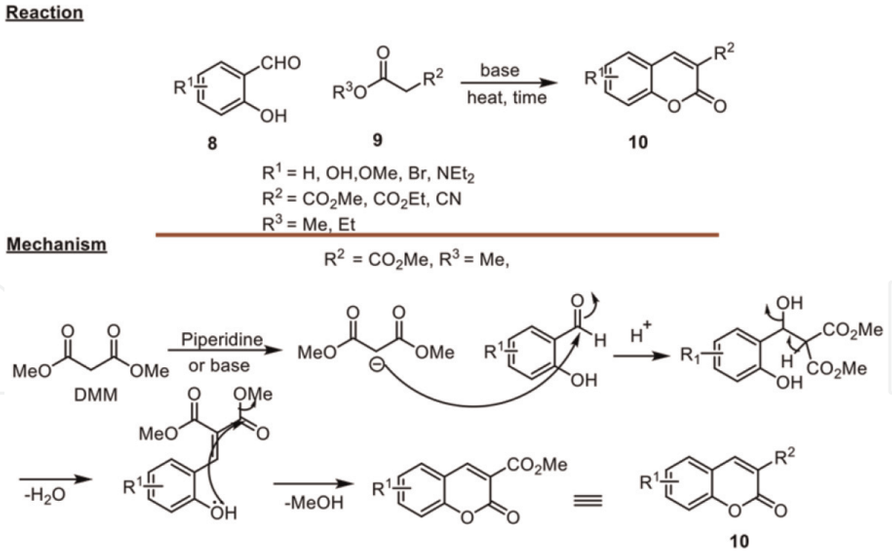


Figure 6.
Synthesis of 3-substituted coumarin via Knoevenagel reaction.

2.4 Knoevenagel reaction

Many coumarin derivatives have been derived from suitable starting materials *via* a Knoevenagel reaction. 3-substituted coumarin derivatives can be synthesized *via* base mediated process. The reaction needs to be carried out in the presence of 2-hydroxy benzaldehydes 8 and coupling partner 9 containing an active methylene group in the presence of the base under heating conditions. The yield obtained from coumarin product 10 is acceptable range [44]. The proposed plausible mechanism of this reaction is shown in **Figure 6**. There are various reports present in the literature regarding the synthesis of scaffolds of coumarin *via* Knoevenagel reaction in the presence of ultrasound solvent-free conditions [45, 46].

2.5 Kostanecki-Robinson coupling reaction

Kostanecki-Robinson coupling reaction could be utilized for the synthesis of derivatives of coumarin. The **Figure 7** shows the reaction between aliphatic anhydride **12** and aryl ketone **11** with a substitution of the hydroxyl group which gives the desired product as coumarin **13** with good to excellent yields. The proposed plausible mechanism of this reaction is described in **Figure 7** [14, 47].

In 2004 Song et al. synthesized 4-arylcoumarins **15** from phenyl ester **14** in the presence of 4-butyl-3-methylimidazolium bromide (phase transfer catalyst), Hf $(OTf)_4$ (metallic catalyst), for 9 h at 80°C the yield of the expected product obtained was good (**Figure 8**) [48].

2.6 Reformatsky reaction

In the Reformatsky reaction of an activated acyl halide first reacts with a zinc metal to offer RZnBr followed 1,2 addition of organometallic zinc reagents to ketone **11** produced a zinc enolate after elimination of Zn [OH(Br)] to form ester. This process converts 3,4-disubstituted coumarins **13** from α, β-unsaturated ester. This synthesis protocol involving reaction steps are as shown in the **Figure 9** with the mechanism as well [49].

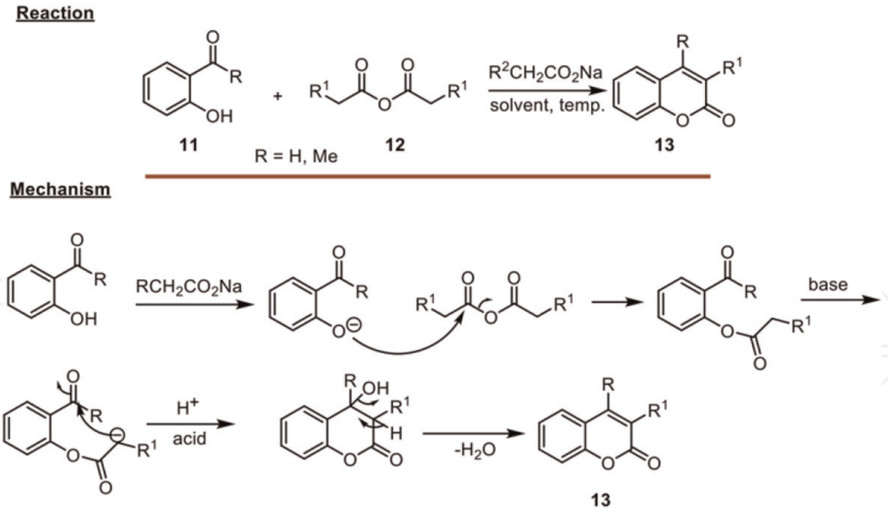


Figure 7.
Synthesis of coumarin derivatives via Kostanecki-Robinson reaction.

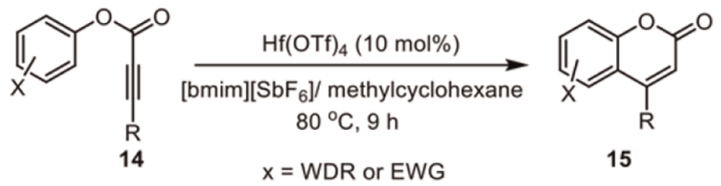


Figure 8.
Synthesis of 4-arylcoumarins.

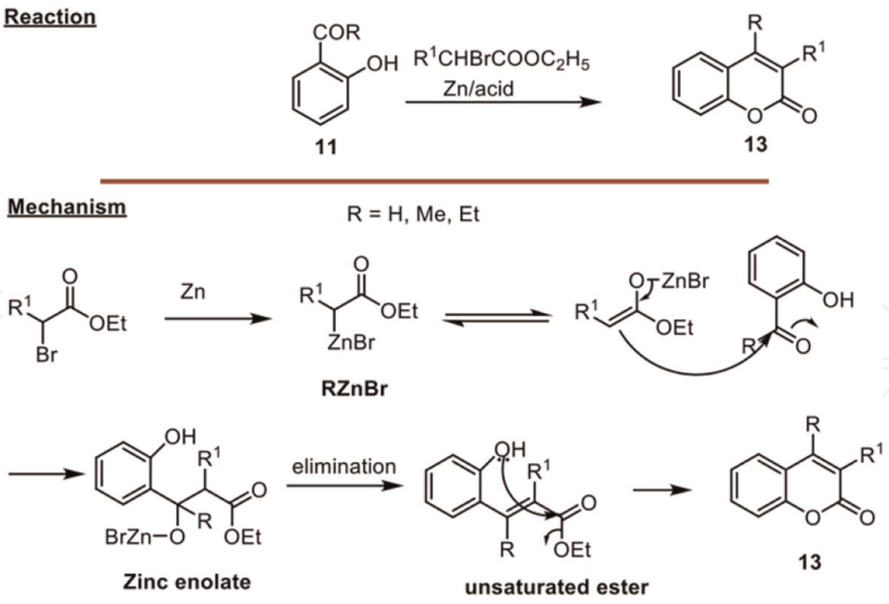


Figure 9.
Synthesis of coumarin via Reformatsky reaction.

2.7 Wittig reaction

Wittig reaction of aldehyde or a ketone **11** is mixed with a Wittig phosphine reagent (a triphenyl phosphonium ylide) to offer the expected olefin 16 in good yields along with phosphine oxide as by-product (**Figure 10**). This Wittig name reaction is

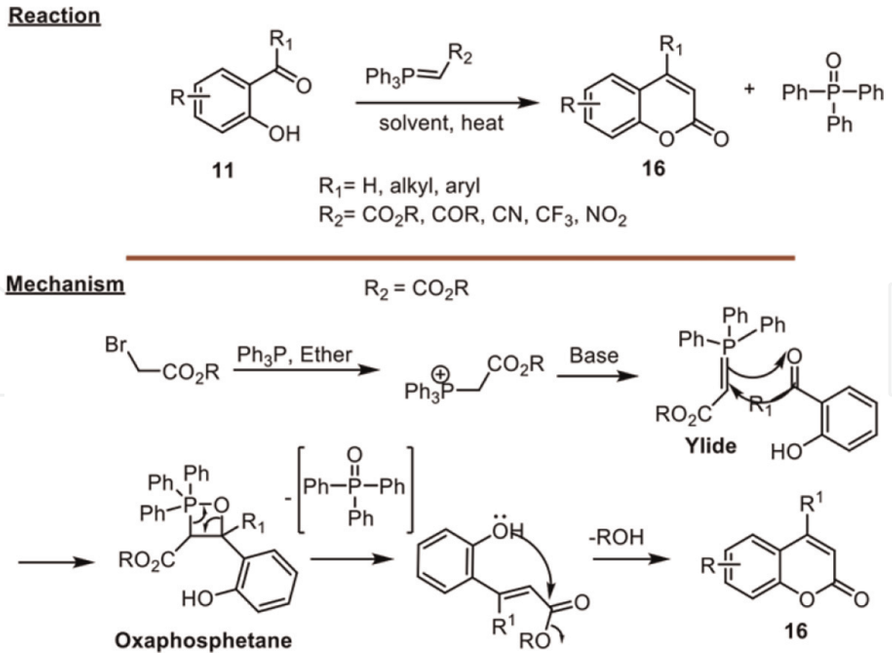


Figure 10.
Preparation of coumarin via Wittig reaction.

discovered by the German chemist Georg Wittig. He received Nobel Prize in Chemistry in 1979 his discovery of this significant olefin synthesis. This system allows the preparation of highly important natural products as well as drug molecules. The preparation of various substituted coumarin **19** derivatives obtained from corresponding phenols **17** having ortho-carbonyl group and triphenyl(α-carboxymethylene) phosphorane imidazole ylide **18** has been carried out by Kumar et al. by following applying the route of Wittig reaction, the yield of olefin reported was good. The mechanism of the reaction suggests that the reaction proceeds through the phosphorane intermediates as shown in **Figure 11** [50]. There are various reports present in the literature regarding the synthesis of coumarin scaffolds via Wittig reaction starting with an aldehyde or ketones with phosphonium ylide.

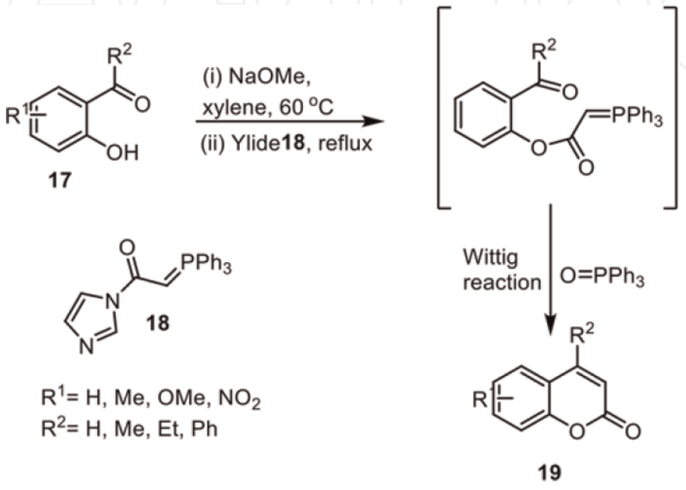


Figure 11.
Synthesis of coumarin via Wittig reaction.

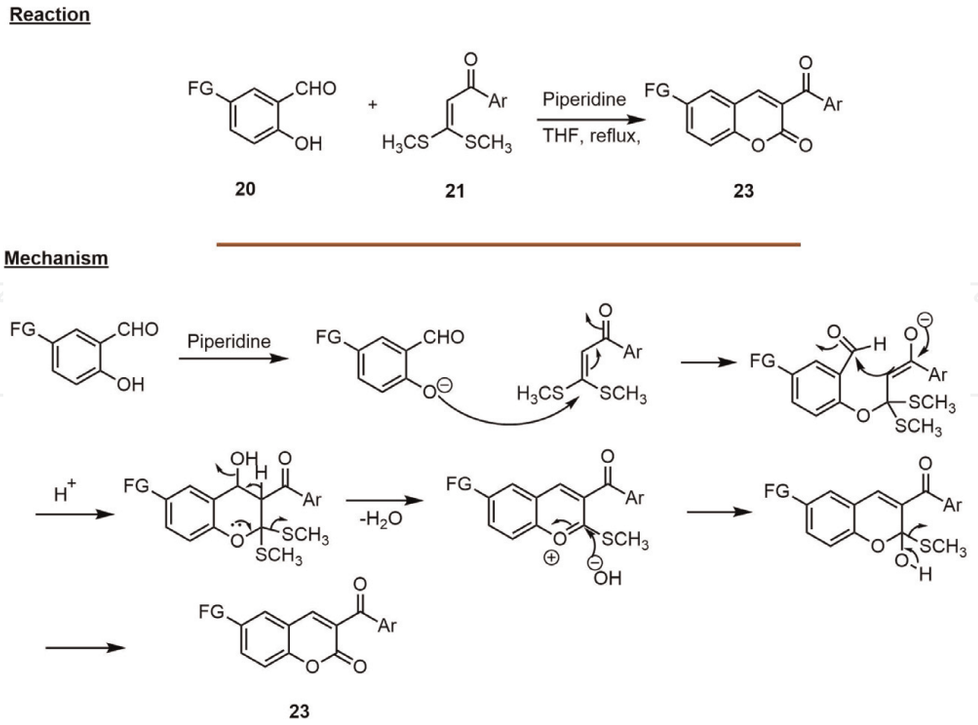


Figure 12.
Synthesis of 3-benzoyl coumarin through Michael addition approach.

2.8 Michael addition

The synthesis of 3-aroylcoumarin **23** could be carried out *via* Michael addition reaction approach from the readily present 2-hydroxybenzaldehyde **20** and α-aroylketene dithioacetals **21** in the presence of piperidine and refluxed condition in THF as a solvent. The mechanism of the reaction shows that the reaction proceeds *via* 2 steps, (i) initially *via* Michael addition (ii) aldol condensation (iii) elimination of water and -SCH_3 as shown in **Figure 12** [51].

2.9 Heck-lactonization reaction

The Heck-Lactonization reaction can be carried out for the synthesis of coumarin analogues **26** *via* Pd catalysis and were examined different reaction conditions tested using aqueous water and organic solvent conditions. Even with 10 mol% of the $PdCl_2$ or Pd $(OAc)_2$-catalysts showed, enoate **25** interacted with iodo compound **24** to produce coumarin **26** in good to moderate yields under conditions A and B with water. The organic solvent condition C was indicating low chemical yield and the proposed catalytic cycle as shown in **Figure 13** [52].

2.10 Baylis-Hillman reaction

As seen in **Figure 14**, the Baylis-Hillman approach was used to create substituted coumarins. In the presence of DABCO, 2-hydroxybenzaldehydes **8** reacts with methyl acrylate **27** to produce a combination of chromene **28** and coumarin **29**. Nevertheless, related interactions between 2-hydroxybenzaldehydes and *tert*-butyl acrylate in the presence of conventional or microwave heating led to respective

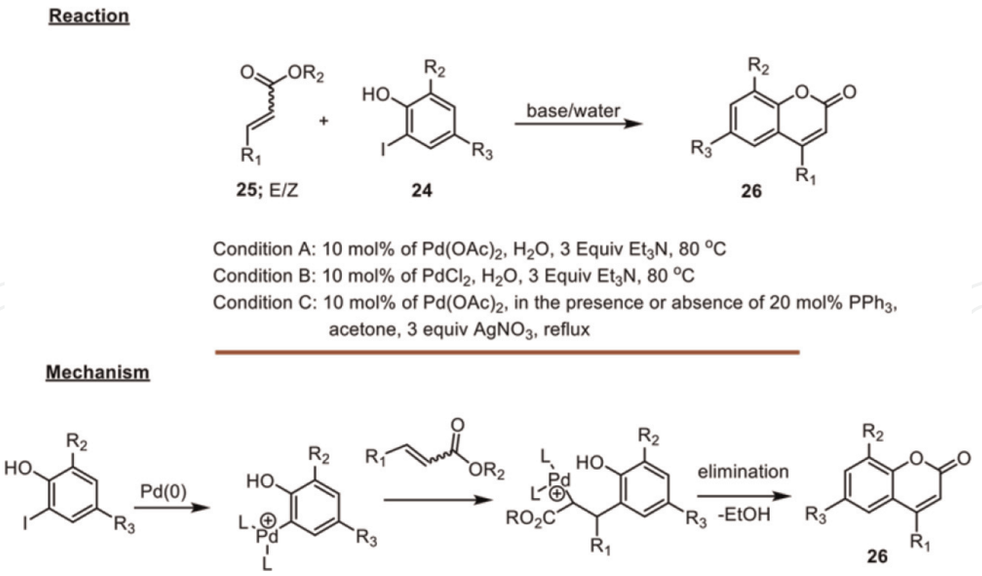
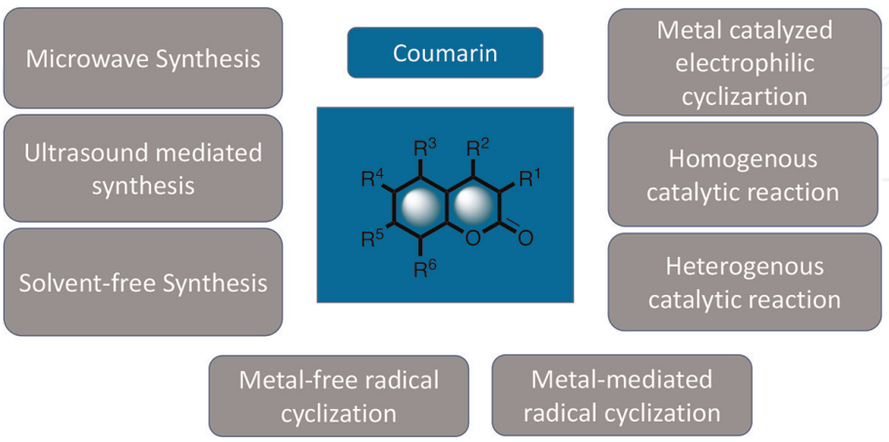


Figure 13.
Synthesis of coumarin via Heck-lactonization reaction.

Baylis-Hillman adducts, that further undergoes cyclization *via* reflux in AcOH to produce a combination of both 3-substituted chromene and coumarin. Decent quantities of 3-(chloromethyl) coumarins **33** are obtained by treating the Baylis-Hillman adducts **30** and strong acid HCl when refluxed in AcOH. Additionally, 3-methyl coumarins **31** are produced by the reaction of compound **30** with HI under reflux in a solution of Ac_2O and AcOH, and these 3-formyl coumarins **32** are produced by a subsequent reaction with SeO_2. The plausible mechanism of the reaction has been shown in the **Figure 14** [53].

3. New approaches for the synthesis of coumarins derivatives



3.1 Microwave mediated innovative synthesis

Recently, microwave-mediated organic synthesis has replaced conventional heating methods. In recent years, the synthesis of organic molecules has increasingly

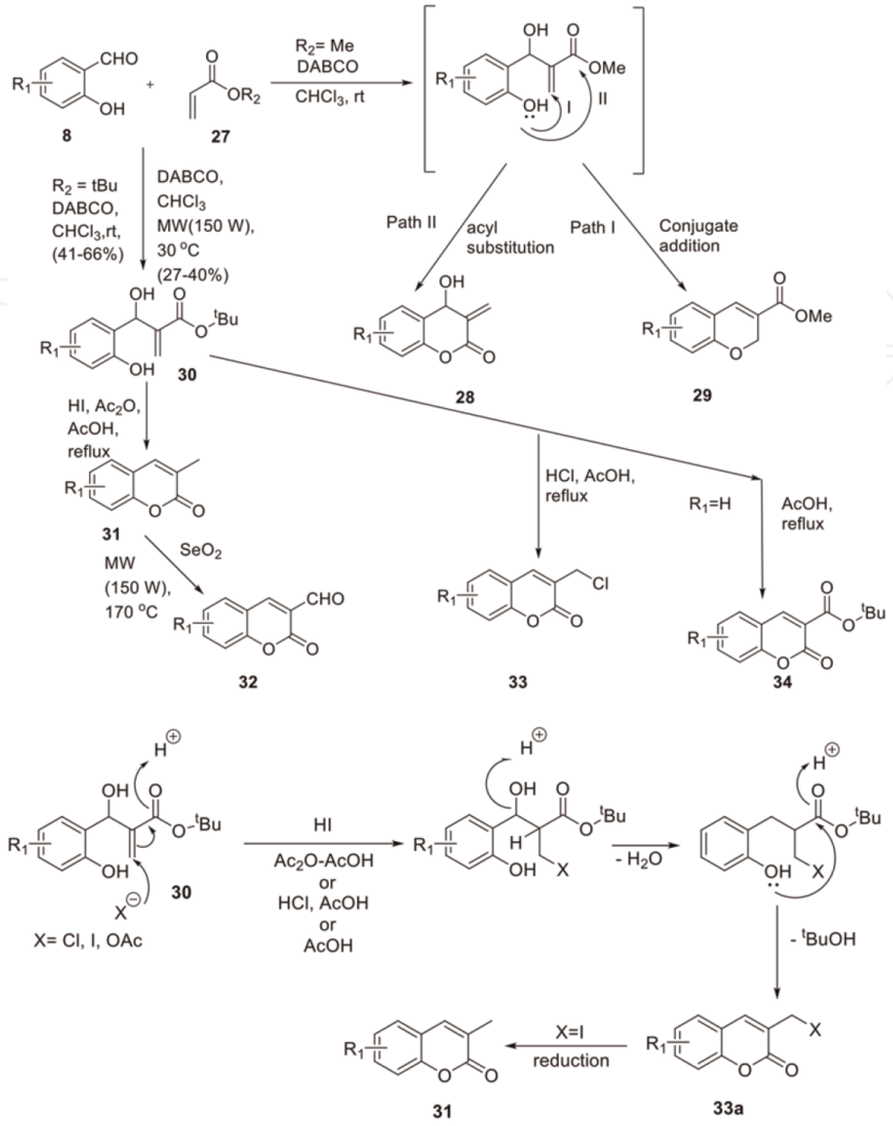


Figure 14.
Baylis Hillman reaction for the synthesis of substituted coumarin.

relied on the use of microwave energy to heat chemical reactions. In contrast to dramatically accelerating chemical reactions, direct microwave heating is known to reduce the formation of side products, increases yield, and improves the reproducibility. Various academic research institutions have already embraced microwave irradiation as a method for fast reaction in order to efficiently synthesize and discover new chemical substances [54].

In the year 2017, Brahmbatt and co-workers demonstrated the microwave- assisted preparation of 3-aryl-furo[3,2-c] coumarins **37**. The time required for the synthesis was just 2–4 minutes and the yield was also good (72–82%) as shown **Figure 15** [55].

In the same year, Desai et al. reported the preparation of 4-(substitutedphenyl)-2-(furan-2-ylmethyleneamino)-6-(2-oxo-2*H*-chromen-3-yl)nicotinonitrile derivatives **42**. The reaction was carried out in a solvent-free condition, the reaction was performed with 2-amino-4-(substitutedphenyl)-6-(2-oxo-2*H*-chromen-3-yl) nicotinenitriles **41** and 2-furfuealdehyde and the microwaves (300 W) were irradiated for 8–10 min. in the presence of acetic acid and a catalytic amount of $ZnCl_2$ (**Figure 16**) [56].

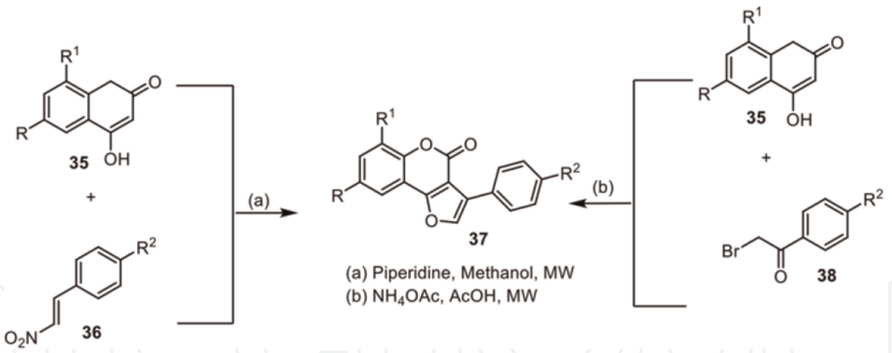


Figure 15.
Microwave assisted synthesis of 3-aryl-furo[3,2-c] coumarins.

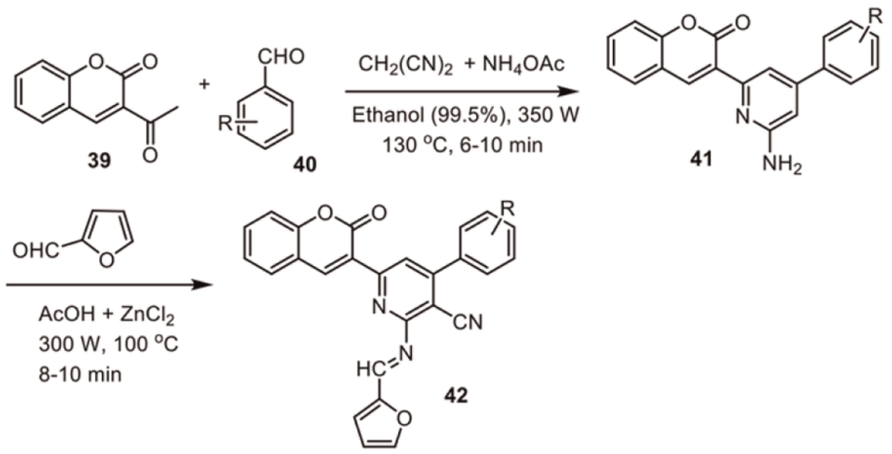


Figure 16.
Synthesis of coumarin-based nicotinonitrile.

[3,4-d]triazole-fused coumarin derivatives were synthesized by Schwendt and co-workers. The yield obtained was best (63–94%) in the presence of DMF (solvent) and at 160°C for 1 min [57].

A variety of coumarin-carbonodithioate and coumarin-maltol derivatives were synthesized, showing antibacterial activity and antitumor in a relatively short period in the presence of microwave radiations. It was stated that this approach was 24 times faster than the traditional technology [58, 59].

Pyrido[3,2-c]coumarins were synthesized in the presence of ammonium acetate, the reaction was carried out with suitable starting materials. The yield obtained was good and the time required for the reaction was about 3–4 mins [60]. Synthesis of coumarin-thiazolidine-2,4-dione was carried out recently by Mangasuli and co-workers. The reaction was performed in the presence of K_2CO_3 (catalyst), the starting material utilized was coumarin and thiazolidinedione.

3.2 Ultrasound helped synthesis

Comparing ultrasonic irradiation to traditional energy sources, there are various benefits like heat, light, and electric potential) [61, 62]. The primary cause of the chemical reactions caused by ultrasound is acoustic cavitation, which is the formation,

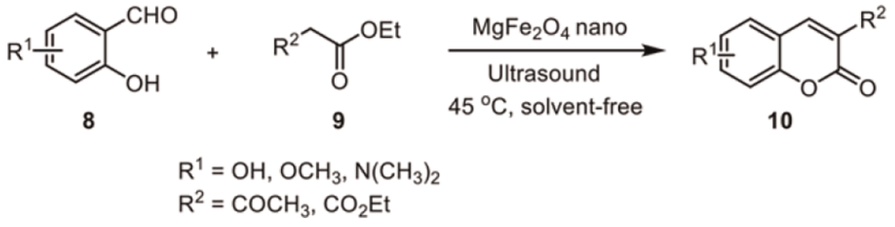


Figure 17.
Ultrasound assisted synthesis of 3-substituted coumarins.

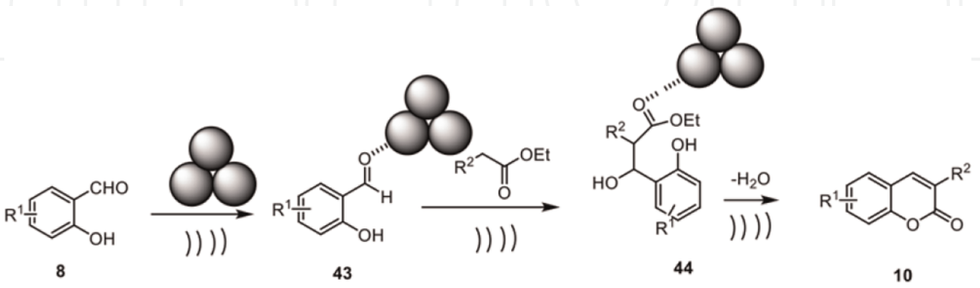


Figure 18.
Mechanism of the synthesis of 3-substituted coumarins.

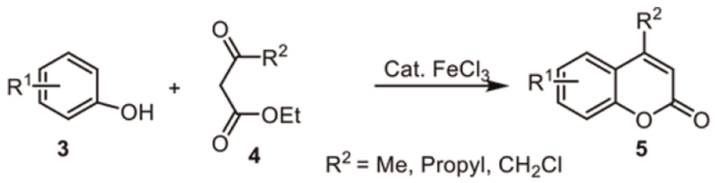


Figure 19.
Synthesis of coumarin via ultrasonic/microwave radiation.

development, and implosive bursting of bubbles. In many fields of chemistry research, including organic synthesis and solid-state materials, ultrasonic-assisted synthesis techniques have gained a lot of interest as shown **Figure 17** [63].

The 3-substituted coumarins **10** can be synthesized in the presence of $MgFe_2O_4$ nanoparticle, and the reaction can be carried out between salicylaldehyde **8** and 1,3-dicarbonyl compound **9** in the existence of the Ultrasound radiation. The mechanism for the syntheis of 3-substituted coumarin **10** was reported by Ghomi and co workers in 2018 and has been shown in the **Figure 18** [64].

The Pechmann condensation reaction for the synthesis of 3- substituted coumarin **5** in the presence of ultrasound radiation as well as in microwave radiation was carried out in the presence of catalyst $FeCl_3$, it was found that the yield reported was better with the methodology used than the conventional method as mentioned in **Figure 19** [65].

Bis-coumarin derivatives have been synthesized in the presence of ultrasound radiation, the reaction was carried out between various aromatic aldehydes and 4-hydroxycoumarin [66].

3.3 Solvent-free synthesis

Large volumes of hazardous and volatile organic solvents are used in numerous conventional chemical reactions. Green chemistry's major objective is to replace such toxic reaction solvents. The design of solvent-free green processes has attracted

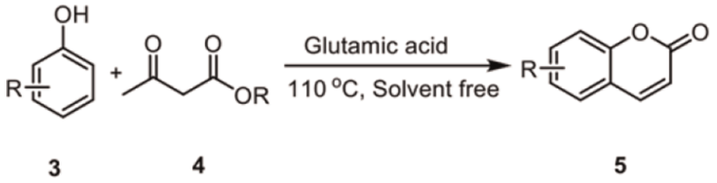
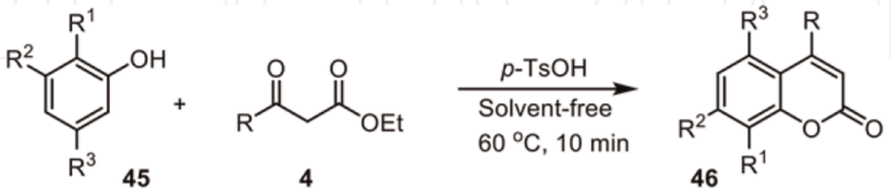


Figure 20.
Solvent-free synthesis of coumarin.



a. R^1 = H; R^2 = OH; R^3 = H R = Me Yield: 98%
b. R^1 = H; R^2 = OH; R^3 = H R = Ph Yield: 92%
c. R^1 = H; R^2 = Me; R^3 = H R = Me Yield: 66%

Figure 21.
Synthesis of substituted coumarin in solvent-free condition.

noticeably more interest from researchers as environmental consciousness on a worldwide scale rises. Many researchers have reported the synthesis of coumarin in a solvent free condition. In the year 2014, Sabetpoor et al. reported the synthesis of simple coumarin analogs **5** in the solvent-free conditions in the presence of glutamic acid as a catalyst. The reaction was carried out between the reactant phenol **3** and keto-ester **4** (**Figure 20**). The yield obtained of the expected product was excellent, in ranging from 83 to 93% [67].

The solvent-free Knoevenagel and Pechmann preparation of coumarin **46** has been carried out by Sugino and Tanaka. Pechmann reaction was carried out between reactant substituted phenol **45** and keto-ester **4** utilizing *p*-toluenesulfonic acid (PTSA catalyst) at 60°C. The yield obtained was good ranging 66–98% with different substituents at Resorcinol **45** and ethyl acetoacetate **4** in **Figure 21**. After heating the mixture for 10 min, it was kept for cooling and then crystalline product was obtained after adding water to the reaction mixture, followed by recrystallization from EtOH [68]. In 2011, a similar type of method has been reported by Makrandi et al. [69].

The same authors have also demonstrated the Knovenagel reaction of salicylaldehyde **47** and β-keto ester **4**, in the presence of piperidine at room temperature for 5 min. The neutralization of the reaction mixture has been carried out using aq. HCl, followed by filtration and recrystallization from EtOH. The 3-ethoxycarbonylcoumarin **48** was obtained with a great yield up to 95%. As well as the other substituted coumarin was also obtained with a high yield [68] as given **Figure 22**.

3.4 Light induced metal-free radical cyclization

In 1912, at the start of the 19th century, Ciamician created a unique technique that used light as a natural source in a chemical reaction. Moreover, utilizing the irradiating method, several organic photochemical processes based on Ultra Violet were developed [70]. In this respect, MacMillan initially investigated in 2008 how a

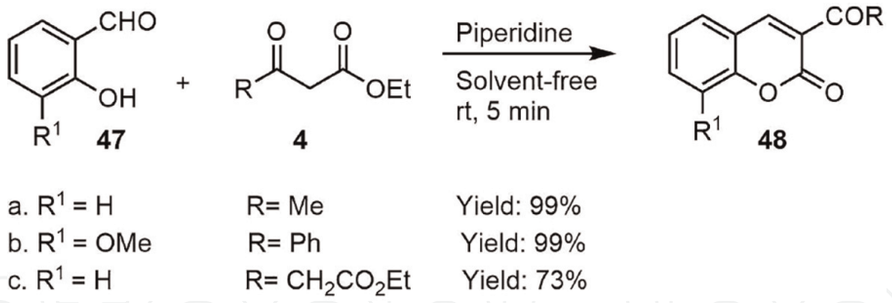


Figure 22.
Synthesis of coumarin via Knovenagel reaction in solvent-free condition.

combination of an organocatalyst and a photosensitive catalyst could enhance the asymmetrical alkylation of aldehydes. Because of its unique single electron transfer (SET) path in very mild reaction circumstances, as well as the fact that it is a secure, economical, and sustainable energy source, visible light-irradiated photoredox catalysis has recently gained a lot of interest. By pairing visible light with metals such as Ruthenium, Iridium, Copper, Nickel, and others, many C-C and carbon-heteroatom bonds can be created. Several studies about how to produce coumarins through metal-free/transition-metal catalyzed inter and intramolecular, radical and electrophilic cyclizations have indeed been reported in the literature, but their practical implementation is constrained by the requirement of a toxic metal, substance, or reagent. In order to synthesize coumarins and other compounds, it is crucial to develop simple, practical, and environmentally friendly techniques [71].

A novel photocatalytic technique to produce (3-acyl 4-arylcoumarin) **51** from aldehyde and aryl alkyne ester was reported in 2018 by Itoh et al. Using visible light, the reaction of phenyl 3-phenyl-2-propynate **49** with *p*-tolualdehyde **50** was conducted in the presence of a AQN catalyst (10 mol%), an oxidant like Bz_2O_2, and K_2CO_3. The necessary 1,2-ester compound was generated in good yields using *p*-substituted phenoxy rings carrying either electron-donating substitution (CH_3, OMe) or electron-poor groups (I, RCOOR', CH_3CO, and OAc). It's noteworthy that the team performed a few straightforward control trials to demonstrate the molecular pathway (**Figure 23**). The method's appealing qualities also include mild reaction conditions, affordable catalysts, and readily available substrates [72].

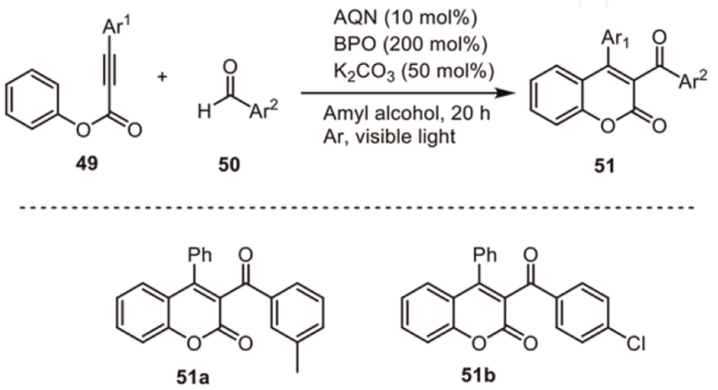


Figure 23.
Synthesis of 3-acyl 4-arylcoumarin.

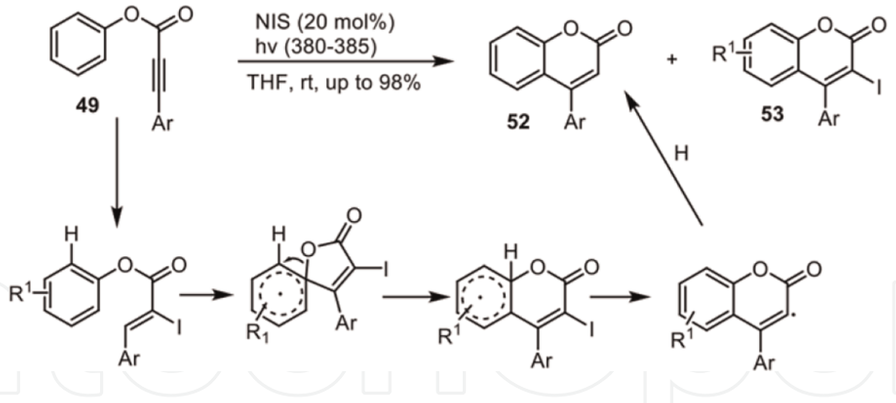


Figure 24.
Synthesis of iodo coumarins via light-assisted metal-free radical cyclization.

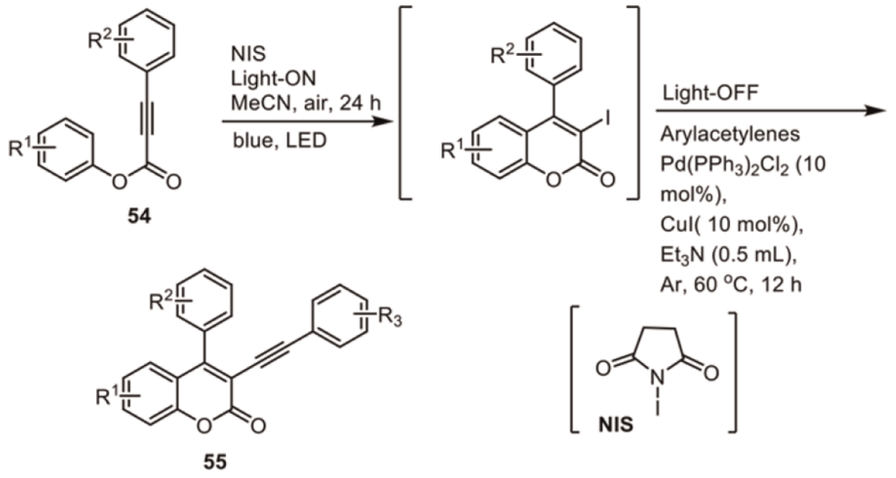


Figure 25.
Synthesis of 3-arylacetylene coumarins.

Li and colleagues described the straightforward photocatalyzed cyclization of alkynoates **49** to iodo coumarins in a THF solvent at 25°C and metal-free circumstances in 2019 (**Figure 24**). After examining the effects of various light sources on the procedure, it was discovered that visible light with a wavelength of 380–385 nm is the most effective. Iodo coumarins **53** were synthesized in high yields using substrates that had substitutions at the *p*-position of the benzene ring [71].

Wu and co-workers very recently reported, in 2020, a simple and practical one-pot reaction to synthesize 3-arylacetylene coumarins **55** from the precursor **54** using thermo-catalysis and photosensitizer-free photocatalytic activity. The basic and effective photocatalytic reactions of *p*-tolyl 3-phenylpropiolate and *N*-iodosuccinimide (NIS) have been conducted in acetonitrile to carry out the one-pot process as given **Figure 25** [73].

3.5 Metal-mediated radical cyclization

Metal-catalyzed reactions have established themselves as one of the crucial steps in the synthesis of organic compounds. There is various methodology reported by chemists for the construction of coumarin derivatives via metal-assisted Radical cyclization reaction. Sulfonyl coumarins **58** can be synthesized from phenyl 3-

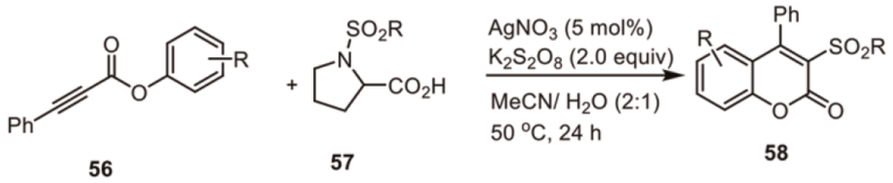


Figure 26.
Synthesis of sulfonyl coumarins.

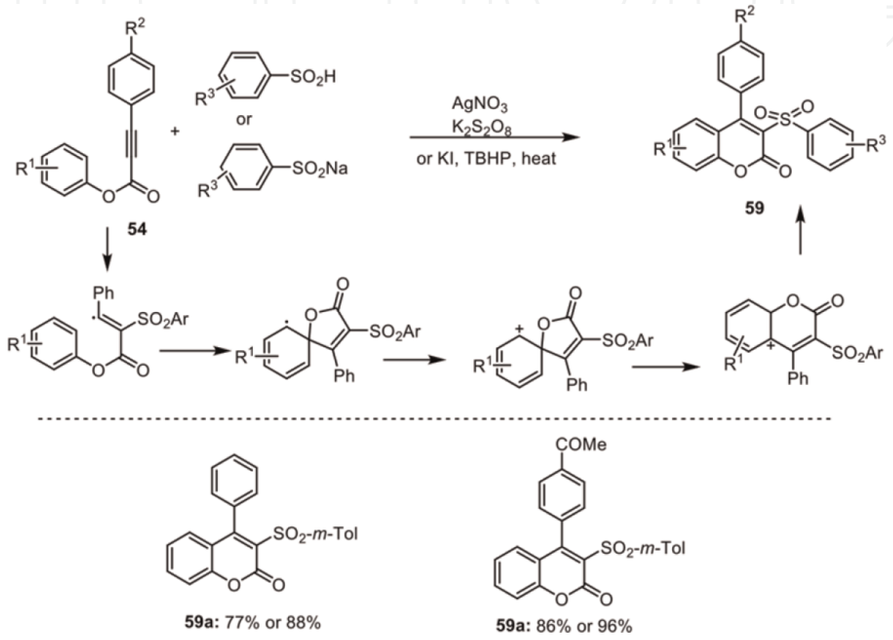


Figure 27.
Synthesis of 4-phenyl 3-sulfonylcoumarins.

phenylpropiolates **56** and tosyl prolines **57** as starting material in the presence of $AgNO_3$ (catalyst), and an oxidant like potassium persulphate in solvent MeCN/H_2O (2:1) at a temperature of 50°C as showed in **Figure 26**. It is to be noticed that the yield is not good with alanine, phenylalanine, and glycine however, it is good with valine or 2-methylalanine sulfomide [74].

In the year 2018, Zhang et al. reported the synthesis of 3-phenyl sulfonyl-coumarins. The reaction is carried out with starting material **54** and sodium sulfinate/sulfinic acids, the reagents required for the reaction are silver nitrate, TBHP, and KI, in solvent (mixture of acetonitrile and water) at 80°C, in the presence of nitrogen atmosphere (**Figure 27**). Various substituted starting materials **54** can be used for synthesizing different derivatives of coumarin **59**. The yield of the product is better with sulfinates than sulfinic acid [75].

Recently in 2019, 3-monofluoromethylated coumarins **60a-c** have been synthesized by Fu and coworkers *via* monofluoromethylation in the presence of a silver catalyst. When used as a CH_2F radical source, phenyl alkynoate **54** and monofluoromethyl benzo[*d*]thiazol-2-yl sulfone were combined with $AgNO_3$(10 mol %) and potassium persulfate (4.0 equiv.) in DMSO (3.0 mL) and heated to 60°C in an environment of nitrogen for 24 h (**Figure 28**). The reaction is compatible with both electron-rich and deficient substituents at the para position of phenyl ring [76].

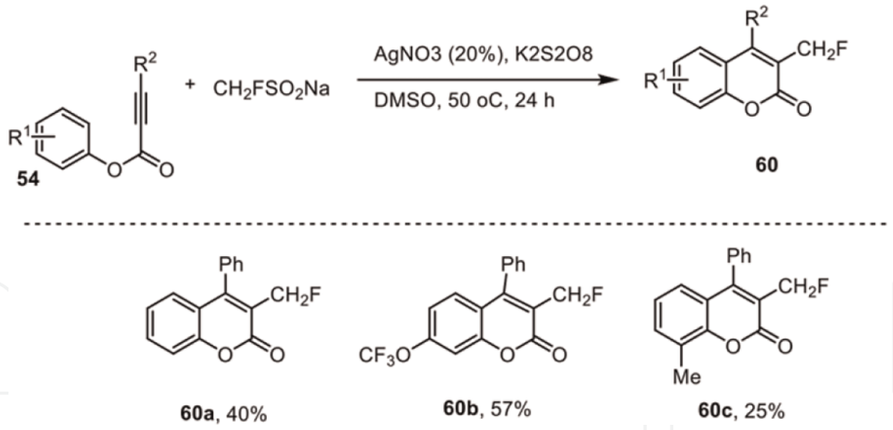


Figure 28.
Synthesis of 3-monofluoromethylated coumarins.

3.6 Metal catalyzed electrophilic cyclization

It has been a challenge for chemists and is crucial in the disciplines of agrochemicals, medicines, and healthcare to activate the C-H bond by a metal-catalyst that results in the novel and advantageous chemically synthesized reaction that creates the C-C bond. A beneficial use relates to organic compounds such as annulated arenes, carbocycles, and heterocycles. Intramolecular hydroarylation is the methodical insertion of arene C-H bonds over numerous bonds in an intermolecular approach. In 2014, it was demonstrated that Au(III) catalyzed electrophilic hydroarylation of aryl alkynoate **61** yielded its respective coumarin analogues **62** through ortho cyclization route and de-aromative ipso-cyclized product in good yield by a modest adjustment in the reaction process. The specific production of coumarin derivatives **62** results from the utilization of an Au-catalyst and AgOTf as additives in an anhydrous DCE solvent, and the presence of a little amount of water results in spirocycles **63** as illustrated in **Figure 29** [77].

Anderson and colleagues demonstrated the electrophilic cyclization-catalyzed formation of 3-organoselenyl-2*H*-coumarins **64a-e** and 3-organoselenylquinolinones from related aryl alkynoates and arylpropiolamides **54**, respectively, in the ideal

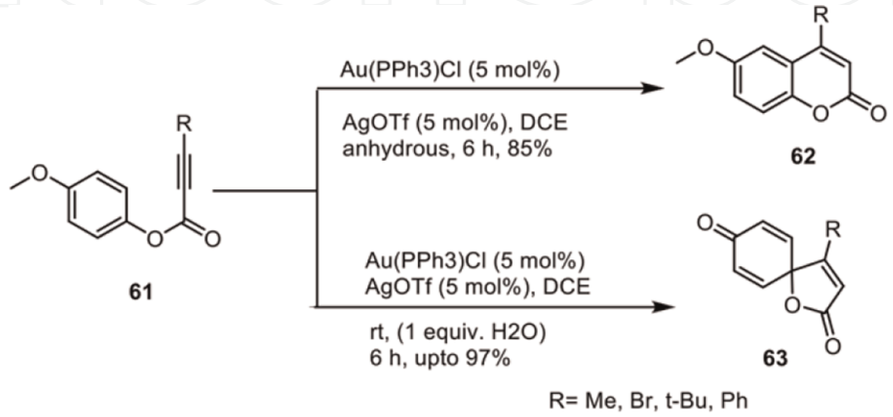


Figure 29.
Au-catalyzed coumarin synthesis.

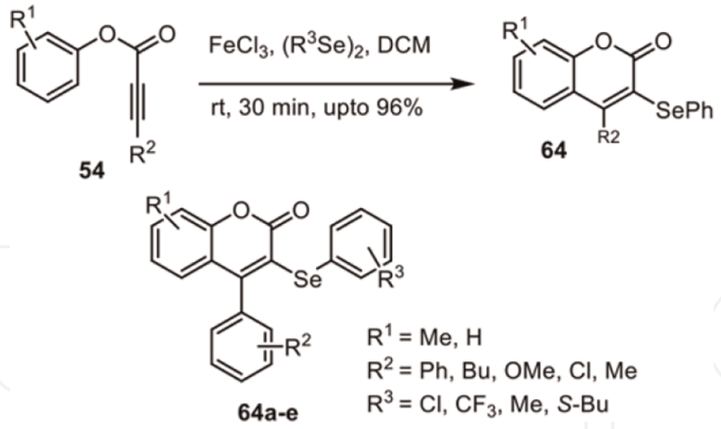


Figure 30.
Fe-catalyzed coumarin synthesis.

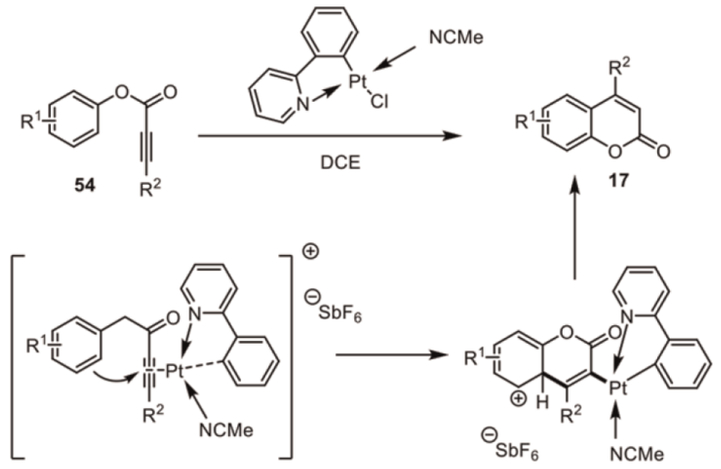


Figure 31.
Pt-catalyzed coumarin synthesis.

reaction conditions attained in a similar manner with organoselenium reagents in dichloromethane solvent as given in **Figure 30** [78].

In 2020, Zaitceva and colleagues showed that cyclometalated (ppy)Pt(II) compounds can catalyze the intramolecular cyclization of phenyl propynoates **54** to produce coumarins **17** and benzocoumarins. A considerable number of substituted coumarins and benzocoumarins were synthesized employing this catalytic approach, and a wide variety of variants were identified to be compatible with the cyclization mechanism (**Figure 31**) [79].

3.7 Homogeneous catalytic reaction

In 2014 Chang et al. proposed a gentle and metal-free approach to synthesize 3-sulfenylated coumarins **66a-c** through cyclization of aryl alkynoates **54** and corresponding *N*-sulfanylsuccinimides **65** promoted by $BF_3{\cdot}Et_2O$ as a Lewis acid (**Figure 32**) [80].

Wu et al. published a practical and flexible approach for functionalizing 3-sulfenylcoumarin **67**a-c and derivatives of 3-sulfenylquinolinone *via* iodine-catalyzed electrophilic cyclization in 2017 (**Figure 33**). The reaction was carried out with phenyl

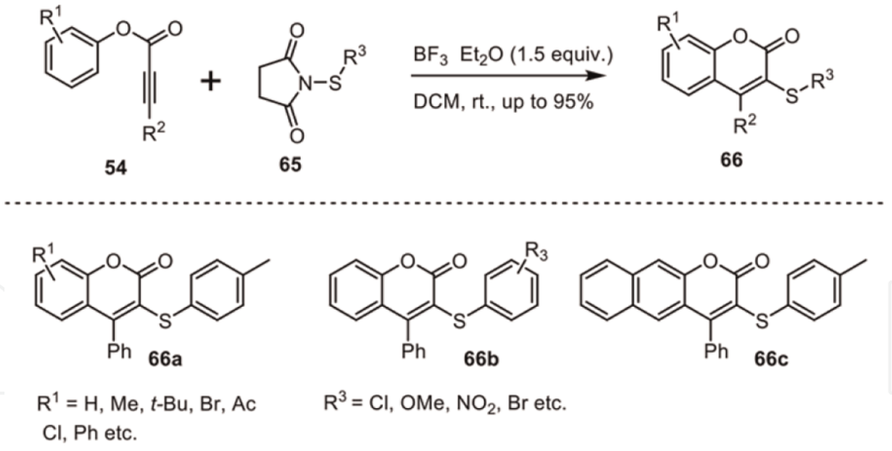


Figure 32.
Preparation of 3-sulfenylated coumarin.

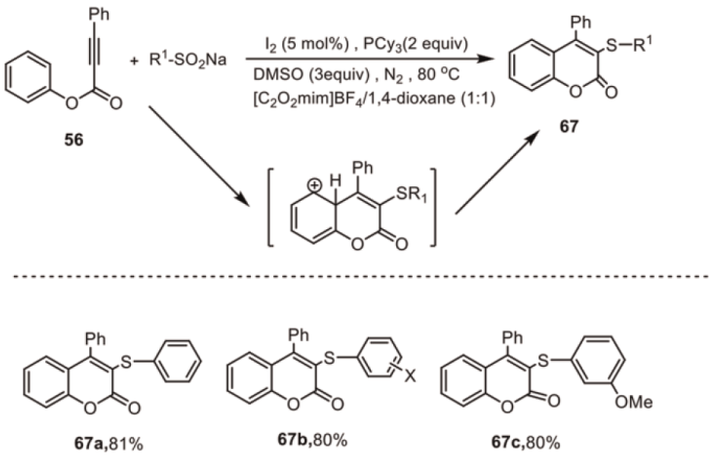


Figure 33.
Iodine-mediated synthesis of 3-sulfenylcoumarin.

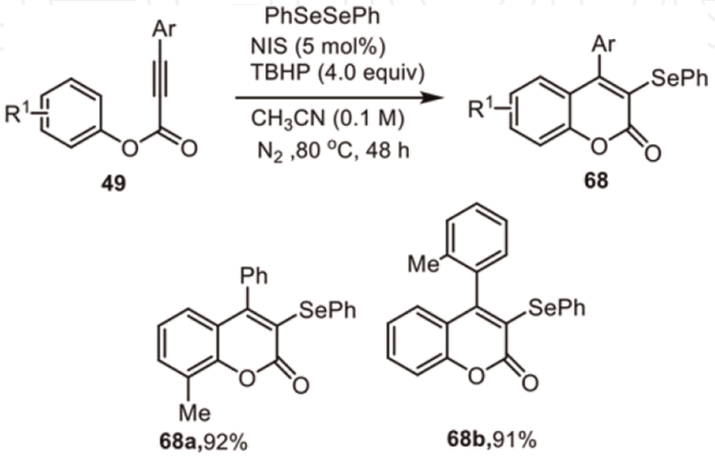


Figure 34.
Formation of 3-organoselenyl-2H-coumarins by propargylic aryl ether.

3-phenylpropiolate **56** and sodium benzenesulfinate, iodine and in DMSO and solvent mixture dioxane and $[C_2O_2mim]BF_4$ were used as co-solvents [81].

Later in 2019, Fang and coworkers reported a methodology for the preparation of 3-organoselenyl-2*H*-coumarins **68** via oxidative radical cyclization of propargylic aryl ethers **49** and diaryl diselenides. The reaction of (3-phenoxyprop-1-yn-1-yl)benzene and diphenyl diselenide was carried in CH_3CN with *tert*-butyl hydroperoxide(4.0 equiv.) at 80°C for 48 h yielded 85% of the expected product **68a-b** as shown in **Figure 34** [82].

3.8 Heterogeneous catalytic reaction

One of the foundational elements of the chemical and energy industries is heterogeneous catalysis will play a key role in facilitating the shift to these sectors' eventual transformation to carbon-neutral operations [83]. Nowadays, heterogenous catalysis is playing an important role in the organic synthesis, and still it is used for converting petroleum as well as natural gas into the cleaner, capable fuels [84, 85].

Researchers have long struggled with the activation of the C-H bond by metal catalysts, which results in the novel and advantageous synthetic organic reaction that creates the C—C bond and is crucial in the agrochemical, pharmaceutical, and medical fields. Intramolecular hydroarylation, which is the systematic introduction of arene C—H bonds over multiple bonds in the intermolecular path way, gives a useful organic products like annulated arene carbocycles as well as heterocycles. A novel method has been demonstrated by Yuzo Fujiwara et al. in the year 2000, for the preparation of coumarins and quinolinones *via* intermolecular hydroarylation substrate. Utilizing the procedure, different aryl alkynoates **54** and alkynanilides can be quickly converted to the required coumarin derivatives **69a-b** at a temperature between 25 and 27°C and with a catalytic quantity of Pd(OAc)2 in a mixture of solvents TFA and DCM as shown **Figure 35** [86].

Dalibor and coworkers in 2004 have also demonstrated $PtCl_4$ catalyzed intramolecular electrophilic hydroarylation of various substrates having different structures which includes alkynoate esters **70**, propargylamines, and propargyl ethers, that results into a great yield of 6-endo cyclized compounds of coumarin derivatives **71** and **72** in DCM as well as in solvent like dioxane at 25°C. This reaction was studied with a variety of transition metals and their salts, and it was determined that $PtCl_2$ and $PtCl_4$ were both successful, however $PtCl_2$ produced lower yields than $PtCl_4$ when used with appropriate organic solvents such as DCM or dioxane (**Figure 36**) [87].

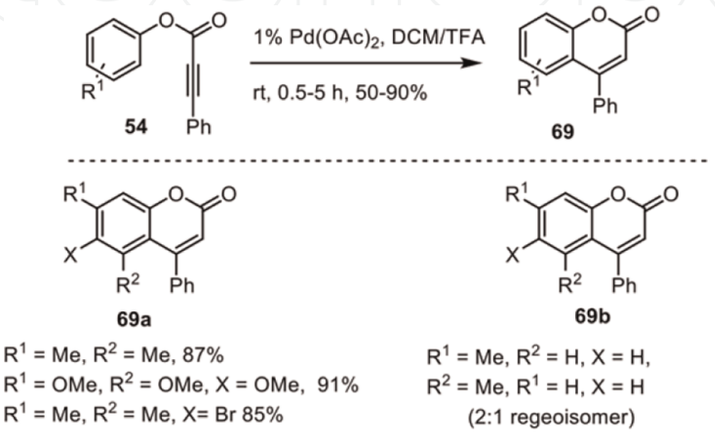


Figure 35.
Synthesis of coumarins by pd-catalyzed intramolecular hydroarylation.

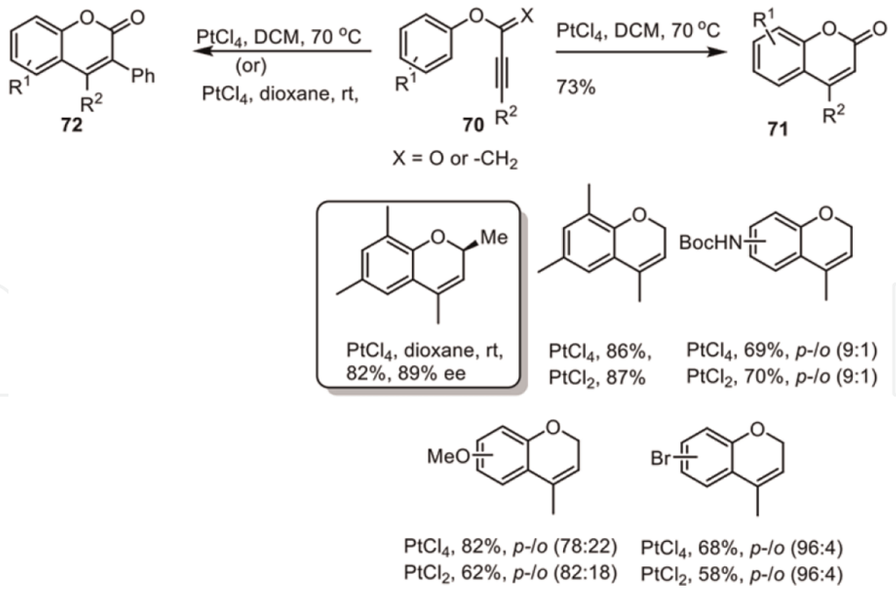


Figure 36.
Preparation of coumarins catalyzed by $PtCl_4$.

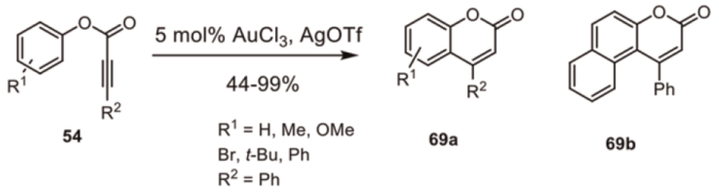


Figure 37.
Method for preparation of coumarins catalyzed by $AuCl_3$.

Later in 2004 Chuan and coworkers have described gold(III)-mediated intermolecular hydroarylation reaction of aryl alkynoates **54** under neat conditions to give coumarin derivatives **69** in high yields (**Figure 37**). In this reaction higher temperature (70°C) was needed in some cases and the process of the reaction is distinct from the same reactions which were catalyzed by Pd(II), Pt(II), Pt(IV), and Ru(II) has been described [88].

4. Recent applications of coumarin based derivatives

Both natural and synthesized coumarins have received a lot of interest recently due to their various biological and pharmacological characteristics, which expand their industrial potential. The usage of coumarins in the creation of biochemical probes has also significantly grown as a result of their photosensitizing and fluorescent capabilities. Umbelliferone, esculetin, and quercetin are coumarins that have anti-oxidant effects and defend against oxidative damage to cellular DNA [89, 90]. Esculetin has been reported best for protecting cells from oxidative damages [91]. By preventing vitamin K from working, the dicumarol exhibits anti-coagulant qualities, whereas angelmarin has been utilized for pancreatic cancer. Sakaguchi and co-workers reported numerous derivatives of coumarin, including 7,7-dihydroxy-coumarins and others, which are known to have anti-oxidant effects. Free radical production results in oxidative damage to DNA, which activates p53. Recently, in 2017 and 2018, Sahu [92] and co-workers and Witaicenis [93] and coworkers respectively, reported the antioxidant property of 4-methylesculetin.

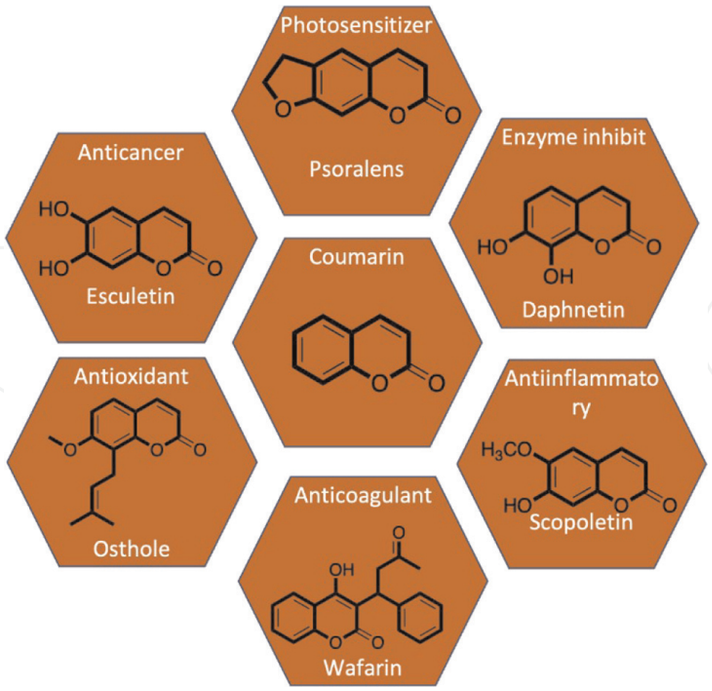


Figure 38.
Coumarin derivatives and their applications.

Coumarin structures like Cloricromene, Warfarin shows good anti-cancer activity and there are being used in the treatment of cancer. Vipirinin, a derivative of coumarin has is used to suppress the Vpr-depended gene (viral) and thus acts as an antagonist [94]. Osthol, a coumarin is well known for its antioxidant property which prevents acetaminophen activation as well as functions in the regulation of the concentration of free calcium that exists in the intracellular space [95]. Coumarins' photosensitivity is beneficial for detecting the activation of particular enzymes as well as bio-molecules including DNA,

S. No.	Activity	Derivative of coumarin	Reference
1	Antioxidant [97–99]	Chrysin Scopoletin Umbelliferone	[97–99]
2	Antiinflammatory [100–102]	Esculetin 4-methyl esculetin Umbelliferone-6-carboxylic acid Scopoletin	[100, 101, 102]
3	Anticancer [103–107]	Esculetin Umbelliferone Scopoletin Cloricromene	[103–106]
4	Anticoagulant [22, 108, 109]	Warfarin Acenocoumarol	[22, 108, 109]
5	Photosensitivity [110, 111]	Furanocoumarins Psoralens	[110, 111]
6	Enzyme inhibitors [105, 112]	Daphnetin Vipirinin	[105, 112]

Table 1.
Coumarin derivatives and their activities.

protein, as well as lipids [96]. Also, they have been utilized in the area of pharmacology to analyze the potency of various drug molecules. Furanocoumarins acts as potent photosensitizing agents by killing bacteria and inactivating virus in a conjugated reaction with Ultraviolet light (**Figure 38**) [13].

5. Conclusions

Coumarin derivatives are highly valuable lactone-based organic molecules for academics and bio-pharma industries due to the unique nature of chemical properties, and flexible design system to access a broad range of functionalized coumarin scaffolds via simple synthetic chemical transformation as a result, a huge number of coumarin derivatives have been successfully developed and produced in single steps. This review permits many protocols of one-pot construction of coumarins and their derivatives, together with well-studied name reactions and other types of coupling reactions as well using different metal-based catalysis, and visible light-mediated photocatalysis. While these aforementioned traditional name reactions have been employed for several decades, new methods developments have been widely achieved in the last few years such as microwave-, ultrasound-helped, light-induced metal-free radical cyclization, metal-mediated radical cyclization, metal-catalyzed electrophilic cyclization, miscellaneous, homogeneous catalytic reaction and heterogeneous catalytic reaction and solvent-free conditions, This new system were applied in a challenge to maximize the single-pot reaction yield, diminish the reaction time, and reduce the unwanted side reactions and as well as making these reactions more bioactive candidates. This review concluded that this catalysis-based new developments can play an increasing role in the preparation of highly substituted coumarin derivatives by modifying the unpleasant typical reaction conditions associated with the standard synthetic routes.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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