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Review Article

A Review of Classical and Advanced Methodologies for Benzocoumarin Synthesis

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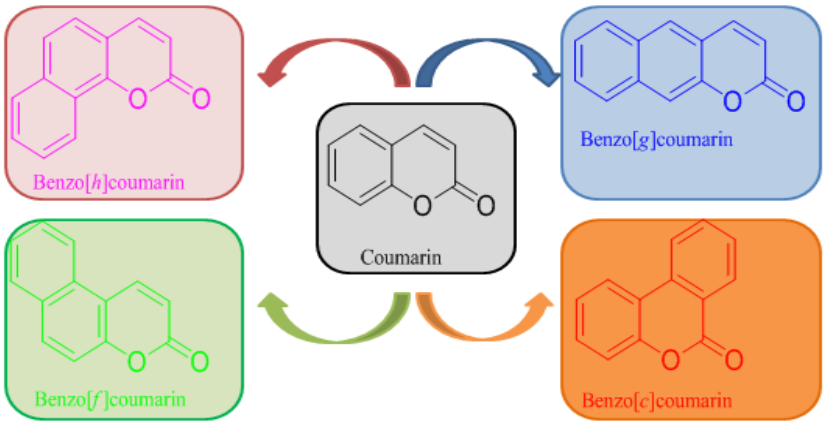
ABSTRACT

Coumarins belong to a worthwhile family of heterocycles that exist naturally and/or synthetically. Benzocoumarins are a type of extended structure of coumarins in which the coumarin core is fused with the benzene ring at 7,8-, 6,7-, 5,6-, or 3,4-positions. Benzocoumarins have a wide range of applications, especially in organic and pharmaceutical chemistries, which makes them of particular interest. Serious efforts have been undertaken over the past decades not only to isolate them from natural resources but also to develop efficient and new approaches to synthesize benzocoumarins with novel or better biomedical properties. Based on the scientific literature, this study outlines the classical methodologies and their advancements that are applied in the synthesis of benzocoumarins.

GRAPHICAL ABSTRACT



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Introduction

Coumarin (**1**) (2*H*-1-benzopyran-2-one), as shown in Figure 1, is an organic compound with the $C_9H_6O_2$ formula that belongs to the benzopyrone family. It was isolated for the first time in 1820 by Vogel from tonka beans and synthesized for the first time in 1868 by Perkin [1]. The coumarin backbone is an intriguing starting point for diverse applications due to its simplicity and versatility [2,3]. It can be found in industrial additives, cosmetics, fragrances, and aroma enhancers. However, medicinal and organic chemistry are the fields where it plays the most significant role [4]. Coumarin derivatives have different biomedical potentials such as antimicrobial [5–9], anticoagulants [10], antioxidant [11–14], anticancer [15–20], and anti-inflammatory [21–23] activities. Nowadays, coumarins isolation, synthesis, and evaluation have become a very appealing and fast-evolving field [4,24,25].

Benzocoumarins (benzochromenones) are a group of the π-extended version of coumarins. Based on the location of the fused benzene ring in the parent coumarin (**1**), benzocoumarin derivatives can be divided into four categories: 7,8-benzocoumarin (**2**) (benzo[*h*]coumarin), 6,7-benzocoumarin (**3**) (benzo[*g*]coumarin), 5,6-benzocoumarin (**4**) (benzo[*f*]coumarin), and 3,4-benzocoumarin (**5**) (benzo[*c*]coumarin), as illustrated in Figure 1 [26].

Benzocoumarins have attained curiosity due to their diverse array of biological properties (e.g., anticancer, antioxidant, antifungal, antibacterial, and antidiabetic) that stimulate pharmaceutical chemistry-related investigations and research. Hence, numerous benzocoumarins have been prepared for screening, and several attractive pharmacological properties identified as a result. Therefore, their scaffolds have become a hot topic in drug discovery in recent years [27]. These results prompted the work team to publish a review to cover the synthetic strategies to prepare benzocoumarins, concentrating on the most significant examples.

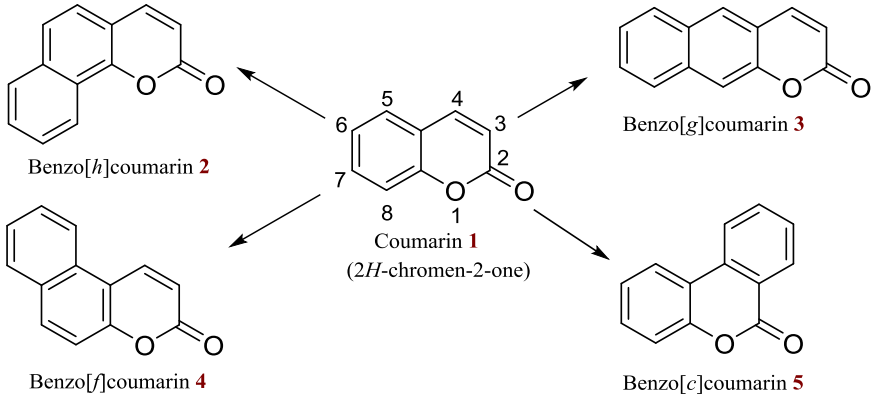
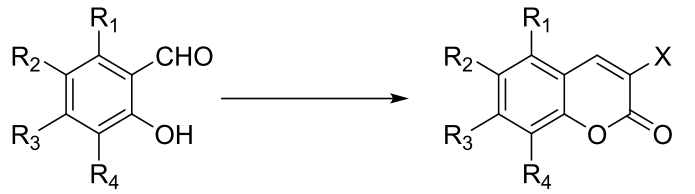


Figure 1: The chemical structures of coumarin and benzocoumarins

Strategies for Synthesis of Benzocoumarins

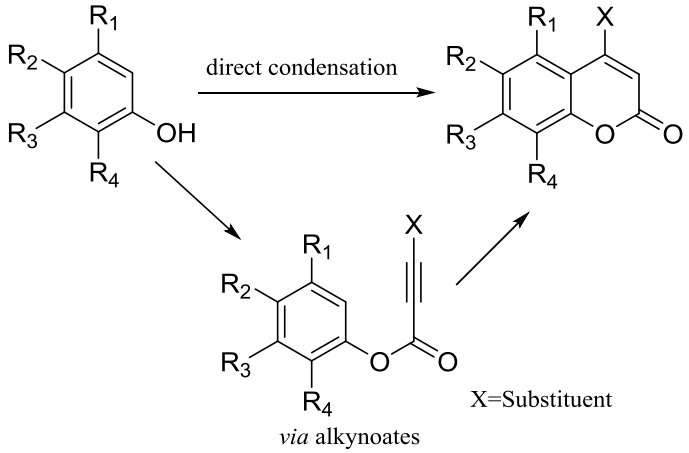
Benzocoumarin derivatives, except benzo[*c*]coumarins, are synthesized utilizing the same approaches as coumarins, like Knoevenagel condensation [28], metal-catalyzed cyclization [29], and Pechmann reaction [25]. Almost all of these synthesis approaches start with one of two chemical groups, namely naphthol or *ortho*-hydroxynaphthaldehyde. The 2*H*-1-Benzopyran-2-one moiety is synthesized from *ortho*-hydroxynaphthaldehyde via intramolecular-cyclization with the OH group after Knoevenagel condensation with an ester of malonic acid or its analog, as illustrated in Figure 1. The creation of distinct types of benzocoumarins (**2**, **3**, and **4**) is therefore dependent on the locations of hydroxyl and formyl groups on the starting *ortho*-hydroxynaphthaldehydes (1-hydroxynaphthalene-2-carbaldehyde or 2-hydroxynaphthalene-1-carbaldehyde or 3-hydroxynaphthalene-2-carbaldehyde) [30].



Symbol	R_1	R_2	R_3	R_4	Product
2	-H	-H	-CH=CH-CH=CH-		Benzo[*h*]coumarin
3	-H	-CH=CH-CH=CH-		-H	Benzo[*g*]coumarin
4	-CH=CH-CH=CH-		-H	-H	Benzo[*f*]coumarin

Scheme 1: The general description of benzocoumarins synthesis from *ortho*-hydroxynaphthaldehydes

Otherwise, via intramolecular cyclization after electrophilic substitution of naphthol compounds with *β*-keto ester compounds, benzocoumarins (**2**, **3**, and **4**) can be directly produced. In the presence of strong Lewis or Bronsted acids, the reaction takes place with the proper electrophile compounds, as shown in the upper pathway in Scheme 2. In another route, by using metal as a promoter, functionalizing the aryl C–H group in alkynoates is also possible, as demonstrated in the lower pathway in Scheme 2. The location of the OH group in the initial naphthol moieties (1-naphthol or 2-naphthol) determines the synthesis of distinct types of benzocoumarins. Two isomers arise in significant proportions from 2-naphthols, and in some situations, their polarity differences allow them to be separated [30].



Symbol	R_1	R_2	R_3	R_4	Product
2	-H	-H	-CH=CH-CH=CH-		Benzo[*h*]coumarin
3	-H	-CH=CH-CH=CH-		-H	Benzo[*g*]coumarin
4	-CH=CH-CH=CH-		-H	-H	Benzo[*f*]coumarin

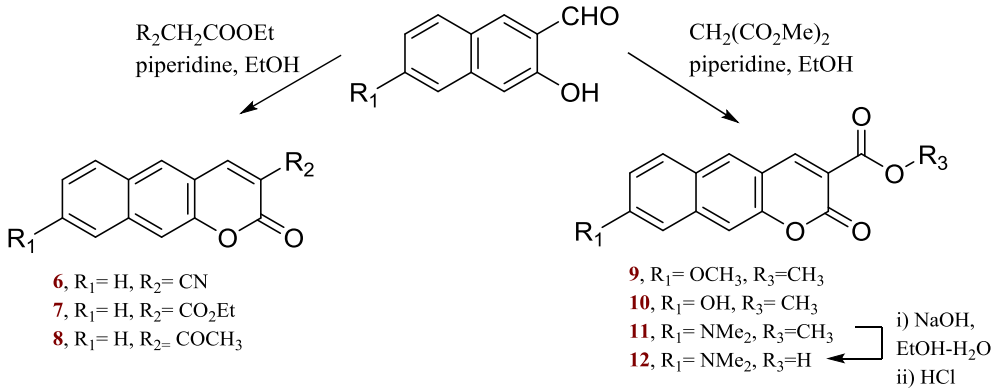
Scheme 2: The general description of benzocoumarins synthesis from phenols

Thus, numerous synthetic approaches for benzo[*f*], benzo[*h*], and benzo[*g*]coumarin derivatives have been established on the basis of the two known strategies stated above, as discussed in the following. Benzo[*c*]coumarins synthesis takes relatively different approaches. For that reason, they will be discussed separately later.

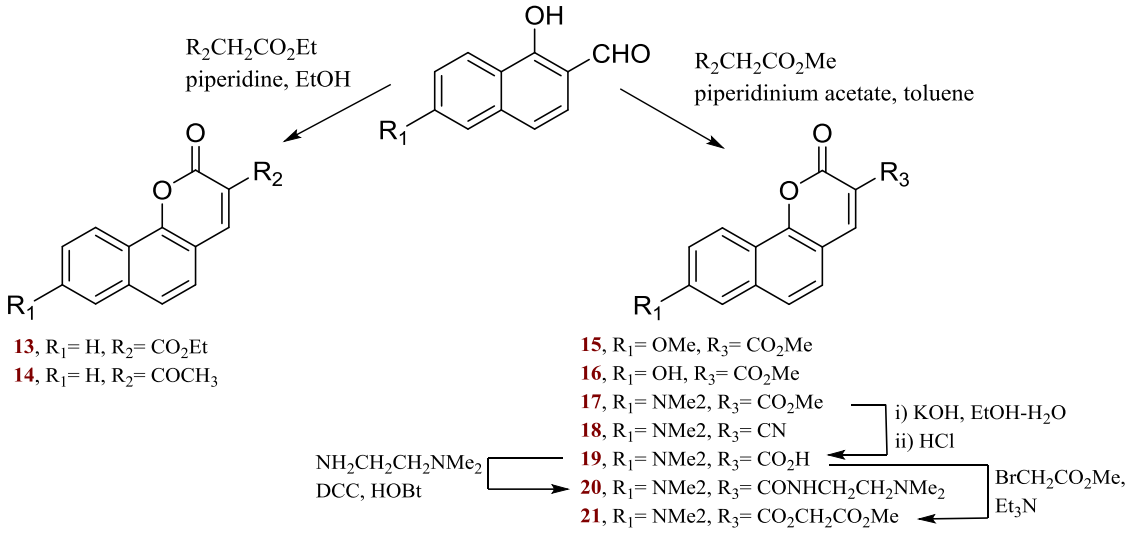
Knoevenagel Condensation

The synthesis of benzocoumarin-based derivatives via the Knoevenagel condensation method is widely used in pharmaceutical chemistry. The *ortho*-hydroxynaphthaldehydes

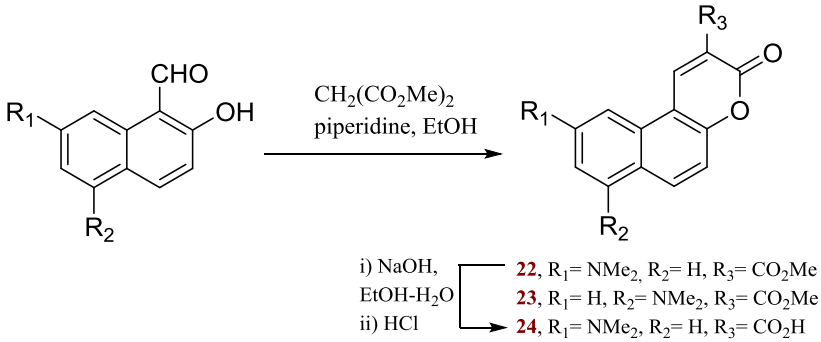
can be used to make benzocoumarins with dialkyl malonates, ethyl acetoacetate, and ethyl cyanoacetate containing an invigorated methylene, using piperidine as a catalyst in dry methanol or ethanol, through cascade Knoevenagel condensation and cyclization reaction [31]. The position of the hydroxyl and formyl groups on the starting *ortho*-hydroxynaphthaldehydes affects the ring formation's regioselectivity. For this reason, to create a particular type of benzocoumarin, this synthetic strategy is favored. As shown, 2-hydroxy-3-naphthaldehyde can be used to make benzo[*g*]coumarin-based compounds (**6-12**) (Scheme 3), 1-hydroxy-2-naphthaldehyde produces benzo[*h*]coumarin-based compounds (**13-21**) (Scheme 4), and 2-hydroxy-1-naphthaldehyde produces benzo[*f*]coumarin-based compounds (**22-24**) (Scheme 5) [30].



Scheme 3: Synthesis of benzo[*g*]coumarin-derived compounds via the reaction of Knoevenagel



Scheme 4: Synthesis of benzo[h]coumarin-derived compounds via the reaction of Knoevenagel



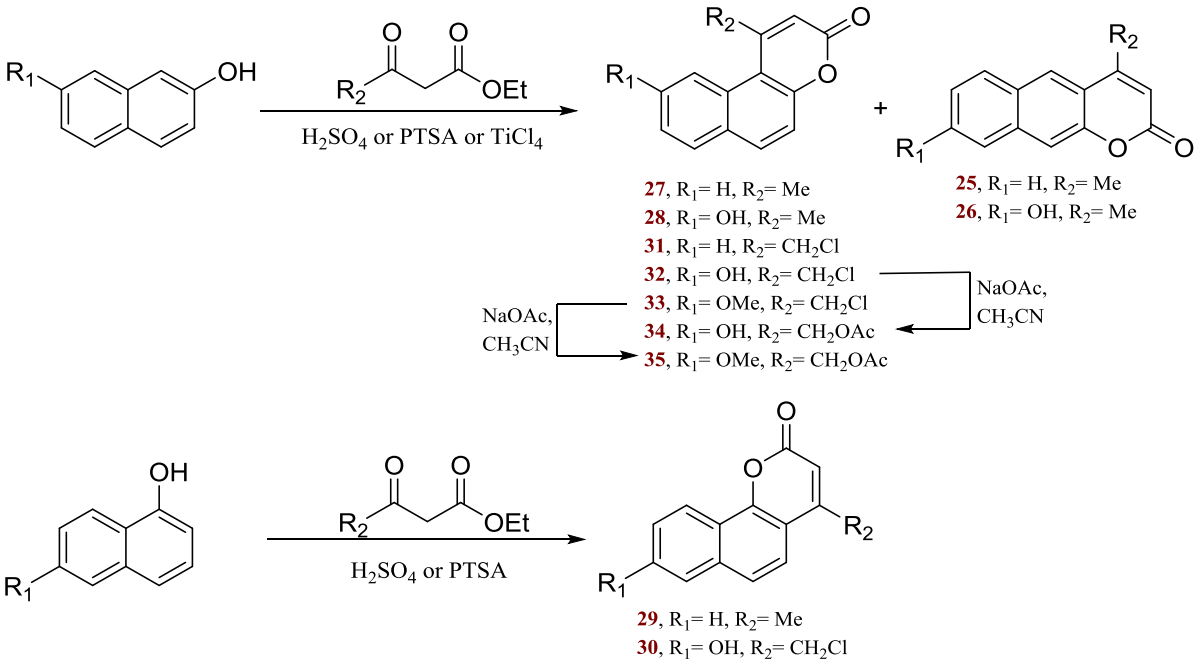
Scheme 5: Synthesis of benzo[f]coumarin-derived compounds via the reaction of Knoevenagel

The *ortho*-hydroxynaphthaldehydes with donor groups (–NMe_2, –OH, –OMe) at the proper position on the naphthalene ring were used to synthesize benzocoumarins containing donor-acceptor groups (**9-12**, **15-21**, and **22-24**) [32, 33].

When more functionalization is required, the 3-carboxy group can be utilized (**19-21**). In general, 3-carboxy benzocoumarins were synthesized in two steps beginning with *ortho*-hydroxynaphthaldehydes and proceeding via Knoevenagel condensation. Then, the corresponding esters are hydrolyzed using a base, as illustrated for (**12**), (**19**), and (**24**) [34, 35]. Also, different organic salts or bases can be used as promoters for the Knoevenagel condensation besides piperidines like sodium acetate [36], pyridine [37], pyrrolidine [38], and piperidinium acetate [34].

Pechmann Reaction

Pechmann condensation is one of the most appealing strategies for the synthesis of bezocoumarin-based derivatives. Under acidic conditions, the Pechmann reaction of naphthols with *β*-keto esters or acids produces benzocoumarins. The mechanism begins with esterification/*trans*-esterification. After that, the new ring is generated by a nucleophilic attack of the activated carbonyl, followed by dehydration [39]. 1-Naphthol compounds react with *β*-keto esters much more readily than 2-naphthol compounds, according to Appel, who discovered this in 1935. This result was supported by the finding that the reaction of ethyl acetoacetate with naphthalene-1,3-diol produced only 5-hydroxybenzo[*h*]coumarin [40]. Wolfbeis' seminal paper later confirmed this assignment. Even in the presence of mild promoters like sulphamic acid [41], 1-naphthols selectively produced benzo[*h*]coumarins in good yields (**29** and **30**) [42, 43]. However, the same reactions with 2-naphthol compounds necessitated the use of a strong acid (70–80% H_2SO_4) and heated to 100°C to yield a mixture of benzo[*g*]coumarins (**25** and **26**) and benzo[*f*]coumarins (**27**, **28**, and **31-35**) [30], as illustrated in Scheme 6.

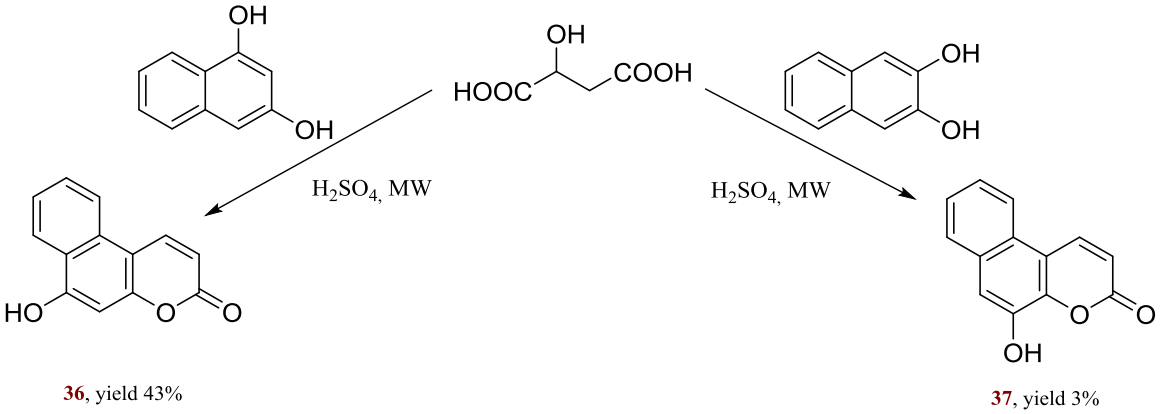


Scheme 6: Synthesis of benzocoumarin-derived compounds via the reaction of Pechmann

Regulating the pH of their aqueous solutions, Tao and his colleagues were able to produce both regioisomers (**26** and **28**) from the Pechmann chemical route of 2,7-naphthalenediol [44]. According to the authors, benzo[*f*]coumarin (**28**) and benzo[*g*]coumarin (**26**) were isolated in yields of 28% and 42%, respectively. Dichtel and his colleagues, on the other hand, discovered the exclusive synthesis of benzo[*f*]coumarin (70% yield) while examining the condensation of

$CF_3COCH_2CO_2Et$ with 2,7-naphthalenediol [45]. In addition, only benzo[*f*]coumarin (40% yield) was produced from the reactions of 2,6-naphthalenediol [46]. In a similar way, only benzo[*h*]coumarin was produced by 1,7-naphthalenediol [30]. Ohwada and his colleagues made similar observations while examining the reaction of ethyl acetoacetate with 7-methoxy-2-hydroxynaphthalene [47].

Numerous modifications were successful in allowing the Pechmann synthetic route to be performed under moderate reaction conditions, such as the iodine-catalyzed reaction [48], *p*-toluenesulfonic acid-catalyzed reaction [49], and poly(4-vinylpyridinium)perchlorate mediated reaction under ultrasound irradiation [50]. Generally, the Pechmann reaction yields benzocoumarin derivatives with substituents in the C4 position. Symeonidis and his colleagues (2009) stated that unsubstituted benzocoumarin derivatives at 4-position might be synthesized under microwave irradiation, using 1,3-naphthalenediol with propiolic acid or its ester produced *in situ* from 2-hydroxybutanedioic acid, as indicated in Scheme 7 [51]. Under these reaction settings, 1,3-naphthalenediol yielded a moderate amount of the corresponding benzocoumarin (**36**), while 2,3-naphthalenediol yielded the corresponding benzocoumarin (**37**) in a very low amount [51].



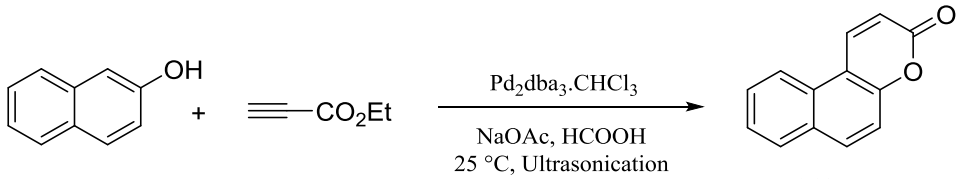
36, yield 43%

37, yield 3%

Scheme 7: Synthesis of unsubstituted benzo[f]coumarins at the C4 position

Metal-Catalyzed Reactions

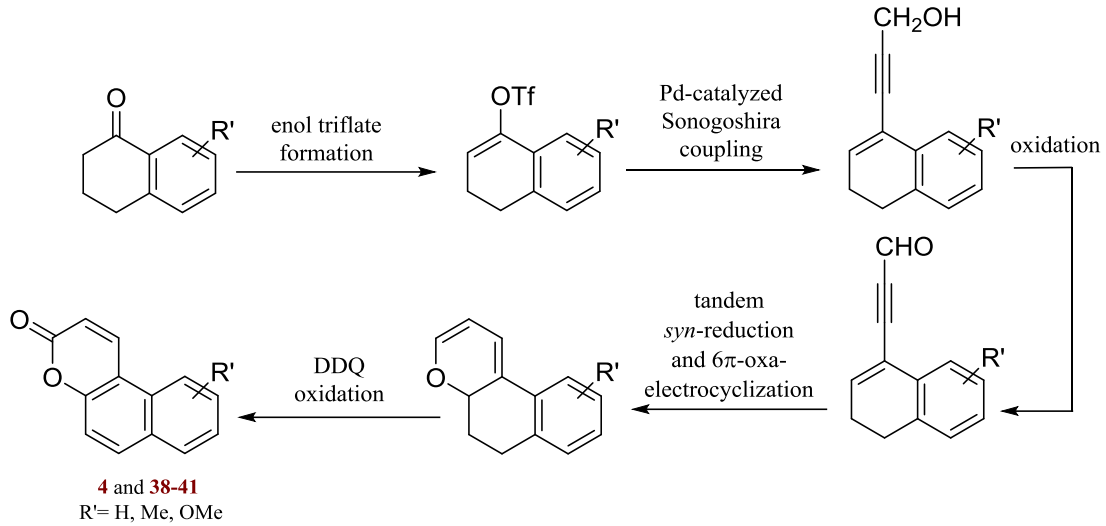
In general, benzocoumarins are formed by metal-mediated cyclization of aromatic rings via C–H functionalization. Naphthol and its derivatives undergo C–H functionalization in the *ortho*-positions. For this purpose, palladium catalysts were widely utilized. Other metals that are effective include nickel, zinc, silver, gold, and platinum. Greenman and his colleagues were the first to demonstrate the addition of phenol and alkynoate compounds via a net C–H insertion utilizing palladium as a reaction promoter. Under sonication, the reaction occurs at room temperature to yield benzo[*f*]coumarin with no substituent (**4**) in high quantities, as indicated in Scheme 8 [52].



4, yield 61%

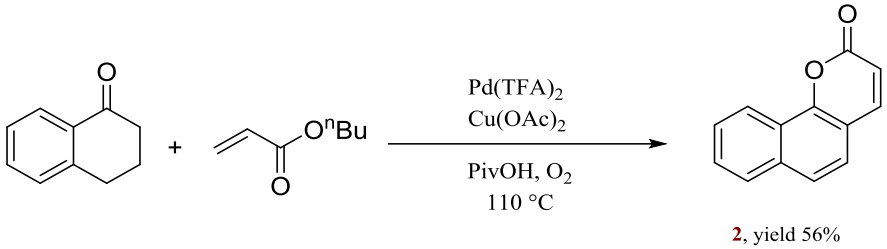
Scheme 8: The synthesis of a benzo[*f*]coumarin via palladium catalyst

Hon and his colleagues (2009) discovered a useful and new technique to synthesize benzo[*f*]coumarins (**4** and **38**-**41**) in the presence of palladium as a promoter by oxidizing the corresponding 2*H*-pyrans produced *in situ* during *cis*-dienals electrocyclization, as shown in Scheme 9 [53].



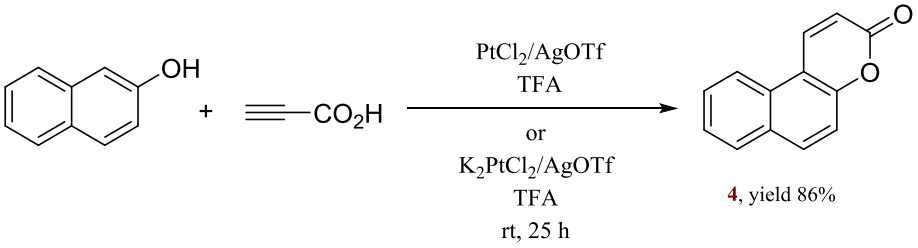
Scheme 9: The synthesis of benzo[f]coumarins via the reaction of cross-coupling promoted by palladium metal

Lately, a one-pot procedure was documented involving palladium-promoted cascade dehydrogenation/Heck oxidative reaction/isomerization/cyclization. In this procedure, butyl acrylate was combined with 3,4-dihydronaphthalen-1(2*H*)-one to produce benzo[*h*]coumarin (**2**), as illustrated in Scheme 10 [54].



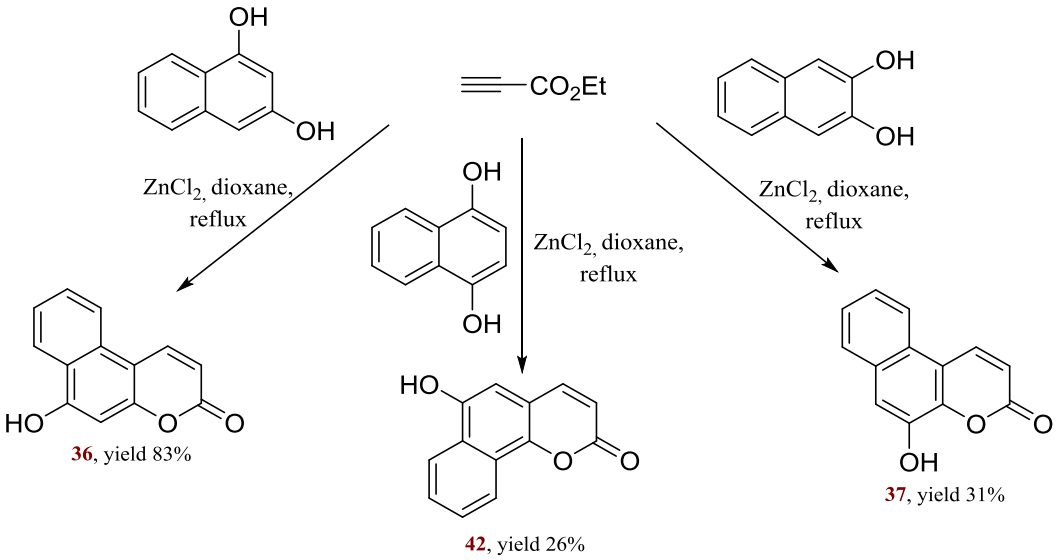
Scheme 10: One-pot reaction for the synthesis of benzo[h]coumarin via a palladium catalyst

Previously, Oyamada and his colleagues demonstrated several C–H functionalization to form the chromone ring via palladium catalyst. Under similar conditions, they recently described the synthesis of benzo[*f*]coumarin (**4**) in good yield by coupling naphthol with propionic acid or its esters using platinum as a promoter, as described in Scheme 11 [55].



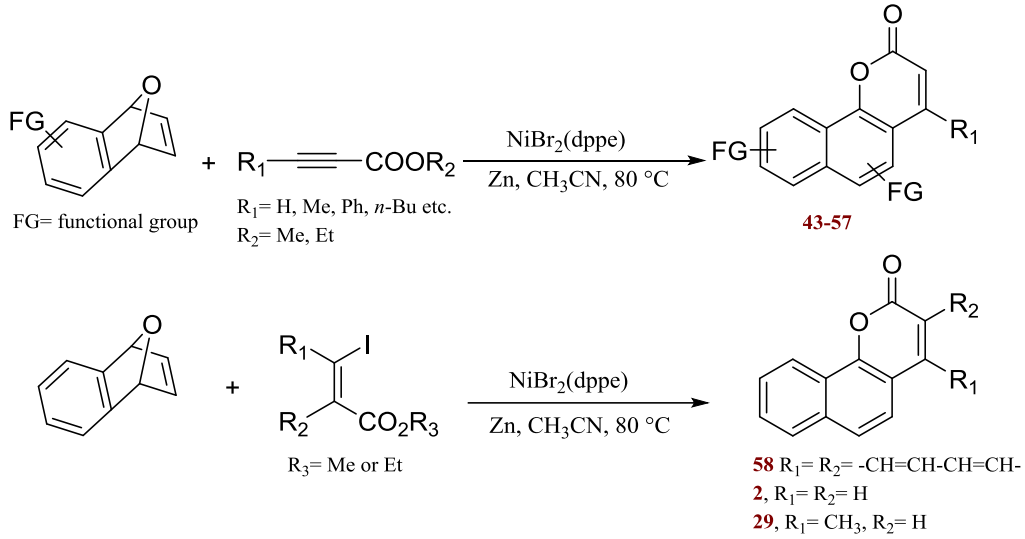
Scheme 11: The utilization of platinum as a promoter for catalyzing the synthesis of benzo[f]coumarin

A similar method to prepare benzocoumarins (**36**, **37**, and **42**) was also reported, involving the coupling of ethyl propiolate with naphthol using $ZnCl_2$ as a metallic promoter. The yields can range from low to high based on the starting naphthol, as indicated in Scheme [51].



Scheme 12: The preparation of benzocoumarins using zinc as a promoter

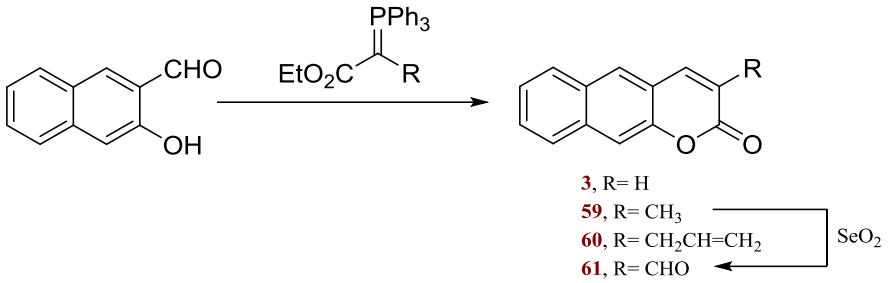
Furthermore, various nickel complexes can be used as catalysts to synthesize highly substituted benzo[*h*]coumarins (**43-58**) in two pathways. As shown in Scheme 13, the first is the cyclization of oxanorbornenes with 2-iodobenzoates or β-iodo-(*Z*)-propenoates [56], and the second is the cyclization of an alkyl propynoate with oxanorbornene [57].



Scheme 13: The synthesis of benzo[*h*]coumarins using nickel complexes as promoters

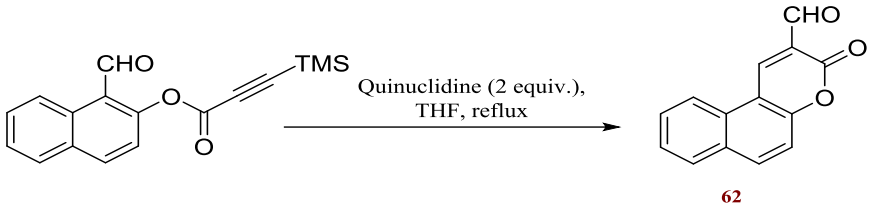
Other Methods for Synthesis of Benzocoumarins

The Wittig reaction was performed on *ortho*-hydroxynaphthaldehydes with phosphorane compounds like carbethoxyethylidene-triphenyllphosphorane or carbethoxymethylene-triphenylphosphorane under heating conditions in aprotic solvents (benzene, diethylaniline, or xylene) to synthesize benzo[*g*]coumarins (**3** and **59-61**), as shown in Scheme 14. In contrast to the reaction of Knoevenagel, which only produced benzocoumarin derivatives with an electron-withdrawing substituent at C3, this method could easily introduce different functional groups at C3 other than an electron-withdrawing group [31, 58].



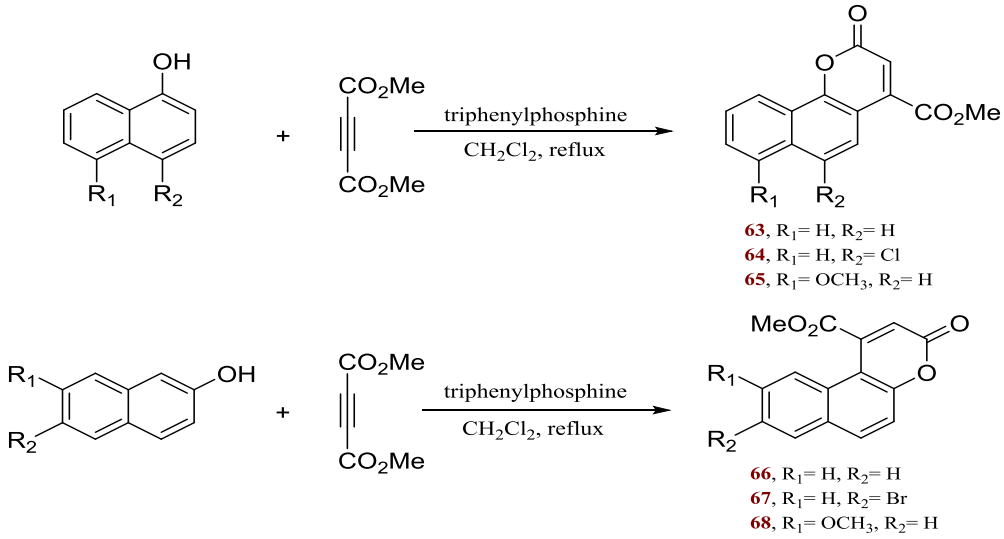
Scheme 14: The reaction of Wittig for the synthesis of benzo[g]coumarin derivatives functionalized at C3

Another example for the synthesis of benzocoumarins was reported by Nemoto and his colleagues. The intramolecular condensation of the *ortho*-formyl with propynoate groups using a base (usually amines) as a promoter to activate the propynoate nucleophile gave benzocoumarins. For example, as shown in Scheme 15, benzo[*f*]coumarin (**62**) could be synthesized from 1-naphthaldehyde bearing propynoate protected by trimethylsilyl via quinuclidine base as a promoter [59].



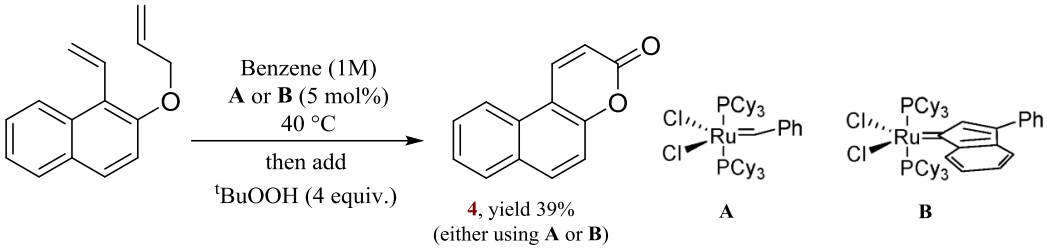
Scheme 15: The condensation between aldehyde and propynoate groups for synthesizing 3-formyl-benzo[*f*]coumarin

Beheshtiha and his colleagues (2002) discovered that the reaction of naphthols with dimethyl acetylenedicarboxylate and triphenylphosphine yielded structurally distinctive benzo[*h*]coumarins (**63-65**) and benzo[*f*]coumarins (**66-68**), as indicated in Scheme 16 [60].



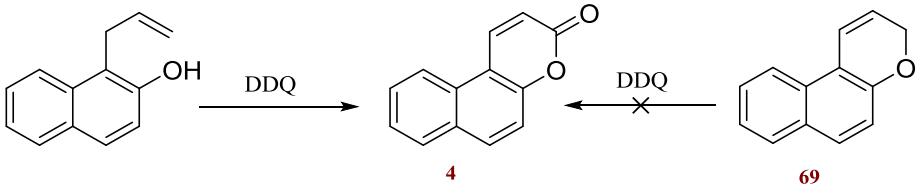
Scheme 16: The synthesis of benzo[h]- and benzo[f]coumarins based on Wittig condensation reaction

A new synthetic method to form benzocoumarin derivatives was described, in 2011, in which benzo[*f*]coumarin (**4**) was produced in moderate yield using cascade ring-closing metathesis-allylic oxidation sequence, as shown in Scheme [61].



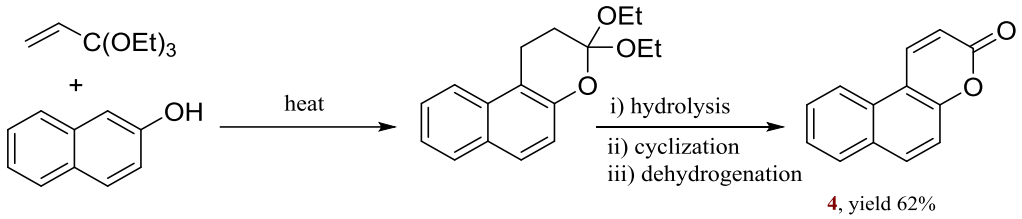
Scheme 17: The ring-closing olefin metathesis method for synthesizing benzo[*f*]coumarin

A benzo[*f*]coumarin (**4**) was also produced as the only product via a direct oxidative cyclization of the 1-allyl-2-naphthol with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, as illustrated in Scheme 18. Surprisingly, benzo[*f*]coumarin (**4**) was not produced by the direct oxidation of chromone (**69**) [62].



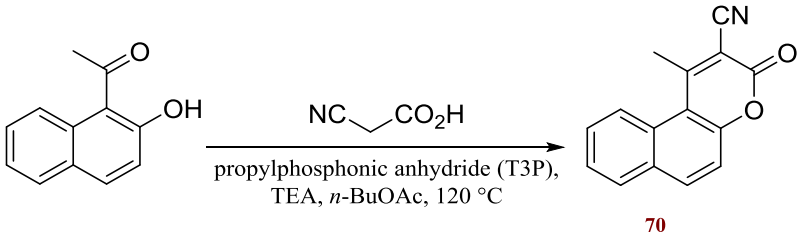
Scheme 18: The Claisen rearrangement for synthesizing benzo[*f*]coumarin

In addition, the Claisen rearrangement reaction of triethyl ortho-acrylate with β-naphthol yielded a benzo[*f*]coumarin (**4**) in a good percentage, as indicated in Scheme 19 [63]. In this method, benzocoumarins were produced in good yield from naphthol compounds, which were poor reactants in the Pechmann condensation reaction.



Scheme 19. The Claisen rearrangement for synthesizing benzo[*f*]coumarin

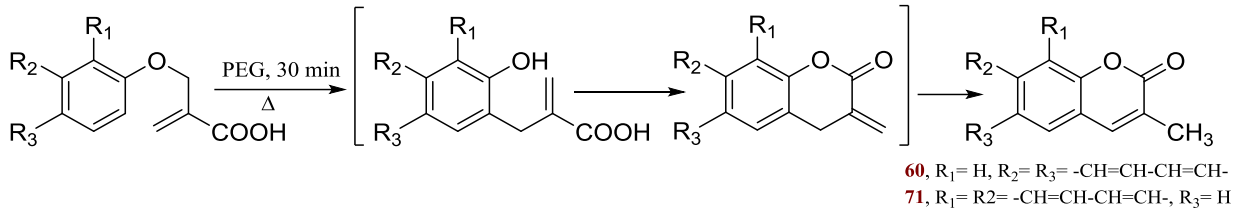
Also, in 2012, Bombrun and his colleagues reported the synthesis of benzocoumarin (**70**) based on the Perkin condensation from cyanoacetic acid and 1-acetyl-2-naphthol in the presence of *n*-butyl acetate, triethylamine, and polyphosphoric anhydride, as illustrated in Scheme 20 [64]. However, because the acetyl group has a lower nucleophilicity than aldehyde, utilized for Knoevenagel condensation, this reaction proceeds only under harsh reaction conditions.



Scheme 20: The Perkin condensation of 1-acetyl-2-naphthol for synthesizing benzo[*f*]coumarin-based compound

Furthermore, Sunitha and his colleagues demonstrated that 3-methyl-benzo[*g*]coumarin (**60**) and 3-methyl-benzo[*h*]coumarin (**71**) can be synthesized easily by thermal rearrangement of α-aryloxy-methylacrylic acids in a medium

containing polyethylene glycol, as seen in Scheme 4 [65].



Scheme 4: Thermal rearrangement of *α*-aryloxy-methylacrylic acids for synthesizing 3-methyl-benzocoumarins

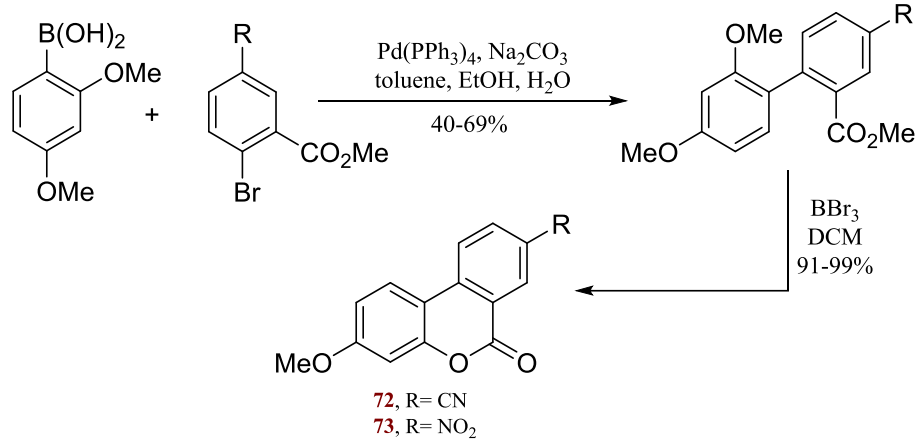
Despite significant progress to improve benzocoumarin derivatives synthetic strategies, the classic Pechmann and Knoevenagel methods remain dominant. The generality and availability of the starting materials of these methods are the main reasons for this [33].

Synthesis of Benzo[c]Coumarin and Its Derivatives

The main mechanism for synthesizing benzo[*c*]coumarins relies on ring-closing reactions. These reactions include the carbon-carbon bond formation (**3.1.**), carbon-oxygen bond formation (**3.2.**), and cyclization (**3.3.**) reactions.

Carbon-Oxygen Bond Formation

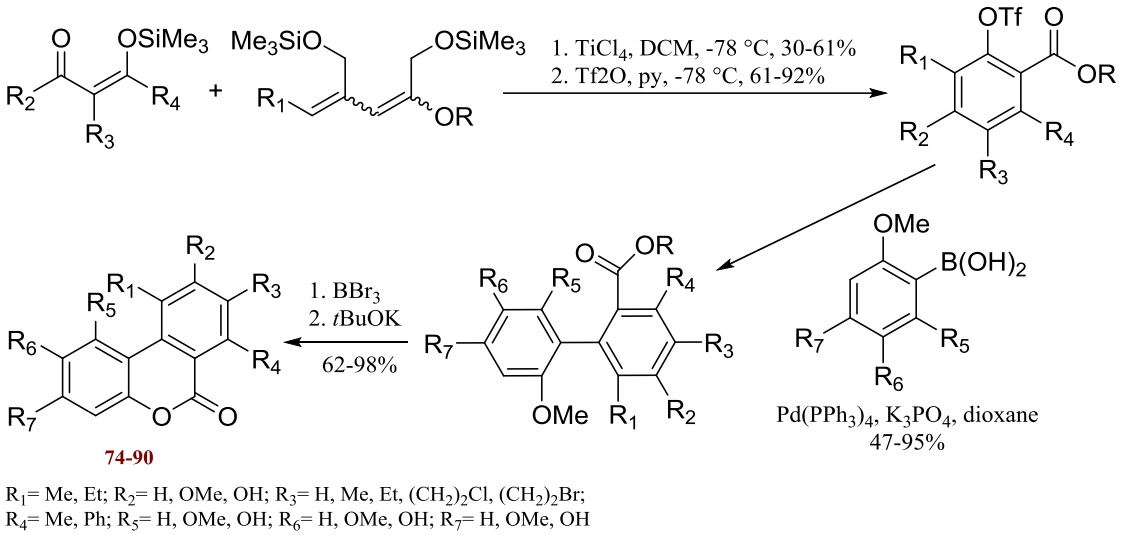
Almost all approaches depend on subsequent reactions on 2,2'-substituted biaryl-containing molecules. The Suzuki reaction between 2,4-dimethoxy-phenylboronic and *ortho*-bromobenzoates resulted in biaryl-based compounds containing ester and methoxy units at 2 and 2' positions. Then, lactonization mediated by boron tribromide yielded the required benzo[*c*]coumarin derivatives (**72** and **73**), as illustrated in Scheme 22 [66].



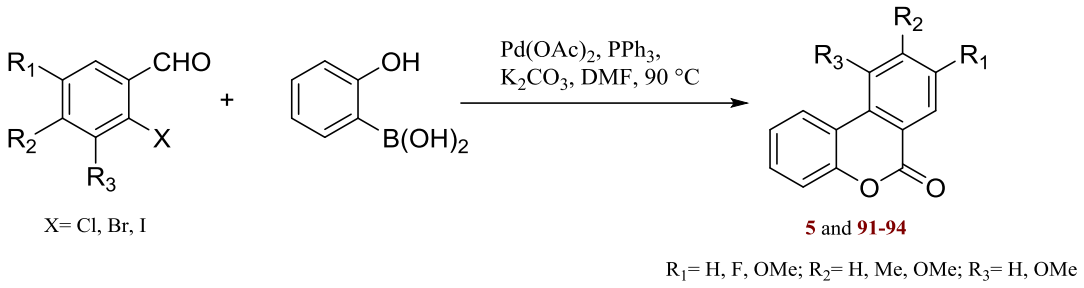
Scheme 22: The synthesis of benzo[c]coumarins using boron tribromide as a promoter

Also, poly-substituted benzo[*c*]coumarins (**74-90**) can be synthesized in three stages, beginning with [3+3] cyclization of 3-silyloxy-2-en-1-one compounds and 1,3-bis (silyl enol ethers). Then, proceeding with Suzuki reaction and lactonization promoted by boron tribromide, as indicated in Scheme [67].

In addition, the reaction of 2-hydroxyphenylboronic acid and substituted *ortho*-halobenzaldehydes resulted in the successful synthesis of benzo[*c*]coumarins (**5** and **91-94**), as shown in Scheme [68]. Suzuki reaction was used in this synthesis, followed by hemiacetals formation and then aerial oxidation.

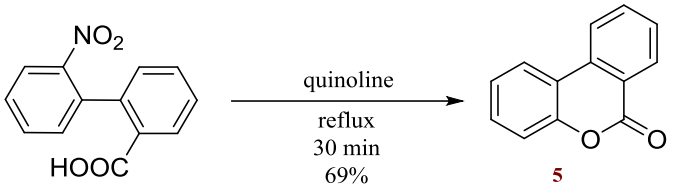


Scheme 23: The synthesis of poly-functionalized benzo[*c*]coumarin derivatives as demonstrated by Nguyen *et al*



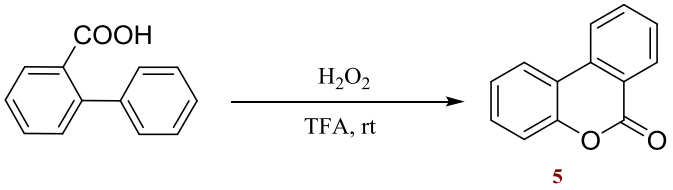
Scheme 24: One-pot synthesis of benzo[*c*]coumarin derivatives as indicated by Singha *et al*

Furthermore, non-functionalized benzo[*c*]coumarin (**5**) could be produced under reflux for half-hours from 2'-nitro-2-biphenylcarboxylic acid in quinoline, as illustrated in Scheme . The hypothesized mechanism for the reaction comprises an intramolecular nucleophilic substitution reaction, with a nitro group acting as a leaving group and the anion carboxylate acting as a nucleophile. Also, Luo and his colleagues developed a technique for obtaining functionalized benzo[*c*]coumarins by utilizing this feature [69].



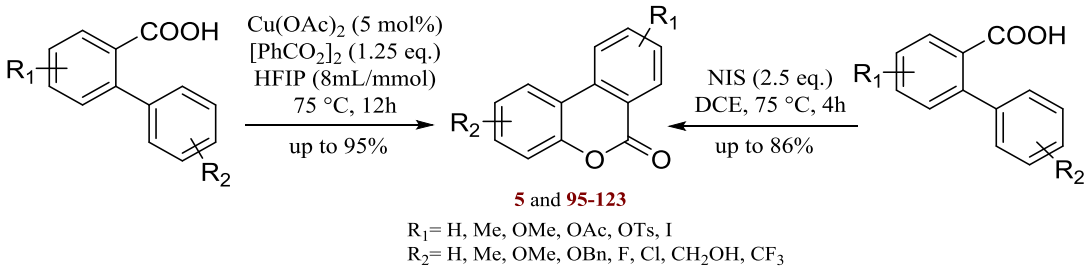
Scheme 25: The synthesis of non-functionalized benzo[*c*]coumarin via intramolecular nucleophilic substitution reaction

Another attractive example is the formation of the carbon-oxygen bond in the 2-biphenylcarboxylic acid through oxidative cyclization, as shown in Scheme 26. The reaction was carried out at room temperature with the presence of H_2O_2 in trifluoroacetic acid. The carboxyl radical generated by H_2O_2 hits the neighboring benzene ring to form lactone ring (**5**) [70].



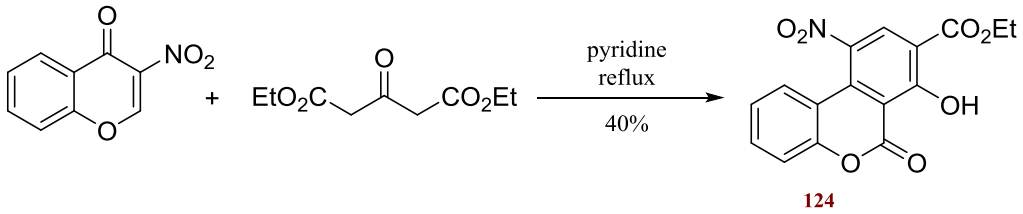
Scheme 26: The synthesis of benzo[*c*]coumarin via oxidative radical cyclization reaction

The lactonization of biphenyl-2-carboxylic acid via copper promoter is another reaction that uses the radical mechanism to form a carbon-oxygen bond. The broad substrate range and the high percentage (95%) of yield are the main benefits of this strategy [71]. Lately, a similar technique has been used to obtain benzo[*c*]coumarins (**5** and **95-123**) without utilizing any promoter by employing N-iodosuccinimide as a radical initiator rather than benzoyl peroxide. This strategy has mild reaction settings and does not employ a transition metal promoter, as indicated in Scheme [72].



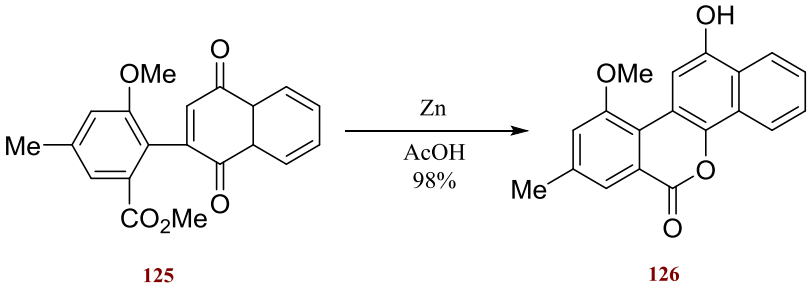
Scheme 27: The synthesis of benzo[*c*]coumarins via oxidative radical cyclization reaction

Also, Ding and his colleagues discovered that biphenyl-2-carboxylic acids could be used to make benzo[*c*]coumarin core easily by forming a carbon-oxygen bond with the help of a palladium catalyst through C–H activation mediated by a carboxyl group [73]. In addition, Hass and his colleagues reported one more important reaction of benzo[*c*]coumarins synthesis. This reaction involves condensation between 1,3-acetonedicarboxylate and 4*H*-1-benzopyran-4-one in pyridine reflux yielded 40% of benzo[*c*]coumarin-based compound (**124**), as shown in Scheme 28 [74].



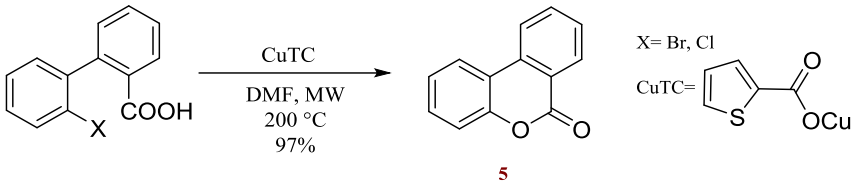
Scheme 28: The synthesis of tri-functionalized benzo[*c*]coumarin, as described by Hass *et al*

When naphthoquinone (**125**) is reductively lactonized by zinc powder in ethanoic acid, it yields 6*H*-dibenzo[*d*]naphtho[1,2-*b*]pyran-6-one (**126**) in a high percentage, which is structurally similar to benzo[*c*]coumarins, as illustrated in Scheme [75].



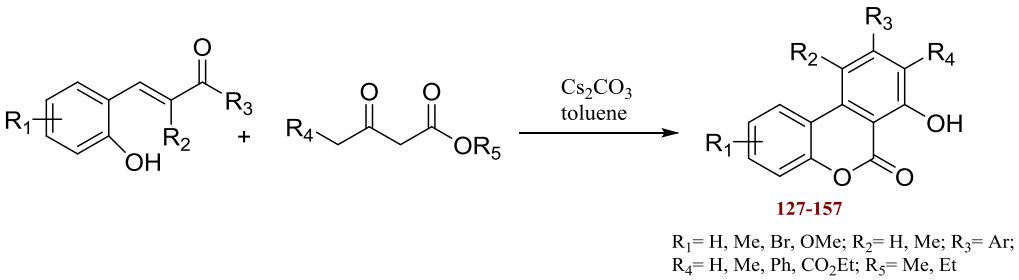
Scheme 29: The synthesis of benzo[*c*]coumarin-based compound via reduction as demonstrated by Jung and Jung

In addition, through an easy and effective carbon-oxygen bond coupling reaction utilizing copper salts under microwave radiation in harsh reaction settings (at 200°C in dimethylformamide), benzo[*c*]coumarin (**5**) was created from 2-halobiarylcarboxylic acids in excellent yield 97%, as indicated in Scheme 30 [76].



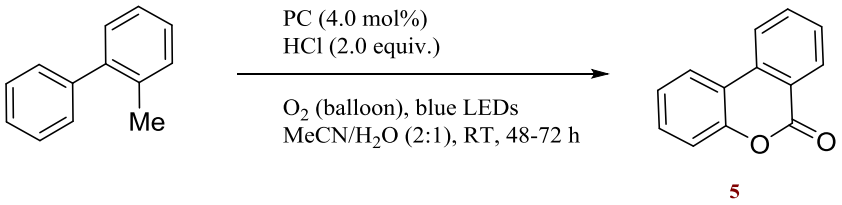
Scheme 30: The synthesis of benzo[*c*]coumarin via copper salt promoter

Also, Poudel and Lee (2014) described an intriguing strategy named domino reaction to produce various benzo[*c*]coumarin derivatives (**127-157**) easily by reacting *β*-ketoester compounds with 2-hydroxy chalcones, as shown in Scheme 31 [77]. The hypothesized mechanism of this strategy comprises sequential Michael addition/intramolecular aldol condensation/ oxidative aromatization/ lactonization.



Scheme 31: The synthesis of benzo[*c*]coumarins through domino reaction

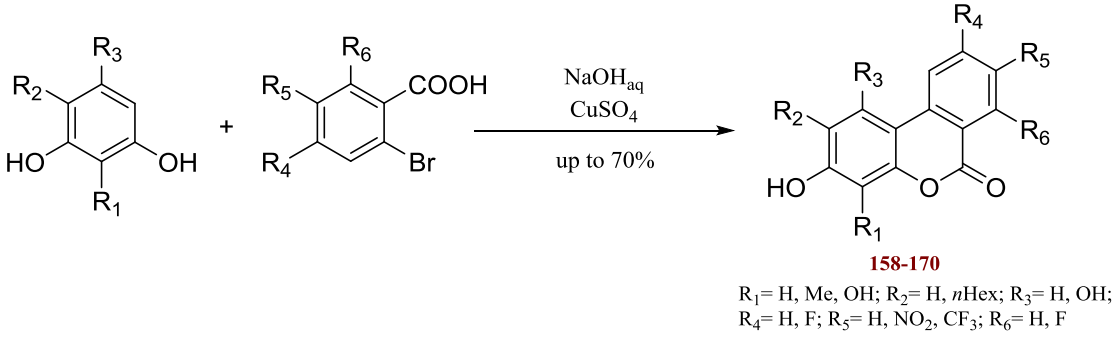
Ye and his colleagues (2019) reported benzo[*c*]coumarin (**5**) synthesis in a good yield from 2-methyl-1,1'-biaryl by using visible light as a photocatalyst, under mild and metal-free conditions, as illustrated in Scheme 32. The proposed mechanism of this strategy involves a cascade reaction that includes multiple carbon-hydrogen bond oxidation and dehydrogenative lactonization [78].



Scheme 32: The synthesis of benzo[*c*]coumarin via photocatalyst

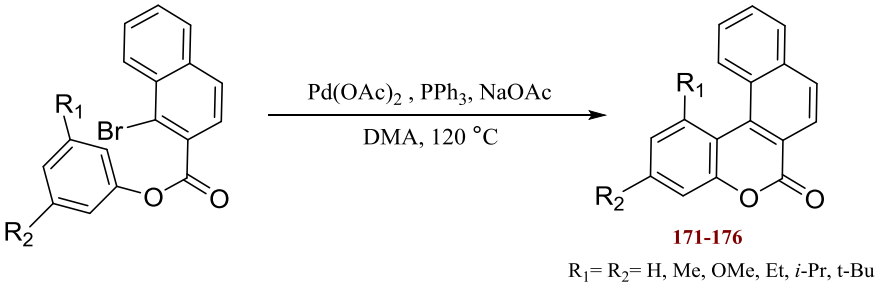
Carbon-Carbon Bond Formation

The formation of a carbon-carbon bond is an alternative method for synthesizing benzo[*c*]coumarins. The Hurtley condensation reaction between electron-rich phenol compounds and *ortho*-bromobenzoic acids is one of the oldest approaches for producing various benzo[*c*]coumarin derivatives (**158-170**); copper salt in aqueous NaOH solution catalyzes the reaction, as indicated in Scheme 33 [79]. Lately, Gryko and his colleagues reported that electron-rich naphthol compounds also undergo this reaction, resulting in π-extended coumarin derivatives like 2-hydroxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-ones and 8-hydroxy-5*H*-dibenzo[*c,f*]chromen-5-ones [79].



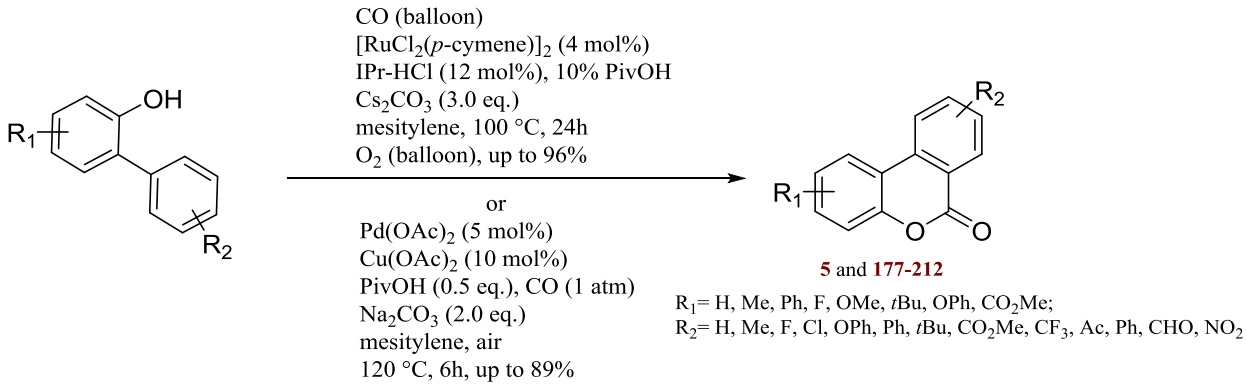
Scheme 33: The synthesis of diverse benzo[c]coumarin derivatives via the Hurtley reaction

Further, transition metals catalyze a variety of intramolecular direct arylation reactions. For example, antimicrobial with a core of 6*H*-dibenzo[*d*]-naphtha-[1,2-*b*]pyran-6-one, isolated from *Streptomyces rutgersensis,* was synthesized totally for the first time in 1994 using palladium as a catalyst [80]. Furthermore, it has been shown that 6*H*-naphtho[2,1-*c*]benzopyran-6-ones (**171-176**), which are structurally similar to benzo[*c*]coumarins, may be synthesized by coupling reaction of 1-bromonaphthalene-2-carboxylate compounds using palladium metal as a catalyst, as shown in Scheme . Also, this reaction was extended to include aryl iodide compounds [81].



Scheme 34: The biaryl bond formation for synthesizing benzo[*c*]coumarins via palladium metal

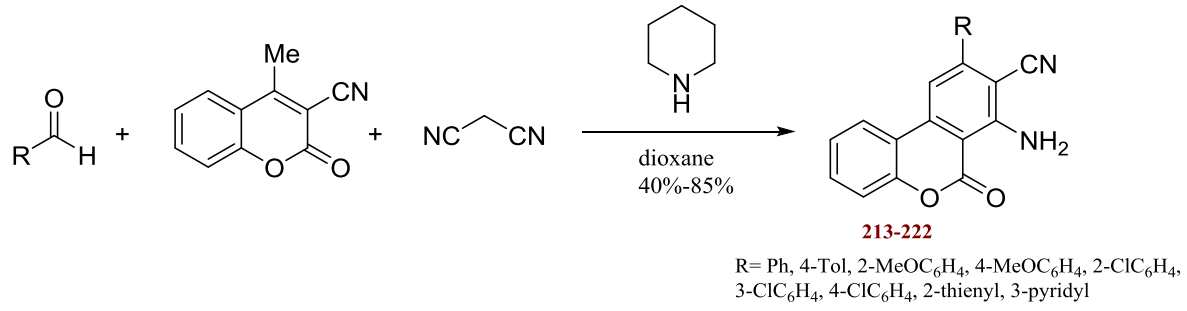
Recently, Inamoto and his colleagues observed carbonylative C-H cyclization of 2-arylphenol compounds via ruthenium catalyst to produce 6*H*-dibenzo[*b,d*]pyran-6-ones (**5** and **177-212**) [82]. In addition, instead of using ruthenium, a palladium catalyst can be used to carbonylate 2-arylphenol compounds, as shown in Scheme 35 [83].



Scheme 35: The use of transition metals as a promoter in the carbonylation of 2-arylphenols to synthesize benzo[c]coumarins

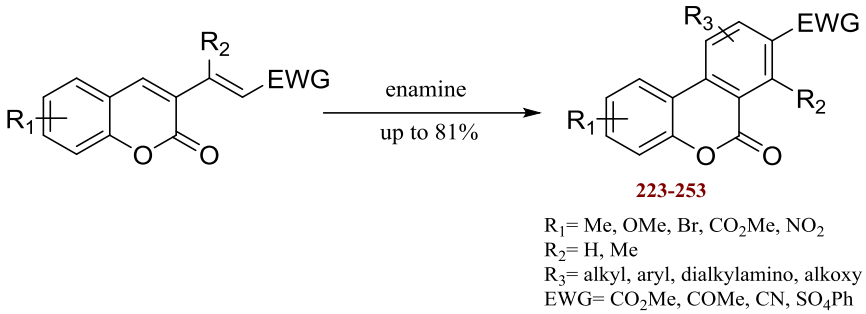
Cyclization Reactions

A benzo[*c*]coumarin backbone was created via a number of multicomponent reactions. The three-component condensation reaction of malononitrile, 3-cyano-4-methylcoumarin, and aromatic aldehyde utilizing piperidine as a reaction promoter resulted in substituted benzo[*c*]coumarins (**213-222**) with amino, cyano, and aromatic groups in one ring, which may be the most surprising result, as illustrated in Scheme [84,85].



Scheme 36: The three-component condensation reaction for synthesizing benzo[*c*]coumarin derivatives

During the standard Diels–Alder reaction, dienes bearing electron-donating groups and dienophiles bearing electron-withdrawing groups undergo cyclo-addition reactions to produce cyclohexene [86]. Nandaluru and his colleagues (2011) used the inverse electron demand Diels–Alder reaction to synthesize various benzo[*c*]coumarin derivatives (**223-253**). This reaction involves the condensation of different electron-rich dienophile compounds (mainly enamine compounds) with coumarin-based electron-poor diene compounds, as indicated in Scheme [87,88].



Scheme *37*: Inverse electron demand Diels–Alder reaction for synthesizing benzo[c]coumarin derivatives

The chemistry of benzo[*c*]coumarins has spawned and developed a slew of complementary strategies over the last ninety years. It appears that the most common procedure techniques are oxidative cyclization of biphenyl-2-carboxylic acid compounds [71] and standard Hurtley condensation [79]. However, the chemistry lately established by Nandaluru and his colleagues [87, 88] and the reaction of β -ketoester compounds with hydroxy chalcones [77] are the most attractive because they result in highly functionalized benzo[*c*]coumarins with both electron-withdrawing and electron-donating groups.

Conclusions

Since Pechmann's first synthesis of benzocoumarins 138 years ago, knowledge about coumarins with π-extended structure has been enhanced. Benzocoumarins are a valued class of heterocyclic compounds, especially in the pharmaceutical and medicinal fields. They have attracted attention due to their notable biological activities. The synthesis of benzo[*f*], benzo[*h*], and benzo[*g*]coumarin derivatives is based in part on classic coumarin approaches like the Knoevenagel condensation, Pechmann reaction, Wittig reaction, and Perkin reaction while the synthesis of benzo[*c*]coumarin derivatives takes relatively different approaches. However, the growing importance of benzocoumarins inspired the discovery of entirely novel paths. This review focused on classical and recent strategies for the synthesis of benzocoumarin derivatives reported in the literature. So, it is a helpful reference for chemists curious about developing novel types of benzocoumarins.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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