Review Article

Classical Approaches and Their Creative Advances in the Synthesis of Coumarins: A Brief Review

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ABSTRACT

Coumarin chemical nucleus is a gift awarded from nature to humanity. The multifarious derivatives and the broad range of their bio-medicinal potentials are the basis for this description. In the last several decades, though numerous coumarin-based products have been primarily separated from their biological origins, the laboratory synthesis of the coumarins is developing. Various synthetic trails namely Knoevenagel, Claisen, Perkin, Pechmann, Wittig, and Reformatsky have been reported. Several advanced innovations have been created to maximize yield, minimize overall reaction time, avoid side products, and make synthetic reactions environmentally friendly. These include the employment of ultrasonic, microwave, and solvent-free conditions. This brief review focuses on the classic methods for synthesizing coumarins, and the advantages derived from the use of creative catalytic tools.

GRAPHICAL ABSTRACT
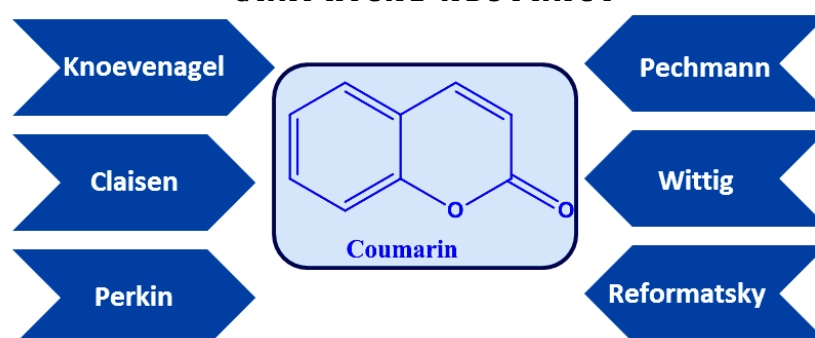
Introduction

Coumarin belongs to the Fabacean family called "Coumarou" which is the plant's derogatory name. Vogel novally separated the primary component, coumarin itself, from this plant that commonly known as tonka bean in 1820 [1].

Coumarin-based products in the plant, animal and microorganism worlds are heavily marketed [2]. But most of these products, notably those found in the plant families named *Rutaceae* and *Umbelliferae*, are isolated from the higher plants Coumarin-derived compounds of varied structural manifestations have been exhibited a distinct role for managing a number of clinical conditions, such as inflammation [8], Alzheimer [9], high protein edema [10], blood coagulation [11], oxidative stress [12], cancer [13–15], and chronic infections [16,17]. Synthesis devised for preparing various coumarin-derived compounds [18].

Chemical synthesis of coumarin-derived compounds

[3]. In various plant components such as the fruits, leaves, roots, and stems, coumarin-derived compounds can attain high levels. The geological and temporal factors can significantly affect the amount of natural coumarins in these plant zones [4].

A number of pharmacologically significant natural coumarins have been separated from various micro-organisms. Form *aspergillus* and *streptomyces* species, for examples, aflatoxins and novobiocin have been identified as antibiotics respectively [5–7].

Up to now, several schematic reactions including the Knoevenagel, Reformatsky, Claisen, Perkin, Pechmann, and Wittig synthetic routes have been
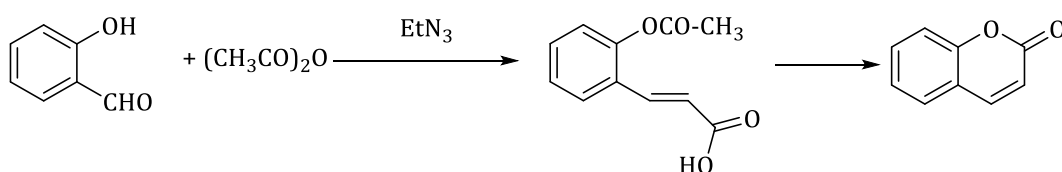
Perkin synthetic route

Perkin first conducted the chemical construction of the parent compound, coumarin. The high - temperature reaction of acetate anhydride with salicylaldehyde, using an alkaline dried salt like sodium acetate, has created the coumarin-derived compound as indicated in Scheme 1. The transitional reaction intermediate named ortho-hydroxycinnamic acid affords the target product via a spontaneous lactonization [19].
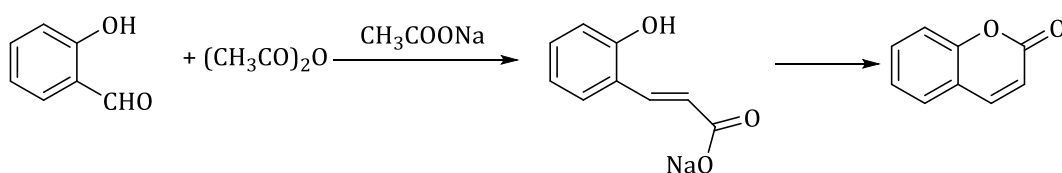
Scheme 1: Perkin synthetic route for the parent compound, coumarin

The Perkin synthetic method offers numerous benefits and downsides in relation to several chemical processes. The described advantage is the unlikely production of the chromane-based isomer as a byproduct. The most notable failure of this reaction is the fakir yield, due to high heating applied, resulting from the production of numerous byproducts. However, the molar content of the used anhydride at aldehyde expense can be adjusted to correct this failure. [20]. Scheme 2 shows one of the most important changes to the Perkin reaction, which is the involvement of tertiary amine as a promoter for initiating the reaction rather than basic salt. [21].


Scheme 2: The utilization of a tertiary amine as a promoter for the chemical reaction of Perkin

Pechmann synthetic route

This reaction, as illustrated in Scheme 3, involves the creation of coumarin-based derivative by conjugating a phenolic compound with dicarboxylic acid-containing derivative using concentrated inorganic acid like HCl or H_2SO_4 as a promoter [22].
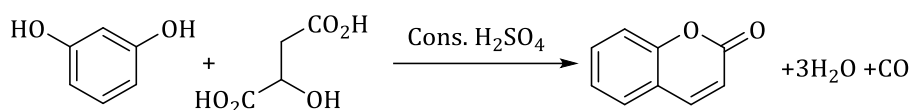

Scheme 3: Pechmann chemical route for synthesizing of 7-hydroxycoumarin

The Pechmann reaction is claimed to be the most suitable synthetic pathway in the synthesis of coumarin-derived compounds which gives a promising yield towards the target product. It may be accomplished by using the homogeneous or heterogeneous acid promoter. Inorganic acids such as trifluoroacetic, hydrochloric, phosphoric, and sulfuric acids as well as Lewis acids such as the chlorides of tin (IV), iron (III), zinc, and titanium may fall in the first category [23]. Cation-exchange resins, Nafion-H, zeolite-HBEA, and other solidified acids may belong to the second category [24].

It has been noted that, in the case of the Pechmann reaction aided by solid promoter such as montmorillonite K-10 or KSF, the produced coumarin-derived compound as indicated in Scheme 4 can attain its greatest yield. This technique is less expensive and environmentally favorable than the use of a homogeneous acid promoter [25]. Regarding this issue, Zhang ZH and his colleagues [26] highlighted three problems; the first worry is that the Pechmann reaction is best conducted with a heterogeneous acid promoter than that belong to the homogeneous phenotype in relation to the match reaction yield and time. The second is that as a promoter, KSF is less efficient than montmorillonite K-10. The last point is that the advanced features such as the minimum environmental hazards are provided by the heterogeneous promoters. Also, the easy of dissociation between the reaction product and the promoter makes the latter to be more usable than once.
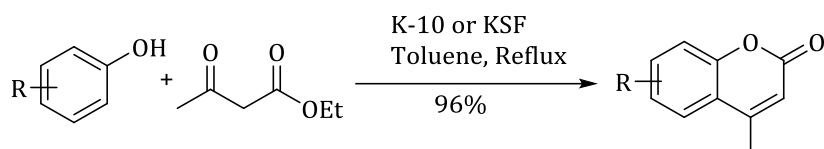

Scheme 4: The application of the heterogeneous promoter for catalyzing the synthesis of coumarin-derived compounds via a schematic pathway of Pechmann

The promoters, such as Amberlite ir-120 and Zeokarb 225, provide numerous benefits with respect to the usage of cation exchange resins as heterogeneous solid promoters for synthetic reaction of Pechmann. The inexpensive, recyclable and easy separation between promoter and product are among these [27]. Besides, the reaction rate can also be improved by using the resin in the ratio of 30% to the total weight of the reagents [28].

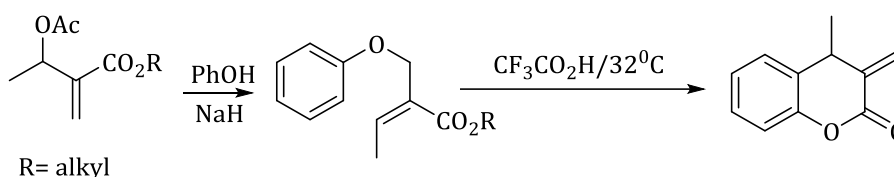It has been shown that 7-hydroxycoumarin may be synthesized by coupling resorcinol with acrylic acid or one of its esterified products. Through the utilization of zeolite H-beta [Si/Al=14] or amberlyst-15 as a heterogeneous promoter, the greatest performance may be attained as equimolar quantities of these reactants are mixed. The hypothesized mechanism as illustrated in Scheme 5 comprises the esterification of phenol derivative for lactonization that produces, along with the target dihydrocoumarin product, the byproduct chemically called 3, 4, 6, 7-tetrahydrobenzo[1,2-b:5,4-b'] dipyran- 2, 8-dione [29].
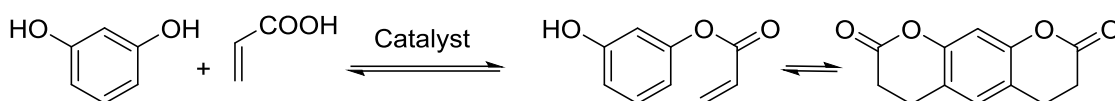
Scheme 5: The synthesis of 7-hydroxycoumarin via synthetic reaction of Pechmann that promoted by heterogeneous catalyst

Claisen synthetic route

The synthesis of 3-methylene-4-methyl-3,4-dihydrocoumarin, as described in Scheme 6, may also be carried out intramolecularly using trifluoroacetic acid as homogeneous promoter via the rearrangement reaction of Claisen [30]. While this synthetic coumarin was produced by others beforehand, Drewes and his colleagues devised a new synthetic route [31]. The intermediate compound was used in situ in the production by acetylating the product named Baylis-Hillman, 3-acetoxy-2-methylene-alkylbutanate.

Trifluoroacetic acid assisted the cyclisation of this intermediate in order to produce a one-pot method affording 86% yield of the target product.


Scheme 6: The preparation of 3-methylene-4-methyl-3,4-dihydrocoumarin using trifluoroacetic acid as homogeneous promoter via Claisen rearrangement reaction

A similar progression for 6-methyl-3-methylenecoumarin production was previously described. This synthesis required rearranging the chemical intermediate, which is the ester of an α-aryloxymethylacrylate, afforded by the reaction of Claisen in presence of the Lewis acid as indicated in Scheme 7. In this procedure the dimer can be provided in a small amount as a byproduct and generally results from the excessive reactivity of the double bond involved in the intermediate referred to the one above [32].
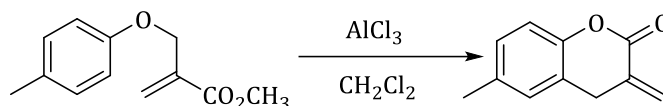
Scheme 7: The synthesis of 6-methyl-3-methylenecoumarin that promoted by a Lewis acid via the rearrangement of Claisen

A new version of the rearrangement of Claisen was described in an approach to solve the challenges associated to the creation of coumarin-derived compounds through the reaction of Pechmann. This amendment, as illustrated in Scheme 8, concerned the use of aryl ethers combined with double or triple bond via their oxygen [33]. This change was implemented in the event that conventional Pechmann reaction may fail to generate a coumarin-based derivative. In view of the mechanism for its reaction, this alteration was done by transforming the reactant into a chemical intermediate named alkoxy-chroman that is afforded the product since it undergoes a spontaneous oxidation [34].
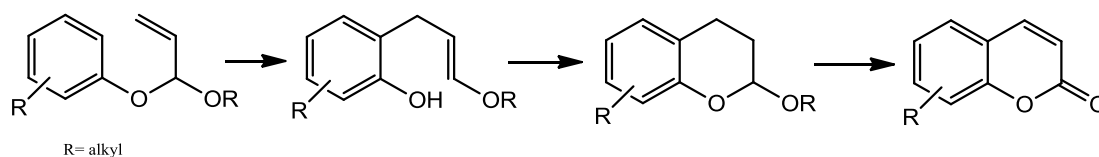

Scheme 8: The new version of the rearrangement reaction of Claisen

Knoevenagel synthetic route

Coumarin-derived compounds can be synthesized by using the schematic route of Knoevenagel. This synthesis, as shown in Scheme 9, involves the coupling of β-ketoester containing product like ethyl malonate, ethyl acetoacetate, or ethyl cyanoacetate, with 2-hydroxy aromatic aldehyde in the presence of organic alkali like piperidine or pyridine as a promoter [35].
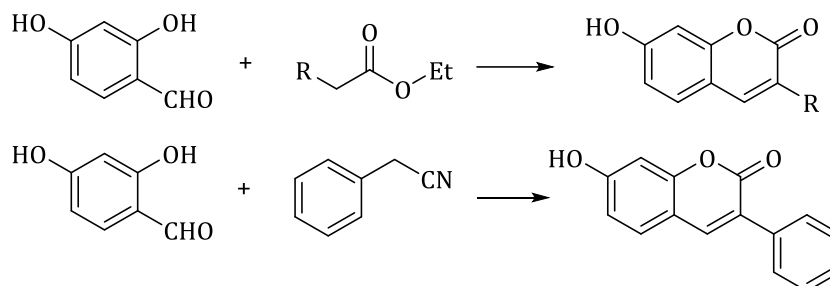
Scheme 9: Two examples for the synthesis of coumarin-derived compounds via the reaction of Knoevenagel

As illustrated in Scheme 10, the reaction of Knoevenagel is generally applied to solve the incidental difficulties related to the synthesis of coumarin-derived compounds by using the reaction of Perkin. The former reaction is less demanding than that indicated in the second one. Despite the differences among these two synthetic reactions, the presence of aromatic aldehyde as a reactant is a fundamental requirement. Also, the presence of the neighboring phenolic hydroxy group is essential since its electron donating capacity directed the reaction, instead of its equivalent cinnamic acid derivative towards the production of coumarin-based compound [36].

$X = COOH, CO_2Et, CONH_2, CN$
$Y = COOH, CO_2Et, CN$
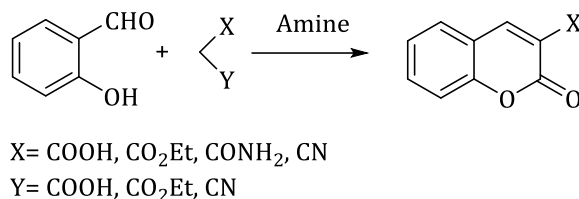
Scheme 10: The general description of the reaction of Knoevenagel

Two distinct mechanisms have been theorized for the reaction of Knoevenagel, as shown by Scheme 11 [37]. Aromatic aldehyde condenses with an organic alkali that gives an iminium or imine salt in the first hypothesized mechanism. Also, the enolate intermediate produces by the deprotonation of the active methylene-containing molecule via the same organic base. Then the last intermediate nucleophile hits the main produced one that eliminates the amine and becomes a derivative based on coumarin. The second proposed mechanism begins as the carbanion that attacks the carbonyl carbon of the aromatic aldehyde by the de-patternation obtained by the organic alkali on the active molecule which contains methylene. The approaching processes follow this order of attack: Proton migration, ring cycling, and finally the elimination of H_2O [38].
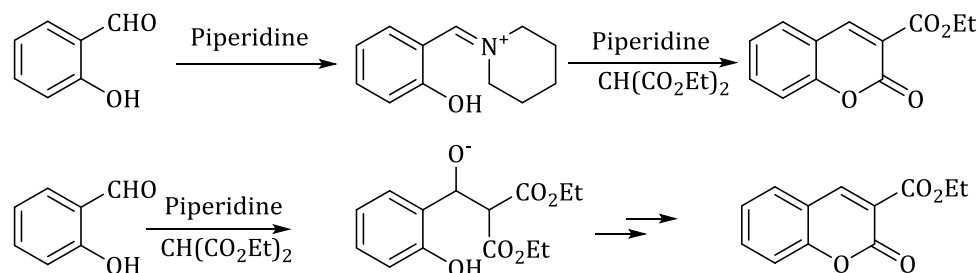

Scheme 11: The two theorized mechanisms for the synthesis of coumarin-derived compounds via the reaction of Knoevenagel

Kostanecki-Robinson synthetic route

Through this reaction, as displayed in Scheme 12, coumarin-based derivative substituted at C3 or C4 can be produced by coupling aromatic ketone containing an ortho phenolic hydroxyl group with an aliphatic anhydride [39,40].
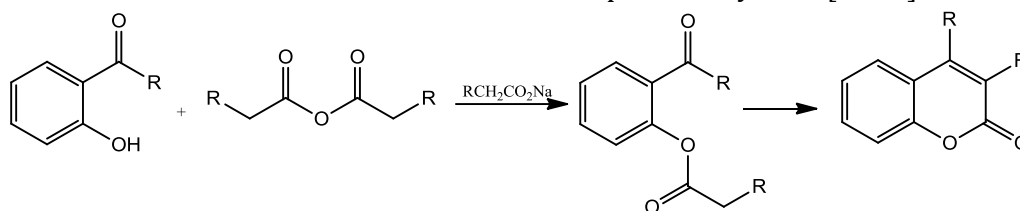
Scheme 12: The schematic description of the synthesis of coumarin-derived compounds via the reaction of by the Kostanecki-Robinson.

In addition, numerous transition metals can be used to facilitate the synthesis of various molecules deriving from coumarin. The two-phase-reaction of Kostanecki-Robinson, for example, was described by Song and his colleagues [41]. The bromide salt named 3-methyl-4-butylimidazolium bromide and $Hf(OTF)_4$ were used as a metallic promoter and phase transfer reagent, respectively. This reaction showed an excellent output of the desired product termed 4-alkylcoumarin, as illustrated in Scheme 13.
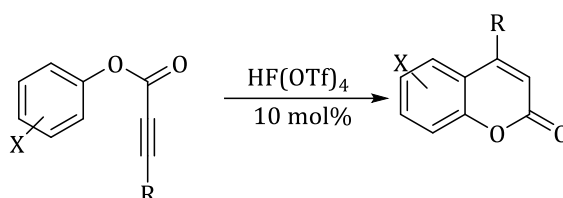
Scheme 13: The two-phase-reaction of Kostanecki-Robinson for the synthesis of various coumarin-derived compounds substituted at C3

In this concern, Sasano and his collaborators [42], as shown in Scheme 14, examined a similar reaction by employing the palladium metal as a promoter. The resultant intermediate named alkenylpalladium can be added nucleophilically to the ambient carbon dioxide that resulted in the synthesis of the target coumarin-based derivative. Besides, an enclosed environment and a solvent with high boiling point are among the requirements of this reaction.
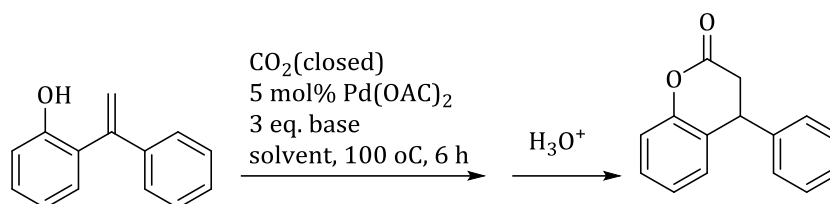
Scheme 14: The synthesis of 4-phenylcoumarin that promoted by Pd-metal as proposed by Sasano his collaborators

In a similar fashion, 4-phenylcoumarins with various substitutions can be produced using the promoter named copper (I) acetate, as shown in Scheme 15. In which, the protected oxygen of the methyl phenylpropiolate-based compounds can be coupled with boric acid to afford the target coumarins [43].
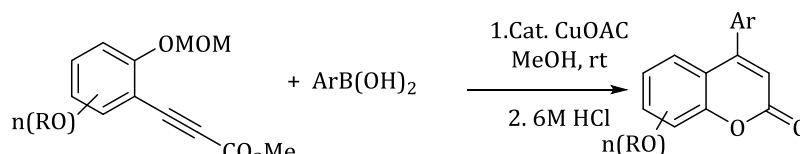
Scheme 15: The synthetic of 4-phenylcoumarins with various substitutions as described via Yamamoto and Kirai

Wang and his collaborators [44] recently examined an efficient technique, which involves the production, as illustrated in Scheme16, of coumarins that are functioning at position 4 with an aromatic ring. In the presence of aromatic boronic acid and metallic palladium, the precursor coumarin reaction resulted in the target 4-phenylcoumarin derivative. This technique was successful when the aromatic ring of the coumarin nucleus functioning with various electron donation or retraction groups.
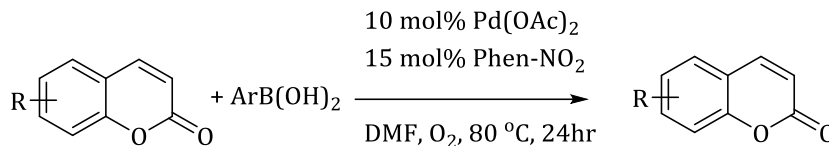
Scheme 16: The preparation of 4-phenylcoumarin derivatives as described via Wang et al.

In the field of promoting the reaction of Kostanecki-Robinson by a transition metal, Yuan et al. [45] examined the synthesis of coumarin-based derivatives functioning with various groups at C3, as shown in Scheme 17.
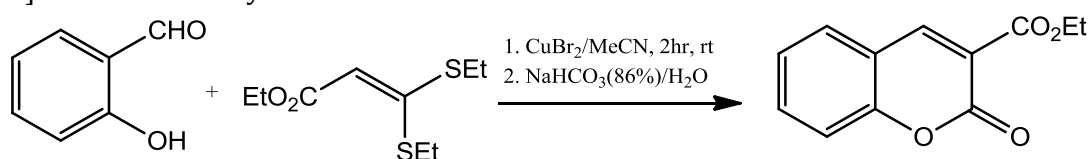
Scheme 17: The preparation of various coumarin-based derivatives functioning with various groups at C3, as indicated by Yuan et al.

Wittig synthetic route

As illustrated in Scheme 18, phosphonium ylide interacts with an aromatic aldehyde/ketone to produce a linked alkene, which is transformed into a coumarin-based derivative through one of the subsequent reactive species: Betaine or oxaphosphetane [46]. Many synthetic coumarin-derived compounds have been produced on the basis of the Witting reaction [47]. In addition, several natural coumarin-based products synthesized based on this reaction, in particular those belonging to coumarin families of prenylates and allyates, have been identified and characterized [48].
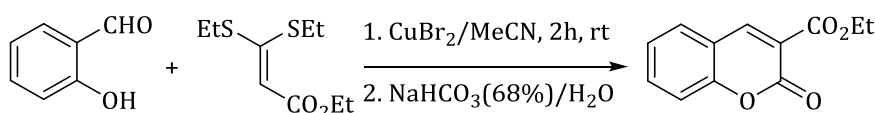
Scheme 18: The general description for the synthesis of coumarin-derived compounds via the reaction of Wittig

The Witting reaction, as indicated in Scheme 19, enables the synthesis of coumarin-derived compounds that are functionalized at C4. The stable phosphorene, like the bromide salt of ethyl ester of (carboxymethyl)triphenylphosphonium, can couple with aromatic aldehyde/ketone having at ortho position a phenolic hydroxyl group affording the target yield [49].
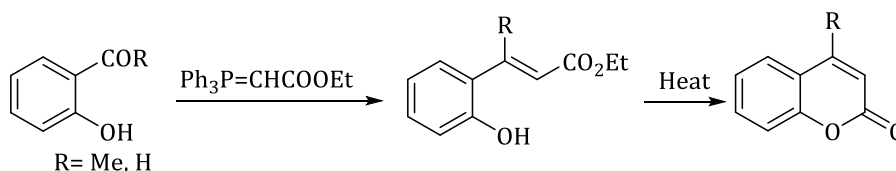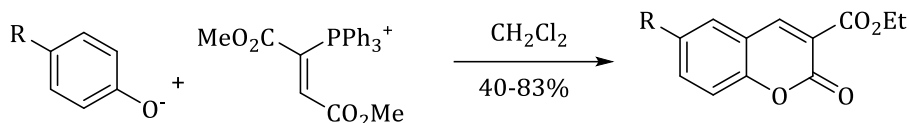
Scheme 19: The synthesis of coumarin-derived compounds that are functionalized at C4 as depicted by Hepwarh and his collaborators

The aryl electrophilic process was used to make a breakthrough in the synthesis of coumarin-derived molecules conjugated with carboxymethyl group at position 4. The synthesis of betaine intermediate was achieved by condensing stable triphenylphospine and dimethyl ester of acetylene dicarboxylic acid, as indicated in Scheme 20 [50]. The target product

was obtained by reacting this intermediate with a phenoxide-containing molecule [51]. This innovation, as compared with existing methods for the synthesis of coumarin-derived compounds, provides a particularly efficient approach for the synthesis of coumarins functioning with acid- or base-sensitive groups [52].

Scheme 20: The synthesis of bi-functionalized coumarins as demonstrated via Yavari and his colleagues

Creative advances in the synthesis of coumarin-derived compounds

Microwave-promoted synthesis

Compared with conventional heating methods, microwave radiation demonstrated several advantages such as the possible internal heating, which reduces significantly the time necessary to complete the process, whilst providing an environmental sustainable source of energy [53]. Furthermore, using microwaves to elicit chemical reactions might result in a significant percent yield owing to a reduction in the possibility of undesired side reactions. As a result, this form of heat may be represented as a part of an international movement towards the use of green organic chemistry [54].

The use of a Pechmann microwave-assisted reaction has been reported to provide an effective system in which coumarin-derived compounds may be synthesized quickly, simply, and inexpensively. For example, the microwave facilitated synthesis of 4,7-dimethylcoumarin, as shown in Scheme 21, by coupling ethyl acetoacetate with 3-cresol using H_2SO_4 as a homogeneous acid promoter [55].
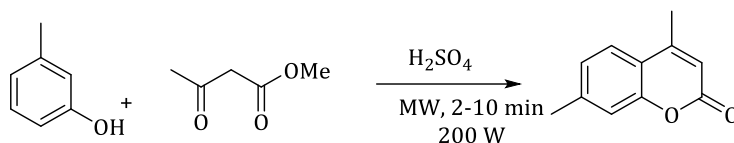
Scheme 21: The microwave-facilitated synthesis of 4,7-dimethylcoumarin

The use of microwave radiation as a power source has been proven to increase the potential for an optimal percentage yield. The microwave-facilitated synthesis of tri-functionalized coumarins, as described in Scheme 22, for example, by condensing various derivatives of salicylaldehyde and carboxylic ester. This condensation is generally carried out in an atmosphere without solvents and promoted via pyridine or piperidine [56].

$$R_1 = H, Et_3N \qquad R_3 = CO_2Et, COMe, CN, p-C_6H_4NO_2$$
$$R_2 = H, OMe$$
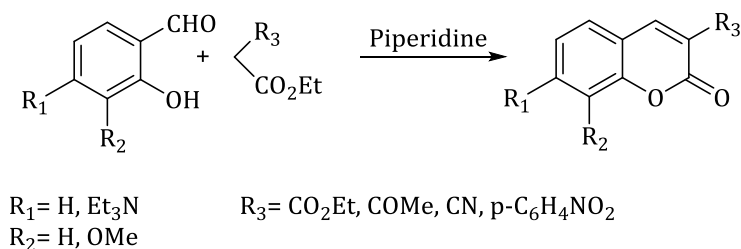
Scheme 22: The microwave-facilitated synthesis of tri-functionalized coumarins, as described by Bogdal

The coupling of ethyl acetoacetate and phenol, as illustrated in Scheme 23, was chosen as a model to study the capacity of $Cr(NO_3)_3.9H_2O$ to function as an effective promoter in the microwave-facilitated reaction of Pechmann. The use of a very modest quantity of this promoter (10 mmol) under microwave radiation has been shown to dynamically boost the completion of the reaction throughout some minutes. However, coumarin-derived compounds functionalized with electron-withdrawing group(s) at the aromatic portion of the coumarin frame were not prepared using the aforementioned technique [57].
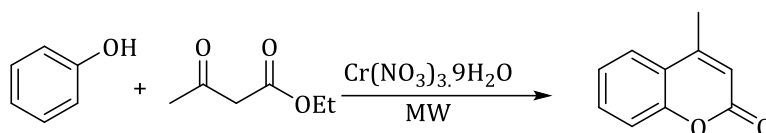
Scheme 23: The use of $Cr(NO_3)_3.9H_2O$ as a promoter in the microwave-aided reaction of Pechmann.

Ultrasound-promoted synthesis

In the last 30 years, the use of ultrasonic radiation in the field of organic chemistry has risen significantly. This is due to the flexibility and efficiency with which this form of energy can be monitored. The ultrasonic radiation appears to be used in a large number of research papers to facilitate several synthetic processes, according to the bibliography [58,59]. Since organic solvents have been used in the majority of the organic reactions, there have been several initiatives to substitute these chemical substances with water. The beneficial qualities of water, such as its accessibility, low cost, sanitation, and environmental friendliness, prompted these initiatives. For example, Scheme 24 shows the ultrasound-facilitated synthesis of tetra-functionalized derivatives of coumarin-3-carboxylic acid in an aqueous medium. [60,61].
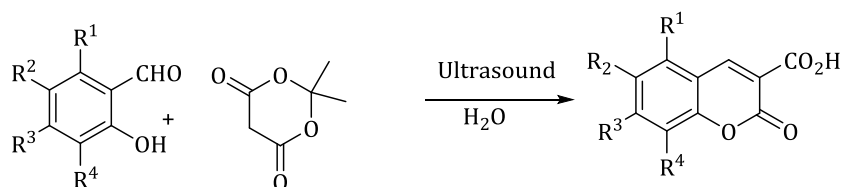
Scheme 24: The ultrasound-facilitated synthesis of tetra-functionalized derivatives of coumarin-3-carboxylic acid in an aqueous medium.

Bismuth-based products have been described as Lewis acid promoters by their tolerable safety, affordability, and stability [62]. They have recently been identified as possible promoters for a variety of organic transformations, including those involved in the synthesis of coumarin-derived molecules [63]. Throughout this respect, it has been recorded that this sort of promoter has been used in a variety of reactions that are managed and executed under ultrasonic radiation, including the halogenation addition reactions [64] and the Heck reaction [65]. For example, the ultrasound facilitated condensation, as illustrated in Scheme 25, between the derivatives β-ketoester and phenol utilizing $BiCl_3$ as a reaction promoter [39,63].
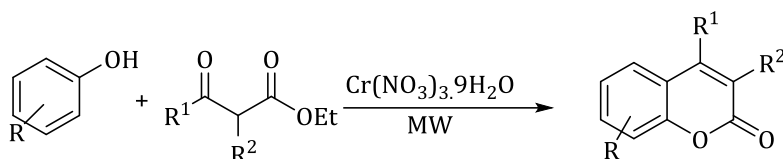
Scheme 25: The ultrasound-facilitated condensation promoted by $BiCl_3$

The conjugation of coumarin functionalized at C4 by a hydroxyl group and benzoic aldehyde, as illustrated in Scheme 26, is another example. This ultrasound-facilitated reaction took place in an aqueous phase for 90 minutes at 40°C, yielding the target product in an extremely high percentage (88%) of yield [66].
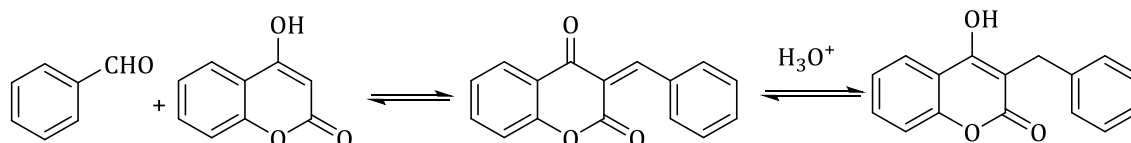
Scheme 26: The condensation between 4-hydroxycoumarin and benzoic aldehyde as described by Palmisano et al

As demonstrated in Scheme 27 utilizing chlorosulfonic acid as an echo-radiation promoter, the effective and easy chemical synthesis the derivatives of pyranopyrimidine was designed to further effectively operate the pyrimidine ring with another mode that is known for the various beneficial medicinal features [67,68].

R = H, Cl, NO$_2$, OCH$_3$, OH   X = S, O
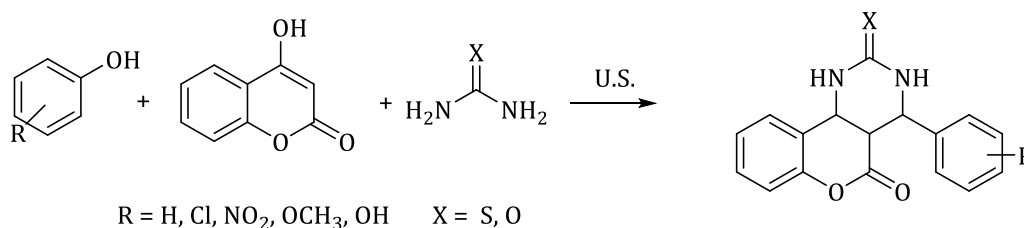
Scheme 27: The sonicated one-pot condensation for synthesizing various derivatives of pyranopyrimidine

In addition, PEG-SO$_3$H can be used as promoter in the synthesis of coumarin-derived compounds. For example as illustrated in Scheme 28, the ultrasonic-aided reaction has demonstrated between the active methylene- and phenol-based chemicals [69,70].
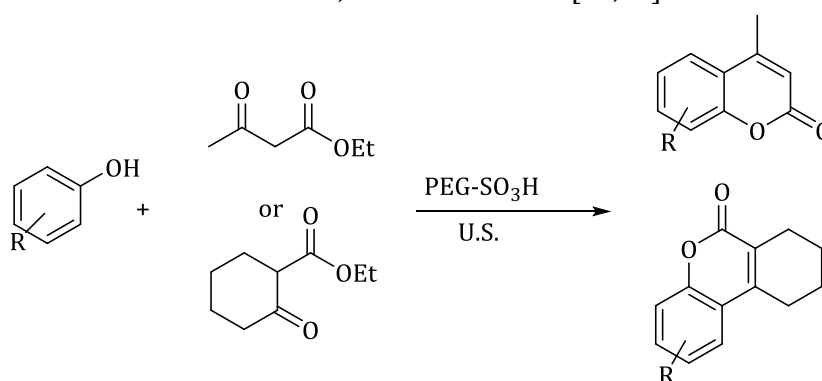
Scheme 28: The sonication-promoted synthesis of coumarin-derived compounds utilizing PEG-SO$_3$H as a promoter

In many scientific articles, a very effective ultrasonic synthesis of the derivatives of biscoumarin in aqueous media has been studied [71–74]. Several efforts have been made to attain this aim by responding to two hydroxycoumarin moles in an aqueous milieu with one mole of the aldehyde-based product have to enhance functionality of these derivatives. The use of ultrasonic radiation in a non-development approach as indicated in Schema 29 is one of the most effective trials [75].
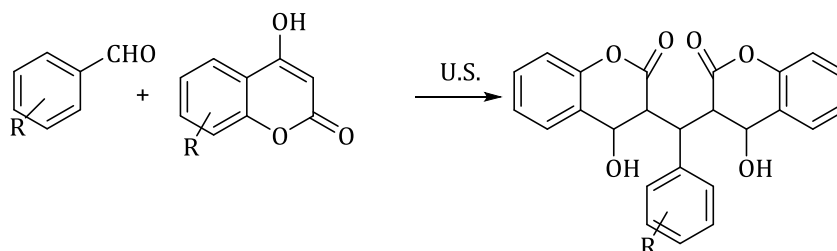

Scheme 29: The sonicated reaction for synthesizing of the derivatives of biscoumarin

Synthesis involving a solvent-free environment
The typical manner in which organic reactions are carried out necessitates the use of organic solvents. The scientific community is now working hard to make these interactions solvent-free owing to their gaseous and hazardous characteristics [76,77].

It has been reported that coumarin-derived compounds can be synthesized using a green methodology by condensing the derivative of phenol with that of β-keto ester. [Msim] HSO$_4$ facilitated and performed this solvent-free reaction, as shown in Scheme 30, at 40°C. In addition, this methodology has provided the promoter with recycling capacity without any

potential influence on its catalytic efficiency for several times [78].
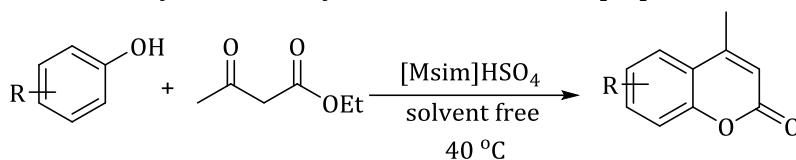
Scheme 30: The solvent-free synthesis of difunctionalized coumarin-derived compounds

In Jalal et al's. [79,80] scientific study, the synthesis of difunctionalized coumarin-derived compounds, as illustrated in Scheme 31, has been analyzed using a special chemical called poly (4-vinylpyridine)-CuI promoter in a solvent-free environment.
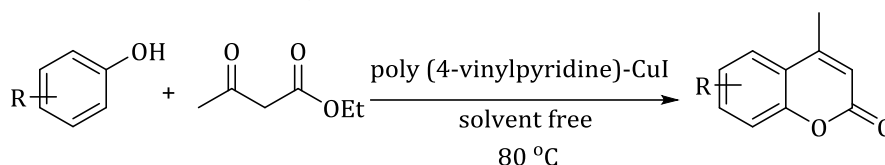
Scheme 31: The synthesis of difunctionalized coumarin-derived compounds via the reaction of Pechmann utilizing poly (4-vinylpyridine)-CuI as a promoter

Conversely, the use of FeF_3 as a promoter is claimed to enable the solvent-free synthesis of coumarin-derived compounds instead of previously mentioned catalysts. As illustrated in Schema 32, this microwave assistance reaction was carried out at a high temperature, yet provided a massive yield [81].
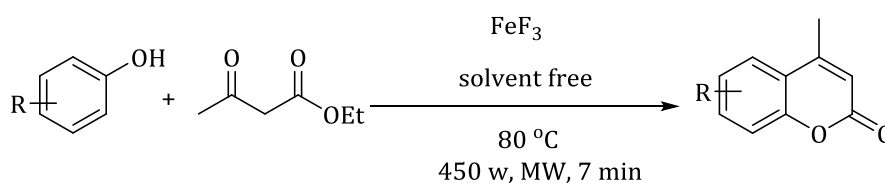
Scheme 32: The employment of FeF_3 as a promoter for the solvent-free synthesis of coumarin-derived compounds

Conclusion

The Knoevenagel, Claisen, Perkin, Pechmann, Wittig, and Reformatsky approaches are among the various synthetic strategies for coumarin-derived compounds. Whilst such reactions have been used for decades, new developments, such as the ultrasound- and microwave-promoted, and solvent-free have been investigated extensively to maximize the outcome, shorten the reaction time, reduce the side reactions, and make these reactions environmentally harmless. This investigation showed that these advancements can play an increasingly important function in the synthesis of coumarin-derived compounds by reducing the unwanted circumstances connected with the conventional pathways.

Authors' contributions

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

Conflict of Interest

We have no conflicts of interest to disclose.

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