A Review of Synthesis Methods of Chalcones, Flavonoids, and Coumarins

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Abstract: Chalcones are the primary building blocks for flavonoids and isoflavonoids production. Chalcones are a three-carbon, -unsaturated carbonyl system. Chalcones form when an aromatic aldehyde reacts with acetophenones in the presence of a catalyst. For the synthesis of these molecules, a variety of methods and approaches have been reported. The Aldol condensation and Claisen-Schmidt condensation reactions are the most commonly referenced synthetic protocols in the literature, but the Suzuki reaction, Witting reaction, and Photo-Fries rearrangement have also been employed as synthetic procedures within the chalcone framework. SOCl₂, natural phosphate, lithium nitrate, aminografted zeolites, zinc oxide, water, K₂CO₃, PEG400, silica sulfuric acid, ZrCl₄, and ionic liquid are among the most commonly used catalysts in the synthesis of the chalcone framework.

Keywords: Chalcones, Aldol Condensation, Claisen-Schmidt Condensation, Suzuki Reaction, Witting Reaction, Photo-Fries Rearrangement

1. Introduction

Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three-carbon α, β-unsaturated carbonyl system (Figure 1). Chalcones are made up of a three-carbon α,β-unsaturated carbonyl system. Condensation of aromatic aldehydes with acetophenones in presence of catalyst yields chalcones [1]. Chalcones are precursors in the synthesis of several beneficial compounds such as flavonoids and isoflavonoids [2].

![Figure 1. General structure of chalcone.](image-url)

Chalcones act as mediators in the synthesis of useful therapeutic compounds. Special consideration has been given to chalcones because of their simple structures and diverse pharmacological activities. Owing to these stated reasons, the synthesis of chalcones and chalcone-based functionalized derivatives is still undertaken. Many researchers around the world have reported schemes for the synthesis of these compounds. Among all the stated methods, Aldol condensation and Claisen-Schmidt condensation still hold the prime position.

The superlative method for the synthesis of chalcones is the conventional Claisen-Schmidt condensation in the presence of aqueous alkaline bases [3], Ba(OH)₂ [4], LiOH, microwave irradiation, and ultrasound irradiation [5]. Other famous techniques include Suzuki reaction [6], Witting reaction, and Photo-Fries rearrangement. Chalcone synthesis via aldol condensation requires two steps, aldol formation, and dehydration. Given that aldol addition is reversible, Claisen-Schmidt condensation using enol ether has come out as an alternative pathway. Aldol reaction is also performed under acidic conditions [7] courtesy of HCl, BF₃, B₂O₃, and p-toluene sulfonic acid. In the past few years, a range of adapted methods for the synthesis of chalcones has been reported. These innovative techniques use various catalysts and reagents including SOCl₂ [8] natural phosphate, lithium nitrate [9], amino grafted zeolites [10], zinc oxide, water [11], K₂CO₃ [12], PEG400 [13], silica sulfuric acid [14], ZrCl₄, and ionic liquid [15]. The accomplishment of these novel methods has been hindered...
by limitations like harsh reaction conditions, toxic reagents, strongly acidic or basic conditions, prolonged reaction times, poor yields, and low selectivity. The development of improved strategies for the synthesis of α, β unsaturated carbonyl compounds is still required.

Chalcones find many applications in organic synthesis, like precursors in the synthesis of several beneficial compounds such as flavanones [2]. Flavanones are important naturally occurring pharmacological compounds and are valuable precursors for the synthesis of flavonoids. Preparation of flavanones (1) has been carried out by intramolecular cycles 2-hydroxy chalcone (2) under various conditions using acids, bases, thermolysis, electrolysis, and photolysis. Different catalysts like acetic acid, [16] piperidine, [17] CH₃COONa, [18] H₃PO₄, [19] PEG-400 [20] have been employed for this conversion (Figure 2).

2. Methods of Synthesis of Chalcones

In 1880-81 L. Claisen [21] and J. G. Schmidt [22] published the reports of their individual research of base-catalyzed condensation between an aldehyde and a ketone, which appear to be the first published report of chalcone preparation. The succeeding century witnessed an ever-increasing interest of chemists and biologists towards the synthesis as well as bioactivity studies of these chalconoids resulting in numerous research publications published and patents filed in different countries. Different variations of Claisen Schmidt condensation (CSC) using different catalysts or reaction conditions have been developed. Amidst these numerous methodologies, the classical aqueous base-catalyzed version of CSC still stands as the most popular method of chalcone synthesis [23].

2.1. Claisen Schmidt Condensation (CSC) Via Enolate Formation

An aldol condensation, an enol, or an enolate ion reacts with a carbonyl compound to form β a hydroxyl ketone, or β-Hydroxyl ketone followed by dehydration to give a conjugated enone. Basically, the CSC is a crossed aldol condensation between a ketone having only one α hydrogen and an aldehyde with no α-hydrogen. The base-catalyzed CSC proceeds via the formation of an enolate of the ketone which attacks the aldehydic carbon to form the adduct (A). Finally, the elimination of a water molecule gives the product chalcone (Scheme 2). Different inorganic and organic bases have been employed for catalyzing CSC under homogeneous and heterogeneous reaction conditions. Among them hydroxides like NaOH, KOH are prominent.

2.1.1. Synthesis of Chalcones Using NaOH

NaOH is one of the most used bases for the synthesis of chalcones. Cabrera et al. [21] synthesized a number of substituted chalcones employing NaOH (3.0 equiv) as a catalyst in anhydrous ethanol (Figure 3). After completion, the reaction mixture is neutralized with dil. HCl and most of the products were recrystallized from methanol.

Sivakumar et al. [25] synthesized a series of chalcones with different substituents on the aryl rings using NaOH in methanol at room temperature in 3 h of reaction time with more than 80% product yields.

2.1.2. Synthesis of Chalcones Using KOH

KOH is another base widely used as a catalyst in CSC to synthesize chalcones. Different reports are there [26] for the synthesis of substituted chalcones using aq. KOH as catalyst (Figure 4).

2.2. Claisen Schmidt Condensation (CSC) Via Enol Mode

The acid-catalyzed version of CSC proceeds through the formation of an enol. The enol attacks the protonated aldehyde to give the additional product. This is followed by the elimination of a water molecule to give the product chalcone (Figure 5).

The advantage of the CSC via enol mode over the enolate mode is that it can be directly applied for the synthesis of hydroxyl chalcones without prior protection of the hydroxyl group. [7]
2.3. Synthesis of Chalcones Using H$_2$SO$_4$ and HCl

Sipos et al. [24] and Co-worker used HCl gas saturated in absolute ethanol for the condensation of 4-hydroxy benzaldehyde with different substituted acetophenones (Figure 6).

![Figure 6. Claisen-Schmidt condensation using HCl in absolute ethanol.](image)

Eun-Jin et al. and Co-worker used a catalytic amount of H$_2$SO$_4$ in methanol for the synthesis of a variety of substituted chalcones. The method was extended for the synthesis of some sulfonamide-N-chalcones and sulfonate-O-chalcones for their biological studies [25] (Figure 7).

![Scheme 7. Synthesis of substituted chalcones using H$_2$SO$_4$.](image)

2.4. SOCl$_2$/EtOH Catalyzed Synthesis of Chalcones

Petrov et al. reported in situ generated HCl was used for carrying out this reaction by using SOCl$_2$/EtOH system. Four hydroxyl-substituted chalcones were also prepared in addition to other substituted chalcones [29] (Figure 8).

2.5. Synthesis of Chalcones Using ZrCl$_4$

Lewis acids provide environmentally benign alternative routes for many hitherto mineral acid-catalyzed organic transformations. [29] Various Lewis acids have been successfully applied for the synthesis of chalcones also.

Kumar et al. [18] used ZrCl$_4$ both in solvent-free and insolvent (dry DCM) reaction conditions to catalyze the CSC (Figure 9). In this fast and clean reaction, substituted chalcones were synthesized in moderate to good yields (70-93%) using 20 mol% of the catalyst.

![Figure 9. Synthesis of chalcones using ZrCl$_4$.](image)

2.6. Synthesis of Chalcone Using Boron trifluoride-Etherate

A new technique was developed by Narender and Reddy (2007) using BF$_3$-Et$_2$O to create a variety of substituted chalcones. Priority has been given to this method because of high yields, simple work-up, short reaction times, and no side reactions. This method has been employed for solvent-free reactions and for reactions concerning liquid reactants which possess base sensitive functional groups like esters and amides.

O-acylated (5) or N-acylated chalcones (8) in high yields were produced by condensation reaction between O-acylated (3) or N-acylated acetophenone (6) and the individual aromatic aldehyde (4) or (7), catalyzed by BF$_3$-Et$_2$O [32] as illustrated in (Figure 10).

![Figure 10. Synthesis of O-acylated and N-acylated chalcones using BF$_3$-Et$_2$O.](image)
2.7. Synthesis of Chromonyl Chalcones Using Zn-(L-proline)$_2$

In a recent report, Siddiqui et al. [29] synthesized a series of chromonyl chalcones employing Zn-(L-proline)$_2$ as a recyclable Lewis acid catalyst in water. The catalyst was reused for five consecutive cycles without any loss of activity (Figure 12).

Figure 12. Synthesis of chromonyl chalcones using Zn-(L-proline)$_2$.

3. Synthesis of Chalcones Using Heterogeneous & Ecofriendly Methods

One of the major drawbacks of these alkali base-catalyzed methods for chalcone synthesis is that 2.5 to 3.0 equivalents of catalyst, as well as the same equivalents of mineral acid for its neutralization, is required in the workup of these methods. Like other homogeneously catalyzed methods of organic syntheses [9], these are also criticized for their highly detrimental environmental impact as a large volume of aqueous waste is generated. Responding to this environmental cry, methods are developed for the synthesis of chalcones using these alkali bases under environmentally benign reaction conditions.

Rateb et al. reported the synthesis of chalcones under solvent-free conditions in quantitative yields by grinding the methyl ketones and aldehydes with solid NaOH (1.4 equiv) in 5-10 minutes of reaction time. [31] The solid catalyst was removed by simple cold aqueous washing and the products were purified by recrystallization (Figure 13).

Figure 13. Synthesis of chalcones using NaOH under solvent-free conditions.

3.1. Synthesis of Chalcones Via Microwave Irradiation

Without using solvents, the blend of supported reagents and microwave irradiation can be used to carry out a variety of reactions in short time intervals and with high conversions and selectivity. This approach is appreciated by researchers because it presents copious advantages over conventional heating methods and fastens the organic reactions. [32]

Solid K$_2$CO$_3$ (10 mol%) in PEG-400 was used to synthesized chalcones. The reaction mixture was stirred at 90-120°C for 1.5-2.5 h and the product was recrystallized after removal of the catalyst by cold aqueous washing (Figure 14).

Figure 14. Synthesis of chalcones using K$_2$CO$_3$, PEG-400.

3.2. Synthesis of Chalcones Via Ultrasound Irradiation

C. J. Duran-Valle and his Co-workers reported two basic activated carbons Na- and Cs-Norit were used to catalyze the CSC under sonochemical irradiation. A new type of catalyst was prepared by grafting amino groups on sodium and cesium exchanged X zeolite. [30] This new catalyst was successfully applied for the synthesis of chalcones in solvent-free conditions under ultrasonic irradiation.

Solhy et al. synthesized reusable hydroxyapatite [Ca$_{10}$(PO$_4$)$_6$(OH)$_2$] and used it with water as a co-catalyst for the synthesis of fifteen substituted chalcones [14] (Figure 15). They studied the impact of water on the catalyst reactivity and high activation of the same was observed in its presence.

Figure 15. Synthesis of chalcones using reusable hydroxyapatite.

3.3. Synthesis of Chalcone Via Grinding Technique

Wang et al. [34] used molecular iodine for catalyzing the CSC between different ketones and aldehydes under solvent-
free and grinding conditions. In this very simple reaction, chalcones were synthesized in 83-95% yield in 5-10 minutes of reaction time (Figure 16).

3.4. Ionic Liquids Catalyzed Synthesis of Chalcones

In recent years, ionic liquids have been emerged as a powerful alternative to conventional organic solvents due to their particular properties, such as undetectable vapor pressure, wide liquid range, as well as ease of recovery and reuse, making them a greener alternative to volatile organic solvents. [41] Different research groups have investigated the applicability of these ionic liquids in the synthesis of chalcones.

Dong et al. [14] used some sulfonic acid functionalized task-specific ionic liquids (TSIL) for catalyzing the CSC to synthesize chalcones. Seven TSILs were studied and found to effectively catalyze the CSC (Figure 17).

Figure 17. Sulfonic acid-functionalized TSIL catalyzed synthesis of chalcones.

Shen et al. [36] reported an efficient and environmentally friendly solvent-free method for the synthesis of chalcone using Brønsted acidic ionic liquids as dual catalyst and solvent. Ionic liquids like [HSO3]BBIM catalyzed the reaction most efficiently at 140°C and the catalyst was reused for three cycles without any appreciable loss of activity.

Four readily available and economic TSILs viz. [TEBSA][HSO4], [TEBSA][NO3], [TEBSA][CF3COO] and [TEBSA][pTSO] have been used as recyclable catalysts for the CSC of benzaldehydes and acetophenones to synthesize chalcones by Qian et al. [44].

Pawar et al. [41] developed a clean and efficient method for the synthesis of chalcones using reusable phosphonium ionic liquid catalyst [PhosILCl]. Chalcones were synthesized in high yields using this eco-friendly method in 2.5 to 3.5 h reaction time. [45]

3.5. ZnO Nanoparticle as the Catalyst for the Synthesis of Chalcone

Subhash Chand et al. [39] reported zinc oxide (ZnO) nanoparticles function as a highly effective catalyst for the synthesis of 3-formyl benzopyranones (11) chalcones by CSC of 2-(2-methoxy-benzoyl)-propenal (9) with 1-Phenylethanal (10) under the solvent-free condition to afford the corresponding chalcones in moderate to good yields (Scheme 23). They reported the advantage of this method solvent-free environmentally co-friend, in the expensive table, can be easily recycled and reused for several cycles with consistent activity.

Figure 18. Synthesis of 3-formyl benzopyran-4-ones chalcones.

4. Miscellaneous Methods of Chalcone Synthesis

Apart from Claisen-Schmidt condensation, some other routes were also developed for the synthesis of chalcones. In particular, Suzuki reaction using phenylboronic acids, Julia-Kocienski olefination, and Wittig reaction was studied for the synthesis of chalcones.

4.1. Synthesis of Chalcone Via Suzuki Reaction

Palladium-catalyzed Suzuki cross-coupling of haloarenes with aryl boronic acid is among the most powerful C-C bond-formation reactions available to synthetic organic chemists. Like in many other organic syntheses, palladium-catalyzed cross-coupling reactions find their application in chalcone synthesis also.

Eddarir et al. [41] developed a method for the synthesis of chalcones based on the Suzuki reaction either between cinnamoyl chlorides and phenylboronic acids or between benzoyl chlorides and phenyl vinyl boronic acids (Figure 19).

Figure 19. Chalcone synthesis via Suzuki reaction.

Mohammad et al. [41] developed a method for direct cross-coupling reaction of benzoyl chlorides and potassium styryl tri fluoroborates to the corresponding α, β-unsaturated aromatic ketones in the presence of PdCl2 (dbdpf) catalyst under microwave irradiation. This method was used for the synthesis of chalcones with a variety of substituents (Figure 20).

Figure 20. Pd (II) catalyzed cross-coupling reaction in the synthesis of chalcone.

4.2. Synthesis of Chalcones Via Julia-Kocienski Olefination

Kumar et al. developed 2-(Benzo[d] thiazol-2-ylsulfonyl)-1-phenylethanones as a new reagent for the synthesis of chalcones via Julia-Kocienski olefination with
aldehydes in presence of a base in good to excellent yields [15] (Figure 21).

4.3. Chalcone Synthesis by Fries Rearrangement

Jeon et al. [16] prepared chalcones using aryl cinnamates by Fries rearrangements catalyzed by TiCl₄ in moderate to good yields (Figure 22).

4.4. Synthesis of via Wittig Reaction

The Wittig reaction is a powerful method for the regio- and stereocontrolled construction of carbon-carbon double bonds. Wittig reaction was also used for synthesizing chalcones. [17, 18]. In these methods reaction of a stable ylide with aldehydes is used for synthesizing the desired chalcones (Figure 23).

Preparation of flavanones (13) has been carried out by intermolecular cyclic 2-hydroxy chalcone (12) under various conditions using acids, bases, thermolysis, electrolysis and photolysis. piperidine, [21] CH₃COONa, (Figure 24).

6. Synthesis Methods of Flavonones

The synthesis of flavanones often involves an intramolecular conjugate addition of 2'-hydroxy chalcone, 2'-aminochalcones, and 2 '- mercaptochalcones to the corresponding cyclic system in the presence of an acid or a base catalyst.

The required chalcones are normally synthesized via Claisen-Schmidt condensation of 2'-hydroxy acetophenone, 2 '-aminoacetophenone, and 2 '- mercaptoacetophenone with various benzaldehydes.

As outlined in (Figure 25), the retrosynthetic analysis consists of two primary disconnections, which can provide a facile and versatile synthetic route to produce a variety of products for the synthesis of flavanones without a lengthy protection-deprotection strategy.

6.1. Acetic Acid-catalyzed Flavanone Synthesis

Cabrera et al. 2007 reported acetic acid is one of the most common solvents (acid catalysts) in organic synthesis due to its commercial availability and reasonable price. It is reported to be a the promising catalyst for the transformation of 2 '-hydroxy chalcones to the corresponding flavanones (Figure 26). [21]
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6.2. L-proline Catalyzed Flavanone Synthesis

An efficient method reported by Chandrasekhar et al. [47] involved a reaction of a variety of aryl aldehydes with substituted 2'-hydroxyl acetophenone in the presence of 30mol% L-proline in DMF (Figure 27).

![Figure 27. Chandrasekhar synthetic route of flavanone.](image)

6.3. Microwave Accelerated Solvent-free Synthesis of Flavanones

Sagara et al. 2003 and Co-workers reported the synthesis of flavanone was carried out by using organic acid (TFA) and mineral support (silica gel) in the microwave. (Figure 28). [48]

They added 0.2ml TFA and 1g silica gel to the reaction mixture of 0.1mmol chalcone in 5ml dry DCM the resulting powder was irradiated by microwave to produce the corresponding flavanones. The advantage of this method minimizes the usage of conventional solvent for flavanone synthesis.

![Figure 28. Microwave Accelerated Solvent-Free Synthesis of Flavanone.](image)

6.4. Jea In Lee Synthetic Method

Lee and Co-workers [22] introduced a method where the reactions proceeded without involving in 2'-methoxy or 2'-hydroxy chalcones. They treated 2' -methoxy benzoic acid with 2 equivalents methyl lithium in THF to produce 2'-methoxyacetophenone which was subsequently treated with 1 equivalent LDA in THF at -20°C to yield the corresponding lithium enolate.

![Figure 29. Synthesis of flavanones using 2'-Methoxy benzoic acid.](image)

6.5. Eco-friendly Polyethylene Glycol Promoted Flavanone Synthesis

Kumar and co-workers employed an eco-friendly method to synthesize flavanones and azaflavanones by reacting 1.4 mmol 2'-hydroxy chalcones or 2'-aminochalcones in 0.5 ml solution of polyethylene glycol (PEG-400) at optimized temperature (130°C) for appropriate time (Figure 30). [64]

![Figure 30. Synthesis of flavanones and azaflavanones in PEG-400.](image)

6.6. Flavanone Synthesis Catalyzed by Anhydrous Potassium Carbonate

Mondal and Co-workers reported by refluxing a mixture of 1mmole of 2'-hydroxy chalcones and anhydrous potassium carbonate (1.5gr) in dry acetone for 3-5hrs to give flavanones. They repeated the same reaction in a microwave by adding 1.5-gram anhydrous potassium carbonate to a solution of 2'-hydroxy chalcones (1mmol) in DCM (Figure 31). [50]
Figure 31. Synthesis of flavanones using anhydrous potassium car.

Condition 1: Anhydrous K$_2$CO$_3$ reflux dry acetone for 3-5 h
Condition 2: Anhydrous K$_2$CO$_3$ microwave irradiation for 3 min.

However, many of the reported methods suffer from disadvantages such as low yields, long reaction times, and strong acidic medium leading to environmental pollution, high cost of the catalyst, and lack of recovery and reusability of the catalysts. In addition, most of the reported synthetic methodologies are not applicable to the synthesis of all subtypes of flavanones.

Hence, there is still a need to develop mild, high-yielding protocols for the cyclization of substituted chalcones to flavanones via environmentally friendly methods. Nowadays, heterogeneous catalysts are preferred over homogeneous processes due to their regenerative ability and reusability, ease of handling, and simplicity of work up.

7. Structural Activity Relationship of Chalcones

7.1. Anticancer Activity

Vogel et al. [51] tested and reported the influence of the A-ring hydroxylation pattern on the cytotoxic activity of the prenylated chalcones (Figure 32) in a HeLa cell line and revealed that non-natural prenylated chalcones, like 12a (IC50 3.2 ± 0.4 M) as well as 3-hydroxyXN, 12b (IC50 2.5 ± 0.5 M), were more active in comparison to XN 13a (IC50 9.4 ± 1.4 M).

7.2. Antimalarial Activity

Awasthi et al [52] synthesized several new chalcone analogs and evaluated them as inhibitors of the malaria parasite. According to the report, inhibitory activity was determined in vitro against a chloroquine-sensitive P. falciparum strain of parasites. The chalcone 3-(4-methoxyphenyl)-1-(4-pyrrol-1-yl-phenyl) prop-2-en-1-one (14) (Figure 33) was found to be the most active with 50% inhibition concentration (IC50) of 1.61 µg/ml. This inhibitory concentration was comparable to licochalcone (15), with an IC50 of 1.43 µg/ml.

7.3. Anti-inflammatory Activity

Yadav et al [53] synthesized a series of five chalcone derivatives and were subjected to anti-inflammatory. According to the report, the compound 4-fluoro/4-chloro chalcone (Figure 34) showed more activity comparable to standard drug indomethacin due to -F/-Cl groups present in the compound. Hence, the anti-inflammatory activity of chalcone derivatives was increased when electron-withdrawing groups (EWG) were present on the chalcone moiety.

7.4. Antifungal Activity

Bag et al [54] synthesized a series of chalcones incorporating sulfur either as part of a hetero-aromatic ring (thiophene) or as a side chain (this methyl group) and tested for their in-vitro activity and the report showed appreciable activity against a fluconazole-sensitive and fluconazole-resistant strain with the chalcone’3-(4 (methylthio)phenyl)-1-(thiophene-2-yl)prop-2-en-1-one’(Figure 35) exhibiting the highest activity.
7.5. Antimicrobial Activity

Yayli et al [55] synthesized N-alkyl derivatives and photochemical dimers of 3 o-, m-, and p-nitro substituted 4-azachalcones. The compounds ‘1-decyl-4-(3-(3-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide’ (16) and ‘1-decyl-4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide’ (17) exhibited broad-spectrum antimicrobial activity. (Figure 36)

According to the report, compounds showed good antimicrobial activity against test micro-organisms E. coli K. pneumoniae, Yersinia pseudotuberculosis, P. aeruginosa, Enterococcus faecalis, S. aureus, Bacillus cereus.

8. Synthesis Methods of Coumarins

Many researchers are reported coumarins (benzopyrones) are a large family of compounds, of natural and synthetic origin, that show numerous biological activities like, antioxidants and enzymatic inhibition properties.

Phenylcoumarins are synthetic compounds in which an additional phenyl ring is attached in any position of the pyrone or the benzenic ring of the coumarin nucleus. The variety of biological activities of the 3-arylcoumarins makes their preparation an interesting topic in synthetic organic chemistry.

Different methods are reported for the synthesis of coumarin’s scaffold such as Wittig reaction Perkin reaction palladium-catalyzed reaction and Microwave irradiation.

8.1. Synthesis of Coumarin Via Perkin Reaction

Reported synthesis of coumarin through Perkin reaction by aldol condensation, of aromatic ortho hydroxybenzaldehyde and acid anhydrides, in the presence of an alkali salt of the acid (Figure 37).

8.2. Synthesis of Coumarin Via Pechmann Reaction

Reported synthesis of coumarins through Pechmann reaction by condensation of phenols with β-ketoesters, in the presence of acid catalysts (Figure 38).

8.3. Synthesis of Coumarin Via Wittig Reaction

Synthesis of coumarin by olefination of ortho-hydroxy carbonyl aromatic compounds, followed by further lactonization. (Figure 39)
8.4. Synthesis of Coumarins Via Pd-Catalyzed Hydroarylation

Jia C et al. [80] reported synthesis of Coumarins by a stereo- and regioselective palladium-catalyzed hydroarylation. This reaction occurs between aryl halides and functionalized alkynes, at room temperature, followed by a fast intramolecular reaction (Figure 40).

8.5. Synthesis of Coumarin Using Ultrasound

S. J. Pradeeba et al. [36] and Co-Workers have reported a fast and highly efficient green method for synthesizing 3-aryl coumarin derivatives from salicylaldehyde and phenyl acetyl chloride in the presence of tetrahydrofuran and K₂CO₃ using ultrasound irradiation is reported. The advantage of this method better yields and faster reaction times of the desired products than when prepared under conventional conditions. (Figure 41).

8.6. ZnO Nanoparticle as a Catalyst for Synthesis of Coumarins

Zinc oxide (ZnO) nanoparticles functions as highly effective catalysts for the reactions of various o-hydroxy benzaldehydes with 1,3-dicarbonyl compounds through Knoevenagel condensation under microwave and thermal conditions to afford the corresponding coumarins (Figure 42).

The advantage of this method is a solvent-free, environmentally friendly, the catalyst is inexpensive, stable, can be easily recycled and reused for several cycles with consistent activity.

9. Conclusion

Chalcone, a favored structure with diverse biological and synthetic utility and adaptable reactive intermediates that are employed to create multiple heterocyclic ring systems, including several types of flavonoids, is the synthetic precursor of many plant-derived secondary metabolites.

Flavonoids have a lot of pharmacological potentials. A variety of synthetic methods have been used to make chalcones and flavonoids, including the Lewis acid-base catalyst, heterogeneous and environmentally friendly approaches, Suzuki reaction, Wittig reaction, and the Jeal Lee synthetic method. The researchers used a variety of catalysts, replacing homogeneously catalyzed classical yield-oriented methods of synthesis with ecologically benign ways and innovative techniques, as catalysts are a necessary component of every approach. As a result, different working groups have created alternative preparation techniques, including an environmentally friendly one.
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