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

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Abstract
Chalcones are the principal precursors for the biosynthesis of flavonoids and isoflavonoids. A three-carbon α, β-unsaturated carbonyl system constitutes chalcones. Chalcones are the condensation products of an aromatic aldehyde with acetophenones in attendance of catalyst. A lot of methods and schemes have been reported for the synthesis of these compounds. Amongst all, Aldol condensation and Claisen-Schmidt condensation reactions are the most cited synthetic protocols in literature, nevertheless, Suzuki reaction, Witting reaction, and Photo-Fries rearrangement have also been utilized as synthetic protocols towards the chalcone framework. Several catalysts have been developed in the synthesis of the chalcone framework among which $SOCl_2$ natural phosphate, lithium nitrate, amino grafted zeolites, zinc oxide, water, K_2CO_3, PEG400, silica sulfuric acid, $ZrCl_4$, and ionic liquid are the most cited ones. The development of better synthetic techniques for the synthesis of α, β- unsaturated carbonyl compounds is still remaining high demand.
Keywords: Chalcones, Aldol condensation, Claisen-Schmidt condensation, Suzuki reaction, Witting reaction, Photo-Fries rearrangement
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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 (Figure1). 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].

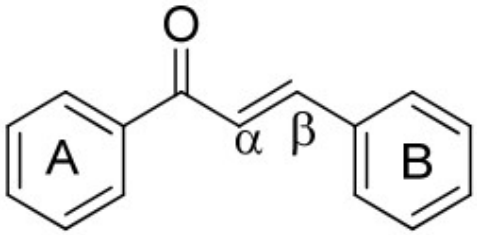
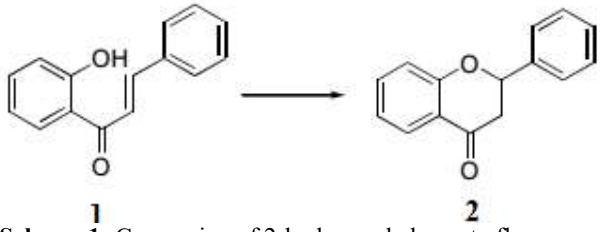


Figure 1: General structure of chalcone

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, BF_3, B_2O_3, and *p*-toluenesulfonic 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 $SOCl_2$ [8] natural phosphate, lithium nitrate [9], amino grafted zeolites [10], zinc oxide, water [11], K_2CO_3 [12], PEG400 [13], silica sulfuric acid [14], $ZrCl_4$ 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] CH_3COONa,[18] H_3PO_4,[19]PEG-400 [20] have been employed for this conversion (Scheme 2).



1 **2**

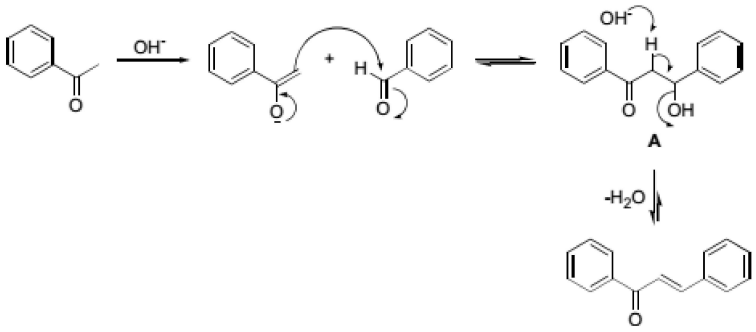
Scheme 1: Conversion of 2-hydroxy chalcone to flavanone.

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.

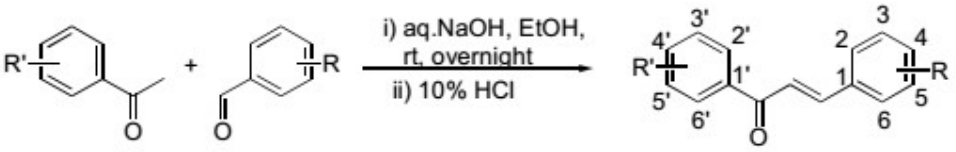


Scheme 2 Mechanism of base-catalyzed Claisen-Schmidt condensation

2.1.1. Synthesis of chalcones using NaOH.

NaOH is one of the most used bases for the synthesis of chalcones. Cabrera *et al*. [24] synthesized a number of substituted chalcones employing NaOH (3.0 equiv) as a catalyst in anhydrous ethanol (Scheme 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.

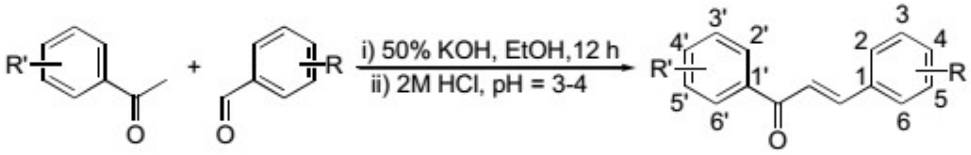


R' = H R = H, 4-Cl, 2-Br, 4-Br, 4-OCH_3, 4-SCH_3, 4-$NHCOCH_3$
R' = 2'-OH R = 4-NO_2, 2-NO_2, 4-Cl, 4-Br, etc.

Scheme 3 Synthesis of chalcones using NaOH.

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 (Scheme 4).



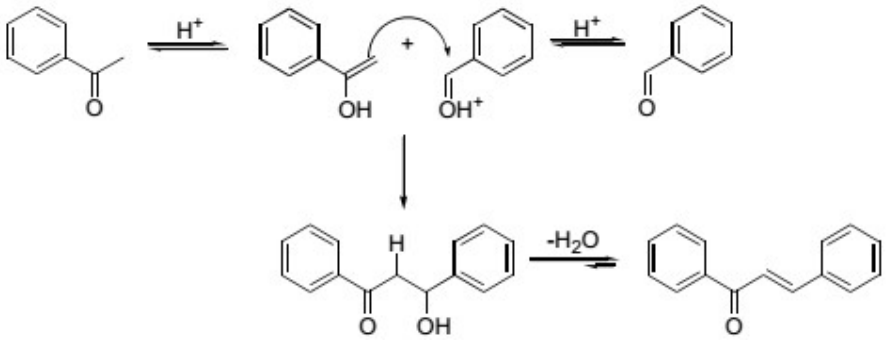
R' = H	R = H
= H	= 4-OMe
= H	= 3,4-O-CH_2-O-
= H	= 3,4,5-OMe
= 3-OMe, 4-OH	= 3,4,5-OMe, etc.

Scheme 4 Synthesis of chalcones using KOH

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 (Scheme 5).

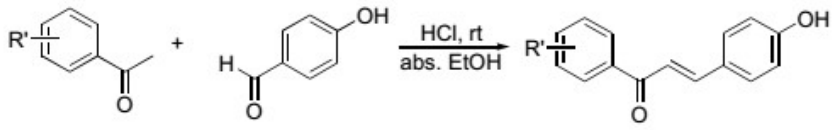
The advantage of the CSC via enol mode over the enolate mode is that it can be directly applied for the synthesis of hydroxyl chalcones without prior protection of the hydroxyl group. [26]



Scheme 5 Mechanism of CSC via enol mode.

2.3. Synthesis of chalcones using H_2SO_4 and HCl

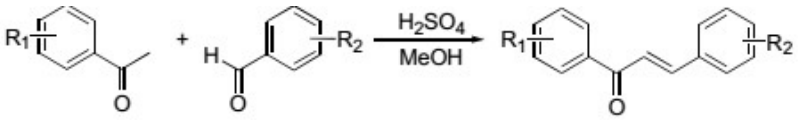
Sipos *et al* [27] and Co-worker used HCl gas saturated in absolute ethanol for the condensation of 4- hydroxy benzaldehyde with different substituted acetophenones (Scheme 6).



R' = 3-NO_2
= 2-OH, 4-NO_2
= 3-OH, 4-NO_2
= 3-OH, 6-NO_2

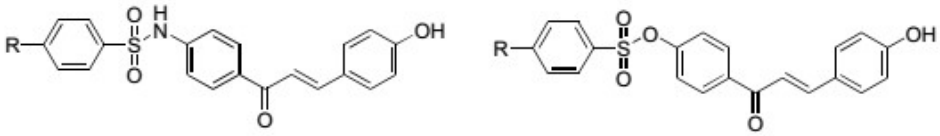
Scheme 6 Claisen-Schmidt condensation using HCl in absolute ethanol.

Eun-Jin *et al*. and Co-worker used a catalytic amount of H_2SO_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 [28] (Scheme 7).



R^1 = H
= OH
= NH_2

R^2 = H
= OH
= OH



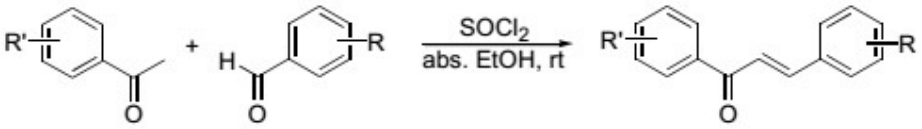
R = H, CH_3, F, NH_2

R = H, CH_3, F, NH_2

Scheme 7 Synthesis of substituted chalcones using H_2SO_4

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] (Scheme 8).



R' = H R = H
= 2-OMe
= 3-OMe
= 4-OMe
= 3-OH
= 4-OH
= 3-Cl
= 4-Cl

R' = 4-OCH_3 R = H
= 4-OMe
= 4-Cl

R' = 4-Cl R = H
= 4-OMe
= 4-OH
= 4-Cl

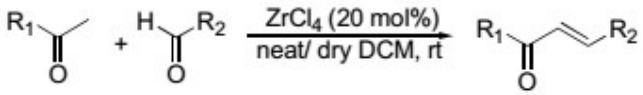
R' = 4-OH R = H

Scheme 8 $SOCl_2$/EtOH catalysed synthesis of chalcones.

2.5. Synthesis of chalcones using $ZrCl_4$.

Lewis acids provide environmentally benign alternative routes for many hitherto mineral acid-catalyzed organic transformations. [30] Various Lewis acids have been successfully applied for the synthesis of chalcones also.

Kumar *et al*. [31] used $ZrCl_4$ both in solvent-free and insolvent (dry DCM) reaction conditions to catalyze the CSC (Scheme 9). In this fast and clean reaction, substituted chalcones were synthesized in moderate to good yields (70-93%) using 20 mol% of the catalyst.



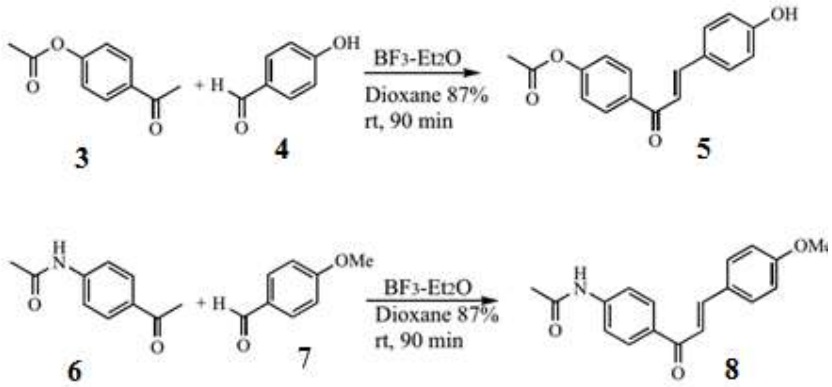
R_1 = Ph	R_2 = Ph	R_1 = 3-NO_2Ph	R_2 = 2-OHPh
= Ph	= 4-OMePh	= 4-NO_2Ph	= Ph
= 4-OMePh	= Ph	= Ph	= 4-OHPh
= 4-OMePh	= 4-OMePh	= 4-OMePh	= 4-OHPh
= 2,6-ClPh	= Ph	= Naphthyl	= Ph
= 2-C_4H_3O	= 4-OMePh	= Naphthyl	= 4-OMePh
= 2-NO_2Ph	= Ph	= Ph	= 4-$OC_2H_4NC_4H_8$Ph

Scheme 9 Synthesis of chalcones using $ZrCl_4$.

2.6. Synthesis of chalcone using Borontrifluoride-Etherate

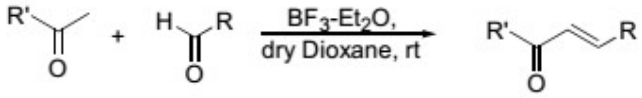
A new technique was developed by Narender and Reddy (2007) using BF_3- Et_2O to create a variety of substituted chalcones. Priority has been given to this method because of high yields, simple work-up, short reaction times, and no side reactions. This method has been employed for solvent-free reactions 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_2O [32] as illustrated in (Scheme 10).



Scheme 10 Synthesis of *O*-acylated and *N*-acylated chalcones using BF_3- Et_2O.

Narender *et al*. used BF3- Et_2O for the synthesis of chalcones in dry dioxane in a very short reaction time with a very good product yield. [33] They applied this method for the synthesis of chalcones with varied substituents (Scheme 11).

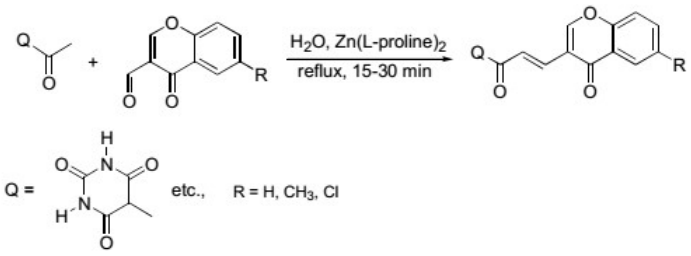


R' = CH_3	R = 3,4-OMePh	R' = 4-NO_2Ph	R = 4-OMePh
= Ph	= Ph	= 2,4-OMePh	= 2-NO_2Ph
= 4-OHPh	= 4-OHPh	= 4-OHPh	= 3,4-OMePh
= 4-OAcPh	= 4-OHPh	= 2,4-ClPh	= 3,4-OMePh
= 4-AcNHPh	= 4-OMePh	= 2,4-OMePh	= 3,4-FPh
= 3-OHPh	= 2-NO_2Ph	= 3-OHPh	= 4-OMePh

Scheme 11. Chalcone synthesis using BF_3- Et_2O.

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

In a recent report, Siddiqui *et al*. [34] 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 (Scheme 12).



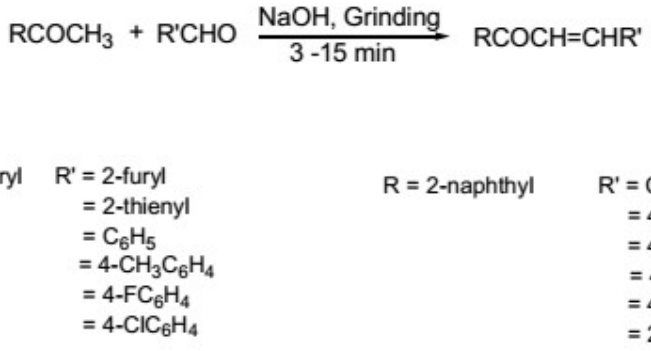
Scheme 12 Synthesis of chromonyl chalcones using Zn-(L-proline)$_2$.

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 [35], 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. [36] The solid catalyst was removed by simple cold aqueous washing and the products were purified by recrystallization (Scheme 13).

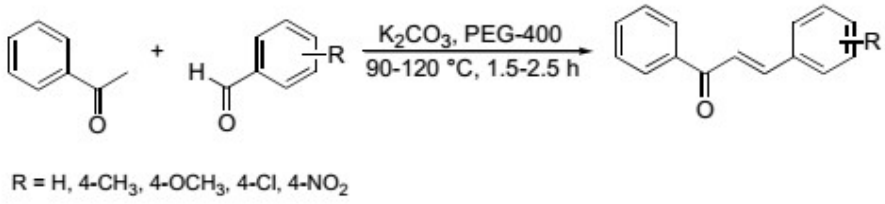


Scheme 13 Synthesis of chalcones using NaOH under solvent-free conditions.

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. [37]

Solid K_2CO_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 (Scheme 14).

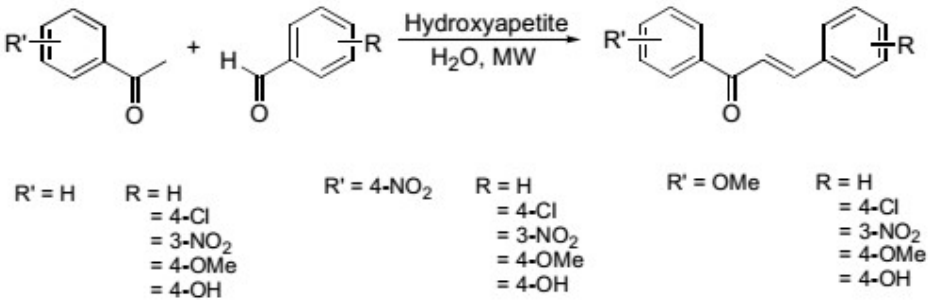


Scheme 14 Synthesis of chalcones using K_2CO_3, PEG-400.

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. [38] This new catalyst was successfully applied for the synthesis of chalcones in solvent-free conditions under ultrasonic irradiation.

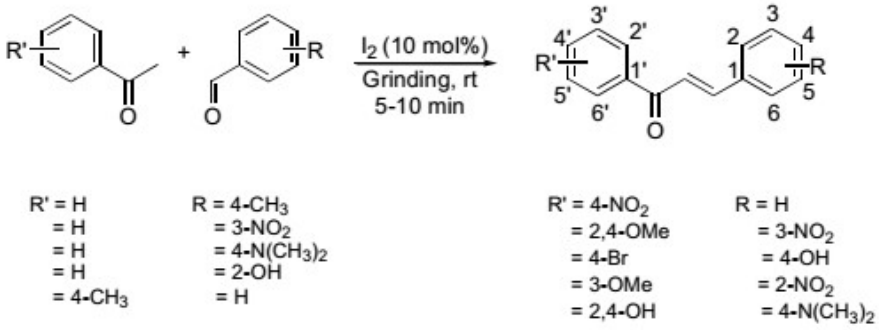
Solhy *et al.* synthesized reusable hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] and used it with water as a co-catalyst for the synthesis of fifteen substituted chalcones [39] (Scheme 15). They studied the impact of water on the catalyst reactivity and high activation of the same was observed in its presence.



Scheme 15 Synthesis of chalcones using reusable hydroxyapatite.

3.3. Synthesis of chalcone *via* Grinding Technique

Wang *et al*. [40] 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 (Scheme 16).

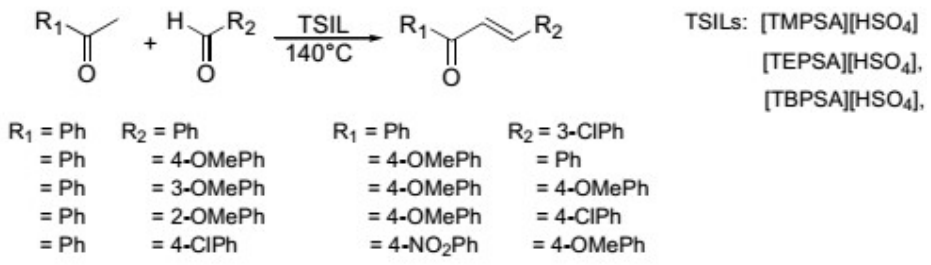


Scheme 16 I_2 catalyzed the synthesis of chalcones by grinding.

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*. [42] 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 (Scheme 17).



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

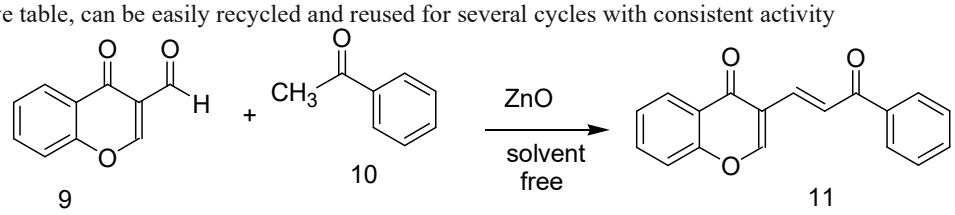
Shen *et al*. [43] reported an efficient and environmentally friendly solvent-free method for the synthesis of chalcone using Brønsted acidic ionic liquids as dual catalyst and solvent. Ionic liquids like [(HSO_3)BBIM]BF_4 catalyzed the reaction most efficiently at 140 °C and the catalyst was reused for three cycles without any appreciable loss of activity.

Four readily available and economic TSILs viz. [TEBSA][HSO_4], [TEBSA][NO_3], [TEBSA][CF_3COO] 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*. was 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*. [46] 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-Phenyl-ethanone(**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



Scheme 18 Synthesis of 3-formyl benzopyran-4-ones chalcones

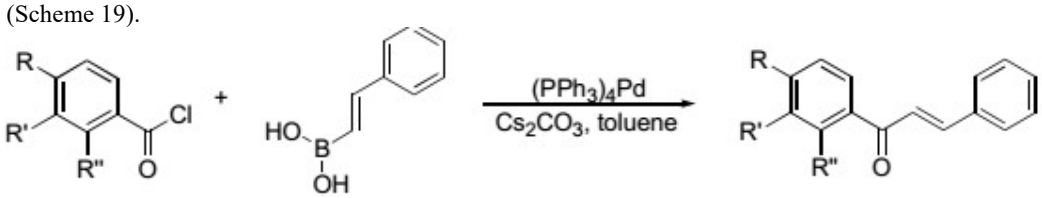
4. Miscellaneous Methods of Chalcone synthesis

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.[47] Like in many other organic syntheses, palladium-catalyzed cross-coupling reactions find their application in chalcone synthesis also.

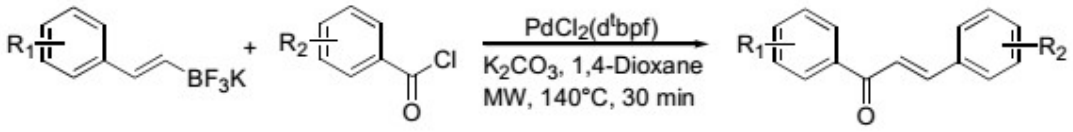
Eddarir *et al*. [48] developed a method for the synthesis of chalcones based on the Suzuki reaction either between cinnamoyl chlorides and phenylboronic acids or between benzoyl chlorides and phenyl vinyl boronic acids (Scheme 19).



R	R'	R''
H	H	H
H	CF_3	H
H	H	CF_3
H	NO_2	H
OMe	H	H
OMe	OMe	H

Scheme 19 Chalcone synthesis via Suzuki reaction.

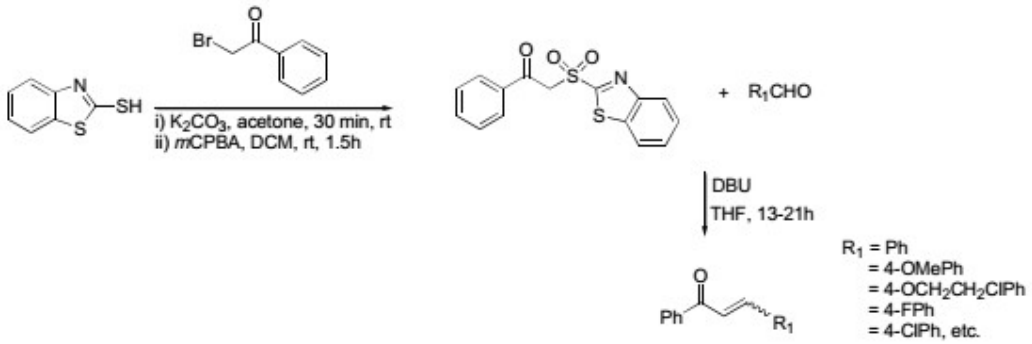
Mohammad *et al*. [49] developed a method for direct cross-coupling reaction of benzoyl chlorides and potassium styryl tri fluoroborates to the corresponding α, β- unsaturated aromatic ketones in the presence of $PdCl_2$(dtbpf) catalyst under microwave irradiation. This method was used for the synthesis of chalcones with a variety of substituents (Scheme 20).



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

4.2. Synthesis of chalcones *via* Julia-Kocienski olefination

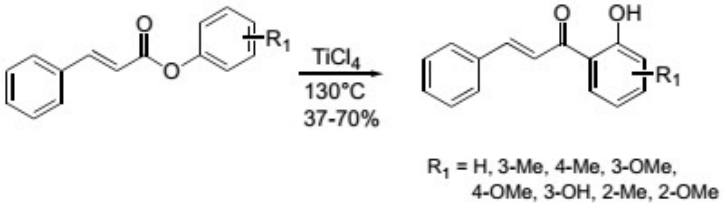
Kumar *et al.* developed 2-(Benzo[*d*]thiazol-2-ylsulfonyl)-1-phenylethanones as a new reagent for the synthesis of chalcones via Julia-Kocienski olefination with aldehydes in presence of a base in good to excellent yields[50] (Scheme 21).



Scheme 21 Julia-Kocienski olefination in the synthesis of chalcones.

4.3. Chalcone synthesis by Fries Rearrangement

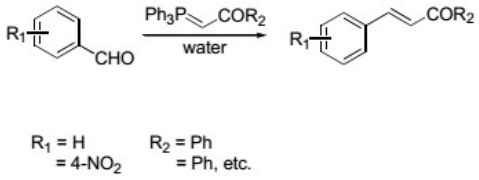
Jeon *et al*. [51] prepared chalcones using aryl cinnamates by Fries rearrangements catalyzed by $TiCl_4$ in moderate to good yields (Scheme 22).



Scheme 22 $TiCl_4$ mediated chalcone synthesis via Fries rearrangement.

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.[52,53] In these methods reaction of a stable ylide with aldehydes is used for synthesizing the desired chalcones (Scheme 23)

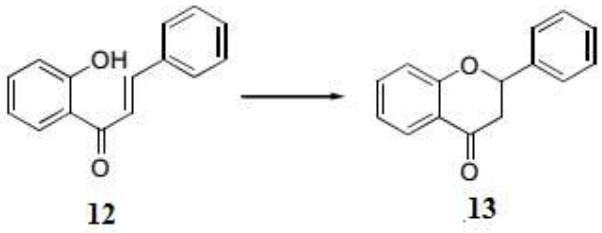


Scheme 23 Synthesis of chalcones using stable ylides.

5. Chalcones in organic synthesis

Chalcones find many applications in organic synthesis as intermediates. Flavanones are important naturally occurring pharmacological compounds and are valuable precursors for the synthesis of flavonoids.

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. [74] Different catalysts like acetic acid,[54] piperidine,[55] CH_3COONa,[56] H_3PO_4,[57] PEG-400 [58] have been employed for this conversion (Scheme 24).



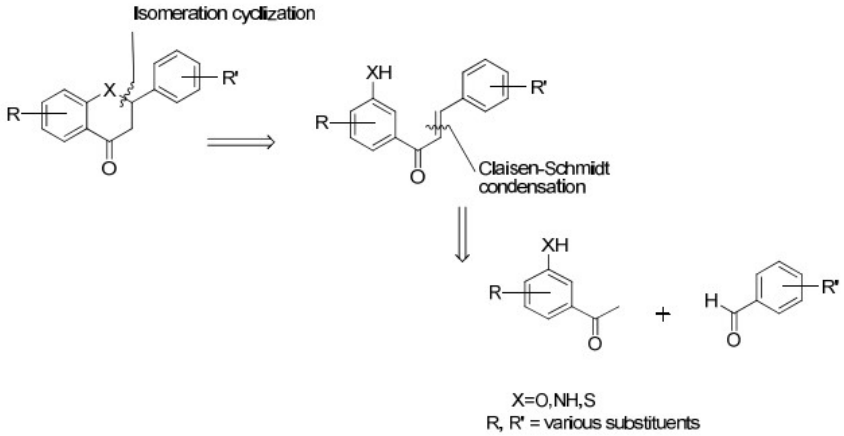
Scheme 24 Conversion of 2 –hydroxy chalcone to flavanone.

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 [59].

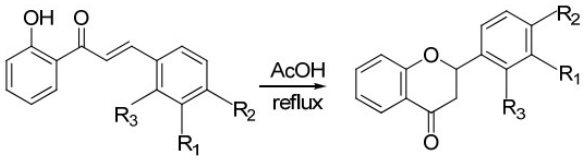
As outlined in (Scheme 25), the retrosynthetic analysis consists of two primary disconnections, which can provide a facile and versatile synthetic route to produce a variety of products for the synthesis of flavanones without a lengthy protection-deprotection strategy.



Scheme 25 Retrosynthesis strategy of flavanone synthesis

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 (Scheme 26).[60]

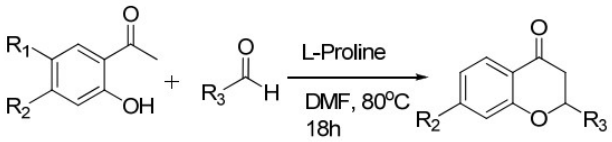


R_1= H, R_2= H, R_3= H
R_1= H, R_2= Br, R_3= H
R_1= H, R_2= H, R_3= Br
R_1= H, R_2= OBn, R_3= H

Scheme 26 Synthesis of flavanones using AcOH

6.2. L-proline catalyzed flavanone synthesis

An efficient method reported by Chandrasekhar *et al*, [61] involved a reaction of a variety of aryl aldehydes with substituted 2′- hydroxyl acetophenone in the presence of 30mol% L-proline in DMF (Scheme 27).



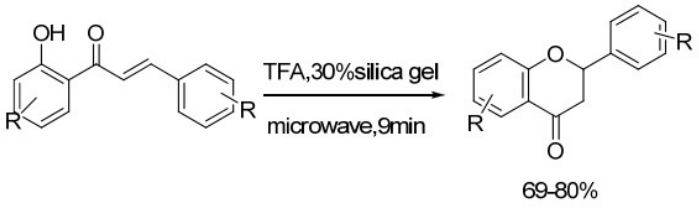
R_1=H, CH_3, OCH_3
R_2=H, Cl
R_3=ph, *p*-NO_2 ph, *p*-OCH_3 ph

Scheme 27. Chandrasekhar synthetic route of flavanone

6.3. Microwave accelerated solvent-free synthesis of flavanones

Sagrera *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. (Scheme 28). [62]

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.



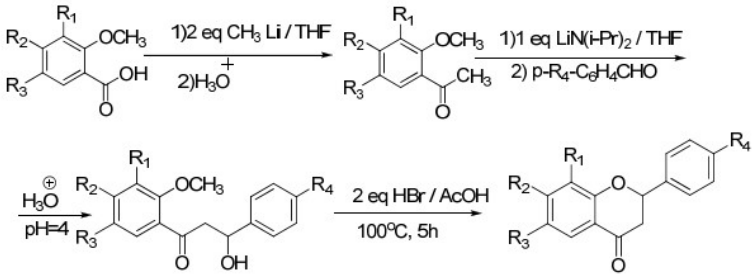
R=MeO,OBn, Br

Scheme 28 Microwave Accelerated Solvent-Free Synthesis of Flavanone

6.4. Jea In Lee synthetic method

Lee and Co-workers [63] 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 methyllithium 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.

They add benzaldehyde to this reaction mixture followed by acidification to produce 1-(2'-methoxyphenyl)-1-oxo-propane-3-(4'- chlorophenyl)-3-ol as a key intermediate. The desired flavanones were obtained by heating this intermediate with 2 equivalents of 48% hydrogen bromide in glacial acetic acid(Scheme 29)

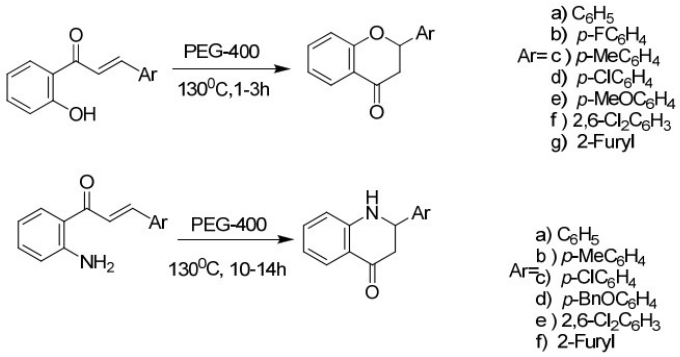


R_1, R_2 , R_3 = H, OCH_3 ; R_4 = H,OCH_3, Cl

Scheme 29 Synthesis of flavanones using 2'-Methoxy benzoic acid.

6.5. Eco-friendly polyethylene glycol promoted flavanone synthesis

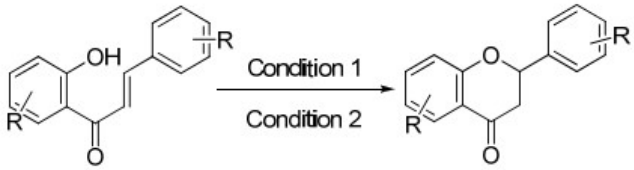
Kumar and co-workers employed an eco-friendly method to synthesize flavanones and azaflavanones by reacting 1.4 mmol 2'-hydroxy chalcones or 2'-aminochalcones in 0.5 ml solution of polyethylene glycol (PEG-400) at optimized temperature (130°C) for appropriate time (Scheme 30).[64]



Scheme 30 Synthesis of flavanones and azaflavanones in PEG-400

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 (Scheme 31).[65]



Condition 1: Anhydrous K_2CO_3 reflux dry acetone for 3-5 h
Condition 2: Anhydrous K_2CO_3 microwave irradiation for 3 min

Scheme 31 Synthesis of flavanones using anhydrous potassium car

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.* [66] tested and reported the influence of the A-ring hydroxylation pattern on the cytotoxic activity of the prenylated chalcones (Figure **2)** 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).

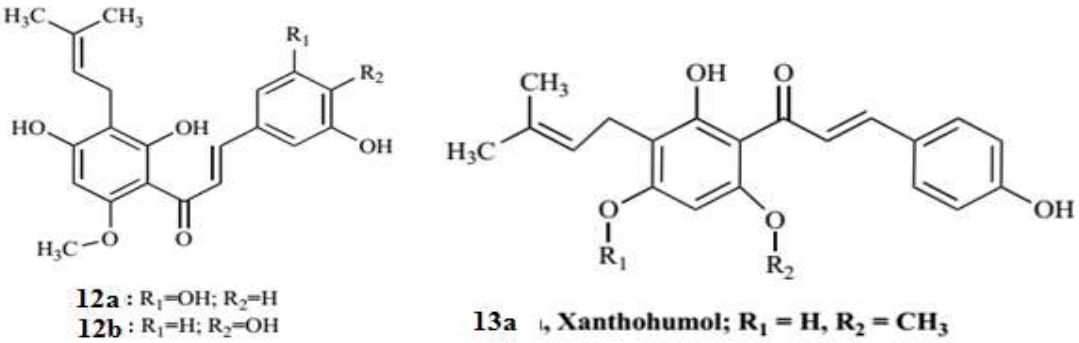


Figure 2

7.2. Antimalarial Activity

Awasthi *et al* [67] 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 4**)** 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.

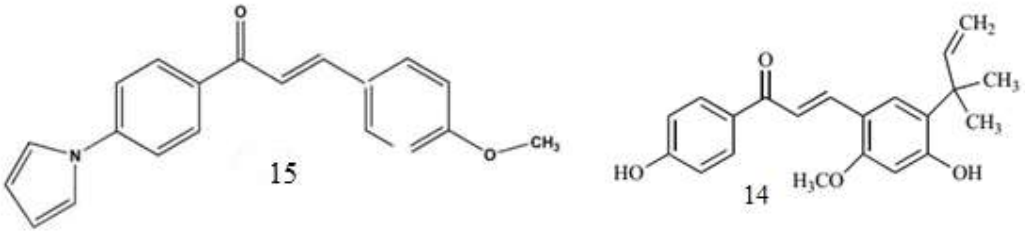


Figure 4

7.3. Anti-inflammatory Activity

Yadav *et al* [68] 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 5) 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.

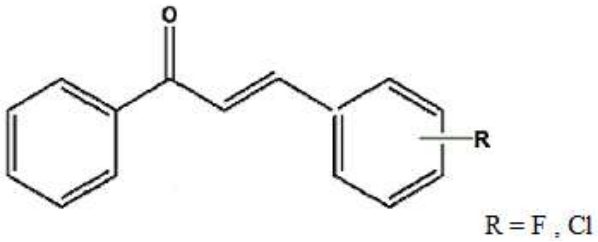


Figure 5

7.4. Antifungal Activity

Bag *et al* [69]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 6) exhibiting the highest activity.

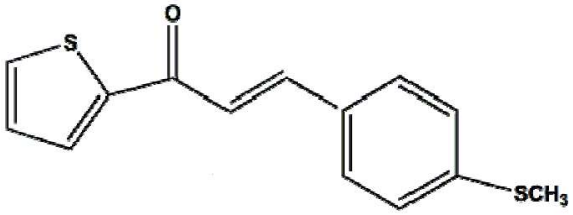


Figure 6

7.5. Antimicrobial Activity

Yayli *et al* [70] 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 7)

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

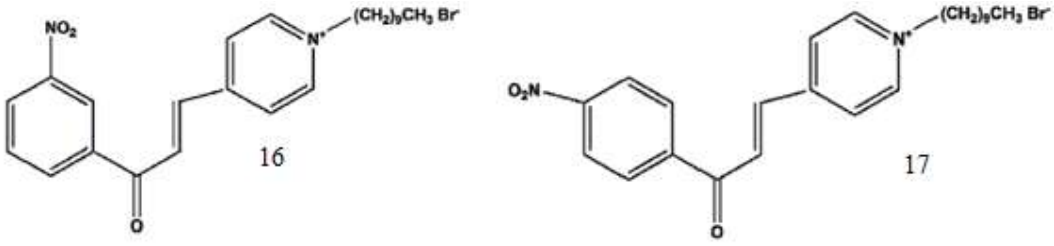


Figure 7

8. Synthesis methods of Coumarins

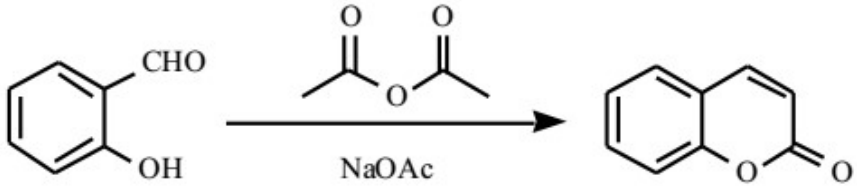
Many researchers are reported coumarins (benzopyrones) are a large family of compounds, of natural and synthetic origin, that show numerous biological activities like, antioxidants [71,72] anticancer[73,74] and enzymatic inhibition properties.

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[75] Perkin reaction[76,77] Pechmann Reaction [78] Ultrasound irradiation [79] palladium-catalyzed reaction[80] and Microwave irradiation.[81]

8.1. Synthesis of Coumarin *via* Perkin Reaction

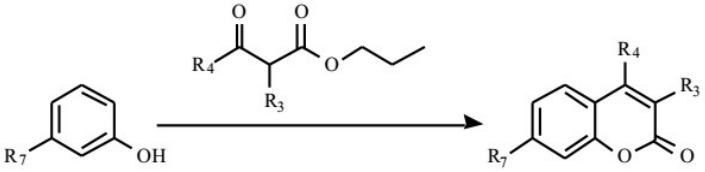
Trkovnik.M *et al.*[82] reported synthesis of coumarin through Perkin reaction by aldol condensation, of aromatic *ortho* hydroxybenzaldehyde and acid anhydrides, in the presence of an alkali salt of the acid (Scheme **32**).



Scheme 32 Synthesis of coumarin *via* Perkin reaction

8.2. Synthesis of Coumarin *via* Pechmann Reaction

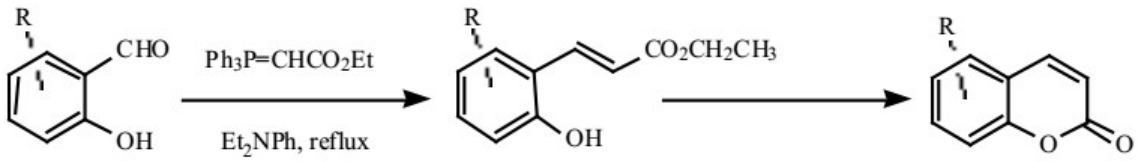
Bose. P *et al.*[78]reported synthesis of coumarins through Pechmann reaction by condensation of phenols with β-ketoesters, in the presence of acid catalysts (Scheme **33**).



Scheme 33 Synthesis of coumarin *via* Pechmann reaction

8.3. Synthesis of Coumarin *via* Wittig Reaction

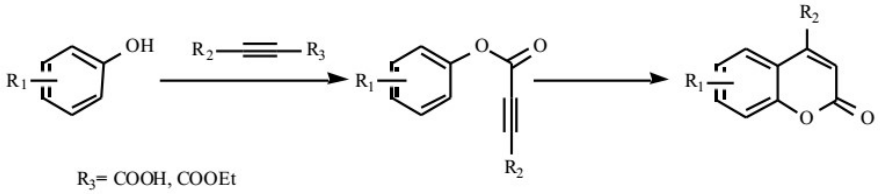
Takeuchi. Y *et al.*[84] reported synthesis of coumarin by olefination of *ortho*-hydroxy carbonyl aromatic compounds, followed by further lactonization.(scheme 34)



Scheme 34 Synthesis of coumarin *via* Wittig reaction

8.4. Synthesis of Coumarins *via* Pd-Catalyzed

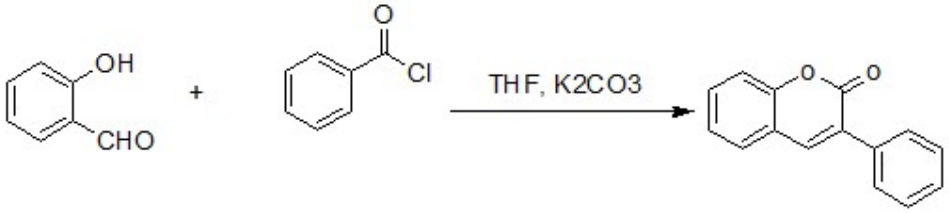
Jia C *et al.*[80] reported synthesis of Coumarins by a stereo- and regioselective palladium-catalyzed hydroarylation. This reaction occurs between aryl halides and functionalized alkynes, at room temperature, followed by a fast intramolecular reaction (Scheme **35**)



Scheme 35 Synthesis of coumarin *via* Pd-Catalyzed

8.5. Synthesis of Coumarin Using Ultrasound

S. J. Pradeeba *et al.*[79] 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 K_2CO_3 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. (Scheme **36**)



Scheme 36 Synthesis of Coumarin Using Ultrasound Irradiation

8.6. ZnO nanoparticle as a catalyst for synthesis of Coumarins

B Vinay Kumar *et al* [81] reported That zinc oxide (ZnO) nanoparticles functions as highly effectivcatalystsst 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 (Scheme **37**)
The advantage of this method is a solvent-free, environmentally co- friend, the catalyst is inexpensive, stable, can be easily recycled and reused for several cycles with consistent activity

Scheme 37. Synthesis of coumarins by Knoevenagel condensation under microwave and thermal conditions.

Conclusion

Chalcone, the synthetic precursor of many plant-derived secondary metabolites, is a privileged structure with varied biological and synthetic utilities, versatile reactive intermediates which are used to synthesize several heterocyclic ring systems including different types of flavonoids.

Flavonoids possess significant pharmacological activity. Chalcones and Flavonoids have been synthesized by a number of synthetic methods such as Lewis acid-base catalyst, Heterogeneous & Eco-friendly methods, Suzuki reaction, Wittig reaction, and Jea In Lee synthetic method As the catalyst is a necessary component of every technique, the researchers have used a variety of catalysts with the replacement of homogeneously catalyzed classical yield-oriented methods of their synthesis with environmentally benign methods and with advanced techniques. Due to these reasons, various preparation procedures were developed by many working groups, including an eco-friendly protocol.

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