



Review Article

A Comprehensive Review On Synthetic Strategies Of Chalcones

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ABSTRACT

Chalcones are the simple chemical structures consisting of α , β unsaturated carbonyl group attached to aromatic or heterocyclic rings. These are naturally occurring compounds and even can be synthesized via various chemical reactions in laboratory conditions. From many decades they attracted the attention of researchers due to their numerous biological activities and clinical potentials, simple method of preparation and for their utility as scaffolds for the synthesis of many pharmacologically active heterocyclic compounds like pyrimidines, pyrazoles, pyridines etc. by simple cyclization and addition reactions. Multiple aspects of chalcones are summarized comprehensively, reviewed critically in this review including development of new synthetic strategies using various methods and catalysts.

INTRODUCTION

Chalcones are phenolic phytochemicals of the flavonoid family that are biosynthesized through the shikimate pathway. They are commonly referred to as 'open chain flavonoids'. Chalcones are thought to be flavonoid's biosynthetic antecedents. Because of the color of most natural chalcones, the word "chalcone" is derived from the Greek word "chalcos," which means "bronze." Chalcones, synthetically they are characterized as α β -unsaturated ketone having center framework of 1,3-diaryl-2-propen-1-one, also known as

chalconoid. They are also called as benzyl acetophenone and benzylidene acetophenone.

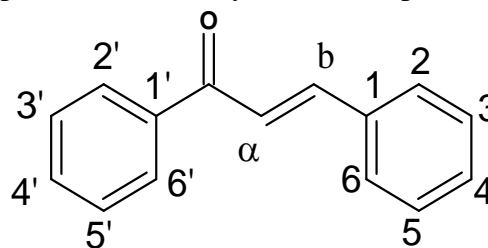


Fig 1: Structure of chalcone

Chalcones are the natural substances present in the vegetables, tea and soya-based staples [1]. The

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presence of reactive keto-ethylenic system in chalcone derivatives have shown reported pharmacological activities including Anti-inflammatory[2], Antioxidant[3], Antimicrobial[4], Antiviral[5], Antiulcer[6], Antifungal[7], Anticancer[8], Antitubercular[9], Antimalarial[10], Antidiabetic[11], Antileishmanial[12] and Antihyperglycemic[13].

Various methods for Synthesis of chalcones:

Chalcones are simpler molecular structures, can be easily synthesized in the laboratories by condensation reactions using acid or base catalysts. Even though chalcones can be easily synthesized in laboratories still there are various different methods are discovered in the literature survey. This is due to the development of different catalysts; reaction conditions lead to the synthesis of some chalcones which cannot be synthesized via conventional methods. The methods for the synthesis of chalcones are discussed in this review.

I. Claisen Schmidt condensation

This is the good old classical condensation technique for the synthesis of chalcones. This method was discovered by the two scientists named R. L. Claisen and J. G. Schmidt in 1881, so the reaction was named after them. It is a condensation reaction between one molecule of aldehyde without α hydrogen and one molecule of a ketone which possess α hydrogen in the presence of acid or base to yield α,β unsaturated carbonyl compound named chalcone. The reaction mechanism for Claisen Schmidt condensation is carbanion derived from aromatic or aliphatic ketone undergoes nucleophilic addition to carbonyl carbon of aromatic aldehyde to form hydroxy ketone. This hydroxy ketone undergoes spontaneous dehydration to form conjugated unsaturated carbonyl compound known as chalcone [14].

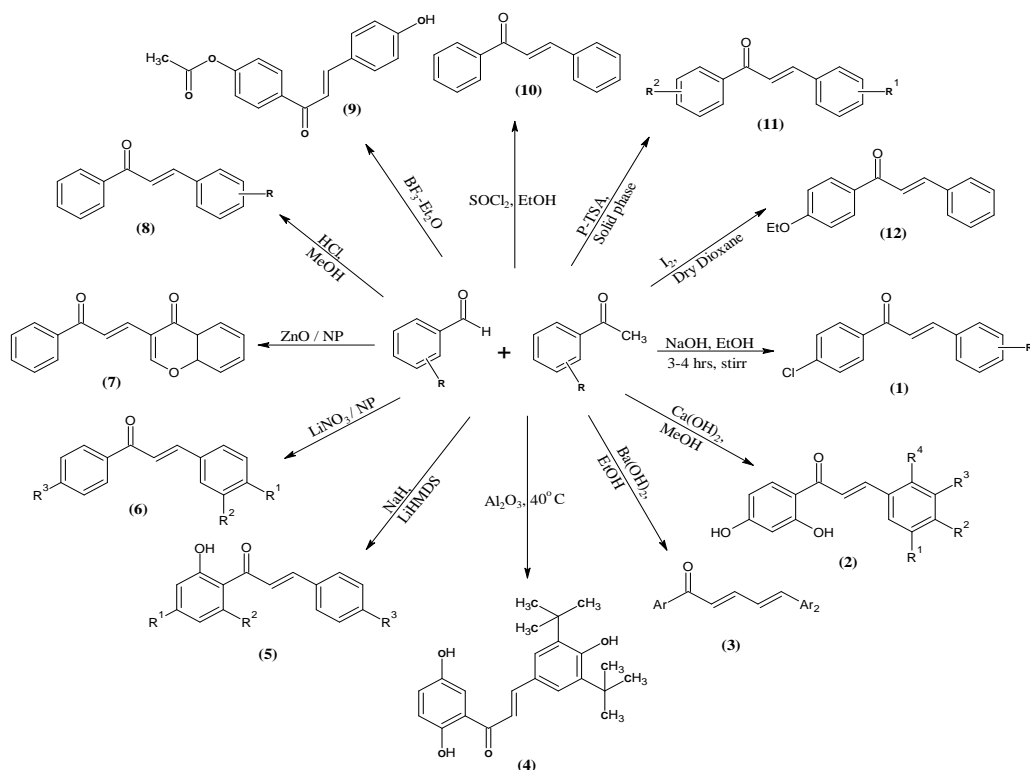


Fig 2: Claisen Schmidt condensation using various acid/base catalysts

1. Sodium hydroxide (NaOH):

Here the mechanical stirring of the mixture of reactants (aldehydes and ketones) and catalyst NaOH was carried out in ethanol medium for 3-4 hours to get the optimal yield of chalcones and further purification was done using ethanol. The yields were around 80%. The reaction is given in fig 2 [14]. Heterocyclic chalcones can also be synthesized by Claisen-Schmidt condensation utilizing NaOH as catalyst. Budak and Yakup et al., synthesized heterocyclic chalcones by reacting 1-(thiophene-3-yl)ethenone and different aldehydes in the presence of NaOH as base catalyst at room temperature for about 3-4 hours. The yields obtained are pretty good ranging 90-99% [15].

2. Calcium hydroxide:

Calcium hydroxide an alkali earth metal can be used as catalyst in the synthesis of chalcones. The reaction is given in fig 2. Synthesis of Polyhydroxy chalcones have some problems like poor yield, sticky oily product, difficult extraction procedure as well as more reaction time while using regular catalysts like NaOH, basic alumina, ZnCl₂, BF₃, AlCl₃ etc. Also, the -OH group is highly reactive, some protection is required so calcium hydroxide can be used. P.S. Kulkarni et al., have synthesized the polyhydroxy chalcones using dihydroxy acetophenone and various substituted aldehydes in the presence of calcium hydroxide catalyst [16].

3. Barium hydroxide:

As discussed, earlier alkali earth metals can be used as catalysts in synthesis of chalcones, sometimes it beneficial to use these catalysts over traditional NaOH. For example: it takes 20 hours to complete the simple Claisen-Schmidt condensation between substituted acetophenones and cinnamaldehyde using NaOH as a basic catalyst and mediocre yields of products from 55 to 81%. [5] by using activated barium hydroxide and ultrasound waves it is possible to reduce the time consumption and improve the product yield.

Ying Xin et al., has synthesized chalcones using activated barium hydroxide under ultrasound waves. The reaction is given in fig 2 [17].

4. Aluminium oxide:

Aluminium oxide can also be used as good catalyst along with ultrasound waves. Chun-Nan Lin et al., they reported synthesis of chalcones from tetrahydropyran-2-yloxyacetophenones and some heterocyclic or aromatic aldehydes. The yield obtained was around 72-74 o C. The reaction is given in fig 2 [18].

5. Lithium bis(trimethylsilyl)amide:

Goncalo P. Rosa et al., reported Claisen Schmidt condensation using lithium bis(trimethylsilyl)amide (LiHMDS) and sodium hydride (NaH) as bases given in fig 2. The reports show that NaH was more potent for the synthesis of 2'-hydroxychalcone compounds, while LiHMDS catalyst used to the synthesis of polyhydroxylated chalcones in one stretch affording good yields in relatively short time. However, for the synthesis of polyhydroxylated chalcones, it is necessary to perform the protection of the -OH groups, which is takes lots of time and the yields of the protected compounds are low [19].

6. Lithium nitrate/NP Catalyst:

The natural phosphate (NP) or activated by an ammonium salt can promote the Claisen-Schmidt condensation. NP modified by NaNO₃ found to give good results in the reaction yield is between 90-98%. LiNO₃/NP is prepared by adding NP to an aqueous solution of lithium nitrate. The mixture was stirred; evaporated to dryness and dried. The solid obtained was calcined to give a new catalyst LiNO₃/NP. Calcination is important process since the catalyst calcinated at lower temperatures gives lesser yields compared to higher temperature. The main disadvantage of this reagent in Claisen Schmidt condensation is the reaction rate is slower. Sad Sebti et al., reported the synthesis of



chalcones using lithium nitrate. The reaction is given fig 2 [20].

7. Zinc oxide nanoparticles:

Under non solvent conditions the Claisen Schmidt condensation can be done. Jagir S Sandhu et al., used the 5 mol% zinc oxide nanoparticles at 120o C is the ideal concentration to get the optimal yields under solvent free conditions. After centrifugation this catalyst can be recycled as well. Nano material zinc oxide has been used because it has basic sites in high density, Nontoxic in nature and efficient green catalyst the reaction is given in fig 2. [21]

8. Hydrochloric acid (HCl):

Not only in basic conditions, Claisen Schmidt condensation can be carried out in acidic catalysts for the synthesis of chalcones. Strong acid like hydrochloric acid can be used in the synthesis of chalcones. The main disadvantage of this method is the removal hydrochloric acid from reaction mixture is difficult. The reaction is given in fig 2. The initial product in every reaction was the hydrogen chloride addition compound, it was indicated by the formation of an unstable HCl on treatment of 4'-iodochalcone with methanolic hydrogen chloride. Leo p. Parads et al., reported the condensation of acetophenone with electron-withdrawing groups and aldehydes in the presence of hydrogen chloride [22].

9. Boron trifluoride (BF₃):

Boron trifluoride gas was firstly used in 1940 by Breslow and Hauser in Claisen Schmidt condensation. Boron trifluoride-etherate (BF₃-Et₂O) can be used in synthesis of chalcones. Boron trifluoride etherate is used mainly if the reactants possess ester or amide functional group because using of traditional NaOH or KOH may lead to hydrolysis of esters and amides. This reagent has got many advantageous over others such as high yields, simple procedure, lesser reaction time, and no side reactions. T. Narender et al., reported condensation reaction between O-

acylated or N-acylated acetophenone and aromatic aldehydes and synthesized O-acylated or N-acylated chalcones in high yields by using BF₃-Et₂O. The reaction is given in fig 2 [23].

10. Thionyl chloride (SOCl₂):

Thionyl chloride along with ethanol can be used as an effective acid catalyst in the Claisen Schmidt condensation. The reaction is given in fig 2. The by-product HCl may accelerate the reaction. Strong electron withdrawing groups on the aromatic rings led to increases yields of the reaction but the electron donating groups decreases yields greatly and only alcohols could catalyze this reaction [24].

11. P-TSA Catalyst ;

p-toluene sulfonic acid is a very useful catalyst in synthesis of chalcones, that ruled out all the limitations of either acid or base catalyzed reactions, a green organocatalyst accelerate the reaction under mild conditions. The acid catalyzed reaction is not only simple but also the Cannizaro's products formation can also be inhibited. Vinod kumar et al., condensed equimolar concentration of benzaldehyde and acetophenone in the presence of p-toluene sulfonic acid under solvent-free conditions at different temperatures to yield chalcones. The reaction is given in fig 2 [25].

12. Iodine (I₂) Catalyst:

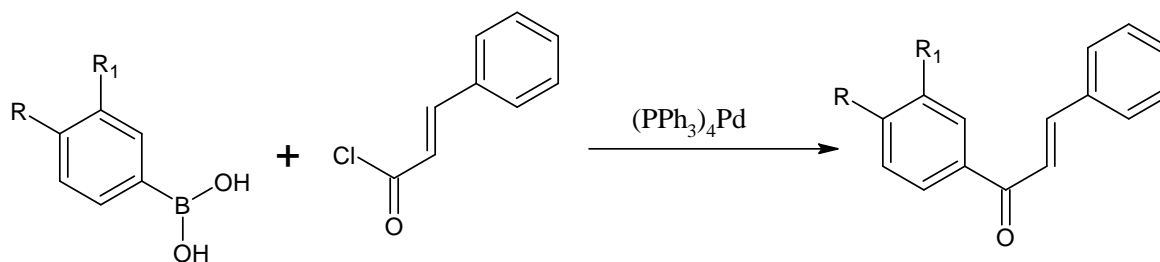
Molecular iodine can be used as efficient catalyst along with dry dioxane at 40o C for the synthesis of chalcones, Because of its low Lewis acidity, it has recently received large interest as an inexpensive, safe, readily available for various organic reaction. Koneni V et al., treated 4-ethoxy benzaldehyde with acetophenone in dry dioxane in the presence of I₂ (5 mol %) at 40 C to form chalcone in 85% yield and characterized the products through NMR, mass, and infrared (IR) spectroscopic studies. To optimize the iodine requirements, 1 mol%, 5 mol%, 10 mol%, and 20 mol % were employed, and the best results were obtained with 5 mol% of iodine in terms of yield



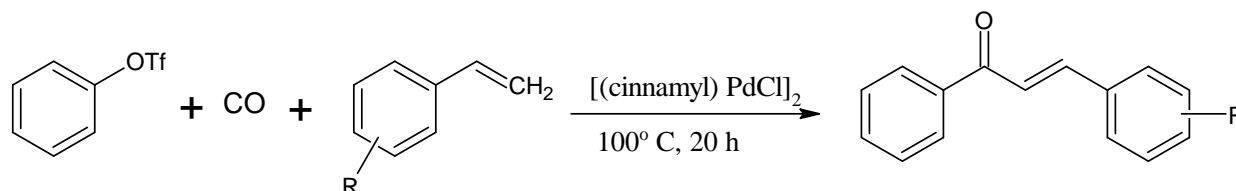
and duration. In the absence of iodine, the reaction did not take place. The reaction is given in fig 2 [26]. In Claisen Schmidt condensation, solid sulfonic acid is also a good catalyst. The catalyst can be synthesized by H₂SO₄ charring and sulfonation of bamboo saw dust. Compared to other catalysts like citric acid, sodium bicarbonate, boric acid, sulfuric acid...etc. bamboo char sulfonic acid has got better yield ranging 95% [27].

II. Organometallic coupling reactions:

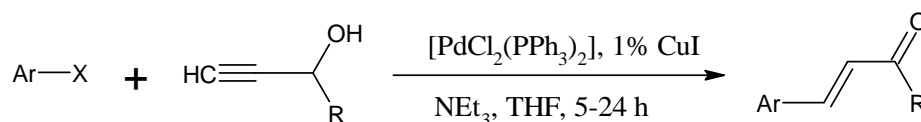
Coupling reactions are a group of reactions where two carbon atoms of different or same compound are joined together with the help of a metal catalyst. Palladium metal is used as the catalyst .this reaction was first reported in 1979 by Akira Suzuki, and shared the Nobel Prize in chemistry with Richard F. Heck and Ei-ichi Negishi in 2010 for the coupling reactions using palladium. In this reaction the alkyl groups with a leaving group and alkyl group with other functional units in the presence of palladium catalyst are made to react for the formation of C-C bond.



Synthesis of chalcones using Suzuki coupling reaction.



Synthesis of chalcones using Heck's coupling reaction



Synthesis of chalcones using Sonogashira coupling reaction.

Fig 3: Synthesis of chalcones by coupling reactions

a. Suzuki coupling reaction:

The chalcones can be obtained by using Suzuki coupling reaction, where it can be achieved in two ways, the coupling between activated cinnamic acids and phenylboronic acids and the coupling between activated benzoic acids and

phenylvinylboronic acids. It is a useful general synthetic strategy for synthesis of biphenyl chalcones. Christian Rolando et al., the coupling between cinnamoyl chloride and various phenylboronic acids using the conditions they employed for the synthesis of fluorinated

resveratrol (solvent: THF; catalyst: PdCl₂(PPh₃)₂/PPh₃ in presence of the non-basic reagent n-Bu₄N⁺, HF₂⁻). This catalytic system may lead to a mixture of complex products. The reaction is given in fig 3 [28].

b. Heck coupling reaction:

In coupling reactions, Heck's coupling reaction is one of the important reactions in organic chemistry for the formation of C-C bonds and C=O bonds. The C=O group can be introduced in between the carbons by adding carbon monoxide into the reaction. In this way Matthias Beller et al., synthesize the chalcones by Heck's coupling between phenyl triflate and styrene along with carbon monoxide in the presence of [(cinnamyl)PdCl]₂ catalyst given in fig 3 [29]. This novel carbonylative Heck reaction first step is oxidative addition of the aryl triflate to the Pd center, migration of CO to give the acyl palladium complex, insertion of styrene and final β-hydride elimination. In most of the cases, only a small amount (< 5%) of the Heck coupling product was detected. Nevertheless, the amount of this product rose when the substrates were sterically inhibited. High yields of the intended products were obtained when arene compounds were replaced with groups that donate or withdraw electrons at the para, meta, or even ortho position.

c. Sonogashira coupling reaction :

The Sonogashira coupling of electron-deficient (hetero)aryl halides and (hetero)aryl or alkenyl 1-propargyl alcohols gives rise to the formation of α,β-unsaturated ketones. Thomas J. J. Muller et al., coupled (hetero)aryl halides and 1-propargyl alcohols the presence of catalytic amounts of [PdCl₂(PPh₃)₂] and CuI in a boiling mixture of triethylamine and THF, gave rise to production of 1-substituted 3-(hetero)aryl propenones. The reaction is given in fig 3 [30].

III. Non-solvent method:

a. Grinding approach:

A classical synthesis of these compounds entails the condensation of acetophenones and aldehydes to give chalcones. The mixture of solvents and lengthy reaction time, highly-priced chemical compounds/catalyst makes this technique environmentally hazardous. This supplied the stimulus to synthesize some new chalcones the use of grindstone method. In grindstone method, reaction takes place through generation of local heat with the aid of grinding of crystals of substrate and reagent by using mortar and pestle. Reactions are initiated by means of grinding, with the small amount of strength through friction. In a few instances, a combination and reagents turns to glassy materials. Such reaction are easy to deal with, lessen pollutants, relatively inexpensive to perform and can be appeared as greater reasonable and ecologically favorable method in chemistry. Solid state reaction takes place extra efficiently and greater selectively than does the solution reaction, due to the fact molecules in the crystal are organized tightly and frequently. The aldehyde and ketone are grinded at the side of catalyst within the absence of solvent to yield chalcone after which the synthesized compound may be recrystallized [31].

b. Microwave irradiation method:

Microwave radiation has gained the attention of chemists because of its unique advantages, such as shorter reaction times, cleaner reaction products, better yields and selectivity's, being a good alternative to accomplish more efficient synthesis of a variety of organic compounds with a considerable simplicity of operation and under milder reaction conditions, when combined with the solvent-free approach, it's an ecofriendly approach. Keeping in view of these discoveries, they describe an easy and convenient method for the synthesis of chalcones in solvent free conditions under microwave irradiation, with improved product yields and lesser reaction time. The catalysts commonly employed in microwave



synthesis of chalcones are NaOH, CaO, anhydrous K₂CO₃, ZnCl₂, Ba(OH)₂, NH₄OH, TiO₂SO₄ [32].

IV. Ultrasound method:

Ultrasound has been used increasingly regularly in organic synthesis in recent decades. Compared with conventional methods, this method is greater handy and without difficulty controlled. Exquisite lots of natural reactions can be carried in better yields, shorter reaction time or milder conditions under ultrasound irradiation Ji-Tai L et al., reacted cyclopentanone or cyclohexanone with various aromatic aldehydes catalysed by using KF/Al₂O₃ using methanol as solvent under ultrasound irradiation, end result the corresponding cyclopentanones or cyclohexanones in proper yield[33]. The Claisen Schmidt condensation of

acetophenone with various aromatic aldehydes catalysed by means of KF/Al₂O₃ under ultrasound irradiation, and the end result are better than that under conventional heating condition [34].

V. Wittig reaction:

Wittig reaction is also an important reaction in the synthesis of chalcones, but the reaction takes place at a slower rate for example, between triphenylbenzoylmethylene phosphorane and benzaldehyde, requiring 3 days of reflux in benzene or 30 hours in THF (70% yield). By implementing the microwave into the system it's possible to increase the yield and reduce the time required for the synthesis dramatically Xian Huang et al., synthesized the above same compound within 5 minutes using microwaves. The reaction is given in fig 4 [35].

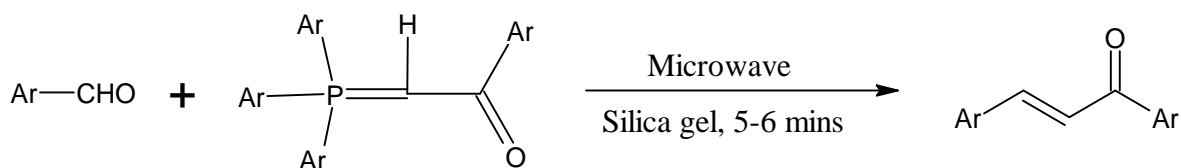


Fig 4: Synthesis of chalcones using Wittig reaction

VI. Julia-Kocienaki olefination:

The modified Julia reaction also known as Julia-Kocienki olefination, which involves direct coupling of heteroarylsulfones with carbonyl compounds in a single step. Julia-Kocienki olefination can be used to synthesize the

chalcones. Atul Kumar et al., reacted (Benzo[d]thiazol-2 ylsulfonyl)(phenyl)methanone with benzaldehyde in DBU and tetrahydrofuran, later the chalcone extracted with solvent like ethyl acetate. The reaction is given in fig 5 [36].

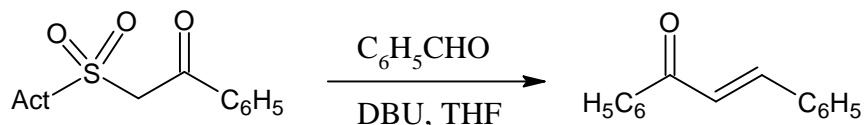


Fig 5: Synthesis of chalcones using Julia-Kocienki olefination

VII. Using potassium tert-butoxide:

Potassium tertiary butoxide can be used as a good catalyst in the synthesis of chalcones. Kazuhiro Yoshizawa et al., reacted 1,3-diphenyl-2-propynyl trimethylsilyl ether with KOt-Bu, THF to form intermediate siloxyallene which upon treatment

with acid to yield chalcone in one pot. in another case, after the formation of intermediate siloxyallene treatment with H₂SO₄ in 1,2-dimethoxyethane at -78o C. yields were found between 80%. The reaction is given in fig 6 [37].

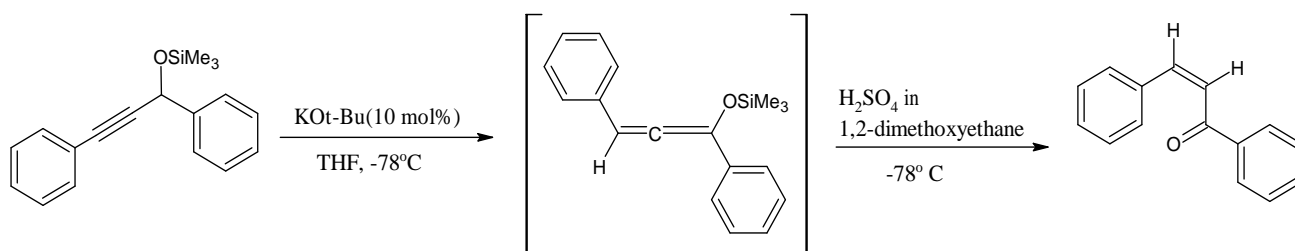


Fig 6: Synthesis of chalcones using potassium tertiary butoxide

CONCLUSION

Chalcones are considered as privileged structures because they can be easily modified into novel compounds by adding side chains and cyclizing the α , β unsaturated carbonyl group, also the modified compounds have greater biological activities. These are the common scaffold found in naturally occurring compounds and can be synthesized in laboratory. These compounds have shown many of interesting biological activities and clinical potential against various diseases. There are many research works are done during past years. The research works including isolation from natural compounds, new synthetic methods, evaluation of biological activity, mechanism of action, structure-activity relationship. Various efforts were made in the synthesis of chalcones however methods need to be optimized because of low yields, critical reaction conditions, longer reaction time, and corrosive catalysts. In medicinal chemistry, chalcones have isolated for biological uses and synthetic analogues should be studied for structure-activity relationship for designing a potential compound via improving physico-chemical properties, due to the fact that chalcones have the problem of poor solubility in water and by this it is difficult for the drug to be given via oral route and the chalcones have huge pool of biological activities also have many adverse reactions including hepatotoxicity so it is necessary for the researchers to find molecules with less adverse effects. The above questions will definitely create a sort of interest among the current researchers and more studies should be

conducted on this molecule via drug discovery strategies and new synthetic route. It is expected that novel chalcones moieties will be discovered/synthesized in future.

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CONFLICT OF INTERESTS:

There is no conflict of interest, according to the authors.

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