A Chalcones: Promising Precursor in Chemistry of Heterocycles -Short Review

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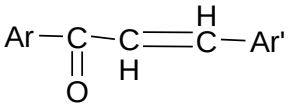
Abstract:

Chalcones derivatives are α, β-unsaturated ketones with the reactive ketoethylenic i.e.1, 3- diaryl-2- propen-1-ones (Ar-CH=CH-CO-Ar) group. They are coloured used as a natural pigment. It is one of the most important classes of flavonoids & iso-flavonoids across the whole edible plant kingdom. It is the oldest but remains popular in the 21st century due to a large number of replaceable hydrogens that allows a large number of derivatives. They bear excellent quality precursors because of this reason a variety of new heterocyclic compounds were synthesized. The purpose of this review is to provide an overview of some derivatives of chalcones.

Keywords: biological activities, Chalcones, flavonoids, pigment, precursor.

Introduction

1,3-Diaryl-2-propen-1-ones are commonly known as chalcones. They are represented as –



Chalcones belonging to the flavonoid family [1]., which have been reported to possess a wide spectrum of biological activities, was including anti-bacterial, anti-fungal, anti-inflammatory, anti-tumour, insect anti-feed ant and anti-mutagenic [2]. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine [3], pyrazolines [4] and flavones [5]. Hence, the synthesis of chalcones has generated vast interest among organic as well as medicinal chemists. Some of their derivatives are used as sweeteners, drugs, and sunscreen agents [6]. Several methods are available for the synthesis of chalcones. The most widely used method is the base-catalysed such as sodium hydroxide (NaOH), potassium hydroxide (K.O.H.),

Further studies using derivatives with various substitutions, and standard assay conditions are likely to be very rewarding. Chalcones constitute an important group of natural products and have been reported to possess varied biological and pharmacological activities [7].

Main Methods for the Synthesis of Chalcones

Many synthetic methods have been described to obtain chalcones. Some of the widely used methods are as described below.

A) By Claisen - Schmidt Condensation

Claisen-Schmidt condensation reaction is one of the most efficient methods for effecting carbon-carbon bond formation and it has wide synthetic applications. It is performed in homogeneous phase or under phase transfer

conditions. Claisen-Schmidt reaction involves the condensation of an aldehyde (without α-H atom) and a ketone (with active methylene group or β-H atoms) in presence of an alcoholic alkali.

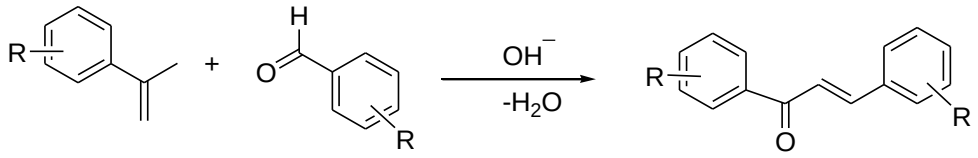


Fig. 1. Synthesis of Chalcone by Claisen -Schmidt Condensation

The alkali used is generally NaOH or K.O.H. in EtOH/MeOH Sometimes piperidine is also used for this reaction.

B) By Aldol Condensation

A novel Aldol type condensation mimic for preparation of *trans*-chalcones has been reported by P.W.H. Chan et al. [8] It involved aromatic γ-vinyl halides readily undergo reaction with aromatic aldehydes at ambient temperatures in presence of catalytic amounts of Lewis acid.

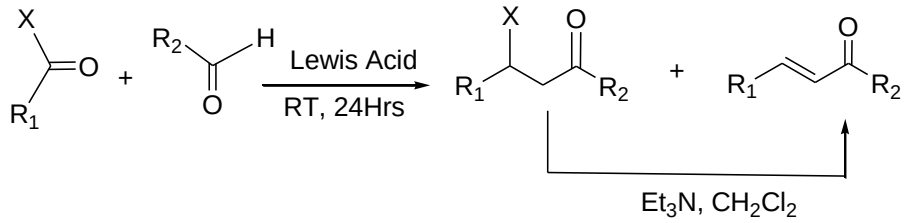


Fig. 2. Synthesis of Chalcone by Aldol condensation

C) By Friedel - Craft Acylation

One of the most attracting approaches would consist in the Lewis acid ($AlCl_3$) catalysed acetylation i.e., the Friedel-Crafts acylation of protected phenols with cinnamoyl chlorides, due to its resemblance to the biosynthetic route.

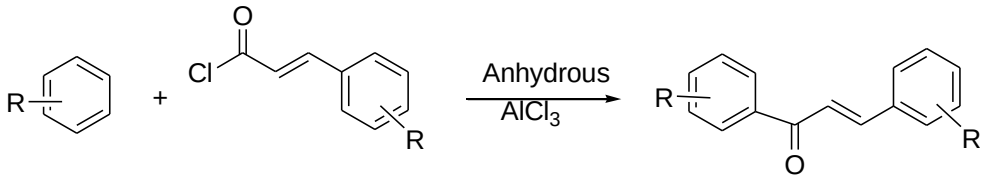


Fig. 3. Synthesis of Chalcone by Friedel- Craft Acylation

D) By Photo - Fries Rearrangement

The photochemical equivalent of Fries rearrangement was first utilised by Obara (1967) in synthesis of simple 2-hydroxychalcones from phenyl cinnamates [9].

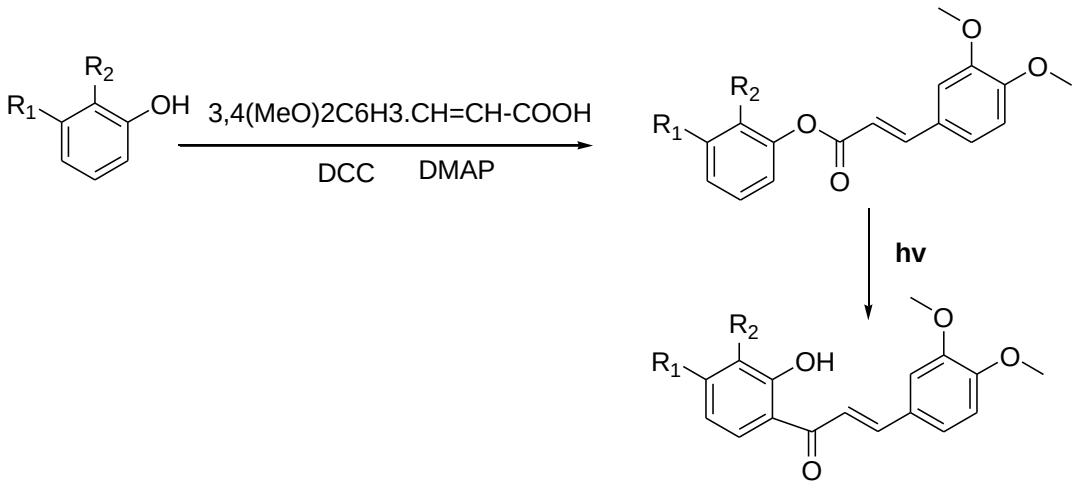


Fig. 4. Synthesis of Chalcone by Photo-Fries Rearrangement.

E) From Phenols

The chalcones were prepared *via* the oxidative cyclisation of the phenols in presence of Pd Cl_2-$CuCl_2$ by Iyer and Trivedi. BF_3. Et_2O-$POCl_3$ catalysed acylation of phenols using α, β- dimethyl acrylic acid was studied by Jain and Krishnamurthy [10]. They observed that condensation between resorcinol and unsubstituted cinnamic acid gave 2',4'-dihydroxychalcone.

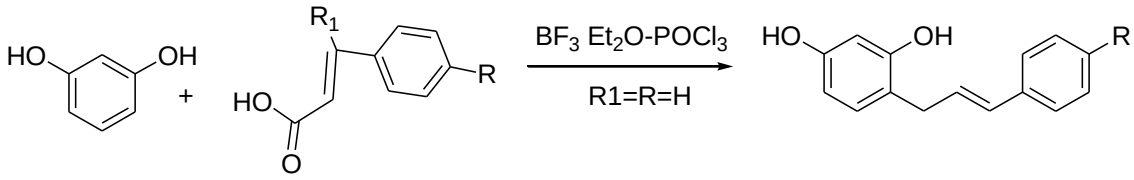


Fig. 5. Synthesis of Chalcone from Phenols

Many of mention synthetic methods, chalcones were synthesized by employing Claisen-Schmidt condensation. The method has been implemented for the synthesis of chalcones due to above merits: 1. this reaction is fairly general, facile and efficient, 2. It has moderate reaction conditions, 3. It gives excellent yield of the product & 4. Work up and isolation is easier.

Shinde (2019, p.1) synthesized chalcone by Claisen-Schmidt condensation reaction. A series of triazine Chalcone derivatives were synthesized by the condensation of 1-(4-(4,6-dimethoxy-1,3,5-triazin-2-yl) amino) phenyl) ethenone with substituted benzaldehyde in methanol solvent. [11]

Padarthi (2013, p. 2630) have synthesized chalcones from 2-Acetyl 5-Methyl furan with various aromatic and hetero aromatic aldehydes using the method of Aldol condensation.[12]

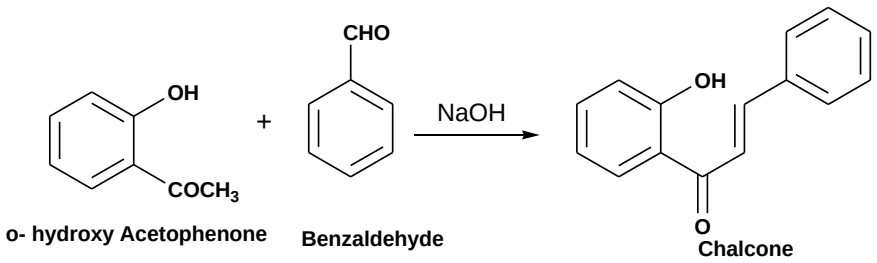


Fig. 6. Synthesis of Chalcone by Shinde (2019, p.1).

Ahmada (2016, p. 933) Synthesized novel chalcone derivatives by conventional and microwave irradiation method and their pharmacological activities. By microwave assisted synthesis, a considerable increase in the reaction rate has been observed and that too, with better yields [13].

The chemistry and pharmacology of thiazoles and thiazolochromenones is of great interest to medicinal chemists because, they are known to possess a wide range of pharmacological properties. 1, 5-benzothiazepines & 1, 5-benzothiazepines have three possible benzo-condensed derivatives, i e., 1, 4, and 1,5-benzothiazepines of the 1, 4-thiazepine. 1, 5-benzothiazepine is a seven membered ring heterocyclic compound containing sulphur and nitrogen as hetero atoms in their nucleus Benzene ring fused with thiazepine is known as benzothiazepine.

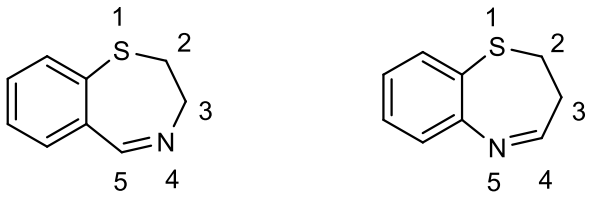


Fig. 7. General Structure of Benzothiazepines.

1, 5 Benzodiazepines & 1, 5 -benzothiazepines were synthesized from chalcones. In this method chalcone derivatives & o-phenylene diamines and o-amino thiophenols in ethanol using few drops of Piperidine synthesizes-1, 5 Benzodiazepines & 1, 5-benzothiazepines.

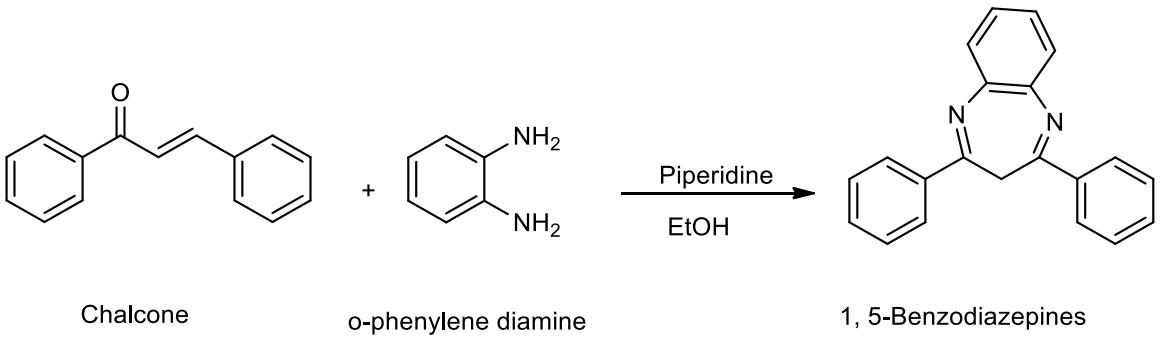


Fig. 8. Synthesis of benzodiazepines from Chalcones

Sharda Sharma et al. [14] synthesised Benzodiazepines derivatives using chalcones and O-phenylene diamines. All the synthesized compounds were evaluated in vitro for antibacterial activities against different strains of bacteria like staphylococcus aureus, Escherichia Coli, Pseudomonas. All compounds test along with standard antibacterial ampicillin were used at 100,200,300,400. Escobar (2009, p.171) synthesized 1,5- benzodiazepines have been synthesised from the corresponding 2' hydroxychalcones and o- phenylenediamine, both in methanol, under reflux and solvent-free microwave irradiation on alumina [15]. This method proved to be advantageous.

Rajani Chauhan et al. [16] applied chalcone derivatives in synthesis of 1, 5-benzodiazepines. They used hetero derivatives indole for this synthesis. They developed novel, convenient and simple method for the preparation of indole-1, 5-Benzodiazepines hybrid compounds. This method utilized the potential of chalcone intermediates in high yield and purity. Anjani Solankee & Rikki Tailor [17] developed a conventional root was designed and synthesised for the pyrazolines & benzodiazepines from chalcones. All synthesised compounds were assessed against selected pathogens. Some of the compounds exhibited excellent antimicrobial activity. Tupare (2017, p. 370) prepared some novel 1, 5-benzodiazepines by using chalcones having pyridazine moiety & o-phenylene

diamine in methoxy ethanol and few drops of piperidine by microwave irradiation [18]. products obtained in high yield. 7-3,8-4,9-5,10-6,

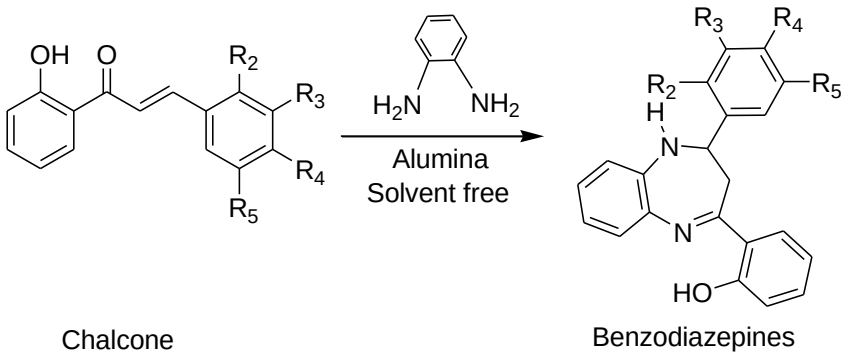


Fig.9. Synthesis of benzodiazepines from Chalcones by Escobar (2009, p.171)

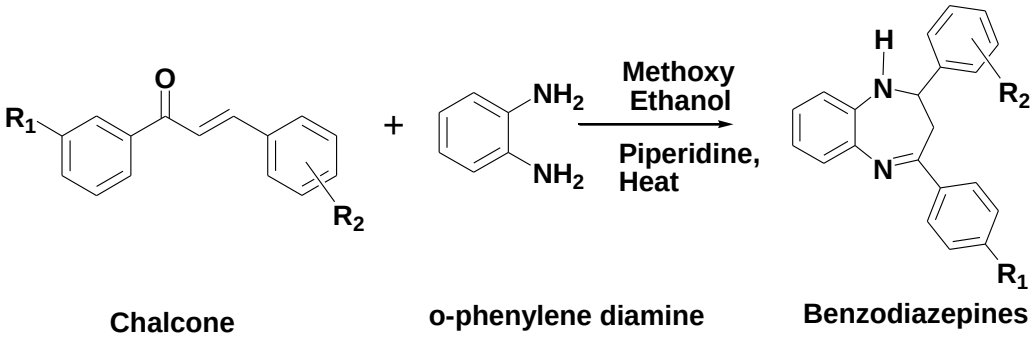


Fig. 10. Synthesis of 1, 5- benzodiazepines by Tupare (2017, p.370)

Reddy et al. [19] prepared 4-aryl-3-methyl-1-phenylpyrazolo [3,4-b] - [1,5] benzothiazepines *via* nucleophilic addition by treating 2-aminobenzenethiol with arylidenes in presence of catalytic amount of acetic acid.

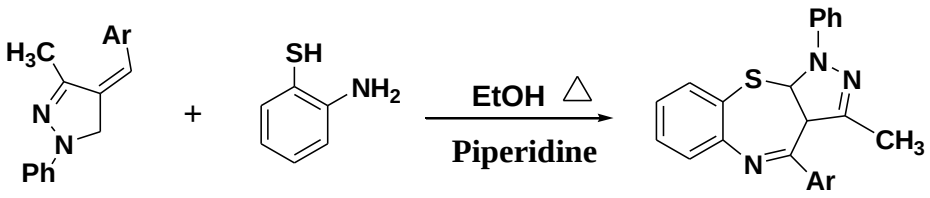


Fig. 11. Synthesis of 1, 5- benzodiazepines by Reddy et al.

Flavones are naturally occurring heterocyclic compound belonging to flavonoid group. It occupies a special place in the realm of natural and synthetic organic chemistry owing to their diversified biological activities. The reaction of 2-hydroxy acetophenone with substituted aromatic aldehydes produced chalcone by trituration (NaOH) and conventional methods (K.O.H./EtOH), which upon further cyclization with dimethyl sulfoxide resulted to form flavone derivatives.

Patel (2016, p. 404) have been synthesized chalcone by Claisen -Schmidt condensation of 2-hydroxy acetophenone and various aldehyde derivatives by solvent free trituration and conventional method [20]. From chalcone derivatives various flavone derivatives were synthesized by cyclization of chalcone with dimethyl sulfoxide. Based on spectral data, it was proved that all synthesized flavones derivatives meet the standard values of various spectral techniques.

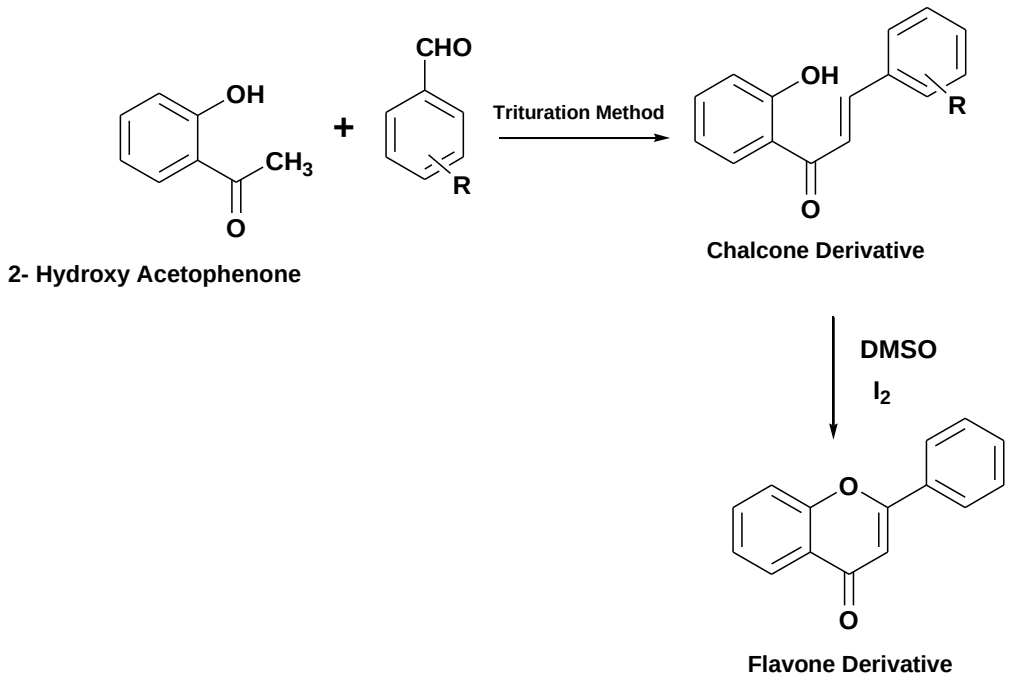


Fig. 12. Synthesis of Flavone by Patel (2016, p. 404)

Das (2014, p. 3841) synthesized flavones from chalcones by oxidative cyclization. Corresponding chalcones were obtained by Claisen Schmidt Condensation of aromatic aldehyde & acetophenone. Chalcone converted into flavone by applying Wacker condition which required the use of stoichiometric amounts of palladium and moderately high temperature. Therefore, alternative method through di-keto derivative undergoes cycloaddition reaction to obtained Flavones in high yield [21].

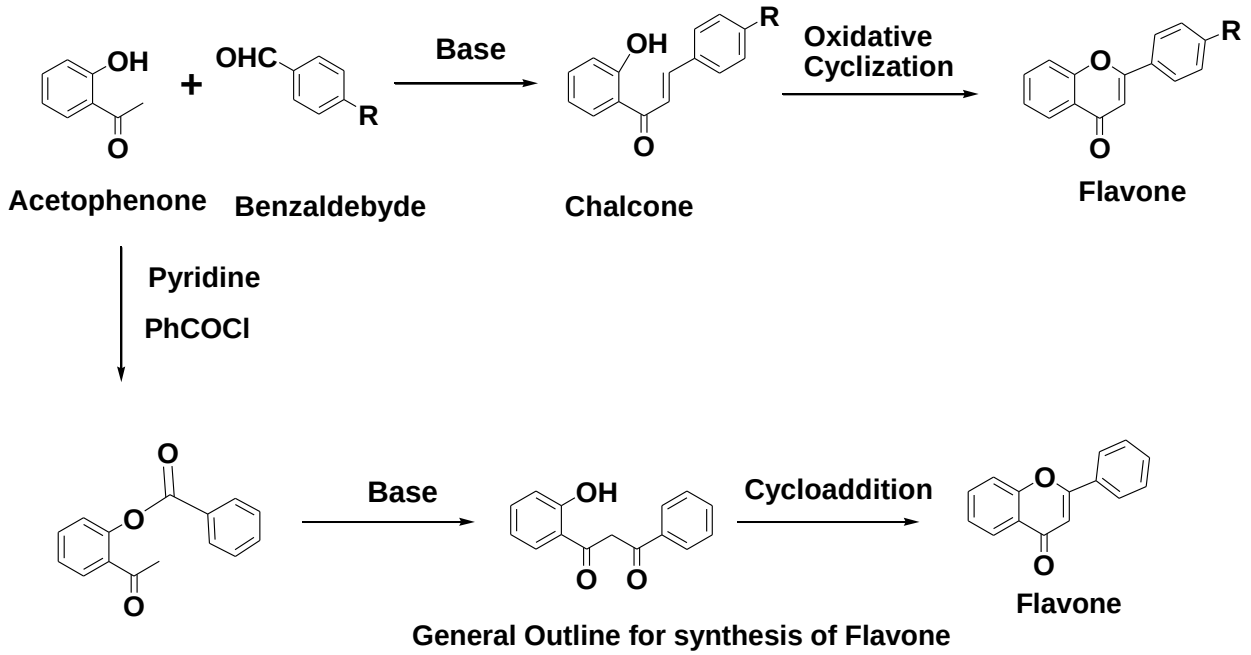


Fig. 13. Synthesis of Flavone by Das (2014, p. 3841)

Sashidhara (2012, p. 2355) have been reported convenient, facile, and alternate synthesis of medicinally important flavone cyclization on heating in the presence of catalytic iodine, generating diversified flavones under solvent – free conditions. All compounds have been synthesized in good yields [22].

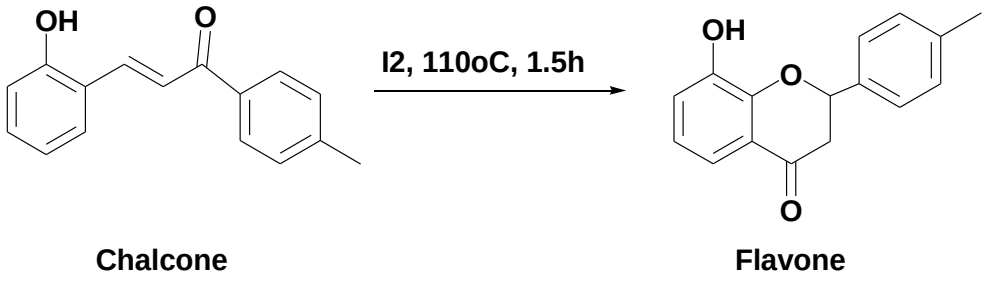


Fig. 14. Synthesis of Flavone by Sashidhar (2012, p. 2355)

Bano (2013) have been synthesized a novel series of chalcones, flavanones and flavone and evaluated for their anti-inflammatory activity in carrageenan induced rat Paw oedema Model. Many of synthesized compounds showed potent anti-inflammatory activity [23]. Cole (2016, p. 2770) have been synthesized chalcones derivatives and some flavonoid derivatives & screened for anti-HIV agents. Chalcones were found to provide the best balance between anti-HIV potency and low host cell toxicity [24].

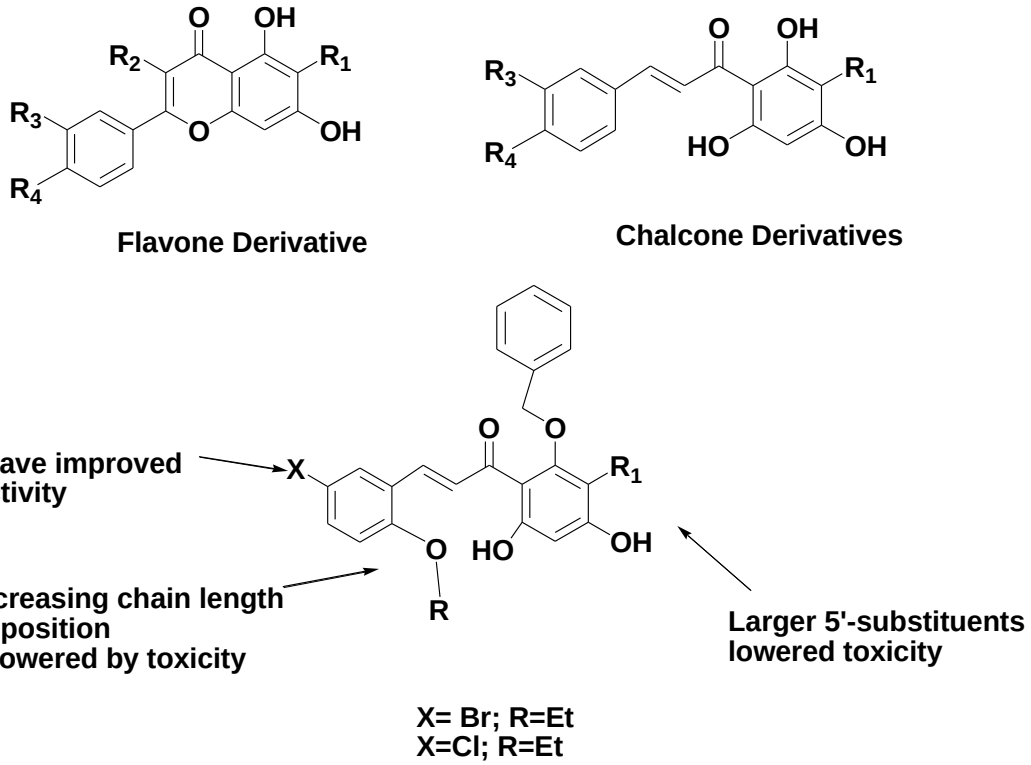


Fig. 15. Synthesis of Flavone by Cole (2016, p. 2770)

Pyrazolines are five membered ring heterocyclic compounds containing three carbon atoms and two adjacent nitrogen atoms. Partially reduced form of pyrazole is called as pyrazoline which exists in tautomeric forms. These pyrazolines possess interesting pharmacological properties and hence they are used as raw materials in drug synthesis.

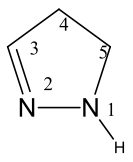


Fig. 16. Structure of Pyrrole.

Tautomers 'A' and 'B' are stable. But for the stability of tautomer 'C' no evidences are found.

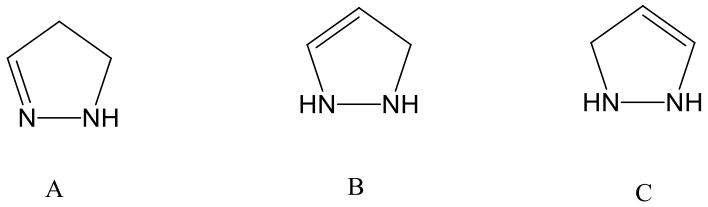


Fig. 17. Tautomeric form of pyrazolines.

These examples play a crucial role in heterocyclic chemistry and extensively used as synthons in organic synthesis. The pyrazolines functions are quite stable and inspired chemists to utilize this stability in bioactive moieties to synthesize new compounds possessing biological activities.

Pyrazolines are the electron rich nitrogen containing important 5- membered heterocyclic compounds possessing diverse biological and pharmacological activities. Which stimulated the research activity in this field? Pyrazolines are usually synthesized by the cyclization reaction between chalcones and hydrazine's or phenyl hydrazine under acidic or basic conditions. In acidic condition they found to good result.

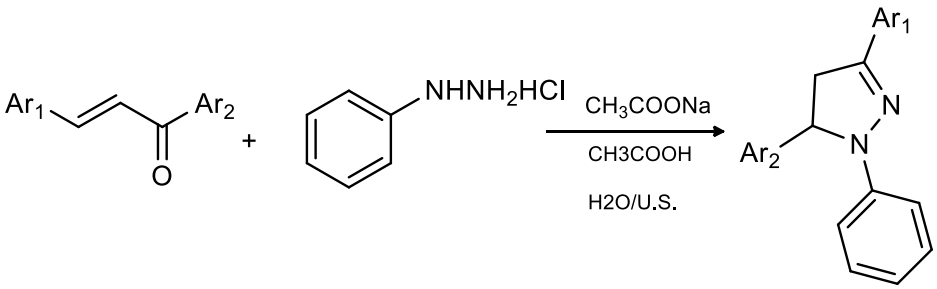
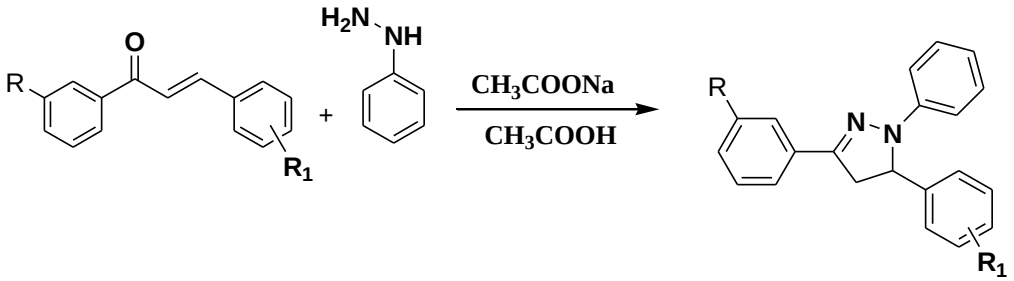


Fig. 18. Synthesis of Pyrazoline from chalcones.

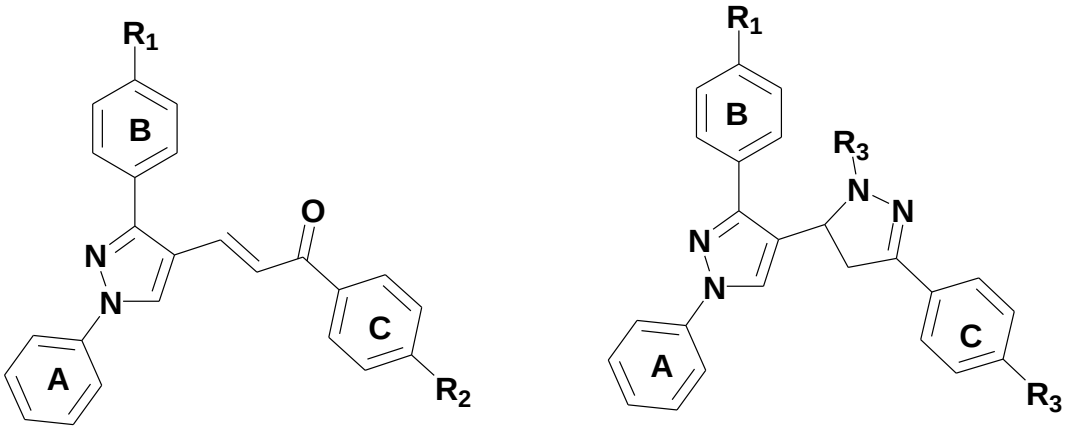
Tupare (2012, p. 372) synthesized different 2*H*- Pyrazoline derivatives from heterocyclic chalcone derivatives using ethyl acetate as a solvent which help to reduces reaction time. 1, 3, 5 triphenyl -1H- Pyrazole containing 6- aminopyridazin-3(2H)-one derivatives [25]. They possess potent biological activities.



R= imido Pyridazone ring; R_1= H, -OH, $-OCH_3$, -Cl, -Br, $-NO_2$ etc.

Fig. 19. Synthesis of Pyrazoline from chalcones by Tupare (2012, p. 372)

Lnsuasty (2010, p. 4965) synthesized novel pyrazolic analogues of chalcones and their 3-aryl-4-(3-aryl-4,5-dihydro-1H-pyrazol-5-yl)-1-phenyl-1H-Pyrazole Derivatives as potential antitumor agents [26]. In this synthesis chalcones were treated with hydrazine afforded the new racemic 3-aryl-4-(3-aryl-4,5-dihydro-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazoles or their N- acetyl derivatives and when reactions were carried out in D.M.F. or acetic acid, respectively.



Chalcone Derivatives **Pyrazoline Derivative**

R_1= NO_2, Cl
R_2 = NO_2, F, Cl, Br, H, CH_3, CH_3O, 3;, 4' -OCH_2O-
R_3= H, $COCH_3$

Fig. 20. Synthesis of Pyrazoline from chalcones by Lnsuasty (2010, p. 4965)

Compounds were screened for their ability to inhibit 60 different human tumour cell lines. They show remarkable activity against leukaemia (K-562 and S.R.), renal cancer (UO-31) and non-small cell lung cancer (HOP-92) cell lines, with the most important GI50 values ranging from 0.04 to 11.4μM, from the in vitro assays.

Tala (2013, p. 808) have synthesized biologically active Chalcone and pyrazole derivatives by reacting 3-isopropyl-4-methoxybenzaldehyde with various aromatic ketones by using alkali as catalyst [27].

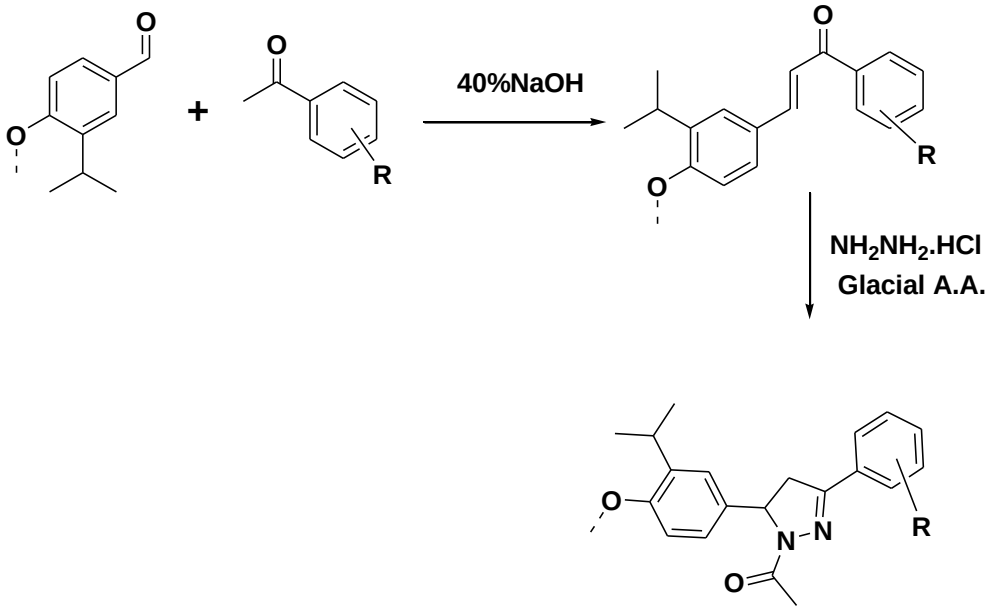


Fig. 21. Synthesis of Pyrazoline from chalcones by Tala (2013, p. 808)

Obtained product were treated with hydrazine hydrate in the presence of glacial acetic acid to give 1-acetyl-3-aryl-5-(3-isopropyl-4-methoxyphenyl) pyrazole. Newly synthesized compounds have been screened for antimicrobial activity. Sattar (2018, p. 4) has given synthesis of some Pyrimidine, Pyrazole, Pyridine derivatives

and their reactivity Descriptors [28]. A series of novel pyrimidine, pyrazole and pyridine derivatives were synthesized using a chalcone-bearing thiophene nucleus. Target compounds were synthesized by reaction of compound with urea, thiourea, malononitrile, hydrazine hydrate, and 2, 4-dinitrophenyl hydrazine, respectively. Molecular electronic structures have been modelled within density functional theory framework (DFT).

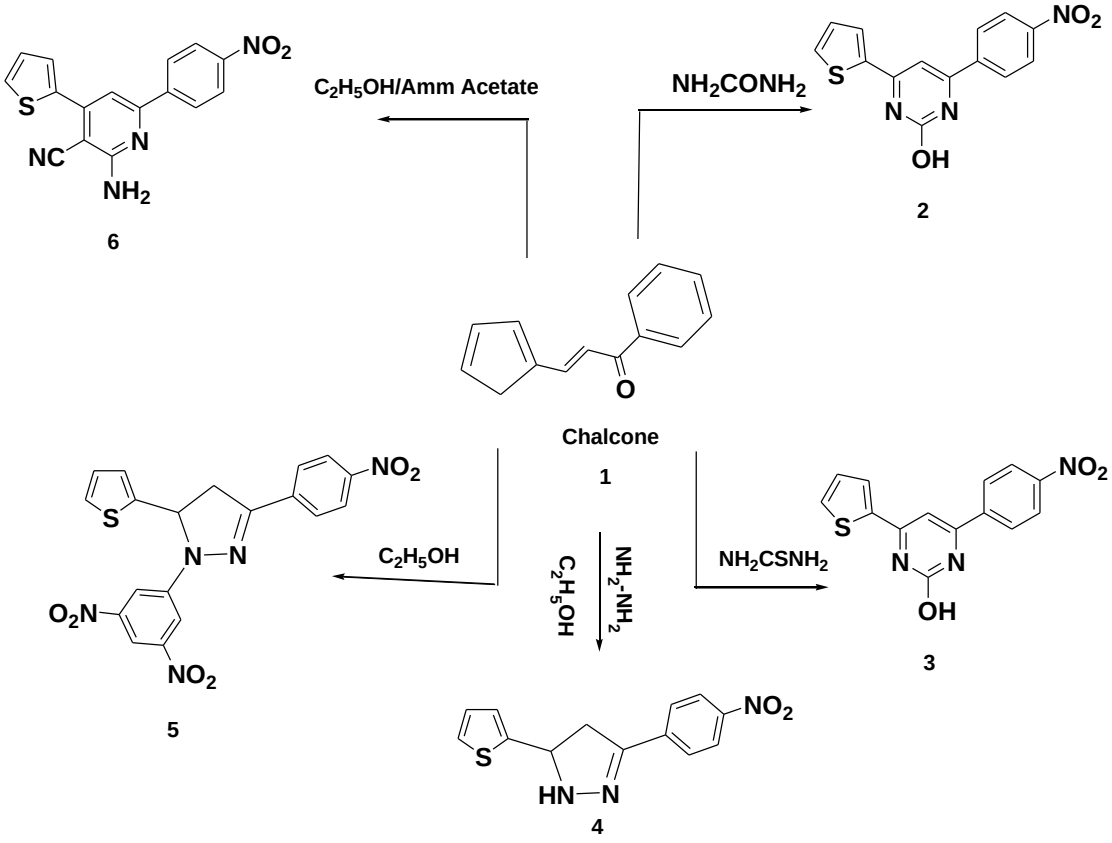


Fig. 22. Synthesis of Pyrazoline from chalcones by Sattar (2018, p. 4)

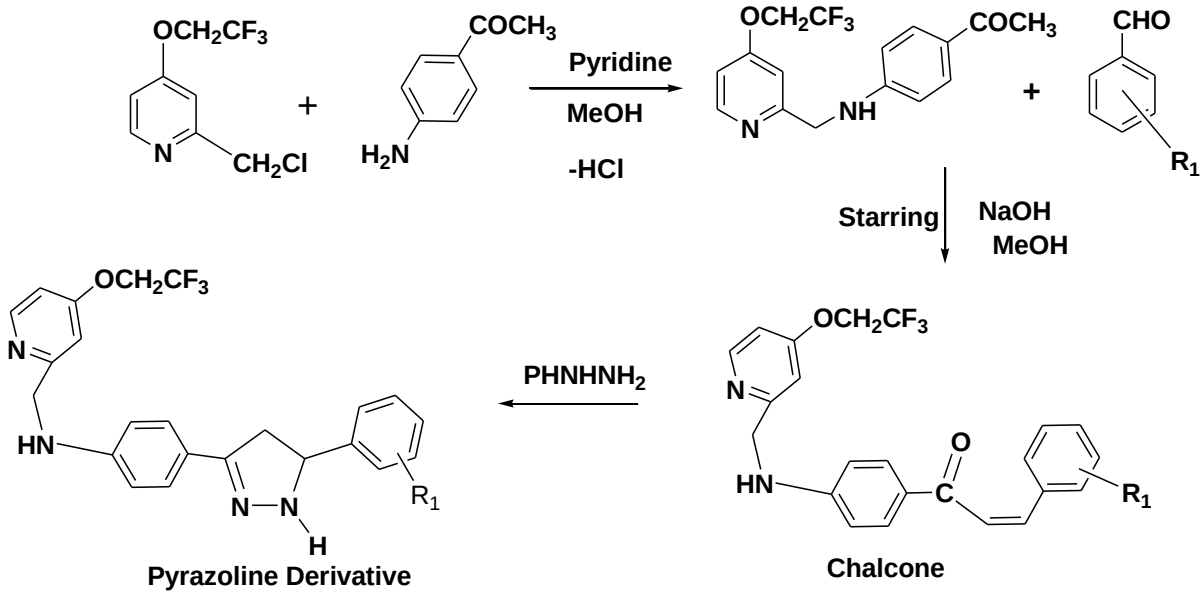


Fig. 23. Synthesis of Pyrazoline from chalcones by Pandya (2017, p. 175)

Reactivity indices and electrostatic surface potential maps (E.S.P. maps) allow us to establish trends that enable making predictions about chemical characteristics of the newly synthesized molecules and their proton transfer tautomer's. Proton transfer is generally more favoured in solution than in the gas phase. In acetonitrile, keto-form tautomer's and thione-form tautomers become more energetically stable than the corresponding enol or thiol tautomer's due to solvent-induced enhancement in the molecular polarity identified by computed dipole moment. Pandya (2017 p.175) synthesized halogenated chalcones in a synthetically affordable route [29]. The pyrazoline derivatives were synthesized by involving of series of chalcones reacts with hydrazine hydrate, catalysed by acetic acid.

All the synthesized molecules were placed for in vitro antibacterial and antifungal activity. Vanillin and other aldehyde containing chalcones, and its pyrazolines are important in pharmaceutical chemistry.

Conclusion

Chalcones, aromatic ketones and enones, are known for their microbial effects. Different varieties of Chalcone derivatives were synthesised and further used in synthesis of many heterocyclic compounds. The current review presents methods for obtaining Flavones, 1, 5- benzodiazepines, 1, 5-benzothiazepines, Pyrazole & pyrazoline from chalcone in moderate to excellent yields by conventical, microwave promoted irradiation, A green chemistry reaction conditions. All mentioned Heterocycles found to be active against human pathogens. In this short review only, few heterocycles were reported with their latest synthetic methods. But there is other derivative of heterocycles which synthesized from chalcones such as Pyrimidines and Thiopyrimidines, Indoles, oxazole etc. Only five and six membered heterocycles are more stable. Therefore in future chalcones have been remaining main precursor in the heterocyclic chemistry. It is found to be effective anticancer agents. In addition to their use as anticancer agents in cancer cell lines, heterocyclic analogues are reported to be effective even against resistant cell lines.

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