The Chalcones are α:β-unsaturated ketones containing the reactive keto ethylene group.

These compounds are also known as benzylidene acetophenones or benzalacetophenones, which are documented as Chalcones by Kostanecki and Tambor (1).

The Chalcones are transitional compounds valuable a choice of flavones, flavanols, anthocyanins, benzal coumaranones.

The Chalcones have found to be useful in providing structure of natural products like plorctin (2) sakuranactin (3) hemlocktanin (4) homocriodicyol and eriodictyol (5) cyanachlorin (6) etc.

In view of their great reactivity and their close relationship to flavanones, flavones and dihydroflavonols, Chalcones are investigated since long. It is of great interest in their study as intermediates for substances of therapeutic importance (7). Schraufstatter and Deutsch (8) and Calcinari (9) have reported antibacterial properties of some Chalcones. The deoxybenzoins derived from Chalcones are found to be good anaesthetics (10) antispasmodics and tranquilizing (11-13); ruchkin, Eaton, Clark et al. [14-16] reported their insecticidal activity. Nakanishi and Tasuda (17) observed that some Chalcone derivatives possess insectrepellent properties. Some Chalcones have suggested as remedy for cancer (18). Laliberte, Campbell and Brederlein (19) reported 3,5-di-phenylisoxazoline derivatives as anthelmintic agents. Vibhute (20) prepared some haloChalcones and flavones and tested for antimicrobial activity. Mishra and Tiwari (21) reported 4-hydroxy-3-nitro-1-naphthyl Chalcone derivatives as potential germicides. Bradsher, brown and blue (22) prepared Chalcones of antifungal activity.
NOMENCLATURE

The Chalcones have given different nomenclatures from time to time. In the numbering system used by Chemical Abstract, the prime numbers are given to the phenyl ring which is nearer to the carbonyl group.

\[ \text{[I]} \]

The British chemical society moreover the academic journal of the chemical society has followed this system.

\[ \text{[II]} \]

In present argument the Chalcones which have set are numbered as per Chemical Abstracts (I).
TECHNIQUES OF PREPARING CHALCONES

CLAISEN SCHMIDT SYNTHESIS

A variety of techniques square measure obtainable for the preparation of Chalcones. the
bulk expedient technique is that the single that involves the Claisen solon condensation of
equimolar quantities of a substituted acetophenone with substituted benzaldehyde within the
presence of liquid alcoholic alkali (23-58). Within the Claisen solon synthesis, the eye of alkali
used usually ranged between ten and hour.

The reaction is meted out at regarding 50°C for 12-15 hours or at temperature for one
week (29). Underneath these conditions, the Cannizaro reaction (59) additionally takes place and
thereby decreases the yield of the required product. To avoid the unbalanced of aldehydes within
the on top of reaction, the employment of b benzylidene diacetate is employed in situ of organic
compound (60).

Scheme – 1.1 Synthesis of Chalcone by Claisen Schmidt condensation

Claisen and Claparede (61) are the earlier workers who condensed the
aliphatic ketones with aromatic aldehydes. They first prepared a simple benzylidene –
acetone on heating with benzaldehyde (1 mol) and acetone (1 mol) in presence of
acetic anhydride (2-mol) and zinc chloride which are found to be identical with
Engler and Leist’s acetocinnamone (62).
Extending the above condensation to an aromatic ketone they prepared benzylideneacetophenone (simple Chalcone) using hydrogen chloride gas a condensing agent. During the condensation of 4-nitrobenzaldehyde with acetone, Bayer and Balker (63) isolated an intermediate aldol type product (I) in pure state which could be easily dehydrated to 4-nitrocinnamoyl methane (II) by the action of acid or alkali.

The isolation of an intermediate is possible in this particular instance because of the presence of nitro group which enhanced the stability of such a compound. The above results clearly indicate that the reaction is an aldol type condensation.

**MECHANISM OF CHALCONE FORMATION:**

Kinetic studies have reported for base catalyzed formation of Chalcone [64-66] and its derivatives [66, 67]
Scheme – 1.4 Mechanism of Chalcone syntheses
DIFFERENT CONDENSING AGENTS APPLIED FOR THE SYNTHESIS OF CHALCONES:

1) Alkali:

The condensation of galloacetophenone and resacetophenone among benzaldehyde in existence of alkali is carried out by Ellison (72) and afterward Mahal, Rai and Venkataraman (73). As a replacement for the expected Chalcones, the consequent flavanones resulted. The condensation of aldehydes excluding benzaldehyde did not thrive but benzyl ether readily gave Chalcones with anisaldehyde, benzaldehyde etc. (74). Alkali is fruitfully used as a condensing agent.
with ethers and its resacetophenone (75-79,29, 42); 2,9-dihydroxyacetophenone and its monomethyl ether (80,82), gallaacetophenone (42, 83,84), phloroacetophenone (85-88) and quinacetophenone; its dimethyl and mono ethers (33,89,90).

Halogen containing Chalcones are prepared by the several workers (41, 96-101) using alkali as condensing agent. Chen and Ueng (102) prepared Chalcones from fluorobenzaldehydes. Merchant, Mehta and Desai (103) prepared Chalcones containing nitro and bromo groups (104-106).

Ambekar, Dandega, Jalod and Rajgopal (107) synthesized 1,2-hydroxy-4-5-methoxyChalcone. Timoney and Vickars (108) condensed 2'-hydroxyacetophenone with heterocyclic aldehydes in the presence of the base and obtained 2-heterocyclic substituted chromones and related Chalcones. Kushwaha, Dinkar and Lal (109) prepared Chalcones having a heterocyclic nucleous.

Shah (110) used 40-50% alkali to derive the Chalcones from 5-hydroxy-6- acetyl-4-methylcoumarin. Chalcones containing pyrrole (111), thiophene (112, 113) pyridine (114,115) and quinoline nuclei (116) have also been reported.

2) **Hydrochloric acid gas:**

In the synthesis of Chalcones from aromatic ketones by condensation with aldehydes, dry hydrochloric acid gas is used as a condensing agent is not successful in all the cases. However, Russell and Todd (117) extensively used to prepare Chalcones required in connection with synthetic preparation of compounds related to natural phlobatannins.

In order to avoid complication arising due to presence of free hydroxyl group, they employed benzoylated ketones and aldehydes as the starting materials and obtained benzoylloxyChalcones which yielded the corresponding hydroxychalcones on debenzylation. They synthesized 3,4-tetrahydroxy-Chalcone from resaceto -phenone dibenzoate and protocatechuic aldehyde dibenzoate to get tetrabenzoyl Chalcone from which from which free Chalcone is obtained on debenzylation.

Lyle and Paradis (118) and Marathey (119) used methanolic solution of dryhydrochloric acid gas at 0°C. Sipos, They synthesized 3,4-tetrahydroxy-Chalcone from resaceto-phenone dibenzoate and protocatechuic aldehyde dibenzoate to get
tetrabenzoyl Chalcone from which free Chalcone is obtained on debenzyolation.

Tsukerman (121) also used this condensing agent in the preparation of Chalcones containing a selenophene nucleus. Caussac and Boucherie (122) reported Chalcones from 3-acetylpyridine with different aldehydes using dilute (1:1) hydrochloric acid while Hermes (123) used concentrated hydrochloric acid and condensed p-methylacetophenone with vanillin. Onoda and Tetsuko (124) used hydrochloric acid as condensing agent for preparation of Chalcone.

PROPERTIES AND TESTS OF CHALCONES

The Chalcones are generally coloured, usually yellow, orange, red or brown. They are comparatively more soluble than flavanones in ethanol and ethylacetate. 2'-hydroxy Chalcones dissolves in dilute alkali with an orange deep red colour.

SIGNIFICANT OF CHALCONES:

i) They have close relationship with flavones, flavonols, flavanones and dihydroflavonols.

ii) Krbechek (133) reported some dihydro Chalcones possessing sweetening property which is 2000 times sweeter than sucrose.

iii) phenylhydrazine resulting ethyl cyclohezanone carboxylate and pyrazoline derivatives.

iv) The Chalcones are valuable for the synthesis of various heterocyclic compounds like flavanones, flavones, flavonols, benzal coumaranones, anthocyanins plus positive compounds like deoxy benzoin and hydrations that are originate to have some therapeutic importance as antispasmodic and mydriatics.

v) The Chalcones have originate helpful in evidencing the structures of natural products like hemlock tannin (4), cyanomaclurin etc.

vi) Schraufstatter and Deutsch (8) and Calcinari (9) observed antibacterial properties of some Chalcones. Mishra and Tiwari (21) reported 2 hydroxy-3 nitro-1-naphthyl Chalcone derivatives as potential germicides. Mishra and Kushwaha (136) have also reported phenanthryl and naphthyl Chalcones as potential germicides. Vibhute (20) have reported antimicrobial activity of
some Chalcones and flavones. Brown and blue (22) prepared Chalcones and tested as remedy for cancer (137, 138).

vii) Chalcones and its synthesized derivatives also find applications as stabilizers photosensitive materials, scintillators, polymerization catalysts fluorescent whitening agents and organic brightening additives.

**Reactivity of Chalcones**

Chalcones are reactive towards a number of reagents. Some of the important reactions are described as below.

**1) Reaction of bromine with Chalcones**

The Chalcone adds a molecule of bromine and under usual conditions α,β- dibromo Chalcone is obtained.

![Scheme – 1.6. Reaction of Bromine with Chalcones](image)

Dibromide of simplest benzylidene acetophenone is prepared by Claisen and Clasparede (139). Action of bromine on Chalcones derived from some o-hydroxyacetophenone is studied by Vanderwalla and Jadhav (140). One molecule of bromine is found to act at the ethylenic bond. Dibormides are prepared using acidic medium (141)

Wheeler and Dodwadmath (142) observed that bromine first enters the double bond very easily and if the reaction is continued, bromine enters the nucleus also. Further, it is seen that styryl nucleus in Chalcones is more reactive than the aryloxy party

**2) Reaction of hydroxylamine hydrochloride on α:β-dibromo - Chalcones**
The alcoholic solution of α-β dibromochalcones when refluxed with molar proportion of hydroxylamine hydrochloride and aqueous potassium hydroxide, followed by acidification, yield that 2-isoxazole derivatives (144, 146, 147).

**Scheme – 1.7 Reaction of Hydroxylamine hydrochloride**

3) **Reaction of benzene -1,2 diamine on α:β - dibromoChalcones:**

Reaction of α-β dibromoChalcones with benzene – 1,2 diamine in methanol in presence of acid catalyst afforded quinoxaline derivatives [143, 148]

**Scheme – 1.8. Reaction of Benzene -1,2-diamine on α:β - dibromoChalcones**

4) **Reaction of hydrazine hydrate with Chalcones:**
Scheme – 1.9. Reaction of hydrazine hydrate with Chalcones

2-pyrazoline derivatives are prepared by using two different techniques. In the first technique, 2-pyrazolines are obtained (149-154). In the second technique 2-pyrazolines are formed by refluxing Chalcones with hydrazine hydrate in ethanol (155-165) or pyridine. Then these compounds are acetylated with acetic acid (156-159,161) or acetic anhydride / pyridine (157, 158), benzyolated with benzoyl chloride in pyridine (156-161). 2-pyrazolines are treated with sulphonylchloride gave sulphonamide derivatives (166) and with sodium nitrite, nitroso derivatives are obtained (167)

5) Reaction of 2,4-dinitrophenyl hydrazine with Chalcones:

Scheme – 1.10. Reaction of 2,4-dinitrophenyl hydrazine with Chalcones

2-pyrazoline derivatives are also synthesized from Chalcones using 2,4-dinitrophenyl hydrazine. The reaction of Chalcones with 2,4-dinitrophenyl hydrazine in glacial acetic acid give the corresponding phenyl hydrazones which on at high temperature converted to 1,3,5-triphenyl-2-pyrazolines (168).

6) Reaction of hydroxylamine hydrochloride with Chalcones:
2-Isoxazoline (159) derivatives are prepared by the reaction of Chalcones with hydroxylamine hydrochloride, probably through the formation of an oxime.

![Scheme 1.11. Reaction of Hydroxylamine hydrochloride with Chalcones](image)

However, the reaction is not simple. Besides the oxime and isoxazoline, other products like hydroxylamine ketone, hydroxylamino oxime, disubstituted hydroxylamine etc.

**Replacement of oxygen by sulphur in 2-isoxazoline derivatives**

Reactions of $P_2S_5$ in pyridine are the replacement of ring oxygen by sulfur atom. Treatment of 2-isoxazoline with phosphorous pentasulfide in pyridine yielded 2-isothiazoline derivatives (171).

**7) Reaction of guanidine nitrate with Chalcones:**

Jain and Gupta (172) prepared 2-amiopyrimidine derivatives by reacting 2-arythydrazone-1-phenylaminobutane-1-3-diones with guanidine nitrate. Greg and Singh (173) also synthesized arylpyrimidines using guanidine nitrate.

2-hydroxyacetophenones are condensed with benzoylechloride to get 2-hydroxy dibenzoyl -methanes (174) which have condensed with urea in ethylene glycol to obtain pyrimidine derivatives (175).
Chalcones when reacted with guanidine nitrate in the presence of aqueous sodium hydroxide (40%) in ethanol gave 2-aminopyrimidine derivatives (176-179), which on treatment with sodium nitrite in presence of glacial acetic acid gave the corresponding 2-pyrimidinone derivatives (180). Further the reaction of 2-amino, pyrimidine derivatives with acetic anhydride in acetic acid gave the corresponding diacetyl derivatives (179).

8) Reaction of 2-aminothiophenol with Chalcones:

Scheme – 1.13 Reaction of 2-aminothiophenol with Chalcones
2-Aminothiophenol on relation with Chalcones in methanol in the presence of glacial acetic acid gave propiophenones which immediately undergo cyclization gave 1, 5-benzothiazepine derivatives (181,182).

9) **Reaction of monoethanolamine with Chalcones:**

![Scheme – 1.14 Reaction of Monoethanolamine with Chalcones](image)

Chalcones reacts with monoethanolamine in absolute alcohol to give corresponding 1,4-oxazapine derivatives (183).

10) **Reaction of p-toluidine with Chalcones:**

![Scheme – 1.15 Reaction of P-toluidine with Chalcones](image)

Chalcones reacts with p-toluidine in absolute alcohol to give corresponding Schiff bases (184).

11) **Reaction of Thiourea with Chalcones:**

![Scheme – 1.16 Reaction of Thiourea with Chalcones](image)
Pyrimidine-2-thione derivatives (185) are prepared by heating benzalacetophenone derivatives with thiourea in ethanolic hydrochloric acid which on treatment with acetylchloride gave the acetyl derivatives (186) of pyrimidine-2-thiones.

12) Reaction of urea with Chalcones:

![Reaction Scheme](image)

Scheme – 1.17 Reaction of Urea with Chalcones

pyrimidinone derivatives (185) are prepared by heating Chalcone derivatives with urea in ethanolic hydrochloric acid.

**BIOLOGICAL ACTIVITY OF CHALCONES:**

During the current century, Chalcones and their derivatives have discovered to be a lot of use. Therefore several Chalcones exhibit therapeutic properties e.g. anticular activity, hypotensive activity etc. Antibiotic activity (280, 281) have shown by some Chalcones owing to presence of AN enone operate. It has discovered that the organic process or antiseptic property gets enhanced with the introduction of a substituent sort of a nitro or bromo cluster at the β-position or a bromo or hydroxyl at the β-position (280). Some substituted Chalcones and their derivatives possess biological properties e.g. they prove prejudicial to the expansion of microbes (282) tubercle bacilli (283, 284) protozoal infection parasites (285) viscus worms (286,287) etc. They additionally inhibit growth of many enzymes (288-289) and fungi (290,291)

**CHALCONES AS ANALYTICAL REAGENTS:**

Chalcones react with a number of metal ions and are reported to be more reactive than the aldehyde or ketone from which they are prepared (292). This reaction have exhibited (293) for the detection of Fe(III) by 2, 4-di-hydroxyChalcone
provided the concentration of interfering ions kept at a minimum 2,3,4 – TrihydroxyChalcone is used as analytical reagent for amperometric estimation of cooper (294) and for spectrophotometric study of the germanium (295) Bhardwaj and Singh (296) introduced 2-hydroxy-2,5 dichloro-4 methylbenzalacetophenone oxime as an analytical reagent.

**Literature review:**

**Naturally Occurring Chalcones**

Naturally occurring Chalcone have been reported to have multiple biological and pharmacological activities. The biological activity is mainly depends on the substitution group of Chalcones. LicoChalcone A (11) is a naturally occurring Chalcone isolated from the roots of Glycyrrhiza inflata (licorice) which was proved to have *in vitro* and *in vivo* antimalarial and antileishmanial activities.

![Scheme 1.19 LicoChalcone A](image-url)
Scheme – 1.20 Original compounds Isorubraisasne (13) and SSumadain (14) and Riubrainee (15)

**Synthetic Chalcones:**

**Creation of Chalcones by the employment of Suzuki coupling synthesis**

An efficient synthesis of Chalcones was carried out based on the Suzuki coupling reaction between benzoyl chlorides and phenylvinylboronic acid. Phenylvinylboronic acid was prepared by dehydrogenative borylation of para-methoxystyrene by pinacolborane oxidative addition-dehydrogenation catalyzed by the rhodium complex, RhCl(cod) to give para-methoxyphenylethenylboronic acid pinacol ester. Oxidative cleavage of using sodium periodate in THF/water to form the para-methoxyphenylethenylboronic required for the Suzuki coupling step. The coupling between and afforded 3',4',4'-trimethoxyChalcone using anhydrous toulene as solvent and catalyzed by tetrakis(triphenylphosphine)palladium(0) and base, cesium carbonate. (Edrarir et al., 2003)
Creation of Chalcones through Microwave Irradiation

The combination of supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short times and with high conversions and selectivity, without the need of solvents. This approach proved beneficial since it offers several advantages over conventional heating techniques and accelerates the organic reactions (Varma, 1999). The air-dried paste of 2'-hydroxyacetophenone, benzaldehyde and anhydrous K$_2$CO$_3$ is subjected to microwave irradiation for 3-5 minutes to 16 produce 2'-hydroxy-Chalcones. This reaction gave a cleaner product with a high yield (80-90%).(Srivastava, 2008)
Scheme – 1.22 Synthesis of Chalcones via Microwave Irradiation

Production of Chalcone via Borontrifluoride-etherate

Narender and Reddy (2007) developed a new techniqueology by using BF$_3$-Et$_2$O to synthesize several substituted Chalcones. The compensation of this technique over the earlier techniques is high yields, simple work-up, short synthesis times, no side synthesis, and partition is desirable to get the products. This technique is solvent free reactions and applicable for reactions involving liquid reactants which are base sensitive functional groups such as esters and amides.

Scheme – 1.23. Synthesis of Chalcones using Borontrifluoride-etherate

The Von-Konstanecki Technique

This is a universal technique for synthesizing flavones which involves a reaction of 2-methoxybenzoate and acetophenone in the presence of sodium to form the diketone compound is formed via Claisen condensation.
Friedel-Crafts Acylation

Besides the Claisen-Schmidt reaction, Chalcones may synthesize directly via Friedel-Crafts acylation of a phenol. The phenol become the A-ring while the acylating agent provides both the B-ring carbons and the three carbon bridge to form C6-C3-C6 unit. (Bohm, 1998) Friedel-Crafts acylation of 3-phenylpropionyl chloride with 2,4-dimethyl-1,3,5-triobenzene gave 2’,4’,6’-trihydroxy-3’,5’-dimethyl-Chalcone. (Bohm, 1998)
PRESENT WORK

Some workers prepared Chalcone from 1-(4-(4-aminophenoxy) phenyl) ethanone (300-305). It is found that heterocyclic derivatives prepared from this compound shows valuable antibacterial activity.

So it is thought interesting to study the reactions of Chalcones with (2, 4- dinitro phenyl) hydrazine, Urea, Benzine-1, 2-diamine, Hydroxylamine hydrochloride, 2-amino benzenethiol, Thiourea, Hydrazine hydrate. The work is taken up to the study of antibacterial activity of compound synthesizing from Chalcones. The following arylaldehydes are used:

1. Benzaldehyde
2. 4-anisaldehyde
3. 2-anisaldehyde
4. Salicyaldehyde
5. 2-chlorobenzaldehyde
6. 4-chlorobenzaldehyde
7. 2-nitrobenzaldehyde
8. 3-bromobenzaldehyde
9. 3,4-dimethoxybenzaldehyde
10. 3,4,5-trimethoxybenzaldehyde