FABAD J. Pharm. Sci., 36, 223-242, 2011

SCIENTIFIC REVIEW

Chemical and Structural Properties of Chalcones I

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Chalcones belong to the flavonoid family and display several pharmacological activities which are very important. They can be used as an initial compound for synthesis of a lot of compounds. Therefore, many researchers have synthesized these compounds and evaluated their biological activities. In this review, we aimed to provide a comprehensive presentation of chemical and structural properties of chalcone derivatives, to the researchers.

Key Words: *Review, chalcones, reactions, synthesize, conformational structure*

Şalkon I'in Kimyasal ve Yapısal Özellikleri

Şalkonlar flavonoid sınıfında yer alan ve önemli biyolojik etkiler gösteren bileşiklerdir. Pek çok sentez reaksiyonunda başlangıç bileşiği olarak kullanılabilmektedirler. Bu yüzden çok sayıda araştırıcı bu bileşikleri sentezleyerek bu bileşiklerin biyolojik etkilerini incelemektedir. Bu derleme ile araştırıcılara şalkon türevlerinin kimyasal reaksiyonlarını ve yapısal özelliklerini bir arada topluca sunmayı amaçladık.

Anahtar Kelimeler: *Derleme, şalkonlar, reaksiyonlar, sentez, konformasyonel yapı*

Received: 10.03.2012
Revised: 26.11.2012
Accepted: 03.04.2013

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1. INTRODUCTION

Chalcones (1,3-diaryl-2-propen-1-ones) are flavonoids found in fruits and vegetables, that attracted attention because of their pharmacological activities such as antiinflammatory (1-7), antibacterial (8-12), antifungal (13-17), antiviral (18-22), antioxidant (23-32), antineoplastic (33-41). Most of aromatic rings of natural chalcones are found as hydroxylated. Chalcones, dihydrochalcones and aurones are composed of pigments whose colour changes from yellow to orange in some *Coreopsis* and *Asteraceae taxa* species. These compounds are found not only in flowers but also in lots of different tissues of the plants. Free radical scavenging properties of phenol groups of chalcones increased the interest in consumption of plants that included chalcones (18).

Chalcones are included dimer, oligomer, Diels-Alder adducts and different conjugates. At the same time because of being precursors of all of other flavonoid groups, chalcones are very important biosynthetic compounds. Essential property that separates chalcones and dihydrochalcones from the other flavonoids is that an open chain with three carbon molecules binds to A and B ring instead of C ring of flavonoids (Figure 1). Chalcones turn to flavanones with a stereospecific reaction catalyzed by chalcone isomerase enzyme in plants. Close biogenetic and structural relation between chalcones and flavanones is the reason for these compounds usually found together in natural products. This is the cause of the identification of chalcone, dihydrochalcone and aurones together with flavanone and dihydroflavonol generally. Chalcones are called as minor flavonoids. But using name of minor flavonoids for chalcones doesn't seem appropriate because of increasing of new species of flavonoids (42).

As flavonoid term, mostly plant pigments are expressed which includes benzo-γ-pirone and flavone (Figure 1). Essential compounds of flavonoids include a phenyl group at 2nd position of benzo-γ-piron (chromone) ring system. Flavonoids differ according to size, saturation and the substituents of γ-pyrone ring which is called C ring (43).

The ethylenic bond between C2 and C3 of C ring of flavones provides conjugation between A and B ring. In this way the ring structure of flavones

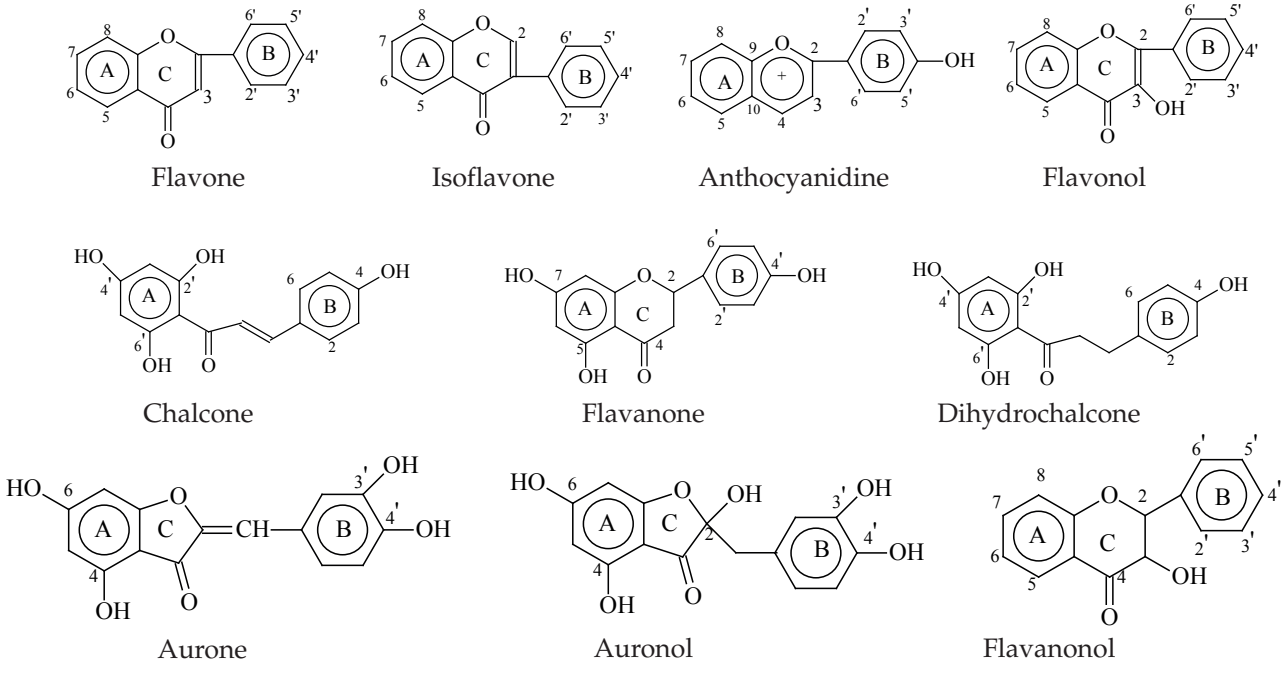


Figure 1. Some flavonoid species

becomes stronger than other flavonoids. Although anthocyanidines differ from other flavonoids by losing carbonyl group in C ring, their biological characteristics are similar to other flavonoids. Chalcone derivatives are ring-chain isomers of flavanone derivatives. Aurone derivatives situates in flavonoids by having benzofuranone structure (42,44,45).

Chalcone containing plants, such as *Glycyrrhiza*, *Angelica*, *Ruscus* and *Piper* species have been used as medicine in Asia, Africa and South America. Several pure chalcones were approved for clinical use. One of the chalcones came on the market is metochalcone (1-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl) -2-propen-1-one), the others are a choleretic drug and an antiulcer drug (sofalcone), (2- [5- [(3-methyl-2-buten-1-yl) oxy] -2- [3- [4- [(3-methyl-2-buten-1-yl) oxy] phenyl] -1-oxo-2-propen-1-yl] phenoxy] acetic acid) (46).

2. CHEMICAL REACTIONS OF CHALCONES

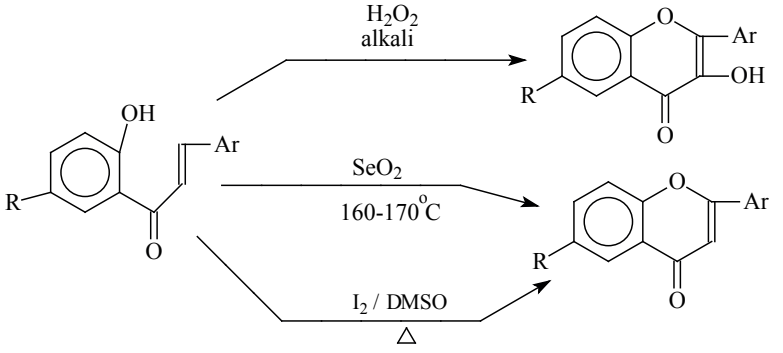
2.1. Oxidation of chalcones

2.1.1. Algar-Flynn oxidation of chalcones

While the reaction of acetaminochalcones with selenium dioxide gives 6-acetaminoflavones, the reaction of acetaminochalcones with alkaline hydrogen peroxide give 6-acetaminoflavonols as the result of Algar-Flynn oxidation (47). Additionally I_2/ DMSO can be used as oxidation reagent to synthesize flavones. (48,49) (Scheme 1). Flavanone derivatives are composed by refluxing 2'-hydroxy chalcones with glacial acetic acid (49) (Scheme 2).

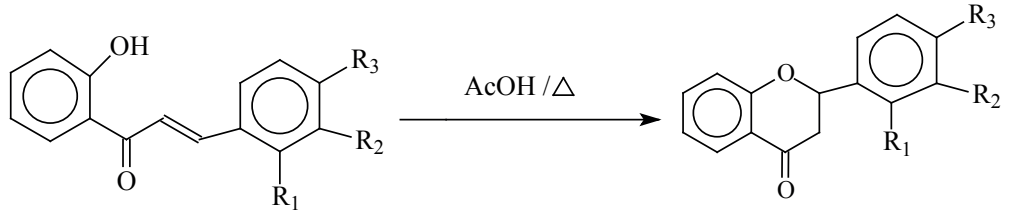
2.1.2. Epoxidation of chalcones

The epoxidation of ethylenic groups of natural compounds such as chromone, chalcone and isoflavone with hydrogen peroxide occurs very fastly and with high yield in 1-butyl-3-methyl imidazolium tetrafluoroborate ([bmim] BF_4) (3) (Scheme 3).

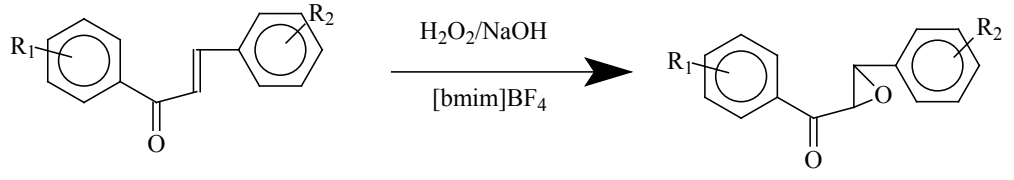


Ar: C_6H_5, p-$C_6H_4OCH_3$, 3,4-C_6H_3 (CH_2O_2), m-C_6H_4OH R:CH_3CONH, H

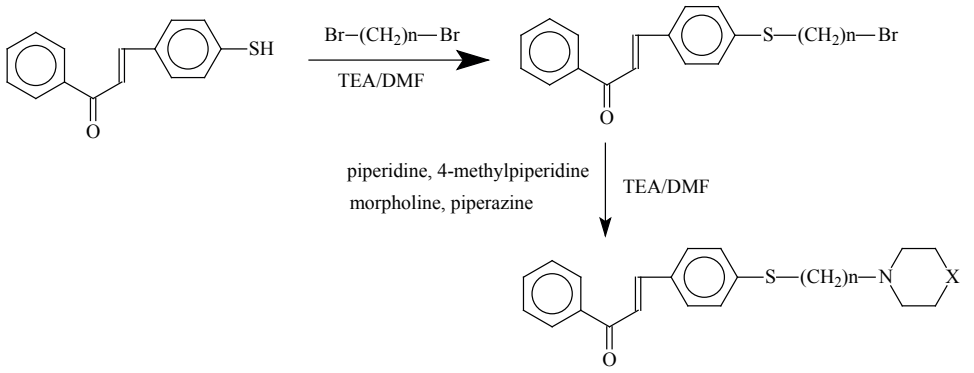
Scheme 1. Oxidation of chalcones



Scheme 2. Oxidation reactions of chalcones



Scheme 3. Epoxidation of chalcones



Scheme 4. S-Alkylation reaction of mercapto chalcones

2.2. Substitution reactions of chalcones

2.2.1. S-Alkylation reactions

S-Alkylation is obtained with the reaction of (*E*)-4-Mercaptochalcones and dibromoalkanes in N,N-Dimethyl formamide in the presence of triethylamine (TEA) at room temperature (7) (Scheme 4).

2.2.2. O-Alkylation reactions

O-Alkylation occurs with the heating reaction of (*E*)-4-hydroxy chalcones and dibromoalkanes in dry acetone in the presence of anhydrous potasium carbonate (7) (Scheme 5).

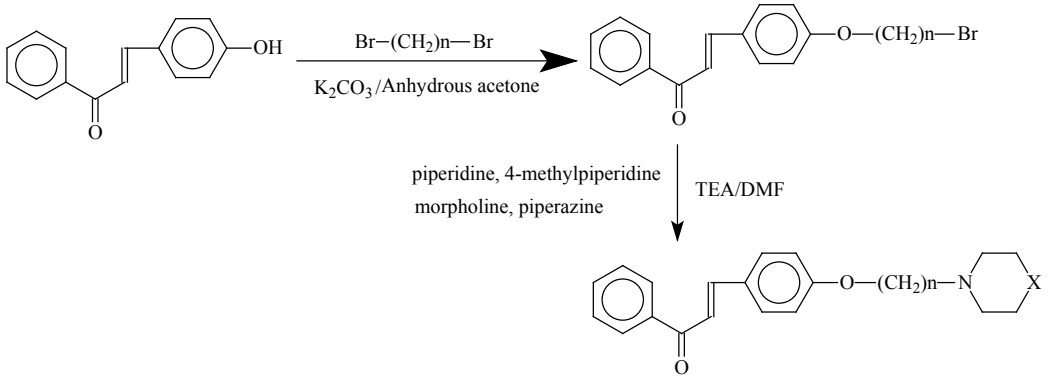
2.3. Addition reactions of chalcones

2.3.1. Michael addition reaction of chalcones

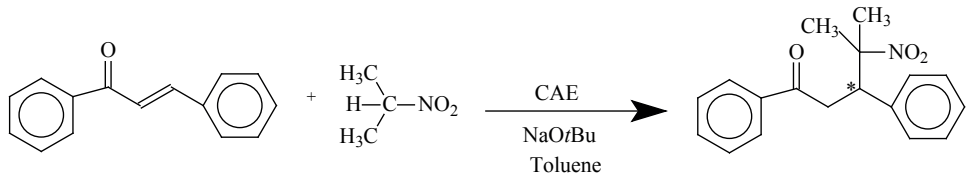
Michael addition is usually made under strong basic conditions. Substituted chalcones give enantioselective Michael addition reaction with 2-nitropropane by using Chiral Azacrown Ether (CAE) as catalyst (Scheme 6). It has been seen that phosphine oxido alkyl compound is formed with %87 yield. The substituent which is on chalcone is effective in determining of reaction's yield and enantioselectivity. Absolute configuration of Michael addition substances is determined with chemical methods and X-ray christallography (50).

1- (1-Alkyl-benzimidazole-2-yl) -4-nitro-3-aryl-butan-1-one is synthesized by addition of nitromethane to the β-carbon atom of benzimidazole chalcone in the presence of K_2CO_3 and tetrabutilamonium bromür (TBAB) (Scheme 7). However, if the reaction occurs under strong basic conditions, a lot of product will be composed such as dehidrating reactions products. However this synthesis reaction can be made with a simple, effective and fast method in the presence of K_2CO_3 and TBAB with no solvent in pestle (51). When the same reaction was carried out in the absence of TBAB, the addition of nitromethane is not succeeded.

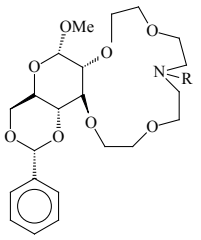
Microwave is used for the addition of compounds having active methylene to the chalcones in the presence of potasium carbonate and water (Scheme 8). In this method organic solvent is not used and pure product is synthesized with high yield (52).



Scheme 5. O-Alkylation reaction of hydroxy chalcones with dibromoalkanes



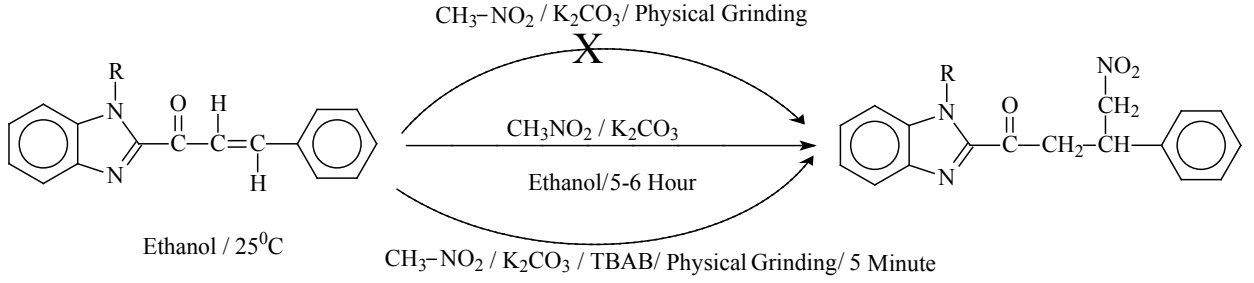
CAE:



R = H,-$CH_2CH_2OCH_3$,–$(CH_2)_4P(O)Ph_2$

NaO*t*Bu: sodium *tert*-butoxide

Scheme 6. Reaction of chalcones with 2-nitropropane

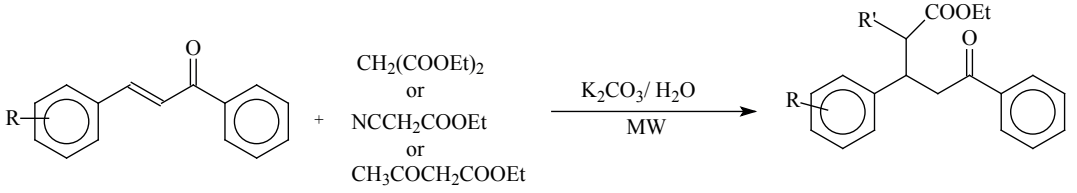


Scheme 7. Reaction of chalcones with nitromethane

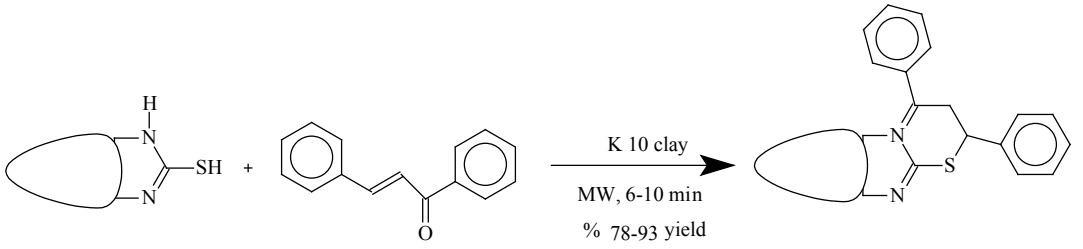
The addition of cyclic thiourea compounds to the chalcones and following cyclodehidrating reaction (Michael addition) give rise to formation of imidazo [2,3-b] 1,3-thiazine ring (53) (Scheme 9).

2.3.2 Bromination of chalcones

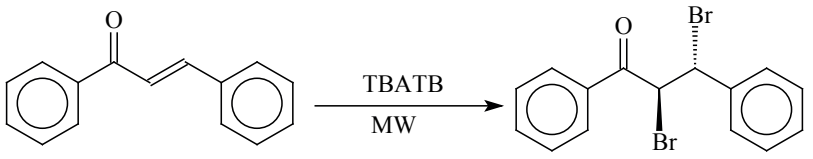
Bromination of chalcones can be made with pure starting substance, special reagents and microwave applications (2450 MHz). The usage of microwave



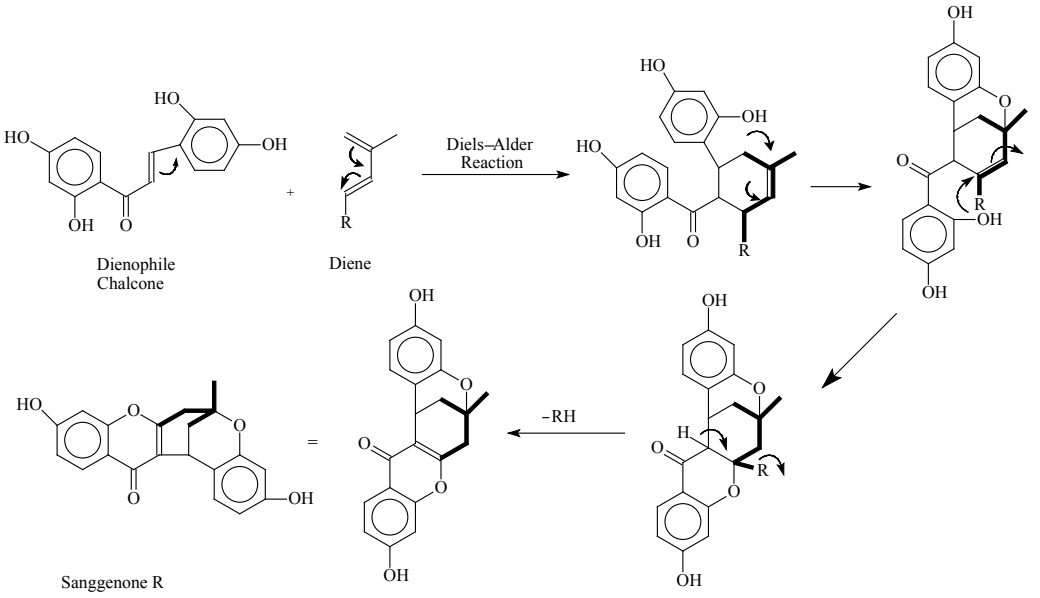
Scheme 8. Reaction of chalcones with the compounds having active methylene group



Scheme 9. Addition reaction of cyclic thiourea compounds to the chalcones.



Scheme 10. Bromination reaction of chalcones



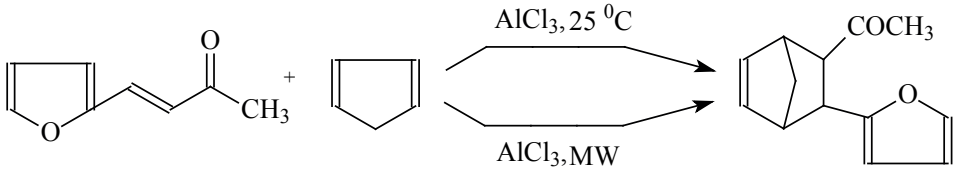
Scheme 11. Diels-Alder reactions via enzyme catalysts

(MW) experiments without solvent make them feasible for synthesis of bromo organic compounds (Scheme 10). Tetrabutylamonium tribromür (TBATB) is used as bromination reagent to avoid from damages of using molecular bromine. Bromination reaction of chalcones at microwave conditions (in 50 seconds) proceeds in 87% yield in the presence of TBATB and without solvent (54).

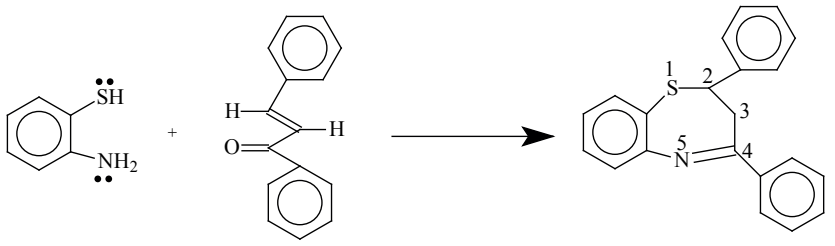
2.3.3. Diels Alder reaction of chalcones

One of the most characteristic chemical feature of chalcones is their action as a dienophile in enzyme catalyzed Diels Alder Reactions (Scheme 11). Dienes that enter into the Diels-Alder adduction reactions are simple structure like isoprene, monoterpene compounds, coumarines and other group flavonoids (42).

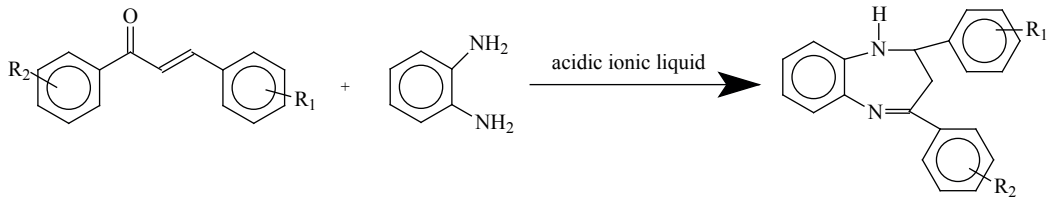
Diels Alder adduction is occurred between chalcones and cyclopentadiene with the polimerization that is composed by inversing ring opening. Most of chalcones give the endo and exo adduct products with high yield by the reaction of cyclopentadiene with furfurylideneacetone and N,N-diethylaminobenzylidene-(4-hydroxy) acetophenone. Chalcone reactions can be made in both of room temperature and microwawe conditions (Scheme 12).



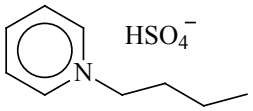
Scheme 12. Diels-Alder reaction with MW and Diels-Alder reaction at room temperature



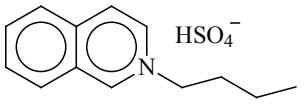
Scheme 13. Addition reaction of chalcones with o-aminothiophenols



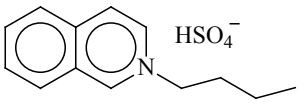
Acidic ionic liquids:



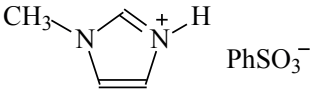
1-Butylpyridinium hydrogen sulfide ([BPy] HSO_4)



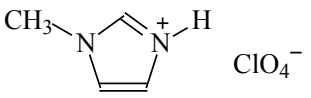
1-Butylpyridinium hydrogen hydrogen sulfide ([iso-BQu] HSO_4)



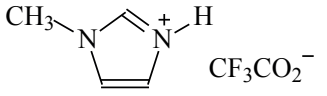
1-Methyl-3-hydro-imidazolium tetrafluoroborate ([HMIm] BF_4)



1-Methyl-3-hydro-imidazolium benzene sulfonate ([HMIm] $PhSO_3$)



1-Methyl-3-hydro-imidazolium perchlorate ([HMIm] ClO_4)



1-Methyl-3-hydro-imidazolium trifluoroacetate [HMIm] CF_3CO_2

Scheme 14. Reactions of chalcones with o-phenylenediamine in acidic ionic liquids

Chalcones are solved in toluen and mixed with cyclopentadiene in the presence of catalytic amounts of $AlCI_3$ at room temperature for three days. The same procedure can be made in 3 minutes by using microwave (55).

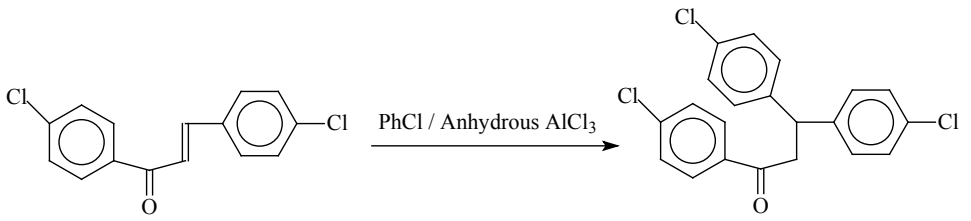
2.3.4. Addition reaction of chalcones with ortho-aminothiophenols and o-phenylenediamine

1,5-Benzothiazepines are synthesized by the reaction of chalcones with o-aminothiophenols under acidic and basic conditions (Scheme 13). The reaction begins with the 1,4-Michael addition of SH group on C-C bond and then it continues with the condensation of NH_2 group to the carbonyl group (56).

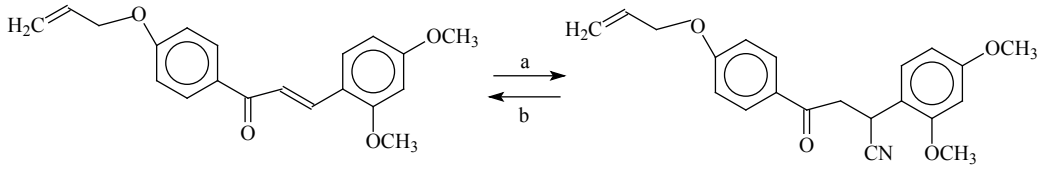
Chalcones give 1,5-benzodiazepines with o-phenylenediamine in acidic ionic liquids (Scheme 14). This method is recognized as a cheap and easy prepared method (57).

2.3.5. Addition reaction of chalcones with chlorobenzene

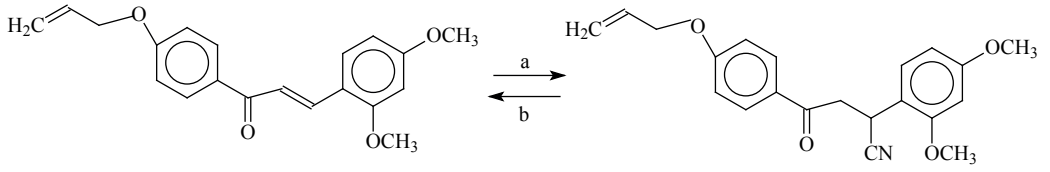
When 4,4'-diclorochalcone is mixed with chlorobenzene in the presence of aluminium chloride at room temperature, conjugate addition product is produced (58) (Scheme 15).



Scheme 15. Reaction of chalcones with AlCl3 and chlorobenzene



Scheme 15. Reaction of chalcones with AlCl3 and chlorobenzene



(a) NaCN, NH_4Cl, DMF, 100°C; (b) NaH, toluene, temperature

Scheme 16. Addition reaction of chalcones with HCN

2.3.6. Addition reaction of chalcones with sodium cyanide (NaCN)

β-Cyanoketones are produced with high yield as a result of conjugate addition reaction of sodium cyanide (NaCN) with the chalcones (8) (Scheme 16).

2.3.7. Addition reaction of chalcones with thiocyanate

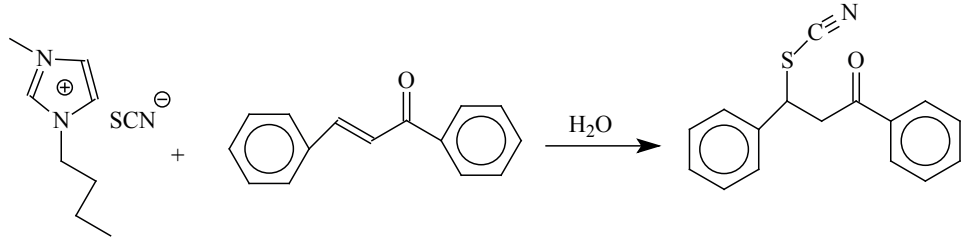
β-Thiocyanoketones are composed by the hydrothiocyanation reaction of chalcones with the 1-N-butyl-3-methylimidazolium thiocyanate ([bmim] SCN) which is one of the ionic liquids (59) (Scheme 17).

2.3.8. Asymmetric conjugate addition of thioglycolate to chalcones

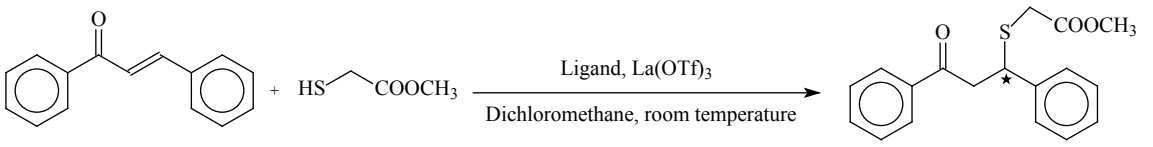
A solution of ligand, La $(OTf)_3$ and chalcone is stirred in anhydrous dichloromethane under microwave irradiation. Then the reaction mixture is cooled to 0°C and the thioglycolate is added (60) (Scheme 18).

2.4. Reduction reactions of chalcones

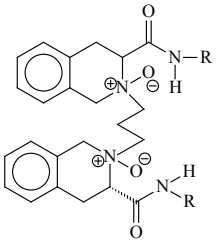
Reduction reactions of chalcones via hydrogenation (Scheme 19) are occurred with rutenium catalysts [(Cp'Ru (PTA) (PR_3) Cl (Cp' = Cp (cyclopentadienyl anion (η^5-$C_5H_5^-$)), Ind (indenyl anion (η^5-$C_9H_7^-$)); PTA



Scheme 17. Addition reaction of chalcones with thiocyanate



Ligand: Ligand: La (OTf) $_3$ = Lantanide triflates

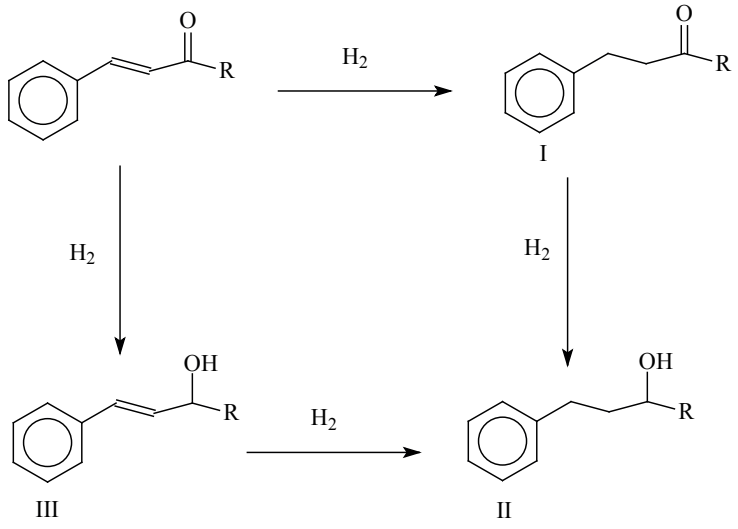


R= 2,6-Diisopropyl phenyl

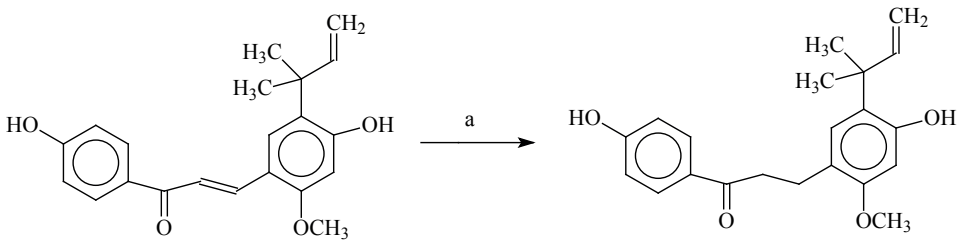
Scheme 18. Asymmetric conjugate addition of chalcones with thioglycolate

(1,3,5-triaza-7-phosphaadamantane); PR_3 = PPh_3 (triphenyl phosphine)] and formic acid, sodium formate or Na_2CO_3/isopropanol serving as the hydrogen source (61). Another catalyst Pd/C (10%) is also used for the hydrogenation of chalcones (62). Because of not only the reduction of ethylenic bond in enone part of the compound but also reduction of carbonyl group or reduction of both group different products are reached with hydrogenation reactions. All of the catalysts cause reduction of ethylenic bond in enonic part of the compound. When CpRu (PTA) (PPh_3) H is used as catalyst, compound I and III are obtained, but when the reaction is made with all the other catalysts without CpRu (PTA) (PPh_3) H in basic conditions, compound I and II are acquired (61) (Scheme 19).

Dihydrochalcones are produced by the reduction of chalcones with trifluoroacetic acid as proton donor and triethylsilane as hydride donor. (Scheme 20). Low polarization of ethylenic group of side chain make this region stable against reactive compound. Using equivalent amounts of chalcone and triethylsilane prevents reduction of carbonyl group. Dihydrochalcone is isolated easily and formed with high yield in reaction medium (8).

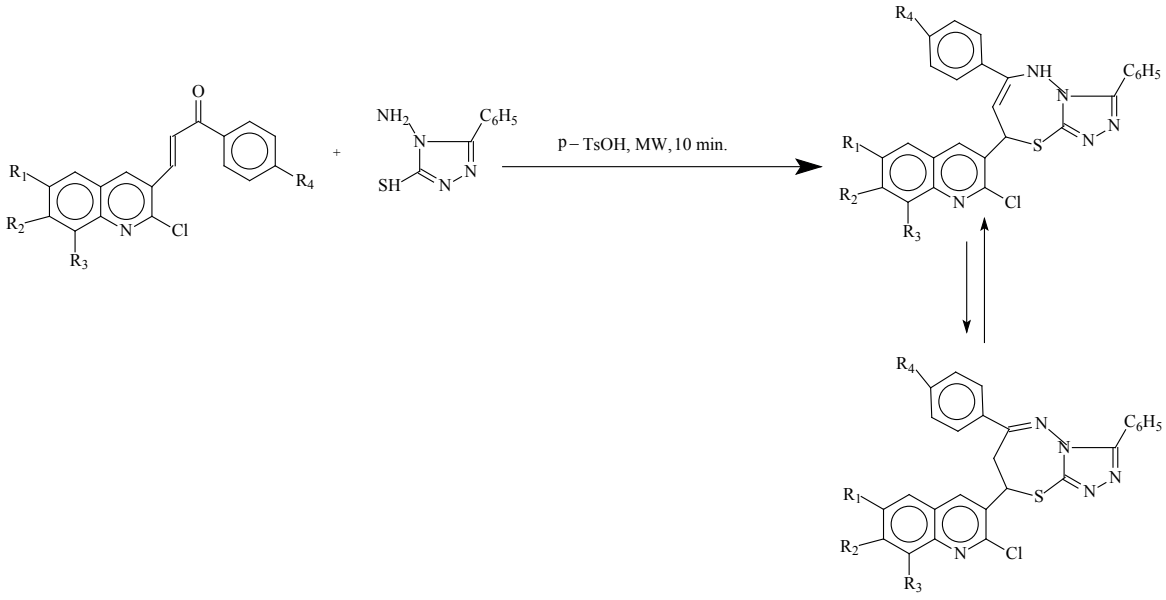


Scheme 19. Reduction reaction products of chalcones



a) CF_3COOH, $(CH_3CH_2)_3SiH$, CH_2Cl_2, 25°C

Scheme 20. Composition of dihydrochalcone derivatives



Scheme 21. Condensation reaction of chalcones

2.5. Condensation reaction of chalcones

[1,2,4] Triazolo [3,4-b] [1,3,4] thiadiazepine derivatives are formed by the condensation reaction of chalcones with 4-amino-5-ethyltriazolo-3-mercaptane in the presence of p-toluensulphonic acid (p-TsOH) at microwave (32) (Scheme 21).

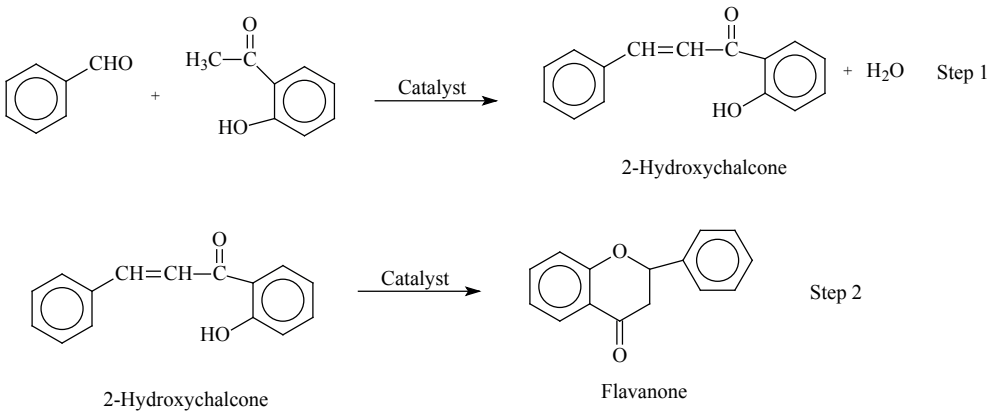
2.6. Cyclisation reaction of chalcones

Flavanones are isomers of chalcones and are usually consisted of the reaction of chalcones with 1-2% acid and basic catalysts and following ring closure to dihydropyran ring (45). 1.5-2.5% NaOH is generally used as basic catalyst. Ethanolic H_2SO_4, dilute HCl (63,64) and ethanolic H_3PO_4 are used as acidic catalysts (65). Additionally, H-ZSM-5 (ZSM = Zeolite Socony Mobil-5) and Mg-ZSM-5, Ba-ZSM-5 can be used as acid catalyst or base catalysts for the cyclisation reaction, respectively. The synthesis of flavanone from benzaldehyde and 2-hydroxy acetophenone with H-ZSM-5, Mg-ZSM-5 and Ba-ZSM-5 at 140°C involves two steps as illustrated in the reaction (66) (Scheme 22).

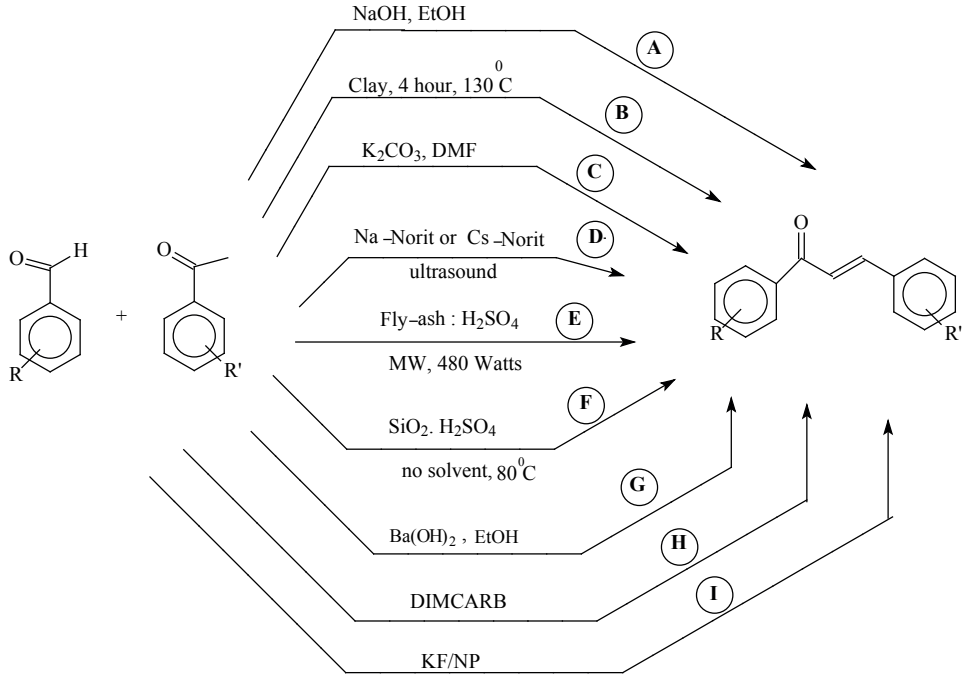
3. SYNTHESIS METHODS OF CHALCONES

3.1. Chalcone synthesis with aromatic aldehydes and acetophenones

Chalcone synthesis are attributed Claisen Schmidt condensation reaction. In this reaction, aromatic aldehydes and ketones are condensed each other in the presence of an acid or basic catalyst. Not only chalcones but also a little quantitiy of flavonones which are the isomers of chalcones are obtained in this reactions (65). Although both of acidic and basic catalysts can be used for this reactions, basic catalysts give higher yield compared to acidic catalysts such as HCl, H_2SO_4 (67,68,69,70). The different catalysts used for chalcone synthesis are shown below (Scheme 23). Using clay minerals as catalysts give best yield (%98).



Scheme 22. Formation of flavanone (66)



Scheme 23. The different catalysts used for chalcone synthesis

METHOD A: Chalcone synthesis with the reaction of aromatic aldehyde and acetophenone in the presence of NaOH in EtOH

Chalcone derivatives can be formed by refluxing of acetophenones and aromatic aldehydes in the presence of NaOH in EtOH (5) (Scheme 23). The same reaction can be made at room temperature (49,71,72) with methanol at room temperature (33,73). During the reaction, KOH can be used instead of NaOH at room temperature (9,74-78), at 0°C (79,80) or at 5-10°C temperature under nitrogen gas or argon gas (81).

In our department we synthesized a number of chalcones using KOH/MeOH at room temperature, which two of them is original, called (*E*)-1-(3,5-dichloro-2-hydroxyphenyl)-3-m-tolylprop-2-en-1-one and (*E*)-1-(4-Bromophenyl)-3-m-tolylprop-2-en-1-one (82).

METHOD B: Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones with clay minerals

Montmorillonite KSF is preferred as clay (83).

Montmorillonite KSF is an acid-activated clay containing relatively high amount of iron. Variation of the initial pH value of the clay suspension changes the clay particle properties such as surface charge, surface area and surface hydroxyl group (84). Although the same experiment can be implemented with basic and neutral clays, best yield is obtained with the Montmorillonite KSF (83) (Scheme 23).

METHOD C: Chalcone Synthesis with the reaction of aldehyde and acetophenone in the presence of potassium carbonate and dimethyl formamide

Chalcones can be synthesized via Claisen Schmidt condensation reaction in the presence of the equivalent mole of acetophenone and aromatic aldehyde with three times mole of K_2CO_3 in DMF at room temperature (10) (Scheme 23).

METHOD D: Chalcone synthesis with the aromatic aldehydes and acetophenones by ultrasound

Norit is an activated carbon and the alkali elements such as sodium (Na) and cesium (Cs) are incorporated in the activated Norit carbon in order to prepare the alkali-Norit samples. Na-norit or Cs-Norit are used as catalysts in chemical reactions because of their extended surface, micropored structure and high surface reactivity (Scheme 23). In this manner this materials are competed with catalysts such as zeolide and clay which are traditionally used in chemical reactions. Yield is increased because of the accelerator effect of ultrasonic irradiation in homogen and heterogen systems. Ultrasonic irradiation potentially activates the chemical systems. Benzaldehyde (5 mmol) and acetophenone (5 mmol) were mixed in the absence of solvent or in 5 ml ethanol in a flask, then norit added and that flask was suspended into the ultrasonic water bath at the reaction temperature (30, 40 and 41°C) (85,86). Amino zeolite can be used as basic catalyst in the same reaction (87).

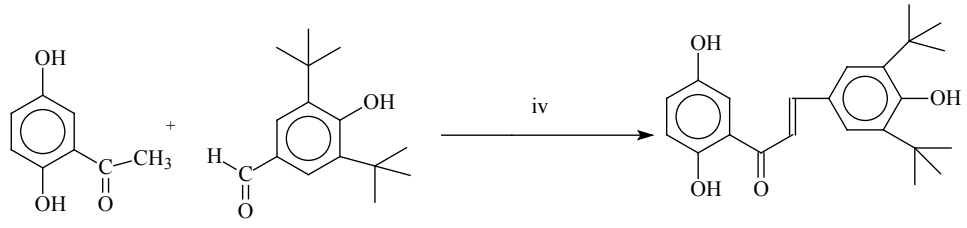
In another method, acetophenone and aryl aldehyde derivatives are solved in acetone in presence of ultrasound irradiation. Then Al_2O_3 is added to the mixture at room temperature (Scheme 24). After one minute, solvent of the mixture is evaporated. Then sonic agitation is carried out to the reaction mixture (28).

METHOD E: Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using Fly-ash:H_2SO4 Reagent

Fly ash is a waste air pollutant, and it has many chemical species such as SiO_2, Fe_2O_3, Al_2O_3, CaO, and MgO, and insoluble residues. The waste fly ash is converted into useful catalyst fly ash: H_2SO_4 by mixing fly ash and sulphuric acid. Sulphuric acid has enhanced catalytic activity (88). A new versatile catalyst Fly-ash:H_2SO_4 is used for chalcone synthesis via Crossed-Aldol condensation in this method. The yield of the reaction is found more than 96% (89) (Scheme 23).

METHOD F: Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using Silica-Sulphuric Acid

Silica sulfuric acid ($SiO_2.H_2SO_4$), a solid acid, is a nonhazardous and versatile catalyst that makes reaction processes more economic, more convenient, and environmentally benign (90). In this reaction aryl aldehyde, aryl ketones and silica-sulfuric acid were heated in an oven at 80°C for 2-3.5h (40) (Scheme 23).



iv: Al_2O_3, 40 °C, 12 hour, % 10.4 yield, ultrasound irradiation

Scheme 24. Synthesis of chalcones with Al_2O_3 via ultrasound

METHOD G: Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using Ba $(OH)_2$

Chalcones are synthesized by refluxing acetophenone with aromatic aldehydes in EtOH in presence of Ba $(OH)_2$. Same reaction can be made in MeOH at 40°C (91), or with barium hydroxide octahydrate at 40°C (28) (Scheme 23).

METHOD H: Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using dimethylammonium dimethylcarbamate

Chalcones are obtained by the reaction of aldehyde with ketones in presence of dimethylammonium dimethylcarbamate (DIMCARB) (Scheme 23) as catalyst (Figure 2).

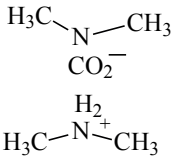


Figure 2. Dimethylamonium dimethyl carbamate (DIMCARB)

DIMCARB is a liquid composed of CO_2 and dimethylamine (Me_2NH), which is stabil until 50°C. It has substantial ionic character and can dissolve salts such as LiCl, NaCl, NaBr, KCl and KI at levels between 2-5% w/v. Although isolation of nonvolatile products from ionic liquid is difficult, this is not valid for DIMCARB because it dissociates to CO_2 and Me_2NH, which can be condensed and reassociated. Thus, since DIMCARB can be recycled during reactions or recovered after using, in many respects it could be considered as a self-associated, "distillable" ionic medium. When DIMCARB is used as the solvent at the temperature up to 50°C, the reaction time varies from 2-32 hours and yields changes between 60-80% (92).

METHOD I: Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using KF/NP as catalyst

Natural phosphate (NP) which belongs to the mineralogical family of phosphocalcic apatite is a naturally occurring material which is brought from the region of Khouribgra in Morocco. NP demonstrates both basic and acidic activity in reactions. The preparation of the KF/NP material involves a simple evaporation of potassium fluoride solution in the presence of NP (93).

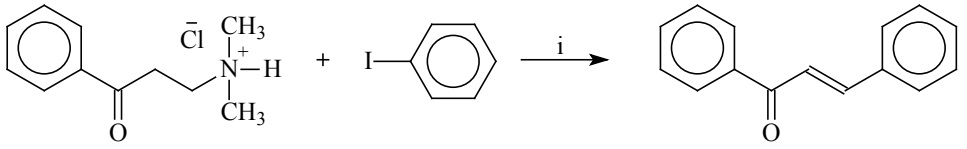
Claisen-Schmidt reaction of 2-hydroxy acetophenones with benzaldehydes occurs because of the strong basic activity of potassium fluoride supported on natural phosphate (KF/NP) (Scheme 23). A lot of synthesis can be made by using the natural minerals such as KF/Al_2O_3, KF/ZnO, $KF/AlPO_4$. High yield (%88 or more) is obtained as a result of the reaction which continues through 1-4 hour at 180°C (93).

3.2. Chalcone synthesis with Mannich bases using palladium as catalyst (Heck Reaction)

Mannich bases and iodoarenes compose chalcones when used with the palladium as catalyst (Heck Reaction) (Scheme 25). Reaction yield changes between 24% and 65% (94).

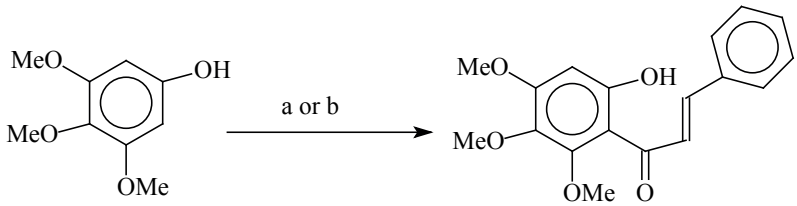
3.3. Chalcone synthesis with trimethoxyphenol

The acylation reaction of trimethoxyphenol is succeeded in the presence of boron trifluoride diethyl ether complex (BF_3-Et_2O) in acetic acid. Then Claisen Schmidt condensation of benzaldehyde is followed



i: 5 mole% Pd $(OAc)_2$, DMF, triethylamine, 140°C, 30 minute.

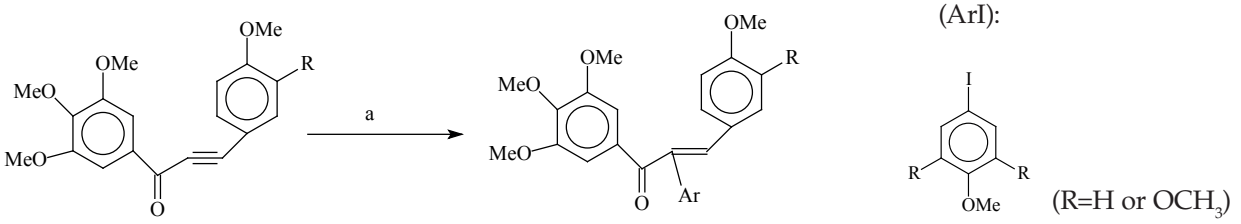
Scheme 25. Chalcone synthesis via Heck reaction



Trimethoxyphenol

(a) acetic acid, BF_3-Et_2O, 15 min.; benzaldehyde, EtOH, KOH, %66 yield (b) cinnamoyl chloride, BF_3-Et_2O,%90 yield

Scheme 26. Chalcone synthesis with trimethoxyphenol



(a): Pd (dba) $_2$, PPh_3, n-Bu_3SnH, THF, Ar-I

Scheme 27. Chalcone synthesis with diarylpropinones

using KOH as catalyst (a) (yield: 66%) (Scheme 26). The same literature reported that the product is alternatively synthesized via direct acylation (b) of trimethoxyphenol with cinnamoyl chloride in the presence of BF_3-Et_2O with a higher yield (90% yield) (48).

3.4. Chalcone synthesis with diarylpropinones

2-Arylchalcones are synthesized by the reaction of diarylpropinones with aryl iodides in the presence of bis (dibenzylideneacetone) palladium ($Pd(dba)_2$), triphenylphosphine (PPh_3), tributyltin hydride (n-Bu_3SnH) (95) (Scheme 27).

3.5. Chalcone synthesis with 4-hydroxy-3-methoxy cinnamaldehyde

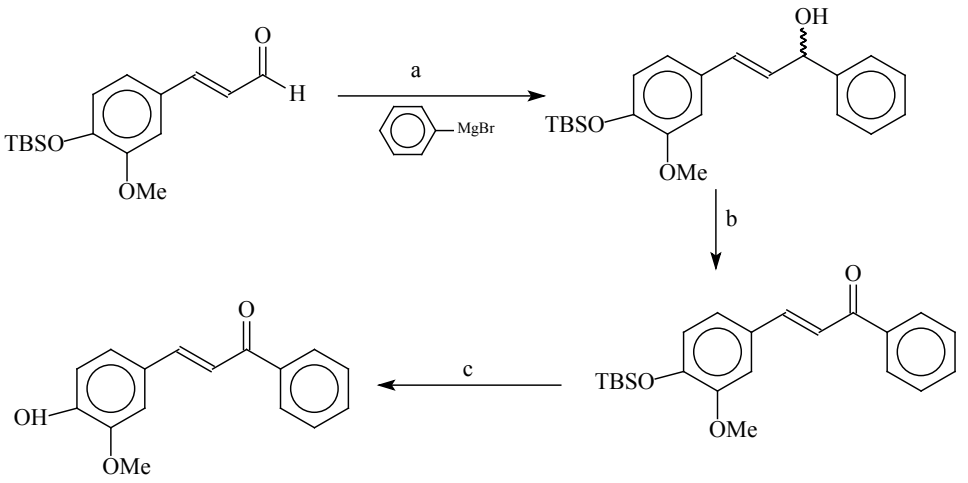
Chalcones are synthesized by the reaction of 4-hydroxy-3-methoxycinnamaldehyde with phenyl magnesium halide via Grignard reaction. Deprotection of aromatic hydroxyl group of 4-hydroxy-3-methoxycinnamaldehyde protected with *tert*-butyldimethylsilyltrifluoromethane sulfonate (TBSOTf) is accomplished with tetrabutyl ammonium fluoride (TBAF) at the end of the reaction (96) (Scheme 28).

3.6. Chalcone synthesis with 2,3-epoxy-l,3-diarylpropan-1-ones

(*Z*)-2-Chloro-1,3-diarylpropen-l-ones are synthesized by treatment of 2,3-epoxy-l,3-diarylpropan-1-ones with Vilsmeier reagent, which is derived from bis (trichloromethyl) carbonate (BTC, triphosgene) and DMF in moderate yields (Scheme 29). The proposed reaction mechanism involves sequential ring-opening, halogenation and elimination reactions (97).

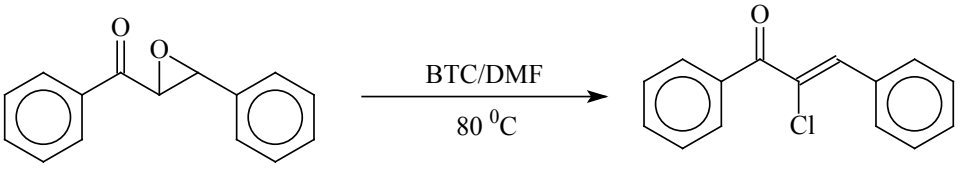
4. Conformational Properties of Chalcones

Chalcones are flexible molecules capable of existing in various conformations and their properties depend on a suitable ring substitution and the presence of α,β-unsaturated ketone moiety (19,98). Chalcones exhibit very interesting stereochemical characteristics such as the existence of the conformational equilibrium illustrated in Scheme 30. The hydrogen atoms of the double $C_\alpha = C_\beta$ bond of chalcones present a *cis* or *trans* configuration, while the C = O bond can present a *s-cis* or *s-trans* conformation with respect to the vinylenic double bond due to free rotation along the single bond between C-carbonylic and C-α (19, 99).



(a) THF, -78°C, 20 minute; then -78°C, 30 minute (yield%82-90);
(b) MnO_2, n-pentane, Δ, 2 hour (%85-92); (c) TBAF, THF, 10 minute, (%86-95 yield)

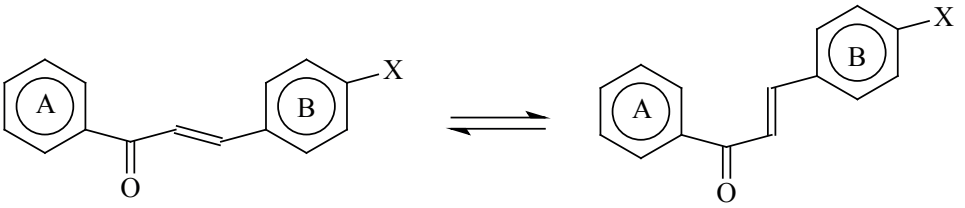
Scheme 28. Chalcone synthesis with 4-hydroxy-3-methoxycinnamaldehyde



Scheme 29. Chalcone synthesis with 2,3-epoxy-l,3-diarylpropan-1-ones

Chalcones exist as either *E*- (*trans*) or *Z*- (*cis*) isomers. The *E*-isomer is the thermodynamically most stable form in most cases, so the *E* isomer is isolated as the majority of the chalcones. Configuration of *Z* isomer is unstable due to the strong steric effects between the carbonyl group and B-ring. So, recrystallisation of an *E–Z* mixture yields *E* isomer as the only stereoisomer (100,101).

S-cis conformation has also been found as the most stable conformer. In contrast, planar and non-planar structures have been reported as the most stable conformers using different computational levels (98). The most stable isomer of chalcone which is experimentally known is *trans*- (*s-cis*) -chalcone. The *s-cis* conformer seems to be fully planar. Whereas steric hindrance between H atoms leads *the s-trans* conformer to be nonplanar. C*is*- (*s-cis*) -chalcone is expected to be non-planar because of steric hindrance between the carbonyl oxygen and a phenyl ring (101,102,103).



4-Substituted chalcone
X = H, OH, N $(CH_3)_2$, F, Cl, OCH_3, NH_2

4- Substituted chalcone *trans-s-trans*

Scheme 30. Conformational equilibrium of *trans* 4- substituted chalcones (99)

A conformational equilibrium between the two conformers is dependent on their structure and the properties of environment, e.g. temperature, solvent (19,102). The relative stabilities of the two conformers' *s-cis* and *s-trans* are considered to be determined by two factors. One of them is steric effect between the substituents present on the ethylenic carbon atoms and carbonyl group and the other is field effects between the C = C and C = O groups (102).

Activity of compounds is affected by steric interactions between chalcones. So, stabilisation of suitable conformations and introduction of suitable substituents could result in a therapeutically useful agent (19,104).

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