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Microwave Assisted Synthesis of Chalcone and Biological Activity

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ABSTRACT

This review explained the microwave assisted synthesis of biologically active Chalcone. Recently the microwave has become the useful nonconventional source for the organic synthesis. Chalcone are widely distributed in nature like fruits, vegetables, tea and spices. Which are polyhydroxylated in the aryl ring due to phenolic group and α, β unsaturated carbonyl group it shows various biological activities, such as antioxidant, antimicrobial, anti-inflammatory, anticancer. Chalcones being natural precursors are obviously important intermediates for the synthesis of flavones. From decades the chalcone had been synthesizing by conventional way of heating which has taking a long time, 24 hrs to complete, So to improve the yield and to minimize the reaction time i.e., Within a second to minutes, this review has given the various microwave assisted methods for the synthesis of chalcone derivatives with diverse structure to have maximum biological activities.

Key words: Chalcone, Claisenschmidth, Microwave, Antiviral, Anticancer, Anti-inflammatory, Antimicrobial.

INTRODUCTION

Microwave radiation shows relatively high wavelength (1 mm to 1 m) and in electromagnetic region it lies between the region of radiofrequency wave and infra-red frequency region. In one half of the century microwave energy had been used for the heating of food material. (Rajendra S. Verma) but now the application of microwave energy has been utilized in organic synthesis [1]. In 1855, Robert Bunsen invented the burner which acts as energy source for heating a reaction vessel and synthesis of organic compound by heating on burner was become a traditional method [2].

Synthesis of organic compound has been accomplished by two ways

Conventional heating

In this energy reaches to reactant molecule from external source through reacting vessel wall and after the heating of reaction vessel thermal energy conventionally reaches to the solvent and reacting molecule. So that it is a very slow and time consuming method.

Microwave or non-conventional heating

This method is not limited by thermal conductivity of the reacting vessel microwaves directly reaches to the reacting mixture and rises the temperature of the system by coupling of microwave to dipole rotation or ionic conductivity of molecule. Only polar molecule can interact with the microwave radiation die to high dipole moment for example, water, ethanol, dichloromethane, chloroform, acetonitrile, DMF, etc. absorb radiation rapidly but nonpolar substances like aromatic and aliphatic hydrocarbon with no dipole moment cannot reacts to microwaves [3] (Table 1).

Table 1: List of common solvents with dielectric constant.

Solvent	Dielectric Constant
Acetic acid	6.20
Acetonitrile	36.64
Chloroform	4.81
Dichloroethane	10.42
Diethylene glycol	31.8
N,N Dimethylformamide	38.25
Ethanol	24.6
Methanol	32.6
Water	78.54
Dimethylsulfoxide	47

The main advantages of microwave assisted organic synthesis are speed up reaction the microwave can use higher temperatures than conventional heating system [4] and consequently the reactions are completed in few minutes instead of hours. Better productivity in which less formation of side product is observed using microwave irradiation, and the product is recovered in higher yield. Consequently, also the purification step is faster and easier. Easy handling availability of high technology and large range of reactor vessels, allows easy handling from few milliliters to one liter without changing reaction parameters. Reproducibility is good due to closed reacting system control the various reaction parameters, such as temperature, pressure and power, always reproduces the same reaction conditions. It is very simple to save and use an optimized synthesis method [5]. Due

to various advantages of nonconventional heating over the conventional heating recently the microwave has become the useful nonconventional source for the organic synthesis [6-9].

Microwave assisted synthesis of chalcone

Chalcone are widely distributed in nature like fruits, vegetables, tea and spices. [9] Naturally occurring chalcones are polyhydroxylated in the aryl ring due to phenolic group and due to presence of α, β unsaturated carbonyl group it shows various biological activities, such as antioxidant, antimicrobial, anti-inflammatory, anticancer, etc. Chalcones being natural precursors are obviously important intermediates for the synthesis of flavones. [8] They are easily prepared by Claisenschmidth reaction of acetophenone with benzaldehyde in ethanol or methanol in basic condition by using sodium or potassium hydroxide (Figure 1). The author Mauricio Cabrera et al. has reported the synthesis of substituted chalcone from 2-hydroxy acetophenone and substituted benzaldehyde in methanol and potassium hydroxide by stirring at room temperature for 24 hours [10]. Chalcones are converted into the corresponding flavones either directly or through flavanones [7].

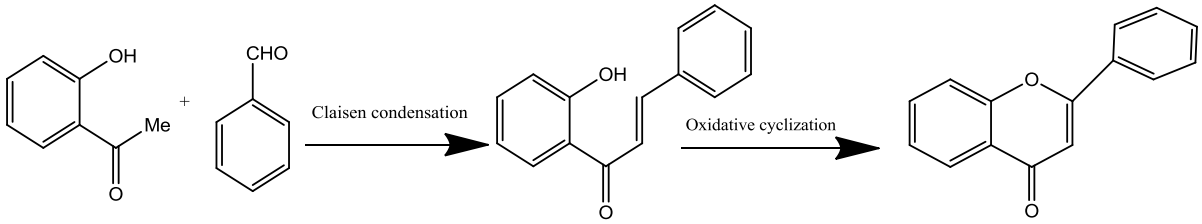
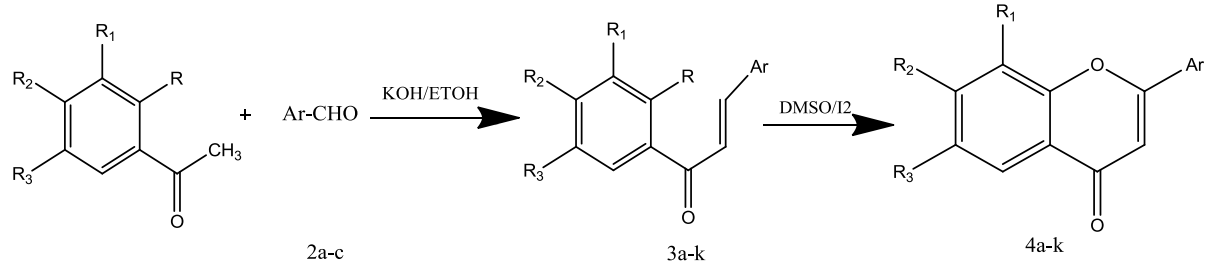


Figure 1: Claisen condensation for the synthesis of flavonoids.

The most conventional and common method for the cyclization is through an oxidative ring closure with iodine and Dimethylsulfoxide which has been reported by Vanita Navale et al. in 2010 in her study has synthesized novel chalcone from 2-hydroxy acetophenone and 2-benzyloxy benzaldehyde, 3-benzyloxy, 4-methoxy benzaldehyde, and 4-benzyloxy, 3-methoxy benzaldehyde (2a-2c) by claisenschmidth condensation and chalcone (3a-3k) was converted to flavones (4a-4k) by oxidative cyclization by using iodine in DMSO (Figure 2) [11,12].

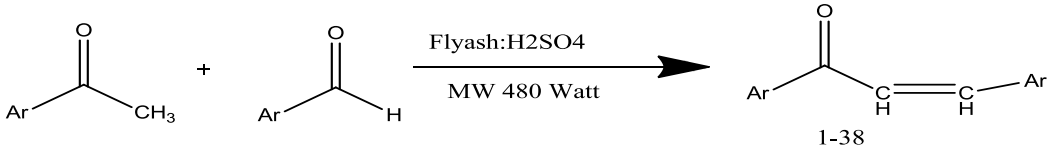


3a, 4a:R-OH, R1,R3-Cl, R2-H,Ar-2a
3b, 4b:R-OH, R1-Br,R2-H,R3-CH3,Ar-2b
3c, 4c:R-OH, R1,R3-Cl, R2-H,Ar-2a
3d, 4d:R-OH, R1,R3-Br, R2-H,Ar-2a
3e, 4e:R-OH, R1,R3-Br, R2-H,Ar-2b
3f, 4f:R-OH, R1,R3-I, R2-H,Ar-2b
3g, 4g:R-OH, R1-I, R3-CH3, R2-H,Ar-2b
3h, 4h:R,R2-OH, R1,R3-Br, Ar-2b
3i, 4i:R-OH, R1-BrR3-Cl, R2-H,Ar-2b
3j, 4j:R,R2-OH, R1,R3-I, Ar-2b
3k, 4k:R-OH,R1,R3-Cl,R2-H, Ar-2c

2a- 2-Benzyloxy Benzaldehyde
2b-3-Benzyloxy, 4-methoxy benzaldehyde
2c- 4-Benzyloxy,3-methoxy benzaldehyde

Figure 2: Synthesis of substituted flavonoids by DMSO/Iodine.

The synthesis of chalcone by conventional heating take longer time to complete so, microwave irradiation procedure for the synthesis of chalcone has been reported recently by researchers to minimize the time and to improve the yield. G. Thirunarayanan et al. in 2012 reported the synthesis of chalcone from aryl methyl ketone and substituted benzaldehyde in green catalyst flyash: H_2SO_4 by microwave irradiation at 160-800 watt, total 38 compounds were synthesized in which compound 30 had more yield (Figure 3) [12] Same chalcone were synthesized by microwave irradiation in 40% sodium hydroxide at 160-320 watt and time required was 60-120 sec [13].



30-Ar-5-Br-C_4H_2-3(2Thienyl)
Ar'-C_6H_5
Yield-96% at 292 watt

Figure 3: Synthesis of chalcone by microwave Irradiation with Flyash: H_2SO_4.

Azachalcone is derivative of chalcone with an annular nitrogen atom in phenyl ring the author Asu Usta et al. has reported the microwave assisted synthesis of azachalcone in microwave by claisenschmidth condensation and further N-alkyl derivatives of azachalcone has been synthesized by corresponding alkyl halide (Figure 4) [14].

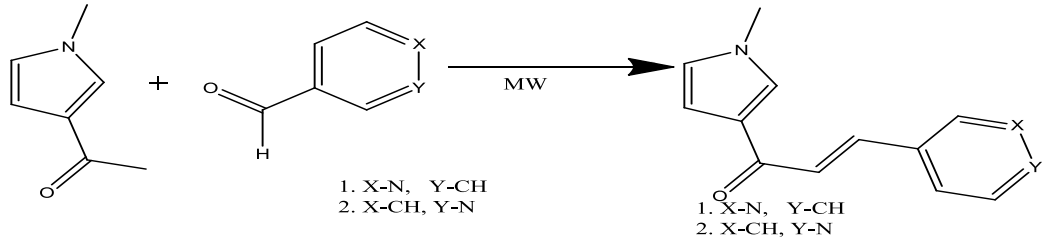


Figure 4: Synthesis of azachalcone by microwave irradiation.

Microwave assisted synthesis of cyno (bis) indolyl chalcone [15] from 3-cynoacetylindole and indole-3-carboxyaldehyde at 100 watt at 80^0c for 5 min. by in presence of ethylene glycol and piperidine. A novel methodology for facile production of α-cyano chalcones (Figure 5) under microwave irradiation is described by Shyam J. Deshpande. They utilized a Knoevenagel condensation between benzoylacetonitriles and aromatic aldehyde, in presence of bases and solvent to get substituted chalcones, duration of reaction was varied from 1-15-min via one-pot synthesis; reaction was reduced in presence of piperidine as a base and 2-pentanol as a solvent [16].

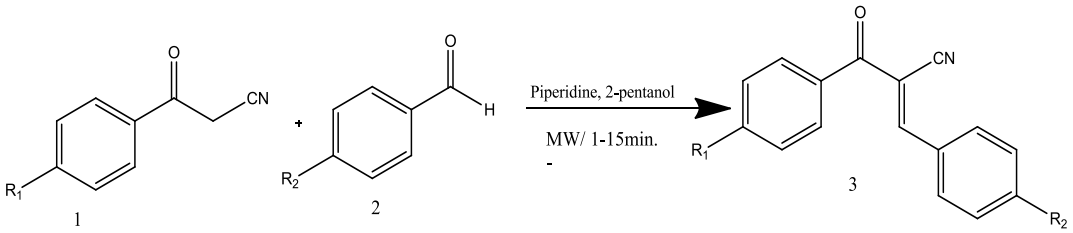


Figure 5: Synthesis of cynochalcone.

Novel chalcone was prepared from 2-acetyl hetero cyclic derivatives and respective aldehyde in aqueous potassium hydroxide solution by microwave irradiation for about 2–6 min at 180 watts (Figure 6) author also synthesized this chalcone conventionally at room temperature reaction was completed in 24 hours [17].

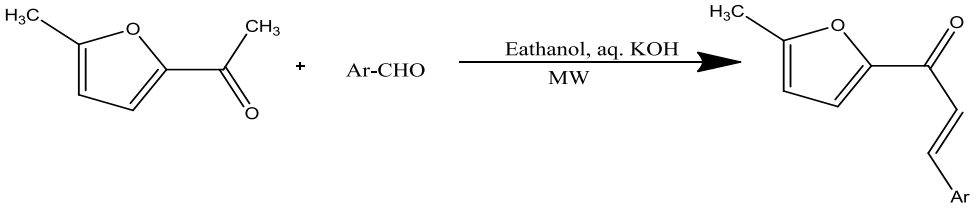


Figure 6: Chalcone with heterocyclic ring.

Dwipen Kakati et al., has synthesized steroidal chalcone from pregnenolone acetate, benzaldehyde and I2-Al_2O_3 by microwave irradiation at 250 W power (Figure 7) [18].

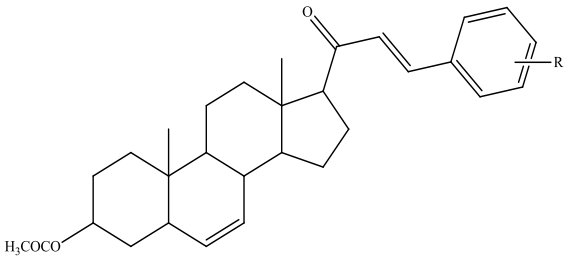


Figure 7: Steroidal chalcone.

Lucas Vieira et al. have reported the Suzuki coupling reaction of chalcone with phenylboronic acid using PEG400 as a solvent under microwave irradiation. [19]. Khan et al. in 2014 has reported the novel chalcone from 3-acetyl-2, 5-dimethylthiophene and the corresponding active aldehyde in dry ethanol with a catalytic quantity of sodium hydroxide by heating inside a microwave oven for 30–50 s. (at 210 W, i.e., 30% microwave power) and yield of chalcone was 80% to 90%. (Figure 8) [20,21].

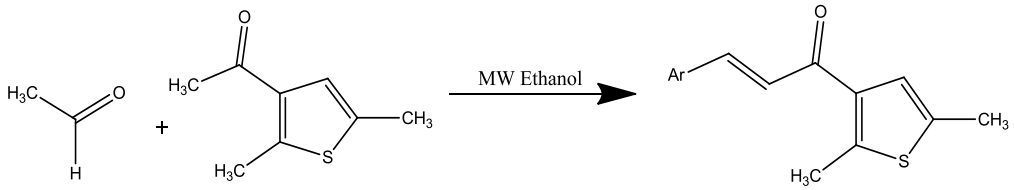


Figure 8: Synthesis of chalcone from 2-acetyldimethylthiophene.

In Green chemistry as like microwave radiation the concentrated solar radiation (CSR) is better as a non-conventional technique for the organic synthesis. Solar energy is available free of cost and it is a renewable source of energy. Solar energy is the unique clean, nontoxic and easily available source. The solar radiations emit a large number of ultraviolet as well as infrared radiations between the range of 280–4000 nm which serves both photochemical and thermal energy respectively. In this regards, solar energy is an able tool for the reaction and offers some advantageous. The usage of solar energy to execute the organic reactions has been reported by Jadhav et al. the green solar assisted synthesis of chalcone (3-(4-fluorophenyl)-1-(4-m ethoxyphenyl)-prop-2-en-1-one) [22-24] Janaki et al. in 2016 reported synthesis of benzimidazole chalcone by fly-ash: H_2SO_4 catalysed aldol condensation from 2-benzimidazole methyl ketone and various substituted benzaldehydes in microwave oven. The yields of these chalcones were more than 70% [25] (Figure 9).

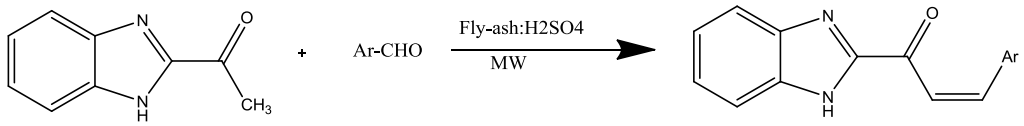


Figure 9: Synthesis of benzimidazole chalcone.

Heterocyclic Chalcones has been synthesized by base catalysed Claisen Schmidt condensation via microwave assisted organic synthesis (MAOS) [26] Researchers reported microwave methods for the synthesis of 1- [2-(2-chloro-6-methyl (3-quinolyl))-5-(4-nitrophenyl)(1,3,4-oxadiazolin-3-yl)]-3-(aryl)-prop-2-en-1-ones. 1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)-3-(aryl) prop-2- en-1-ones were synthesised by microwave assisted method as well as conventional method. When the reaction durations were compared among microwave assisted synthesis (4–6 min) and the conventional method (12 h) again to prove the reduced reaction time and increase yield by microwave irradiation has reported the synthesis of Chalcones, cyclohexenone and indazoles by using self-designed microwave method and already reported non-microwave method [26] through study authors has found that reaction time for microwave irradiation was 6-8 minutes, (Cyclohexanone) and 3 minutes (Indazole) and yield was 60-95% (Figure 10).

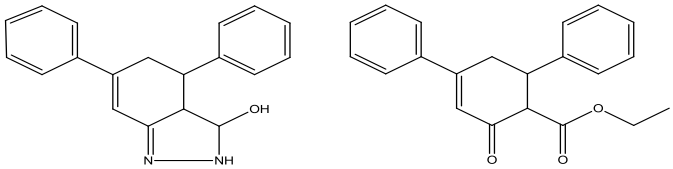
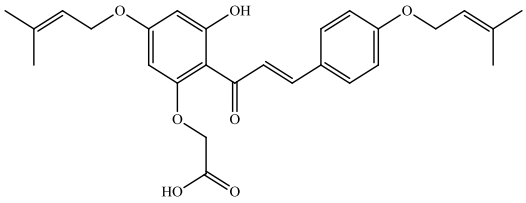
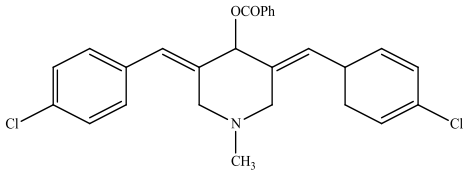
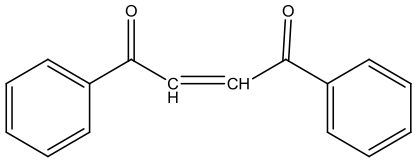


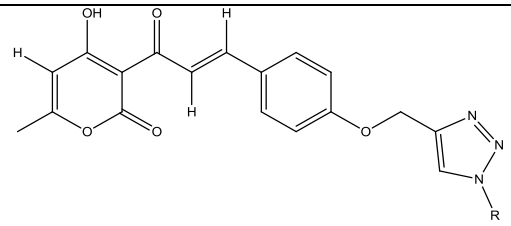
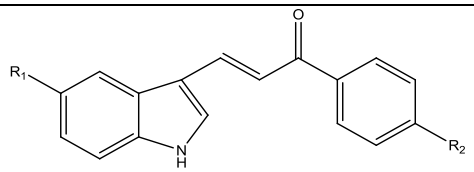
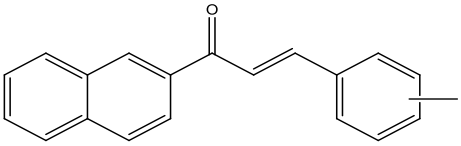
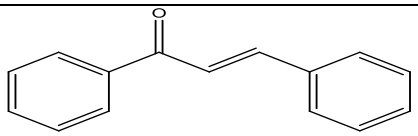
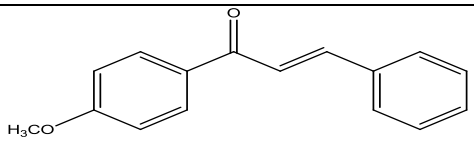
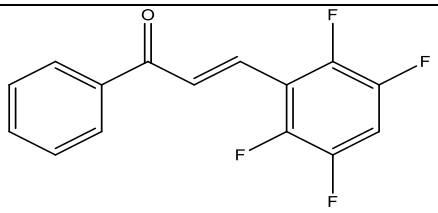
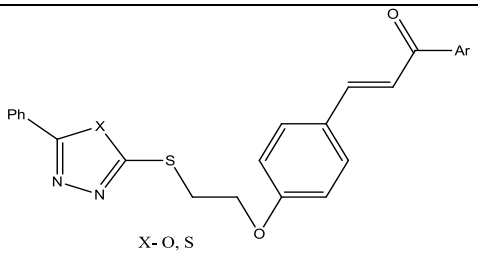
Figure 10: Cyclohexanone and indazole derivatives of chalcone.

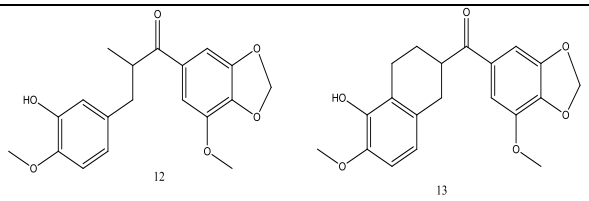
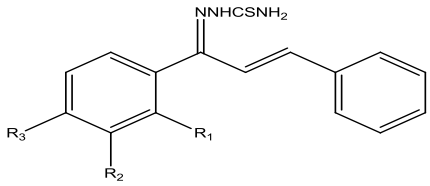
Biologically active chalcones

Chalcones are abundantly present in nature from ferns to higher plants. They are aromatic compounds with an unsaturated side chain and are often cytotoxic *in vitro* [27-29]. Chalcones are structural analogues of benzalacetophenone (BAP). Several derivatives have been identified in plants and anticarcinogenic and anti-inflammatory properties were attributed to the compounds - analgesic and antipyretic [30]. Some chalcones possess bactericidal, antifungal and insecticidal activity and some of their derivatives are reported to be antimutagenic [30]. Table 2 indicates the various biological activities of chalcones.

Table 2: Chalcone derivatives with various biological activities.

Structure of Chalcone	Name and Author	Activity
	Di-O-Prenylated Chalcone by Kyogoku et al. [31,32].	Antiulcer
	Benzoic acid 3,5-bis-(4-chloro-benzylidene)-1- methyl-piperidin-4-yl esterby Aneta Modzelewska, et al. [33].	Inhibit Breast Cancer cell line
	Synthetic chalcone by Ruby John Anto, [34].	Antioxidant and Anticancer

	Dehydroacetic acid-chalcone-1,2,3-triazole Kashmiri Lal, et al. [35].	Antimicrobial
	New indole-based chalcones Ahmet Ozdemir et al. [36].	COX1 and COX2 Inhibitor (Anti-inflammatory)
	2-Acetyl naphthalene Chalcone, Varun Arora et al. [37].	Antifungal, Antimicrobial
	Novel Chalcone, Sandip Sen et al. [38], Nasir Tajuddeena, et al. [39].	Antioxidant, Antimicrobial Antileishmanial activity
	Methoxy substituted chalcone Bijo Mathew, et al. [40]	Monoamine oxidase inhibitors
	1-(phenyl)-3-(2,3,5,6-tetrafluorophenyl)-prop-2-en-1-one, Otavio Augusto Chaves, et al. [41]	Tyrosinase stimulant activity
	1, 3, 4, oxadiazole/thiadiazole Chalcone conjugates. Xiuhai Gan, et al. [42]	Antiviral

 12 13	α-methyl chalcone [12] complexed with tubulin to form 1, 2, 3, 4-tetrahydronaphthalen-2-yl aryl ketones (13) as a conformational mimetics [43]	Anti-proliferative activity against tumor and endothelial cells
	Thiosemicarbazide derivative of chalcone et al. Jinbing Liu [44].	Tyrosinase Inhibitors

CONCLUSION

This review has explained about the biological activity of chalcone and the advantages of nonconventional method of heating over the conventional heating for the synthesis of modified chalcone through derivatization via microwave assisted synthesis with better yield to develop a biologically active molecule.

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