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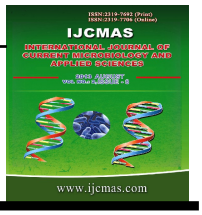


## Original Research Article

# Green synthesis of Flavanone by Using Ionic Liquid EAN (Ethyl Ammonium Nitrate)

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**A B S T R A C T**

A high yielding and efficient method for smooth conversion of substituted α-β-unsaturated carbonyl compounds (*E*) chalcones to corresponding substituted 2-phenylchroman-4-one i.e. flavones promoted by ionic liquid catalyst, ethyl ammonium nitrate $[EtNH_3]NO_3$ under microwave irradiation in excellent yield with shorter reaction time . The ionic liquid can be recycled and reused several times. Flavanone was synthesized and tested for antibacterial effects against *Bacillus Subtilis, Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The antibacterial screening of the synthesized compounds were performed in vitro by the filter paper disc diffusion method.

**Keywords**

Dehydrate cyclization; α-β-unsaturated antibacterial activity; Flavanone.

## Introduction

Flavanones are a group of common and naturally occurring polyphenolic compounds that are widely found in the plant kingdom (Geissman *et al.*, 1969). They occur naturally as plant pigments in a broad range of fruits and vegetables as well as beverages such as tea, red wine, coffee (Murray *et al*., 1996). Flavanone have been reported to exert multiple biological effects including antimicrobial (Proestos *et al.*, 2005), cytotoxicity (Yenjai, 2004),anti-inflammatory (Furuta *et al.*, 2004) as well as anti-tumor activities(Xia *et al.*,2000). In this regard, several flavanones bearing hydroxyl groups on the A or B ring have been reported to be potential antioxidant agents. It is now well established that such potency is mainly due to the ability of hydroxyl groups to donate hydrogen which enable the flavanone to undergo a redox reaction that helps them to scavenge free radicals(Hertog *et al.*,1993). In addition, the presence of hydroxyl groups in the skeleton also contribute to high affinity for proteins and therefore acts as inhibitors of microbial enzymes(Prusky *et al.*,1993) and inhibition of NADH dehydrogenase of mitochondrial inner membranes(Ravanel *et al.*,1989). Prenylated flavanones are a unique class of naturally occurring flavanone characterized by the presence of a prenylated side chain in the flavonoid skeleton. It was reported that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonones (Laks *et al.*,1989). Substitution of the flavanoid ring system with prenyl groups would increase their lipophilicity and consequently enhance their interaction

with cellular membranes (Baron *et al.,* 1989). Different methods are used for the synthesis of flavones, includes Allan-Robinson synthesis (Banerji *et al.,* 1980), synthesis from chalcones (Hoshino *et al.,*1986) and via intramolecular witting reaction (LeFloch'h *et al.,*1986). The most common method used involves Baker-Venkatramn arrangement. In this method 2- hydroxy acetophenone are converted to benzoyl ester, which in presence of base (pyridine/KOH) form 1,3 diketones. The diketones are further cyclized under strong acidic condition to afford the flavones (Balogh *et al.,* 1993, Chisen *et al.,* 1997) .

In recent development of such dehydrative cyclization it includes the use of Amberlyst15 (Hoshino *et al.,*1987), $Co^{III}$(sulpr)OH (Nishinaga *et al.,*1982), $FeCl_3$ (Zubaidha *et al.,*2005), $Br_2/CHCl_3$ (Garg *et al.,*1994), EtOH/HCl (Jung *et al.,*2001) ,clay (Verma *et al.,*1998), NaOAc/AcOH (Kumar *et al.,*1999) and $H_2SO_4$ under microwave irradiation(Tsukayama *et al.,* 2003) . Prenylated flavanone is a unique class of naturally occurring flavonoids characterized by the presence of a Prenylated side chain in the flavonoid skeleton. It was reported that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonoids(Baron *et al.,*1989) Substitution of the flavonoid ring system with prenyl groups would increase their lipophilicity and consequently enhance their interaction with cellularmembranes4′,5,7-Trihydroxy-3′-prenylflavanone (1) has been isolated for the first time in 1989 from the chloroform extract of the stem bark of Erythrina eriotriocha(Nkengfack *et al.,*1989) .The chemical and pharmaceutical industries are always under the pressure to find out environmental friendly organic reaction methodologies. Microwave irradiation is used for a variety of organic reactions due to their use in a rapid and cleaner synthesis of organic compounds (Varma *et al.,*1993 and Marrero-Terrero *et al.,*1996 and Benalloum *et al.,*1998 and Lerestif *et al.,*1997).

Ionic liquids are possible green catalyst acts as alternatives for several catalytic reactions. Ionic liquids attracted attention of researchers due to their mild reaction conditions, short reaction times and better yield, solvating ability and easy recylibility(Welton*et al.,*1999 and Wassercheid *et al.,* 2000 and Sheldon *et al.,*2001 and Zhao *et al.,*2002) .Various reactions have been reported recently using ionic liquids as an catalyst, reaction media(Rajgopal *et al.,*2003 and Jarikote*et al.,*2003 and Gholap *et al.,*2004 and Panchgalle,2004) and as rate enhancers (Madje*et al.,*2004). (Sarda *et al.,*2006) synthesized a high yielding and fast method for smooth conversion of substituted 1-(2-hydroxy phenyl)-3-phenyl-1,3-propane diones to corresponding chromen-4-one under microwave irradiations using ionic liquid$[EtNH_3]NO_3$ is firstly reported.

## Experimental

The α-β-unsaturated carbonyl compounds 1 (1 mmol ) was added in ionic liquid EAN ( 2 mmol ) and irradiate into a domestic microwave oven at $250^0$C for 20-25 sec. The reaction was monitored on TLC. After completion on the reaction, the mixture was extracted 5 X 20 ml. of ethyl acetate: petroleum ether (50%+50%). Compound comes in organic layer, was again treated with water, brine & dried over MgSO4. Organic solvent is evaporated to afford pure flavanones 2. Further, Ionic liquid was dried under

reduced pressure and reused for another reaction gives same yield.

The recovery percentage of ionic liquid is satisfactory. The obtained products 2a-p were identified by comparison with authentic samples $^{1}$H NMR and their melting points.

## Results and Discussion

From the observations of the literature it is noted that the yield is low to moderate in the conventional methods some time due to catalyst or due to solvent therefore we choose a novel methodology in which we used IL as catalyst as well as solvent so it will become green synthesis.(Scheme-1). We used EAN ethyl ammonium nitrate.

Herein we wish to report for the first time a novel synthesis of flavanones 2 promoted by ionic liquid catalyst, ethyl ammonium nitrate $[EtNH_3]NO_3$ under microwave irradiation in excellent yield with shorter reaction time (Scheme 1). The ionic liquid can be recycled and reused several times. The ionic liquid $[EtNH_3]NO_3$ was prepared as per literature method.

The effect of microwave heating was studied considering different solid supports and catalyst. After some experimentation the best procedure for the irradiation is described as follows. The reaction mixtures were heated successively for 10 sec periods followed by a 5 sec cooling interval between irradiations. The method was designed to avoid over heating of reactants. Since the unmodified house hold microwave oven lacks the special attributes of commercial reactors in terms of power and temperature control. In addition, because a slandered house hold microwave oven was used, a experiment to test the homogeneity of the irradiating field was conducted. In a typical reaction, the 2'-hydroxychalcone (1) in ionic liquid $[EtNH_3]NO_3$ was irradiated under domestic microwave oven in a specified time. The progress of the reaction was monitor by TLC. After completion of reaction, aqueous work up afforded pure flavanones **(2)** in 85% yield. To evaluate the synthetic utility of the process, various substituted chalcones were prepared by the previous (scheme1) and subjected to the reaction under microwave irradiation. The results are shown in Table-1.

### Antimicrobial activity

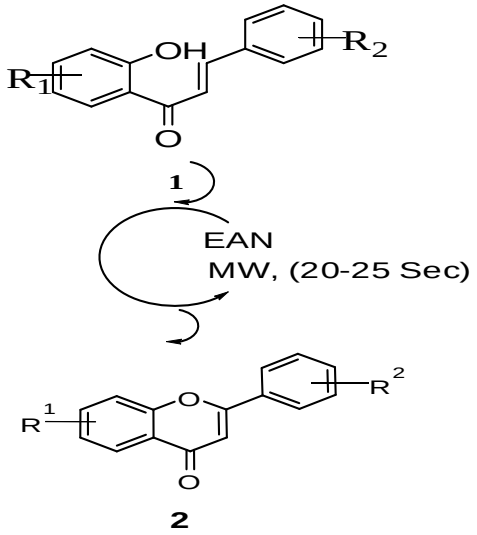
The antibacterial activities of the synthesized compounds (d) and (f) were studied against four bacteria, viz. *Bacillus subtilis* (G+), *Escherichia coli* (G–), *Staphylococcus aureus* (G+) and *Pseudomonas aeruginosa* (G–). For the detection of antibacterial activities, the filter paper discs diffusion method was used (Tsukayama *et al.*, 2003). Streptomycin sulphate was used as positive control. Nutrient agar (NA) was used as basal medium for test bacteria. The discs were prepared by impregnating them in methanol solution of each sample (1 mg/1 mL). Each culture was prepared to a turbidity equivalent to McFarland and spread on the test tube. The paper disc containing the compound were placed on the agar surface previously inoculated with suspension of each microbes to be tested.

All determinations were made in duplicate. Inhibition diameters were determined after incubation at 37°C ± 1 for 24 h. The antimicrobial activity was indicated by the presence of the clear inhibition zones around each disc.

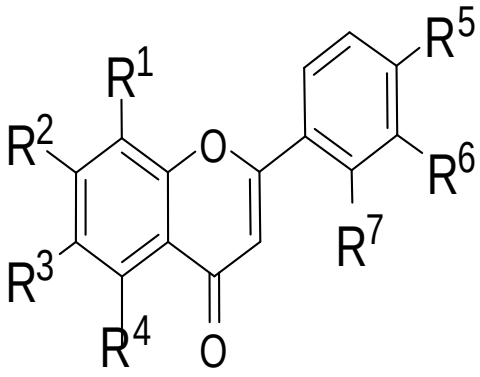
**Scheme.1** Synthesis of flavanone using EAN ionic liquid


1 2

**Scheme.2** Plausible mechanism for the synthesis of flavanone




2




**2**

**Table.1** Synthesis of Flavanone 2 by using EAN ionic liquid in microwave oven

| Pdt | R1 | R2 | R3 | R4 | R5 | R6 | R7 | T sec | [a]Y% |
|---|---|---|---|---|---|---|---|---|---|
| 2a | H | H | H | H | H | H | H | 10 | 89 |
| 2b | H | H | H | H | Cl | H | H | 12 | 90 |
| 2c | H | H | H | H | OMe | H | H | 14 | 87 |
| 2d | H | H | Me | H | OMe | H | H | 16 | 86 |
| 2e | H | H | H | H | OMe | OMe | H | 12 | 92 |
| 2f | H | OH | H | H | H | H | H | 15 | 93 |
| 2g | H | H | H | H | H | H | cl | 17 | 95 |
| 2h | H | H | H | H | H | OMe | H | 13 | 89 |
| 2i | H | H | H | H | Br | H | H | 10 | 93 |
| 2j | H | H | H | H | H | H | No2 | 12 | 90 |
| 2k | H | H | H | H | H | H | OMe | 11 | 90 |
| 2l | H | H | H | H | H | H | Br | 13 | 89 |
| 2m | H | H | H | H | $OC_6H_{13}$ | H | H | 14 | 91 |
| 2n | H | H | H | H | $OC_9H_{17}$ | H | H | 17 | 92 |
| 2o | H | OMe | H | Me | Br | H | H | 18 | 90 |
| 2p | H | $OC_4H_9$ | H | H | $OC_4H_9$ | H | H | 20 | 89 |

[a] isolated yield

**Table.2** Antibacterial screening for the compounds (b) and (g)

| Organism | chalcones | flavanone | Streptomycin sulphate |
|---|---|---|---|
| *Bacillus subtilis* | – | – | 22·0 ± 0·3 |
| *Staphylococcus aureus* | – | – | 22·5 ± 0·7 |
| *Escherichia coli* | – | 12·5±0·3 | 22·0 ± 0·0 |
| *Pseudomonas aeruginosa* | – | - | 22·0 ± 0·0 |

Diameter of the zone of inhibition (mm)

**Minimum inhibition concentration**

The determination of the minimum inhibitory concentration (MIC), the serial dilution technique were followed using nutrient broth medium. The MIC was defined as the lowest concentration of samples that had restricted the growth of microbial . The MIC value of compound (c) were determined against *Escherichia coli* (G–).

In summary we have demonstrated an efficient and mild protocol for the synthesis of flavanones by cyclization of chalcones using EAN under microwave irradiation and dehydrative cyclization of 1,3-(diaryl) diketones to flavanones in presence of ionic liquids . Shorter reaction time, simple reaction conditions and higher yield render this microwave irradiation method superior. The method is clean and simple, which can be used as an alternative to the existing methods.

**Antimicrobial screening**

The antibacterial activity of compounds (d) and (f) has been assayed at the concentration 1000 μg/mL against four human pathogenic bacteria. Among them two were gram-positive and the other two were gram negative. The inhibitory effect of compounds (d) and (f) against these organisms are given in table 2.The screening results indicate that only compound (f) was active against a gram-negative bacteria, Escherichia coli with a mean zone of inhibition 12·5 ± 0·3 mm (table 3).

**Determination of the minimum inhibitory concentration (MIC)**

The active sample in the disc diffusion method was then tested for its activity by the serial dilution method to determine the minimum inhibition concentration (MIC-value). The MIC value obtained for flavanone (f) was 1000 μg/mL against *Escherichia coli*.

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