

## Ferric sulphate solid acid catalyst for cyclization of 2'-hydroxychalcone to flavanone under microwave condition

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**Abstract:** Ferric sulphate was found to be an efficient solid Lewis acid for conversion of 2'-hydroxychalcone to flavanone under microwave condition. Using this condition we prepared various substituted flavanone with electron donating and electron withdrawing groups present at 2', 3', and 4' positions on the benzene ring. This method has various merits compared to other reported methods, including short reaction time, high yield; avoid use of hazardous organic solvent, and inexpensive and easily available catalyst.

**Keywords:** Ferric sulphate, Flavanone, 2'-Hydroxychalcone, Microwave irradiation, Solvent free.

### Introduction

Flavonoids are naturally occurring oxygen containing heterocyclic compounds and they are classified into flavanone, flavones, isoflavones, flavonols, anthocyanin. Flavanone is a key intermediate for synthesis of flavones or isoflavones and flavonols [1]. Naturally occurring flavanones are found in glycosylated or aglycon form and pyrano and furano form. Natural and synthetic flavanone shows various biological activities like antitumoral [2], anti-tyrosinase [3], anti-sindbis [4], anti-inflammatory [5], antileishmanial and antitrypanosomal [6], antioxidant properties [7], antimalarial [8], anti-atherosclerosis [9], Vasorelaxant agents [10] and oviposition stimulants [11]. Due to these wide ranges of biological activity of flavanones, they attract many researchers for their synthesis. Flavanones are generally synthesized by the treatment of 2'-hydroxy chalcones with acidic or basic reagent or oxidative cyclization of it. Cyclization of 2'-hydroxychalcone to flavanone is reported using methane sulphonic acid [12], amino acid [13], Celite supported potassium fluoride in Methanol [14], trifluoroacetic acid [15], sulfuric acid in methanol [16],

polyphosphoric acid [17], Amberlyst A-21 [18], Basic reagent using triethyl amine under reflux condition [19], NaOH [20], KOH in methanol [21], and Potassium carbonate in acetone under reflux condition [22]. This cyclization is also brought out using an oxidizing agent like Co (salpr) in methanol under oxygen [23], Potassium ferricyanide using phase transfer catalyst [24] and photochemical irradiation [25]. However, these reported methods suffer from disadvantages like low yield; require longer reaction time, high temperature, expensive catalyst, strongly acidic or basic conditions. Hence there is scope to develop a new method which should have advantageous such as eco-friendly, use of inexpensive and easily available catalyst, high yield and short reaction time.

In the last twenty years, microwave radiation has attracted many organic chemists to use its application in organic synthesis due to the rapid transformation of reactant into product, reaction time reduced from hours into minutes or seconds, generally high yield compared to conventional heating, solvent free reaction, use of unconventional heating and ecofriendly method. Recently Microwave radiation is used in the synthesis of 2,4-disubstituted quinolines [26], homopropargylic

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alcohols [27], N-methylamides [28],  $\alpha$ -amino Ketones [29], and synthesis of 1,3-diphenylpropenones [30]. From literature, use of microwave radiation in the synthesis of flavonoids is very limited; it is used in the synthesis of flavones by a dehydrative cyclization of o-hydroxydibenzoyl methanes using  $\text{CuCl}_2$  as a catalyst [31], synthesis of flavanones with TFA over silica gel [32], synthesis of functionalized flavones brought out by microwave irradiation condensation between phloroglucinol and  $\beta$ -keto esters [33].

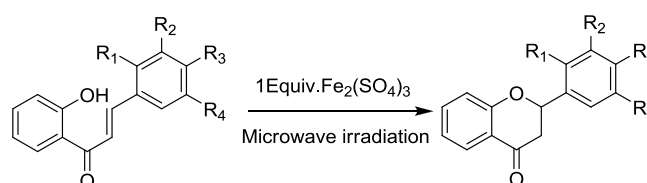
Ferric sulphate is inexpensive, non-toxic to the environment and easily available. Ferric Sulphate is used as efficient Lewis acid in Knoevenagel condensation [34], the Ferrier reaction of per-O-acetylated/benzylated glycals with alcohols to give 2,3-unsaturated  $\alpha$ -glycosides in a few minutes under microwave irradiation [35], an efficient heterogeneous catalyst for the tetrahydropyranylation of alcohols and phenols at ambient or near ambient temperature [36] and in synthesis of imines [37]. Here we report an efficient, practical environmentally benign and high yielding method for the synthesis of flavanones using Ferric sulphate as a catalyst under microwave irradiation.

## Results and discussion

First, we studied solvent free cyclization of 2'-hydroxychalcone to flavanone using ferric sulphate under microwave radiation. 2'-Hydroxychalcone (1a) was adsorbed over ferric sulphate with the help of ethanol, after evaporation of ethanol we got free flowing powder. The resulting powder was exposed to microwave irradiation at 400W at power level 4 and progress of the reaction was monitored by TLC using (1:9) ethyl acetate and pet ether for an interval of 2 min. and after 10 min. We observed that reaction proceed in the forward direction and formation of a new product that is flavanone (2a). After completion of the reaction, the product was separated from the catalyst by dissolving it in 10ml of ethyl acetate and filter it. The product was present in filtrate that is an ethyl acetate layer, after evaporation of ethyl acetate layer we got crude flavanone and purified by recrystallization from ethanol afforded pure flavanone. The structure of the product was confirmed by spectroscopic method and spectral data match with flavanone (2a). Next we have decided to optimize reaction condition; we vary the amount of ferric sulphate 5, 10, 20 mol% and 1:1 catalyst. It was found that 1:1 catalyst showed a maximum yield in short time interval. There was no reaction when cyclization was carried out without ferric sulphate which indicates that

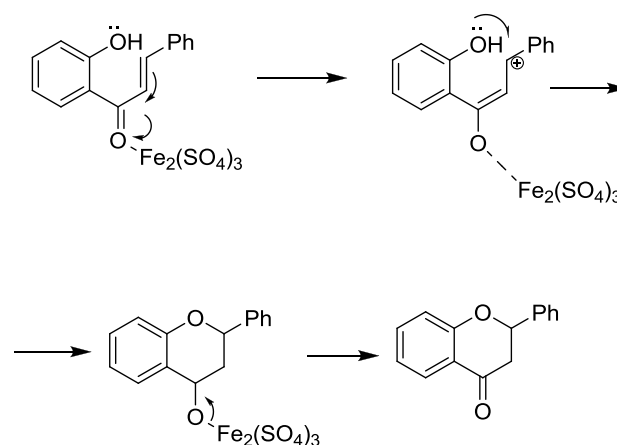
a catalyst is necessary for the cyclization reaction even under microwave conditions.

Next we explored the scope of reaction using various substituted 2'-hydroxychalcone by varying the substituted B ring of benzene from electron donating groups to withdrawing groups. The results are presented in Table 1. From table 1, it is clear that, the cyclization of chalcones proceeds healthy to give flavanones in good yield. As usual electron donating groups present on ring B, cyclization proceeds very smoothly to afford flavanones in good yield while electron withdrawing groups and steric effects generate cyclization slow leading to moderate yield of flavanone (Scheme 1).



**Scheme 1:** Ferric Sulfate Catalyzed Cyclization of 2'-Hydroxychalcone to Flavanone under microwave irradiation

The possible mechanism of this transformation is shown in following scheme 2.



**Scheme 2:** Mechanism of Ferric Sulfate Catalyzed Cyclization of 2'-Hydroxychalcone to Flavanone under microwave irradiation.

## Conclusion

In conclusion, here in we report an inexpensive, eco-friendly synthesis of flavanones using ferric sulphate as a catalyst. This method has merits over other reported methods like inexpensive and easily available catalyst, high yield and short reaction time, and avoid use of toxic solvent.

## Experimental

**General:**

All reagents, chemicals and solvents were purchased from Loba, Merck and Sigma Aldrich. Microwave reactions were carried out using synthesized catalyst, India. TLC (pre-coated silica gel 60 F254, Merck) was used to monitor the progress of the reaction. Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded as KBr pellets

using shiznude FTIR. The  $^1\text{H}$  NMR spectra were obtained on a Bruker DRX-300 Avance instrument using  $\text{CDCl}_3$  as solvent and TMS as internal standard at 300MHz. All products are known compounds and their authenticity was ensured on the basis of spectroscopic data and on comparison with authentic samples.

**Table 1:** Ferric sulphate Catalyzed Cyclization of various 2'-hydroxychalcone to Flavanone.

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Flavanone(2)	% Yield <sup>a</sup>	Melting Point °C[Ref]
1	H	H	H	H	<b>2a</b>	86	75-76[38]
2	H	OMe	OMe	OMe	<b>2b</b>	83	132-133[38]
3	H	H	Cl	H	<b>2c</b>	78	93-94[38]
4	H	H	Me	H	<b>2d</b>	81	65-66[18]
5	H	OMe	H	H	<b>2e</b>	74	76-78[22]
6	Cl	H	Cl	H	<b>2f</b>	62	93-94 [39]
7	H	H	Br	H	<b>2g</b>	68	117-118[22]
8	Cl	H	H	H	<b>2h</b>	59	83-85[40]
9	H	H	F	H	<b>2i</b>	75	78-79 [38]
10	H	NO <sub>2</sub>	H	H	<b>2j</b>	74	143-144 [41]
11	H	H	OMe	H	<b>2k</b>	81	88-89[38]
12	H	OMe	OMe	H	<b>2l</b>	76	125[38]
13	H	H	NO <sub>2</sub>	H	<b>2m</b>	56	161-162[41]
14	H	H	NMe <sub>2</sub>	H	<b>2n</b>	67	122-124[21]

a: Yields refers to isolated and pure product

*General Procedure for Cyclization of 2'-Hydroxychalcone to Flavanone under microwave Radiation:*

2'-Hydroxychalcone 1(5mmol) was dissolved in 5mL ethanol. To this solution ferric sulphate (5mmol) was added and well swirled. The solvent was removed under reduced pressure using a rotatory evaporator. Resulting free-flowing powder was taken in a 10mL beaker and irradiated in microwave oven at 400 W for 10 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled, added to ethyl acetate (10mL) and the supernatant organic layer decanted and evaporate under reduced pressure using a rotatory evaporator to yield flavanone (2). A pure sample was obtained by recrystallization from ethanol.

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