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FORM 2
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COMPLETE SPECIFICATION
(See section 10 and rule 13)

1. TITLE OF THE INVENTION: - PROCESS FOR SYNTHESIS OF CHALCONES AND USES THEREOF

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3. PREAMBLE OF THE DESCRIPTION

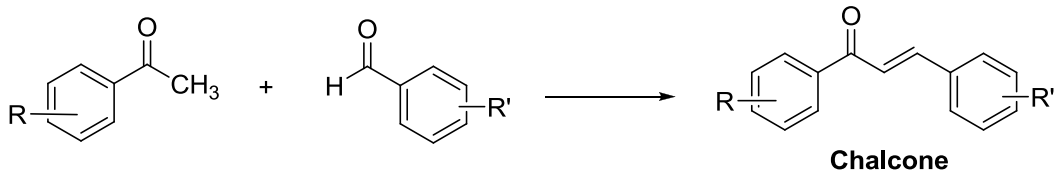
The following specification particularly describes the invention and the manner in which it is to be performed

Field of the Invention:

The present invention relates to provide an extremely simple, rapid and high yielding practical synthetic approach for a variety of chalcones using of *p*-toluenesulfonic acid (*p*-TSA) as an efficient catalyst for the synthesis of chalcones under solvent-free conditions that ruled out all the limitations of either acid or base catalysed reactions as well as microwave conditions.

Background of the invention:

The most widely used method for the synthesis of chalcones is the base catalysed Claisen-Schmidt reaction between aryl aldehydes and substituted acetophenones (**Scheme 1**).



Scheme 1: Claisen-Schmidt condensation

The earlier used methods for the synthesis of chalcones comprises expensive catalysts and involve stringent and/or dry conditions, use of organic solvents, extended reaction times, formation of side products, complex work-up procedures, poor yields and the use of stoichiometric and/or relatively expensive reagents. Also most of these methods when used for the synthesis of 2-hydroxy chalcones generally are accompanied by the formation of flavanones and aurones via cyclization. Some acid catalysed reactions have also been reported by using dry HCl gas, BF_3 and $AlCl_3$ as reagents which make the process further difficult to handle. Thus, development of more efficient methods is required which uses proper catalysts to make the available procedures more convenient and simple that can be used for compounds containing base sensitive functionalities.

1306/MUM/2009 is related to the synthesis and characterization of novel coumarin chalcones chromophores prepared from condensation of 8-acetyl-1,4,-dialkyl-1,2,3,4-tetrahydro-7H-pyrano [2,3-g] quinoxalin-7-one with various substituted benzaldehyde derivatives but the application has been withdrawn.

2462/DEL/2007 is related to novel antimalarial acylhydrazones of chalcones and process for the preparation thereof. The invention involves mixing a ketone and an aldehyde in the molar ratio of 1:1 to 1:5 in 1-3 N alcoholic NaOH or KOH at room temperature for 40-240 minutes, ii.washing the reaction mixture with acidic water to obtain the product chalcones. This invention is evidently different from the present application which claims the use of *p*-toluenesulfonic acid (*p*-TSA) as an efficient catalyst instead of using alcoholic NaOH or KOH in the above mentioned prior art.

2724/DEL/2005 provides process using aqueous NaOH in methanol at room temperature to obtain chalcones which again is different from the present application.

6511/DELNP/2010 provides method for preparing 3-Trifluoromethyl chalcones using alkaline earth metal hydroxides and compounds capable of forming said alkaline earth metal hydroxides on contact with water and the said method is based on forming a low boiling azeotrope with water or by using a Grignard reagent.

(CN102093274) relates to Chalcone-containing acylthiourea compounds and preparation method and use thereof. The compounds are prepared by reacting acyl chloride with ammonium thiocyanate in the presence of a phase transfer catalyst in a protonic solvent to obtain acylisosulfocyante, reacting acylisosulfocyante with aminoacetophenone to obtain N-benzoyl-N'-acetylphenylthiourea, and performing condensation of N-benzoyl-N'-acetylphenylthiourea and aromatic aldehydes under an alkaline condition to obtain target compounds. This is different from the present application.

(WO2011064726) Method for the synthesis of aspalathin and analogues thereof provides for the step of coupling a sugar to a dihydrochalcone, chalcone or flavanone, or coupling the sugar to an intermediate for producing a dihydrochalcone, chalcone or flavanone followed by coupling of the sugar-intermediate adduct to a further intermediate for producing a dihydrochalcone, chalcone or flavanone, and transforming the product thereof into a compound of formula 1 or an analogue or derivative thereof.

(CN102850202) Method for preparing chalcone by fluorous biphasic catalysis with fluoride-free solvent discloses a method for preparing chalcone by fluorous biphasic catalysis with fluoride-free solvent. The method comprises the following steps: dissolving DMAP (dimethylamino pyridine) and fluorine-containing alkyl iodide into dichloromethane,

stirring at room temperature for reaction to generate white solid, drying at high temperature in vacuum to obtain fluorine-containing DMAP; adding fluorine-containing DMAP into a reactor containing normal octane, and then adding acetophenone and benzaldehyde to perform condensation reaction, and raising the temperature for heating; cooling and filtering the mixed solution obtained from the condensation reaction to recycle the catalyst; evaporating out the solvent to recycle; recrystallizing the product to obtain pure chalcone. In this invention, the catalyst is fluorous based whereas the present application deals with p-TSA as the catalyst.

None of the cited references above disclose or teach what the present invention discloses or teaches. The present invention distinguishable over these cited prior art references.

The present invention is related to the novel application of *p*-toluenesulfonic acid (*p*-TSA) as an efficient catalyst for the synthesis of chalcones under solvent-free conditions. The catalytic reaction using (*p*-TSA) overcomes the limitations of either acid or base catalysed reactions as well as microwave conditions. The present invention focuses on the catalytic evaluation of *p*-toluenesulfonic acid by taking benzaldehyde and acetophenones as model substrates.

The present protocol has also been found to be highly useful for the condensation between 2-hydroxy acetophenones and aryl aldehydes which selectively led to the formation of 2-hydroxy chalcones without any cyclized side products. Further, the reaction time has also been reduced from hours to few minutes and the yields achieved are much better than those used in the prior arts.

It is for the first time when only *p*-toluenesulfonic acid has been used for Claisen Schmidt condensation reaction without the use of any expensive reagents or apparatus like microwave etc. to synthesize a wide variety of chalcones derivatives vehemently under solvent-free mild conditions.

Another important advantage is isolation of *p*-TSA catalyst which can be used again.

Summary of the Invention

The present invention results in a very simple, solvent free and highly expeditious method to prepare a wide variety of chalcone derivatives using *p*-toluene sulfonic acid (*p*-TSA), thereby

disclosing the use of *p*-TSA as a green organocatalyst which accelerates the Claisen Schmidt condensation reaction dramatically under very mild conditions affording high yields.

The invention provides an acid catalysed protocol which is not only simple but also eliminates the formation of cannizaro's products. The present approach is an elegant and highly useful for the condensation reaction specifically between 2-hydroxy acetophenones and aryl aldehydes which selectively leads to the formation of 2-hydroxy chalcones without any cyclized side products.

Detailed description of the invention

Chalcones represent an important class of natural compounds with a variety of biological activities and are represented by the following structural formula (Fig.1).

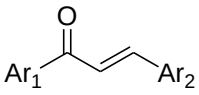
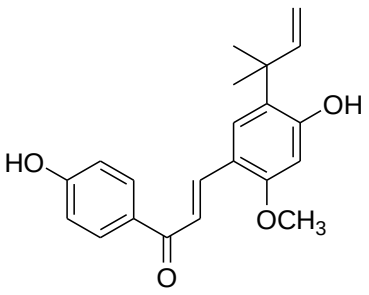


Fig.1

In recent years, chemistry of both natural and synthetic chalcones have has attracted more attention because these compounds have been found to exhibit various biological activities like anticancer, antimalarial, antimicrobial, anti-inflammatory activities, anti-HIV, antiviral, anti-hyperglycemic and tyrosinekinase inhibitory activities.

Licochalcone A (Fig.2) isolated from the roots of *Glycyrrhiza inflata* (licorice) possesses in vitro as well as in vivo antimalarial and antileishmanial activity. 3-Methoxy-4-hydroxyloncocarpin (Fig.3) obtained from the roots of *Lonchocarpusutilis* inhibits NADH-ubiquinone oxidoreductase activity (Narender, T., Reddy, K.P., *Tetrahedron Letters*, 2007, 48, 3177-3180).



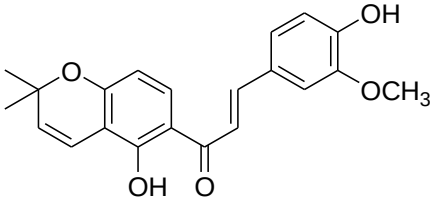
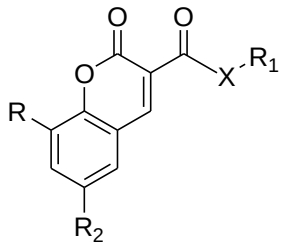


Fig.2 Fig.3

Recently, it has been reported that coumarin chalcones (Fig.4) act as potent anticancer agents used in treatment and prevention of cervical, oral squamous, lung, prostate carcinoma and brain tumors. Moreover, these chalcone derivatives are selective for the cancerous cell and did not harm normal cells (Sashidhara, K., Sashidhara, V., Kumar, A., Kumar, M., Sarkar, J., Sinha, S., Sinha, K., WO 2012/017454A1 (2012). Poter *et al* have reported that substituted 1-(4-methoxyphenyl)-3-(3,5-dimethoxyphenyl)prop-1-en-3-ones (Fig.5) exhibited anti-proliferative and anti-inflammatory activities (Poter, G.A., Butler, P.C., Wanogho, E., US6787672 B2 (2004).



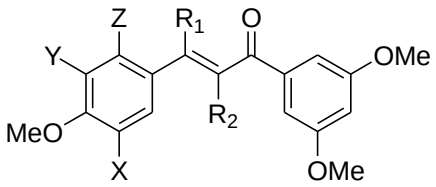
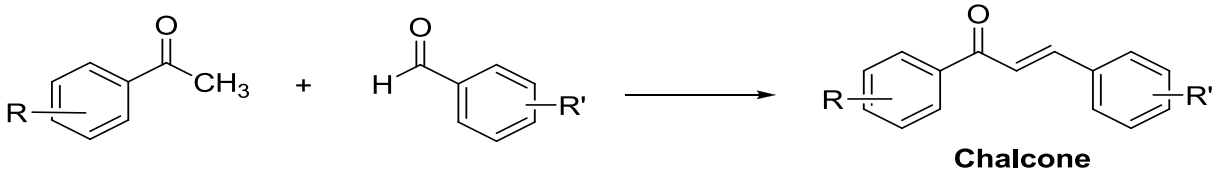


Fig.4 Fig.5

Apart from medicinal uses, they are also used in food additives and ingredients in cosmetic formulations (Bertrand, K., Roudot, A., Rool, P., WO 2011/144579A1 (2011)). Some derivatives are used as sweeteners, drugs, and sunscreen agents. Chalcones are the main precursors for the biosynthesis of flavonoids which are frequent components of the human diet. They are abundant in commonly consumed fruits and vegetables such as apples, pears, strawberry, bearberry and tomatoes respectively. In addition, they are also present in wheat and wheat products. The most common chalcones occur in fruits and vegetables include phloretin, phloridzin, chalconaringenin and arbutin. These derivatives also act as useful precursors for the synthesis of many medicinally important heterocyclic moieties like pyrazolines, benzodiazepines, 1, 4-diketones and flavones (Siddiqui, Z.N., Musthafa, T.N.M., *Tetrahedron Letters*, 2011, 52, 4008-4013).

Of the numerous synthetic approaches available for chalcones, the most widely used is the base catalysed Claisen-Schmidt reaction between aryl aldehydes and substituted acetophenones (Scheme 1).



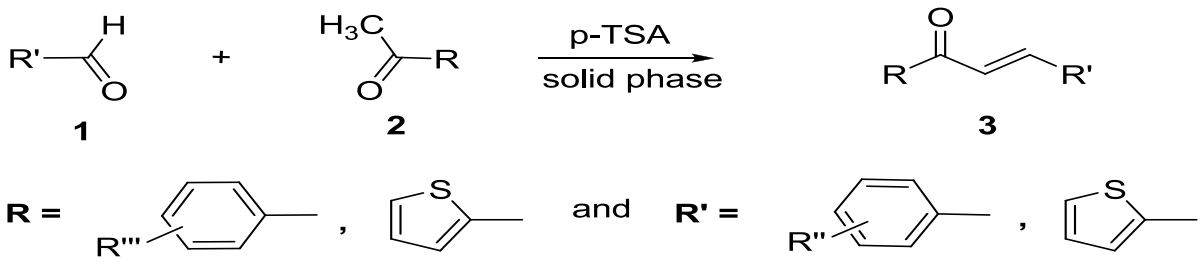
Scheme 1: Claisen-Schmidt condensation

Besides drawbacks of using expensive catalysts, some of the methods involve stringent and/or dry conditions, use of organic solvents, extended reaction times, formation of side products, complex work-up procedures, poor yields and the use of stoichiometric and/or relatively expensive reagents. Also most of these methods when used for the synthesis of 2-hydroxy chalcones generally are accompanied by the formation of flavanones and aurones via cyclization. Some acid catalysed reactions have also been reported by using dry HCl gas, BF_3 and $AlCl_3$ as reagents which make the process further difficult to handle. Thus, development of more efficient methods and exploring proper catalysts are still in demand to make the available procedures more convenient and simpler that can be used for compounds containing base sensitive functionalities.

Methodology of reaction

Owing to widespread availability and therapeutic potential of chalcones and in continuation of our work related to explore efficient and novel greener synthetic methodologies for important key intermediates and biologically active heterocycles it was envisaged to perform and study the Claisen Schimdt reaction using *p*-TSA under solid phase conditions.

Herein, we report the novel application of *p*-toluenesulfonic acid (*p*-TSA) as an efficient catalyst for the synthesis of chalcones under solvent-free conditions that ruled out all the above-mentioned limitations of either acid or base catalysed reactions as well as microwave conditions. Preliminary efforts were mainly focused for the catalytic evaluation of *p*-toluenesulfonic acid by taking benzaldehyde and acetophenones as model substrates. To observe the effect of temperature, as well as the amount of *p*-toluenesulfonic acid required, different reactions were carried out using 1 equiv. of benzaldehyde (1a) and 1 equiv of. acetophenone (2a) in the presence of *p*-toluenesulfonic acid under solvent-free conditions at different temperatures (Scheme-2, Table 1).



Scheme 2: Claisen-Schmidt condensation using p-TSA

Initially, a reaction between 1a and 2a was performed at room temperature for 60 minutes and resulted the recovery of starting materials without the traces of the product 3a (entry 1). After the analysis of ^{1}H NMR spectrum of a crude mixture it has been confirmed that reaction between 1a and 2a could not succeed.

Table 1. Reaction of **1a** and **2a** under different temperatures[a]

Entry	***p*-TSA (equiv)**	**Temp(°C)**	**Time (min.)**	**3a** (%)
1	0	25	60	0
2	1	25	15	35
3	2	25	15	90
4	1	50	2	97
5	2	50	2	98

[a]Condition: 1 equiv of **1a** was treated with 1equiv of **2a** under a solvent-free condition.
[b]Reaction was monitored on the basis of TLC.

To explore the catalytic potential of *p*-toluenesulfonic acid (p-TSA), a similar reaction was carried out at room temperature in the presence of 1 equiv of p-TSA for the preparation of 3a, in which 35% of 3a has been formed within 15 minutes (entry 2), however with 2.0 equivalents *p*-TSA, 90 % conversion of reactants into product has been achieved at the same temperature with in 15 minutes.

But the reaction surprisingly resulted into the exclusive formation of the product 3a in 97% yield (entry 4) at 50-60 °C in presence of 1.0 equivalent *p*-TSA within 2-4 minutes. In order to optimize the amount of *p*-TSA required for the above transformation, different experiments were carried out by varying the amount of *p*-TSA at different temperatures. It has been found that either using 1 or 2 equivalents of *p*-TSA at 50-60 °C always resulted in

the exclusive formation of 3a in 90-98 % yields. These results clearly indicated that the use of 1 equivalent catalyst is sufficient to synthesize the chalcone derivatives in excellent yields. After choosing the best condition using bezaldehyde (1a) and acetophenones (2a), the generality of the *p*-toluenesulfonic acid catalyzed reaction was examined by selecting a number of aryl aldehydes as well as various substituted acetophenones (Table 2). As expected, excellent yields were obtained for compounds3 generated under solvent-free condition at 50-60 $^{\circ}$C within 2-5 minutes. All the synthesized compounds were characterized on the basis of IR, ^{1}H, ^{13}C NMR and Mass spectral data.

The present protocol has also been found to be highly useful for the condensation between 2-hydroxy acetophenones and aryl aldehydes which selectively led to the formation of 2-hydroxy chalcones without any cyclized side products. The reaction time was reduced from hours to few minutes and the yields were achieved much better (Table 2). To the best of our knowledge it is for the first time when only *p*-toluenesulfonic acid has been used for Claisen Schmidt condensation reaction without the use of any expensive reagents or apparatus like microwave etc. to synthesize a wide variety of chalcone derivatives (3) vehemently under solvent-free mild conditions.

Another important advantage is isolation of *p*-TSA catalyst which can further be used. Further research work on such types of condensation reactions and others (e.g. reaction of pyrazole aldehydes with acetophenones or aliphatic acyclic or cyclic ketones and reaction of DHA with acetophenones) is still continued in our lab with an aim to explore the further synthetic utility of *p*-TSA in the field of organic synthesis.

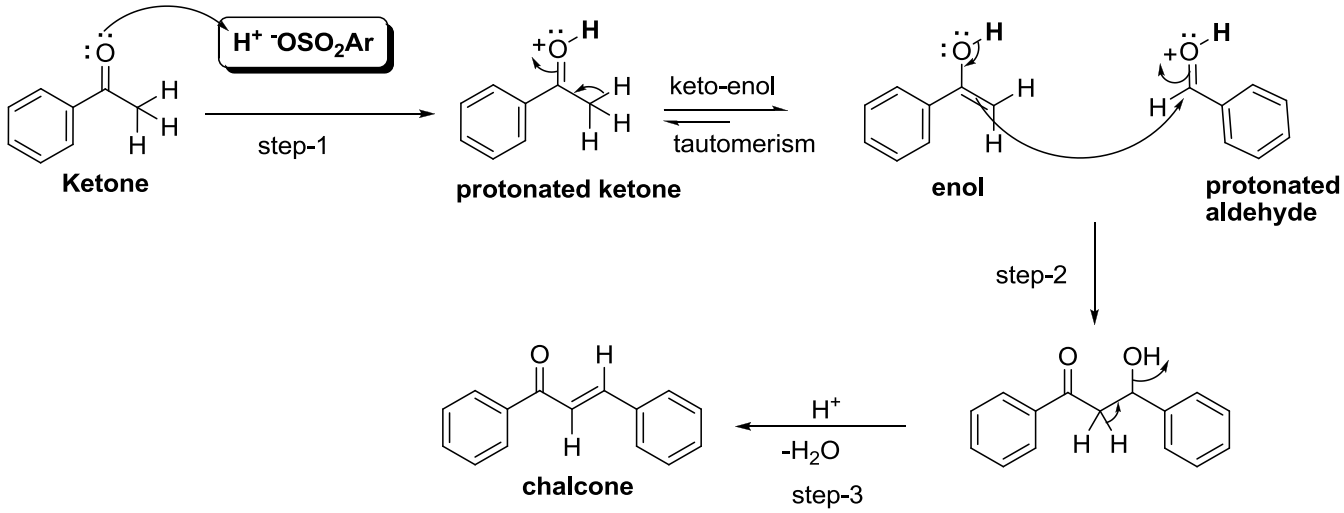
Table 2. Physical data of chalcones **3** obtained by solvent-free conditions in presence of *p*-TSA

Entry	**Products (3)**	**R= R$^{''}$**-C_6H_5-, Or **thienyl**	**R$^{'}$ = R$^{'''}$**-C_6H_5-,Or **thienyl**	**Time (minutes)**	**Isolated yield (%)**	**Mp. ($^{\circ}$C)**	**R_f value**
-	-	**-R$^{''}$**	**-R$^{'''}$**	-	-	-	
1	**3a**	H	4-CH_3	5	66.66%	94	0.5
2	**3b**	H	4-Cl	5	66.46%	156	0.6

3	**3c**	H	4-F	4	73.26%	166	0.4
4	**3d**	H	4-NO_2	4	94.78%	101	0.4
5	**3e**	H	4-Br	4	97.5%	106	0.5
6	**3f**	4-Cl	4-CH_3	4	70.25%	145	0.6
7	**3g**	4-Br	4-CH_3	4	63.74%	165	0.5
8	**3h**	4-F	4- CH_3	5	74.87%	120	0.7
9	**3i**	4-NO_2	4- CH_3	2	94.54%	169	0.3
10	**3j**	4-Cl	4-Cl	5	90.86%	157	0.66
11	**3k**	4-NO_2	4-NO_2	5	83.155	155	0.5
12	**3l**	4-F	4-F	5	79.43%	119	0.43
13	**3m**	4-Cl	4-F	5	89.22%	136	0.42
14	**3n**	4-F	4-OH	5	90.80%	199	0.45
15	**3o**	4-NO_2	4-OH	5	80.36%	182	0.5
16	**3p**	2-F	4-F	5	85.71%	101	0.4
17	**3q**	2-F	4-NO_2	5	86.66%	166	0.4
18	**3r**	4-NO_2	2-Ethoxy	5	84.92%	194	0.4
19	**3s**	Thein-2-yl	Thein-2-yl	5	94.82%	124	0.4
20	**3t**	Thein-2-yl	4-CH_3	4	95.01%	140	0.4
21	**3u**	-H	2-OH	4	90.23%	89-90	0.4
22	**3v**	4-CH_3	2-OH	2	91.21%	105-106	0.5
23	**3w**	4-OCH_3	2-OH	3	85.21%	90-91	0.5

Mechanism of Claisen-Schmidt Reaction Using *p*-TSA

A plausible mechanism for the Claisen-Schmidt condensation between acetophenone and benzaldehyde in presence of *p*-TSA may involve the steps shown in Scheme-3.



Scheme 3: Plausible mechanism

In conclusion, a very simple, solvent free and highly expeditious method to prepare a wide variety of chalcone derivatives (3) using *p*-toluene sulfonic acid (*p*-TSA) has been developed. For first time it disclosed the use of *p*-TSA as a green organocatalyst which accelerates the Claisen Schmidt condensation reaction dramatically under very mild conditions. The syntheses of chalcone derivatives which have already been reported earlier in solvent medium and/or in presence of bases result poor yields besides the formation of side products. Herein, we provide an acid catalysed protocol which is not only simple but also eliminates the formation of cannizaro's products. The present approach is an elegant and highly useful for the condensation reaction specifically between 2-hydroxy acetophenones and aryl aldehydes which are selectively led to the formation of 2-hydroxy chalcones without any cyclized side products. Mild reaction conditions, clean reaction media, very simple workup, exclusive formation of products without side products, easy purification and recycling of the catalyst are advantages of the present methodology.

We claim;

1. A process for synthesis of chalcones comprising the steps of reacting aryl aldehydes to substituted acetophenones in presence of catalyst *p*-TSA (*p*-Toluene sulfonic acid) under solvent free conditions., without formation of any side product.

2. The process as claimed in claim 1, wherein by using 1 or 2 equivalents of *p*-TSA at 50-60 $^{\circ}$C results in the exclusive formation of product in 90-98 % yields in 2-4 minutes.

Dated this January 17, 2014

(Ashish Sharma)
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