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Simple and solvent free practical procedure for chalcones: An expeditious, mild and greener approach

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ABSTRACT

An extremely simple, expeditious and greener synthetic method for a variety of chalcone derivatives (**3**) under mild and solvent free reaction conditions has been developed. The present protocol discloses the use of *p*-toluenesulfonic acid (*p*-TSA) as a solid phase organocatalyst which accelerates the Claisen–Schmidt condensation reaction dramatically under mild conditions. Various aryl aldehydes (**1**) were treated with differently substituted aryl ketones (**2**) in the presence of *p*-TSA at 50–60 °C to yield the desired products in a very short period of reaction time. Mild reaction conditions, clean reaction media, expulsion of hazardous solvents, simple work-up, exclusive formation of products in high yields without side products, and easy purification are advantages of the present methodology.

1. Introduction

Chemistry of chalcones has always been the most demanded and focused area of research among the scientific community [1]. Chalcones (Fig. 1) represent an important class of natural compounds with a variety of biological activities such as anticancer [2–5], antimalarial [6,7], antimicrobial [8–10], anti-inflammatory [11,12], anti-HIV [13], antiviral [14,15], anti-hyperglycemic [16], tyrosinekinase inhibitory [17] properties. 2-Hydroxy chalcones are natural compounds which have been used as key intermediates for the synthesis of various flavonoids [18–22]. Furthermore, they are considered as important precursors for various biologically active heterocyles [23–27].

Some of the medicinally important chalcones are represented in Fig. 2. The chalcone derivative, Licochalcone A (**I**) extracted from *Glycyrrhiza inflata* (licorice) roots displayed *in vitro* as well as *in vivo* antimalarial and antileishmanial activities. Whereas, 3-methoxy-4-hydroxyloncocarpin (**II**) obtained from the roots of *Lonchocarpusutilis* inhibited NADH-ubiquinone oxidoreductase activity [28]. The coumarin chalcones (**III**) act as selective anticancer agents used in treatment and prevention of cervical, oral squamous, lung, prostate carcinoma and brain tumors without harming normal cells [29]. Substituted 1-(4-methoxyphenyl)-3-(3,5-dimethoxyphenyl)prop-1-en-3-ones (**IV**) exhibited anti-proliferative and anti-inflammatory activities [30].

Apart from medicinal uses, chalcones are also used in food additives and ingredients in cosmetic formulations [31]. In view of the importance, numerous synthetic methods for chalcones have been reported in the literature [1]. Generally, they are synthesized via Claisen Schmidt condensation between arylaldehydes and substituted acetophenones in presence of alkalies or sodium ethoxide [32] (Scheme 1).

Use of several reagents and conditions such as basic alumina [33], zinc chloride, Lewis acid such as dry HCl gas, BF_3, $AlCl_3$ [34], Mg–Al-OBu hydrotalcite [35], strong alkalies with phase transfer catalysts [36], barium hydroxide in ethanol [37], calcined $NaNO_3$/phosphate [38], potassium phosphate, the use of chlorinated solvents while work-up, microwave conditions [39–41] and ultrasonic conditions [42–44] have also been reported. Most of the reported methods have been explored by using organic solvents either during chemical reactions or while isolating the products. Further, most of the organic solvents are considered as hazardous materials to humans and the environment. Moreover, most of the available methods for the synthesis of 2-hydroxychalcones are generally associated with the formation of flavanones and aurones *via* cyclization. Furthermore, using expensive and toxic metal based

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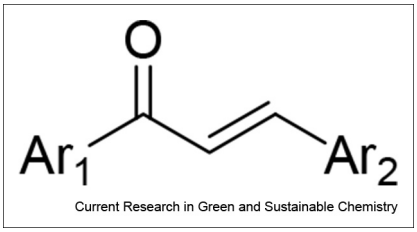


Fig. 1. General chemical skeleton of chalcones.

precursors not only confines the applicability of such methods, but also generates a serious concern in view of green chemistry. In addition to the above mentioned drawbacks, some of the methods also require acidic or basic work-up treatments to obtain the products, catalysts using stringent and/or dry conditions, prolonged reaction times, poor yields, and complex work-up procedures. Thus, development of more practical methods with efficient catalysts are still in demand to make the available procedures more convenient, greener and simple that can be used for compounds containing base sensitive functionalities.

2. Results and discussion

Owing to widespread availability and therapeutic potential of chalcones and in continuation of our earlier work in order to explore efficient and novel greener synthetic methodologies [45–51] 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, applicability of *p*-toluenesulfonic acid (*p*-TSA) as an efficient solid phase catalyst for the synthesis of chalcones under solvent-free conditions has been explored and reported (Scheme-2).

Initially, feasibility of the reaction between aldehyde and ketone was studied and then preliminary efforts were mainly focused on the catalytic potential of *p*-toluenesulfonic acid by taking benzaldehyde and acetophenone as model substrates. In order to optimize the reaction conditions, different sets of reactions were carried out by using equimolar concentration of benzaldehyde (**1a**) and acetophenone (**2a**) in the presence of *p*-toluenesulfonic acid under solvent-free conditions at different temperatures (Table 1).

Firstly, a reaction between **1a** and **2a** was performed at room temperature for 60 min that resulted the recovery of starting materials without the traces of the product **3a** (**entry 1**). The reaction was monitored by thin layer chromatography (TLC). In order 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** and it was found that only 35% of **3a** is formed within 15 min (**entry 2**), however, with 2.0 equivalents *p*-TSA, 90% conversion of reactants into product has been achieved at the same temperature within 15 min.

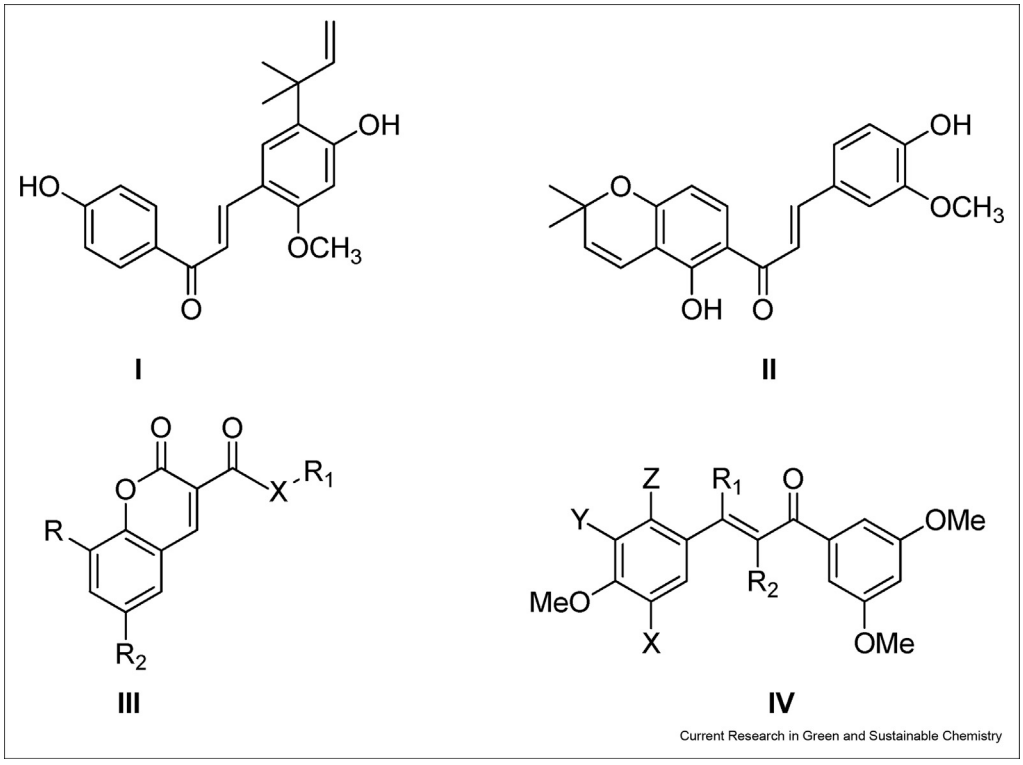
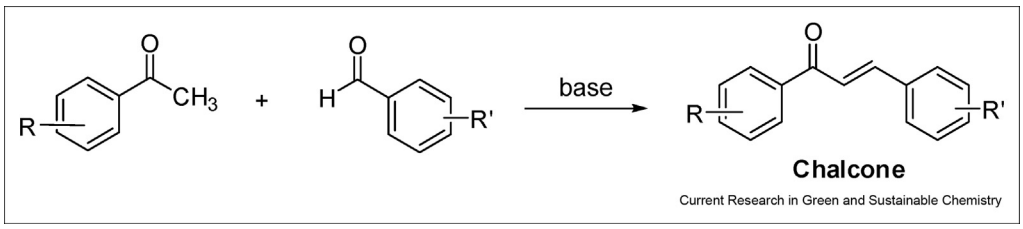
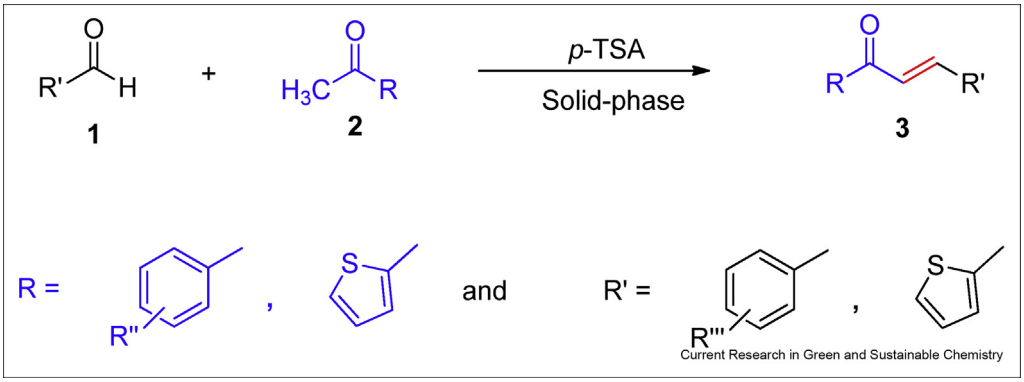


Fig. 2. Some important bioactive chalcones.



Scheme 1. Claisen–Schmidt condensation.



Scheme 2. Solid-phase synthesis of chalcones using *p*-TSA.

Table 1
Reaction of **1a** with **2a** at different temperatures[a,b].

Entry	*p*-TSA (equiv)	Temp(°C)	Reaction Time (min.)	Product (3a)[52]in %
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

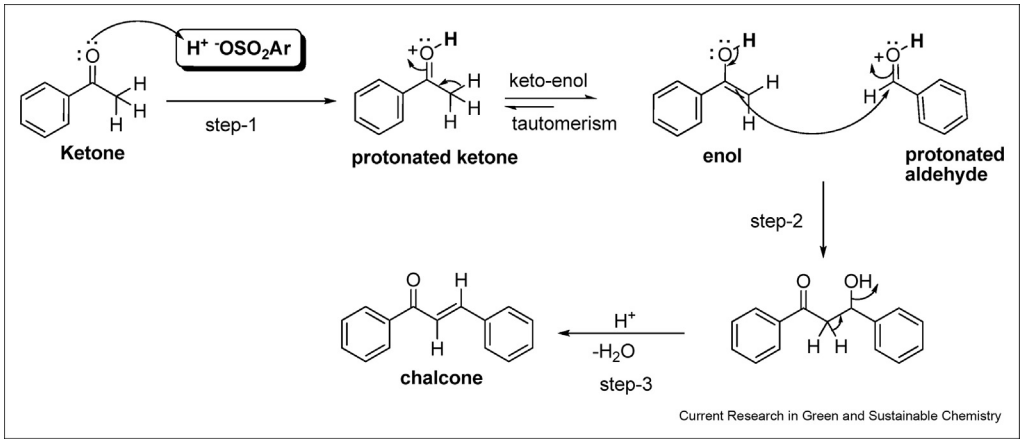
[a] Condition: 1 equiv. of **1a** was treated with 1equiv. of **2a** under a solvent-free condition.
[b] Reaction was monitored on the basis of TLC.

Interestingly, the reaction resulted into the exclusive formation of the product **3a** in 97% yield (**entry 4**) at 50–60 °C in the presence of 1.0 equivalent *p*-TSA within 2–4 min. In order to optimize the amount of *p*-TSA required for the above mentioned chemical transformation, different experiments were also carried out by varying the amount of *p*-TSA at different temperatures. It has been found that either using 1 or 2 equivalent of *p*-TSA at 50–60 °C always resulted in the exclusive formation of **3a** in good yield. 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 acetophenone (**2a**), generality of the *p*-toluenesulfonic acid catalyzed reaction was examined by considering a number of arylaldehydes as well as various substituted acetophenones (Table 2). Expectedly, excellent yields were obtained for compounds **3** generated under solvent-free condition at 50–60 °C within 2–5 min. All the products were characterized by comparing their melting points with those reported in literature and on the basis of IR, ^{1}H and ^{13}C NMR spectral data.

The present protocol has also been found to be highly useful for the condensation between 2-hydroxyacetophenones and arylaldehydes which selectively led to the formation of 2-hydroxychalcones without any cyclized side products. The reaction time was reduced from hours to few minutes and the yields were achieved much better (Table 2). It is important to mention here that *p*-toluenesulfonic acid has been used for Claisen Schmidt condensation reaction without using any expensive reagents or chlorinated solvents or apparatus like microwave [40,41] to synthesize a wide variety of chalcone derivatives (**3**) vehemently under

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

Entry	Products (3)	R = R″-C_6H_4- Or thienyl	R' = R‴-C_6H_4- Or thienyl	Time (minutes)	Isolated yield (%)	M.pt. (°C)	Lit.M.pt. (°C)
-	-	-R″	-R‴	-	-	-	-
1.	3a	H	H	4	97	53	55–57[52,53]
2.	3b	H	4-CH_3	5	77	93–94	95–96[41]
3.	3c	H	4-Cl	5	75	110–111	112–113[41]
4.	3d	H	4-NO_2	4	92	160–162	160–163[41]
5.	3e	H	4-Br	4	87	106–108	109–110[53]
6.	3f	H	4-F	4	73	82	82–83[53]
7.	3g	H	4-OCH_3	5	67	75–76	78–79[53]
8.	3h	4-F	4-CH_3	5	75	137–139	140[54]
9.	3i	4-F	H	4	90	86	87[54]
10.	3j	4-Cl	4-Cl	5	91	157	–
11.	3k	4-F	4-Cl	5	89	134	134[54]
12.	3l	4-F	4-F	5	79	113	112–113[55]
13.	3m	Thien-2-yl	4-CH_3	4	85	99–100	101–102[53]
14.	3n	4-CH_3	2-OH	2	91	105–106	165–167[56]
15.	3o	4-OCH_3	2-OH	3	85	90–91	151–153[56]
16.	3p	4-OCH_3	4-F	5	90	111–112	112–114[57,58]
17.	3q	4-OCH_3	4-OH	5	88	180–182	181–184[58]
18.	3r	2-OH	4-CH_3	2	86	114–116	115–117[59]
19.	3s	2-OH	4-OCH_3	3	87	91–92	93–94[59]
20.	3t	4-NO_2	4-OCH_3	5	80	192–193	192–194[28]
21.	3u	4-Br	4-CH_3	4	93	162–163	163–164[60]
22.	3v	4-NO_2	H	2	92	145–146	146–147[54]
23.	3w	4-NO_2	4-NO_2	5	83	175–176 dec.	175–178[55]
24.	3x	Br	4-OCH_3	5	85	144–145	145–146[60]
25.	3y	Thien-2-yl	Thien-2-yl	5	84	124	–



Scheme 3. Plausible mechanism.

solvent-free mild conditions. 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 acetophenone) is still continued in our lab with an aim to explore the further synthetic utility of *p*-TSA in the field of organic synthesis.

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.

3. Conclusion

A very simple, solvent free and highly expeditious method to prepare a wide variety of chalcone derivatives (**3**) using *p*-toluenesulfonic acid (*p*-TSA) has been developed that ruled out all the limitations of either acid or base catalysed reactions, use of chlorinated solvent while work-up as well as microwave conditions. It discloses the use of *p*-TSA as a green organocatalyst which accelerates the Claisen Schmidt condensation reaction dramatically under mild conditions. The acid catalysed protocol 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-hydroxyacetophenones and aryl aldehydes which are selectively led to the formation of 2-hydroxychalcones without any cyclized side products.

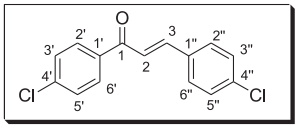
4. Experimental

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a Buck Scientific IR M500 instrument using KBr pellets (cm^{-1}). The ^{1}H and ^{13}C NMR spectra were run on a Brucker instrument at 400 and 100 MHz, respectively. Chemical shifts are expressed in δ-scale downfield from TMS as an internal standard using $CDCl_3$ or d_6-DMSO as a solvent. Compounds **1** and **2** were purchased from commercial suppliers and used as such without further purification.

4.1. Synthesis of chalcones (3)

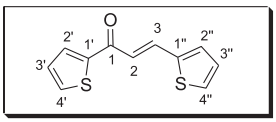
General procedure: To a mixture of acetophenone (1 g, 0.0083 mol) and *p*-methylbenzaldehyde (1 g, 0.0083 mol), added *p*-TSA(1.58 g, 0.0083 mol) in a pestle. The resulting mixture immediately was allowed to grind vigorously with the help of mortar for an appropriate time at appropriate temperature. Added water (50 ml) and separated crystals were filtered through Buchner funnel using cotton cloth, washed with water and dried. Noted the m.pt. and compared with that reported in literature.

Other derivatives were prepared by adopting the similar procedure. **Spectral data of the representative compounds are given below: (*E*)-1, 3-*bis* (4-Chlorophenyl)prop-2-en-1-one (3j**).



Yield: 91%; **M.pt.**: 157 °C; **IR**(ν_{max}, cm^{-1}): 1681 (C=O str.), 1603.9 (C=Cstr.); **^{1}H NMR** (400 MHz, DMSO-d_6, δ_H): 8.06 (d, 2H, 2' & 6'-H, J_o = 8.52 Hz), 7.73 (d, 1H, 3-H, $^{3}J_{trans}$ = 15.8 Hz), 7.71 (d, 2H, 3' & 5'-H, J_o = 8.50 Hz), 7.65 (d, 1H, 2-H, $^{3}J_{trans}$ = 15.6 Hz), 7.51 (d, 2H, 2″ & 6″-H, J_o = 8.40 Hz), 7.42 (d, 2H, 3″ & 5″-H, J_o = 8.32 Hz); **^{13}C NMR** (100 MHz, DMSO-d_6, δ_c): 121.67, 128.48, 128.70, 129.63, 129.71, 132.89, 135.69, 135.81, 138.54, 142.96, 187.92.

(*E*)-1,3-*bis*(Thiophen-2-yl)prop-2-en-1-one (3y)



Yield: 84%; **M.pt.**: 124 °C; **IR**(ν_{max}, cm^{-1}): 1679 (C=O str.), 1602 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$, δ_H): 7.94 (d, 1H, 3-H, $^{3}J_{trans}$ = 15.2 Hz), 7.20 (d, 1H, 2-H, $^{3}J_{trans}$ = 15.2 Hz), 7.05–7.83 (m, 6H, 2′, 3′, 4′, 2″, 3″, 4″ –H); **^{13}C NMR** (100 MHz, $CDCl_3$, δ_c): 120.26, 128.30, 128.40, 129.00, 131.81, 132.26, 133.98, 136.48, 140.02, 145.39, 181.63.

Credit author statement

Duha Adnan: Investigation, Methodology, Writing- Original draft preparation; **Bijender Singh:** Conceptualization, Methodology, Writing-Original draft preparation; **Surinder K Mehta:** Visualization, Writing-Reviewing; **Ramesh Kataria:** Conceptualization, Visualization, Writing-draft preparation; **Vinod Kumar:** Conceptualization, Validation, Methodology, Writing- Original draft preparation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crgsc.2020.100041.

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