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# Zirconium chloride catalyzed efficient synthesis of 1,3-diaryl-2-propenones in solvent free conditions via aldol condensation☆

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**Abstract**

Zirconium chloride has been found to be a new and highly efficient catalyst for the aldol condensation of aldehyde and ketone under solvent free conditions, at room temperature. The reaction is very fast, clean and environmentally benign for the synthesis of variety of 1,3-diaryl-2-propenones. Zirconium chloride also found to be compatible with various solvents and gave the aldol product in acceptable yield (56–70%) but the excellent yield was obtained in solvent free condition. The higher mol% of the catalyst (zirconium chloride) yielded the 1,4-Michael adduct along with the aldol product.


*Keywords:* 1,3-Diaryl-2-propenone; Zirconium chloride; Aldol condensation; 1,4-Michael adduct

## 1. Introduction

1,3-Diaryl-2-propenones (chalcones) belong to flavanoid family, have displayed an impressive array of biological activities, among which anti-malarial [1], anti-cancer [2,3], anti-tuberculosis [4], cardiovascular [5], anti-leishmanial [6], anti-mitotic [7], anti-hyperglycemic [8], nitric oxide inhibition [9,10], anti-inflammatory [11], tyrosinase inhibition [12], activities have been reported. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine [13], pyrazolines [14], 1,4-diketones [15], and flavones [16]. Thus the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemists. The traditional methods for the synthesis of 1,3-diaryl-2-propenones involves the use of strong bases such as NaOH [17,18], KOH [19], $Ba(OH)_2$ [20,21], hydrotalcites [22], LiHMDS [23], calcined $NaNO_3$/natural phosphate [24]. There are also some reports of acid-catalyzed aldol condensations, e.g. $AlCl_3$ [25], $BF_3$ [26], dry HCl [27], $Zn(bpy)(OAc)_2$ [28], $Cp_2ZrH_2/NiCl_2$ [29] and $RuCl_3$ (for cyclic and acyclic ketones) [30]. Chalcone synthesis has also been achieved employing Suzuki reaction [31]. The previously reported procedures have various disadvantages such as long reaction times (14 h–5 days), special efforts needed to prepare the catalysts and starting materials, high temperatures, requirement of special apparatus, use of expensive reagents, generation of noxious substances, subsequent neutralization process and use of hazardous solvents, necessitate the development of newer method.

Solvent free reaction are of great importance in organic synthesis as it reduces the environmental pollution and bring down the handling costs due to simplification of work up technique [32].

Here we wish to report the synthesis of chalcone using zirconium chloride as catalyst in solvent free conditions. Recently, zirconium chloride chemistry has attracted much attention because $ZrCl_4$ has emerged as a safe, economical, air and moisture tolerant alternative Lewis acid. To best of our knowledge, there are no earlier reports for the zirconium chloride catalyzed synthesis of 1,3-diaryl propen-2-ones.

## 2. Results and discussion

Chalcones are usually synthesized using the Claisen–Schmidt reaction in basic medium in polar solvent and involves cumbersome purification process as the reaction often led to a complex mixture [17,18]. The aim of present study was to

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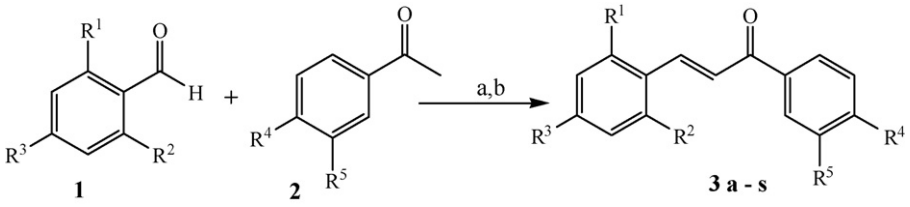



Scheme 1. Reagent and conditions: (a) $ZrCl_4$ (20 mol%) and (b) neat/dry DCM at room temperature.

develop an efficient protocol for a zirconium catalyzed aldol reaction of appropriately substituted aromatic aldehydes (**1**) with a broad variety of aromatic ketones (**2**) to obtain the corresponding 1,3-diaryl-2-propenones (**3**) with good to excellent yields in short span of time without the formation of any side product.

Our initial investigations were concerned the zirconium chloride catalyzed aldol reaction of benzaldehyde with acetophenone as a model system. We chose this system in order to optimize the reaction conditions in terms of the yield, time and reaction temperature (Scheme 1).

A variety of solvents were surveyed to establish the influence of the reaction medium on zirconium chloride catalyzed reaction (Table 1). The use of relatively less polar solvents furnished **3a** in moderately good yields (Table 1, entries 1 and 2). We also performed zirconium chloride catalyzed reaction in high boiling solvent DCE (Table 1, entry 3) at 50–60 °C but no further improvement in yield was observed. The use of solvents of relatively higher polarity (MeOH), with the exception of MeCN (Table 1, entry 7), either trace product formation was observed or no reaction was detected. The poor results in DMF were obtained probably due to the solvation effect, which interferes in coordinating the zirconium chloride with the carbonyl oxygen. Excellent yields were obtained under solvent free condition with 20 mol% of zirconium chloride.

In order to establish the best reaction conditions, we performed an optimization study using acetophenone and benzaldehyde as the model substrate in the presence of varying amounts of catalyst $ZrCl_4$ (Table 2). The best results were obtained with the use of 20 mol% of catalyst. While three to five fold excess in mol% of $ZrCl_4$ (60–80 mol%) was found to increase rate of reaction but some side products like 1,4-Michael adducts (**4**) was also obtained (Scheme 2).

Table 1
Effect of various solvents on the reaction of (**1a**) with (**2a**) in catalytic influence of zirconium chloride

| Entry | Solvent | Time (h) | Yield[c] (%) |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 2 | 70 |
| 2 | $CHCl_3$ | 2 | 68 |
| 3 | DCE | 2 | 67 |
| 4 | MeOH | 1.5 | 20 |
| 5 | DMF | 1.2 | 12 |
| 6 | Toluene | 5 | 25 |
| 7 | MeCN | 2.5 | 56 |
| 8 | Neat[a] | 1 | 92 |

[a] Conditions: benzaldehyde (1 mmol) and acetophenone (1 m mol) was taken in solvent free condition and stirred in presence $ZrCl_4$ (20 mol%) at r.t.
[c] Isolated yield (%).

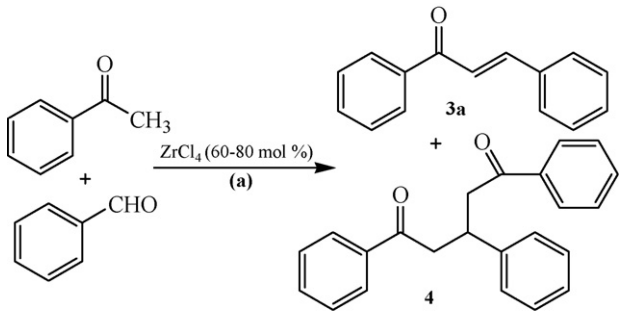
Table 2
Effect of catalyst loading on the synthesis of 1, 3 -diaryl propen-2-one[a,b]

| Entry | $ZrCl_4$ (mol%) | Solvent | Time (h) | Yield[c] (%) |
|---|---|---|---|---|
| 1 | – | DCM | 6 | nr |
| 2 | 2–5 | DCM | 4 | 45 |
| 3 | 10 | DCM | 2.5 | 57 |
| 4 | 15 | DCM | 1 | 65 |
| 5 | 20 | DCM | 1 | 70 |
| 6 | 15 | DCE | 2.0 | 58[b] |
| 7 | 20 | DCE | 1.6 | 64[b] |
| 8 | 5 | Neat | 1 | 56 |
| 9 | 10 | Neat | 1–1.5 | 80 |
| 10 | 15 | Neat | 1.2 | 88 |
| 11 | 20 | Neat | 1 | 92 |

[a] Reaction conditions: benzaldehyde reacted with acetophenone in presence of $ZrCl_4$ at room temperature.
[b] Heated at 50–60 °C.
[c] Isolated yield (%).

We investigated the generality and scope of the method with a variety of substituted aceophenones and aldehydes using our optimized reaction conditions. We required a methodology, which, should be amenable to various substitution patterns on both aryl rings of aldehyde as well as on ketone. Reaction under solvent free condition at room temperature gave excellent yields (Table 3). $ZrCl_4$ was found to be one of the most efficient Lewis acid catalysts in terms of handling, time, and yield and reaction temperature.

Zirconium chloride catalyzed synthesis of 1,3-diaryl-2-propenones is attractive since it specifically generates (*E*)-isomer. This was confirmed with the spectral data ($^1H$ NMR, $^{13}C$ NMR) of the corresponding chalcones and also by comparing with the reported literature data. It was found from $^1H$ NMR spectra, all chalcones were geometrically pure and with *trans*-configuration (J Hα–Hβ = 15.50–15.60 Hz).




1,4 - conjugate addition product

Scheme 2. (a) Neat/dry DCM at room temperature.

Table 3
$ZrCl_4$ catalyzed synthesis of 1,3-diaryl propen-2-one in solvent free condition[a,b]

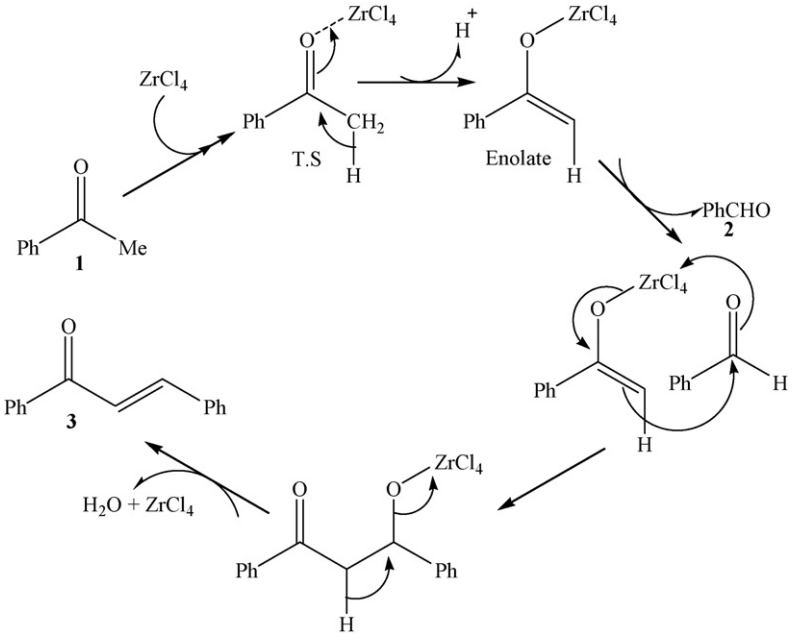
| Entry | (1) $R^1$ | (2) $R^2$ | (3) Yield[c] | % | Time (h) | mp (°C)/lit ref |
|---|---|---|---|---|---|---|
| 1 | Ph | Ph | 3a | 92 | 1 | 56–58 [33] |
| 2 | Ph | 4-OMe Ph | 3b | 93 | 1.2 | 72–74 [18,28] |
| 3 | 4-OMe Ph | Ph | 3c | 88 | 1.2 | 75–76 [28] |
| 4 | 3-OMePh | Ph | 3d | 85 | 1.5 | Oily |
| 5 | 4-OMePh | 4-OMe Ph | 3e | 90 | 1 | 102–105 |
| 6 | 2, 6-Cl Ph | Ph | 3f | 87 | 1 | 62–65 |
| 7 | 3-Cl Ph | 4-Me-Ph | 3g | 90 | 1.4 | 80–82 |
| 8 | 2-$C_4H_3O$ | 4-OMe Ph | 3h | 68 | 1.8 | 42–46 |
| 9 | 2-$NO_2$Ph | Ph | 3h | 83 | 1.2 | 133–140 |
| 10 | 3-$NO_2$Ph | Ph | 3i | 86 | 2 | 143–144 [28] |
| 11 | 3-$NO_2$Ph | 2-OH Ph | 3j | 80 | 2 | Oily |
| 12 | 4-$NO_2$Ph | Ph | 3k | 70 | 1.5 | 158–161 [28] |
| 13 | Ph | 4-OH Ph | 3l | 92 | 1 | 178–179 |
| 14 | 4-OMePh | 4-OH Ph | 3m | 52 | 2 | 188–189 [34] |
| 15 | 2-OH Ph | 4-Ph | 3n | 92 | 2 | 152–153 [28] |
| 16 | Napthyl | Ph | 3o | 80 | 2 | 90–92 |
| 17 | Napthyl | 4-OMe Ph | 3p | 82 | 2 | 148–151 |
| 18 | Ph | 4-$OC_2H_4NC_4H_8$ Ph | 3q | 87 | 2.2 | 89–90 |
| 19 | Ph | 4-$OC_2H_4NC_5H_{10}$ Ph | 3r | 86 | 2.8 | 77–79 |
| 20 | Ph | 4-$OC_2H_4NC_2H_6$ Ph | 3s | 86 | 2.5 | Oily |

$R^1CH=CHCOR^2$ (3).
[a] Reaction conditions aldehyde (1 mmol) acetophenone (1 mmol), and $ZrCl_4$ at room temperature, solvent free, stir.
[b] Anhydrous DCM was used as a solvent for entry (5, 7, 9, 10, 12 and 14).
[c] Product characterized by spectroscopic (IR, $^1H$ and $^{13}C$ NMR, mass) data.

Present methodology works efficiently with a wide variety of substrates. In most cases the reaction proceeded smoothly to produce the corresponding 1,3-diphenyl-2-propen-one. The reaction was found to be clean and the products were obtained in the excellent yields without the formation of any side products.

The proposed mechanism of $ZrCl_4$ catalyzed reaction may proceed, through the enolate intermediate generated via the initial addition of zirconium chloride to the carbonyl carbon of aryl ketone. The plausible role of $ZrCl_4$ in catalyzing the reaction in solvent free condition can be rationalized through the catalytic cycle depicted in Scheme 3.

It was proposed that $Zr^{4+}$coordinate with the carbonyl oxygen of the ketone and form an orange–violet colored transition metal complex (this color varied accordingly the aryl ketone was used), it generates the enolate intermediate by the abstraction of proton from the α-carbon of the aryl ketone. This transition metal complex further coordinate with the arylaldehyde and increases the electrophilicity of carbonyl carbon of aldehyde and make




Scheme 3. $ZrCl_4$ catalyzed synthesis of diaryl-2-propenone.

it susceptible for intramolecular nucleophillic attack of enolate ion. Further dehydration process generates the resultant product (**3**).

## 3. Conclusions

In conclusion, we have successfully developed a simple and efficient methodology to prepare a wide variety of 1,3-diaryl-2-propenones using zirconium chloride in catalytic amounts. The powerful catalytic activity of zirconium chloride for these transformations can be sustained by the less reaction time as well as high product yields. This is the environmentally acceptable, economical, and solvent less process for the synthesis of chalcones. However even in solvents like DCM, chloroform yields are good.

## 4. Experimental

### *4.1. General procedure for the preparation of 1,3-diaryl-2-propenones*

*Method A*: Benzaldehyde (106 mg, 1.0 mmol) and acetophenone (120 mg, 1 mmol) were mixed together and then anhydrous $ZrCl_4$ (46.6 mg, 20 mol%) was added and the solution stirred at room temperature under an air atmosphere for 60 min. After the completion of the reaction (monitored by TLC and IR), the crude mixture was worked up in ice cold brine solution and then extracted with etylacetate solution (3× 10 mL). The combined ethyl acetate extract was dried over anhydrous $Na_2SO_4$, filtered and then concentrated in vacuo, and the resulting product was purified by simple crystallization in ethyl acetate/*n*-hexane (1:25) to afford the pure product **3a** as a yellow solid (192 mg, 92% yield). The product was recrystallized by methanol.

*Method B*: In critical case when one or both the reactants are solid (Table 3, entries 5, 7, 9, 10, 12 and 14), we used 1–2 ml of dry DCM, i.e. minimal amount of solvent required to dissolve the solid reactant and make the reaction feasible. Except this all methodology used is same as mentioned above.

All the synthesized compounds were properly characterized by their spectroscopic data (Table 3). The compounds that are known are identified by comparison of their spectroscopic data with those reported in the literature.

#### *4.1.1. Spectral data for selected compounds*

*4.1.1.1. 1,3-Bis-(4-methoxy-phenyl)-propenone (entry 5, Table 3).* $^1$H NMR (200 MHz, $CDCl_3$)—*δ*: 8.05 (d, *J* = 8.6 Hz, 2H), 7.82(d, *J* = 15.5Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 15.5 Hz, 1H), 7.00 (t, *J* = 8.6 Hz, 4H), 3.88 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$)—*δ*: 189.1, 163.6, 161.9, 144.2, 131.7, 131.1, 130.5, 128.2, 119.9, 114.7, 114.1, 55.8. IR (KBr) 1654, 1594 $cm^{-1}$. MS (FAB) *m/z*: 269 ($M^+$H).

*4.1.1.2. 3-Furan-2-yl-1-(4-methoxy-phenyl)-propenone (entry 8, Table 3).* $^1$H NMR (200 MHz, $CDCl_3$)—*δ*: 8.06 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 15.2Hz, 1H), 7.51 (d, *J* = 2.9 Hz, 1H), 7.49 (d, *J* = 15.2Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 2.7 Hz, 1H), 6.50 (s, 1H), 3.87 (s, 3H); $^{13}$C NMR—*δ*: 188.5, 163.8, 152.2, 145.1, 131.4, 131.1, 130.3, 119.6, 116.2, 114.2, 113.0, 55.8. IR (KBr) 1656, 1600 $cm^{-1}$. MS (FAB) *m/z*: 229 ($M^+$H).

*4.1.1.3. 1-(4-Hydroxy-phenyl)-3-(4-methoxy-phenyl)-propenone (entry 14, Table 3).* $^1$H NMR (200 MHz, $CDCl_3$)—*δ*: 7.99 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 15.6 Hz, 1H), 6.93(d, *J* = 7.2 Hz, 4H), 5.85 (brs, 1H), 3.86 (s, 3H), IR (KBr) 3371,1654, 1583 $cm^{-1}$. MS (FAB) *m/z*: 254 ($M^+$H).

*4.1.1.4. 1-(4-Methoxy-phenyl)-3-napthalene-2-yl-propenone (entry 17, Table 3).* $^1$H NMR (300 MHz, $CDCl_3$)—*δ*: 8.64 (d, *J* = 15.4 Hz, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.93-7.88 (m, 3H), 7.63 (d, *J* = 15.4 Hz, 1H), 7.59–7.49 (m, 3H), 7.00 (d, *J* = 8.6 Hz, 2H), 3.89 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$)—*δ*: 187.9, 163.7, 139.6, 133.7, 131.7, 131.4, 131.0, 130.6, 129.1, 127.5, 126.6, 126.1, 125.8, 124.7, 123.2, 114.4, 55.9; IR (KBr) 1654, 1600 $cm^{-1}$. MS (FAB) *m/z*: 289 ($M^+$H).

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