Synthesis of chalcone derivatives by using ammonium chloride

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Abstract: A simple, efficient and environmentally benign one-pot multicomponent synthesis of *E*-chalcones was developed using an inexpensive, readily available, Non- polluting ammonium chloride catalyst.

Keyword: aromatic aldehyde; aromatic ketones; aromatic amines; chalcones; ammonium chloride; ethanol

I] Introduction:

Organic syntheses are composed of two main types of reactions: carbon-carbon bond formations and functional group transformations. C-C bond formation is the essence of organic synthesis and provides the foundation for generating more complicated organic compounds from simpler ones. [1] The aldol reaction is an important reaction for the creation of carbon-carbon bonds. The condensation reactions of active methylene compounds such as acetophenone or cyclohexanone with aryl aldehydes under basic or acidic conditions gave good yields of aldol along with the dehydration compounds called chalcone.[2] Chalcone compounds are a group of natural organic compounds present in many medicinal plants [3], such as licorice and safflower, with a basic skeleton structure of 1,3-diphenyl acrylone, due to its molecular structure with greater flexibility can be combined with different receptors [4]. The chalcone family has attracted much interest not only from the synthetic and biosynthetic perspectives but also due to its broad interesting biological activities. Therapeutic applications of chalcones trace back thousands of years through the use of plants and herbs for the treatment of different medical disorders, such as cancer, inflammation, and diabetes [5-9]. Several chalcone-based compounds have been approved for clinical use. For example, metochalcone was once marketed as a choleretic drug, while sofalcone was previously used as an antiulcer and mucoprotective drug. Modern pharmacological studies have shown that chalcone derivatives have a variety of biological activities including: anti-tumor, anti-oxidation, platelet aggregation, antiparasitic, anti-virus, anti-ulcer, anti-bacterial, anti-inflammatory, inhibition, Liver and other effects [10]. They are main precursors for the biosynthesis of several flavonoids and isoflavonoids [11]. Flavonoids are the regular constituents of human diet. Flavonoids which are synthesized in plants performing diverse physiological functions such as attractants of pollinators, UV protectors, and insect repellents. They have found numerous applications as pesticides, photo protectors in plastic, solar creams, food additives. Because of its conjugated system, chalcones with proper electron-pulling and electron-pushing functional groups on the benzene ring(s) can be fluorescent [12-18] making them potential chemical probes for mechanistic investigations and imaging/diagnosis. Traditionally, chalcones could be obtained via the Claisen–Schmidt condensation carried out in basic or acidic media under homogeneous conditions. In the most recent decades, heterogeneous catalysis is widely accepted as an environmental friendly alternative for fine chemicals synthesis. There are many solid basic catalysts that have been applied in the synthesis of chalcones, such as MgO [19] hydrotalcites [20], natural phosphates modified with $NaNO_3$ or KF [21], metal doped carbon catalysts [22] and amino propylated mesoporous silica [23] Even though these reactions provide advantages due to its heterogeneous nature, the major drawback is associated with poor selectivity to chalcone in strong basic conditions. It is widely accepted that there is a need to develop clean and economical processes, where the use of noxious substances and the generation of wastes can be avoided. Ammonium chloride as an inexpensive and commercially available reagent has been used in various reactions. It efficiently foster the Ugi reaction [24], Biginelli reaction [25], claisen rearrangement [26], isocyanides-based MCRs for the synthesis of 4-imino-4H-3,1-benzoxazines [27]. So it is used as promoter in the oxidation [28] or reduction of organic compounds [29].

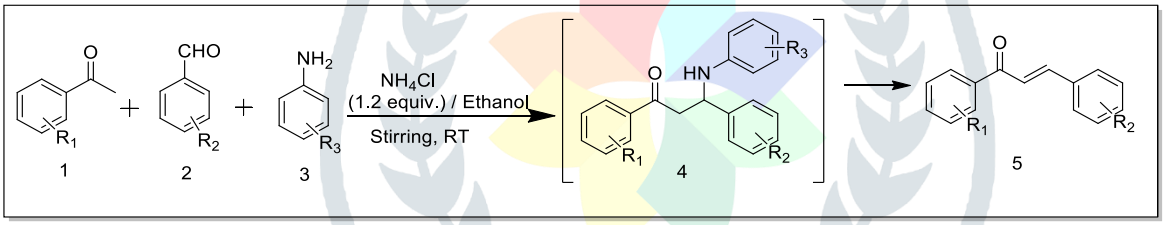
II] Results and Discussion:

Initially our focus was to synthesize *β*- amino ketones with aromatic ketones, aromatic aldehydes, and aromatic amines. For this synthesis we optimized different reaction condition. When reaction occurred with 0.1 mmol of ammonium chloride in ethanol at room temperature for 48h, the product **4** was afforded in 25% yield. When the amount of ammonium chloride was increased up to 0.5 mmol the yield of product **4** greatly increased to 95% within 24h. However, further increases in the amount of ammonium chloride (0.6-0.8 mmol) no significant yield improvement was observed (Table 1, entries 5 and 6). We also added 1mmol of ammonium chloride; in this case on TLC we observed another spot than *β*- amino ketones. So we continued this reaction at 48 hr, surprisingly we obtained chalcone. So we increases amount of NH_4Cl up to 1.5 mmol the product 4 was in 25% and the product 5 was in 75% yield.

Table No. 1:- Optimization of reaction condition

Entry	NH_4Cl (equi)	Temp (°C)	Solvents	Time	Yield (%) 4	5
1.	0.1	RT	EtOH	48h	25	-
2.	0.2	RT	EtOH	48h	40	-
3.	0.3	RT	EtOH	48h	55	-
4.	0.4	RT	EtOH	24h	70	-
5.	0.5	RT	EtOH	24h	95	-
6.	0.8	RT	EtOH	24h	95	-
7.	1.0	RT	EtOH	24 h	80	20
8.	1.2	RT	EtOH	48h	50	50
9.	1.5	RT	EtOH	48h	25	75
10.	2.0	RT	PEG	48h	20	50
11.	2.5	RT	CH_2Cl_2	48h	-	-

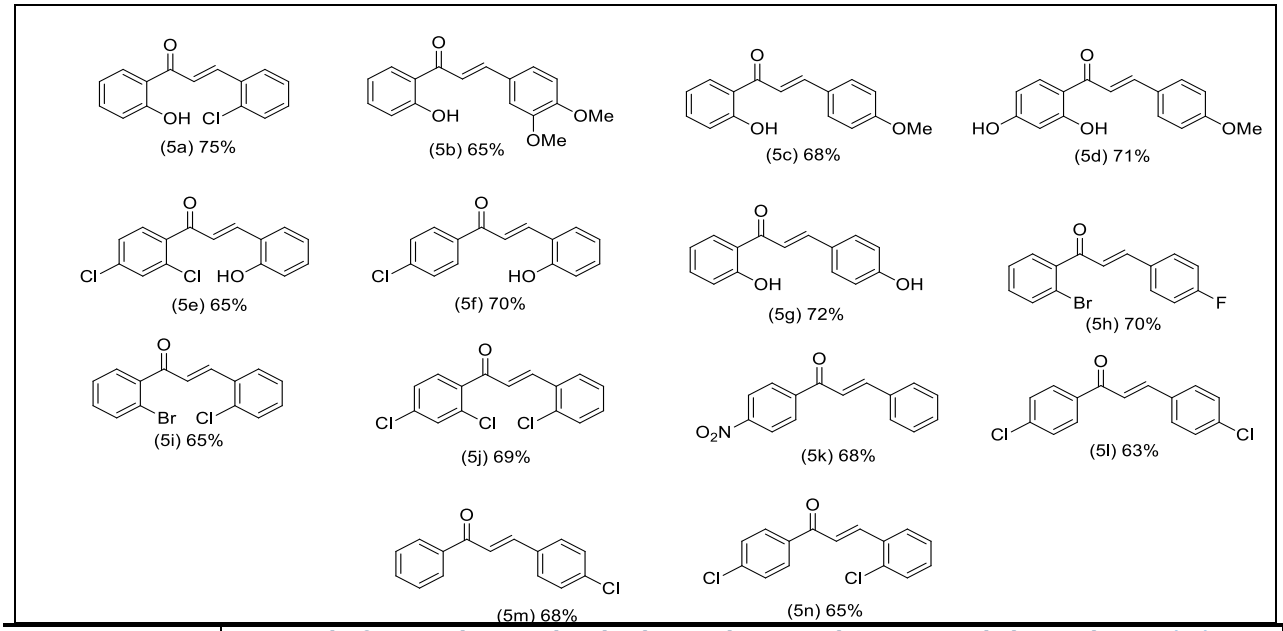
In present reaction condition chalcone is formed after elimination of aniline (Scheme 1). Formation of chalcone can easily controlled by amount of ammonium chloride and reaction time. As per our knowledge, such type of environmental friendly chalcone formation is not observed in the literature.



Scheme 1: Formation of chalcone via mannich base.

Optimistic by these results, we next turned to explore the scope and generality of the present method with variety of aromatic aldehydes, aromatic ketones and amines. Various aromatic aldehydes, ketones and amines having electron withdrawing group viz., NO_2, Cl, Br as well as electron donating groups like OMe, Me were chosen for screening. In all cases, the reaction proceeds smoothly with 1.5 mmol of NH_4Cl in ethanol. Ammonium chloride acts as a mild Bronsted acid to induce the reaction is highly stereoselective, affording α-β unsaturated ketones (chalcone) in excellent yield with *E*-geometry.

Table 2: synthesis of chalcone derivatives in one pot



[a] Reaction condition: 1(1mmol), 2(1mmol), 3(1mmol),and NH_4Cl (1.5mmol) in ethanol at room temperature for 48h. isolated yield are given.

III] Conclusion:

In conclusion, a new method was developed for the synthesis of chalcones using easily available, cheap and easy to handle general laboratory reagent NH_4Cl in mild reaction conditions. Further, this protocol was successfully applied for the synthesis of several electron donating and electron withdrawing chalcone derivatives.

IV] General procedure for the synthesis of Chalcone:

The mixture of aromatic ketone (10 mmole), aromatic aldehydes (10 mmole), aromatic amines (10mmole) and ammonium chloride (1.5mmol) was stirred at room temperature for 30-48 hrs in ethanol solvent. When reaction was completed as indicated by TLC. The product precipitated from reaction mixture. The precipitate was filtered off, dissolved in hot ethanol. The filtrate was kept at room temperature and the resulting crystallized product was collected by filtration. The product was identified by IR, ^{1}HNMR, ^{13} CMR, LCMS, HRMS.

V] Spectral analysis:

(E)-3-(3,4-dimethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (5b) :
Yellow solid, **m.p.:** 170^{0}C**, IR**(KBr): 3062, 1670,1588, 1398,750, 523 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ; 12.93 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.91 (d, *J* = 15.4 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.29 (d, *J* = 6.2 Hz, 1H), 7.07 – 6.96 (m, 1H), 3.97 (s, , 3H), 3.95 (s, , 3H).; **^{13}C NMR (**101 MHz, $CDCl_3$)**.;** MS (EI, 70eV) m/z 284.31 (M^+).

(E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (5c):
Yellow solid, **m.p.:** 162^{0}C**, IR**(KBr): 3270, 1635, 1558, 1204,753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ12.96 (s, 1H), 7.94 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 15.4 Hz, 1H), 7.52 (s, 1H), 7.07 – 6.96 (m, 4H), 3.90 (s, 3H).; **^{13}C NMR (**101 MHz, $CDCl_3$) δ 193.70, 163.58, 162.06, 145.37, 136.15, 130.56, 129.54, 127.40, 120.16, 118.76, 118.61, 117.66, 114.55, 55.47**;** MS (EI, 70eV) m/z 254.28 (M^+).

(E)-1-(2, 4-dichlorophenyl)-3-(2-hydroxyphenyl) prop-2-en-1-one (5e):
Yellow solid, **m.p.** 130^{0}C **IR** (KBr): 3405, 3053, 1689, 1595, 1509, 1445, 1329, 743, 688 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 16.2 Hz, 1H), 7.51 (dd, *J* = 5.2, 1.6 Hz, 2H), 7.48 – 7.42 (m, 2H), 7.41 – 7.36 (m, 1H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.03 – 6.83 (m, 2H), 6.72 (s, 1H).**^{13}C NMR (**101 MHz, $CDCl_3$) δ 195.93, 194.43, 165.98, 155.99, 154.06, 143.56, 137.38, 136.86, 132.48, 132.45, 130.43, 130.23, 130.12, 127.21, 126.63, 121.59, 121.01, 116.64. **MS** (EI, 70eV) m/z 293.14 (M^+). Anal. Calcd. for $C_{15}H_{10}Cl_2O_2$: C, 61.46; H, 3.44; Cl, 24.19; O, 10.92; Found: C,61.40; H, 3.48; Cl,24.22; O,10.95

(E)-3-(2-chlorophenyl)-1-(2,4-dichlorophenyl)prop-2-en-1-one (5j) :
Yellow solid, **m.p.**120^{0}C**, IR**(KBr): 1660, 1593, 1172.95, 1445,1070.93, 879.28, 537 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ. 7.93 (d, *J* = 16.1 Hz, 1H), 7.72 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.48 (ddd, *J* = 14.2, 7.9, 1.6 Hz, 3H), 7.39 (dd, *J* = 8.3, 1.9 Hz, 2H), 7.34 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.12 (d, *J* = 16.1 Hz, 1H); **^{13}C NMR (**101 MHz, $CDCl_3$) δ 192.27, 142.09, 137.20, 137.18, 135.59, 132.63, 132.49, 131.66, 130.59, 130.33, 130.27, 128.11, 127.87, 127.35, 127.21, MS (EI, 70eV) m/z 311.59 (M^+).

(E)-1-(4-nitrophenyl)-3-phenylprop-2-en-1-one (5k):
Yellow Solid, Melting Point: 152^{0}C **IR**(KBr) (ν_{max}/ cm^{-1}): 3053, 1689, 1595, 1509, 1445, 1329, 743, 688 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.7 Hz, 2H), 8.20 – 8.14 (m, 2H), 7.87 (d, *J* = 16 Hz, 1H), 7.70 (m, 2H), 7.51 (d, *J* = 16 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H)**.: ^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.04, 150.12, 143.09, 142.32, 134.35, 129.28, 129.22, 129.15, 129.14, 128.95, 128.71, 123.87, 121.39. **MS** (EI, 70eV) *m/z* 253.07 (M^+).

(E)-1,3-bis (4-chlorophenyl)prop-2-en-1-one (5l):
Yellow solid, **m.p.**120^{0}C**, IR**(KBr): 1660, 1593, 1172.95, 1445,1070.93, 879.28, 537 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 2H), 7.78 (d, *J* = 15.7 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.50 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H) ; **^{13}C NMR (**101 MHz, $CDCl_3$) δ 188.94, 144.00, 139.30, 136.43, 131.00, 130.96, 130.38, 129.88, 129.52, 128.97, 121.23; MS (EI, 70eV) m/z 277.15 (M^+).

(E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (5m):
Yellow solid, **m.p.:** 110^{0}C**, IR**(KBr): 3062, 1670,1588, 1398,750, 523 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ; 8.03 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.77 (d, *J* = 15.7 Hz, 1H), 7.62 – 7.57 (m, 3H), 7.52 (dd, *J* = 11.5, 4.2 Hz, 3H), 7.43 – 7.39 (m, 2H).**^{13}C NMR (**101 MHz, $CDCl_3$) δ190.22, 143.28, 138.07, 136.44, 133.43, 132.92, 129.59, 129.25, 128.68, 128.50, 122.54.**;** MS (EI, 70eV) m/z 242.70 (M^+).

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