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Ammonium chloride catalyzed microwave-assisted Claisen-Schmidt reaction between ketones and aldehydes under solvent-free conditions

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Abstract: *It has been found that ammonium chloride, which is a very inexpensive and readily available reagent, can efficiently catalyzed Claisen-Schmidt reaction between ketones and aldehydes. α,α′-Bis(arylmethylene)cycloalkanones, α,α′-bis(cinnamylidene)cycloalkanones, α-cinnamylideneacetophenones and chalcones were afforded by reaction of ketones and aldehydes under microwave assisted solvent-free conditions in presence of ammonium chloride in good to excellent yields.*

Keywords: *Claisen-Schmidt reaction, Ammonium chloride, Microwave irradiation, Solvent-free conditions, Eco-friendly*

I. Introduction

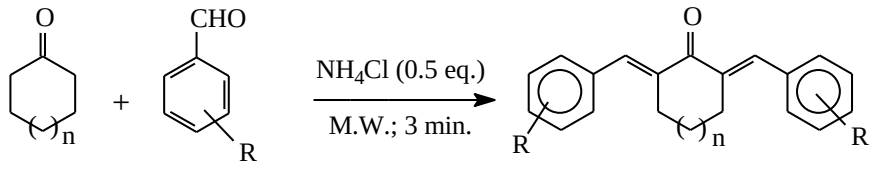
It is well known that α,α'-bis(arylmethylene)cycloalkanones, chalcones and related compounds are used as starting materials for synthesis of a variety of other interesting compounds[1-3] and exihibit a wide range of biological activities such as antibacterial and antitumor properties[4]. The principal synthetic routes avenues to these compounds comprise the base, protic and Lewis acid catalyzed reaction of ketomethyl or ketomethylene compounds with aldehydes. In view of that, several synthetic methods for the preparation of such compounds have been reported by using catalysts such as: solid NaOH[5], $BF_3.OEt_2$[6], $InCl_3$[7], $InCl_3$/TMSCl[8], $TiCl_3(SO_3CF_3)$ [9], TMSCl/NaI[10], $Yb(OTf)_3$[11], $Cu(OTf)_2$[12], $RuCl_3$[13], $FeCl_3$[14], SmI_3[15], silica surfuric acid[16], KF/inorganic solid support[17], Co(II)-bipyridyl[18], Molecular Iodine[19] and $SOCl_2$[20]. Microwave irradiation methods were also reported using KF-Al_2O_3[21], NaOH[22], acidic alumina[23], Na_2CO_3-TBAB (PTC condition)[24] and bis(*p*-methoxyphenyl)telluroxide[25] as catalysts. Most of these methods suffer from various disadvantages such as long reaction periods [*e.g.* 10 hrs using Cp_2ZrH_2/$NiCl_2$[26]], use of expensive Lewis acids [*e.g.* amberlyst-15[27] and B_2O_3/ZrO_2 or SO_4^{2-}/ZrO_2[28]], use of hazardous catalyst [*e.g.* iodine[19]]. Moreover, none of these methods is environmentally friendly, since always an excess of solvent and often toxic or hazardous chemicals are employed. Due to these problems, development of an efficient and versatile method for the preparation of α,α'-bis(arylmethylene)cycloalkanones, chalcone and related compounds are an important aspect and which is an active going on research area and there is a scope for the further improvement towards mild reaction conditions and improved yields.

Ammonium chloride has been reported as catalyst for synthesis of various organic compounds. It is efficiently promoted Ugi four-component reactions[30], four-component synthesis of pyrrolo[3,4-*b*]pyridones[31] and one-pot synthesis of imidazole[1,2-*a*]pyridines[32]. Moreover ammonium chloride was effectively used as catalyst for aliphatic Claisen rearrangement[33], reduction of azo compounds to their corresponding hydrazine[34], reduction of nitrophenols in aqueous media[35] and under ultrasound[36], reductive cleavage of azo compounds[37], synthesis of diindolylmethanes[38], synthesis of spirochromenes and spiroacridines compounds[39] and Biginelli synthesis of 3,4-dihydropyrimidinones under solvent-free conditions[40]. Recently, Teimouri *et al*.[41] were synthesized α,α'-bis(substituted benzylidene)cycloalkanones using ammonium chloride in ethanol under refluxing conditions within 3.5 to 5 hrs. There is an increasing interest in the use of environmentally feasible regents particularly in solvent-free conditions and also reduction of reaction times. Prevention of organic solvents during reactions in organic synthesis leads to a clean, efficient, and economical technology; not only with the reduction of cost, but also increased amounts of reactants can be achieved in the same equipment without huge modification. A survey of the literature revealed that the reaction between cycloalkanones and aromatic aldehydes using ammonium chloride under microwave irradiation has not been studied so far.

In continuation of this research, I herein report the rapid synthesis of α,α'-bis(arylmethylene)cycloalkanones, α,α'-bis(cinnamylidene)cycloalkanones, α-cinnamylideneacetophenones and chalcones using ammonium chloride as a environmentally friendly catalyst using microwave irradiation under solvent-free conditions (Scheme 1 & 2).

II. Results And Discussion

In this methodology, **s**everal aromatic aldehydes were rapidly reacted with cyclohexanone and cyclopentanone when subjected to microwave irradiation in presence of ammonium chloride under solvent-free conditions. The condensation proceeded smoothly to form α,α′-bis(arylmethylene)cyclohexanones (**3a-f**) and α,α′-bis(arylmethylene)cyclopentanones (**3g-k**), respectively, in very good yield (73-95%) (Scheme 1, Table 2). Furfuraldehyde and cinnamaldehyde also reacted with the said cyclic ketones in the similar way.



n = 1, 0

1 **2** **3a-f : n= 1**
3g-k : n= 0

Scheme 1

To achive the best results for this reaction (Scheme 1) we have studied the synthesis of α,α′-bis(phenylmethylene)cyclohexanone (**3a**, entry a**,** Table 2) as a model substrate with using various amount of catalyst (0.25, 0.50 and 0.75 mmol) in different reaction times. For each reaction condition, conversion of benzaldehyde (2 mmol) and cyclohexanone (1 mmol) to **3a** was realized by TLC using silica-gel G of SRL Pvt. Ltd.

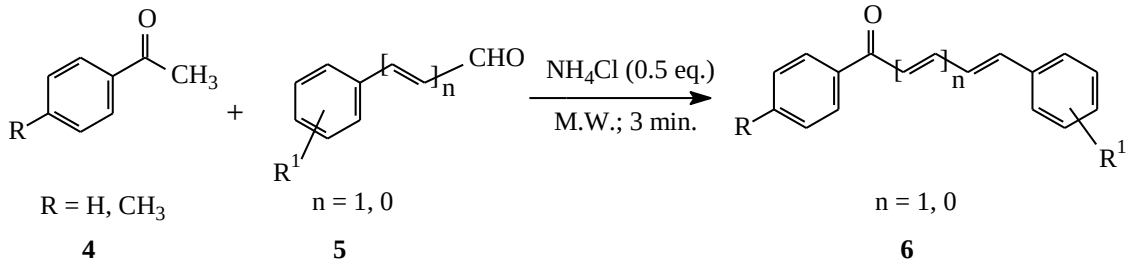
Table 1. Optimization of catalyst content and reaction time.

Catalyst (eq.)	Reaction time (min)	Conversion (%)
0.25	1	40
0.25	2	55
0.25	3	63
0.5	1	71
0.5	2	90
0.5	3	99
0.75	1	75
0.75	2	94
0.75	3	98

As shown in Table 1, the most satisfactory results were obtained with a 2:1:0.5 ratios of benzaldehyde, cyclohexanone and ammonium chloride for 3 min.

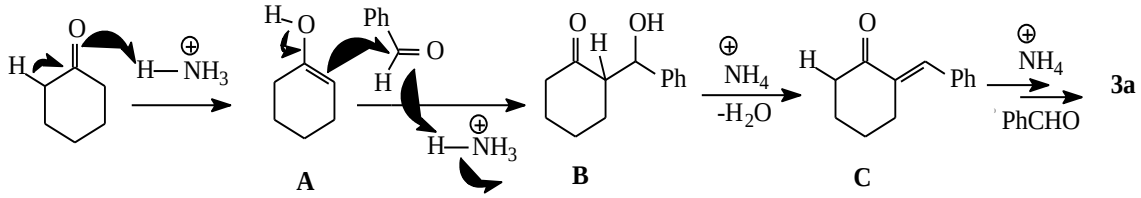
The experimental procedure is very simple and the conversion occurs in short irradiation time of *ca*. 3 min. After irradiation the mixture was cooled, poured in ethanol, and filtered. After evaporation of the solvents corresponding condensation products were recovered in crystalline forms. The reactions were clean and free from side products such as self condensation of ketones. The presence of electron donating or electron withdrawing group in the aromatic aldehyde did not show any significant effect on the rate of conversion under the present experimental condition. When this reaction was carried out under thermal condition in refluxing acetonitrile a longer time (6 hrs.) was required and the yields of the products were also low (40-50%).

After getting success in condensation of cycloalkanones with aromatic aldehydes and related compounds, I turned my attention to apply this methodology for synthesis of chalcones and related compounds which are also well-known for their biological activities as well as for their easy transformation to other biologically active compounds. Thus, when acetophenone and benzaldehyde or cinnamaldehyde were used, the desired chalcones and related compounds were obtained in 70-88% yield (Scheme 2, Table 3).



Scheme 2

The catalytic role of ammonium chloride in the above process was clearly evident from the observation that in its absence no reaction took place. Neutral alumina used acted as solid support only, and this view corroborates the findings of Esmaeili *et al*.[23]



Scheme 3

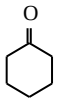
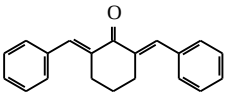
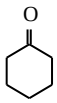
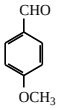
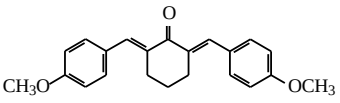
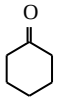
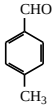
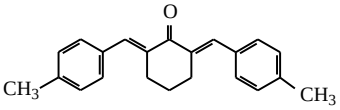
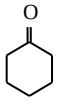
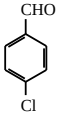
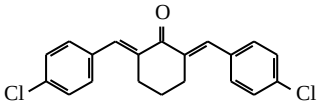
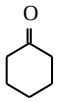
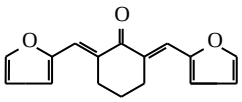
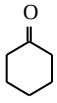
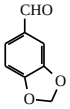
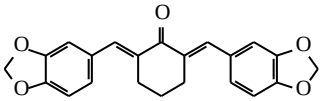
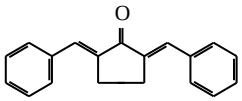
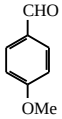
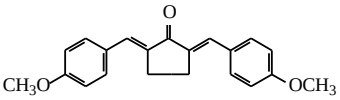
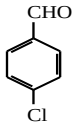
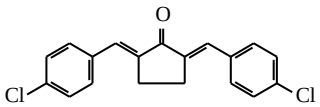
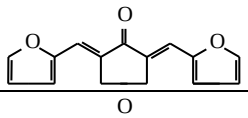
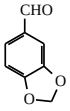
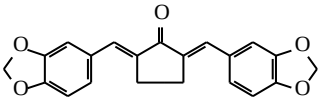
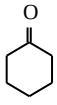
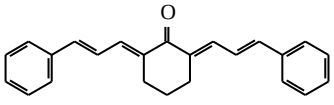
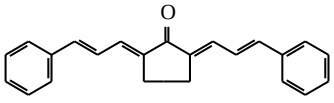
Scheme 3 briefly shows the catalytic behavior of ammonium chloride throughout the predicted mechanistic pathway for the preparation of **3a**. Ammonium chloride could activate the carbonyls of cyclohexanone for formation of enol **A** as well as the nucleophilic attack of **A** to benzaldehyde which formed an intermediate **B**. The intermediate **B** again activated for dehydration by formation of hydrogen bonding of its hydroxyl group with NH_4Cl which formed **C**. Repetition of these processes formed **3a**.

My findings (Table 2 & 3) reflect the wide applicability and usefulness of the method. Some previously reported data (Table 4) on reaction conditions and yield of product for preparation of α,α′-bis(phenylmethylene)cyclohexanone (entry a, Table 2) were compared with this results. As one can see the results show a very good comparability with previously reported data particularly Teimouri *et al*.[41] in order to yields and reaction times.

Table 4. Comparison own result with reported previously data for synthesis of α,α′-bis(phenylmethylene)-cyclohexanone (**3a**).

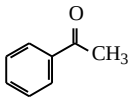
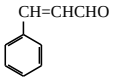
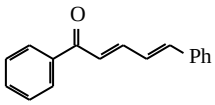
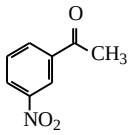
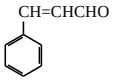
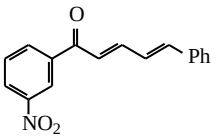
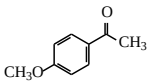
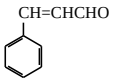
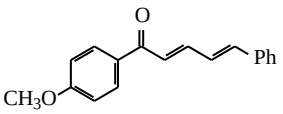
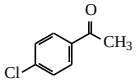
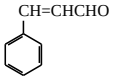
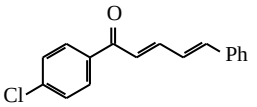
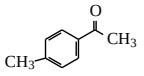
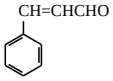
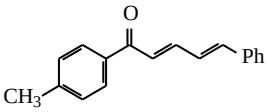
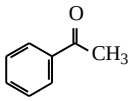
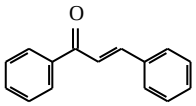
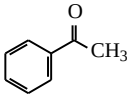
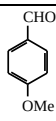
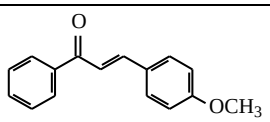
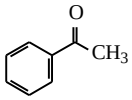
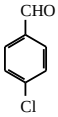
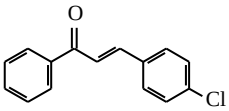
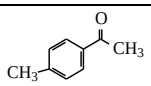
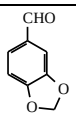
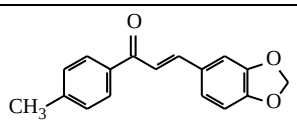
Catalyst	Reaction condition	Time	Catalyst content	Yield (%)	Ref.
Indium trichloride	Solvent-free, 110ºC	6 hr	0.1 mmol	95	7
Copper triflet	Solvent-free, 80ºC	6 hr	0.05 mmol	94	12
Iodine	Solvent-free, 60-65ºC	10 min	0.1 mmol	93	19
Ytterbium triflet	Solvent-free, 90ºC	6 hr	0.025 mmol	92	11
Ruthenium trichloride	Solvent-free, 120ºC	6 hr	0.1 mmol	95	13
Silica sulfuric acid	Solvent-free, 80ºC	2.5 hr	4 mmol	91	16
SO_4^{2-}/ZrO_2 or B_2O_3/ZrO_2	Solvent-free, MW	18 min	unspecified	96	28
Amberlyst-15	Solvent-free, MW	3 min	100 mg	80	27
$KF\text{-}Al_2O_3$	Solvent-free, MW	4 min	37 % (w/w)	90	21
Acidic alumina	Solvent-free, MW	3.5 min	4 gm	97	23
Ammonium chloride	Ethanol, Reflux	5 hr	0.5 mmol	91	41
Ammonium chloride	Solvent-free, MW	3 min	0.5 mmol	95	Present work

Table 2. Results of Microwave assisted Claisen-Schmidt reaction between cycloalkanones and aldehydes catalyzed by ammonium chloride.

Entry	Ketone (**1**)	Aldehyde (**2**)	Product (**3**)[a]	Isolated Yield (%)[b]	Mp/ ºC	
					Found	Reported
a				95	114	115-116[21]
b				81	203-205	205[23]
c				79	164-166	168[16]
d				90	137	138[27]
e				78	140-142	143-145[23]
f				79	180-182	184[27]
g				82	190	190-191[16]
h				73	213-215	212-215[16]
i				87	227-239	225[16]
j				80	204	204-205[19]
k				74	259-261	262[27]
l				81	178	178-180[21]
m				84	219-221	222-224[21]

[a]All products were identified by their melting points and spectral data; [b]Isolated yields.

Table 3. Results of Microwave assisted Claisen-Schmidt reaction between acetophenones and aldehydes catalyzed by ammonium chloride.

Entry	Ketone (**4**)	Aldehyde (**5**)	Product (**6**)[a]	Yield (%)[b]	Mp/ ºC	
					Found	Reported
a				70	84-85	86[27]
b				75	122	120-121[27]
c				78	74-75	76-78[27]
d				82	133-135	136[27]
e				85	77	78-80[27]
f				96	56	56-57[20]
g				87	68-70	69-71[5]
h				78	110-112	111-113[5]
i				90	110	112[27]

[a]All products were identified by their melting points and spectral data. [b]Isolated yields after crystallization in ethanol.

III. Experimental

1.1. Chemicals and Apparatus

All the chemicals used in the present study are of analytical grade and were obtained from local suppliers. Melting points were determined on a Kofler block and uncorrected. IR spectra were recorded on Perkin Elmer FT-IR Spectrophotometer (Spectrum RX 1) and Jasco FT-IR-4200 Spectrophotometer as KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker AV-300 (300 MHz) spectrometers using TMS as an internal standard. Analytical samples were dried *in vacuo* at room temperature. Microanalytical data were recorded on two Perkin-Elmer 2400 Series II C, H, N analyzers. Column chromatograpy were performed on silica gel (100-200 mesh) using petroleum ether (60-80ºC)-ethyl acetate mixture as eluents. TLC was carried out on silica gel G.

1.2. General procedure

Ketone (1 mmol), aldehyde (2 mmol for **3a**-**m** or 1 mmol for **6a**-**i**) neutral alumina (2 g), and ammonium chloride (0.03 g, 0.5 mmol) were mixed thoroughly with the help of mortar pastle and the mixture was taken in a Pyrex beaker (10 mL). The solid mixture was irradiated under a microwave (LG, MH-4048GW, 480 W, 3 min). After completion of reaction indicated by TLC, the reaction mixture was cooled to room temperature, poured in ethanol, and filtered. After evaporation of the solvents corresponding condensation products were recovered in crystalline forms. The products were characterized from their IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The characteristics data of some representative compound are given below.

1.3. Analytical and Spectral data of some selected compounds

2,6-Bis(piperanyl)cyclohexanone (**3f**): Yellow crystalline solid. m.p. 180-182ºC. FT-IR (KBr): 3050, 2930, 1682 (C=O), 1595 (C=C), 1210, 756 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (br. s., 2H), 7.00 (br. d., 2H, *J* = 7.5 Hz), 6.98 (s, 2H, =CH), 6.85 (d, 2H, *J* = 8.4 Hz), 6.01 (s, 4H, -OCH_2O-), 2.87-2.92 (dt, 4H), 1.76-1.84 (quintet, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz); δ 190.1 (C=O), 148.1, 147.7, 136.6, 134.6, 130.2, 125.8, 110.1, 108.4, 101.3, 28.5, 22.9. Anal. Calcd for $C_{22}H_{18}O_5$ (362): C, 72.92; H, 5.01. Found: C, 72.68; H, 5.12%.

2,5-Bis(cinnamylidene)cyclopentanone (**3m**): Yellow crystalline solid. m.p. 219-221ºC. FT-IR (KBr): 3019, 2909, 1674 (C=O), 1615 (C=C), 1203, 755 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.03-7.52 (m, 12H), 6.95-7.02 (m, 4H), 2.92 (s, 4H).

α-Cinnamylidene-4-methylacetophenone (**6e**): Yellow crystalline solid. m.p. 77ºC. FT-IR (KBr)): 3041, 2953, 1652 (C=O), 1600 (C=C), 1199, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 (d, 2H, *J* = 8.1 Hz), 7.60 (ddd, 1H, *J* = 15.3, 7.2 & 3.0 Hz), 7.50 (dd, 2H, *J* = 6.9 & 1.3 Hz), 7.27-7.40 (m, 5H), 7.10 (d, 1H, *J* = 17.2 Hz), 6.97-7.05 (m, 2H), 2.43 (s, 3H, CH_3).

4'-Methyl-α-piperanylacetophenone (**6i**): Yellow crystalline solid. m.p. 110ºC. FT-IR (KBr)): 3060, 2933, 1675 (C=O), 1590 (C=C), 1220, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (d, 2H, *J* = 8.1 Hz), 7.73 (d, 1H, *J* = 15.6 Hz), 7.37 (d, 1H, *J* = 15.6 Hz), 7.29 (d, 2H, *J* = 8.1 Hz), 7.17 (d, 1H, *J* = 1.5 Hz), 7.11 (dd, 1H, *J* = 8.0 Hz & 1.5 Hz), 6.83 (d, 1H, *J* = 7.8 Hz), 6.00 (s, 2H, -OCH_2O-), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.9 (C=O), 149.8, 148.3, 144.2, 143.4, 135.8, 129.7, 129.2, 128.5, 125.1, 120.2, 108.6, 106.6, 101.6, 21.65 (CH_3). Anal. Calcd for $C_{17}H_{14}O_3$ (266): C, 76.68; H, 5.30. Found: C, 80.55; H, 5.21%.

IV. Conclusions

In Conclusion, I have developed an economically and environmentally friendly catalyser for simple and efficient synthesis of α,α'-bis(arylmethylene)cycloalkanones, α,α'-bis(cinnamylidene)cycloalkanones, α-cinnamylideneacetophenones and chalcones in relatively short reaction times using microwave irradiation under solvent-free reaction conditions. This involves the use of NH_4Cl as a very inexpensive and easily available catalyst under neutral and solvent free conditions. Present methodology offers very attractive features such as reduced reaction times, higher yields and economic viability of the catalyst, when compared with other catalysts, which will have wide scope in organic synthesis.

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