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CALCIUM CHLORIDE/HCl AN EFFICIENT CO-CATALYTIC SYSTEM FOR SYNTHESIS OF 3-(ARYLIMINOMETHYL)-CHROMONES UNDER SONOCHEMICAL CONDITION

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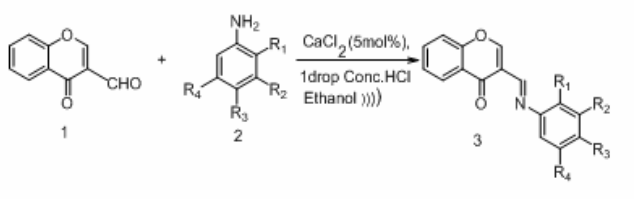
Calcium Chloride and one drop concentrated HCl has been found to be an efficient catalyst for the synthesis of 3-(Aryliminomethyl)-Chromones (**3**) from 3-Formylchromones (**1**) and amines (**2**) under ultrasound condition. The reaction under ultrasound condition proceeds in high yields at ambient temperature in a short time. A variety of imines have been synthesized by varying substituent on aromatic amines in good yields.



INTRODUCTION

In the last decade sonochemistry has been attracting many organic chemists to develop new organic transformation since it accelerates chemical reactions, improved fields, and improved selectivity. Sonochemistry involves the use of ultrasound technique to promote organic reactions. A huge number of ultrasonic reactions can be carried out in higher yield, shorter reaction time or milder reaction condition. Ultrasound irradiation has been confirmed as an unconventional energy source for organic reactions which can be generally accomplished by heating. Due to the thermal effect of ultrasound wave, large amount of molecules can meet the demand for the active energy in a given reaction, leading to the apparent improvement of the reaction efficiency with increased rates and reduced reaction time. It is also observed that reactions performed under ultrasound irradiation are commonly easier to work-up as compared to the conventional reactions.[1]

Chromones are a group of naturally occurring, oxygen containing heterocyclic compounds. They are widely spread in the plant kingdom and form the basic nucleus of important compounds such as anthocyanin and flavonoids. Chromones are also well known for their antimicrobial,[2,3] antitumor,[4,5] and antiviral activities.[6,7] 3-Formylchromones are important synthons in synthetic chemistry for incorporating chromone moieties into other heterocyclic systems for creating new heterocyclic systems based on chromone ring[8,9] and transition metal chelates. [10] They contain three electron deficient sites (C-2, C-4, CHO) appropriate for nucleophilic attack and as a synthetic manipulation consequence of rivalry between these centers.[11]

The synthetic and therapeutic significance of imines is well familiar. The condensation of amines with carbonyl compounds is an esteemed and valuable organic transformation[12] as the resultant imines are used as versatile components in nucleophillic addition with organometallic reagents,[13] in cylcoaddition reactions[14] and have potential for therapeutic application such as lipoxygenase inhibitors, anti inflammatory agents[15] and anticancer agents.[16] Recently it has been

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reported the biological activity of Schiffs bases of 3-formylchromones as a bovine cytosolic carbonic anhydrse and anti-inflammatory agents, Thymidine phosphorylase inhibitors[17] and Optical selective chemosensor for Al^{3+} ion.[18] 3-(aryliminomethyl) chromones undergo various addition reactions like the variety of alcohols and thiols, and certain thiol adducts can be cyclised to thiazepine derivatives. The action of manganese dioxide on 3-(aryliminomethyl)-chromones leads to 3-(arylamino- methylene) chroman-2,4-diones,[19] and undergoes cycloaddition reaction with benzonitrile oxide and nitrilimine of 4-oxo-4h-1-benzopyran-3-carboxaldehydes with alkenes to give Δ^2-1,2,4 oxadiazolinyl chromones.[20]

A very few reports are available for the synthesis of imines of 3-formylchromones in the literature. The reaction between equimolar quantities of 3-formylchromones and a primary aromatic amine in benzene leads to a mixture of the 3-(aryliminomethyl)chromone and 2-arylamino-3-(arylaminomethylene)chroman-4-one, making the isolation of pure compounds difficult.[19, 21] The reason for this quite unusual ring addition of a second aromatic amine molecule to the imine is due to the formation of a stable ketoamine hydrogen bond.[22] A much improved yield of 3-(aryliminomethyl) chromones can be obtained from the condensation of reactants in the presence of 4-toluene sulfonic acid.[17a, 21, 23] Pure 3-(aryliminomethyl) chromones can be prepared from 2-alkoxy-3-(arylaminomethylene)chroman-4-ones via elimination of a molecule of alcohol by heating the compounds to their melting point under vacuum.[24] Primary aromatic amines having a nucleophilic functionality at their *ortho* position react with 3-formylchromones giving fused seven-membered heterocycles,[25-27] (aryliminomethyl)chromones[25-27] or dihydrotetraaza [1]-anulenes.[28-29] However, these methods suffer from drawbacks like low yield, tedious work-up and hazardous solvent. Hence there is scope for development of new methodology for the synthesis of 3-(aryliminomethyl) chromones.

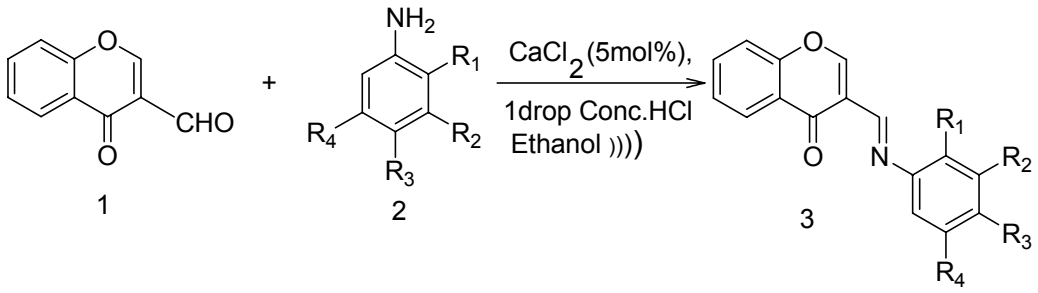
In recent years, there has been substantial attention in developing more economical and environmental-friendly conversion processes. $CaCl_2$ is an inexpensive and commercially available reagent and as it has been shown recently to be a very excellent catalyst in organic reactions like the aldol reaction of dimethyl silyl(DMS)enolates,[30] in the Bigineli reaction,[31] in the synthesis of α-Aminophosphonic esters,[32] in three component Mannich reaction for synthesis of β-amino ketone[33] and in synthesis of flavanone.[34] We here in report an efficient, practical environmentally benign and high yielding method for the synthesis of imines of 3-Formylchromones using $CaCl_2$/HCl as catalyst under ultrasound condition.

RESULTS AND DISCUSSION

There are two possible pathways for the formation of 3-(arylimino- methyl)chromones. The first is a straight-forward 1,2-addition of the amine to the aldehyde function of 1, while the second is a 1,4-addition of the amine with the simultaneous opening of the pyrone ring and successive recyclization of the intermediate.

In 3-formyl chromone, the electrophilic character of aldehyde group reduced due to it is in conjugation with C═C double and oxygen. But when the electrophilicity of the carbonyl and nucleophilicty of amine groups are reduced, the condensation of carbonyl and an amine group requires a catalyst. Calcium chloride has an affinity for water and acts as dehydrating agent and used as drying agent for solvents. Here, we explored this principle for the condensation of between 3-Formylchromones with anilines to afford 3-(aryliminomethyl)chromones under sonochemical condensation. It was expected that calcium chloride would co-ordinate with carbonyl oxygen of aldehyde group and increase the electrophilicity of carbonyl group of aldehyde and facilitate the nucleophilic attack of amine on aldehyde carbonyl and also serve as dehydrating agents to facilitate the removal of water generated in the final step. Use of conc. HCl increases the catalytic activity of calcium chloride due to this reaction time decreases and yield of product increases. As envisaged the reaction proceeded very smoothly to afford the imines in good yield (Scheme 1).

To establish the scope and limitations of Calcium chloride as a catalyst for 3-(aryliminomethyl)chromone formation, 3-Formylchromones were treated with various amines such as aniline, 4-chloroaniline, 4-nitroaniline, 2-nitroaniline, 2,4-disubstitued aniline, 3,4-disubsistued aniline under the catalytic influence of Calcium chloride and the results are summarized in Table 1. Excellent result is obtained in most of the studied cases.



Scheme 1 – Synthesis of chromone Schiff's bases.

Table 1

Condensation reaction between 3-Formyl chromone and various mono- and di-substituted aniline for synthesis of chromone Schiff bases catalyzed by $CaCl_2$/Conc. HCl under ultrasound condition[a]

Entry	Substituted Aniline	Product (3)	% Yield[b]	M.P. ^oC
1	Aniline	**3a**	93	135
2	4-nitroaniline	**3b**	85	181
3	2-nitroaniline	**3c**	67	130
4	3-nitroaniline	**3d**	92	210
5	2-chloroaniline	**3e**	74	107
6	2,3-dichloroaniline	**3f**	84	178
7	3,5-dichloroaniline	**3g**	90	184
8	2,4-dichloroaniline	**3h**	77	139
9	3,4-dichloroaniline	**3i**	88	177
10	3-chloro-4-nitro aniline	**3j**	84	148
11	2-methyl-4-nitroaniline	**3k**	74	162
12	4-methoxy aniline	**3l**	89	172
13	3,4,5-trimethoxyaniline	**3m**	82	202
14	4-bromo-2-methyl aniline	**3n**	78	109

a: Reaction condition 1mmole of 3-formylchromone, 1mmole of substituted aniline and 0.05mmole of calcium chloride/ 1drop of conc. HCl in 10mL ethanol, under ultrasound condition b: isolated after purification.

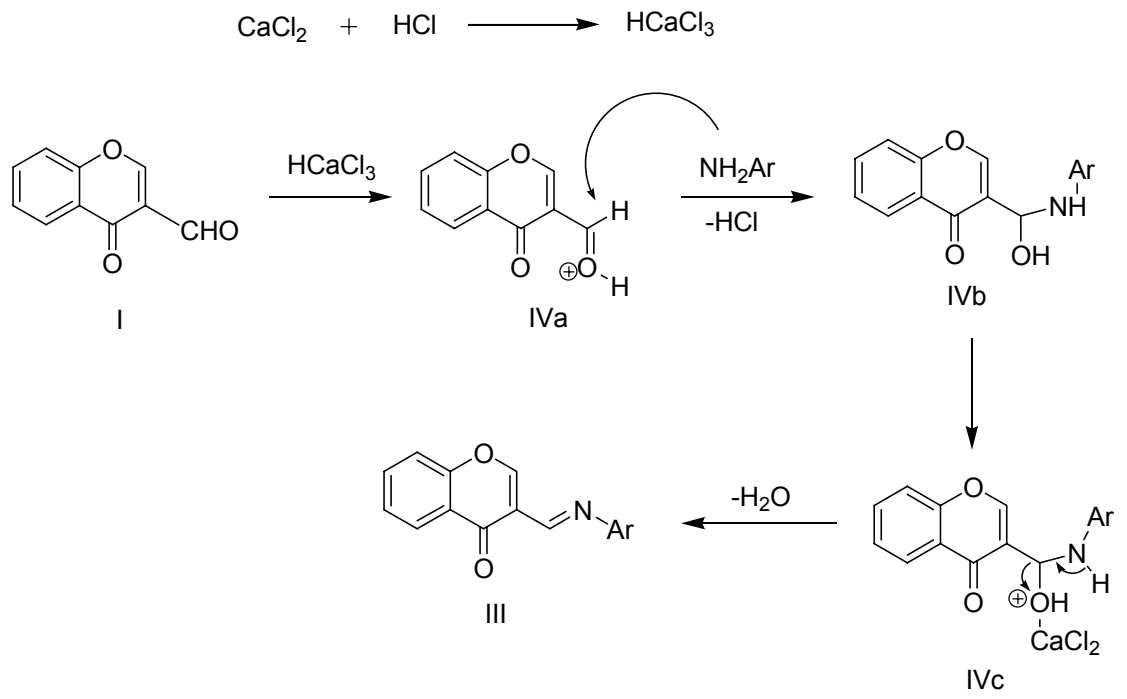
The probable mechanism of imine formation using calcium chloride/Conc. HCl as a co-catalytic system is shown in Scheme 2. In the first step hydrogen atom coordinates with the oxygen of aldehyde carbonyl and in the second step, nucelophilic attack of amine nitrogen on carbonyl carbon yield intermediate IVb and in third step calcium coordinates with oxygen resulting in the removal of water as calcium chloride dihydrate $CaCl_2.\ 2H_2O$ to form product III.

EXPERIMENTAL

All purchased chemicals were of analytical grade and used without further purification. 3-Formylchromone (1) was prepared by the Vilsmeier-Haack synthesis.[11] Melting points are determined by open capillary method and uncorrected. The ^1H NMR spectra were obtained on a Bruker DRX-300 Avance instrument using $CDCl_3$ as solvent and TMS as internal standard at 300MHz.

Typical procedure for imine formation

3-Formylchromoes (1mmole) was treated with substituted aniline (1 mmole), anhydrous calcium chloride (0.05 m mol/ 5 mol %), one drop of conc. HCl was dissolved in ethanol (10 ml). This reaction mixture was irradiated under sonochemical condition at 33KHZ for 2-3 hours. The progress of reaction was monitored by TLC. After the completion of reaction ice cold water was added in the reaction mixture and solid was precipitated out, filtered on Buckner funnel, washed with water followed by ice cold ethanol. The products were purified by recrystalization from ethanol and dried.



Scheme 2 – Probable mechanism for imine formation using calcium chloride/Conc. HCl as a co-catalytic system.

Spectral data of synthesized compound

3-[(phenylimino) methyl]-4H-Chromen-4-one **(3a):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.12 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.52 (m, 1H), 7.46 (m, 1H), 7.32 (m, 1H), 7.07-7.12 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 118.43, 120.24, 125.25, 126.51, 134.69, 160.47, 175.44, 188.43ppm; IR (KBr): $\bar{\nu}$ =1593, 1656 cm^{-1}; HRMS: 250.08 (positive ESI scan)

3-[(4-nitrophenylimino) methyl]-4H-Chromen-4-one **(3b):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56(s, 1H), 8.17(s, 1H), 7.79(d, J=7.5Hz, 1H), 7.72(d, J = 7.1Hz, 2H), 7.55 (m, 1H), 7.46(d, J = 7.1Hz, 2H), 7.44(m, 1H), 7.32(m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 118.62, 120.25, 125.23, 126.16, 126.52, 134.85, 156.17, 160.69, 176.27, 188.68ppm; IR (KBr): $\bar{\nu}$ =1598, 1664 cm^{-1} HRMS: 295.06 (positive ESI scan)

3-[(2-nitrophenyl)imino]methyl]-4H-chromen-4-one **(3c):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55(s, 1H), 8.17 (s, 1H), 7.78(d, J = 7.5Hz, 1H), 7.66(m, 1H), 7.53(m, 1H), 7.42(m, 1H), 7.32(m, 1H), 6.82(m, 1H), 6.78(m, 1H)ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ= 118.72, 120.27, 125.17, 126.14, 126.42, 134.78, 156.10, 160.46, 176.10, 188.53 ppm; IR (KBr): $\bar{\nu}$ =1597, 1662 cm^{-1}; HRMS: 295.06 (positive ESI scan)

3-[(3-nitrophenyl)imino]methyl]-4H-chromen-4-one **(3d):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55(s, 1H), 8.17 (s, 1H), 7.80 (d, J = 7.5Hz, 1H), 7.77(d, J = 7.5Hz, 1H), 7.54(d, J = 7.2Hz, 1H), 7.45(m, 1H), 7.38(m, 1H), 7.13(d, J = 7.2Hz, 1H), 7.05(d, J = 7.2Hz, 1H), 6.8 (m, 1H)ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.60, 120.21, 125.10, 126.14, 126.42, 134.70, 156.08, 160.50, 176.08, 188.46 ppm; IR (KBr): $\bar{\nu}$ =1593, 1655 cm^{-1}; HRMS: 295.06 (positive ESI scan).

CONCLUSIONS

In summary, the present protocol on the use of calcium chloride/HCl as an efficient catalyst for the synthesis of 3-(aryliminomethyl) chromone under ultrasound condition offers advantages in terms of inexpensive and easily available catalyst; condensation of deactivated amines and 3-formylchromones proceeded very smoothly to afford 3-(aryliminomethyl)chromone in high yields compared to reported methods. Reaction conditions and work up procedure are mild and easy to handle.

The present eco-friendly protocol represents an attractive alternative to the existing methods for synthesis of imines.

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