A Conventional and Micro wave Assisted Synthesis of 3-(3-(4-chlorophenyl)acryloyl)-2H-chromen-2-one Using Eco-Friendly Catalyst And Its Characterisation

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Abstract

A convenient and efficient method of Chloro substituted 3-(4-chlorophenyl) acryloyl)-2H-chromen-2-one derivatives were achieved by following two stage. In a first stage 3-Acetyl coumarin were synthesised by a Microwave assisted Method. The mixture of salicylaldehyde and ethyl aceto acetate by a Von Pechmann condensation using Zn [(L)-Proline]₂ as solvent free catalyst. The Organo metallic Catalyst Zinc amino complex was prepared by adding tri ethyl amine and L-Proline in Methanol followed by adding zinc acetate, after completion of reaction getting white Zn [(L)-Proline]₂ complex. In a second stage 3-acetyl coumarin and 4-chloro benzaldehyde were allowed to react with PEG-600 as a solvent by Claisen-Schmidt condensation which gives 3-(3-(4-chlorophenyl) acryloyl)-2H-chromen-2-one by green chemistry approach. In Previous methods of synthesis both conventional and microwave irradiation. The progress of the reaction was monitored by TLC and separated the compound using column chromatography. The synthesized compound structures were identified and confirmed by UV-Visible, FT-IR and ¹H NMR and Mass spectral analysis respectively.

Keywords: Pechmann Condensation; Coumarins; Organo Metallic Catalyst; PEG-600; MWI; Green Synthesis

Introduction

Coumarins have been synthesized as a well-known naturally occurring heterocyclic compounds isolated from various plants. They belong to the family of lactones having 1-benzo pyran-2-one system [1]. Coumarin is a versatile pharmacophore which exhibits wide variety of biological activities [2] like antibacterial [3-4] and antimicrobial [5]. Coumarins have been synthesized by several routes including pechmann [6], Perkin [7], knoevenagel [9], reformatsky [10] and Wittig [11] reactions.

The century-old Pechmann reaction is widely used method for preparing Coumarins [12] and it is an example of exothermic reaction. A commonly used protocol for conducting this reaction involves heating together a mixture of a salicylaldehyde (1) and beta-keto ester such ethyl aceto acetate (2) and a large amount of sulphuric acid [6] as a condensing agent. The major product (4)

obtained in low to good yield is a substituted coumarin. In Pechmann reaction most of the researcher used acidic agents, such as chloro sulphuric acid [12], melamine formaldehyde resin supported H⁺ ion catalyzed [14], ionic liquid catalyzed [15], oxalic acid catalyzed [16], silica triflate catalyzed, heterogeneous catalyst, zirconium supported catalyst etc. Recently, Pechmann reaction has been carried out by using CuFe₂O₄ [17] nano particle and molecular iodine catalyst.

The organo metallic biodegradable Zn[(L)-Proline]₂ [17-28] as a catalyst has found very vast applications in reactions such as, aldol condensation [29], cross aldol coupling reactions [30], rearrangement reaction, condensation reaction, usually acts as strong Lewis acid catalyst and dehydrating agent [31].

Von-Pechmann condensation reaction Zn(L-proline)₂ exhibited the highest catalytic activity with regard to the transformation of Salicylaldehyde (1) and ethyl aceto acetate (2) into 3-acetyl-2H-chromen-2-one (4). Zn(L-proline)₂ which was efficient, inexpensiveness, eco-friendly as well as easy to handle and re usable catalyst in excellent yields. And its higher solubility in water, insolubility in organic solvents.

The synthesis of 3-(3-(4-chloro phenyl) acryloyl)-2H-chromen-2-one (6) achieved by Using PEG-600 [21] green chemistry approach. In this stage 3-acetyl coumarin were condensed with 4-chloro benzaldehyde through Claisen-Schmidt condensation [33] using piperidine and PEG- 600 as a solvent for both conventional and microwave irradiation respectively. In our work MWI using the PEG-600 [34] like Zn (L-proline)₂ is non-toxic, eco-friendly, in-expensive, water soluble and potentially recyclable solvent. Based on the careful analysis of the literature, present investigation was aimed to focus on the PEG-600 solvent system. The series of 3-acetyl coumarin and coumarin chalcone compounds were synthesized by both conventional and microwave irradiation methods. The synthesized compounds were characterized on the basis of UV-visible, FTIR, ¹H NMR and mass spectral data.

Experimental

Methods and materials

The chemicals Salicylaldehyde (1), Ethyl acetoacetate (2), Et₃N (3), L-Proline (4), Zinc acetate (5), 4-chloro benzaldehyde (6), PEG-600 and sodium hydroxide were purchased from Merck (India), Sigma-Aldrich and Avra chemicals. They were used without further purification. Silica gel (TLC and Column grade) was purchased from Merck. The solvents were purified as per the standard procedure reported elsewhere. Melting points were measured in open capillary tubes on Mettler FP51 melting point apparatus and are uncorrected.

The IR spectra were recorded on a Bruker Vertex 70 spectrometer and frequencies were expressed in cm⁻¹. UV-visible spectra were also recorder using Alpha Bruker UV spectra-photometer. The ¹H NMR spectra were recorded on a Bruker 400 MHz instrument in DMSO-d₆ or CDCl₃ using TMS as an internal standard (chemical shifts were reported in ppm units, coupling constants (J) in Hz).

All the compounds were checked for purity by Thin Layer Chromatography (TLC). Mass-spectral analysis was performed by electron ionization on a mass-spectrometer at 20 eV. Microwave reactions are carried out commercially available IFB domestic microwave oven having a maximum power out put of 300W operating at 2450Hz.

Synthesis of Zn [(L) proline]₂

The Zinc amino complex was prepared by adding Et₃N (0.6 ml) to the amino acid (4.34 mmol) in MeOH (10 ml), after 15 min, followed by zinc acetate (2.17 mmol). After stirring for 1 hour a white precipitate was collected by filtration (98 % yields). (Fig 1)

General experimental procedure for Synthesis of 3-acetyl-2H-chromen-2-one (Scheme 1)

Method-A (conventional method): The mixture of Salicylaldehyde (1) (0.2M, 4.28 ml) and ethyl aceto acetate (2) (0.2M, 5.13 ml) was taken in a beaker, with continuous stirring. After 2 mints 5 to 6 drops of catalyst piperidine was added in the reaction mixture with vigorous shaking. After 15 minutes yellow precipitate was separated out. The precipitate was filtered off, washed and re crystallized with ethanol. The purity of compounds was established on the basis of TLC. **Yield: 68-71%** (M.P. 119-121 °C).

Method-B (microwave irradiation method): A mixture of salicylaldehyde (1) (10mmol), ethyl aceto acetate (2) (10mmol) and Zn [(L)-Proline]₂ (3) (20 mol %) were subjected to

microwave irradiation at 300W for appropriate time 3-5 mints. After completion of reaction, as monitor by TLC, the reaction mixture was cooled to room temperature, water was added as a solvent and stirred for another two minutes, and precipitation was filtered off and re crystallized from ethanol to obtained pure 3-acetyl-2 H-chromen-2-one (4) as yellowish crystal.

Yield: 92 % (M.P. 119-121 °C)

Scheme 1

Synthesis of 3-(3-(4-chloro phenyl) acryloyl)-2H-chromen-2-one (Scheme 2)

Method-A (conventional method): A mixture of 3-acetyl-2H-chromen-2-one (4) (0.01mol) and 4-Chloro benzaldehyde (5) (0.01mol) and 10 mL ethanol taken in a round bottom flask. Then 4 to 5 drops of Piperidine was added to it. The reaction mixture allowed refluxing on 5-8 hour at 80°C (The formation of product was monitored by TLC). The reaction mixture was poured into ice cold water and then it was neutralized by hydrochloric acid. The yellow colour solid product was filtered and re crystallized by using ethanol as solvent. (Yield: 71 % and melting point: 222-223 °C)

Method-B (microwave irradiation method): A mixture of 3-acetyl-2H-chromen-2-one (4) (0.01mol) and 4-chloro benzaldehyde (5) (0.01mol) and NaOH (0.02 mol) were grinded in to the mortar. Then it was mixed with 20 mL of PEG-600. The mixed compounds were taken in a100 mL beaker and it was irradiated with microwave oven for the 3-5 min at 300W operating at 2450Hz at 30s of intervals. After completion of reaction as followed by TLC examination, ice water was added to the reaction mixture and neutralized by an acid. The solid product was obtained, which was filtered, dried and crystallized from an ethanol. The filtrate was evaporated to dryness to remove water leaving behind PEG-600. (Yield - 87.5 % and melting point: 222-223 °C).

Scheme 2

Mechanism Of the 3-acetyl-2H-chromen-2-one formation using Zn[(L)-Proline]₂ as a Catalyst (Scheme 1)

The mechanism of formation of 3-acetyl-2H-chromen-2-one can be visualized as shown in Scheme 1. Probably the reaction

initiates by nucleophilic attack of nitrogen of Zn (L-proline)₂ complex on 2-hydroxy Benzaldehyde (**1**) to form A, in which aldehydic oxygen is bonded with Zn(L-proline)₂ complex. A is then converted to B through the displacement of lone pair of electron and opening of carbon-oxygen bond.

The Active Methylene Carbon containing Ethyl aceto acetate X which on enolated, Carbon-carbon double bond of enolized diketone Y then attacks on carbon of B to give C, ethanol as a leaving group in this stage then D undergoes cleavage process to expel out Zn(L-proline)₂ complex (**3**) and water so as to result in 3-acetyl-2H-chromen-2-one (**4**).

Results

Figure 1: FT-IR Spectrum of 3-acetyl-2H-chromen-2-one .

Table 1: Spectral details of 3-acetyl-2H-chromen-2-one (**4**)

Melting point :	119-121 °C	C ₁₁ H ₈ O ₃
UV-visible (λ max: nm) :	298 (π → π* transition), 340 (n → π* transition)	
FTIR (cm ⁻¹) :	2945(Aromatic C-H stretching), 1728.29(C=O(ester)), 1627.29 (C=O(Exo cyclic ketone)), 1599.23 C=C str.(Aromatic),1351(C-Cstr), 752(C-H out plane bending), 1157.28 (C-O str).	(Fig: 1)
¹ H NMR(ppm) :	δ 2.51 (s, 3H, CH ₃), 7.32- 7.95 (m, 4H, Benzo fused coumarin-H), 8.65(s, 1H, Coumarin-H).	(Fig: 2)
Mass (m/z) :	Calculated M.W 188.18	Ob-served M.W 189.60 (Fig: 3)

Table 2: Spectral details of 3-(3-(4-Chloro phenyl)acryloyl)-2H-chromen-2-one (**6**)

Melting point :	246-249 °C	
UV-visible (λ max: nm)	306 (π → π* transition)	
FT-IR (cm ⁻¹) :	1618, ν(C=O, α, β-unsaturated ketone), 1742, ν(C=O, lactone carbonyl of coumarin).	(Fig: 4)
¹ H NMR (DMSO-d ₆ 400 MHz):	δ 6.86 (1H, m, C ₆ -H), δ 7.12 (2H, d, p-substituted phenyl ring), δ 7.23 (1H, m, aromatic protons), δ 7.39 (2H, m, aromatic proton), δ 7.63 (2H, d, p-substituted phenyl ring), δ 7.88 (1H, d, J = 7.8 CH=CH- protons), δ 7.90 (1H, d, CH=CH- protons), δ 8.52 (1H, s, C ₄ -H).	(Fig: 5)
¹³ C-NMR (CD ₃ OD, 400 Hz):	δ 183.7, 159.4, 153.0, 147.2, 142.2, 134.2, 133.5, 133.3, 129.0, 129.0, 128.7, 128.7, 128.3, 127.9, 125.4, 125.4, 118.1, 116.1 ppm.	(Fig 6)
ESI-MS (m/z):	Calculated M.Wt 310.04	Ob-served M.Wt 310.6, 312.7 (Fig: 7)

Figure 2: ^1H NMR Spectrum of 3-acetyl-2H-chromen-2-one.

Figure 3: Mass Spectrum of 3-acetyl-2H-chromen-2-one.

Figure 4: FT-IR Spectrum of 3-(3-(4-Chloro phenyl)acryloyl)-2H-chromen-2-one.

Figure 5: ^1H NMR Spectrum of 3-(3-(4-Chloro phenyl)acryloyl)-2H-chromen-2-one.

Figure 6: ^{13}C NMR Spectrum of 3-(3-(4-Chloro phenyl)acryloyl)-2H-chromen-2-one.

Figure 7: Mass Spectrum of 3-(3-(4-Chloro phenyl)acryloyl)-2H-chromen-2-one.

Discussion

A mixture of Salicylaldehyde (1) and ethyl aceto acetate (2) was subjected to microwave irradiation (300W) in presence of $\text{Zn}[(\text{L})\text{-Proline}]_2$ (3) under solvent free condition with different mol%. (Scheme 1). The Progress of reaction was checked by chromatography (TLC). Optimization of reaction condition was achieved by using varying amounts of $\text{Zn}[(\text{L})\text{-Proline}]_2$ catalyst and best results of yields could be obtained by using 20 mol % of $\text{Zn}[(\text{L})\text{-Proline}]_2$ catalyst. Increasing the ratio, above 20 mol % of $\text{Zn}[(\text{L})\text{-Proline}]_2$ was found to increase rate of reaction but afforded products in low yield due to the formation of side products. (Table 3).

In summary ,for synthesis of 3-acetyl-2H-chromen-2-one by Pechmann condensation is highly efficient as it avoid use of organic solvents at any stage of reaction, under microwave irradiation technique at very low power (300W) and presence of organo metallic biodegradable $\text{Zn}[(\text{L})\text{-Proline}]_2$ as a catalyst.

The (Scheme 1) progressive of the reaction employed $\text{Zn}[(\text{L})\text{-Proline}]_2$ at different Optimised condition furnishing very good yield 92% instead of acid /base catalysts. Our investigation revealed that the catalytic activity of various acidic/basic catalysts in water was found to be in the order $\text{Zn}(\text{L-proline})_2 >$

Table 3: Optimization of reaction condition for synthesis of 3-acetyl-2H-chromen-2-one under Solvent free condition by microwave irradiation technique at low power (300W) using Zn [(L)-Proline]₂ catalyst.

Catalyst	Mol %	Yield
Zn[(L)-Proline] ₂	5	Below 20%
Zn[(L)-Proline] ₂	10	42.2%
Zn[(L)-Proline] ₂	15	69%
Zn[(L)-Proline] ₂	20	92%
Zn[(L)-Proline] ₂	25	84.3%
Zn[(L)-Proline] ₂	30	76.5%

piperidine > L-proline > diethyl amine > FeCl₃ > ZnCl₂ in terms of yield and selectivity.

However, in polar protic solvents MeOH, EtOH, and AcOH relatively high yield of the product (74–78%) was obtained under reflux condition in more period of time, whereas when reaction was performed in water in the presence of Zn(L-proline)₂, it completed within 15 min whole reaction with increase in yield of the product (92%) (Table 4)

UV absorption and FT- IR spectra of compound (4) and (6) has been provided a preliminary idea in confirmation the formation of product. According to the UV spectrum, presence of peaks at 286 nm and 306 nm clearly showed that the compound (6) has –CH=CH– group and hetero atom respectively. According to the FT-IR, presence of peak at 1627.29 cm⁻¹ has clearly, the utilization of starting materials transform in to the product. Further, the corresponding peaks at 2945, 1728.29, 1627.29, 1599.23, 1351.752 and 1157.28 cm⁻¹ have been related to – Ar C-H str, C=O ester (str), C=O Exo cyclic ketone (str), C=Cstr.(Aromatic), C-C str. (exo cyclic), (C-H out plane bending) and (C-O str) respectively in the compound (4) (Fig.1). The concerned mass of the compound (4) is in good agreement with the observed (189.6 m/z) and calculated value (188.18 m/z). (Fig.3) similarly, proton NMR strongly revealed for the formation of the product by its δ value at 2.51, 7.32–7.95, and 8.65 ppm corresponding to the aliphatic C–H, Ar–H and Benzo fused coumarin–H protons of compound (4) were mentioned in (Fig.2).

Similarly, (Scheme-2) to the FTIR, presence of peak at 1618 cm⁻¹ has clearly, the utilization of starting materials transform in to the product. Further, the corresponding peaks at 1618, ν(C=O, α, β-unsaturated ketone), 1742, ν(C=O, lactone carbonyl of coumarin) respectively, in the compound (6). (Fig.4) The concerned mass of the compound (6) is in good agreement with the observed (310.6 m/z) and calculated value (310.04 m/z) (Fig.7).

Table 4: Different solvents effect on the synthesis of 3-acetyl-2H-chromen-2-one in the presence of Zn(L-proline)₂ Catalyst.

Solvent	Time	Yield (%)
H ₂ O	15	92
MeOH	75-80	78.5
EtOH	92-98	78.2
AcOH	120	74-76

Similarly, proton NMR strongly revealed for the formation of the product by its δ value at δ 6.86 (1H, m, C₆-H), δ 7.12 (2H, d, J = 7.2, p-substituted phenyl ring), δ 7.23 (1H, m, Ar-H), δ 7.39 (2H, m, aromatic proton), δ 7.63 (2H, d, J = 7.2, p-substituted phenyl ring), δ 7.88 (1H, d, J = 7.8, CH=CH- protons), δ 7.90 (1H, d, J = 7.8, CH=CH- protons), δ 8.52 (1H, s, C₄-H) of compound 6 were mentioned in (Fig.5). [13]. C NMR (DMSO-d₆ 100 MHz): δ 114.8 (C-4a), 116.5 (C-8), 118.6 (C-10, -CO-CH=), 124.2, 125.1, 126.2, 127.9, 129.8, 130.0, 133.5, 134.6 (8 different types of aromatic carbons), 147.1 (C-11, -CH=CH-), 147.6 (C-4), 151.5 (C-8a), 159.7 (C=O, lactone carbonyl of coumarin), 190.2 (C=O, α, β-unsaturated ketone). (Fig.7)

Conclusions

- ❖ In our conclusion, clear that first step, Pechmann condensation reaction Zn (L-proline)₂ exhibited the highest catalytic activity with regard to the transformation of Salicylaldehyde (1) and ethyl acetoacetate (2) into 3-acetyl-2H-chromen-2-one (4).
- ❖ Zn (L-proline)₂ which was efficient, inexpensiveness, eco-friendly as well as easy to handle and re usable catalyst in excellent yields and its higher solubility in water, insolubility in organic solvents.
- ❖ Similarly, Second step the synthesis of 3-(3-(4-Chloro phenyl) acryloyl)-2H-chromen-2-one (6) achieved by using PEG-600 green chemistry approach. In this stage 3-acetyl coumarin (4) were condensed with 4-chlorobenzaldehyde (5) through Claisen–Schmidt condensation using piperidine and PEG- 600 as a solvent for both conventional and microwave irradiation respectively.
- ❖ In our work MWI using the PEG-600 like Zn (L-proline)₂ is non-toxic, eco-friendly, in-expensive, water soluble and potentially recyclable solvent. Generally most of the researchers have been synthesized by 3-acetylcoumarin and coumarinyl chalcones using by Piperidine as catalyst. But Piperidine as catalyst is used hazarder us as well as dangerous to handle. Therefore both step used amino acid Zn (L-proline)₂ catalyst and PEG 600 solvent fulfils the green chemistry approaches.
- ❖ The chemical structures of compounds (4) and (6) have been confirmed using standard spectral techniques viz., FT-IR, UV-visible, Mass and ¹H-NMR spectra and were found to be in agreement with the chemical structures as expected.

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