An efficient and novel synthesis of chromonyl chalcones using recyclable Zn(l-proline)$_2$ catalyst in water

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A R T I C L E   I N F O

A B S T R A C T

A novel approach was adopted for the synthesis of a series of chromonyl chalcones (3a–o) from 3-formylchromones (1a–c) and different cyclic active methyl compounds (2a–e), employing Zn(l-proline)$_2$ as a recyclable Lewis acid catalyst in water. In each conversion, the catalyst was successfully recovered and reused several times without significant loss in yield and selectivity. All the newly synthesized compounds were characterized using elemental analysis and spectral data (IR, $^1$H NMR, $^{13}$C NMR and mass spectrometry).

Molecules containing chromone moiety form an important component of pharmacophores of a number of biologically active molecules of synthetic as well as natural origin having significant medicinal applications. They are also key precursors in the synthesis of many biologically important heterocycles, such as benzodiazepines, pyrazolines, 1,4-diketones, and flavones. Chalcones are generally synthesized via Claisen–Schmidt condensation carried out in basic or acidic media under homogeneous conditions. The reactions carried out in the presence of bases include aqueous NaOH, KOH, Ba(OH)$_2$, zeolites, hydrotalcites, LiHDM, calcined NaNO$_3$, natural phosphates, etc. A number of acid-catalyzed methods are also placed in the literature which includes the use of AlCl$_3$, dry HCl, Zn[bpy$_2$(OAc)$_2$, TiCl$_4$, Cp$_2$ZrH$_2$/NiCl$_2$, and RuCl$_3$. In contrast to the common organic reaction media, water is used as an environmentally benign solvent as it is nontoxic, nonflammable and cheap. Ever since the exploration of water soluble Zn(l-proline)$_2$ complex by Darbre's group, a few reports have so far appeared employing Zn(l-proline)$_2$ as a Lewis acid catalyst for different organic reactions. Thus, there is a lot of scope to further explore the catalyst for its application in forming various heterocyclic rings. To the best of our knowledge Zn(l-proline)$_2$ has not been used as a catalyst for the synthesis of heterochalcones. In continuation of our earlier studies on chromone derivatives and development of new catalysts and subsequent application for various organic transformations herein we report the first time an efficient synthesis of chromonyl chalcones catalyzed by recyclable Lewis acid complex Zn(l-proline)$_2$ in pure water.

As preliminary study attempts were made to synthesize a series of chromonyl chalcones 3a–o employing 3-formylchromones 1a–c and various cyclic active methyl compounds 2a–e in the presence of mild base under conventional solvents. The chalcones 3a–o synthesized in the presence of pyridine using ethanol/methanol as a solvent in conventional method, took longer period for completion of reaction (7–18 h) with relatively low yields (56–79%). Then, we used Zn(l-proline)$_2$ as a recyclable, efficient catalyst for achieving the targeted products using environmentally friendly water as the reaction medium (Scheme 1). The results were quite interesting as it was giving pronounced increment in the yields of products within shorter time. All reactions were found to be completed within 15–30 min with considerable increase in the yields of products (79–92%) (Table 1). The used catalyst can be recycled, and used for the next reaction without any further purification. The mechanism of formation of chromonyl chalcones can be visualized as shown in Scheme 2. Probably the reaction initiates by nucleophilic attack of nitrogen of Zn(l-proline)$_2$ complex on aldehydic oxygen of heteroaldehydes (1a–c) 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. Carbon–carbon double bond of enolized ketone (2a–e) then attacks on carbon of B to give C which undergoes cleavage process to expel out Zn(l-proline)$_2$ complex and water so as to result in heterochalcones (3a–o).

In order to optimize the reaction conditions, including catalysts and solvents, in terms of yield and time, the reaction of 6-chloro-3-
formylchromone (1c) with 3-acetyl-4-hydroxycoumarin (2e) was selected as a model reaction under various acidic/basic catalysts and in different solvents. The results are listed in Tables 2 and 3. In order to establish superiority of Zn(L-proline)$_2$ over other catalysts the model reaction was carried out under various Lewis acid catalysts and also in the presence of basic catalysts. Our investigation revealed that the catalytic activity of various acidic/basic catalysts in water was found to be in the order Zn(L-proline)$_2$ > AlCl$_3$ > piperidine > L-proline > NiCl$_2$ > FeCl$_3$ > ZnCl$_2$ > PTS (Table 2) in terms of yield and selectivity. It is, thus, clear that Zn(L-proline)$_2$ exhibited the highest catalytic activity with regard to the transformation of heteroaldehydes into heterochalcones.

To compare the efficiency as well as capacity of the reactions under aqueous condition, the model reaction was also examined in the presence of Lewis acid catalyst in different solvents, such as CH$_2$Cl$_2$, CHCl$_3$, MeOH, EtOH, AcOH, and H$_2$O. The use of relatively less polar aprotic solvents CH$_2$Cl$_2$ and CHCl$_3$ furnished the product in good yield (65–68%), after long period of time (Table 3). However, in polar protic solvents MeOH, EtOH, and AcOH relatively high yield of the product (76–78%) was obtained under reflux condition in less period of time, whereas when reaction was performed in water in the presence of Zn(L-proline)$_2$, it completed within 15 min with considerable increase in yield of the product (92%) (Table 3). Thus, our study revealed that water is the best solvent for the Zn(L-proline)$_2$-catalyzed formation of heterochalcones in terms of reduced reaction time and the maximum yield of the products.

In order to establish the best reaction conditions, we performed an optimization study using model substrates in the presence of varying amounts of catalyst Zn(L-proline)$_2$ (Table 4). The best results were obtained with the use of 10 mol% of catalyst. While two to 5-fold excess in mol% of Zn(L-proline)$_2$ (20–50 mol%) was found to increase rate of reaction but afforded products in low yield due to the formation of side products.

For recycling studies, the reaction of 6-chloro-3-formylchromone (1c) with 3-acetyl-4-hydroxycoumarin (2e) in the presence of Zn(L-proline)$_2$ in water was selected as the model reaction. After completion of reaction in specified time the crude product...
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obtained was extracted by dichloromethane and the catalyst was recovered by separation of aqueous and organic phases. The catalyst present in the aqueous medium was used for the subsequent cycle. The same procedure was applied for all recycling studies. The results (Table 5) revealed that catalyst exhibited good catalytic activity up to five consecutive cycles. The scope of the reaction was further investigated with different cyclic active methyl compounds and the results obtained were encouraging.

Infrared (IR) spectrum of 3o exhibited chromone and coumarin carbonyl groups at 1648 and 1719 cm⁻¹, respectively, whereas a broad band for the OH group was present at 3354 cm⁻¹. The ¹H NMR spectrum of 3o showed trans olefinic protons Hₐ and Hₖ as ortho coupled doublets at 9.04 (J = 15.2 Hz) and 7.90 (J = 16.5 Hz), respectively. The value of spin–spin coupling constant J₉₀ in the range 15–16 Hz is indicative of the E-configuration of chalcone. Seven aromatic protons (three protons of chromone...
moeity and four protons of coumarin unit) were discernible in the form of multiplet at δ 8.66. The 13C NMR spectrum showed signal for α,β unsaturated carbonyl group at δ 182.60 whereas olefinic carbons C2 and C3 were appeared at δ 137.19 and 129.19, respectively. Further, the structure was confirmed by mass spectrum, which showed M+ at m/z 394.61. The spectral data of other compounds followed similar pattern and as obtained are given in Supplementary data.

In conclusion, we have developed a simple, efficient, and ecofriendly method for the synthesis of a series of chromonyl halcones in excellent yields using recyclable and reusable Zn[(proline)2] Lewis acid catalyst in water. Higher solubility in water, insolubility in organic solvents, inexpensiveness, ecofriendly nature, uncomplicated handling, convenient workup, and recyclability are the advantages associated with the catalyst.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.118.

References and notes

8. (a) Nielsen, S. F.; Christensen, S. B.; Cruciani, G.; Kharazmi, A.; Liljefors, T.
Ten millimoles of L-proline was dissolved in 25 mL absolute ethanol containing 10 mmol potassium hydroxide and stirred well for 15 min. In order to maintain the metal to ligand ratio 1:2, 5 mmol of Zn(NO₃)₂·6H₂O was dissolved in a small quantity of double distilled water and this solution was added in drops to the solution of l-proline. The contents were vigorously stirred at room temperature for 8 h. The Zn[(L-proline)]₂ complex was obtained as white solid, was filtered and dried. Yield: 91%.
25. General method for the preparation of chromonyl chalcones (3a–o)
To a partially suspended Zn[(L-Proline)]₂ (10 mol %) in water (10 mL), 3-formylchromones (1a–c) (4 mmol) and heteroaryl active methyl compounds (2a–e) (4 mmol) were added successively and heated under reflux condition for appropriate time (Table 1). After the completion of reaction, as monitored by TLC, the product was extracted with dichloromethane (3 × 15 mL) until complete removal of organic component, dried over anhydrous Na₂SO₄, concentrated to furnish crude product, which was then recrystallized from chloroform or methanol–DMF mixture. The catalyst was recovered by precipitating the aqueous layer by addition of acetone. The catalyst recovered from the aqueous layer was used for the subsequent cycle.