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Zn(L-proline)$_2$ as a powerful and reusable organometallic catalyst for the very fast synthesis of 2-amino-4*H*-benzo[*g*]chromene derivatives under solvent-free conditions

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An efficient route for the synthesis of 2-amino-4*H*-benzo[*g*]chromenes via a three-component coupling reaction of aldehydes, malononitrile and 2-hydroxy-1,4-naphthaquinone in the presence of Zn(L-proline)$_2$ is reported. High yields, short reaction times, non-toxicity and recyclability of the catalyst, and easy work-up are the main merits of this protocol. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: Zn(L-proline)$_2$; 2-amino-4*H*-benzo[*g*]chromenes; aldehydes; malononitrile; 2-hydroxy-1,4-naphthaquinone; recyclable catalyst

Introduction

The development of methodologies that involve the use of inexpensive and reusable catalysts under mild and environmentally friendly reaction conditions is one of the major goals in green and sustainable chemistry. Methodologies leading to various heterocyclic structures are in high demand for both academic and industrial applications.[1]

2-Hydroxy-1,4-naphthoquinone has been known for the past 4000 years, is found in many natural products and has been employed as a synthetic intermediate for the preparation of numerous heterocyclic compounds. Molecules containing the heterocyclic quinone group constitute one of the most important classes of compounds in organic chemistry because of their biological properties such as antitumor, antibacterial, antifungal and anti-inflammatory activities.[2–8]

Multicomponent reactions (MCRs) have emerged as a powerful synthetic strategy because of their efficiency, atom economy, high selectivity and convenience in the construction of diverse chemical libraries of 'drug-like' molecules.[9] MCRs are convergent reactions, in which three or more starting materials react to give a highly complex product in one pot. Typically, purification of products resulting from MCRs is also simple because all the organic reagents employed are consumed and incorporated into the target compound.

Zn(L-proline)$_2$ is an efficient, inexpensive, non-toxic, stable and reusable catalyst which is not dissociated under reaction conditions. Also, many advantages such as higher solubility in water, insolubility in organic solvents, eco-friendly nature and convenient work-up make Zn(L-proline)$_2$ a green catalyst in organic synthesis.[10]

To the best of our knowledge, only a few methods are available for the preparation of 4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-5,10-dione derivatives. Recently, many catalysts have been used for this preparation such as triethylbenzylammonium chloride (TEBA),[11] DMF/AcOH under microwave irradiation,[12] Et_3N,[13] 1,8-diazabicyclo[5.4.0]undec-7-ene,[14] ionic liquids[15] and potassium phthalimide-*N*-oxyl.[16] However, several of these methods suffer from certain drawbacks such as prolonged reactions times, use of volatile or hazardous organic solvents, tedious work-up conditions, use of extra energy sources and employment of large amount of catalyst, which lead to difficulty in product separation and non-recyclability of the catalyst. Therefore, it is desirable to develop a more efficient and a general method for the synthesis of 2-amino-4*H*-benzo[*g*]chromene derivatives.

Experimental

General

All chemicals were obtained from Merck and Sigma-Aldrich and used as received. Infrared (IR) spectra were recorded with a Shimadzu 435-U-04 spectrophotometer (KBr pellets). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-300 Avance spectrometer in DMSO-d_6 or $CDCl_3$, and shifts are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Melting points were determined using an Electrothermal 9200 instrument.

General Procedure for Synthesis of 2-Amino-4*H*-benzo[*g*]chromene Derivatives

A mixture of aldehydes (1 mmol), malononitrile (1 mmol) and 2-hydroxy-1,4-naphthaquinone (1 mmol) was stirred with Zn(L-proline)$_2$ (20 mol%) at 60°C for the required period of time (for solid aldehydes, 0.1 ml of ethanol was added). Upon completion of the reaction as indicated using TLC (hexane–ethyl acetate,

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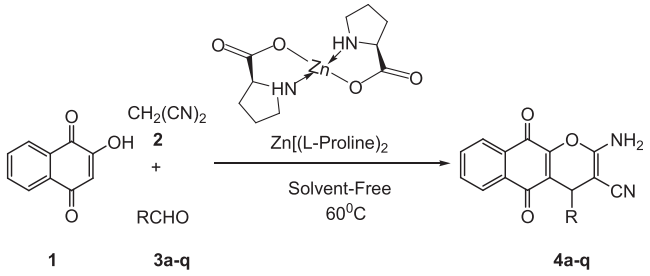
4:1), an appropriate amount of hot EtOH (96%, 2 ml) was added and the mixture stirred for 2 min. The resulting crude product was poured into crushed ice and the solid product that separated was filtered and recrystallized from ethanol (96%, 2 ml) to afford pure 2-amino-4*H*-benzo[*g*]chromene derivatives.

Results and Discussion

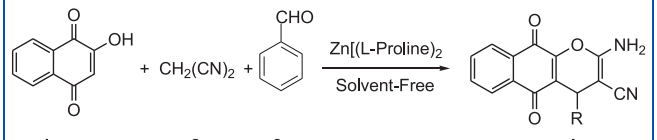
In continuation of our efforts towards the development of greener methodologies,[17] we report herein a simple, clean and environmentally friendly process for the synthesis of 2-amino-4*H*-benzo[*g*]chromene derivatives by reaction of various aldehydes, malononitrile and 2-hydroxy-1,4-naphthaquinone in the presence of Zn(L-proline)$_2$ under solvent-free conditions (Scheme 1).

For the present study, the catalyst Zn(L-proline)$_2$ was prepared following a literature procedure.[9i] Initially, benzaldehyde (1 mmol), malononitrile (1 mmol) and 2-hydroxy-1,4-naphthaquinone (1 mmol) were selected as representative substrates to investigate the reaction conditions. The catalyst plays an important role in the formation of 2-amino-4-(phenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (**4a**). Without the catalyst, it is observed that there is no conversion to product even after 2 h (Table 1, entries 1 and 2). Then, we focused our attention on using Zn(L-proline)$_2$ catalyst, which might help to reduce the reaction time and improve the yields of the target compounds. Our studies show that



Scheme 1. Synthesis of 2-amino-4*H*-benzo[*g*]chromene derivatives catalysed by Zn(L-proline)$_2$.

Table 1. Screening of reaction conditions for synthesis of 2-amino-4-(phenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile (**4a**)



Entry	Zn(L-proline)$_2$ (mol%)	Temp. (°C)	Time (min)	Yield (%)[a]
1	None	r.t.[b]	120	No reaction
2	None	60	120	No reaction
3	30	r.t.[b]	5	22
4	30	50	5	76
5	30	60	5	90
6	30	70	5	85
7	20	60	5	91
8	10	60	5	82

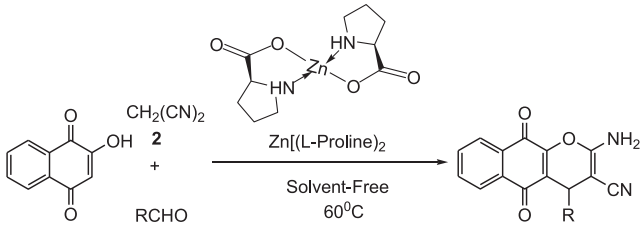
[a]Isolated yield.
[b]Room temperature.

in the presence of Zn(L-proline)$_2$ (30 mol%) under solvent-free conditions at room temperature and after 5 min, 32% of product is observed, and the yield of the reaction increases as the reaction temperature increases (entries 3–6). As evident from entries 3 and 5, the temperature is necessary for the synthesis of **4a**. Using 30 mol% of Zn(L-proline)$_2$ at 70°C, the yield unexpectedly decreases to 85% (entry 6). A possible explanation for the trace product yield is that the starting material or the product may be destroyed during the reaction. The best results are obtained at 60°C (entry 5). To determine the optimal amount of Zn(L-proline)$_2$, the model reaction was carried out using various amounts (entries 7 and 8). The results show that 20 mol% of Zn(L-proline)$_2$ is sufficient to obtain the best yield (entry 7).

Encouraged by this success, a study of the substrate scope was carried out. The results are summarized in Table 2. It can be seen from the results that a wide range of aromatic aldehydes are suitable for this MCR. Aromatic aldehydes tethered with both electron-donating and electron-withdrawing substituents afford the desired products in very good yields.

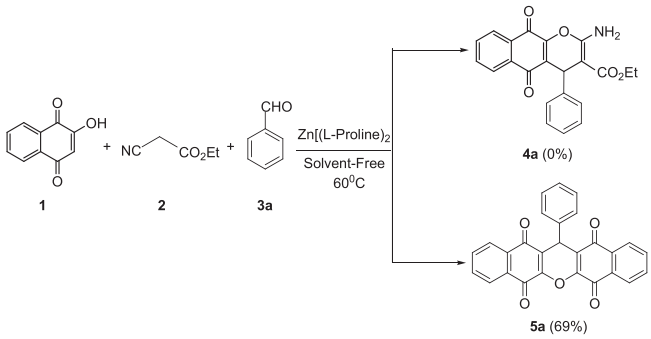
There is no effect on the reaction time and the yield of the corresponding products when electron-donating groups and electron-withdrawing groups on benzaldehydes are used. Furthermore, we examined aliphatic aldehydes such as butanal instead of benzaldehydes in the reaction. All the starting materials in the

Table 2. Three-component synthesis of 2-amino-4*H*-benzo[*g*]chromene derivatives from the reaction of 2-hydroxynaphthalene-1,4-dione (1 mmol), malononitrile (1 mmol) and aldehydes (1 mmol) in the presence of Zn(L-proline)$_2$ (20 mol%)



Products (**4a–q**)	RCHO (**3a–q**)	Time (min)	Yield (%)[a]	Ref.
4a	C_6H_5	4	91	[15b)]
4b	4-$OCH_3C_6H_4$	5	90	[15b)]
4c	3-$OCH_3C_6H_4$	9	90	[15b)]
4d	3,4-$OCH_3C_6H_3$	5	92	[15b)]
4e	4-ClC_6H_4	6	93	[15b)]
4f	2-ClC_6H_4	10	86	[15b)]
4g	4-BrC_6H_4	8	89	[15b)]
4h	4-FC_6H_4	12	82	[15c)]
4i	4-$CH_3C_6H_4$	15	78	[11]
4j	3-$NO_2C_6H_4$	4	93	[10]
4k	2-$NO_2C_6H_4$	6	89	[15b)]
4l	2,4-ClC_6H_3	8	90	[15b)]
4m	4-OHC_6H_4	14	80	[15b)]
4n	2,3,4-$OCH_3C_6H_3$	6	87	[15b)]
4o	4-$NO_2C_6H_4$	5	94	[15b)]
4p	2-Thienyl	7	90	[12]
4q	4-Pyridyl	7	86	[16]

[a]All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with those of authentic samples.



Scheme 2. Reaction between benzaldehyde, 2-hydroxy-1,4-naphthaquinone and ethyl cyanoacetate in the presence of Zn(L-proline)$_2$ (20 mol%).

reaction are intact without formation of any desired product and side products after 1 h. In addition to the aromatic aldehydes, the reaction also proceeds smoothly using heterocyclic aldehydes in high yield.

The applicability of the catalyst was further extended by reaction between benzaldehyde (1 mmol), 2-hydroxy-1,4-naphthaquinone (1 mmol) and ethyl cyanoacetate (1 mmol) under solvent-free conditions at 60°C. The reaction is complete in 30 min and 69% of 13-phenyl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraone (**5a**) is obtained after work-up (Scheme 2).[18] Subsequently, reactions of other aromatic aldehydes (such as with 4-methoxy, 4-nitro substituents) with ethyl cyanoacetate also give the corresponding derivatives of **5a** in good yields.

To show the merit of the present work, we summarize the results for the synthesis of 2-amino-4*H*-benzo[*g*]chromenes obtained by other workers in Table 3. In contrast to other existing methods, the present methodology offers several advantages such as excellent yields, simple procedure, short reaction times, easy synthesis, simple work-up and greener conditions using Zn(L-proline)$_2$ as an efficient catalyst (Table 3).

Finally, the recycling of Zn(L-proline)$_2$ was investigated during the synthesis of **4a**. After completion of the reaction, the solid product was collected by filtration. Then, water was removed under reduced pressure, and diethyl ether was added to the solidified mixture in order to separate the catalyst from the mixture, being insoluble in organic solvents. Then the catalyst was filtered, washed with diethyl ether and dried at 80°C for 2 h to afford Zn(L-proline)$_2$ which was reused directly for the next run. It is found that Zn(L-proline)$_2$ can be used for the reactions for up to three runs without any appreciable loss of efficiency (Fig. 1).

Table 3. Comparison of the efficiencies of various catalysts used in the synthesis of 2-amino-4*H*-benzo[*g*]chromenes

Entry	2-Amino-4*H*-benzo[*g*]chromene	Conditions	Time (min)	Yield (%)
4b	4-$OCH_3C_6H_4$	DMF/AcOH/MWI[12]	6	81
		Et_3N/rt/CH_3CN[13a)]	1440	70
		[bmim]OH/rt/EtOH[15c)]	120	80
		This work	5	90
4e	4-ClC_6H_4	TEBA/85°C/solvent free[11]	190	93
		Pyrr[CH_3COO]/rt/solvent free[15a)]	12	90
		[bmim]OH/rt/EtOH[15c)]	50	92
		This work	6	93
4o	4-$NO_2C_6H_4$	TEBA/85°C/solvent free[11]	180	94
		Et_3N/rt/CH_3CN[13a)]	1440	75
		[bmim]OH/rt/EtOH[15c)]	40	93
		[Et_3NH][HSO_4]/rt/solvent free[15d)]	12	91
		This work	4	94

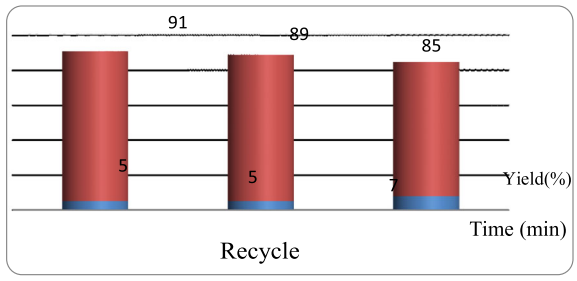
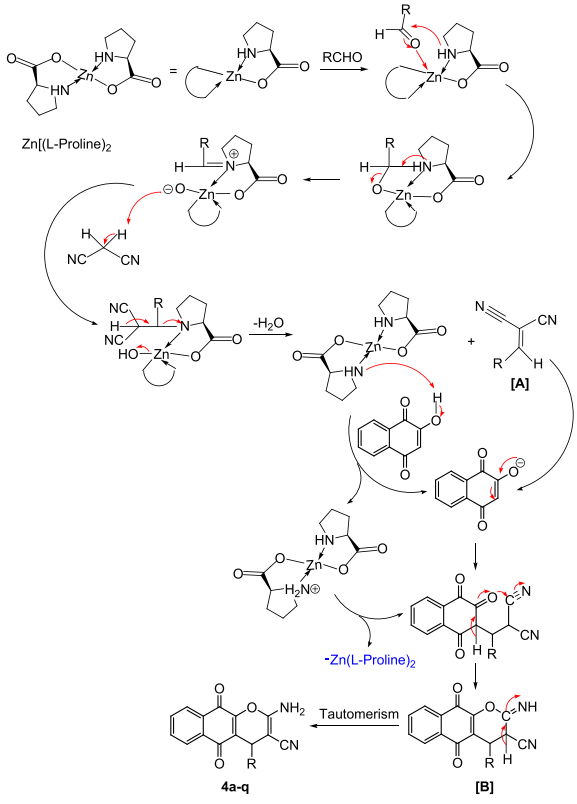


Figure 1. Reusability of Zn(L-proline)$_2$ for the synthesis of 2-amino-4-(phenyl)-5,10-dihydro-5,10-dioxo-4*H*-benzo [*g*]chromene-3-carbonitrile (**4a**).



Scheme 3. Proposed mechanism.

A plausible mechanism of the reaction is presented Scheme 3. We believe that Zn(L-proline)$_2$ facilitates cyanoolefin formation and synthesis of 2-amino-4*H*-benzo[*g*]chromenes. The reaction occurs via initial formation cyanoolefin [**A**] from condensation of aldehydes and malononitrile, which reacts with 2-hydroxynaphthalene-1,4-dione to give intermediate [**B**] which subsequently undergoes cyclization to afford the desired products (**4a–q**).

Conclusions

We have developed an efficient and environmentally friendly method for the synthesis of 2-amino-4*H*-benzo[*g*]chromenes in excellent yield within short reaction times. This procedure provides several advantages such as cleaner reactions, easier work-up and being an eco-friendly and promising strategy. It is expected that

the present methodology will find application in organic synthesis. In addition, it is easy to separate and recover the catalyst for another catalytic cycle.

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