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Zn[(*L*)-proline]$_2$: A Novel and Recyclable Catalyst for the Synthesis of 2-Aryl-4(3H)-quinazolinones in Solvent-Free Conditions

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ABSTRACT

An efficient, solvent-free and facile synthesis of 3-aryl quinazolinones from cyclocondensation of 2-aminobenzamides with aryl aldehydes catalyzed by Zn[(*L*)-proline]$_2$ in the presence of $CuCl_2$ is described. The salient features of the reaction include good yields , mild reaction conditions , low loading of catalyst , and operational simplicity. The catalyst is reusable and can be applied several times without considerable decrease in the yields and rates of the reactions.

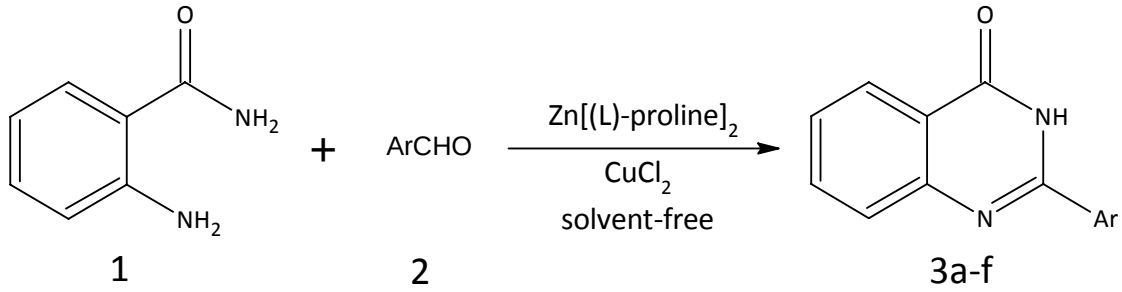
Key words: 2-Aryl quinazolinones , Zn[(*L*)-proline]$_2$, Solvent-free Conditions, Recyclable Catalyst.

INTRODUCTION

4(3H)-Quinazolinone derivatives have attracted great attention recently in synthethic organic chemistry due to their wide range of biological activity and pharmacologically property[1-5], such as anti-inflammatory[6,7], anti-bacterial[8], anti-malarial[9], anti-tumor[10], antagonist[11], anti-microbial[12], analgesic[13], anti-pyretic, and diuretic activity[14]. In addition, quinazolinone moiety is a bulding block for approximately 150 naturally occurring alkaloids, such as glycosminine[15], deoxyvasicinone[16], and drug like methaqualone[17] and piriqualone[18]. Quinazolinones are normally prepared by treatment of O-acyl anthranil with primary amines at temperatures above 200 ^0C[19]. Other synthetic methods includes treatment of phosphoranes with NaH/CH_3CN[20], pyrolysis of Schiff bases derived from 3-amino-1,2,3-triazine-one in paraffin oil at 300 ^0C[21]. The most general method for synthesis of these compounds involves cyclocondensation of anthranilamides with aldehydes in the presence of various promoting agents, such as p-toluenesulfonic acid/DDQ[22], I_2/KI in water[23], $CuCl_2$ in ethanol[24], DDQ/DMF[25], $Sc(oTf)_3$[26], $NaHSO_3$[27], $SnCl_4.4H_2O$[28], TBAB[29], and

$KMnO_4$ under microwave irradiation[30]. Lewis-acid catalyzed organic reactions in water have attracted much attention in organic synthesis because they allow environmentally friendly processes under mild reaction conditions[31]. Proline is the most prominent amino acid for the coordination of Zn, its secondary amino group and carboxylate function being ideally suited for Zn^{2+} in low coordination number, which makes Zn complex a moderately soft lewis acid. Recently, darbre·s group have showed that Zn[(*L*)-proline]$_2$ are efficient and enantioselective catalysts for the direct aldol reaction[32]. There are also a few reports that show Zn[(*L*)-proline]$_2$ can act as an efficient recyclable and inexpensive lewis acid catalyst for the preparation of heterocyclic compounds such as hantzch 1,4-dihydropyridine derivatives[33], 1,5-benzodiazepines under microwave conditions[34], 1,2-disubstituted benzimidazoles[35], quinoxaline derivatives and knoevenagel condensation under solvent-free/ aqueous conditions[36]. Although, the catalytic applications of Zn[(*L*)-proline]$_2$ for organic synthesis have been established, to the best of our knowledge, there is no reported in the literature on the use of Zn[(*L*)-proline]$_2$ in synthesis of 4(3H)-quinazolinone derivatives under solvent-free conditions.

In continuation of our interest in finding environmentally benign method for the synthesis of various heterocyclic compounds[37-42], here in we want to report for first time, a new and efficient synthesis of 4(3H)-quinazolinones in the presence ofZn[(*L*)-proline]$_2$ as a lewis acid catalyst under solvent-free conditions (Scheme 1).



Scheme 1: Synthesis of 2-Aryl-4(3H)-quinazolines

EXPERIMENTAL

Melting points were recorded on electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300-Shimadzu spectrophotometer in KBr disks. The ^{1}HNMR (500MHz) spectra were recorded on a Bruker-Ac-500 spectrometer. The catalyst was synthesized according to the literture[31].

Preparation of the catalyst (Zn[(*L*)-proline]$_2$)

(*L*)-proline (20mmol) was dissolved in absolute ethanol (50ml) containing potassium hydroxide (20mmol) and magnetically stirred for 15min in a round-bottomed flask at room temperature. $Zn(NO_3)_2.6H_2O$ (10mmol) was dissolved in a small quantity of double distilled water and added in drops to the (*L*)-proline solution. The contents were vigorously stirred at room temperature for 6h by using a magnetic stirrer. The Zn[(*L*)-proline]$_2$ complex was obtained as a white solid. It was collected by filtration and dired at 70°C in vacuum for 6h[31].

General procedure for the synthesis of 2-aryl-4(3H)-quinazolinones(3a-f)

A mixture of 2-aminobenzamide (1mmol), aromatic aldehyde (1mmol) $CuCl_2$ (0.4mmol), and Zn[(*L*)-proline]$_2$ (0.25mmol) as catalyst was heated on the oil bath at 100°C for 3h. The reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was cooled to room temperature and then water was added. The precipitate was filtered off and recrystallized from ethanol to give compounds **3a-f** in good yields. The structure of the products were confirmed by ^{1}HNMR and IR spectroscopy, and comparison with authentic samples prepared by reported methods[23,29].

Recycling and reusing of the catalyst

The catalyst is soluble in water and could therefore be recycled as the filtrate. The catalyst was recovered by evaporation of the water, washed with chloroform, dried at 70°C under vacuum for 1h and reused in another reaction without appreciable reduction in the catalytic activity.

RESULTS AND DISCUSSION

At the onset of the research, we investigated the model reaction between 2-aminobenzamide and benzaldehyde in the presence of a catalytic amount of Zn[(*L*)-proline]$_2$ under solvent-free conditions. The reaction was carried out by heating a mixture of 2-aminobenzamide (1mmol), and benzaldehyde (1mmol), under various amount of the catalyst and at different temperatures under solvent-free conditions (Table 1). It was found that the yield of compound 3a was strongly affected by the catalyst amount and reaction temperature. Trace product was obtained in the absence of the catalyst (Entry 1) or in the presence of the catalyst at room temperature (Entry 2), indicating that the catalyst and temperature are necessary for the reaction. Increasing the amount of the catalyst and reaction temperature up to 25mol% and 100°C, respectivity, increased the yield of the product 3a, where as further increase in both catalyst amount and temperature was found to have an inhibitory effect on formation of the product (Entries 5,8,9-11).

The model reaction was also examined in various solvents such as ethanol, water, chloroform, dichloromethane and acetonitrile and also under solvent-free conditions by using 25mol% catalyst. The yield of the reaction under solvent-free conditions was the highest and the reaction time was shortest under above optimized conditions, the scope of this reaction was next examined using various aromatic aldehydes. In all cases the yield obtained were good without formation of any side products. The results are given in Table 2. As shown, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in good yields. The results also revealed that electron-donating or electron-withdrawing groups on the aromatic ring did not seen to affect the reaction significantly either in the yield of the product or the rate of the reaction.

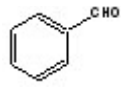
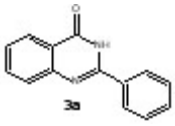
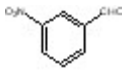
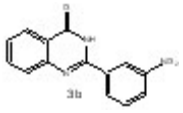
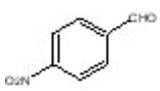
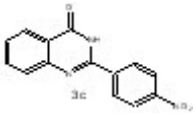
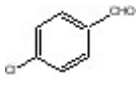
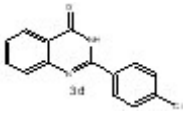
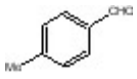
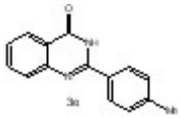
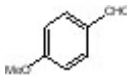
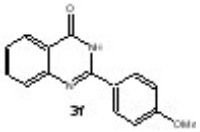
To explore the reproducibility of the catalyst recycle study was carried out. Therefore, in this work, the reusability of Zn[(*L*)-proline]$_2$ in model reaction was also investigated. After the completion of the reaction, the reaction mixture was cooled to room temperature and water was added. The catalyst is soluble in water and could be recycled as the filtrate.

Table 1: Effect of Zn[(*L*)-proline]$_2$ amount and temperature on the model reaction[a]

Entry	Catalyst (mol%)	T (°C)	Time (h)	Yield (%)[b]
1	None	100	4	Trace
2	25	r.t.	4	Trace
3	20	90	3	61
4	20	100	3	66
5	20	110	3	65
6	25	90	3	67
7	25	100	3	74
8	25	110	3	72
9	30	90	3	63
10	30	100	3	65
11	30	110	3	64

[a]1mmol 2-aminobenzamide, 1mmol benzaldeyde, 0.4 mmol $CuCl_2$ under solvent-free conditions; [b] Isolated yields.

Table 2: Synthesis of 2-aryl-4(3H)-quinazolinones 3a-f using Zn[(*L*)-proline]$_2$ as catalyst[a]

Entry	Ar	Product[b]	Time (h)	Yield (%)[c]	m.p. (°C)	
					Found	Reported
1			2	74	233-235	235-236[29]
2			3	75	352-354	351-353[23]
3			2	75	363-365	363-364[23]
4			2	71	306-308	305-308[29]
5			2	73	240-243	241-243[23]
6			3	77	249-251	248-249[23]

[a]2-aminobenzamide, 1mmol aromatic aldehyde, 0.4mmol $CuCl_2$, and 25mol% Zn[(L)-proline]2 under solvent- free conditions. [b]All products were characterized by comparision of theirspectroscopic and physical data with authentic samples synthesized by reported procedures. [c] Isolated yields.

The catalyst was recovered by evaporation of the water, washed with chloroform, dried at 70°C under vacuum for 1h. The catalyst could be used at least three times with only slight reduction in catalytic activity. The three recycles showed the yields 74, 71, and 67% respectively.

CONCLUSIONS

In conclusion, we have developed an efficient, and mild method for the synthesis of 2-substituted-4(3H)-quinazolinones through reaction of 2-aminobenzamide and aromatic aldehydes using Zn[(*L*)-proline]$_2$ as catalyst. The catalyst can be reused after a simple work-up, with only slight reduction in the catalytic activity. Good yields, simple operation, recyclable of catalyst, and easy work-up are some advantages of this protocol.

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