



Short communication

## LaCl<sub>3</sub>/nano-SiO<sub>2</sub>: A novel nanocatalyst for efficient synthesis of functionalized 2,3-dihydroquinazolinones

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## ABSTRACT

The novel LaCl<sub>3</sub>/nano-SiO<sub>2</sub> catalyst was synthesized by adsorption of LaCl<sub>3</sub> on nano-SiO<sub>2</sub> and characterized by powder XRD, FE-SEM, TEM, EDX, FT-IR spectra, BET surface area, TPD of ammonia and ICP-AES analyses. It was found as an efficient catalyst for the one-pot synthesis of 2,3-dihydroquinazolinones. All reactions proceeded with high efficacy under solvent-free conditions and gave excellent yields avoiding tedious workup and purification of products.

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### 1. Introduction

The major goals of 'Green Chemistry' are nowadays embraced by maximising the use of starting materials and reducing environmentally challenging reaction waste streams [1]. The toxic effluent produced by chemical processes has stimulated extensive efforts to develop more environmentally friendly processes. Approaches towards achieving these goals include the use of alternative reagents and catalysts, atom-economic processes, simplification of the purification step, easy recovery and recycling of catalysts [2]. In this context, substantial research efforts have been devoted to develop catalysts with high efficacy. In the case of heterogeneous catalysis, the catalytic ability of materials mainly depends on their microscopic structure which directly impacts the activity, selectivity and thermal or chemical stability of the catalyst [3]. The use of efficient nanocatalysts plays a promising role towards achieving these objectives of green chemistry [3,4].

2,3-Dihydroquinazolinones represent a family of drugs that are used as anticancer, antibiotic, anti-inflammatory, analgesic, diuretic, antidepressant, and antitubercular agents [5–10]. Since 2,3-dihydroquinazolinone scaffolds are of specific interest for drug discovery, many synthetic methods developed include the reaction of anthranilamide with benzil, reductive cyclization of *o*-nitrobenzamides and *o*-azidobenzamide with aldehydes and ketones, reactions of 2-aminobenzonitriles and aromatic aldehydes, and the most popular, preparation from isatoic anhydrides [11–14].

Lewis acid catalysed reactions are of great current interest because of the readily availability, inexpensiveness, and unique reactivities under mild conditions. A few examples of Lewis acid catalysts used for the 2,3-dihydroquinazolinones synthesis are Sc(OTf)<sub>3</sub>, Ga(OTf)<sub>3</sub>, SrCl<sub>2</sub>, Bi(NO<sub>3</sub>)<sub>3</sub>, KAl(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O, I<sub>2</sub>, and SnCl<sub>2</sub> [15–21]. Although some of procedures are environmentally friendly, many others have drawbacks such as the use of toxic solvents, difficulties in separation of catalysts from products, and long reaction time. In this regard, the design of new heterogeneous Lewis acid catalysts that are nontoxic, easily separable from products, and reusable, would be appreciable for environmentally benign chemical processes.

Because of the pharmaceutical significance of 2,3-dihydroquinazolinone motif in bioactive compounds, we wish to report a powerful approach for its synthesis using LaCl<sub>3</sub>/nano-SiO<sub>2</sub> as environmentally benign and recyclable heterogeneous catalyst. It is worthy to mention here that aldehydes having pharmaceutical relevance viz pyrazole-4-carbaldehyde and 3-formylchromone were used in the particular reaction in the expectation of getting 2,3-dihydroquinazolinones with improved and altered biological activities. The newly synthesized catalyst was characterized with the help of powder XRD, FE-SEM, TEM, EDX, FT-IR spectra, BET surface area, TPD of ammonia and ICP-AES analyses.

### 2. Experimental

#### 2.1. Preparation of LaCl<sub>3</sub>/nano-SiO<sub>2</sub> and LaCl<sub>3</sub>/SiO<sub>2</sub>

1 g of lanthanum chloride was added to a suspension of nano-SiO<sub>2</sub>/SiO<sub>2</sub> (1 g) in ethanol (30 mL). The mixture was stirred at 100 °C till the evaporation of the solvent. The solid was repeatedly washed with

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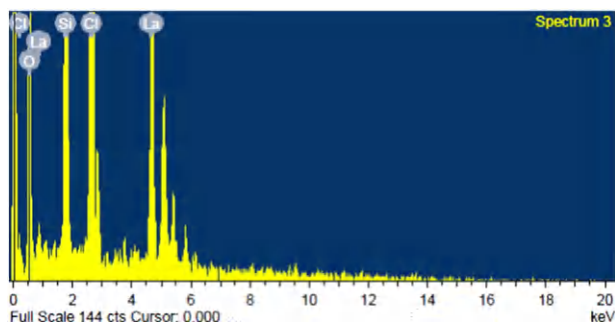


Fig. 1. EDX analysis of LaCl<sub>3</sub>/nano-SiO<sub>2</sub>.

ethanol to remove any unadsorbed lanthanum chloride, filtered off and dried at 120 °C in an oven for 2 h to furnish catalyst as a white free-flowing powder.

## 2.2. General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones

A mixture of isatoic anhydride (10 mmol), aromatic amine (10 mmol), 5-chloro-3-methyl-1-phenylpyrazol-4-carbaldehyde/3-formyl chromone (10 mmol) and 0.3 g of LaCl<sub>3</sub>/nano-SiO<sub>2</sub> was stirred at 80 °C under solvent-free condition for the appropriate time (Table 2). Upon completion of the reaction (confirmed by TLC), ethyl acetate (5 mL) was added to the reaction mixture and the catalyst was recovered by filtration, washed with ethanol (2 × 5 mL) and reused for subsequent cycles. After evaporation of the solvent of the filtrate,

Table 1  
Effect of different catalysts for the model reaction.<sup>a</sup>

Entry	Catalyst	Time <sup>b</sup>	Yield <sup>c</sup> (%)
1	No catalyst	24 h	No product formation
2	CuCl <sub>2</sub> (10 mol%)	4.3 h	30
3	AlCl <sub>3</sub> (10 mol%)	3.6 h	38
4	ZnCl <sub>2</sub> (10 mol%)	4 h	34
5	FeCl <sub>3</sub> (10 mol%)	3 h	40
6	NiCl <sub>2</sub> (10 mol%)	2.3 h	50
7	SnCl <sub>2</sub> (10 mol%)	4.3 h	34
8	I <sub>2</sub> (10 mol%)	5 h	30
9	BiCl <sub>3</sub> (10 mol%)	1.2 h	62
10	LaCl <sub>3</sub> (10 mol%)	1 h	68
11	LaCl <sub>3</sub> /SiO <sub>2</sub> (30 mg)	35 min	74
12	LaCl <sub>3</sub> /nano-SiO <sub>2</sub> (30 mg)	10 min	90
13	Nano-SiO <sub>2</sub> (30 mg)	5 h	Incomplete

<sup>a</sup> Reaction of isatoic anhydride (1 mmol), *p*-anisidine (1 mmol) and 5-chloro-3-methyl-1-phenylpyrazol-4-carbaldehyde (1 mmol) in the presence of different catalysts under solvent-free condition.

<sup>b</sup> Reaction progress monitored by TLC.

<sup>c</sup> Isolated yield.

products (**4a–j**) were obtained which were further purified by recrystallization from ethanol. The identity of the products was confirmed by NMR and mass spectra (See Supplementary information).

## 3. Results and discussion

The XRD pattern of the catalyst recorded at  $2\theta = 5\text{--}80^\circ$  range (Fig. S1) showed amorphous nature of the catalyst. A broad peak in the range  $2\theta = 10\text{--}30^\circ$  was attributed to silica. The surface morphology

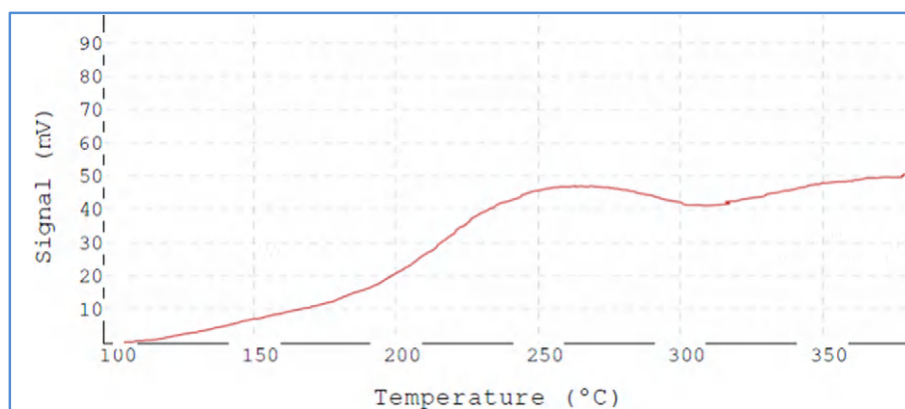


Fig. 2. NH<sub>3</sub>-TPD profile of catalyst LaCl<sub>3</sub>/nano-SiO<sub>2</sub>.

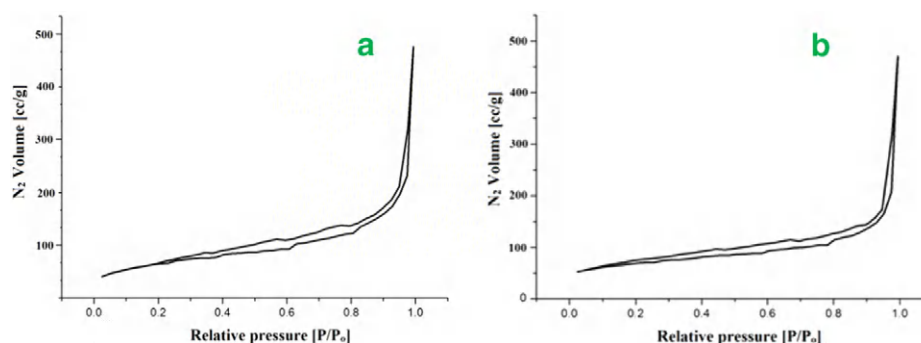


Fig. 3. Nitrogen adsorption isotherms of (a) nano-SiO<sub>2</sub> (b) LaCl<sub>3</sub>/nano-SiO<sub>2</sub>.

and spherical structure of nano-SiO<sub>2</sub> and catalyst were investigated by FE-SEM and TEM analysis. The images showed that the particle size (mean particle diameter of about 150 nm) and shape of nano-SiO<sub>2</sub>

were retained after adsorption of LaCl<sub>3</sub> (Figs. S2 and S3). The presence of elements Si, O, La and Cl in LaCl<sub>3</sub>/nano-SiO<sub>2</sub> was confirmed by EDX analysis (Fig. 1).

**Table 2**

The reaction of isatoic anhydride, aromatic amines and pyrazole-4-carbaldehyde/3-formylchromone under thermal solvent-free conditions.

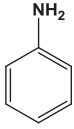
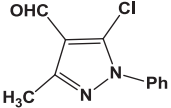
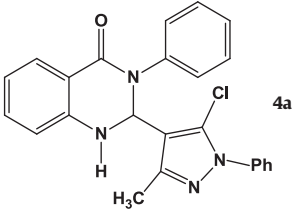
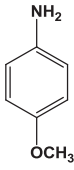
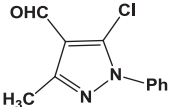
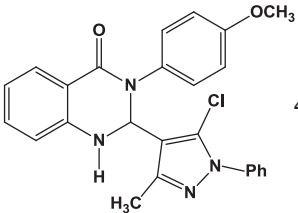
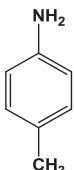
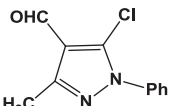
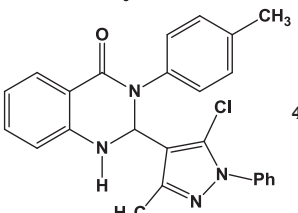
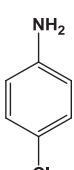
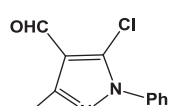
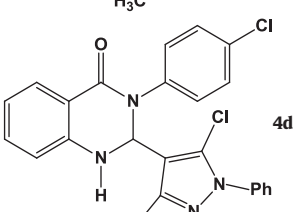
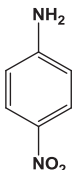
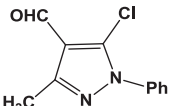
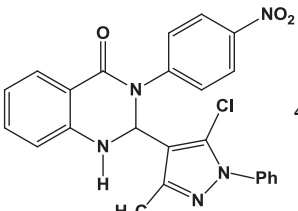
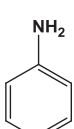
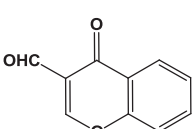
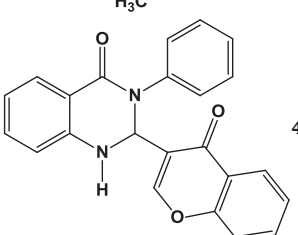
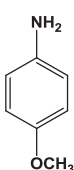
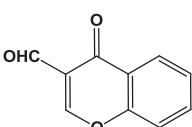
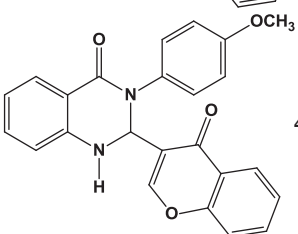
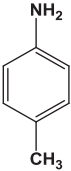
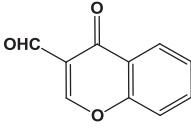
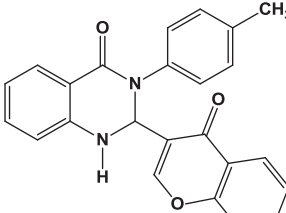
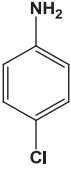
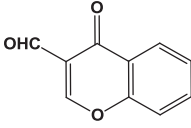
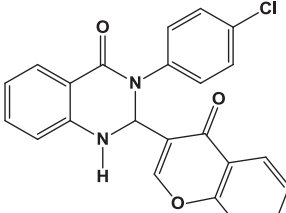
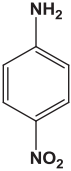
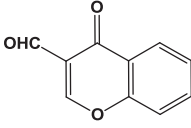
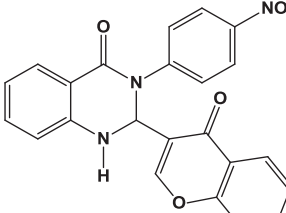
Entry	Amines	Aldehydes	Products	Time (min) <sup>a</sup>	Yield (%) <sup>b</sup>
1				10 <sup>c</sup> /40 <sup>d</sup>	86 <sup>c</sup> /68 <sup>d</sup>
2				10 <sup>c</sup> /35 <sup>d</sup>	90 <sup>c</sup> /74 <sup>d</sup>
3				10 <sup>c</sup> /35 <sup>d</sup>	90 <sup>c</sup> /73 <sup>d</sup>
4				15 <sup>c</sup> /40 <sup>d</sup>	90 <sup>c</sup> /68 <sup>d</sup>
5				20 <sup>c</sup> /50 <sup>d</sup>	86 <sup>c</sup> /64 <sup>d</sup>
6				15 <sup>c</sup> /35 <sup>d</sup>	90 <sup>c</sup> /68 <sup>d</sup>
7				15 <sup>c</sup> /35 <sup>d</sup>	90 <sup>c</sup> /72 <sup>d</sup>
8				10 <sup>c</sup> /40 <sup>d</sup>	90 <sup>c</sup> /70 <sup>d</sup>

Table 2 (continued)

Entry	Amines	Aldehydes	Products	Time (min) <sup>a</sup>	Yield (%) <sup>b</sup>
				4 h	
9				15 <sup>c</sup> /45 <sup>d</sup>	86 <sup>c</sup> /70 <sup>d</sup>
10				20 <sup>c</sup> /45 <sup>d</sup>	84 <sup>c</sup> /66 <sup>d</sup>

<sup>a</sup> Reaction progress monitored by TLC.

<sup>b</sup> Isolated yield.

<sup>c</sup> Reaction time and yield in the presence of LaCl<sub>3</sub>/nano-SiO<sub>2</sub>.

<sup>d</sup> Reaction time and yield in the presence of LaCl<sub>3</sub>/SiO<sub>2</sub>.

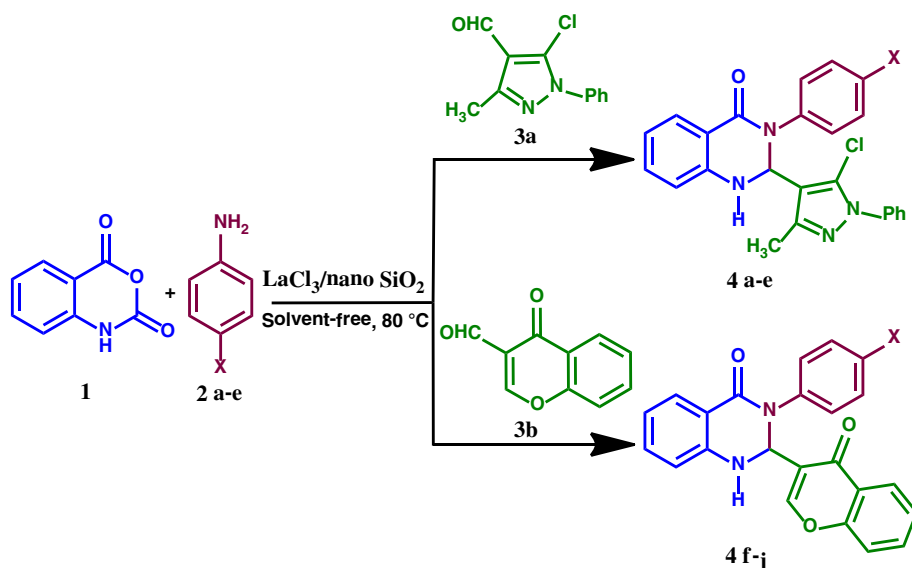
Temperature-programmed desorption of ammonia was used to determine acid strength of LaCl<sub>3</sub>/nano-SiO<sub>2</sub>. A broad peak appearing in the low-temperature region indicates the acidic properties of the catalyst (Fig. 2) [22].

The surface areas of nano-SiO<sub>2</sub> and LaCl<sub>3</sub>/nano-SiO<sub>2</sub> were determined by BET method. The surface area of catalyst was 450 m<sup>2</sup>/g (Fig. 3b), which was lower than that of nano-SiO<sub>2</sub> (482 m<sup>2</sup>/g) (Fig. 3a). The adsorption of LaCl<sub>3</sub> on nano-SiO<sub>2</sub> may account for the BET surface area drop.

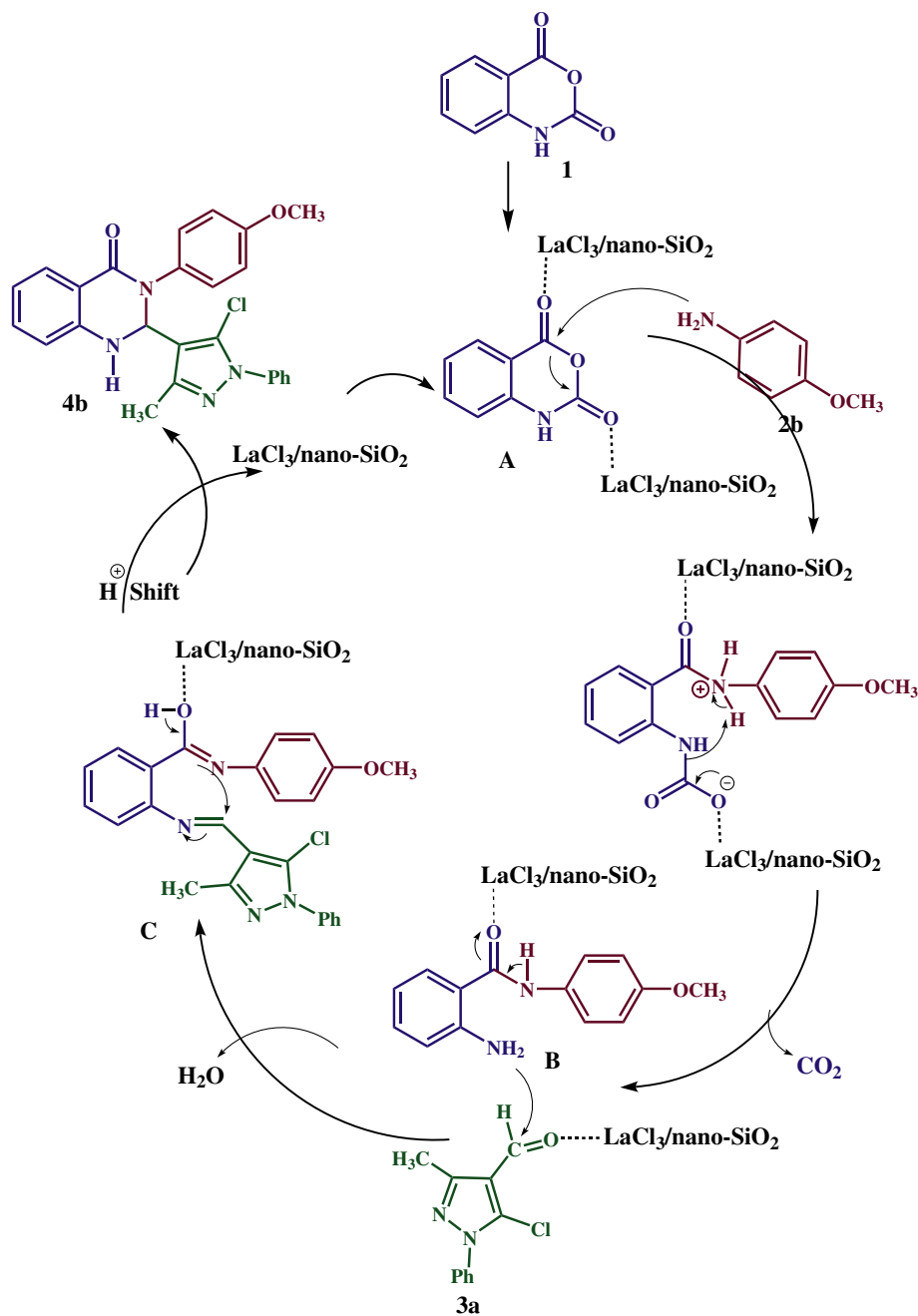
The weight percentage of La was found to be 18.8% by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis.

### 3.1. Optimization of reaction conditions

In order to explore suitable reaction conditions, a multicomponent reaction involving isatoic anhydride **1** (1 mmol), *p*-anisidine **2b** (1 mmol) and 5-chloro-3-methyl-1-phenylpyrazol-4-carbaldehyde **3a** (1 mmol) was designed to get 2,3-dihydroquinazolinone **4b** and



Scheme 1. Synthesis of 2,3-dihydroquinazolinones (4a-j).



Scheme 2. Proposed mechanism for the formation of 4b.

subsequently efforts were focused on optimization of various reaction parameters such as effect of various acidic catalysts, different solvents, percentage of  $\text{LaCl}_3$  loading on nano- $\text{SiO}_2$ , amount of  $\text{LaCl}_3/\text{nano-SiO}_2$  and temperature in terms of yield and time period.

Our initial investigation was focused on the model reaction under solvent-free condition in the absence of catalyst (Table 1) and no product formation was observed after prolong heating (entry 1). Using metal halides low yields of the product were obtained (entries 2–7). Between  $\text{BiCl}_3$  and  $\text{LaCl}_3$ ,  $\text{LaCl}_3$  was found to be more efficient with respect to reaction time and yield of the product (entries 9, 10). When the model reaction was carried out with  $\text{LaCl}_3/\text{SiO}_2$ , the reaction time was reduced and product yield enhanced (entry 11). However, maximum yield of the product (90%) in minimum time period (10 min) was obtained when the model reaction was conducted with  $\text{LaCl}_3/\text{nano-SiO}_2$  (entry 12). The rate enhancement of the reaction is attributed to the increased surface area of nano- $\text{SiO}_2$  (482  $\text{m}^2/\text{g}$ ) as support in the catalyst as

compared to bulk  $\text{SiO}_2$  (300–350  $\text{m}^2/\text{g}$ ) [23]. The reaction was also conducted with nano- $\text{SiO}_2$  in order to evaluate role of  $\text{LaCl}_3$  and reaction was found incomplete (entry 13).

The model reaction was examined in the presence of different solvents (Table S1). In  $\text{CH}_3\text{OH}$ ,  $\text{C}_2\text{H}_5\text{OH}$ ,  $(\text{CH}_3)_2\text{CHOH}$ ,  $\text{H}_2\text{O}$  and  $\text{CH}_3\text{COOC}_2\text{H}_5$ , the yield of product was low. Green solvents were again not suitable for the protocol, as the reaction did not lead to completion. The model reaction when screened under solvent-free grinding condition, afforded lower yield of the product whereas, best result was obtained when the reaction mixture was heated at 80 °C under solvent-free condition. In the presence of different loadings of  $\text{LaCl}_3$  on nano- $\text{SiO}_2$ , maximum yield of the product was obtained with 50% w/w  $\text{LaCl}_3/\text{nano-SiO}_2$ . Increasing the loading of  $\text{LaCl}_3$  to 60% did not improve yield of the product (Table S2). The percentage yield of the product increased gradually when the amount of the catalyst ( $\text{LaCl}_3/\text{nano-SiO}_2$ ) was increased from 10 to 30 mg. Further, increase in the amount of

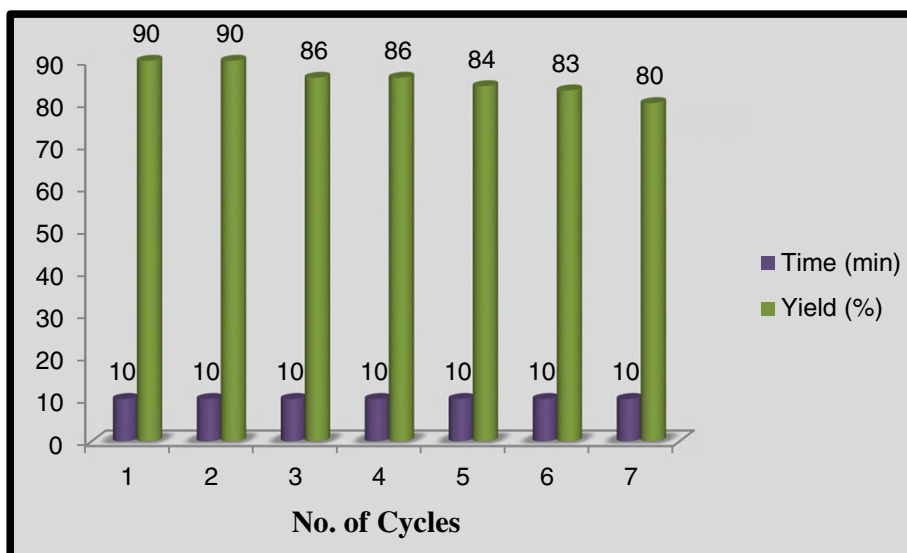


Fig. 4. Recyclability of the catalytic system.

catalyst showed no effect on the yield or reaction time (Table S3). The reaction temperature has a significant effect on the rate of the reaction. For model reaction, it was observed that there was no sign of the product formation when the reaction was carried out at room temperature. Increase in temperature affects the conversion positively, up to temperature of 80 °C and further increase could not improve the yield or reaction time (Table S4).

### 3.2. Synthesis of 2,3-dihydroquinazolinone

To assess advantages and efficacy of the protocol, reactions of isatoic anhydride, different aromatic amines and pyrazole-4-carbaldehyde/3-formylchromone were conducted in the presence of  $\text{LaCl}_3/\text{nano-SiO}_2$  under the optimized reaction conditions. Irrespective of the presence of an electron withdrawing or releasing substituent on aniline moiety, the reaction proceeded fairly well and afforded the desired products in excellent yields in short time periods (Table 2) (Scheme 1). The reactions were also carried out using  $\text{LaCl}_3/\text{SiO}_2$  as a catalyst to provide a comparative analysis with results obtained by using  $\text{LaCl}_3/\text{nano-SiO}_2$  (Table 2).

The plausible mechanism for the formation of **4b** is shown in Scheme 2. The carbonyl group of isatoic anhydride (**1**) is activated through coordination with acidic  $\text{LaCl}_3/\text{nano-SiO}_2$  to give **A**, which facilitates the nucleophilic attack of *p*-anisidine (**2b**) on the carbonyl carbon followed by decarboxylation to give 2-amino-*N*-substituted benzamide **B**. Imine formation takes place by condensation of  $\text{NH}_2$  group of **B** with  $\text{LaCl}_3/\text{nano-SiO}_2$  activated hetero-aldehyde **3a** to give **C**, which undergoes intramolecular cyclization to form the final product **4b** [24].

### 3.3. Reusability of the catalyst

The level of reusability was examined for the heterogeneous nature of the catalyst (Fig. 4). The recovered catalyst successfully catalysed the synthesis of **4b** for seven consecutive times with good activity. The morphology and particle size of catalyst were almost unchanged as shown by XRD and TEM analysis of the recovered catalyst (Figs. S1 and S3). The weight percentage of La of recycled catalyst was found to be 18.3% by ICP-AES analysis. This indicates that leaching of lanthanum does not take place during the course of reaction.

## 4. Conclusion

We have designed a new heterogeneous catalyst and developed a conceivably powerful approach for the synthesis of 2,3-dihydroquinazolinones. Compared with  $\text{LaCl}_3$ ,  $\text{LaCl}_3/\text{nano-SiO}_2$  is found more active and efficient catalyst for one-pot catalytic process. Short reaction times, clean reaction profiles, rational optimization, high conversions and air stability of the catalyst make this method a promising one. This protocol may be an effective contribution to the existing methodologies of 2,3-dihydroquinazolinones.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.catcom.2015.03.013>.

## References

- [1] P.T. Anastas, J.C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.
- [2] B.M.L. Dioso, I.F.J. Vankelecom, P.A. Jacobs, *Adv. Synth. Catal.* 348 (2006) 1413.
- [3] V. Polshettiwar, R.S. Varma, *Green Chem.* 12 (2010) 743.
- [4] D. Astruc, F. Lu, J.R. Aranzas, *Angew. Chem. Int. Ed.* 44 (2005) 7852.
- [5] A. Kamal, E.V. Bharathi, J.S. Reddy, M.J. Ramaiah, D. Dastagiri, M.K. Reddy, A. Viswanath, T.L. Reddy, T.B. Shaik, S.N.C.V.L. Pushpavalli, M.P. Bhadra, *Eur. J. Med. Chem.* 46 (2011) 691.
- [6] R.J. Alaimo, H.E. Russel, *J. Med. Chem.* 15 (1972) 335.
- [7] D.S. Badiger, R.B. Nidavani, R.S. Hunoor, B.R. Patil, R.S. Vadavi, V.M. Chandrashekar, I.S. Muchchandi, K.B. Gudasi, *Appl. Organometal Chem.* 25 (2011) 876.
- [8] H.A. Parish Jr., R.D. Gilliom, *J. Med. Chem.* 25 (1982) 98.
- [9] J.I. Levin, P.S. Chan, T. Bailey, A.S. Katocs Jr., A.M. Venkatesan, *Bioorg. Med. Chem. Lett.* 4 (1994) 1141.
- [10] S. Rajasekaran, G. Rao, H.S. Niranjana, *IJPSR* 3 (2012) 4394.
- [11] J.A. Moore, G.J. Sutherland, R. Sowerby, E.G. Kelly, S. Palermo, W. Webster, *J. Org. Chem.* 34 (1969) 887.
- [12] W. Su, B. Yang, *Aust. J. Chem.* 55 (2002) 695.
- [13] X.F. Wu, S. Oschatz, A. Block, A. Spannenberg, P. Langer, *Org. Biomol. Chem.* 12 (2014) 1865.
- [14] S. Santra, M. Rahman, A. Roy, A. Majee, A. Hajra, *Catal. Commun.* 49 (2014) 52.
- [15] T. Deng, H. Wang, C. Cai, *J. Fluor. Chem.* 169 (2015) 72.

- [16] J. Chen, D. Wu, F. He, M. Liu, H.Wu, J. Ding, W. Su, *Tetrahedron Lett.* 49 (2008) 3814.
- [17] M. Wang, T.T. Zhang, Y. Liang, J.J. Gao, *Chin. Chem. Lett.* 22 (2011) 1423.
- [18] I.M. Baltork, A.R. Khosropour, M. Moghadam, S. Tangestaninejad, V. Mirkhani, S. Baghersad, A. Mirjafari, *C. R. Chimie.* 14 (2011) 944.
- [19] M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary, A.A. Mohammadi, *Tetrahedron Lett.* 46 (2005) 6123.
- [20] S.K. Panja, N. Dwivedi, S. Saha, *Tetrahedron Lett.* 53 (2012) 6167.
- [21] C.L. Yoo, J.C. Fettinger, M.J. Kurth, *J. Org. Chem.* 70 (2005) 6941.
- [22] X. Ma, J. Gong, S. Wang, N. Gao, D. Wang, X. Yang, F. He, *Catal. Commun.* 5 (2004) 101.
- [23] S. Radi, S. Tighadouini, M. Bacquet, S. Degoutin, F. Cazier, M. Zaghrioui, Y.N. Mabkhot, *Molecules* 19 (2014) 247.
- [24] J. Safari, S. Gandomi-Ravandi, *J. Mol. Catal. A Chem.* 371 (2013) 135.