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Short Communication

Nano-indium oxide: An efficient catalyst for one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones with a greener prospect

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ABSTRACT

Nano-In_2O_3 is found to be a remarkable efficient catalyst for the one-pot three-component condensation of isatoic anhydride, primary amine or ammonium salts and aromatic aldehydes for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in aqueous media. In_2O_3 nanoparticles are easily recyclable without the significant loss of catalytic activities.

1. Introduction

The last decade has witnessed tremendous growth in the field of nanoscience and nanotechnology. The easy accessibility to nanoparticles has prompted investigations on their applications in catalysis. Several reports showed an amazing level of their performance as catalysts in terms of selectivity, reactivity, and improved yields of products [1,2]. In addition, the high surface-to-volume ratio of nanoparticles provides a larger number of active sites per unit area compared to their heterogeneous counterparts. Thus, in recent times, interest in nanoparticle catalysis has increased considerably because of their high efficiency under environmentally benign reaction conditions [3]. As a part of the continuous interest in indium catalysis [4,5], we have demonstrated the catalytic activity of indium in various multicomponent reactions (MCRs) leading to molecules of biological and pharmaceutical importance. Indium(III) compounds are mild and water-tolerant Lewis acids and show high regio-, stereo-, and chemoselectivity [6–8]. However, until now, the use of nano-In_2O_3 as a catalyst is limited in organic synthesis [9–12]. Recently, we found that nano-In_2O_3 is a very effective and reusable catalyst for useful chemical transformations [10–12]. This inspired us to focus on the use of nano-In_2O_3 as a catalyst in multicomponent reactions.

Recently, multicomponent reactions (MCRs) are one of the most powerful and efficient tools in organic synthesis for the synthesis of biologically important compounds in the perspective of green chemistry. In addition, MCRs offer molecular diversity and complexity in a fast and often experimentally simple fashion [13–15]. For this reason, MCRs are particularly well suited for diversity oriented synthesis and library synthesis of drug like compounds, which are an essential part of the research performed in agrochemical and pharmaceutical companies [16]. Indeed, the concept of environmental factor (E-factor) and atom economy has been gradually included into conventional organic synthesis in both industry and academia. The use of solvent is the main reason for an insufficient E-factor, especially in synthesis of fine chemicals and pharmaceutical industries [17].

Quinazolinone derivatives are a class of fused nitrogen containing heterocycles that have drawn much attention due to their potential biological and pharmaceutical activities including antifertility, antibacterial, antitumor and monoamine oxidase inhibitory activity [18,19]. In addition, these compounds can easily oxidize to their quinazolin-4(3*H*)-one analogs, which are themselves important biologically active heterocyclic compounds and can also be found in some natural products [20]. Quinazolinone scaffolds are also important for the establishment of some commercially available drugs (Fig. 1) [21].

Due to their immense biological activities, synthesis of quinazolinone derivatives is a demanding task. Numerous protocols have been developed for the synthesis of quinazolinone derivatives using silica sulfuric acid [22], zinc(II) perfluorooctanoate [$Zn(PFO)_2$] [23], gallium(III) triflate [24], $KAl(SO_4)_2 \cdot 12H_2O$ [25], MCM-41-SO_3H [26], nano-Fe_3O_4 [27], 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) [28], molecular I_2 [29], β-cyclodextrin [30], etc. Regardless of their efficiency and reliability, most of these methods suffer from one or more of these disadvantages, such as the use of hazardous organic solvents, low yields, strongly acidic conditions, expensive moisture-sensitive catalysts, and tedious work-up procedure.

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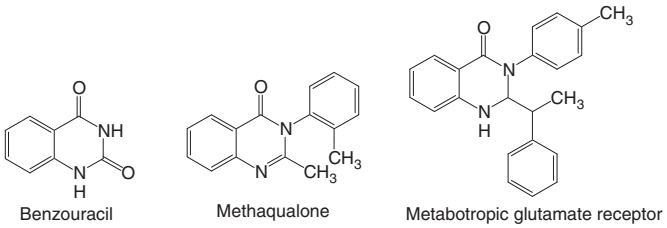


Fig. 1. Some important drugs with quinazolinone skeleton.

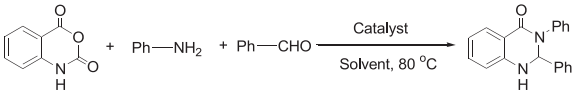
Very recently, we have developed an environmentally benign nano-CuO catalyzed "on-water" strategy for the one-pot synthesis of isoindolo[2,1-*a*]quinazolines by a three-component coupling of isatoic anhydride, 2-carboxybenzaldehyde and amines (Scheme 1a) [31]. So, in continuation of our efforts in the field of nanocatalysis [10–12,31] herein, we report a remarkable catalytic activity of nano-In_2O_3 in one-pot protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives by a three-component condensation of isatoic anhydride with primary amines or ammonium salts and aromatic aldehydes in aqueous medium (Scheme 1b).

2. Experimental section

2.1. General procedure for the synthesis of 2,3-dihydro-2-phenylquinazolin-4(1H)-one

To a mixture of isatoic anhydride (1 mmol), primary amine (1.1 mmole) or ammonium salt (ammonium carbonate, 0.6 mmol, ammonium acetate, 1.2 mmol, or ammonium chloride, 1.2 mmole) and aldehyde (1 mmol) were stirred in the presence of commercially available In_2O_3 nanopowder (5 mol%, 0.013 g) in water/ethanol (2:1, 3 mL) under 80 °C for 4 h. After completion of the reaction, the reaction mixture was cooled to room temperature and nano-In_2O_3 was recovered by centrifugation. Then the ethanol was evaporated in rotary evaporator and the solid separated was filtered under suction.

Table 1
Optimization of the reaction conditions.[a]



1 2a 3a 4a

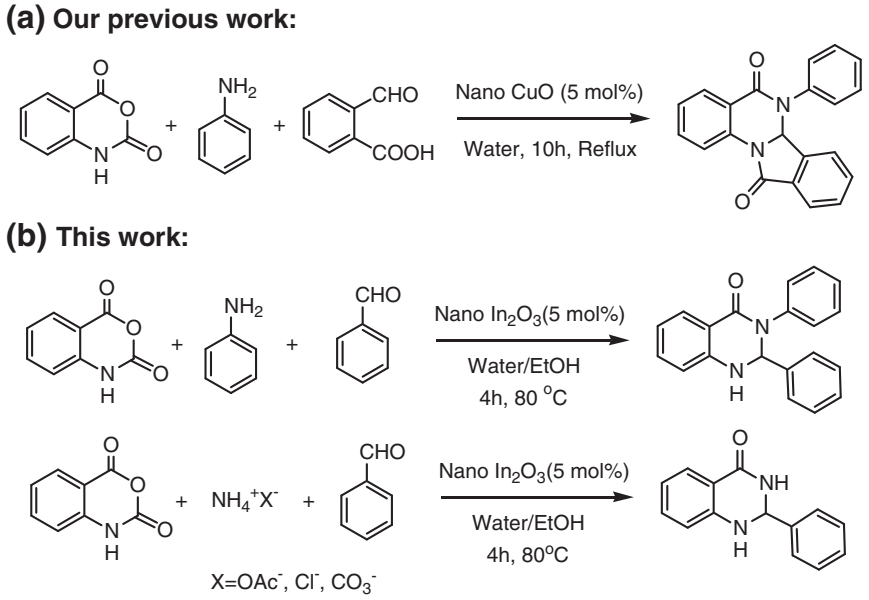
Entry	Catalyst (mol%)	Solvents	Time (h)	Yield[b] (%)
1	Nano-In_2O_3 (5)	EtOH	4	72
2	Nano-In_2O_3 (5)	H_2O	4	75
3	Nano-In_2O_3 (5)	MeOH	6	68
4	Nano-In_2O_3 (5)	H_2O/EtOH (1:1)	4	80
5[c]	**Nano-In_2O_3 (5)**	**H_2O/EtOH (2:1)**	**4**	**87**
6	Nano-In_2O_3 (5)	H_2O/EtOH (1:2)	4	77
7	Nano-In_2O_3 (5)	H_2O/MeOH (1:1)	6	74
8	Nano-In_2O_3 (5)	H_2O/MeOH (2:1)	6	76
9	Nano-In_2O_3 (5)	H_2O/MeOH (1:2)	6	74
10	Nano-In_2O_3 (2)	H_2O/EtOH (2:1)	6	76
11	Nano-In_2O_3 (10)	H_2O/EtOH (2:1)	4	87
12	Nano-In_2O_3 (5)	DMF	6	44
13	Nano-In_2O_3 (5)	MeCN	6	48
14	Nano-In_2O_3 (5)	Toluene	6	36
15	Nano-In_2O_3 (5)	1,4-Dioxane	6	40
16	Nano-In_2O_3 (5)	1,2-DCE	6	46
17	In_2O_3 powder (5)	H_2O/EtOH (2:1)	6	62
18	Nano-NiO 5)	H_2O/EtOH (2:1)	6	55
19	Nano-ZnO (5)	H_2O/EtOH (2:1)	6	58
20	Nano-CuO (5)	H_2O/EtOH (2:1)	6	65
21	–	H_2O/EtOH (2:1)	6	<25

[a] Reaction conditions: 1 mmol of **1** and 1.1 mmol of **2a** and 1 mmol of **3a** in the presence of catalyst in solvent (3 mL) at 80 °C.
[b] Isolated yields.
[c] Optimized reaction conditions.

The solid crude was washed with cold water and recrystallized from EtOH to afford the analytically pure product.

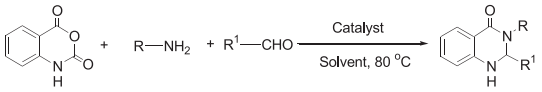
2.2. Procedure for recycling the catalyst

After completion, the nano-In_2O_3 was separated from the reaction mixture by ultra centrifugation, washed with water, dried under vacuum followed by at 110 °C for 2 h and reused for further catalytic reactions.



Scheme 1. Synthesis of quinazolinone derivatives.

Table 2
Substrates scope.[a]



Entry	R	R^1	Product	Yield[b] (%)	Mp (°C)	
					Found	Reported [ref]
1	Ph	Ph	**4a**	87, 82[c]	203–204	203–205 [23]
2	Ph	4-MeC_6H_4	**4b**	88	213–214	214 [27]
3	Ph	4-$MeOC_6H_4$	**4c**	83	204–205	204–205 [23]
4	Ph	4-BrC_6H_4	**4d**	81	221–222	222–225 [23]
5	Ph	4-$NO_2C_6H_4$	**4e**	79	193–194	195–196 [23]
6	Ph	2-BrC_6H_4	**4f**	81	218–220	
7	Ph	4-ClC_6H_4	**4g**	83	213–214	214–217 [29]
8	4-MeC_6H_4	Ph	**4h**	87	195–196	196–198 [23]
9	4-ClC_6H_4	Ph	**4i**	80	214–215	216–218 [29]
10	4-$NO_2C_6H_4$	Ph	**4j**	78	183–184	185–187 [23]
11	4-BrC_6H_4	Ph	**4k**	81	223–224	224–226 [23]
12	2-ClC_6H_4	Ph	**4l**	80	212–214	215–216 [27]
13	4-$MeOC_6H_4$	Ph	**4m**	80	214–215	215–216 [29]
14	4-MeC_6H_4	4-$MeOC_6H_4$	**4n**	85	246–248	247–249 [27]
15	4-MeC_6H_4	Piperonyl	**4o**	87	238–240	

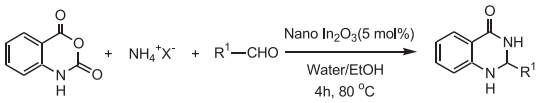
[a] Reaction conditions: 1 mmol of **1** and 1.1 mmol of **2** and 1 mmol of **3** in the presence of nano-In_2O_3 (5 mol%) in water/ethanol (2:1, 3 mL) at 80 °C for 4 h.
[b] Isolated yield.
[c] Isatoic anhydride (**1**, 20 mmol), aniline (**2a**, 22 mmol) and benzaldehyde (**3a**, 20 mmol) in the presence of nano In_2O_3 (5 mol%) in water/ethanol (2:1, 60 mL) at 80 °C for 4 h.

3. Results and discussion

We commenced our study taking isatoic anhydride (**1**), benzaldehyde (**2a**) and aniline (**3a**) as the model substrates in the presence of catalytic amount of nano-In_2O_3 (5 mol%) in EtOH at 80 °C for 4 h (Table 1, entry 1). To our delight, desired quinazolinone derivative was obtained in 72% yield after 4 h and no further improvement was noticed by increasing reaction time. Encouraged by this initial result, we proceeded to optimize the reaction conditions which are summarized in Table 1. Water/ethanol (2:1) mixture appeared to be the best choice among the common solvents such as MeOH, CH_3CN, toluene, dioxane, and 1,2-DCE. Lower conversions were obtained when indium oxide powder. Nano-In_2O_3 was found to be the most effective catalyst among the various metal nanocatalysts tested (In_2O_3, NiO, ZnO, CuO) and 5 mol% nano-In_2O_3 proved to be optimal. With respect to the quantity of the catalyst, there was no significant enhancement in yields when the amount of catalyst was increased from 5 to 10 mol% while decreasing the amount of catalyst decreased the yield. In the absence of catalyst, negligible amount of desired product was observed. Thus, optimal reaction conditions were obtained using isatoic anhydride (**1**, 1 mmol), benzaldehyde (**2a**, 1 mmol) and aniline (**3a**, 1.1 mmol) in the presence of 5 mol% of nano-In_2O_3 in a mixture of water and EtOH (2:1) at 80 °C (entry 6, Table 1) for 4 h.

After optimization, we explored the scope of this reaction by using various substituted aromatic aldehydes and amines to prove the general applicability of the reaction conditions (Table 2). The bromo- and chloro-substituted benzaldehydes afforded the corresponding products **4f** and **4g** in 81% and 83% yields respectively. We were pleased to notice that under the stated conditions, anilines substituted with halogens such as –Cl and –Br (**4i**, **4k** and **4l**) smoothly reacted with benzaldehyde without forming any dehalogenated products. Aldehyde as well as amine containing electron donating –OMe group on the aromatic ring have shown also good efficiency (**4c** and **4m**). We are delighted to find that the acid sensitive aldehyde such as piperonal is well tolerated under our catalytic conditions with 87% isolated yield (**4o**). It is well known that ammonium salts (carbonate, chloride, and acetate) are the source of ammonia in the synthesis of nitrogen-containing heterocyclic compounds. Accordingly, corresponding 2,3-dihydroquinazoloin-4-(1*H*)-ones (**6a**–**6f**) were synthesized efficiently using ammonium carbonate or ammonium chloride or ammonium acetate (**5**), isatoic anhydride **1** and aldehyde **5** (Table 3). This methodology is also applicable

Table 3
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using ammonium salts.[a]



Entry	Ammonium salts (**5**)	R^1	Product	Yield[b] (%)	Mp (°C)	
					Found	Reported [ref]
1	NH_4OAc	Ph	**6a**	89	223–224	225–226 [29]
2	NH_4OAc	4-MeC_6H_4	**6b**	88	228–230	229–231 [29]
3	NH_4OAc	4-ClC_6H_4	**6c**	83	206–207	207–208 [29]
4	NH_4Cl	Ph	**6d**	87	225–227	225–226 [29]
5	NH_4Cl	4-MeC_6H_4	**6e**	88	231–233	229–231 [29]
6	$(NH_4)_2CO_3$	Ph	**6f**	86	223–225	225–226 [29]

[a] Isatoic anhydride (1 mmol), ammonium salts (ammonium carbonate, 0.6 mmol, ammonium acetate, 1.2 mmol, or ammonium chloride, 1.2 mmol) and aldehyde (1 mmol) in the presence of nano-In_2O_3 (5 mol%) in water/ethanol (2:1, 3 mL) under 80 °C for 4 h.
[b] Isolated yield.

Table 4
Recycling of In_2O_3 nanoparticle for synthesizing **4a**.[a]

No. of cycle	Yield[b] (%)	Catalyst recovery (%)
1	87	98
2	85	96
3	82	94
4	82	91
5	79	90
6	76	88

[a] Carried out with 1 mmol of **1** and 1.1 mmol of **2a** and 1 mmol of **3a** in the presence of catalyst in water/ethanol (2:1, 3 mL) at 80 °C for 4 h.
[b] Isolated yields.

on a gm-scale synthesis also. We have successfully prepared the quinazolinone **4a** in 82% yield by the reaction of isatoic anhydride (**1**, 20 mmol), aniline (**2a**, 22 mmol) and benzaldehyde (**3a**, 20 mmol). In addition, we have developed a greener reaction condition bearing lower E-factor [17,32]of 0.42 and 0.39 in cases of synthesizing **4a** and **4b** respectively (see Supplementary data).

To check the recyclability of the catalyst, it was separated from the reaction mixture by ultra centrifugation, washed with water, dried under vacuum followed by drying at 110 °C and reused for further reactions. The catalyst maintained its high level of activity even after being recycled six times for synthesizing **4a** as shown in Table 4.

The morphology of nano-In_2O_3 was determined by HRTEM and powder XRD. A comparative study of the HRTEM and powder XRD of the fresh catalyst and the recovered catalyst after six cycles (Figs. 2 and 3) shows that the catalyst does not undergo agglomeration during the recycling process.

Based on the literature reports [23,24] a plausible mechanism for the formation of 2,3-dihydroquinazolin-4(1*H*)-ones is exposed in Scheme 2. At first the isatoic anhydride is activated by nano-In_2O_3 followed by the *N*-nucleophilic amine attacks on the carbonyl to form T.S.-I. T.S.-I gets more stability which in turn leads to the formation of intermediate **A** by elimination of CO_2. After that intermediate **A** reacts with the aldehydes in the presence of nano-In_2O_3 to form the intermediate **B** which upon intramolecular cyclization afforded the final product **4**. Nano-In_2O_3 might activate the aldehyde through coordination with the oxygen of the corresponding carbonyl group which facilitates the subsequent nucleophilic attack by the nitrogen atom on the carbonyl carbon. Nano-In_2O_3 is the most efficient among the nanometal oxides for this transformation (Table 1) probably due to its low and selective heterophilicity [6–8,33].

4. Conclusions

In conclusion, we have developed an efficient nano-In_2O_3 catalyzed one-pot three-component condensation reaction of isatoic anhydride, aldehydes, and amines or ammonium salts under environmentally benign reaction conditions. A library of quinazolinone derivatives was prepared from easily available starting materials. The catalyst was recovered and reused for six times without

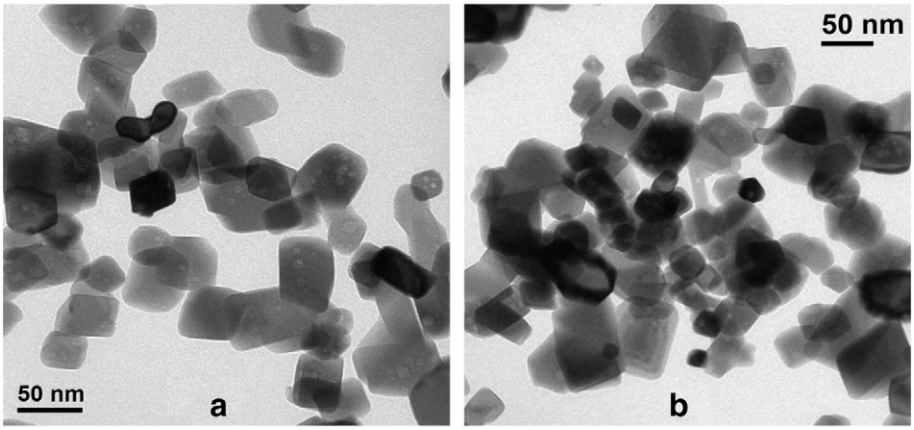


Fig. 2. HRTEM images of (a) fresh In_2O_3 nanoparticles and (b) In_2O_3 nanoparticles after the sixth cycle.

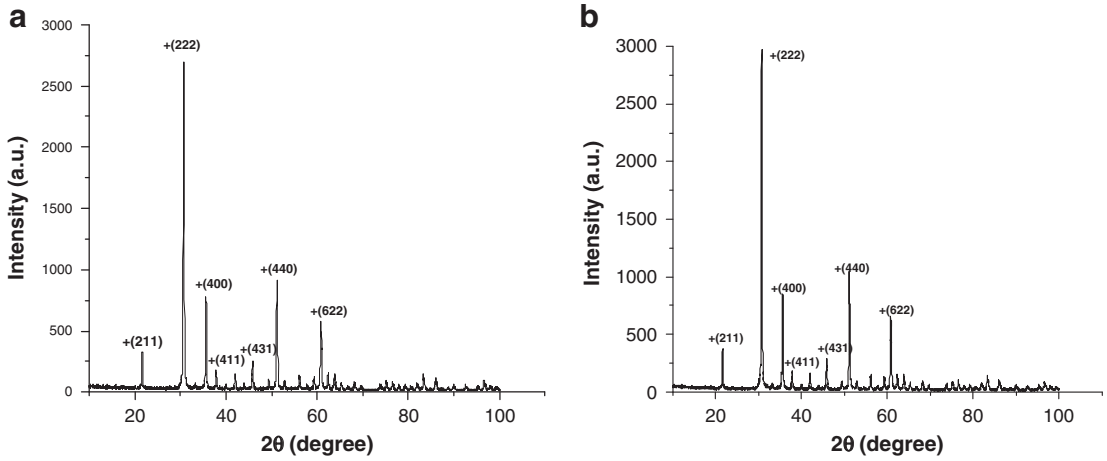
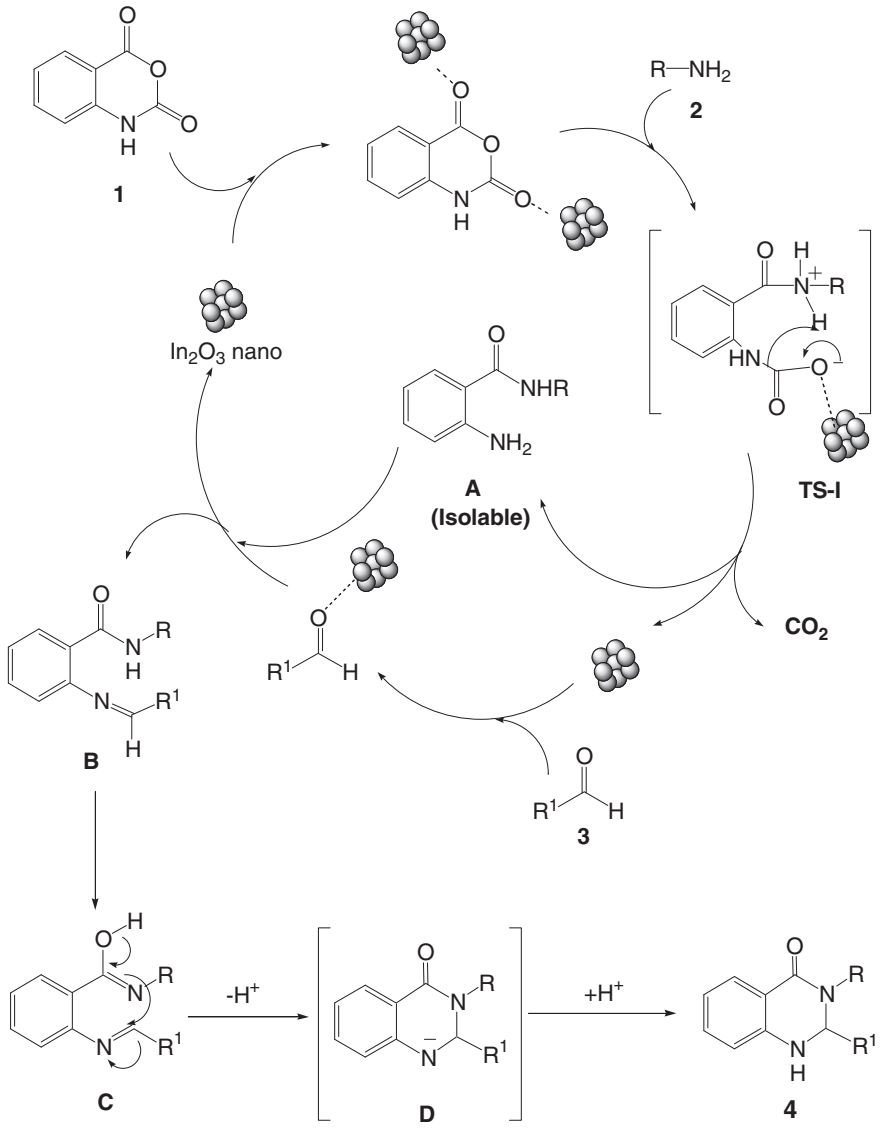


Fig. 3. Powder X-ray diffraction patterns of (a) fresh In_2O_3 nanoparticles and (b) In_2O_3 nanoparticles after the sixth cycle.



Scheme 2. Plausible mechanism.

significant loss of catalytic activities. This protocol is also applicable on gram-scale synthesis. The significant advantages offered by this method are: (i) use of greener solvent, (ii) good yields, (iii) benign byproducts, (iv) low catalyst loading, (v) simple operation, and (v) lower E-factor. We believe that our new protocol using nano-In_2O_3 will find widespread applications in academic laboratories and industry and the above features makes this procedure truly environmentally benign.

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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.2014.01.032.

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