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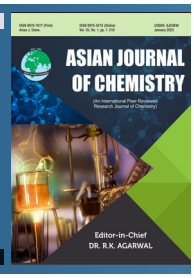

Hydrothermal Synthesis of In_2O_3-SiO_2 as Recyclable Mesostructured Catalyst Utilized for 2,3-Dihydrophthalazine-1,4-dione (DHP) Derivatives

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Mesostructured In_2O_3-SiO_2 as recyclable heterogeneous catalyst material was synthesized by an aqueous solution based wet chemistry method, *i.e.* hydrothermal method and utilized for the reaction between pathalic anhydride and substituted hydrazine hydrate in DMF medium to synthesize 2,3-dihydrophthalazine-1,4-dione (DHP) derivatives. The advantages of this protocol are cost effective, ease of handling and environmental friendly. This catalytic material were characterized by using X-ray diffraction spectroscopy, scanning electron microscopy, energy dispersive spectroscopy, Fourier transform infrared spectroscopy, temperature-programmed desorption and Brunauer–Emmett–Teller. The proposed synthetic method results in a high yield, has an easy work-up procedure, is non-toxic and clean, and facilitates the simple recovery and reusability of the catalytic system.

Keywords: Mesostructured, Reusability, Hydrothermal method, Phthalzine-1,4-diones.

INTRODUCTION

Worldwide, several modern green methodology for the synthesis of the heterocyclic compounds has been developed [1]. Consequently, nitrogen containing heterocyclic compounds has a unique and valuable position in the organic and inorganic chemistry. Numbers of the heterocyclic drug molecules those are approved by the FDA, are having significant physico-chemical properties and promising applications in the pharmaceutical world [2,3].

2,3-Dihydrophthalazine-1,4-dione (DHP) is a versatile molecule and employed in the pharmaceutical industries as an intermediary in the production of chemical compounds and medicinal molecules. This molecule exhibit unique biological activities like anticonvulsant agents [4] and effective against osteosarcoma [5], glioma [6], hypolipidemic [7] and as antibacterials [8]. Normally, the starting materials play an important role for the chemical reactions that lead to the production of useful pharmaceutical and medical compounds. Several compounds based on 2,3-dihydrophthalazine-1,4-dione such as 2-(5-(subs-tituted)-2,6-dioxo-1,2,5,6-tetrahydropyrimidin-4-yl)-2,3-dihydrophthalazine-1,4-diones having anticancer activity [9], dihydralazine (1,4-dihydrazinophthalazine) (B) as anti-hypertensive agent [10], 5-amino-2,3-dihydro-1,4-phthalazinedione (C) as anti-aging agent [11], 3-(substituted amino)thiocarbonyl-phthalazine-1,4-diones (D) as antimicrobial activity [12], *etc*. are crucial in the field of medicinal chemistry.

Various available catalysts such as polymer embedded Fe_2O_3 nanospheroids [13], a strong acidic mixture of acetic acid and hydrochloric acid [14], montmorillonite KSF clay [15], PCl_5 in $POCl_3$ [16], were used for the synthesis of 2,3-dihydrophthalazine-1,4-dione derivatives. As a result, the synthesis of 2,3-dihydrophthalazine-1,4-dione presents a major challenge in terms of developing a green, efficient and environmentally friendly catalyst material that has not been employed previously.

The nano form of mixed metal oxides have emerging applications such as fluorescent imaging, bio tagging and bio labeling, drug delivery, regenerative medicine, wound healing and so on [17,18]. As well as the synthesis of the mixed metal

oxides are utilized in the synthesis of heterocyclic compounds those are having very good medicinal properties [17,18]. The active center, structural morphology and oxidation state of mixed metal oxides is play crucial role to show its efficiency in organic transformation [19].

The binary mixture of mixed metal oxides which consist of two types of surface acidic sites, like Brønsted and Lewis acidic sites. As a result, such a material, which may have both positive and negative charges in its component structure, might provide the synergistic effects and integrate the best physico-chemical properties of its constituent components [20]. Due to the unique properties of the binary mixture of mixed oxides as catalyst [21-23], in this work, recyclable mesostructured In_2O_3-SiO_2 mixed oxide with different ratios were synthesized by a hydrothermal method and studied the physico-chemical properties of In_2O_3-SiO_2 metal oxides. Moreover, using 2,3-dihydrophthalazine-1,4-diones as a model compound, the utility of the prepared In_2O_3-SiO_2 mixed oxide as a potential catalyst for this synthesis is also evaluated.

EXPERIMENTAL

Synthesis of In_2O_3-SiO_2: In first step, a mixture of 10 mL distilled water were stirred vigorously with tetraethylortho-silicate (TEOS) to from silicate solution. Now, TEOS solution was mixed with aqueous indium solution and a suspension solution of SiO_2 (2 g in 50 mL of CH_3OH) dropwise while being vigorously stirred followed by the addition of 1 g cetyl trimethyl ammonium bromide (CTAB) as structural directing. The solution was then adjusted to a pH of 9-10 by adding NH_3 in a desired volume. After 30 min of stirring, a thick pale yellow gel had formed in the suspension which was transformed into a Teflon-lined stainless steel autoclave and close tightly for hydrothermal treatment at 150 ºC for 24 h. After that the material was cooled at room temperature, washed thoroughly with double distilled water for several times and then dried in an oven at 110 ºC for 2 h. Finally, the product was calcined at 500 ºC for 2 h in a muffle furnace. The prepared suspension was used for synthesis of DHP derivatives.

General method for the synthesis of DHP derivatives: A mixture of phthalic anhydride (5 mmol) and substituted hydrazine hydrate (5 mmol) and 1 g of In_2O_3-SiO_2 catalyst were mixed thoroughly. After that the volume of the reaction mixture was adjusted to 15 mL with DMF and then refluxed at 90 ºC for 1 h (**Scheme-I**). The reaction was monitored by thin layer chromatography. After the completion of the reaction, the white colour crude product was precipitated from the reaction mixture and recrystallized from ethanol. The purity of all the product determined by comparison of melting point in literature and representative compound were characterized by ^{1}H NMR, FTIR and mass spectrum.

Scheme-I

Spectral data of representative compound

2,3-Dihydrophthalazine-1,4-dione (4a): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.39 (d, 2H, Ar-H), 8.0 (d, NH), 7.54 (d, 2H, CH); IR (KBr, ν_{max}, cm^{-1}): 2893 (NH), 1658 (C=O), 1558 (C=C). *m/z* 163.19 (M^{+2}).

2,3-Dihydro-2-phenylphthalazine-1,4-dione (4b): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 6.70-7.50 (m, 5H), 8.12 (s, NH), 7.90-8.15 (m, 4H); IR (KBr, ν_{max}, cm^{-1}): 2750 (NH), 1580 (C=O), 1460 (C=C).

2,3-Dihydro-2-(4-nitrophenyl)phthalazine-1,4-dione (4c): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 6.50-7.05 (m, 4H), 8.00 (s, NH), 7.05-8.14 (m, 3H); IR (KBr, ν_{max}, cm^{-1}): 2810 (NH), 1609 (C=O), 1566 (C=C).

2,3-Dihydro-2-(2,4-dinitrophenyl)phthalazine-1,4-dione (4d): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 6.47-7.15 (m, 4H), 8.05 (s, NH), 7.83-8.32 (m, 4H); IR (KBr, ν_{max}, cm^{-1}): 2720 (NH), 1530 (C=O), 1530 (C=C).

RESULTS AND DISCUSSION

XRD studues: The powder XRD pattern of SiO_2, In_2O_3 and In_2O_3-SiO_2 are given in Fig. 1. In Fig. 1a, the broad peaks were obtained at 2θ = 21.74º corresponding to the plane 100 indicate the hexagonal phase of SiO_2. At Fig. 1b, an intense peak were observed at 2θ = 21.56º, 30.67º, 35.55º, 51.12º and 60.77º corresponding to the planes (211), (222), (400), (440) and (622) indicate the cubic phase of In_2O_3 (JCPDS card no. 76-0152), while the highly intense peaks (Fig. 1c) were obtained at 2θ = 21.51º, 30.58º, 35.46º, 37.66º, 41.85º corresponding to the planes ($\bar{1}01$), ($\bar{2}11$), (120), ($\bar{2}31$), ($\bar{3}20$), respectively which indicate the monoclinic phase powder diffraction pattern of In_2O_3-SiO_2 samples are crystalline in nature indicating the strong interaction between the In_2O_3 and SiO_2 support.

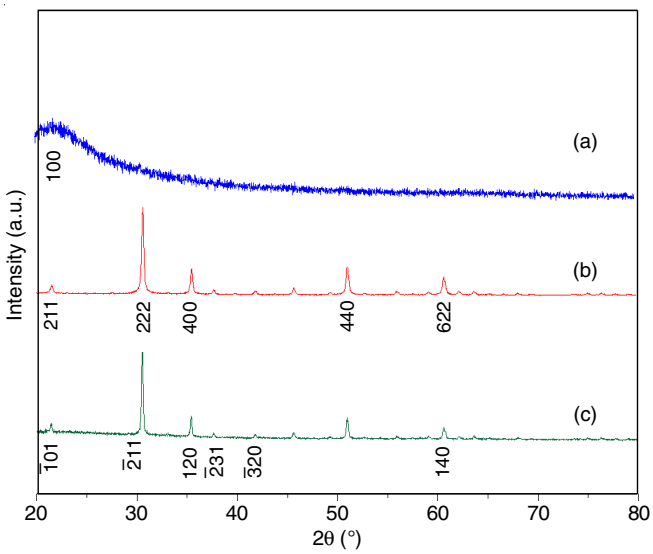

Fig. 1. XRD patterns of (a) SiO_2 (b) In_2O_3 and (c) In_2O_3-SiO_2

FTIR studies: The IR spectrum of SiO_2 (Fig. 2a) shows five intense peaks such as 3400 cm^{-1} for Si-OH stretching vibra-

tion, 2337 cm^{-1} for SiO_2, 1527 cm^{-1} for bending Si-OH, 1095 cm^{-1} for stretching Si-O vibration and 802 cm^{-1} for Si-O-Si bending vibration. Whereas the IR spectrum of In_2O_3 (Fig. 2b) exhibits two intense peaks *i.e*. a peaks at 3390 cm^{-1} for In-OH stretching vibration and at 493 cm^{-1} for antisymmetric In-O-In vibrational. In the IR spectrum of In_2O_3-SiO_2 (Fig. 2c), the peaks at 3410, 1689, 1087, 810 and 462 cm^{-1} is exact matches with Fig. 2a-b with their stretching, bending and antisymmetric vibration [24-26].

SEM-EDAX analysis: The SEM image of SiO_2 indicate flake like morphology (Fig. 3a) whereas Fig. 3b indicate the grain like morphology of In_2O_3. In Fig. 3c, the deposition of In_2O_3 on the surface of SiO_2 is clearly observed. In EDX spectra (Fig. 4), the peaks of the elements *viz*. In, Si and O indicates that no impurity found during the formation of In_2O_3-SiO_2 binary metal oxide and the capping agent is completely remove from the material. The elemental composition was found to be indium (2.75%), silicon (46.74%) and oxygen (50.51%) (Table-1).

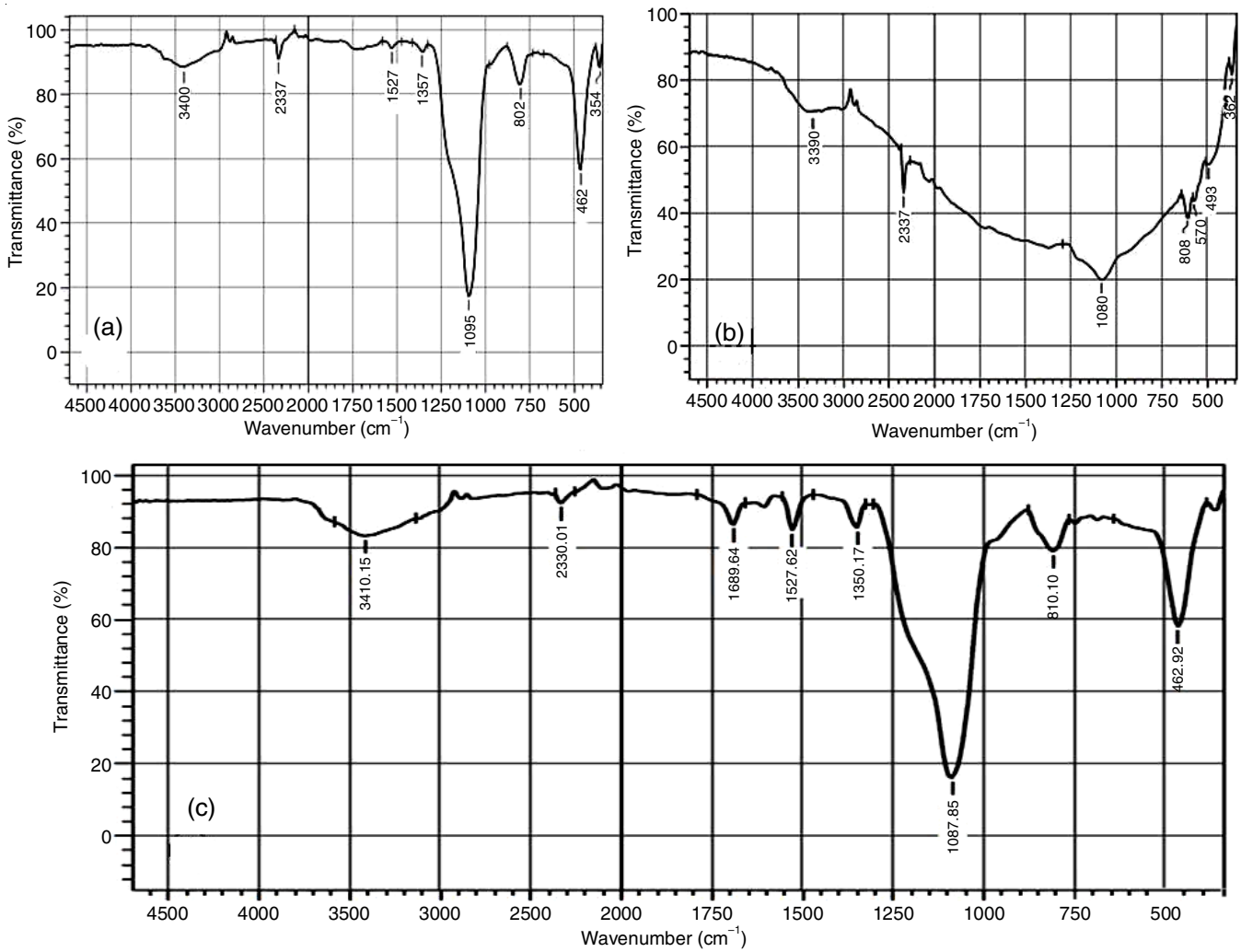

Fig. 2. FTIR spectrum of (a) SiO_2, (b) In_2O_3 and (c) In_2O_3-SiO_2

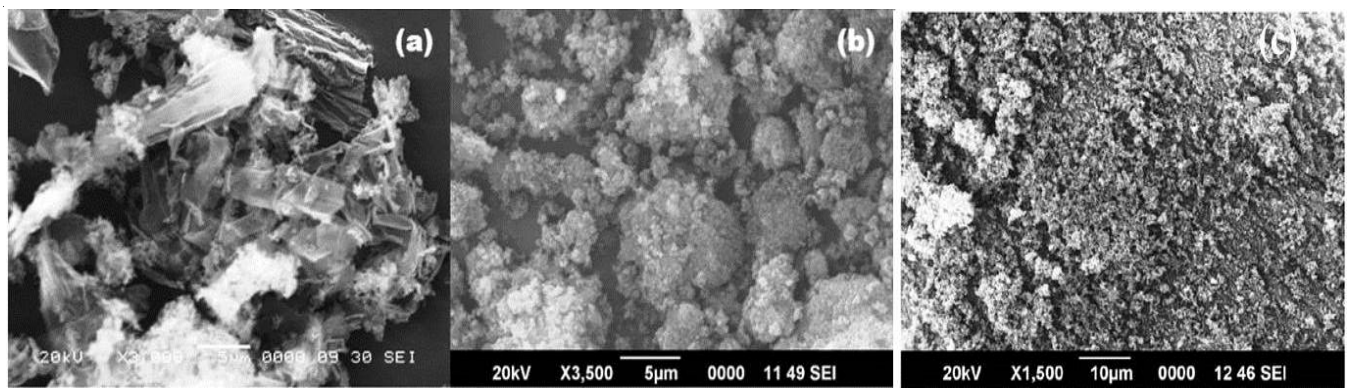

Fig. 3. SEM image of (a) SiO_2 and (b) In_2O_3 (c) In_2O_3-SiO_2

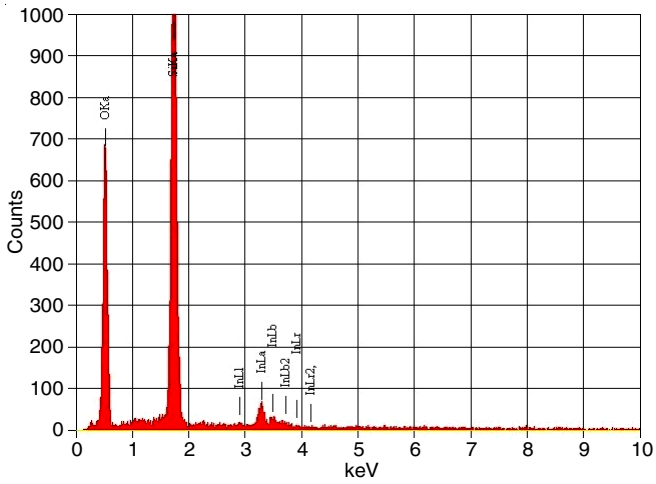

Fig. 4. EDAX spectrum of In_2O_3-SiO_2

TABLE-1
EDAX ELEMENTAL QUANTITATIVE ANALYSIS OF In_2O_3-SiO_2

Elements	Weight (%)	Atom (%)
In	12.97	2.75
Si	53.87	46.74
O	33.17	50.51
Total	100.00	100.00

Temperature programmed desorption (NH_3-TPD): Temperature programmed desorption method revealing information about the acidity and adsorption sites. According to the calculation of the TPD analysis as shown in Fig. 5, the desorption peak was observed at 190.38 ºC at 0.7236 mmol/g which indicate that In_2O_3-SiO_2 is a weak acidic site (0.02957 mmol/g).

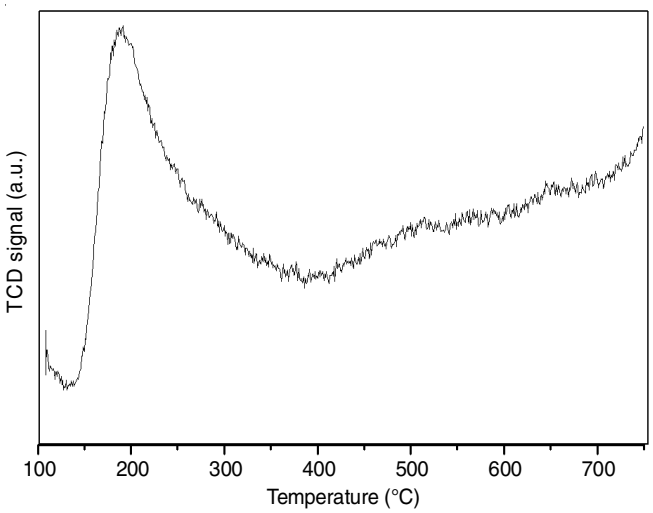

Fig. 5. NH_3-TPD profiles of In_2O_3-SiO_2

BET analysis: According to the BET analyis, the surface area of In_2O_3-SiO_2 was found to be 96.6984 m^2/g (Fig. 6) and the average pore diameter of In_2O_3-SiO_2 was 7.95 nm (Fig. 7). In contrast to the surface area of pure silica (39.7 m^2/g) and the prepared catalyst generated in this work had a large surface area, thus catalysts possessing a high surface area lead to high catalytic activity for the organic synthesis [27].

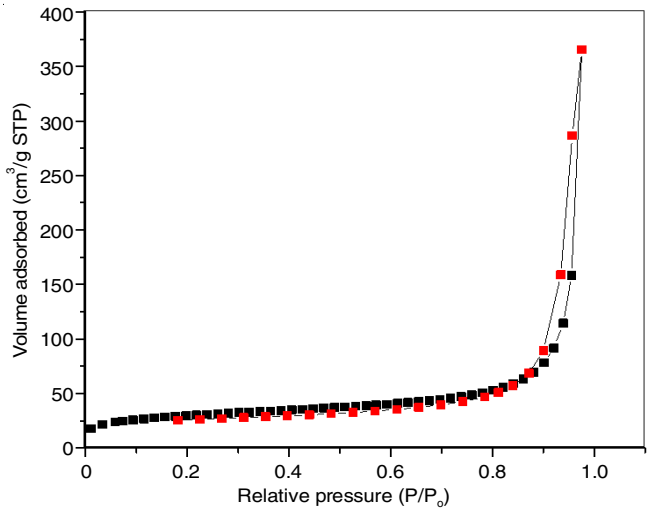

Fig. 6. N_2 adsorption/desorption isotherm of In_2O_3-SiO_2

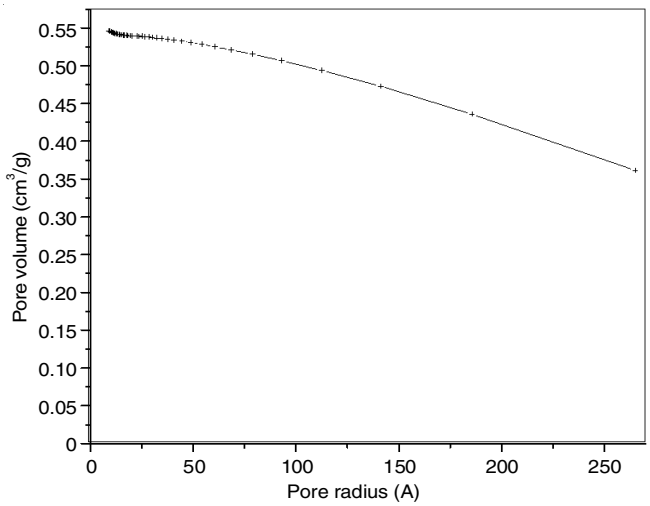

Fig. 7. BJH adsorption cumulative pore diameter In_2O_3-SiO_2

Catalytic activity: The present communication reports the synthesis of 2,3-dihydrophthalazine-1,4-diones (DHPs) from pathalic anhydride and hydrazine hydrate using In_2O_3-SiO_2 as a catalytic material. The effect of different organic solvents such as methanol, toluene, acetonitrile, THF, ethanol and DMF on synthesis of DHP were carried out. The results showed that DHP yields were moderate when methanol, acetone, acetonitrile, THF and acetone were employed in the procedure, but the yields improved significantly when DMF was used (Table-2, entry 6). Therefore, DMF was selected as a solvent for the further reaction derivatives.

TABLE-2
STUDY OF VARIOUS SOLVENTS[a]

Entry	Solvents	Time (min)	Yield (%)[b]
1	Methanol	120	40
2	Toluene	100	65
3	Acetonitrile	140	67
4	Tetrahydrofuran	90	70
5	Acetone	140	57
6	Dimethyl formamide	60	95

[a]All reactions were run by using In_2O_3-SiO_2 reflux at 90 °C; [b]Isolated yields.

The screening of various amounts of catalyst was studied. In the absence of any catalyst, no results are observed for up to 120 min (Table-3, entry 1). On the other hand, in the presence of neat SiO_2 and In_2O_3 as catalyst only the moderate yield was observed (Table-3, entry 2 & 3). By using non-calcined In_2O_3-SiO_2 metal oxide as a catalyst, acceptable yields are obtained, but the time required to complete the reaction is increased (Table-3, entry 4). Now, evaluating the In_2O_3-SiO_2 calcined powder composites has been the last step since, for the same reaction, it drastically decreases the time required to achieve the final product while simultaneously increasing the yield (Table-3, entry 5). Therefore, In_2O_3-SiO_2 mixed metal oxide was selected as a catalyst for the further reactions.

TABLE-3
STUDY OF VARIOUS AMOUNTS OF CATALYST[a]

Entry	Catalyst	Time (min)	Yield (%)[b]
1	Without catalyst	120	–
2	SiO_2	80	45
3	In_2O_3	70	70
4	In_2O_3-SiO_2	100	90
5	In_2O_3-SiO_2	60	95

[a]Reaction conditions: Phthalic anhydride (5 mmol), hydrazine hydrate (5 mmol) and DMF with 1 g of In_2O_3-SiO_2 (1:1) under reflux condition. [b]Isolated yield.

A variety of different substituted hydrazine possessing electron withdrawing groups were investigated and obtained the desired products in excellent yields (85-95%). Of additional importance was that the reactions were completed within 60-70 min in DMF reflux at 90 ºC (Table-4).

TABLE-4
SYNTHESIS OF 2,3-DIHYDROPHTHALAZINE-1,4-DIONE DERIVATIVES USING In_2O_3-SiO_2

Entry	R	Time (min)	Yield (%)[b]	m.p. (°C)	
				Found	Lit.
a	H	60	95	340	343 [28]
b	C_6H_5	60	90	215	211 [28]
c	4-NO_2-C_6H_4	70	89	348	345 [28]
d	2,4-Dinitro-C_6H_3	75	90	320	312 [28]

[a]Reaction conditions: Phthalic anhydride (5 mmol), hydrazine hydrate (5 mmol) and DMF with 1 g of In_2O_3-SiO_2 under reflux condition. [b]Isolated yield.

Recyclability studies: From the perspectives of both industrial uses and environmental protection, the catalyst recycling is of essential significance. Hence the prepared catalyst In_2O_3-SiO_2 was separated by simple filtration by washing with *n*-hexane and dried at 80 ºC for 2 h before the next catalytic run. This catalyst is reused at least three times to get similar yield under same reaction condition (Fig. 8).

Conclusion

In conclusion, a mesostructured In_2O_3-SiO_2 as recyclable heterogeneous catalyst material was successfully synthesized by hydrothermal route and characterized by XRD, SEM-EDS and FTIR, TPD and BET surface area analysis. The catalyst was used to synthesize 2,3-dihydrophthalazine-1,4-dione (DHP) reaction between pathalic anhydride with hydrazine hydrate in DMF at reflux at 90 ºC. This approach has several benefits, including a rapid reaction time, a high product yield and the ability to recycle and reuse the catalyst at least three times without a significant loss of activity.

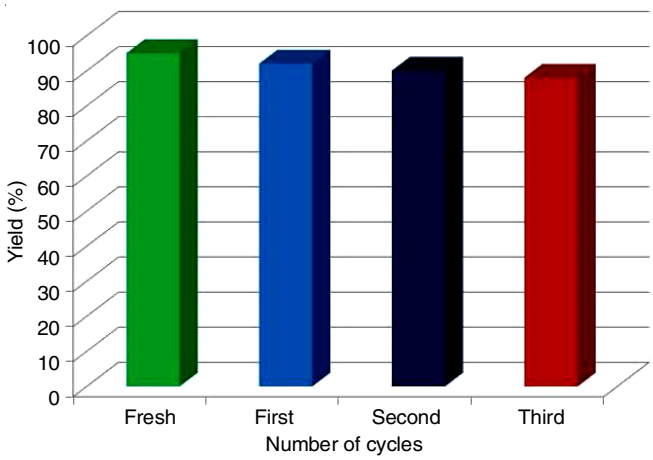

Fig. 8. Recyclation of In_2O_3-SiO_2 for synthesis of DHP (**3a**)

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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