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Hydrothermal Synthesis of $\text{In}_2\text{O}_3\text{-SiO}_2$ as Recyclable Mesostructured Catalyst Utilized for 2,3-Dihydrophthalazine-1,4-dione (DHP) Derivatives

D. TAYDE^{1,*}, U. GAWAI², R. NIKAM¹, V. INGALE³ and M. LANDE⁴

¹Department of Chemistry, M.J.M. Arts, Commerce and Science College, Karanjali-422208, India

²Department of Chemistry, Late Annasaheb R.D. Deore Arts and Science College, Mhasadi-424304, India

³Department of Chemistry, Arts, Commerce College, Warvat Bakal-444202, India

⁴Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004, India

*Corresponding author: Tel/Fax: +91 258 234666; E-mail: dtt_chem@yahoo.com

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Mesostructured $\text{In}_2\text{O}_3\text{-SiO}_2$ 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, Phthalazine-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 anti-bacterials [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-(substituted)-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 anti-microbial 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].

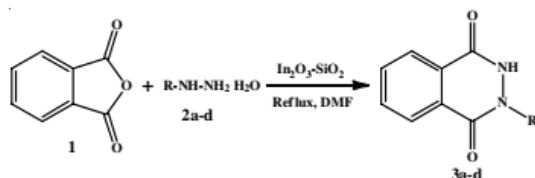
The binary mixture of mixed metal oxides which consist of two types of surface acidic sites, like Brønsted and Lewis acidic sites. As a result, such a material, which may have both positive and negative charges in its component structure, might provide the synergistic effects and integrate the best physico-chemical 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 $\text{In}_2\text{O}_3\text{-SiO}_2$ mixed oxide with different ratios were synthesized by a hydrothermal method and studied the physico-chemical properties of $\text{In}_2\text{O}_3\text{-SiO}_2$ metal oxides. Moreover, using 2,3-dihydrophthalazine-1,4-diones as a model compound, the utility of the prepared $\text{In}_2\text{O}_3\text{-SiO}_2$ mixed oxide as a potential catalyst for this synthesis is also evaluated.

EXPERIMENTAL

Synthesis of $\text{In}_2\text{O}_3\text{-SiO}_2$: In first step, a mixture of 10 mL distilled water were stirred vigorously with tetraethylorthosilicate (TEOS) to form 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 °C 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 °C for 2 h. Finally, the product was calcined at 500 °C 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 $\text{In}_2\text{O}_3\text{-SiO}_2$ catalyst were mixed thoroughly. After that the volume of the reaction mixture was adjusted to 15 mL with DMF and then refluxed at 90 °C 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 litera-



ture and representative compound were characterized by ^1H NMR, FTIR and mass spectrum.

Spectral data of representative compound

2,3-Dihydrophthalazine-1,4-dione (4a): ^1H 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^+).

2,3-Dihydro-2-phenylphthalazine-1,4-dione (4b): ^1H 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): ^1H 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): ^1H 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 studies: The powder XRD pattern of SiO_2 , In_2O_3 and $\text{In}_2\text{O}_3\text{-SiO}_2$ are given in Fig. 1. In Fig. 1a, the broad peaks were obtained at $2\theta = 21.74^\circ$ corresponding to the plane 100 indicate the hexagonal phase of SiO_2 . At Fig. 1b, an intense peak were observed at $2\theta = 21.56^\circ, 30.67^\circ, 35.55^\circ, 51.12^\circ$ and 60.77° 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 $2\theta = 21.51^\circ, 30.58^\circ, 35.46^\circ, 37.66^\circ, 41.85^\circ$ corresponding to the planes (101), (211), (120), (231), (320), respectively which indicate the monoclinic phase powder diffraction pattern of $\text{In}_2\text{O}_3\text{-SiO}_2$ samples are crystalline in nature indicating the strong interaction between the In_2O_3 and SiO_2 support.

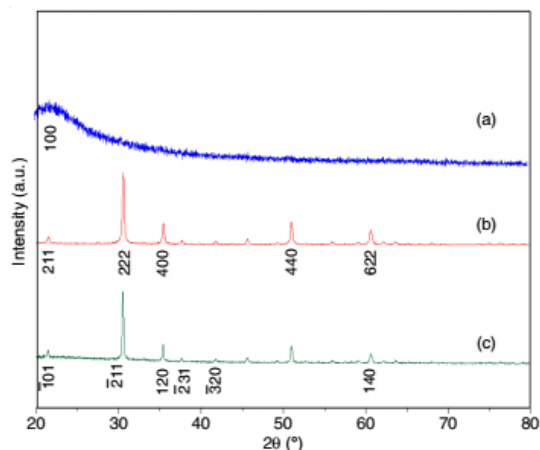


Fig. 1. XRD patterns of (a) SiO_2 (b) In_2O_3 and (c) $\text{In}_2\text{O}_3\text{-SiO}_2$

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 $\text{In}_2\text{O}_3\text{-SiO}_2$ (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 $\text{In}_2\text{O}_3\text{-SiO}_2$ 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).

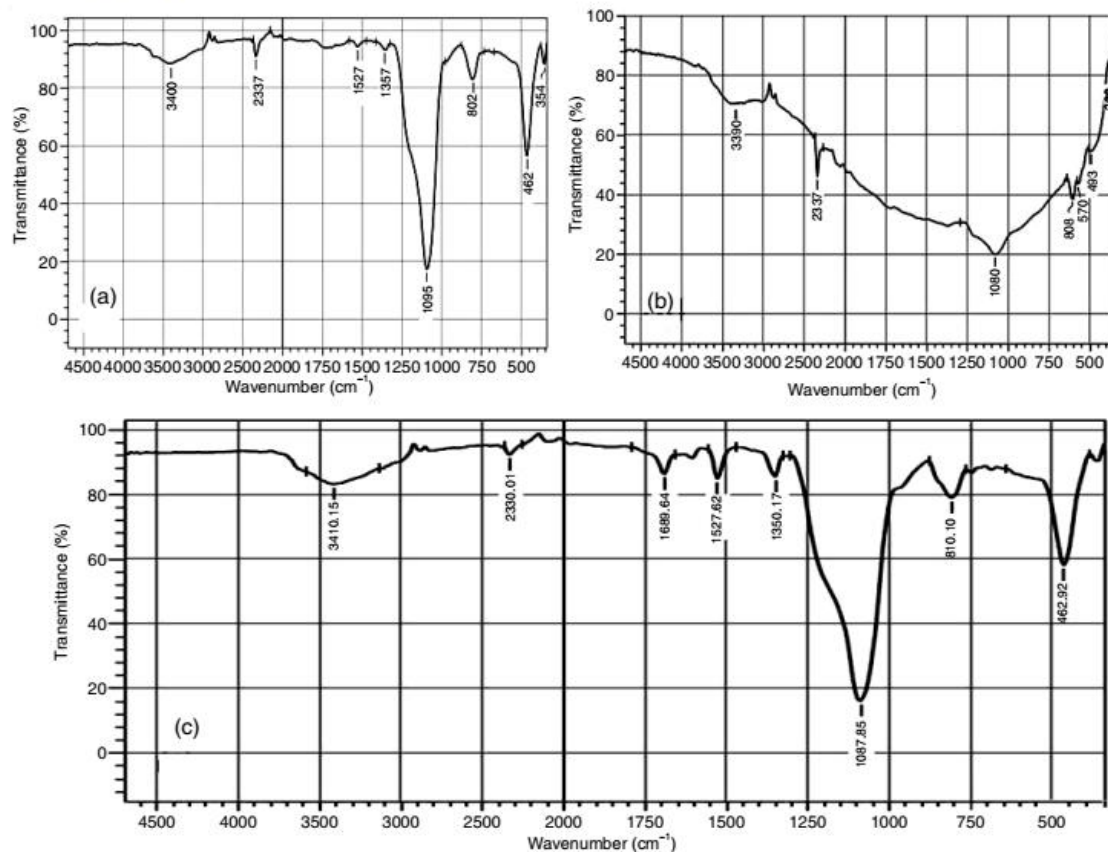


Fig. 2. FTIR spectrum of (a) SiO_2 , (b) In_2O_3 and (c) $\text{In}_2\text{O}_3\text{-SiO}_2$

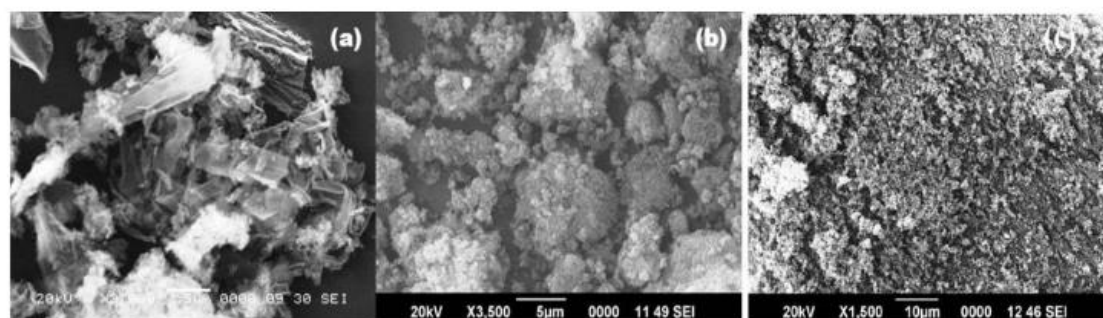


Fig. 3. SEM image of (a) SiO_2 and (b) In_2O_3 (c) $\text{In}_2\text{O}_3\text{-SiO}_2$

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 SiO₂ and In₂O₃ as catalyst only the moderate yield was observed (Table-3, entry 2 & 3). By using non-calcined In₂O₃-SiO₂ 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 In₂O₃-SiO₂ 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, In₂O₃-SiO₂ 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 ₂ O ₃	70	70
4	In ₂ O ₃ -SiO ₂	100	90
5	In ₂ O ₃ -SiO ₂	60	95

^aReaction conditions: Phthalic anhydride (5 mmol), hydrazine hydrate (5 mmol) and DMF with 1 g of In₂O₃-SiO₂ (1:1) under reflux condition. ^bIsolated 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 °C (Table-4).

TABLE-4
SYNTHESIS OF 2,3-DIHYDROPHthalazine-1,4-DIONE DERIVATIVES USING In₂O₃-SiO₂

Entry	R	Time (min)	Yield (%) ^b	m.p. (°C)	
				Found	Lit.
a	H	60	95	340	343 [28]
b	C ₆ H ₅	60	90	215	211 [28]
c	4-NO ₂ -C ₆ H ₄	70	89	348	345 [28]
d	2,4-Dinitro-C ₆ H ₃	75	90	320	312 [28]

^aReaction conditions: Phthalic anhydride (5 mmol), hydrazine hydrate (5 mmol) and DMF with 1 g of In₂O₃-SiO₂ under reflux condition. ^bIsolated yield.

Recyclability studies: From the perspectives of both industrial uses and environmental protection, the catalyst recycling is of essential significance. Hence the prepared catalyst In₂O₃-SiO₂ was separated by simple filtration by washing with *n*-hexane and dried at 80 °C 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 In₂O₃-SiO₂ 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 phthalic anhydride with hydrazine

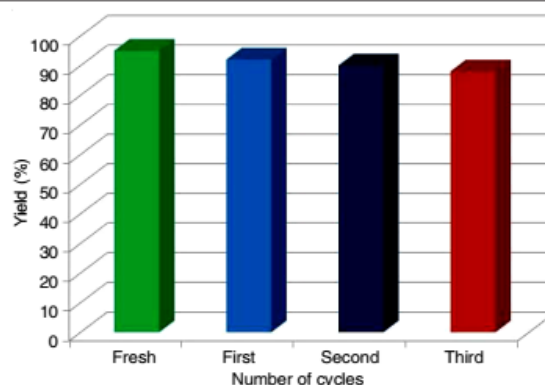


Fig. 8. Recyclability of In₂O₃-SiO₂ for synthesis of DHP (3a)

hydrate in DMF at reflux at 90 °C. 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.

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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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