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FULL PAPER

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Mesoporous silica supported ytterbium as catalyst for synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles

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The benzimidazole ring is an important pharmacophore in contemporary drug discovery. Thus, effort to identifying new compounds containing benzimidazole scaffolds have gained much attention in recent years. In the present study, MCM-41 type mesoporous silica with large pore (*l*-MSN) supported ytterbium was successfully prepared by wet impregnation method. Among rare earth metal salts, ytterbium triflate has already been widely investigated as a catalyst in organic synthesis but less toxic ytterbium oxide has yet to be explored. Relatively high abundance and low cost of ytterbium with respect to many catalytically active metals (e.g. Pd, Au, Ru, Ir, Pt) offer an opportunity to develop sustainable catalysts for organic conversions. The catalyst has been characterized by various techniques including nitrogen adsorption, FT-IR, TEM, SEM, EDX technique and elemental mapping. The obtained materials exhibit high surface area and a narrow distribution of mesoporosity. The catalytic performance of the Yb@*l*–MSNs was tested by synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles through the coupling of aldehydes with *o*-phenylenediamine. The catalyst resulted in excellent yields in short reaction times and the reaction showed tolerance toward both electron-donating and electron-withdrawing functional groups at room temperature. A particularly interesting finding was the solvent selectivity of this reaction; namely, 1,2-disubstituted benzimidazoles generated as major product in water-ethanol, while the 2-substituted benzimidazoles was generated exclusively in non-polar solvents like toluene.

KEYWORDS
1,2-disubstituted benzimidazoles, 2-substituted benzimidazoles, heterogeneous catalyst, mesoporous silica, solvent dependent synthesis, ytterbium loading

1 | INTRODUCTION

Among benzofused nitrogen-containing heterocyclic compounds, the benzimidazole scaffold is an important core unit in drug discovery due to the broad range of biological activities exhibited by compounds bearing this structural unit.[1] The benzimidazole moiety is isostructural to the purine bases and found in a variety of natural products.[2] Commercially available medicines having a benzimidazole ring comprise proton-pump inhibitors (omeprazole, esomeprazole, lansoprazole, rabeprazole), direct thrombin inhibitor dabigatran, AT1

receptor antagonists (candesartan, telmisartan), H1 receptor antagonist mizolastin, anthelmintic agent for the management of veterinary heart failure pimobendan, chemotherapeutic drug to treat chronic lymphocytic leukemia bendamustine etc. Moreover benzimidazole-quinolinonebased potent EGFR-3 inhibitor, Dovitini is currently in phase-III clinical trials for the treatment of metastatic renal cell cancer.[3] Benzimidazole derivatives also exhibit biological activities such as antimicrobial,[4] antioxidant,[5] anti-leishimanial,[6] antitubercular,[7] antifungal[8] and activity against several viruses[9] and human cytomegalovirus (HCMV). In addition, benzimidazole based structural frameworks are explored as electron-transporting hosts for phosphorescent organic light-emitting diodes (PHOLEDs).[10] Thus, owing to the vast importance of benzimidazole moiety in pharmaceutical industries, synthesis of benzimidazoles are therefore of continuing interest.

Generally, direct one-pot condensation of 1,2-diaminoarenes with aldehydes followed by oxidative cyclization is the most straightforward approach to prepare benzimidazoles.[11] The other common procedures include condensation of 1,2-diaminoarenes with carboxylic acids,[12] carboxylic acid derivatives and nitriles under dehydrating conditions.[13] Though the reported protocols are quite efficient, many of those have several limitations such as use of perilous organic solvents, require elevated temperature and costly reagents. Moreover, one of the major drawbacks of these protocols are that they show poor selectivity towards N-1 substitution, which results in the formation of 1,2-disubstituted benzimidazole as a side product along with 2-substituted benzimidazole (Scheme 1).

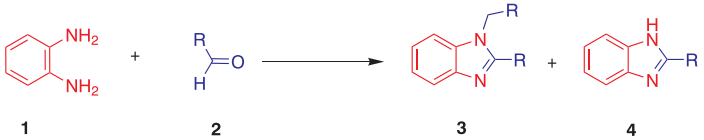
As a part of our current research in this area,[14] we report here a MCM-41 type mesoporous silica-supported ytterbium catalyzed synthesis of regio-defined 1,2-disubstituted benzimidazole and 2-substituted benzimidazole (Scheme 1). During the last two decades, ytterbium triflate has been found as unique Lewis acid that has exhibited high catalytic activity in many organic reactions, including Michael, aldol, Friedel-Crafts, Mannich, Diels-Alder, Povarov reactions, imino ene reaction etc.[15] Other ytterbium salts or ytterbium oxides have not been investigated so far. This motivates us to explore the opportunity of making a less hazardous MCM–41 type mesoporous silica loaded with ytterbium possessing high surface area and large pore diameter. Among different mesoporous silica materials, MCM–41 have attracted much attention as adsorbents and catalysts due to their remarkably high surface area, large pore volume, uniform pore structure, and tailored pore size up.[16] Different metal incorporated or loaded MCM–41 materials have been studied focussing on their application as catalysts and adsorbents. Despite these advances, the efficacy of this material in fine chemical synthesis is not well explored due to its poor intrinsic activity as well as lower pore diameter. Lin and his co-worker reported a MCM–41type MSN (*l*-MSN) material with a large pore diameter to study uptake and release profiles of cytochrome *c*.[17] Very recently, Trewyn *et al.* have studied activity of re-associated concanavalin A released from *l*-MSN.[18] The high surface area and large pore diameter of *l*-MSN could be attractive for supported metal catalysts.

Moreover, in organic chemistry, solvent-selective reactions offer unique synthetic methodology.[19] Combining the same reactants in different solvents selectively generates different products.[19] Thus, solvent can be considered as one of the most important stimuli that can direct the course of reactions from one product to another. Considering the importance of benzimidazole moiety in pharmaceutical industries, heterogeneous catalytic activity of ytterbium loaded mesoporous silica has been explored here for the solvent selective synthesis of 1,2-disubstituted benzimidazole and 2-substituted benzimidazole. To the best of our knowledge, single catalyst furnishing both 1, 2-disubstituted benzimidazole and 2-substituted benzimidazole selectively in different solvents under similar reaction conditions is not known so far.

2 | EXPERIMENTAL

2.1 | Materials and methods

Cetyl trimethyl ammonium bromide (CTAB, 99%), tetraethyl orthosilicate (TEOS, 99%) and ytterbium nitrate pentahydrate (99.9%) were purchased from Sigma-Aldrich. All chemicals were used as received without any purification. All solvents were of analytical grade and distilled before use. Large pore MCM-41 type mesoporous silica with (*l*-MSN) was synthesized via the method of Slowing *et al.*[17,18] using CTAB and mesitylene as template and pore-expanding agent, respectively.



SCHEME 1 Competitive formation of 1,2-disubstituted and 2-substituted benzimidazoles

2.2 | Characterization techniques

Nitrogen adsorption–desorption isotherms of the samples were measured at liquid nitrogen temperature with a Micromeritics Tristar 3020 surface area and porosity analyzer. The samples were degassed under nitrogen flow at 373 K for 6 h. The surface areas were calculated by the Brunauer–Emmett–Teller (BET) method and the pore size distribution were calculated by the Barrett–Joyner–Halenda (BJH) method.

Scanning Electron Microscopy (SEM) was performed using a JEOL JSM 7610F instrument. The samples were dispersed on a conductive carbon tape and analyzed using an accelerating voltage of 15 kV. EDS and particle mapping were performed using an Oxford Instruments X-Max^N 50 X-ray detector attached with the aforementioned SEM instrument.

Transmission Electron Microscopy (TEM) imaging was done on a Philips FEI CM 200 transmission electron microscope operated at 200 kV. TEM samples were prepared by sonicated the samples in ethanol for 15 min. 2 μL of this suspension was drop-casted onto carbon-coated, 300 mesh copper grids.

Ytterbium content in the samples were measured using a Perkin Elmer inductively coupled plasma atomic emission spectrometer (ICP-AES) model NexION 300Q. 5 mg of catalyst was dissolved in 10 mL aliquot of 500 mL solution prepared from mixing 50 μL of 36% HF and 500 μL of aqua regia.

^{1}H NMR spectra were recorded on a Bruker Avance III 300, 400 and 500 MHz NMR spectrometer. NMR spectra were recorded at room temperature with $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts (δ) of ^{1}H NMR spectra are reported in ppm relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: δ = 7.26 ppm, DMSO in DMSO-d_6: δ = 2.50 ppm); data are reported as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; *J* values are given in Hz.

FT-IR spectra were recorded using KBr disks with JASCO FTIR-460 Plus spectrophotometers.

2.3 | Synthesis of mesoporous silica nanoparticle with large pores (*l*-MSN)

Cetyltrimethylammonium bromide (CTAB, 1.0 g, 2.7 mmol) was dissolved in 480 ml water and 3.5 ml of 2 M NaOH in aqueous medium was added to it followed by mesitylene (5.87 gm, 48.8 mmol). The mixture was stirred vigorously at 80 °C for 2 h and then tetraethyl orthosilicate (4.56 gm, 21.9 mmol) was added to the solution dropwise. The reaction was heated to 80 °C with vigorous stirring and continued for another 2 h. The white precipitate was isolated by filtration, washed with methanol, and dried under vacuum at 100 °C for 12 h. The synthesized material (1.0 gm) was stirred in a mixture of methanol (100 ml) and concentrated hydrochloric acid (0.75 ml) at 50 °C for 6 h to remove the structure-templating CTAB and mesitylene molecules. The template-removed product was then filtered and dried under vacuum at ambient temperature for 12 h.

2.4 | Catalyst synthesis

A series of ytterbium-containing *l*-MSN samples with spherical morphology were synthesized in the following manner. Yb $(NO_3)_3{\cdot}5H_2O$ was completely dissolved in 10 ml ethanol and 0.5 g of *l*-MSN was suspended in Yb $(NO_3)_3{\cdot}5H_2O$/ethanol solution. The suspension was left to dry in air at 30 °C with constant stirring. The solid obtained was then calcined in air at 550 °C for 5 h. The synthesized catalysts are referred to as Xm-Yb, where Xm represents the amount of ytterbium precursor added in mmol during the synthesis.

2.5 | General experimental procedure for the synthesis of 1, 2-disubstituted benzimidazole

A mixture of aldehyde (2 mmol), *o*-phenylenediamine (1 mmol) and catalyst (15 mg) was taken in a single neck round bottom flask in water/ethanol (2:1, 5 ml). The reaction mixture was stirred for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was recovered by centrifugation and solvent was evaporated at reduced pressure. The product was purified by column chromatography using ethyl acetate and hexane (30:70) mixture as eluent.

2.6 | General experimental procedure for the synthesis of 2-substituted benzimidazole

A mixture of aldehyde (1 mmol), *o*-phenylenediamine (1 mmol) and catalyst (15 mg) in toluene (5 ml) was taken in a round bottom flask. The reaction mixture was stirred for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by centrifugation and solvent was evaporated at reduced pressure. The product was purified by column chromatography using ethyl acetate and hexane (30:70) mixture as eluent to obtain the desired product.

3 | RESULTS AND DISCUSSION

3.1 | Characterization of Catalyst

The MSN with large pores has been synthesized by adding mesitylene as a pore-expanding agent to a CTAB-templated base-catalyzed condensation reaction of silicate as reported previously.[17,18] The catalysts were obtained by impregnating the *l*-MSN support in the ethanolic solution of Yb $(NO_3)_3{\cdot}5H_2O$, followed by calcination.

The nitrogen adsorption–desorption isotherm and BJH pore size distribution determined for *l*–MSN and *l*–MSN supported ytterbium catalysts are displayed in Figure 1 and textural characteristics are summarized in Table 1. The samples exhibited type IV adsorption–desorption isotherm, which is characteristic of mesoporous materials. The parent *l*–MSN support was characterized by a relatively high surface area and pore volume of 743 $m^2\ g^{-1}$ and 1.18 $cm^3\ g^{-1}$, respectively (Figure 1a). The isotherm exhibits a double plateau shape which can be attributed to the heterogeneous pore expansion and the results are consistent with previously reported pore expanded mesoporous silica.[17] Barrett–Joyner–Halenda (BJH) pore size distributions data show (Table 1) narrow pore size distribution with peak at 5.6 nm. The BJH pore size distributions of *l*-MSN shows only one peak unlike two peaks reported previously (Figure 2b). As shown in Figure 1a, ytterbium loaded samples show only one hysteresis loop (H_2 type) in the 0.4 to 0.75 P/P_0 range. The surface area and pore volume gradually decreased with the increase in ytterbium loading. This may be due to the blocking of pores of parent *l*–MSN by ytterbium ions. Accordingly, the pore volume decreases with increases in ytterbium loading (Table 1). The synthesized catalysts exhibit a narrow pore size distribution at around 4.6 nm, which are slightly reduced in comparison to parent *l*-MSN.

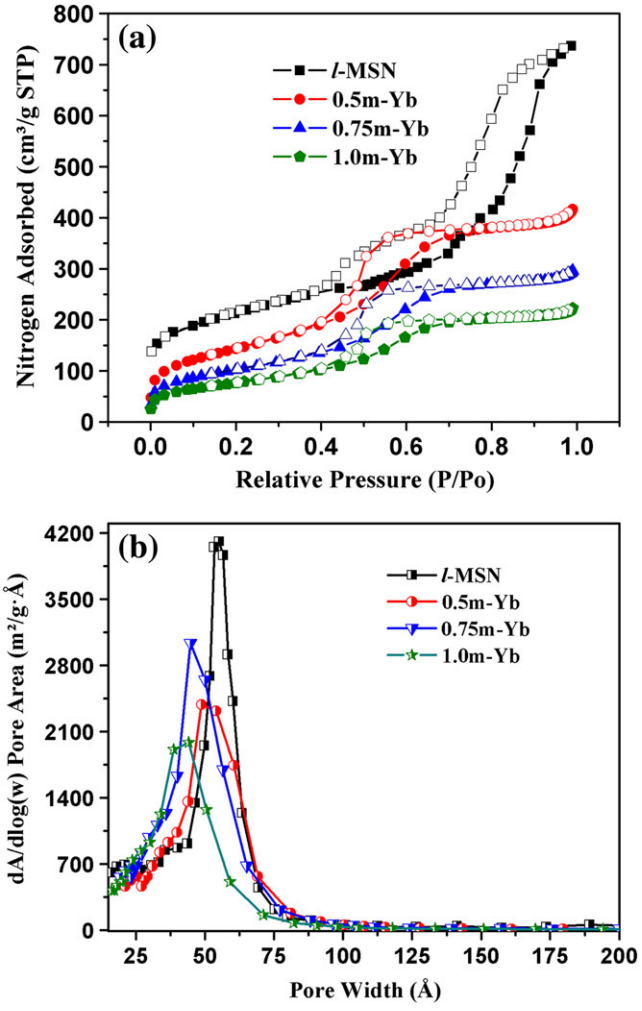


FIGURE 1 (a) Nitrogen adsorption and desorption isotherm (closed symbol: adsorption and open symbol: desorption) and (b) BJH pore size distribution of catalysts

As shown in Figure 2, *l*-MSN, 0.75 m-Yb and 1.0 m-Yb were characterized by low angle XRD. The diffraction pattern of *l*-MSN exhibits a sharp peak for d_{100} plane as well two low intensity peaks for d_{110} and d_{200} planes of hexagonally ordered pores common to MCM-41 type materials.[20] In the ytterbium loaded samples, most intense d_{100} diffraction is observed clearly, but higher peaks are broadened and not clearly observed. In high angle X-ray diffraction pattern of 0.75 m-Yb, no characteristics peak for Yb_2O_3 is observed (Figure S1) indicating the uniform dispersion of ytterbium in the silica matrix.

Figure 3 presents the scanning electron micrographs of parent *l*-MSN and 0.75 m-Yb. Micrographs of *l*-MSN and 0.75 m-Yb are showing spherical particles and the size of these particles is in a range from 0.3 to 0.8 μm. The energy dispersive X-ray (EDX) spectroscopy of 0.75 m-Yb shows the presence of Yb (Figure S2). The ytterbium dispersion was measured by EDS mapping of the catalyst sample (Figure 4). The result shows that ytterbium is homogeneously dispersed throughout the surface of the silica support. TEM micrograph of the 0.75 m-Yb obtained is shown in Figure 5. The image clearly displays spherical nature and the radial porosity of the silica frame. Figure S3 exhibit FT–IR of 0.75 m-Yb. The exact metal loading of these MSN catalysts was analyzed by ICP-OES technique and the results were summarized in Table 1. The measured loading is very close to the amount introduced.

3.2 | Synthesis 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles

Initial optimization of the reaction conditions for the synthesis of substituted benzimidazoles, were performed

TABLE 1 Summary of physical properties of supported catalysts

Entry	Catalyst	Amount of Yb $(NO_3)_3 \cdot 5H_2O$[a] (mmol)	(gm)	S_{BET} ($m^2\ g^{-1}$)[b]	W_{BJH} (nm)[b]	Pore volume ($cm^3\ g^{-1}$)[b]	Yb/Si[c]
1	*l*-MSN	-	-	743	5.6	1.18	-
2	0.5 m-Yb	0.5	0.22	537	4.8	0.81	0.061
3	0.75 m-Yb	0.75	0.34	365	4.6	0.63	0.091
4	1.0 m-Yb	1.0	0.45	275	4.3	0.34	0.12

[a]Amount of Yb $(NO_3)_3 \cdot 5H_2O$ used per 0.5 gm of *l*-MSN.

[b]Specific surface area (S_{BET}) and mean pore diameter (W_{BJH}) were obtained from nitrogen sorption analysis. The specific surface area was calculated by BET method and the mean pore diameter was calculated by BJH method.

[c]The molar ratio of Yb/Si determined by ICP-AES analysis.

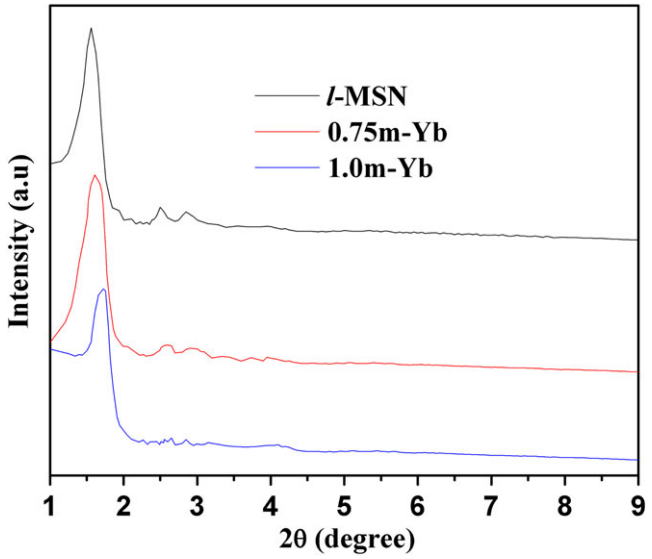


FIGURE 2 Low angle XRD of *l*-MSN, 0.75 m-Yb and 1.0 m-Yb

with 4-methylbenzaldehyde as a model substrate in presence of *o*-phenylenediamine in ethanol using ytterbium containing *l*-MSN as catalysts (Table 2). In a typical experiment, a mixture of *o*-phenylenediamine (1 mmol) and 4-methylbenzaldehyde (1 mmol) in 5 ml solvent was reacted in presence of 15 mg catalyst for 1 h at room temperature. The conversion percentage increased with the increase in ytterbium loading from 14 wt% to 17 wt%. With further increase in ytterbium loading, the percentage of conversion diminished. It seems that, with 17 wt% ytterbium loading there is monolayer coverage of Yb_2O_3 on the support. But with increased ytterbium percentage there is excess loading of metal and some pores of *l*-MSN are blocked. Poor yield was obtained with unmodified solid support *l*-MSN. No product is obtained when the reaction was carried out without any catalyst.

Then the effect of solvent on the reaction was evaluated thoroughly using 0.75 m-Yb as the catalyst. It is evident from Table 3 that polar solvents like ethanol, methanol, DMF and DMSO (entries 1–4) exhibit high conversion with very good selectivity towards 1,2-disubstituted benzimidazole whereas water shows poor conversion rate with excellent selectivity towards 1, 2-disubstituted benzimidazole (entry 5). When the reaction was performed in ethanol/water (2:1) mixture, 92% conversion obtained with excellent selectivity towards 1, 2-disubstituted benzimidazole (entry 9). Other solvents such as acetonitrile, THF exhibits a poor conversion rate as well as selectivity (entries 6, 7). Interestingly, toluene demonstrates 95% conversion with absolute selectivity

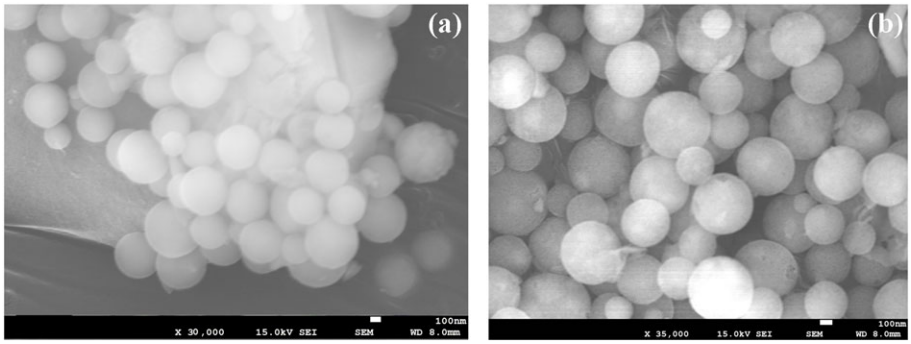


FIGURE 3 Scanning electron microscope images of (a) *l*-MSN and (b) 0.75 m-Yb

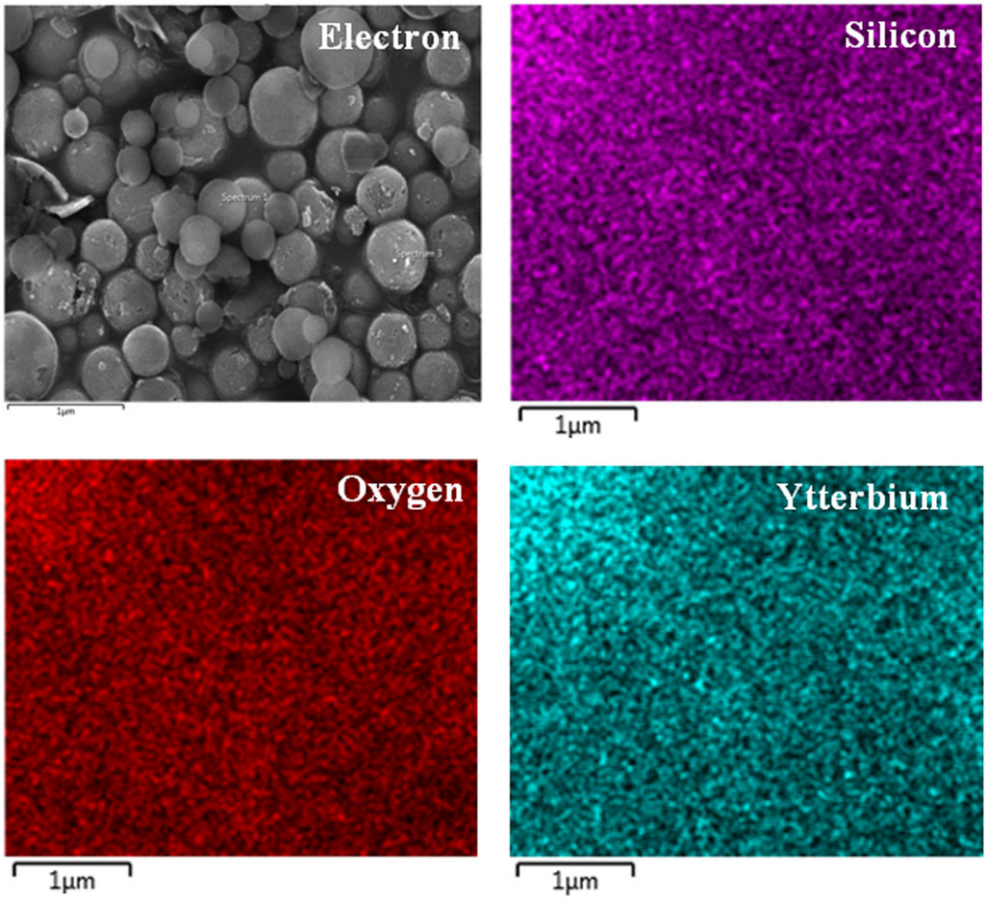


FIGURE 4 EDS mapping of 0.75 m-Yb used to measure dispersion of active species within the catalyst

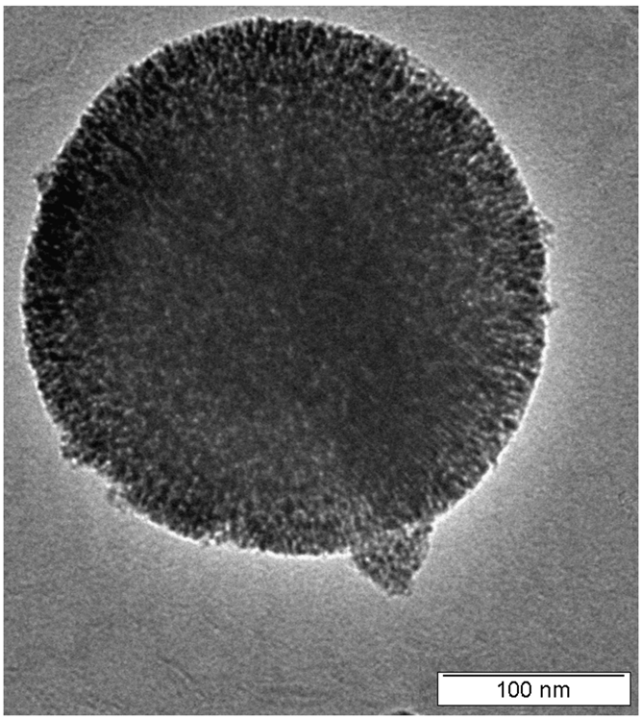


FIGURE 5 TEM image of ytterbium containing porous silica sphere of 0.75 m-Yb

TABLE 2 Comparison of catalytic performance of catalysts on benzimidazole synthesis[a]

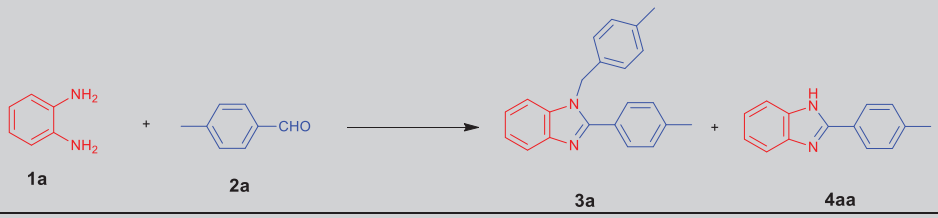
Entry	Catalyst	Conversion (%)[b]
1	0.5 m-Yb	70
2	0.75 m-Yb	90
3	1.0 m-Yb	85
4	*l*-MSN	30
5	None	Trace

[a]Reaction condition is detailed in the experimental section.

[b]Percent conversion of *o*-phenylenediamine.

for 2-substituted benzimidazole (entry 8). There was no noticeable increase in the yield on prolonging the time span or increasing the metal loading (entries 10–13). Lower conversions were obtained when Yb $(NO_3)_3 \cdot 5H_2O$, $YbCl_3 \cdot 6H_2O$ and ytterbium oxide powder were used (entries 14–16). Ytterbium loaded *l*-MSN (0.75 m-Yb) was better suited to afford 1,2-disubstituted benzimidazoles in ethanol/water (2:1) mixture at room temperature. Whereas toluene emerged as the best choice

TABLE 3 Optimization of reaction conditions for the synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles[a]



1a 2a 3a 4aa

Entry	Solvent	Catalyst	Catalyst Amount (mg)	Time (h)	Conversion(%)[b]	Selectivity (%)[c]	
						3a	4aa
1	ethanol	0.75 m-Yb	15	1.0	90	75	25
2	DMF	0.75 m-Yb	15	1.0	65	60	40
3	DMSO	0.75 m-Yb	15	1.0	82	70	30
4	methanol	0.75 m-Yb	15	1.0	90	80	20
5	water	0.75 m-Yb	15	1.0	40	90	10
6	ACN	0.75 m-Yb	15	1.0	43	55	45
7	THF	0.75 m-Yb	15	1.0	34	60	40
8	toluene	0.75 m-Yb	15	1.0	95	0	100
9	EtOH/H_2O	0.75 m-Yb	15	1.0	92	90	10
10	EtOH/H_2O	0.75 m-Yb	15	2.0	90	90	10
11	EtOH/H_2O	0.75 m-Yb	15	4.0	92	90	10
12	EtOH/H_2O	0.75 m-Yb	20	1.0	90	90	10
13	EtOH/H_2O	0.75 m-Yb	10	1.0	82	90	10
14	EtOH/H_2O	Yb $(NO_3)_3 \cdot 6H_2O$	15	4.0	65	90	10
15	EtOH/H_2O	$YbCl_3 \cdot 6H_2O$	15	4.0	63	90	10
16	EtOH/H_2O	Yb_2O_3	15	5.0	56	90	10

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (2 mmol), catalyst in solvent (5 ml), room temperature.

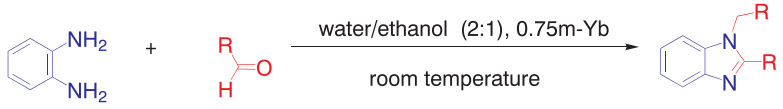
[b]Percent conversion of *o*-phenylenediamine.

[c]Isolated yield.

amongst other solvents to obtain 2-substituted benzimidazoles utilizing 0.75 m-Yb as catalyst.

To examine the versatility of this reaction, a series of aromatic aldehydes were introduced to the optimal reaction conditions (Scheme 2). By using ethanol/water (2:1) as solvent at room temperature, 1,2-disubstituted benzimidazoles were obtained in excellent yields. Most aromatic aldehydes bearing both electron-donating and electron-withdrawing groups in the *para*-position were well resilience under the same reaction condition affording high yields (Scheme 2, **3b–3g**). Aromatic aldehydes having substitution on *ortho*-position furnished moderate yield due to steric hindrance (Scheme 2, **3h–3j**). Heteroaromatic thiophene-2-carbaldehyde, 2-pyridyl benzaldehyde and 3-pyridyl benzaldehyde (Schme 2, **3 k–3 m**) were also furnished corresponding 1,2-disubstituted benzimidazoles in decent yields. To the contrary, the reaction of aliphatic aldehydes needed extended reaction time to achieve moderate yields.

The scope of the catalyst was broadened successfully to the synthesis of 2-substituted benzimidazoles in toluene. The optimised protocol was 1, 2-phenylenediamine (1 mmol) and aldehyde (1 mmol) in the presence of 15 mg catalyst in toluene at 25 °C. The electronic effect of substituent groups on the yield of reaction was thoroughly examined and is shown in Scheme 3. Aldehydes bearing electron withdrawing as well as electron donating groups (Scheme 3, **4aa**, **4 ac–4aj**) produced very good to excellent yield (78—95%) under the optimal reaction conditions. The presence of both electron withdrawing and donating groups does not affect the yield of the reaction considerably. Inactivated aliphatic aldehyde also shows good yield (Scheme 3, **4al**). 2-Pyridine aldehyde and 1,2-dihydroanthracene-9-carbaldehyde also furnished moderate yield (Scheme 3, **4ak** and **4 am**). 1,2-Phenylenediamine having electron donating groups (Scheme 3, **4bb–4db**) also gave very good yield whereas diamine with electron withdrawing furnished much inferior yield.



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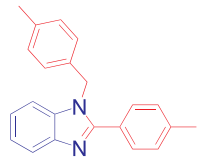
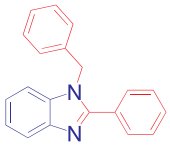
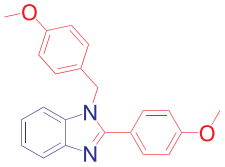


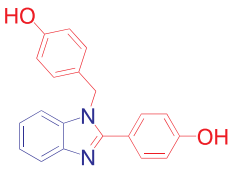
3a, 92% conv
83% yield, select 90.2%
TON: 34



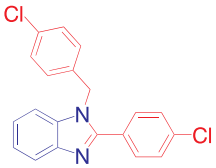
3b, 90% conv
80% yield, select 88.9%
TON: 33



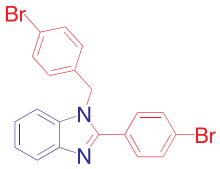
3c, 90% conv
83% yield, select 90.2%
TON: 34



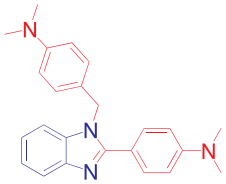
3d, 85% conv
77% yield , select 90.6%
TON: 32



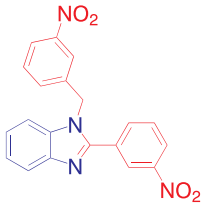
3e, 86% conv
77% yield, select 89.5%
TON: 32



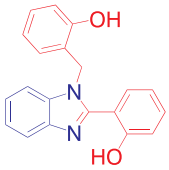
3f, 86% conv
78% yield, select 90.7%
TON: 32



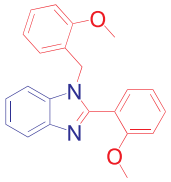
3g, 81% conv
73% yield, select 90%
TON: 30



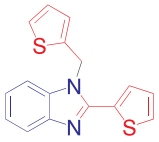
3h, 80% conv
72% yield, select 90%
TON: 30



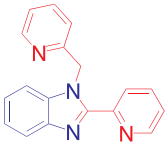
3i, 84% conv
70% yield, select 83.3%
TON: 29



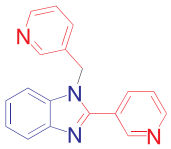
3j, 82% conv
65% yield, select 79.3%
TON: 27



3k, 85% conv
72% yield, select 84.7%
TON: 30



3l, 80% conv
72% yield, select 90%
TON:30

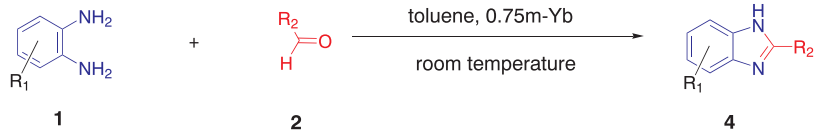


3m, 82% conv
70% yield, select 85.4%
TON: 29

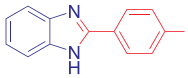
Reaction conditions (untill otherwise specified): **1** (1.0 mmol), **2** (2 mmol), 15 mg 0.75m-Yb, water/ethanol (2:1, 5 mL), room temperature, 1 h. Percent conversion of *o*-phenylenediamine is reported. Isolated yields are reported. TON = The moles of 1, 2-disubstituted benzimidazole formed per mol catalyst. Reaction temperature was 40 °C for **3h**-**3j**.

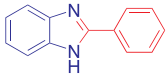
SCHEME 2 Substrates scope in 1,2-disubstituted benzimidazole formation

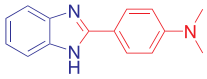
To test the recyclability of the catalyst, a reaction with 4-methylbenzaldehyde and *o*-phenylenediamine was performed in the presence of 0.75 m-Yb in ethanol/water (2:1). Figure 6 shows the recyclability of the *l*-MSN catalyst for five cycles. Both conversion and yield were maintained as >90% in the first three cycles

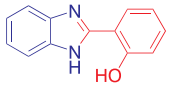


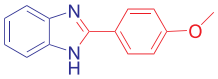
1 2 4

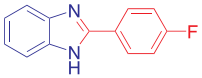

4aa, 95%, TON: 39

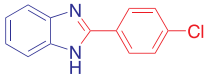

4ab, 95%, TON: 39

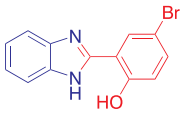

4ac, 86%, TON: 35

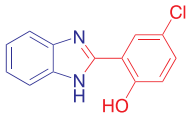

4ad, 85%, TON: 35

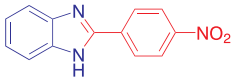

4ae, 92%, TON: 38

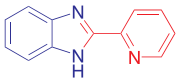

4af, 80%, TON: 33

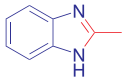

4ag, 82%, TON: 33

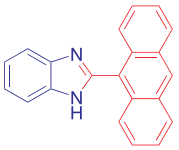

4ah, 84%, TON: 35

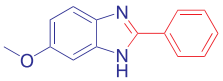

4ai, 82%,TON: 33

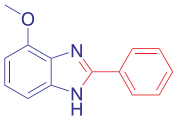

4aj, 78%, TON: 32

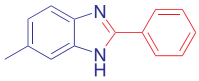

4ak, 76%, TON: 31

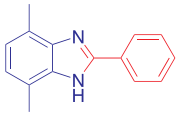

4al, 73%, TON: 30


4am, 76%,TON: 31


4bb, 85%, TON: 35


4cb, 84%, TON: 35


4db, 90%, TON: 37


4eb, 80%, TON: 33

Reaction conditions: **1** (1.0 mmol), **2** (1 mmol), 15 mg 0.75m-Yb, toluene (5 mL), room temperature, 1 h. Isolated yields are reported. TON = The moles of 2-substituted benzimidazole formed per mol catalyst.

SCHEME 3 Substrates scope in 2-substituted benzimidazole formation

and then started decreasing during the fourth run and dropped significantly for the next cycle. The reused catalyst (after five cycles) was also characterized by BET and TEM after five consecutive runs. The results demonstrated that the catalyst suffered no observable changes in mesoporosity (Figure 7a), although pore volume and BET surface area reduces to 0.22 cc g^{-1} and 140 m^2 g^{-1}, respectively (Figure 7b), pore diameter remained unchanged. The reduction in pore volume can be attributed to blocking of the pore channels by reaction species in the mixture. To prove the blocking of pore channel, the reused catalyst after five cycle was calcined at 550 °C and BET surface area of the calcined sample was measured. BET surface area and pore volume (Figure 7c) of the calcined sample were found to be 0.55 cc g^{-1} and 326 m^2 g^{-1}. These values are very close to the BET surface area and pore volume of catalyst 0.75 m-Yb (Table 1).

In addition, leaching of metal ion has been a concern for metal catalysts incorporated in mesoporous silica. To discard the contribution of homogeneous catalysis, the reaction with 4-methylbenzaldehyde and *o*-phenylenediamine was conducted in the presence of 0.75 m-Yb in ethanol/water (2:1) for 30 min to obtain a yield of 68%. The solid catalyst was removed by filtration and the filtrate was then transferred to another vessel.

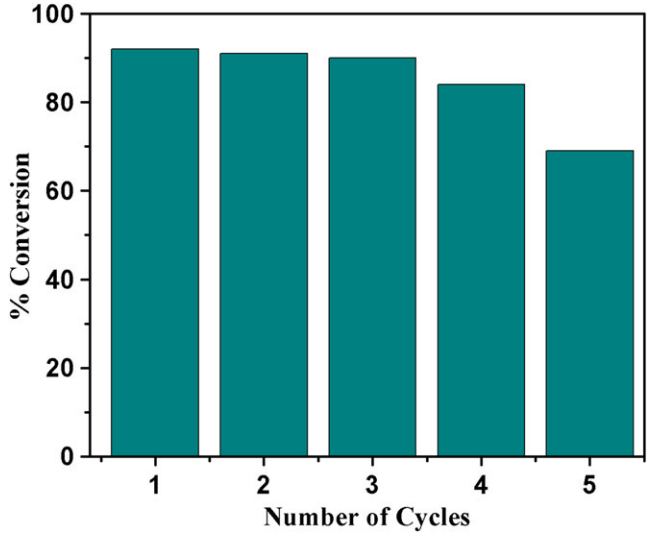


FIGURE 6 Reusable profiles of the 0.75 m-Yb catalyst for the synthesis of 1-(4-methylbenzyl)-2-(*p*-tolyl)-1Hbenzo[d] imidazole (**3a**)

Stirring of the catalyst-free solution was continued for additional 1 h at room temperature, but no further reaction took place. The reaction solution was then subjected to ICP-AES analysis and no metal ion were detected within the detection limit.

In order to examine the efficiency of 0.75 m-Yb, we compared the results for the synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles in the presence of this catalyst with few heterogeneous catalysts[11v,21] reported so far in the literature (Table 4). As evident from Table 4, these catalysts furnished either 1-benzyl-2-phenyl-1H-benzo [d] imidazole or 2-phenyl-1H-benzo [d]imidazole.

To rationalize the role of solvent on selectivity control, we move toward the mechanism of the Yb incorporated mesoporous silica catalyzed synthesis of 1,2-disubstituted benzimidazole and 2-substituted benzimidazole. Scheme 4 illustrates a plausible reaction pathway for this reaction. The Yb^{3+}, is assumed to accelerate the nucleophilic attack by *o*-phenylenediamine. Solvents with low polarity such as toluene facilitate the formation of monoimine (**5**), whereas in highly protic polar solvent such as ethanol/water mixture, bisimine (**6**) is formed. Cyclization of monoimine (**5**) followed by oxidative dehydrogenation by air leads to 2-substituted benzimidazole. The higher polarity and hydrogen bonding ability of ethanol/water mixture facilitate it to act as effective electrophilic co-activating agents for bisimine formation and stabilizes bisimine through formation of hydrogen bonding. 1,2-Disubstituted imidazoles formed by intramolecular nucleophilic attack in bisimine (**6**) followed by a 1,3-hydride shift.

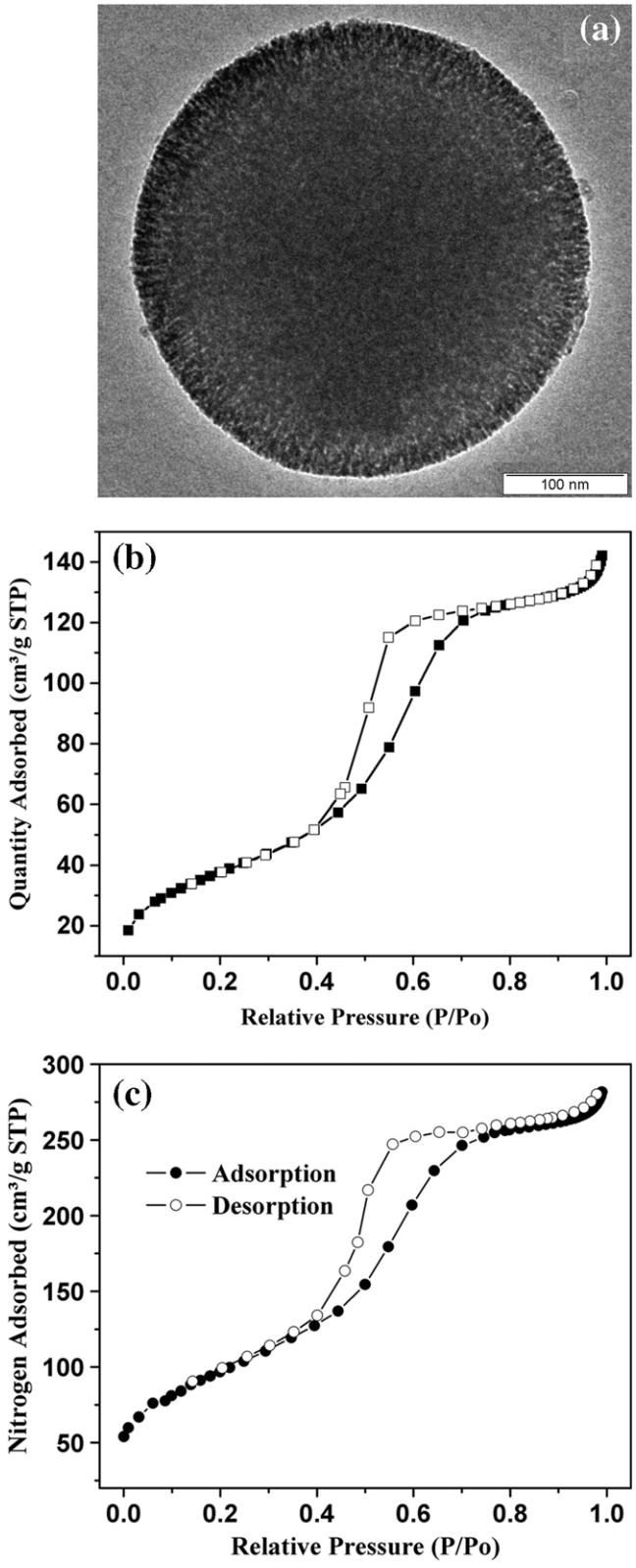
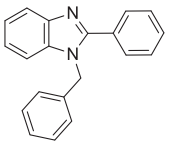
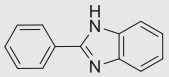
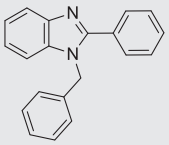
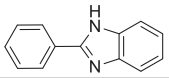


FIGURE 7 (a) TEM and (b) BET isotherms of the reused 0.75 m-Yb after five runs of the 1-(4- ethylbenzyl)2-(*p*-tolyl)-1H-benzo [d] imidazole synthesis (**3a**) and (c) BET isotherms of the five times reused 0.75 m-Yb after calcination

TABLE 4 Comparison of results for 0.75 m-Yb with heterogeneous catalysts for the synthesis of 1-benzyl-2-phenyl-1H-benzo [d] imidazole or 2-phenyl-1H-benzo [d]imidazole

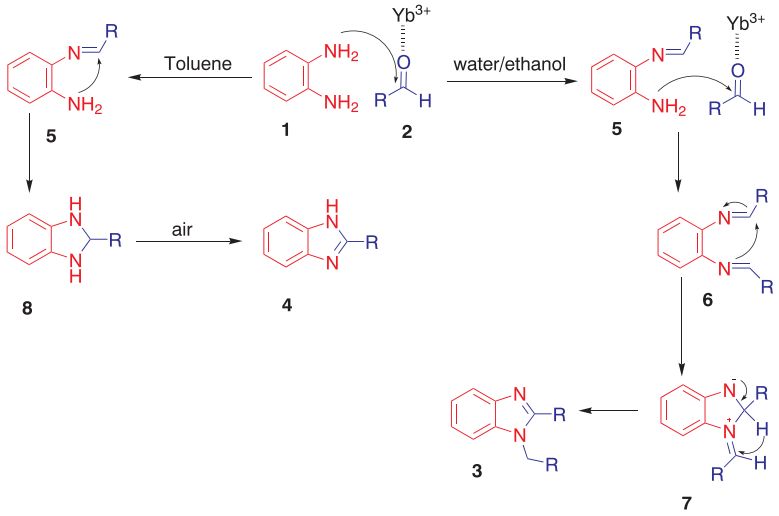
Entry	Catalyst	Solvent	Temperature (°C)	Time (min)	Product	Yield[a] (%)	Ref.
1	Nano indium oxide	EtOH/H_2O (2:1)	60	120		89	[11v]
2	N,N-Dimethylaniline/ graphite,	EtOH	75	240		69	[21a]
3	*p*-Toluensufonic acid/ graphite	Solvent free	75	40	Mixture (1:2.9)[b]	89[c]	[21a]
4	0.75 m-Yb	EtOH/H_2O (2:1)	RT[d]	60		80	This work
5	0.75 m-Yb	Toluene	RT	60		95	This work

[a]Isolated yield.

[b]Both 1-benzyl-2-phenyl-1H-benzo [d] imidazole (66%) and 2-phenyl-1H-benzo [d] imidazole (23%).

[c]Total yield.

[d]Room temperature.



SCHEME 4 Mechanism for formation of 1,2-disubstituted benzimidazole and 2-substituted benzimidazole

4 | CONCLUSIONS

A series of ytterbium loaded mesoporous silica nanoparticles (Xm-Yb) as catalysts for synthesis of substituted benzimidazoles have been synthesized through wet impregnation methods. It has been shown that catalysts prepared by this approach exhibit homogeneous distributions of ytterbium within the mesoporous catalyst support. Synthesized catalysts have been found to be efficient for the synthesis of substituted benzimidazoles by the condensation of diamine with aldehyde at room temperature. The condensation of diamine with aldehyde in the presence of ytterbium loaded catalyst was found to be solvent selective, generating 1,2-disubstituted benzimidazoles in water/ethanol medium (2:1) and 2-substituted benzimidazoles exclusively in toluene. Thus, the present study offers a simple procedure for the selective synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzimidazoles promoted by a reusable, non-toxic and environmentally benign mesoporous silica supported ytterbium catalyst (0.75 m-Yb). Moreover, the methodology reported here are highly

chemoselective, requiring short reaction time, can be performed at room temperature and exhibit a wide functional group tolerance. We believe the current protocol using 0.75 m-Yb will find widespread applications in academic laboratories and industry.

ACKNOWLEDGMENTS

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