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MCM-41-SO_3H-catalyzed synthesis of highly substituted 3-amino-imidazo[1,2-*a*]pyridines or pyrazines via the Groebke-Blackburn-Bienaymé multicomponent reaction under grinding conditions at ambient temperature

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KEYWORDS
Groebke-Blackburn-Bienaymé;
Multicomponent reactions;
Grinding;
Imidazo[1,2-*a*]pyridines;
Pyrazines.

Abstract. A highly efficient method, which is environmentally-friendly, has been developed by a sequential one-pot, three-component reaction between isocyanides, aldehydes, and 2-aminopyridines or 2-aminopyrazines under solvent-free and grinding conditions at room temperature in the presence of nano-ordered MCM-41-SO_3H.

1. Introduction

Nowadays, chemists are constantly challenged to develop green synthetic methodologies to meet the criteria of sustainable and environmentally-friendly development. Consequently, several newer strategies, such as multicomponent reactions under solvent-free conditions and solid-state organic reactions, have attracted much interest not only for the laboratory synthesis, but also in the chemical industry, because of reduced pollution, lower costs, mild conditions, and simple purification.

Many organic reactions occur more efficiently in the solid state than in solution due to a tighter and more regular arrangement of the substrate molecules. As the typical representative of mechanochemical solid-state reactions, the grinding technique is the simplest and has been widely used in organic synthesis and applied to reactions, such as Dieckmann condensation [1a], Knoevenagel condensation [1b], Aldol condensation [1c], Claisen-Schmidt reaction [1d], and imines formation [1e].

Imidazo[1,2-*a*]pyridines and the related imidazo [1,2-*a*] pyrazines have received significant attention from the pharmaceutical industry owing to their interesting biological applications [2a]. These compounds are known to display bioactivity over a broad range of therapeutic classes and have demonstrated anti-inflammatory [2b], antiprotozoal [2c], antiviral [2d], antiulcer [2e], antibacterial [2f], antifungal [2g], an-

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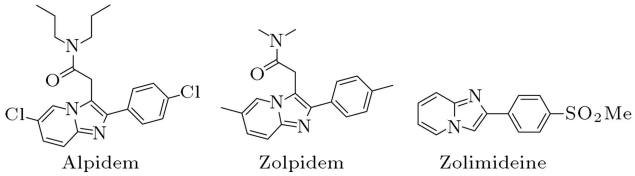


Figure 1. A few selected therapeutic agents containing the imidazo[1,2-*a*]pyridine core.

tiherpes [2h], and anti-proliferative2i properties, as well as being good candidates for the treatment of hepatitis C [2j], HIV [2k], and c-Met inhibitor [2l]. There are also several therapeutic agents currently available on the market containing the imidazo[1,2-*a*]pyridine core, including anxiolytic drug Alpidem, hypnotic drug Zolpidemand, and an anti-ulcer agent Zolimidine (Figure 1) [3].

There is a large number of potential synthetic routes for the synthesis of imidazo[1,2-*a*]pyridines. The most important approaches include:

(i) Condensation of 2-aminopyridine with α-halocarbonyl compounds [4], or pyridines with enamides **4f**;

(ii) Three-component reactions of 2-aminopyridines, aldehydes, and alkynes [5];

(iii) One-pot condensations of isocyanides, aldehydes, and 2-aminopyridines [6] termed as Groebke-Blackburn-Bienaymé multicomponent reaction (GBB MCR) [7].

Among all the methods which can be employed for the synthesis of the imidazo[1,2-*a*]pyridine core, only (i) and (iii) allow for diversity in the final products. Method (i) is a popular approach for synthesizing the imidazo[1,2-*a*]azine core, since a variety of substituted 2-aminopyridines and α-halocarbonyl compounds are commercially available or can be readily synthesized [4]. However, one of the biggest drawbacks of this method is the inability to form 3-amino-monosubstituted imidazo[1,2-*a*] pyridines by this ring closing procedure. Hence, the GBB MCR is the method of choice for the synthesis of 3-aminoimidazo [1,2-*a*] pyridine/pyrazine ring systems as it is the only method known to date to allow for significant diversity at the 3-position [7].

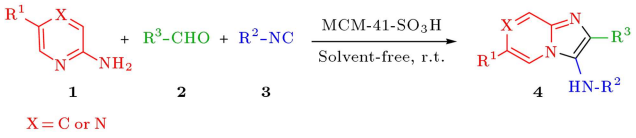
A variety of acid catalysts including acetic acid [7a], perchloric acid [7b], scandium (III) triflate [7c], ammonium chloride [7d], and also some basic ionic liquid [7e] have been used in the Groebke-Blackburn reaction. These catalysts all homogeneously catalyze the GBB reaction and show many limitations such as the use of expensive reagents and excess amount of catalyst [7,8a,8b], harmful organic solvents [6b,8c], long reaction times [7,8d], high temperatures [8e,8c], harsh reaction conditions [8f,8g], and sometimes only give poor yields [8h].

In order to simplify catalyst removal and minimize the amount of waste formed, the utilization of heterogeneous or solid acid catalysts as an alternative to this process is an emerging topic in the field of green-chemical processes. In fact, normally, the heterogenization procedure causes a decrease in stereoselectivity and activity in comparison with the homogeneous counterparts. To address this decline in the activity of heterogeneous catalysts over homogeneous ones, the use of high surface area materials, such as MCM, has been widely investigated [9]. Mesoporous silica, known as MCM-41, had been the most commonly used; however, it soon became apparent that the use of mesoporous silica and aluminosilicates as solid acids did not produce the desired results due to the low acid strength of their acid sites [10]. A better alternative would be to use the mesoporous silica with their mild acid sites in an aluminosilicate framework as supports to which strong acid sites could be covalently anchored. Among the various covalently anchored solid acids, MCM-41 was functionalized with sulfonic acid groups (MCM-41-SO_3H) functions more efficiently in organic synthesis [11].

The focus of the present work concerns the application of atom-economic, multicomponent reactions, and the use of nano-ordered, heterogeneous acid catalysts that can be run under green conditions. In connection with our ongoing work on the application of MCRs to the synthesis of biologically active compounds [12], we report a simple and efficient route for the synthesis of highly substituted 3-amino-imidazo[1,2-*a*]pyridines or pyrazines **4** *via* the GBB MCR of 2-aminoazines **1**, isocyanides **2**, and aldehydes **3** under solvent-free conditions at ambient temperature in the presence of nano-ordered MCM-41-SO_3H [13] (Scheme 1). To the best of our knowledge, no investigations or studies on MCM-41-SO_3H-catalyzed synthesis of imidazoazines have been reported to date.

2. Results and discussion

In the initial phase of this study, 2-aminopyridine (**1a**), 4-chlorobenzaldehyde (**2a**), and cyclohexylisocyanide (**3a**) (molar ratio: 1:1.2:1.1), as a model reaction (Scheme 2), were mixed and ground in a mortar at room temperature. As a result, only a trace amount of the desired product **4a** is detected, as monitored by Thin-Layer Chromatography (TLC) after 180 min (entry 1, Table 1).



Scheme 1. The Groebke-Blackburn-Bienaymé reaction catalyzed by MCM-41-SO_3H.

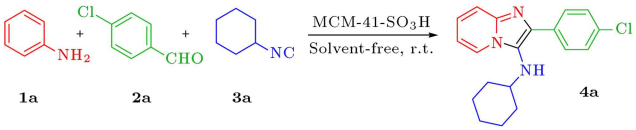
Table 1. Effect of catalyst and its loading on the synthesis of **4a** at room temperature under grinding conditions.

Entry	Catalyst	Amount of catalyst (mg)	Time (min)	Yield (%)[a]	TON[b]	TOF[c] (h^{-1})
1	———	—	180	trace	—	—
2	MCM-41-SO_3H	20	30	90	37.5	75
3	**MCM-41-SO_3H**	**15**	**30**	**90**	**50**	**100**
4	MCM-41-SO_3H	10	30	83	69.2	138
5	MCM-41-SO_3H	5	30	74	123	246
6	MCM-41	15	120	40	—	—
7	Zn-MCM-41	15	120	51	37.5	18.75
8	Fe-MCM-41	15	120	40	28.7	14.35
9	Al-MCM-41	15	60	60	44.7	44.7

[a]: Isolated yield;

[b]: Turnover number: moles of product per mole of catalyst;

[c]: Turnover frequency: moles of product per mole of catalyst per hour.



Scheme 2. The model reaction for the synthesis of imidazo[1,2-*a*]pyridines *via* the Groebke-Blackburn-Bienaymé reaction.

In order to improve the grinding process, 20 mg of MCM-41-SO_3H was added to the mortar. After the mixture was ground for 30 min at room temperature, the researchers were surprised to discover that the desired product **4a** was obtained at a 90% yield (entry 2, Table 1). Subsequently, the amount of required MCM-41-SO_3H was investigated to find the optimal catalyst loading. The results showed that 15 mg of catalyst was sufficient for an excellent yield (entry 5, Table 1).

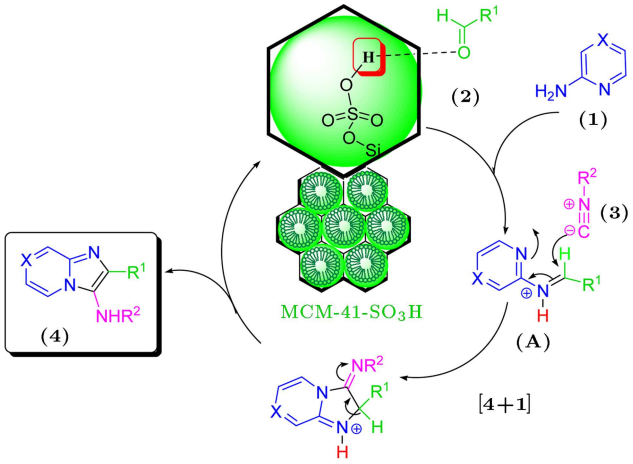
In order to further evaluate and establish the superior catalytic activity of MCM-41-SO_3H, the effects of other mesoporous compounds, such as MCM-41, Zn-MCM-41, Fe-MCM-41, and Al-MCM-41, were investigated in this model reaction. As shown in Table 1 (entries 6-9), when the mixture was reacted under solvent-free conditions in the presence of these mesoporous compounds, the yield was lower and longer reaction times were required, which show the superior catalytic activity of MCM-41-SO_3H in this transformation. This superior catalytic activity may be attributed to the higher acid strength of their acid sites. The surface acidity measurement of MCM-41-SO_3H was performed by an inverse acid-base titration of the catalyst which showed that the acid content was 0.02 mmol g^{-1} of catalyst (1.7 mg/g of catalyst).

This study also examined the effects of some organic solvents (EtOH or CH_2Cl_2) as well as water for the purpose of demonstrating the high efficiency of the grinding method. Initial screening studies

Table 2. Solvent effect on the synthesis of **4a** in the presence of 15 mg MCM-41-SO_3H at room temperature.

Entry	Solvent	Time (min)	Yield (%)[a]
1	EtOH 96%	180	76
2	CH_2Cl_2	480	45
3	H_2O	210	53
4	Solvent-free[b]	30	90

[a]: Isolated yield; [b]: Grinding conditions.



Scheme 3. The proposed mechanism for the synthesis of imodazoazines *via* the Groebke-Blackburn-Bienaymé reaction at room temperature in the presence of MCM-41-SO_3H as catalyst.

confirmed that solvent-free conditions were optimal for this reaction (Table 2). The results showed that the efficiency and the yield of the reaction under solvent-free conditions were higher than those obtained in the presence of solvents [14]. It is noteworthy that the use of non-polar solvent like dichloromethane in reaction requires longer time (entry 2). According to the proposed mechanism (Scheme 3), protic solvents

such as H_2O and EtOH could favor the formation of iminium ion **A**, but could not avoid the competitive side reaction of nucleophilic attack of 2-aminopyridine or 2-aminoazine, as well as that of the solvent itself to the imine intermediate.

Moreover, to expand the scope of the method with respect to reactants, different 2-aminopyridines **1a-c**, aldehydes **2a-k**, and isocyanides **3a,b** were used under the optimized conditions. The results are given in Table 3. It can be seen that a wide range of substrates were able to participate in the reaction. As it is shown, different aromatic aldehydes bearing both electron withdrawing (Table 3, entries 1-4) and electron releasing groups (Table 3, entries 8 and 13) afforded the corresponding imidazoazines in high to excellent yields. The aliphatic aldehyde, such as isobutyraldehyde (**2k**), has also proved to be efficient by producing the product **4p** in 55% yield (Table 3, entry 17).

The suggested reaction mechanism for this transformation catalyzed by MCM-41-SO_3H is outlined in Scheme 3. It could reasonably be expected that the protonated schiff base (**A**) is generated through condensation of aminoazines **1** with activated aldehyde **3** in the presence of nanocatalyst. The final product of 3-amino-imidazo[1,2-*a*]azine **4** is formed by a nonconcerted [4+1] cycloaddition reaction between protonated schiff base **A** and isocyanide **2** followed by imine-enamine tautomerisation.

The reusability of the catalyst was also investigated in further runs of the model reaction, and the results showed that the catalyst was active for at least four reaction cycles without considerable loss of activity (Figure 2).

The morphology of MCM-41-SO_3H was specified by Scanning Electron Microscopy (SEM) (Figure 3). The powder X-Ray Diffraction (XRD) measurement of MCM-41-SO_3H was also carried out (Figure 4). The EDX and FTIR spectrum of MCM-41-SO_3H was also provided in supplementary data. EDX analysis revealed the presence of acid groups in the framework of the materials.

To demonstrate that our method outperforms those of some other published works, a comparison has been drawn with some recently published methods in Table 4.

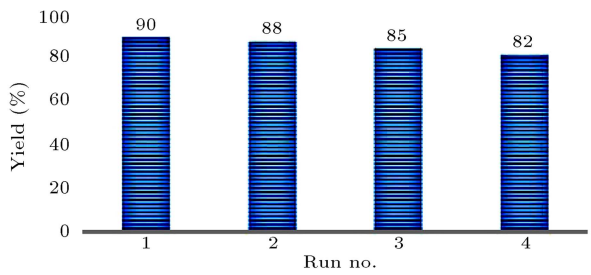


Figure 2. Reusability of the catalyst in the model reaction.

3. Experimental

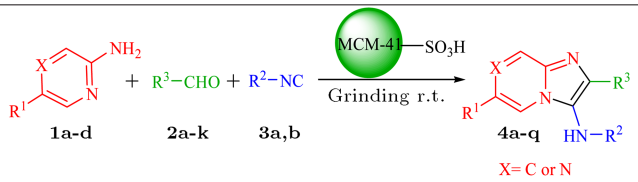
3.1. General procedure for preparation of MCM-41

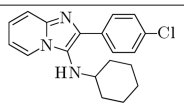
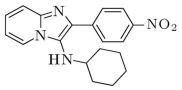
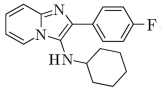
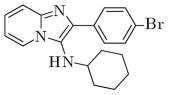
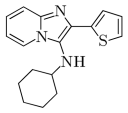
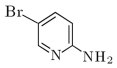
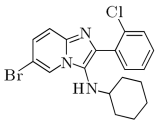
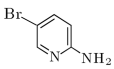
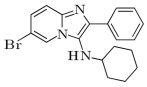
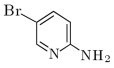
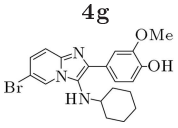
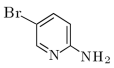
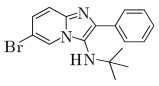
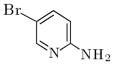
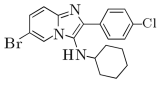
7.2 g diethylamine was added to 42 mL deionized water and stirred for 10 minutes. Then, 1.47 g cetyltributylammonium bromide (CTAB) was added to the solution and stirred for 30 minutes until the surfactant was completely dissolved, and a clear solution was obtained. 2.1 g Tetraethyl orthosilicate as the silica source was added drop-wise to the solution, and the pH was fixed at 8.5 by addition of 1M HCl solution and stirred for 2 hours under mild conditions. The white precipitate was filtered and washed several times with deionized water and dried at 45°C for 12 hours [13a]. The organic template in the as-synthesized MCM-41 was removed and recovered through extraction by refluxing the solid (1.5 g) in 1 M hydrobromic acid ethanolic solution (500 mL) at 75°C for 24 h. The template-free MCM-41 was filtered, washed with ethanol, and dried for 10 h at 100°C in vacuum [13b].

3.2. General procedure for the preparation of MCM-41-SO_3H

Grafted hydrogen sulfate groups (MCM-41-SO_3H) were synthesized according to the reported method [15]. MCM-41 (1 g) was suspended in CH_2Cl_2 (5 mL) in a 100 mL round bottom flask equipped with a gas outlet tube and a dropping funnel containing a solution of chlorosulfonic acid (2 mL) in dichloromethane (15 mL). The chlorosulfonic acid solution was added drop-wise to obtain suspension over a period of 30 minutes at room temperature. The HCl gas evolved from the reaction mixture was conducted via the gas outlet tube into a NaOH solution. After the completion of the reaction, the solvent was evaporated under reduced pressure and the MCM-41-SO_3H was collected as a white solid. Morphology was specified by Scanning Electron Microscopy (SEM) (Figure 3). SEM micrographs were obtained using Philips model XL-30 microscope. The powder X-Ray Diffraction (XRD) measurement was carried out on Philips Xpert instrument with Cu Kα radiation (λ = 0.15406 nm) at 40 kV and 40 mA (Figure 4). The surface acidity of MCM-41-SO_3H was determined by a reported titration method [16]. The concentration of acid sites of catalyst was determined by titration: 0.5 g of the catalyst sample was added to 50 mL of NaCl solution (200 g/L) and stirred at room temperature. The ion exchange between H^+ and Na^+ was allowed to proceed for 24 h. The catalyst was filtered off and washed with distilled water, then the mixture was titrated with 0.01 N NaOH solution using phenolphthalein as pH indicator. The turnover numbers are expressed as the molar ratio of converted substrate to the milliequivalent of the sulfonic acid group.

Table 3. Synthesis of imodazoazines **4a-q** in the presence of MCM-41-SO_3H under solvent-free conditions at room temperature.



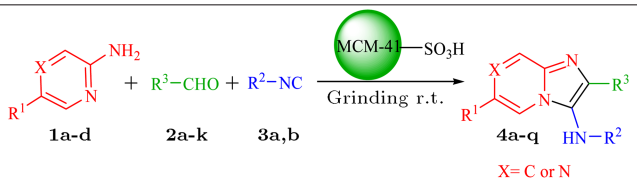
Entry	Amino.[a]	Iso.[b]	Ar	Product	Time (min)	Yeild[c] (%)	Mp (°C)	Mp (°C)[lit]	TON[d]	TOF[e](h^{-1})
1			4-Cl-C_6H_5		30	90	197-199	198-199 [14a]	50	100
	1a	**3a**	**2a**	**4a**						
2			4-NO_2-C_6H_5		30	85	203-205	203-205 [8c]	47.2	94.5
	1a	**3a**	**2b**	**4b**						
3			4-F-C_6H_5		30	93	170-173	167-169 [8c]	51.7	103.3
	1a	**3a**	**2c**	**4c**						
4			4-Br-C_6H_5		45	90	166-168	166-168 [8c]	50	66.7
	1a	**3a**	**2d**	**4d**						
5			Thiophen-2 -carbaldehyde		60	89	176-178	165-166 [14b]	49.4	49.4
	1a	**3a**	**2e**	**4e**						
6			2-Cl-C_6H_5		20	82	149-152	144-146 [8c]	45.5	138.1
	1b	**3a**	**2f**	**4f**						
7			C_6H_5		30	93	207-208	207-208 [14c]	51.7	103.3
	1b	**3a**	**2g**	**4g**						
8			Vanilinyl		45	90	234-236	Present work	50	66.7
	1b	**3a**	**2h**	**4h**						
9			C_6H_5		30	86	202-204	206-208 [14d]	47.8	95.5
	1b	**3b**	**2g**	**4i**						
10			4-Cl-C_6H_5		60	80	209-211	213-214 [14e]	44.4	44.4
	1b	**3a**	**2a**	**4j**						

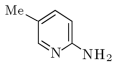
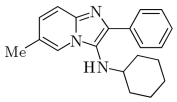
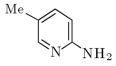
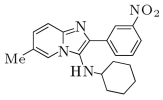
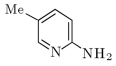
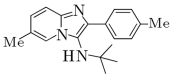
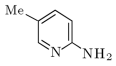
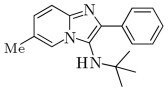
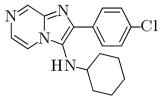
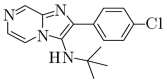
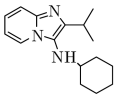
[a]Amino.: Aminopyridine; [b]Iso.: Isocyanide; [c]: Isolated yield;

[d]: Turnover number: molar ratio of converted substrate to the milliequivalent of the sulfonic acid group;

[e]: Turnover frequency: molar ratio of converted substrate to the milliequivalent of the sulfonic acid group per hour.

Table 3. Synthesis of imodazoazines **4a-q** in the presence of MCM-41-SO_3H under solvent-free conditions at room temperature (continued).



Entry	Amino.[a]	Iso.[b]	Ar	Product	Time (min)	Yeild[c] (%)	Mp (°C)	Mp (°C)[lit]	TON[d]	TOF[e](h^{-1})
11			C_6H_5		30	90	197-201	203-206 [14d]	50	100
	1c	**3a**	**2g**	**4k**						
12			3-NO_2-C_6H_5		45	87	208-210	208-210 [14c]	48.33	64.4
1c	**3a**	**2i**	**4l**							
13			4-Me-C_6H_5		30	89	210-212	210-212 [14f]	49.4	98.9
	1c	**3a**	**2j**	**4m**						
14			C_6H_5		30	80	217-219	217-220 [14d]	44.4	88.8
	1c	**3b**	**2g**	**4n**						
15			4-Cl-C_6H_5		45	85	136-138	130-133 [14g]	47.2	63
	1d	**3a**	**2a**	**4o**						
16			4-Cl-C_6H_5		45	85	151-153	150-152 [14g]	47.2	63
	1d	**3b**	**2a**	**4p**						
17					60	55	117-118	116-118 [8c]	30.5	30.5
	1a	**3a**	**2k**	**4q**						

[a]Amino.: Aminopyridine; [b]Iso.: Isocyanide; [c]: Isolated yield;

[d]: Turnover number: molar ratio of converted substrate to the milliequivalent of the sulfonic acid group;

[e]: Turnover frequency: molar ratio of converted substrate to the milliequivalent of the sulfonic acid group per hour.

Table 4. Comparison between the proposed method and some published methods.

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yields	Ref.
1	—	—	160	1.5-3	80-97	[60]
2	NH_4Cl (1 mmol)	—	150	2	58-83	[61]
3	—	H_2O	70	7	85-97	[51]
4	I_2 (1 mol %)	MeOH	r.t.	12	82-85	[62]
5	Cellulose sulfuric acid	MeOH	r.t.	2	87-98	[63]
6	Silica sulfuric acid	MeOH	r.t.	3	77-99	[54]
7	**MCM-41-SO_3H**	—	**r.t.**	**0.33-1**	**80-93**	**This work**

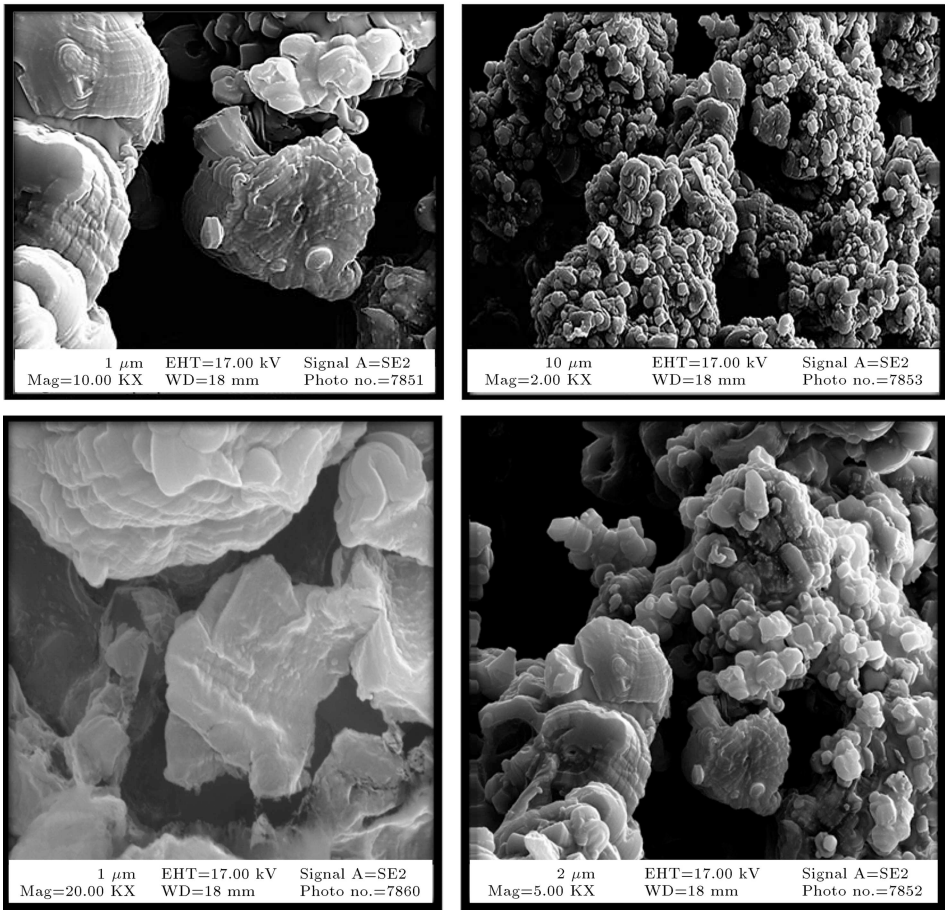


Figure 3. SEM micrographs of MCM-41-SO_3H sample.

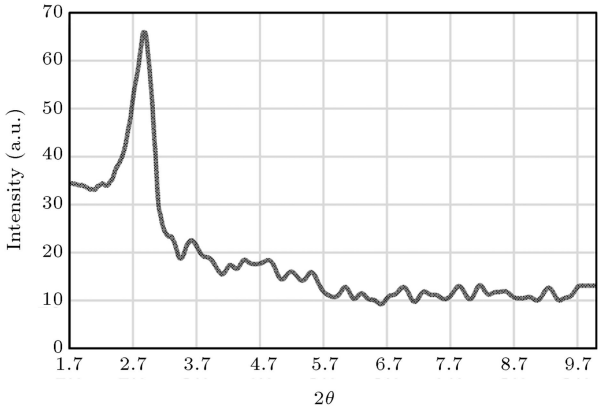


Figure 4. The XRD pattern of MCM-41-SO_3H.

3.3. General procedure for the synthesis of imodazoazines (4a-q)

2-aminoazines **1** (1 mmol), aldehyde **2** (1.2 mmol), and isocyanide **3** (1.1 mmol) were mixed (as a mixture) and ground in a mortar in the presence of MCM-41-SO_3H (15 mg) at room temperature. After completion of the reaction (indicated by TLC), the product was purified by recrystallization from hot ethanol. All the compounds are known while the characterization data of new compounds (**4h**) are given below.

6-Bromo-3-(cyclohexylamino)-2,3-difydroimidazo[1,2-*a*]pyridin -2-yl)-2-methoxyphenol (4h):

Cream powder (90%); mp: 234-236°C; IR (KBr): 3300 cm^{-1}(OH), 3296 cm^{-1} (NH), 3080, 2923, 2852, 1652 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 1.01-1.65 (10H, m, $5CH_2$ of cyclohexyl), 2.82 (1H, m, CH of cyclohexyl), 3.79 (3H, s, OMe), 4.73 (1H, bs, NH), 6.78-7.6 (4H, m, H-Ar), 7.7 (1H, s, H-Ar), 8.4 (1H, s, H-Ar), 9.02 (1H, s, OH). ^{13}C NMR (125 MHz, DMSO-d_6): 24.6, 25.4, 33.5, 55.5, 56.4, 105.3, 110.4, 115.4, 117.6, 119.5, 122.9, 125.1, 125.6, 126.0, 135.8, 138.6, 146.0, 147.4. MS, m/z (%): 417 (MH^+, ^{81}Br, 22), 415 (MH^+, ^{79}Br, 24), 332 (40), 305 (50), 156 (35), 55 (70); Anal. Calcd for $C_{20}H_{22}BrN_3O_2$ (416.31): C, 57.70; H, 5.33; N, 10.09; Found: C, 58.01; H, 5.61; N, 9.86%.

4. Conclusion

In summary, MCM-41-SO_3H was found to be a highly efficient nano catalyst for the one-pot three-component synthesis of 3-amino-imidazo[1,2-*a*]pyridines or pyrazines via the condensation of

isocyanides, 2-aminopyridines, and aldehydes under solvent-free conditions at room temperature on grinding. This method offers several advantages, such as omitting toxic solvents or catalyst, high yields, short reaction time, no waste production, very simple work-up, and needs no chromatographic method for purification of the products.

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Supplementary data

Supplementary data associated with this article can be found in in the online version at: https://drive.google.com/file/d/0B9842hDGewJHOV95Xzlmd1AydXc/view?usp= sharing

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