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Efficient multicomponent synthesis of 2-aminopyridines catalysed by basic mesoporous materials

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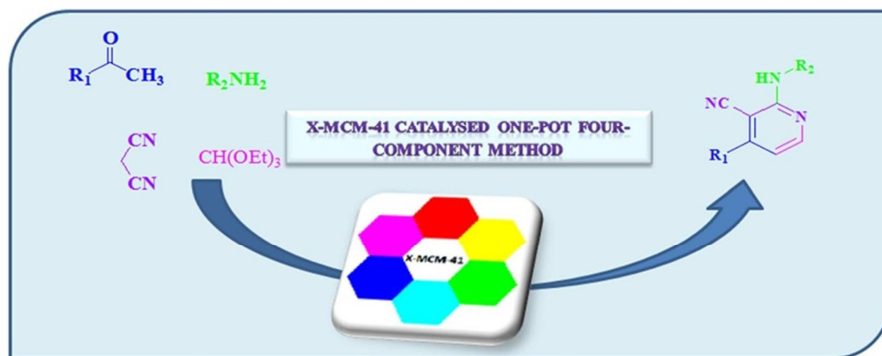
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Abstract

An efficient and green procedure for the synthesis of 2-aminopyridines derivatives via four-component reaction of acetophenone, malononitrile, triethoxymethane and different primary amines has been developed using different surfactant-containing mesoporous catalysts. The advantages of this approach are easy operational method, high product yields and reusable catalysts without losing their catalytic activity.

Graphical abstract



Keywords Multicomponent reactions of 2-aminopyridines synthesis · Solvent-free · Mesoporous materials · MCM-41 · Catalyst reuse

Introduction

Multicomponent reactions (MCRs) have received considerable attention and are known as some of the most important reactions in organic and medicinal chemistry [1–11]. One-pot multicomponent reactions are the useful path for the facile synthesis of heterocycles with a biological value [12–15]. In recent years, the challenge in organic synthesis has been the development of new MCRs using catalytic systems as well as MCM-41, clean, environmentally benign, efficient basic recyclable catalysts for the synthesis of heterocyclic compounds [16–18]. The structures of 2-aminopyridines and its derivatives are a class of nitrogen heterocyclic compounds that have drawn much attention, due to their biological and pharmaceutical activities [19–24]. The development of clean synthetic routes towards nitrogen-containing heterocycles is of great importance to both synthetic and medicinal chemists [25–27]. So, it is important to find simple and convenient procedures for the synthesis of 2-aminopyridines with different substitutes in their moiety, with the aim of obtaining some novel heterocyclic compounds with potentially enhanced properties.

In the continuation of our research program on the development of green methodologies in the synthesis of biologically important compounds using readily available, inexpensive and environmentally friendly catalysts [28–34], we wish to report in this work a new multicomponent reaction of 2-aminopyridines using mesoporous catalysts.

In the last decades, a particular interest was set on the use of the mesoporous silica in catalysis and adsorption [35–46], due to their higher specific surface areas and pore size compared to the zeolites. These catalysts may be easily recovered at the end of a reaction and can be reused in several cycles. Among these materials, the mesoporous silica MCM-41 has known very wide applications due to its bi-dimensional structure and its ordered pores [47, 48]. The mesoporous silica MCM-41 has been applied in several catalytic reactions as acid/base and/or redox catalysts. However, due to the surface of the mesoporous silica MCM-41 containing only the silanol groups, several efforts have been made in order to activate its surface and make it useful in basic catalysis.

Among the most used methods for modifying the surface of the mesoporous silica, there is the dispersion of the metal oxides, the dispersion of the polymers having a basic character and the functionalization by amine groups. However, some of these methods can affect the structural and textural properties of the modified material. A particular interest has been devoted to the use of mesoporous silica containing its own surfactant without any modification, the non-calcined mesoporous silica with a strong basicity from the siloxy group bonded with CTA⁺ [47]. These attractive catalysts have also been tested in different reactions which require basic catalysts such as Knoevenagel and Claisen–Schmidt condensations [48], Michael additions–cycloaddition reactions of CO₂ with epoxides [48], cycloaddition of 4-nitrophenyl azide [34] and condensation of acetophenone with ethyl cyanoacetate [48]. Herein, we report a facile and rapid one-pot four-component route to the synthesis of 3-cyano-2-aminopyridines in the presence or absence of Al, Ga or Si-MCM-41 as-synthesized catalysts under free solvent conditions. The comparative studies have been performed between homogeneous and heterogeneous catalysis for the synthesis of 2-aminopyridines derivatives.

Experimental

Materials and physical measurements

All products were prepared in our laboratory and analysed by spectroscopic methods. The melting points were measured using a Bank Kofler Heizbank apparatus standard WME 50–260 °C without particular correction. IR spectra were performed on solid samples using a Fourier transform PerkinElmer Spectrum with ATR accessory. Only significant absorptions are listed. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 400 spectrometers at 400 and 100 MHz, respectively. Samples were recorded in CDCl_3 solutions using TMS as an internal standard. The chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS. The multiplicities are reported as: *s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet (Scheme 1).

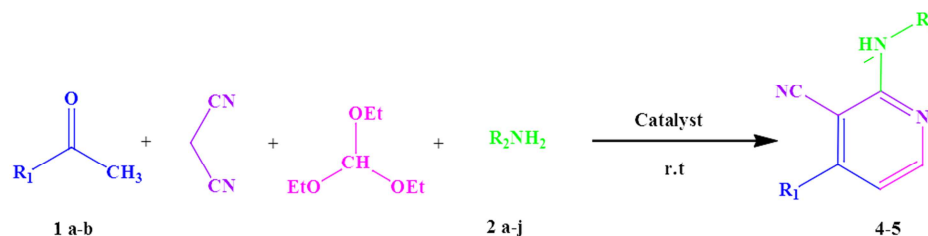
Synthesis

General synthesis of 2-aminopyridines without catalyst

A mixture of acetophenone (10 mmol), 10 mmol of malononitrile, 10 mmol of triethoxymethane and primary amine (10 mmol) was heated for 3 h at 100 °C. After the completion of the reaction, the residue was purified by column chromatography over silica gel using a mixture of *n*hexane–EtOAc (8:1) as the eluent to give desired compounds.

General synthesis of 2-aminopyridines with catalyst

A mixture of equimolar amount of the four compounds: acetophenone; malononitrile, triethoxyethane and benzylamine with 0.001 mol of (X-MCM-41), was stirred at room temperature without solvent. After the completion of the reaction, the catalyst was separated by filtration.



1a: R= Ph

1b: R= 4- CH_3 -Ph

Scheme.1. Four-component reaction of 2-aminopyridines derivatives

X-MCM-41: Si-MCM-41, Al-MCM-41, Ga-MCM-41

2-(Benzylamino)-4-phenylnicotinonitrile 4_a White solid, mp 95 °C; IR ν_{\max} (neat/ cm^{-1}): 1575 (C=C); 1531 (C=C); 2215 (CN); 3361 (NH); NMR ^1H (CDCl_3) δ_{H} ppm : 4.6 (2H, *d*, $J_{\text{H-H}}=5.2$ Hz, NH-CH₂); 5.60 (1H, *t*, $J_{\text{H-H}}=4.6$ Hz, NH-CH₂); 6.69 (1H, *d*, $J_{\text{H-H}}=4.6$ Hz, CH=CH); 7.28–7.30 (5H, *m*, H_{arom}); 7.46–7.58 (5H, *m*, H_{arom}); 8.30 (1H, *d*, $J_{\text{H-H}}=4.6$ Hz, CH=CH); RMN ^{13}C (CDCl_3) δ_{C} : 45.6; 90.1; 113.1; 116.9; 128.7–129.8; 136.7; 152; 154.50; 159.2; EIMS *m/z* (% relative abundance): 286 (M^+H , 100), 208 (23), 91 (93); HRMS (ESI-QTOF): Calcd for: C₁₉H₁₆N₃ M + H 286,1339; Found: 286,1345.

2-(Cyclohexylamino)-4-phenylnicotinonitrile 4_b Yellow solid, mp 189 °C; IR ν_{\max} (neat/ cm^{-1}): 1572 (C=C); 1533 (C=C); 2217 (CN); 3362 (NH); RMN ^1H (CDCl_3) δ_{H} : 1.49–1.75 (*m*, 2H, -(CH₂)₄-); 1.75 (1H, *q*, CH-NH); 5.22 (1H, *s*, NH); 6.33 (1H, *d*, $J_{\text{H-H}}=5.8$ Hz, CH=CH-N); 7.325–7.56 (5H, *m*, H_{arom}); 8.26 (1H, *d*, $J_{\text{H-H}}=5.7$ Hz, CH=CH-N); RMN ^{13}C (CDCl_3) δ_{C} : 11.1; 23.6; 46.5; 88.3; 105.1; 117.0; 127.3–129.3; 152.3; 155.3; 156.2; EIMS *m/z* (% relative abundance): 277 (M^+H , 100), (19), HRMS (ESI-QTOF): Calcd for: C₁₈H₂₀N₃ M + H 277,1324; Found: 277,1122.

2-(Hexylamino)-4-phenylnicotinonitrile 4_c Yellow solid, mp 120 °C; IR ν_{\max} (neat/ cm^{-1}): 1571 (C=C); 1532 (C=C); 2215 (CN); 3360 (NH); RMN ^1H (CDCl_3) δ_{H} : 0.98 (3H, *t*, $J_{\text{H-H}}=7.2$ Hz, -(CH₂)₅-CH₃); 1.29 (2H, *m*, -N-CH₂-CH₂-CH₂-CH₃); 1.30 (2H, *m*, N-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃); 1.33 (2H, *t*, $J_{\text{H-H}}=4.20$ Hz N-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃), 1.52 (2H, *t*, $J_{\text{H-H}}=4.20$ Hz N-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃), 3.53 (2H, *t*, $J_{\text{H-H}}=4.20$ Hz, *m*, N-CH₂-CH₂-CH₂-CH₂-CH₃); 5.36 (1H, *t*, $J_{\text{H-H}}=4.20$ Hz, NH); 6.63 (1H, *d*, $J_{\text{H-H}}=5.8$ Hz, CH=CH-N); 7.35–7.56 (5H, *m*, H_{arom}); 8.31 (1H, *d*, $J_{\text{H-H}}=5.7$ Hz, CH=CH-N); RMN ^{13}C (CDCl_3) δ_{C} : 14.1; 22.6; 26.5; 32.6; 44.5; 88.3; 105.1; 113.4; 117; 126.2–127.5; 136.4; 152.3 155.3; 155.3; EIMS *m/z* (% relative abundance): 280 (M^+H , 100), 200 (19), HRMS (ESI-QTOF): Calcd for: C₁₈H₂₂N₃ M + H 279,1422; Found: 279,1345.

2-(Propylamino)-4-phenylnicotinonitrile 4_d Yellow solid, mp 111 °C; IR ν_{\max} (neat/ cm^{-1}): 1583 (C=C), 1554 (C=C); 2219 (CN); 3383 (NH); RMN ^1H (CDCl_3) δ_{H} : 1.01 (3H, *t*, $J_{\text{H-H}}=7.4$ Hz, -(CH₂)₂-CH₃); 1.56 (2H, *m*, -N-CH₂-CH₂-CH₃); 3.11 (2H, *m*, -N-CH₂-CH₂-CH₃); 5.22 (1H, *t*, $J_{\text{H-H}}=4.20$ Hz, NH); 6.64 (1H, *d*, $J_{\text{H-H}}=5.8$ Hz, CH=CH-N); 7.325–7.56 (5H, *m*, H_{arom}); 8.26 (1H, *d*, $J_{\text{H-H}}=5.7$ Hz, CH=CH-N); RMN ^{13}C (CDCl_3) δ_{C} : 11.1; 23.6; 46.5; 88.3; 105.1; 117; 127.3–129.3; 152.3; 155.3; 156.2; EIMS *m/z* (% relative abundance): 237 (M^+H , 100), (20), HRMS (ESI-QTOF): Calcd for: C₁₅H₁₆N₃ M + H 237,1422; Found: 237,1235.

2-(Butylamino)-4-phenylnicotinonitrile 4_e White solid, mp 159 °C; IR ν_{\max} cm^{-1} : 1583 (C=C), 1554 (C=C); 2219 (CN); 3383 (NH); RMN ^1H (CDCl_3) δ_{H} : 0.91 (3H, *t*, $J_{\text{H-H}}=7.2$ Hz, -(CH₂)₃-CH₃); 1.32 (2H, *m*, -N-CH₂-CH₂-CH₂-CH₃); 1.33 (2H, *m*, N-CH₂-CH₂-CH₂-CH₃); 2.64 (2H, *t*, $J_{\text{H-H}}=4.20$ Hz N-CH₂-CH₂-CH₂-CH₃); 5.36 (1H, *t*, $J_{\text{H-H}}=4.20$ Hz, NH); 6.63 (1H, *d*, $J_{\text{H-H}}=5.8$ Hz, CH=CH-N); 7.35–7.56 (5H, *m*, H_{arom}); 8.31 (1H, *d*, $J_{\text{H-H}}=5.8$ Hz, CH=CH-N); RMN ^{13}C (CDCl_3) δ_{C} : 13.71 (CH₃); 21.3; 32; 41.5; 88.3; 113.42; 117.01; 126.25–129.86; 136.88; 152.08; 155.34; 160.12. EIMS *m/z* (% relative abundance): 251 (M + H, 100), (19), HRMS (ESI-QTOF): Calcd for: C₁₆H₁₈N₃ M + H 251,1348; Found: 251,1356.

2-(Benzylamino)-4-p-tolylnicotinonitrile 5_a White solid, mp 189 °C; IR ν_{\max} (neat/ cm^{-1}): 1578, 1533 (C=C); 2217 (CN); 3363 (NH); RMN ^1H (CDCl_3) δ_{H} : 2.41 (3H, *s*, Ph-

CH₃); 4.68 (2H, d, J_{H-H} = 4.6 Hz, NH-CH₂); 5.66 (1H, t, J_{H-H} = 4.6 Hz, NH-CH₂); 6.70 (1H, d, J_{H-H} = 4.6 Hz, CH=CH); 7.25–7.30 (5H, m, H_{arom}); 7.46–7.58 (4H, m, H_{arom}); 8.35 (1H, d, J_{H-H} = 4.6 Hz, CH=CH); RMN ¹³C (CDCl₃) δ_C: 24.5 (Ph-CH₃), 45.6 (CH₂); 91.1 (C=C-CN); 113.4 (CH=CH); 116.8 (CN); 127.3–127.9 (5x C_{arom}); 128.1–129.5 (5x C_{arom}); 136 (C_{arom}); 139.2 (C_{arom}); 153.1 (CH=CH); 154.6 (C=C-CN); 160.1 (N=C-NH); EIMS m/z (% relative abundance): 300 (M⁺H, 80), 150 (25), HRMS (ESI-QTOF): Calcd for: C₂₀H₁₉N₃ M⁺H 300,1244; Found: 300,1345.

2-(Cyclohexylamino)-4-p-tolynicotinonitrile 5_b Yellow solid, mp 189 °C; IR ν_{max} (neat/cm⁻¹): 1575,1533 (C=C); 2221 (CN); 3365 (NH); RMN ¹H (CDCl₃) δ_H: 1.48–1.76 (m, 2H, -(CH₂)₄-); 1.75 (1H, q, CH-NH); 2.35 (3H, s, -CH₃); 5.22 (1H, s, NH); 6.32 (1H, d, J_{H-H} = 5.8 Hz, CH=CH-N); 7.325–7.56 (5H, m, H_{arom}); 8.26 (1H, d, J_{H-H} = 5.7 Hz, CH=CH-N); RMN ¹³C (CDCl₃) δ_C: 11.1; 23.6;24.4; 46.5; 88.3; 105.1; 117; 127.3–129.3;152.4; 155.3; 156.2; EIMS m/z (% relative abundance): 291 (M⁺H, 100), (19), HRMS (ESI-QTOF): Calcd for: C₁₉H₂₂N₃ M + H 291,1224; Found: 291,1155.

2-(Hexylamino)-4-p-tolynicotinonitrile 5_c Yellow solid, mp 220 °C; IR ν_{max}(neat/cm⁻¹):1572,1532 (C=C); 2219(CN); 3363 (NH); RMN ¹H (CDCl₃) δ_H: 0.99 (3H, t, J_{H-H} = 7.2 Hz, -(CH₂)₅-CH₃); 1.27 (2H, m, -N-CH₂-CH₂-CH₂-CH₃); 1.30 (2H, m, N-CH₂-CH₂-CH₂-CH₂-CH₃); 1.32 (2H, t, J_{H-H} = 4.20 Hz N-CH₂-CH₂-CH₂-CH₂-CH₃), 1.52 (2H, t, J_{H-H} = 4.20 Hz N-CH₂-CH₂-CH₂-CH₂-CH₃), 2.35 ((3H, s, -CH₃); 3.42 (2H, t, J_{H-H} = 4.20 Hz, m, N-CH₂-CH₂-CH₂-CH₂-CH₃); 5.29 (1H, t, J_{H-H} = 4.20 Hz, NH); 6.63 (1H, d, J_{H-H} = 5.8 Hz, CH=CH-N); 7.33–7.52 (5H, m, H_{arom}); 8.28 (1H, d, J_{H-H} = 5.7 Hz, CH=CH-N); RMN ¹³C (CDCl₃) δ_C: 14.1; 22.61; 24.3; 26.5; 32.6; 43.4; 88.2; 105.1;113.3;117; 127.5–136.4;152.3; 155.3; 155.6; EIMS m/z (% relative abundance): 293 (M⁺H, 100), 200 (19), HRMS (ESI-QTOF): Calcd for: C₁₉H₂₄N₃ M + H 293,1322; Found: 293,1115.

2-(Propylamino)-4-p-tolynicotinonitrile 5_d Yellow solid, mp 181 °C; IR ν_{max} (neat/cm⁻¹): 1570,1531 (C=C); 2217 (CN); 3365 (NH); NMR ¹H (CDCl₃) δ_H ppm 1.49–1.75 (m, 2H, -(CH₂)₄-); 1.75 (1H, q, CH-NH); 2.35 (3H, s, -CH₃); 5.31(1H, s, NH); 6.29 (1H, d, J_{H-H} = 5.8 Hz, CH=CH-N); 7.25–7.49 (5H, m, H_{arom}); 8.23 (1H, d, J_{H-H} = 5.7 Hz, CH=CH-N); RMN ¹³C (CDCl₃) δ_C: 10.1; 23.3; 24.3; 45.4; 88.4; 105.1; 117; 127.3-129.3;151.3; 155.3; 156.5; EIMS m/z (% relative abundance): 251 (M⁺H, 100), (19), HRMS (ESI-QTOF): Calcd for: C₁₆H₁₈N₃ M + H 251,1324; Found: 251,1223.

2-(Butylamino)-4-p-tolynicotinonitrile 5e White solid, mp 147 °C; IR ν_{\max} cm^{-1} : 1582 (C=C), 1553 (C=C); 2222 (CN); 3381 (NH); RMN ^1H (CDCl_3) δ_{H} : 0,91 (3H, t, $J_{\text{H-H}}=7.2$ Hz, $-(\text{CH}_2)_3-\text{CH}_3$); 1.33 (2H, m, $-\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$); 1.34 (2H, m, $\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$); 2.40 (3H, s, $\text{Ph}-\text{CH}_3$); 2.66 (2H, t, $J_{\text{H-H}}=4.8$ Hz, $\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$); 5.34 (1H, t, $J_{\text{H-H}}=4.8$ Hz, NH); 6.61 (1H, d, $J_{\text{H-H}}=5.9$ Hz, $\text{CH}=\text{CH}-\text{N}$); 7.36–7.58 (5H, m, H_{arom}); 8.27 (1H, d, $J_{\text{H-H}}=5.9$ Hz, $\text{CH}=\text{CH}-\text{N}$); RMN ^{13}C (CDCl_3) δ_{C} : 13.5; 21.33; 24.51; 33.5; 42.4; 87.9; 113.6; 117.51; 126.3–130.1; 137.9 (C_{arom}); 153.1 ($\text{CH}=\text{CH}-\text{N}$); 155.3 (C=C–CN); 159.5; EIMS m/z (% relative abundance): 251 (M^+H , 100), (19), HRMS (ESI-QTOF): Calcd for: $\text{C}_{17}\text{H}_{20}\text{N}_3$ $\text{M}+\text{H}$ 265,1667; Found: 251,1670.

Results and discussion

So we wish to report an efficient one-pot four-component method for the preparation of 2-aminopyridines. Moreover, to the best of our knowledge, this paper is the first report on the synthesis of some 2-aminopyridines using as-synthesized mesoporous catalyst.

Initially, we have synthesized Al, Ga or Al-MCM-41 mesoporous materials containing CTA^+ by a direct method of crystallization according to the literature [37]. The detailed experimental procedures for the preparation of different as-synthesized mesoporous materials are well detailed and characterized in our previously published work [39].

Among the various methods developed for that purpose, multicomponent reactions involving domino processes answer perfectly to the green chemistry principles. In this context, and in connection with our recent investigation on the synthesis of nitrogen heterocycles under solvent-free conditions, firstly, we describe one-pot four-component approach to synthesis 2-aminopyridines efficiently without catalyst. This approach is a process in which four easily accessible components are combined together in a single reaction 1 to produce a final product 4–5 (Table 1).

Table 1

However, using acetophenone with benzylamine gives good yields. After 3 h of heating at 100 °C all, the products 4–5 were purified by column chromatography and isolated in yields ranging from 66 to

76% (Table 1). From this result, and in continuation of our interest in using solid catalysts in the synthesis of heterocycles, we describe here a simple and green strategy based on the new MCRs using MCM-41 as a powerful, recyclable and safe catalyst for the preparation of novel and known 3-cyano-2-aminopyridines **4–5** derivatives. Initially, a model reaction was conducted using acetophenone (0.1 mol), malononitrile (0.1 mol), triethoxymethane (0.1 mol) and benzylamine (0.1 mol) at room temperature in the presence of 0.001 mol (X-MCM-41) as catalyst under solvent-free conditions (Table 2); the product **4a** is confirmed by their NMR, IR and MS analysis.

Table 2

The reaction proceeded best at ambient temperature without heating in the presence of Si-MCM-41 to provide good yield 89% in a short time (15 min), and the results are summarized in Table 2, by against studying this reaction without heterogeneous catalyst leads to a product mixture.

Table 1 Four-component reaction of 2-aminopyridines derivatives without catalyst

To develop the scope of this reaction, and in order to evaluate the generality of this model reaction, we encouraged to extend this reaction to a variety of **1a–b** with different primary amines **2a–j**, so we have examined this reaction employing the optimized conditions, and the results are summarized in Table 3.

Table 3

It was clearly observed that the best results were obtained in the presence of Si-MCM-41 as catalyst at room temperature. Then, the generality of the procedure was evaluated using various primary amines under optimized reaction conditions. It was found that both using benzylamine as primary amine and Si-MCM-41 reacted well in this process to afford the corresponding products in

good to excellent yields 92% (Table 3). So we can note that these MCRs are a selective synthesis of 2-aminopyridines using mesoporous catalyst.

The evolution of the yields is carried out in the following sequence: Si-MCM-41 > Al-MCM-41 > Ga-MCM-41, and the as-synthesized Si-MCM-41 presents the best catalytic performance.

As shown in Fig. 1, all the catalysts have the same vibration bands of the as-synthesized MCM-41, the bands appeared between 2800 and 2900 cm^{-1} corresponding to the groups $-\text{CH}_2$ and $-\text{CH}_3$, and these bands also confirm the presence of surfactant (CTA^+) linked with siloxy anions ($\equiv \text{SiO}^-$) inside the pores of MCM-41 which are considered as basic sites [36, 39, 48]. The choice of incorporating Al and Ga into the framework of Si-MCM-4 was to generate a bifunctional acid/base catalyst. But according to the catalytic reaction, the MCRs were well governed by the Si-MCM-41. This also shows that the reaction takes place with the basic catalyst Si-MCM-41 due to the presence of higher density of the siloxy groups [49–56].

It is also necessary to take into account the factor of the morphology which can affect the properties of catalyst. As shown in Fig. 2, it is clearly indicated that the catalysts Si- and Al-MCM-41 have a spherical morphology, while the catalyst Ga-MCM-41 has morphology in the form of aggregates probably due to the incorporation of the gallium leading subsequently to a slight deconstruction of obtained catalyst.

Fig. 2

In order to examine the influence of amount for heterogeneous catalysts on MCRs, we have mixed 1a, 1 Eq of acetophenone, 1 Eq of malononitrile, 1 Eq of tri-ethoxymethane and 1 Eq of propylamine using different amounts of as-synthesized Si-MCM-41 (Fig. 3). T

Fig. 3

The use of 10 mol% of as-synthesized Si-MCM-41 led to 80% yield for 25-min reaction time. We note in Fig. 1 that increasing the amount of catalyst has an impact on the reaction yield. Indeed, a 25-min reaction time led to a 89% yield using 20 mol% (and 90% yield using 40 mol%) of as-synthesized Si-MCM-41. The yield obtained after 10 min of reaction in the presence of 50% of catalyst is about 98%.

Thus, the reaction time can be minimized due to an increase in catalytic amount of synthesized Si-MCM-41 catalyst and best results were obtained by performing the reaction in the presence of 50 mol% of catalyst.

Furthermore, the reusability of Si-MCM-41 was also examined with the optimized experiment conditions of the model reaction for the synthesis of product **5a**: acetophenone (1 mmol), malononitrile (1 mmol), triethoxymethane (1 mmol) and 0.1 mol of benzylamine or cyclohexylamine in the presence of Si-MCM-41 (10 mol %) at room temperature and reaction time for as-synthesized Si-MCM-41 being 15 min. After completion of the reaction, the catalyst was isolated by simple filtration than the catalysts were filtered, washed with DMF and dried before use in the following cycles, and the results are represented in Fig. 4. This study demonstrated that Si-MCM-41 could be effectively used as a recyclable catalyst for this new four-component reaction. The decrease in the activity of this catalyst during its reuse is strongly linked to the leaching of surfactant following its exposure on various occasions to treatment with solvents during cleaning. These results are in agreement with our work published previously [56, 57].

Fig. 4.

Conclusion

In conclusion, we have described a novel and efficient protocol for one-pot synthesis of 3-cyano-2-aminopyridines via a reaction between acetophenone derivative, malononitrile and triethoxymethane, using mesoporous materials as catalysts. The reaction time and product yields have been improved in the following order: Si-MCM-41 > Al-MCM-41 > Ga-MCM-41; as-synthesized Si-MCM-41 is particularly efficient for this reaction at room temperature due to its higher number of ionic pairs $\text{SiO}^- - \text{CTA}^+$. Mild conditions, good to excellent yields, reusable catalysts and short reaction time are the advantages of the present method.

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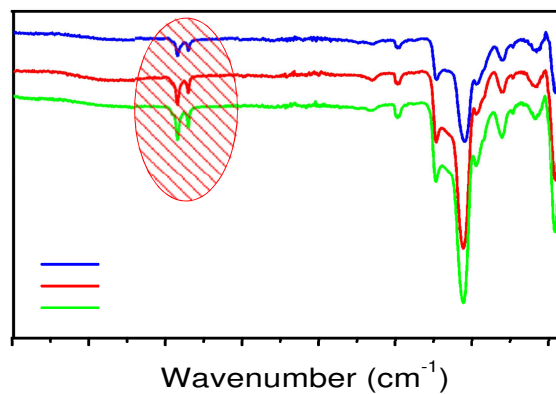


Fig. 1 FTIR spectra of as-synthesized Si-MCM-41 and its modified counterparts

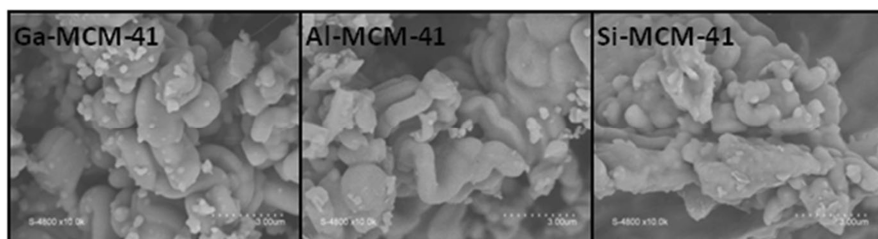


Fig. 2 SEM images of as-synthesized Si-MCM-41 and its modified counterparts

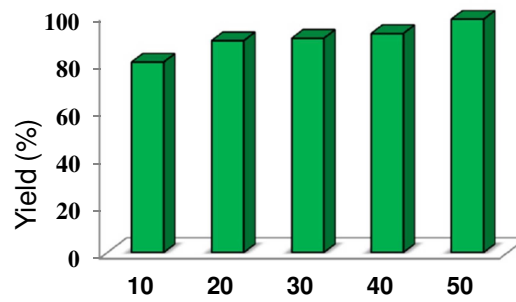


Fig. 3 Effect of the catalyst amount (as-synthesized Si- MCM-41) on the yield of 5a

mol % mol % mol % mol % mol %
amount of catalysts

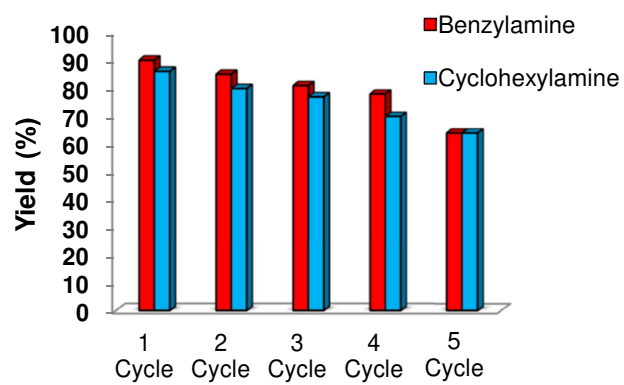
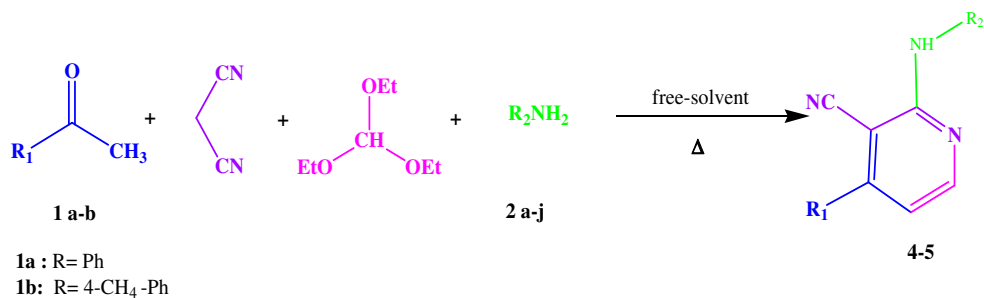
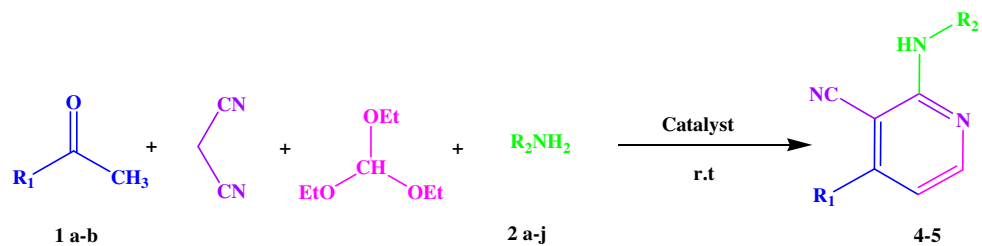


Fig. 4 Catalyst reusability

Table 1: Four-component reaction of 2-aminopyridines derivatives without catalyst

Entry	R1	R2	Product	Yield (%)
1		Benzyl-	4 _a	73
2		Cyclohexyl-	4 _b	68
3	C ₆ H ₅ -	Hexyl-	4 _c	70
4		Propyl-	4 _d	62
5		Benzyl-	5 _a	76
6		Cyclohexyl-	5 _b	65
7	p-CH ₃ C ₆ H ₄ -	Hexyl-	5 _c	72
8		Propyl-	5 _d	66

Reaction conditions: acetophenone (1, 1 mmol), malononitrile (1mmol), triethoxymethane (1 mmol), and (2, 1 mmol) amine, 100°C, 3h.

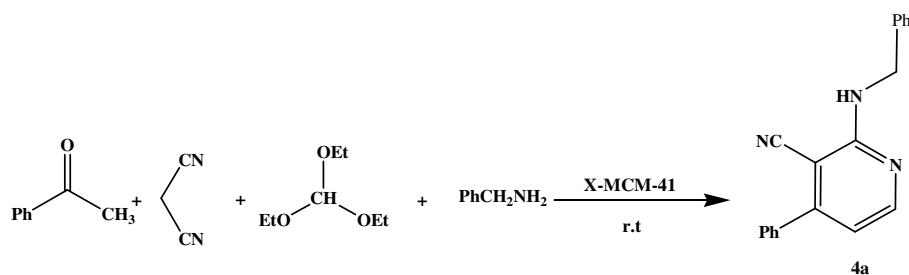


1a: R= Ph

1b: R= 4-CH₄-Ph

Scheme.1. Four-component reaction of 2-aminopyridines derivatives

Table.2. Optimization of the reaction conditions in the synthesis of **4a**



X : Ga, Al or Si

Entry	Catalyst	Time (min)	Yield (%)
1	Al-MCM-41	30	67
2	Ga-MCM-41	20	75
3	Si-MCM-41	15	89

Table.3. Synthesis of 2-aminopyridines catalyzed by Al- Ga or Si-MCM-41 under solvent free-conditions

Entry	R ₁	R ₂	Catalyst	Product	Time(min)	Yield (%)
1	C ₆ H ₅ -	Benzyl-	Al-MCM-41	4 _a	30	67
2		Cyclohexyl-		4 _b	35	70
3		Hexyl-		4 _c	40	73
4		Propyl-		4 _d	50	70
5	C ₆ H ₅ -	Benzyl-	Ga-MCM-41	4 _a	28	75
6		Cyclohexyl-		4 _b	30	79
7		Hexyl-		4 _c	38	80
8		Propyl-		4 _d	45	73
9	C ₆ H ₅ -	Benzyl-	Si-MCM-41	4 _a	15	89
10		Cyclohexyl-		4 _b	20	80
11		Hexyl-		4 _c	25	82
12		Propyl-		4 _d	30	75
13	p-CH ₃ C ₆ H ₄ -	Benzyl-	Al-MCM-41	5 _a	28	70
14		Cyclohexyl-		5 _b	22	83
15		Hexyl-		5 _c	20	85
16		Propyl-		5 _d	28	79
17	p-CH ₃ C ₆ H ₄ -	Benzyl-	Ga-MCM-41	5 _a	22	78
18		Cyclohexyl-		5 _b	20	80
19		Hexyl-		5 _c	17	82
20		Propyl-		5 _d	25	75
21	p-CH ₃ C ₆ H ₄ -	Benzyl-	Si-MCM-41	5 _a	13	92
22		Cyclohexyl-		5 _b	18	88
23		Hexyl-		5 _c	20	85
24		Propyl-		5 _d	25	80