Article

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Application of MCM-41-SO_3H as an Advanced Nanocatalyst for the Solvent Free Synthesis of Pyrano[3,2-c]pyridine Derivatives

Shahnaz Rostamizadeh,[a]* Nasrin Shadjou[a] and Mohammad Hasanzadeh[b]
[a]*Department of Chemistry, K. N. Toosi University of Technology, P.O. Box 15875-4416, Tehran, Iran*
[b]*Drug Applied Research Center, Tabriz University of Medical Science, Tabriz, Iran*

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MCM-41-SO_3H, an ordered mesoporous silica material in which MCM-41 with covalently anchored sulfonic acid groups was used as an acidic catalyst for the rapid and 'green' synthesis of pyrano[3,2-c]pyridine derivatives under solvent-free conditions. Reusability of the catalyst, high yields, short reaction times, simplicity and easy workup are advantages of this novel synthetic procedure compared to the conventional methods reported in the literature.

Keywords: Nanocatalyst; MCM-41-SO_3H; Pyrano[3,2-c]pyridine; Solvent free conditions.

INTRODUCTION

Various pyrano[3,2-c]pyridine and their derivatives are important heterocyclic compounds with a broad range of biological, medicinal, and pharmacological properties. They are constituents of antitumor, anti-inflammatory and antifungal drugs.[1-3] In view of these useful properties of pyrano[3,2-c]pyridine, a number of reports for the synthesis of these molecules have been published. El-Subbagh et al. have reported the synthesis of pyrano[3,2-c]pyridine derivatives through two component reactions between α,β-unsaturated ketones and malononitrile in BuOH.[1] Recently new method have also been reported in the literature for the synthesis of these useful heterocycles using microwave irradiation in the presence of DMF as a solvent.[4,5] Also these compounds have been synthesized in the presence of solid sodium ethoxide as catalyst under solvent-free condition,[6] in methanol containing sodium,[7] hexadecyltrimethyl ammonium bromide in aqueous media and 110 °C,[8] KF-Al_2O_3,[9] and sodium hydroxide or piperidine under microwave irradiation.[10]

However, these methods are time-consuming and use a lot of toxic solvents and reagents through classical conditions with microwave irradiation. Most importantly, the catalysts that have been used for the synthesis of these compounds are not reusable. Thus, the development of a green, simple, efficient, and general method for the synthesis of these widely used organic compounds, from readily available reagents, remains one of the major challenges in organic synthesis.

Recently, more attractive possibilities have been arisen by the development of various new silica materials with ordered structure.[11,12] One of the best-known examples is Si-MCM-41, which is a structurally well-ordered mesoporous material with a narrow pore size distribution between 1.5 and 10 nm, depending on the surfactant cation, and a very high surface area up to 1500 m^2g^{-1}.[13] It has been proven that Si-MCM-41 lacks Brönsted acid sites and exhibits only weak hydrogen-bonding type sites.[14,15] An additional possibility to develop acidic solids is the modification of the surface of suitable support materials, as the chemical functionalities of these materials can be uniformly modified by covalent anchoring of different organic moieties.[16] While several types of solid sulfonic acids have been created in recent years, there have been only a few reports about their applications as catalyst in chemical transformations.

Herein, we report, for the first time, the preparation of pyrano[3,2-c]pyridine derivatives *via* the novel recently reported MCM-41-SO_3H as a nanocatalyst from the reaction of (E)-3,5-bis(benzylidene)-4-piperidones and malononitrile under solvent-free conditions (Scheme I).

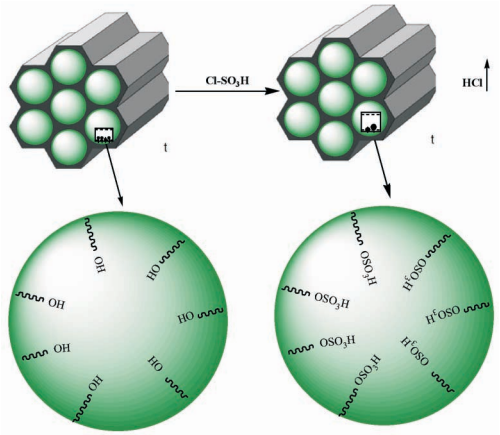
Scheme I Synthesis of pyrano[3,2-*c*]pyridine derivatives *via* MCM-41-SO_3H

* Corresponding author. Fax: +98(21)22853650; E-mail: rostamizadeh@kntu.ac.ir, shrostamizadeh@yahoo.com

RESULTS AND DISCUSSION

At first, MCM-41 was synthesized according to the previously described method using cetyltrimethylammonium bromide (CTMABr), as the templating agent.[17] Then MCM-41 was modified using a 100-mL suction flask equipped with a constant pressure dropping funnel containing $ClSO_3H$ (81.13 g, 0.70 mol) and a gas inlet tube for conducting HCl gas over an adsorbing solution. Into it was charged MCM-41 (60.0 g) and $ClSO_3H$ was then added drop wise over a period of 30 min at room temperature. HCl gas was released from the reaction vessel immediately. After completion of the addition, the mixture was shaken for 30 min and a white solid (MCM-41-SO_3H) was obtained (115.9 g) (Scheme II).

Scheme II Functionalization of MCM-41with SO_3H groups



MCM-41-SO_3H was characterized by scanning electron microscopy (SEM), Xray diffraction (XRD), and acid-base titration. The SEM image of mesoporous MCM-41-SO_3H that had been coated with gold for two minutes was taken to show the surface at high magnification (Figure 1a). The SEM image display regular chemically clean uniform porous structure. It is evident from the micrograph that the calcined and functionalized MCM-41 powder has a uniform size and shows little tendency to agglomerate. XRD analysis was performed from 1.5° (2θ) to 10.0° (2θ) at a scan rate of 0.02° (2q)/sec. The XRD patterns of the synthesized MCM-41-SO_3H sample are presented in Figure 1b. The sample of MCM-41-SO_3H showed relatively well-defined XRD patterns, with one major peak along with three small peaks identical to those of MCM-41 materials.

To verify this appearance, the N_2 adsorption isotherms after grafting of SO_3H group were recorded and shown in Figure 2. The specific surface area and pore volume obtained by the N_2 adsorption isotherms and calculated by the Brunauer-Emmett-Teller (BET) method[18] were 704 m^2g^{-1} and 0.69 cm^3g^{-1}, respectively. The pore diameter of the MCM-41-SO_3H was 3.48 nm derived from the adsorption and desorption branches by the Broekhoff and de Boer model.[19]

To obtain the optimum amount of the catalyst, at first, we chose 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one (0.33 mmol) and malononitrile (0.33 mmol) under solvent-free conditions as model reactants and examined the effect of the amount of MCM-41-SO_3H. According to these data, the optimum amount of catalyst was 0.015 g. Increasing the amount of catalyst did not improve the yield and the reaction time, while by decreasing it, the reaction time increased and the yield was lower. Also in the present of bare MCM-41 the yield and the time of the reaction was not pleasing (Figure 3).

In continuation of our work, in order to evaluate the effect of solvent, we examined different solvents for the synthesis of **5e** in the presence of MCM-41-SO_3H as a catalyst. According to our findings, solvent-free conditions gave the best result for this transformation (Table 1).

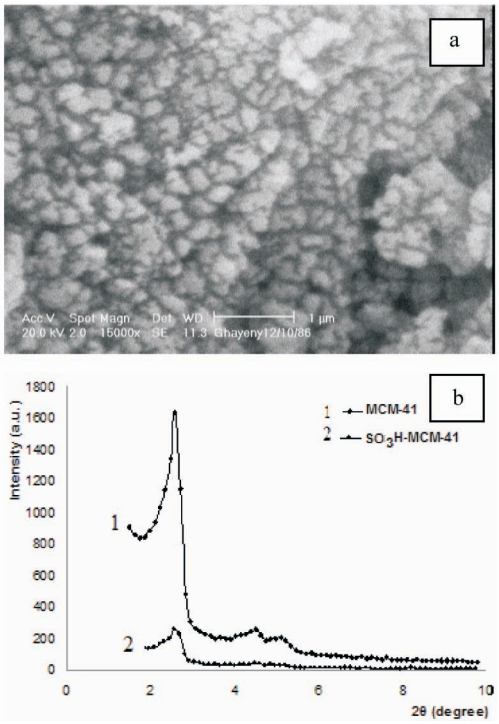


Fig. 1. (a) The SEM image of MCM-41-SO_3H (b) The XRD pattern.

With these results in hand, a variety of aromatic aldehydes, possessing both electron-donating and electron-withdrawing groups were employed for pyrano[3,2-c]pyridine formation and the results indicated that for 3,5-dibenzylidenepiperidin-4-one bearing different functional groups, the reaction proceeded smoothly in all cases. The products were obtained in relatively short reaction time, and no impurities were observed by TLC. We have also observed that 3,5-dibenzylidenepiperidin-4-one with electron-withdrawing groups such as 2,3-dichloro, 2-chloro, 4-fluoro, 4-nitro, 3-nitro, 4-bromo, and 2,4-dichloro reacted rapidly whereas with electron-rich groups such as 4-benzyloxy, 4-methoxy, and 4-methyl the reactivity decreased and longer reaction time has been required and the yield of the product decreased (Table 2).

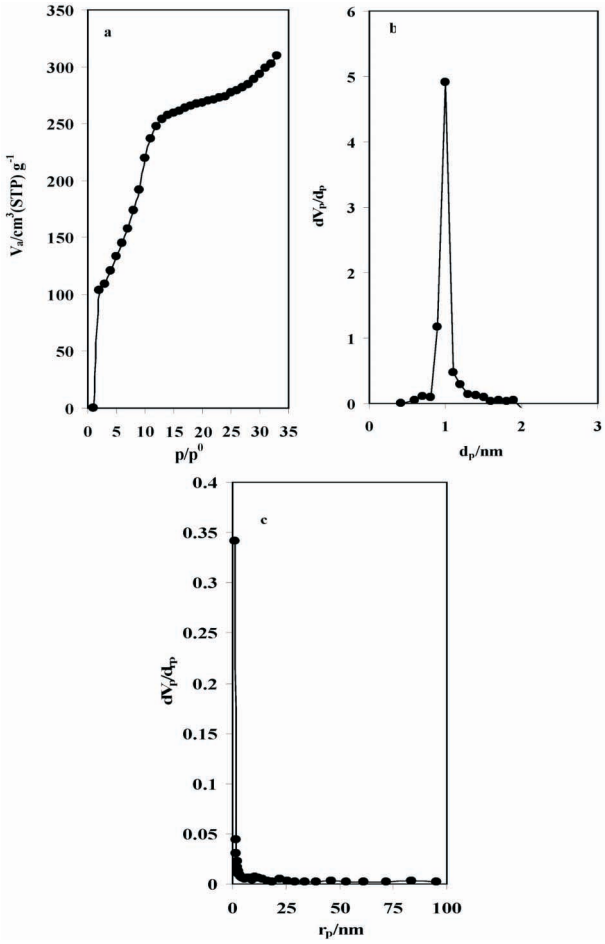


Fig. 2. (a) Nitrogen adsorption/desorption isotherm, (b) Pore size distribution and, (c) BJH of MCM-41-SO_3H.

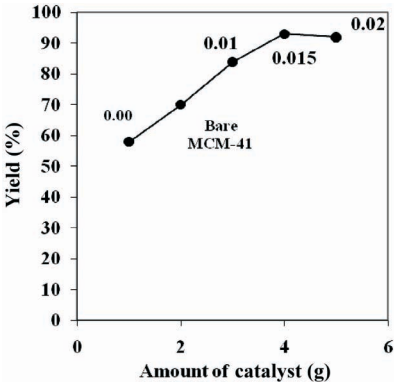


Fig. 3. Comparison of the amount of the catalyst and yields for the synthesis of **5e**.

Table 1. The effect of the solvents for the synthesis of **5e** in the presence of 0.015 g catalyst

Solvent	Reaction conditions	Time (min)	Yield (%)
EtOH	Reflux	240	75
H_2O/DMF	Reflux	30	80
H_2O	Reflux	240	No reaction
BuOH	Reflux	300	65-97 [1]

MCM-41 has two-dimensional pore structures, thus, it is easy for the reactant and product molecules to transfer into it. It seems that at first the insertion of reactants toward nanocatalyst channels occurs, and they are accompanied by the inherent Brönsted acidity of -SO_3H groups, which are capable of bonding with the carbonyl of the 3,5-dibenzylidenepiperidin-4-one moiety. In other words, ionic intermediates (**3**, **4**) are generated inside the nanoreactor by sufficient energy released during the collapse and strong polarity of the -SO_3H groups. Finally, by using this nanocatalyst, the reaction rates and yields under the reaction condition are enhanced (Scheme III).

Scheme III Proposed mechanism in the presence of MCM-41-SO_3H

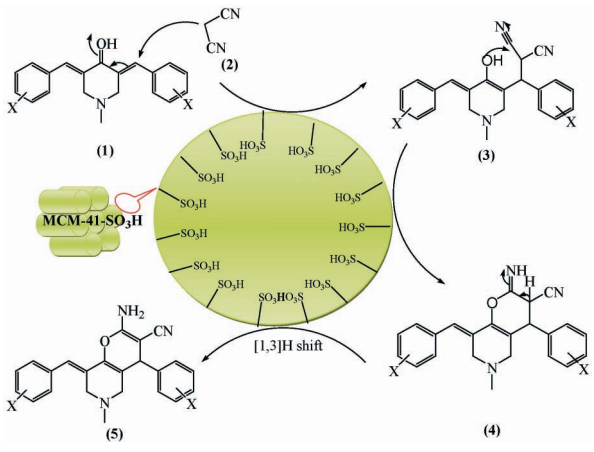
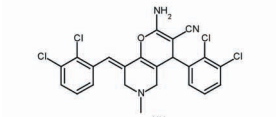
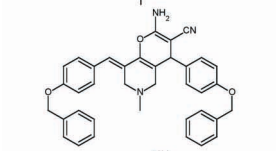
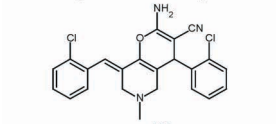
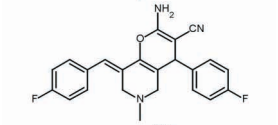
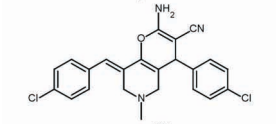
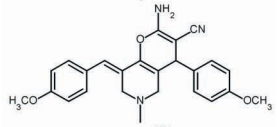
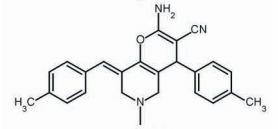
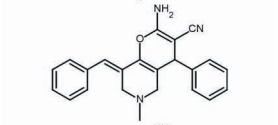
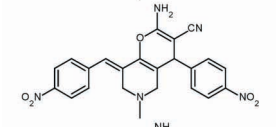
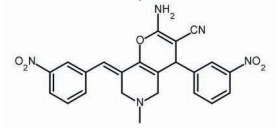
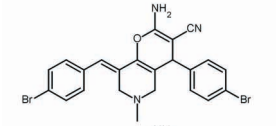
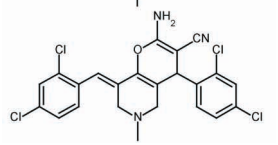


Table 2. The reaction time (min) and the yield (%) of pyrano[3,2-c]pyridine product

Entry	Product	Time (min)	Yield (%)	M.P (°C)	Ref
5a		10	98	213-215	–
5b		40	95	193-195	–
5c		10	96	213-216	208-210 [20]
5d		5	98	204-205	197-198 [20]
5e		10	93	238-239	238-240 [5]
5f		45	70	203-204	203-204 [1]
5g		25	80	226-228	215-217 [5]
5h		5	78	211-212	200-202 [5]
5i		8	80	238-240	238-240 [5]
5j		15	91	225-226	225-227 [5]
5k		10	95	245-246	245–246 [5]
5l		8	93	198-200	199-200 [6]

Finally, in order to check the reusability of our catalyst, after completion of the reaction, the solid catalyst was dried and reused for at least four cycles. It is very efficient with reusability for a four times with consistent activity

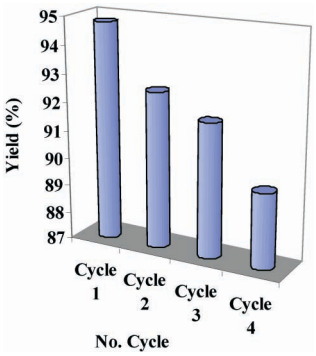


Fig. 4. Catalytic recyclability of MCM-41-SO_3H.

(Figure 4).

In conclusion, this novel synthetic method is especially favoured because it provides a synergy of the nano-sized MCM-41-SO_3H and solvent-free condition which offers the advantages of high yields, short reaction times, simplicity and easy workup compared to the conventional methods reported in the literature. Most significantly, this solid acidic catalyst is found to be very efficient with reusability for a number of times with consistent activity.

EXPERIMENTAL

General procedure for the synthesis of 3,5-dibenzylidenepiperidin-4-one

In a 50-mL reaction vial, a mixture of the 4-piperidone (10 mmol), the appropriate aldehyde (20 mmol), 10% NaOH (1 mL) and 95% EtOH (30 mL) was stirred at room temperature for 0.5-2 h. The separated solid was collected by filtration and for further purification was recrystallized from ethanol.[1]

General procedure for the synthesis of pyrano[3,2-c]pyridine derivatives

A mixture of 3,5-dibenzylidenepiperidin-4-one (0.33 mmol), malononitrile (0.33 mmol), was added to MCM-41-SO_3H (15 mg, 0.09 mmol H^+); it was then stirred at 115 °C for an appropriate period of time. After completion of the reaction (monitored by thin-layer chromatography, TLC; petroleum ether and EtOAc, 2:1), the reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from 95% EtOH to give pure product.

(8E)-8-(2,3-dichlorobenzylidene)-2-amino-4-(2,3-dichlorophenyl-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5a, $C_{23}H_{17}Cl_4N_3O$)

M.p = 213-215 ºC; ^{1}HNMR (300 MHz; DMSO-d_6): δ 2.09 (3H, s, N-CH_3), 2.51 (1H, d, *J* = 14.0 Hz), 3.02 (1H, d, *J* = 16.2 Hz), 3.15 (1H, d, *J* = 14.0 Hz), 3.31 (1H, d, *J* = 14.8 Hz), 4.7 (1H, s, CH), 6.94 (1H, s, C=CH), 7.05 (2H, s, NH_2), 7.24-7.44 (4H, m), 7.58 (2H, d, *J* = 8.0 Hz); ^{13}CNMR (75 MHz, DMSO-d_6): 44.2, 53.7, 54.2, 118.8, 119.9, 128.0, 128.9, 129.2, 129.4, 129.6, 130.3, 130.6, 132.0, 136.3, 139.5, 142.7, 160.1; MS (EI): *m/e* = 42 (100), 81 (46), 113 (30), 149 (70), 181 (60), 216 (53), 250 (91), 293 (12), 346 (11), 390 (14), 449 (19), 492 (22).

(8E)-8-(4-(benzyloxy)benzylidene)-2-amino-4-(4-(benzyloxy)phenyl)-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5b, $C_{37}H_{33}N_3O_3$)

M.p = 193-195 ºC; ^{1}HNMR (300 MHz; DMSO-d_6): 2.13 (3H, s, N-CH_3), 2.54 (1H, d, *J* = 14.4 Hz), 2.94 (1H, d, *J* = 14.0 Hz), 3.25 (1H, d, *J* = 14.4 Hz), 3.45 (1H, d, *J* = 14.0 Hz), 3.97 (1H, s, CH), 5.06 (2H, s, OCH_2), 5.10 (2H, s, OCH_2), 6.75 (2H, s, NH_2), 6.83 (1H, s, C=CH), 7.00 (2H, d, *J* = 8.7 Hz), 7.03 (2H, d, *J* = 8.7 Hz), 7.12 (2H, d, *J* = 8.7 Hz), 7.18 (2H, d, *J* = 8.7 Hz), 7.29-7.46 (10H, m): ^{13}CNMR (75 MHz, DMSO-d_6): 44.4, 53.9, 54.4, 55.7, 113.0, 115.3, 115.5, 120.3, 120.4, 127.4, 129.4, 129.5, 130.9, 131.0, 132.3, 132.4, 139.1, 139.6, 139.7, 159.5, 159.6, 159.7, 162.8: MS (EI): *m/e* = 42 (16), 65 (63), 91 (100), 131 (40), 174 (44), 198 (19), 222 (23), 250 (63), 382 (86), 410 (54), 473 (30), 501 (75), 567 (16).

(8E)-8-(2-chlorobenzylidene)-2-amino-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5c, $C_{23}H_{19}Cl_2N_3O$)

M.p = 213-216 ºC; ^{1}HNMR (300 MHz; DMSO-d_6): δ 2.09 (3H, s, N-CH_3), 2.48-2.53 (1H, d, *J*=14.6 Hz), 2.96-3.02 (1H, d, *J* = 16.1 Hz), 3.15-3.20 (1H, d, *J* = 14.0 Hz), 3.28-3.34 (1H, d, *J* = 17.0 Hz), 4.6 (1H, s, CH), 6.95 (1H, s, C=CH), 6.98 (2H, s, NH_2), 7.25-7.52 (8H, m); ^{13}CNMR (75 MHz, DMSO-d_6): 44.3, 53.9, 54.3, 54.5, 56.0, 127.1, 128.1, 128.9, 129.0, 129.2, 129.4, 129.6, 130.5, 130.8, 131.0, 132.3, 132.8, 133.3, 133.9, 134.0, 139.4, 140.1, 159.5: MS (EI): *m/e* = 51 (36), 81 (62), 115 (66), 182 (100), 216 (89), 379 (53), 422 (74), 423 (45).

(8E)-8-(4-chlorobenzylidene)-2-amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (5e, $C_{23}H_{17}Cl_4N_3O$)

M.p = 238-239 ºC; ^{1}HNMR (300 MHz; DMSO-d_6): δ 2.16 (3H, s, N-CH_3), 2.98 (1H, d, *J* = 16.0 Hz), 3.2 (1H, d, *J* = 14.3 Hz), 3.28 (1H, d, *J* = 14.0 Hz), 3.46 (1H, d, *J* = 14.0 Hz), 4.16 (1H, s, CH), 6.87 (1H, s, C=CH), 6.88 (2H, s, NH_2), 7.25 (4H, d, *J* = 8.0 Hz), 7.43 (4H, d, *J* = 8.0 Hz).

ACKNOWLEDGEMENTS

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