Research article
International Journal of Heterocyclic Chemistry, Vol. 9, No. 3, pp. 58-64 (Summer 2019)

An Efficient One-Pot Synthesis of 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-dione Derivatives using MCM-41

Adel Ghasemi[1*], Haleh Sanaeishoar[2]

[1] Department of Chemistry, Damghan University, Damghan, Iran

[2] Department of Chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran,

Recieved:28 November 2018 Revised: 22 January 2019 Accepted: 26 February 2019

ABSTRACT

Aza heterocyclic compounds are major interest for organic chemists because of their mainly pharmacological activities and clinical applications such as antianxiety, antitumor, anticonvulsant, cardiotonic and vasorelaxant. This work a new and efficient synthesis of phthalazine drivatives from the three-component condensation reaction of malononitrile, phthalhydrazide and aromatic aldehydes using MCM-41 as catalyst. The features of this procedure are mild reaction conditions, good to excellent yields, short reaction times and operational simplicity.

Keywords: MCM-41, Phthalazine, Malononitrile, Multi Component, Aza Hetrocyclic

1. INTRODUCTION

Mesoporous solids synthesized using micelles as structure directing agents have been found to posses' large specific surface area, large pore volume, regular order of pore structure and tuneable pore characteristics [1, 2].

Recently, the discovery of a new family of mesoporous molecular sieves designated as MCM-41 has been reported by researchers at the Mobil Corporation [3]. The MCM-41 material possesses a uniform hexagonal array of cylindrical pores embedded within a silica-based matrix. The material is synthesized through a hydrothermal reaction of silicate gel in the presence of a surfactant. The pore diameter can be tailored within the range of 1.6-10 nm by the choice of the surfactant molecular size. The large pore size of MCM-41, compared with that of zeolite pores, has led to a great focusing of potential applications of the materials for the adsorption, separation and catalytic conversion of large molecules.

The development of new efficient methods for synthesizing structurally diverse aza heterocyclic is of major interest for organic chemists. Among a large variety of nitrogen-containing heterocycles, derivatives whit a bridgehead phthalazine are common and these moieties are continually receiving much attention from organic and medicinal chemists, mainly due to its the pharmacological activities and clinical applications such as antianxiety [4], anticonvulsant [5], cardiotonic [6] and vasorelaxant [7].

Solvent-free organic reactions have attracted much interest particularly from the viewpoint of green chemistry. The solid-state reaction (or solvent-free reaction) has many advantages such as: reduced pollution, low costs, and simplicity in process and handling [8].

The protocol of green chemistry involves the ecofriendly transformations and environmental concerns in research and industry [9] using heterogeneous catalysts. In organic synthesis and medicinal chemistry multicomponent reactions are having the most important protocols [10].

Multi-componet reactions (MCRs) are defined as one-pot processes that three or more substrates combine either simultaneously (so called tandem or domino reactions), or through a sequential addition procedure that does not require any change of solvent. MCRs are gaining more and more importance especially in the total synthesis of natural products, and medicinal heterocyclic compounds, because of their simplicity, higher yield of the products, and lower reaction times [11, 12].

2. Experimental observations

All chemical reagents were purchased from commercially available vendors and used without further purification. Reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. Melting points were determined in open capillaries. IR spectra were recorded on a BOMEM MB-series 1998 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO on Bruker Advanced DPX 400 MHz. spectrometer using TMS as internal standard. The crystalline structures were analyzed by X-ray diffraction (XRD, X'Pert Pro MPD, PANalytical) using Cu Ka radiation (40 kV and 40 mA). N2 adsorption/desorption isotherms of calcined samples were performed at 77 K (BELSORP-mini II, MicrotracBEL, Corp.).

Scanning electron microscope (SEM) model VEGA//TESCAN-XMU instrument and operated at 20 kV, Energy dispersion X-ray (EDX) spectroscopic analysis was attached to the transmission electron microscopy (TEM) which was performed by JEOL, JEM-2100 and operated at 200 kV.

General procedure for the preparation of MCM-41

The micro-mesoporous silica samples were synthesized using tetraethyl orthosilicate (TEOS) as the silica source, CTAB and [N-bupy]Br were used as the dual templates and pH of solution was controlled by ethylamine (EA). In a typical synthesis, an aqueous solution of CTAB and cationic [N-bupy]Br was used as template solution and the Ph value was maintained constant (pH = 12), then required amount of TEOS was added drop-wise to the solution. The molar compositions of the mixed gel were: (SiO2:CTAB:IL:EA:H2O) =(1:0.2:0.2:0.6:100). After addition of the TEOS, the mixture was stirred vigorously at room temperature for 2 h, and the solutionwas transferred into a stainless-steel autoclave and heated for 48 h at 353 K. The solid product was washed once with EtOH and twice with deionized water and dried at 373 K to obtain as-synthesized sample. The as-synthesized sample was calcined in air at 823 K for 6 h with a heating rate of 1 K min^{-1}. [13]

General Procedures for One-Pot Preparation of 1H-Pyrazolo[1,2-b]phthalazine-5,10-dione Using MCM-41 as a Catalyst

A mixture of malononitrile (0.066 g, 1 mmol), aldehyde (1 mmol), and phthalhydrazide (0.16 g, 1 mmol), and MCM-41 (0.08g) was heated 150°C for 15 min. Completion of the reaction was indicated by TLC [TLC n hexan/ethylacetate (3:1)]. After completion of the reaction the insoluble crude product was dissolved in hot ethanol and MCM-41 was filtered. The crude product was purified by recrystallization in ethanol to afford the pure product.

Spectroscopic Data of Representative Compound

3-Amino-5, 10-dioxo-1-phenyl-5, 10-1H-pyrazolo[1,2-b]phthalazine-2- carbonitrile (4a)

IR (KBr): 3362, 2198, 1660, 1601 cm^{-1}. ^{1}HNMR (DMSO,d6,300MHz): 6.21 (s,1H,CH), 7.4-7.53 (m,5H,Ar-H), 8.03 (bs,2H.NH2), 8.17 (t,3H,Ar-H), 8.34 (q,1H,Ar-H). ^{13}CNMR (DMSO,d6,75MHz): 61.87, 63.51,100.02, 116.31, 127.18, 127.24, 127.77, 128.72, 128.93, 129.09, 134.10, 135.04,138.69, 151.09, 154.09, 157.04 ppm.

3-Amino-1-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo- 1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (4b)

IR (KBr): 3420,1650, 2193 cm^{-1}. 1H NMR (300 MHz, DMSO-d6) d = 6.13 (1H,s, CH), 7.44-7.58 (4H, m, ArH), 7.90-8.39 (4H, m, ArH), 8.23 (2H, s, NH2). ^{13}C NMR (300 MHz, DMSO-d6) C 61.6, 62.5, 116.7, 127.3, 127.8, 129.1, 129.6, 133.8, 135.0, 135.3, 137.2, 152.3, 154.6, 157.4 ppm.

3. DISCUSSION

The micro-mesoporous silica samples were synthesized using tetraethyl orthosilicate (TEOS) as the silica source, CTAB and [N-bupy]Br were used as the dual templates and pH of solution was controlled by ethylamine (EA). In a typical synthesis, an aqueous solution of CTAB and cationic [N-bupy]Br was used as template solution and the Ph value was maintained constant (pH = 12), then required amount of TEOS was added drop-wise to the solution. The molar compositions of the mixed gel were: (SiO2:CTAB:IL:EA:H2O) =(1:0.2:0.2:0.6:100). After addition of the TEOS, the mixture was stirred vigorously at room temperature for 2 h, and the solutionwas transferred into a stainless-steel autoclave and heated for 48 h at 353 K. The solid product was washed once with EtOH and twice with deionized water and dried at 373 K to obtain as-synthesized sample. The as-synthesized sample was calcined in air at 823 K for 6 h with a heating rate. The quality and structural ordering of MCM-41 were identified by powder X-ray diffraction. (Figure. 1)

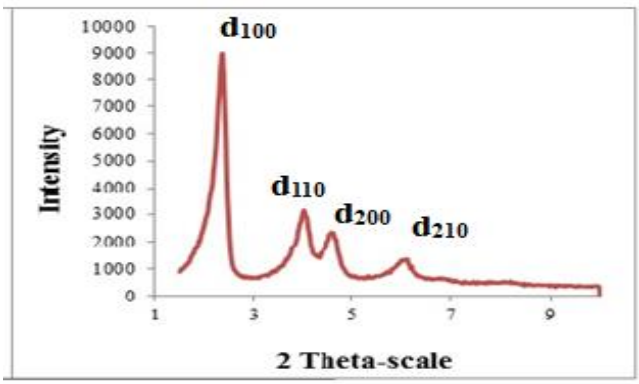

Fig 1. XRD for the synthesized solids

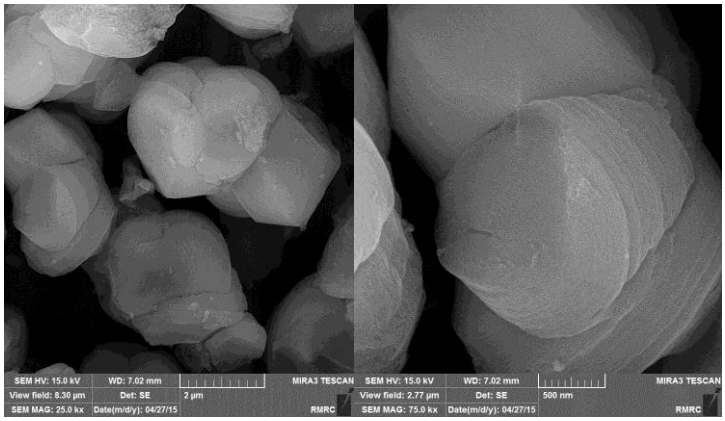

Fig 2. SEM images of synthesized solids

Nitrogen sorption isothermals of all calcined sample is presented in Figure 3. This sample present type IV isotherm patterns Furthermore, the sample shows type H4 hysteresis loops which generally observed with solids containing both micropores and mesopores. Table 1 shows the specific BET surface areas, pore volumes and pore diameters for MCM-41.

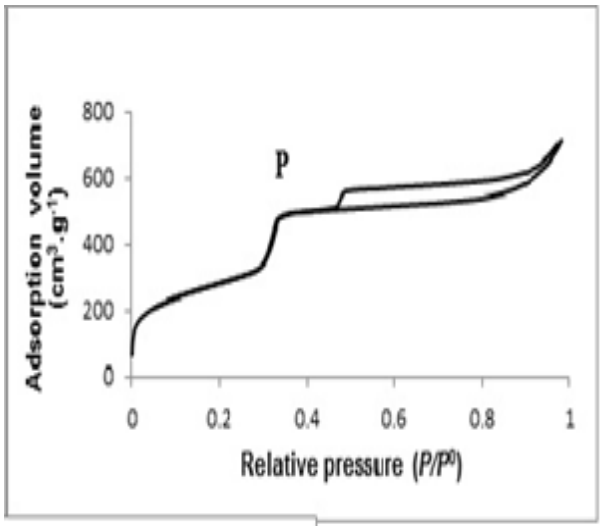

Fig 3. N_2 adsorption-desorption isotherm curves of.MCM-41

Table 1. Structural parameters of the MCM-41

Sample	S_{BET} (m^2/g)	V_P (cm^3/g)[a]	Mean pore diameter (nm)
MCM-41	1151	1.05	4.49

[a] Total pore volume

To extend the scope of the reaction and to investigate the generality of this procedure, we established the reactions of a series of aromatic aldehydes with malononitrile and phthalhydrazide in the presence of MCM-41 at 150 °C under solvent-free conditions (figure 4).

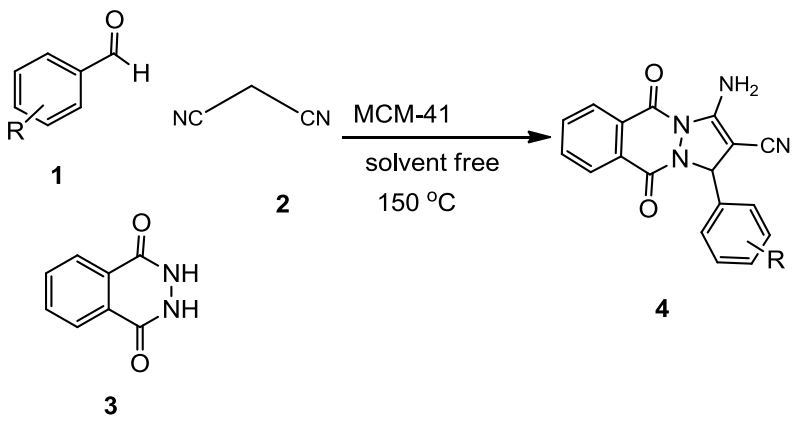

Fig 4. Three component reaction

In all cases studied, the three-component reaction proceeded smoothly to give the corresponding 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-dione in satisfactory yields. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted efficiently and gave excellent yields. The results of these investigations are summarized in Table 2. As can be seen, all reactions were carried out successfully within 1h to afford phthalazine which are also of much interest because of their biological activities in excellent yields.

Table 2. The one-pot Preparation of phthalazine derivatives promoted by MCM-41

Comp	R	Time (min)	Yield (%)	m. p. (°C) obs	Ref
4a	H	15	90	276	276-278 [14]
4b	4-Cl	30	92	269	270-272 [14]
4c	4-NO_2	60	87	231	230-232 [15]

4. Conclusion

In summary, we have described a simple and facial protocol for the synthesis of 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives from the one-pot three-componet

condensation reaction of aromatic aldehydes, malononitrile, phthalhydrazide using MCM-41 as a novel environmentally safe hetrogeneous catalyst under solvent-free condition. The method offers several advantages including high yields, applicarion of an inexpensive catalyst, short reaction times, easy wokup and performing multicomponent reaction under solvent free conditions that is considered to be relatively environmentally benign.

REFERENCES

[1] W. Zhang, T. Pauly, R. Pinnavaia, (1997) *Chemistry of Materials*, 9 ,2491.

[2] C. T. Kresge, M. E. Leonowicz , W.J. Roth, J. C. Vartul, J. S. Beck, (1992) *Nature*, 359, 71.

[3] J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt. Chu, C. T.W., D. H. E. W. Olson Sheppard, S. B. McCullen, J. B. Higgins, J. L. Schlenker, (2001) Journal of the American Chemical Society, 44-45, 581.

[4]Y. Imamura , A. Noda, T. Imamura, T. Okawara,H. Noda (2003). *Life Sci*. 74, 29.

[5]S. Grasso, G. De Sarro, A. De Sarro, N. Micale, M. Zappala, G. Puja, M. C. Baraldi, J. De Micheli, (2000) *Journal of medicinal chemistry*. 43 2,851.

[*6*]Y. Nomoto, H. Obase, H. Takai, Teranishi,M. Nakamura, K. Kubo, (199) *J. Chem. Pharm. Bull*. (Tokyo) 38, 2179.

[7]N. Watanabe, Y. Kabasawa, Y. Takase, M. Matsukura, K. Miyazaki, H. K. Ishihara, Kodama, H. Adachi, (1998) 5″ *Journal of medicinal chemistry*. 41, 3367.

[8] K. Tanaka, F. Toda, (2000)

[9] W Xie, Y Jin, PG Wang(1999) *Chemtech.* 29, 23.

[10] L Weber. Drug Disc. Today, 7 (2002)143, (b) A Domling, Curr. Opin. Chem. Biol, 6 (2002) 306.

[11]J. Zhu, H. Bienayme, *Weinheim*, 2005.

[12] N. Shajari, A. R. Kazemizadeh, A. Ramazani, (2012) *J. Serb. Chem. Soc*. 77, 1175.

[13] H. Sanaeishoar, M. Sabbaghan, F. Mohave, (2015) *Microporous and Mesoporous Materials*, 217, 219

[14]R. Ghahremanzadeh, G. I. Shakibaei,A. Bazgir, (**2008** Synlett. 8 ,1129.

[15] A. Mulik, M. Deshmukh, Dattatraya Chandam,. (2013) *Der Pharma Chemica*, 5 19.