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Multi-component one-pot reaction of aldehyde, hydroxylamine and sodium azide catalyzed by Cu-MCM-41 nanoparticles: A novel method for the synthesis of 5-substituted 1*H*-tetrazole derivatives

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Simple and efficient procedure for the synthesis of 5-substituted 1*H*-tetrazole derivatives has been developed by one-pot three-component reaction of various aldehydes, hydroxylamine and sodium azide in the presence of catalytic amount of Cu-MCM-41 as a nanostructured, heterogeneous and reusable catalyst. In this research, Cu-MCM-41 nanoparticles with three Cu/Si molar ratios were prepared and characterized by various techniques. The characterization and optimization results show that the catalyst with Cu/Si molar ratio of 0.050 has the best catalytic activity.

Keywords: 5-substituted 1*H*-tetrazoles; multi-component; heterogeneous catalyst; Cu-MCM-41; nanoparticle.

Introduction

Tetrazoles are an important class of the synthetic heterocyclic compounds with wide range of practical applications in major areas of sciences such as medicine, chemistry and material sciences. From pharmaceutical chemistry viewpoint, tetrazole derivatives have many biological activities such as antihypertensive,¹ anti-allergic,² antibiotic,³ anti-diabetic,⁴ anti-arrhythmic,⁵ activity and have also potential for drug development as inhibitor for HIV or other immune

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diseases.^{6, 7} The high physiological activity of tetrazoles, such as lower toxicity and higher lipophilicity makes them as substances of versatile biochemical and pharmaceutical destinations especially in drugs as isosteric replacement of carboxylic acid moiety.⁸ Moreover, this functional group has significant roles as ligand in coordination chemistry,⁹ in photography¹⁰ and specialty in explosives.^{11, 12}

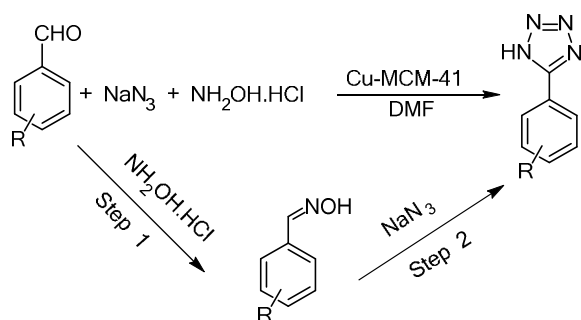
General method for the synthesis of 5-substituted 1*H*-tetrazole derivatives is based on the [2+3] cycloaddition (two-component reaction) of various nitriles with sodium azide (NaN₃) or trimethylsilylazide (TMSN₃) in polar aprotic solvents.¹³⁻¹⁵ Many catalysts have been used for this type of reaction such as Brønsted acids,¹⁶ Lewis acids including BF₃.OEt₂,¹⁷ AlCl₃,¹⁸ metal oxides such as Cu₂O,¹⁹ ZnO,²⁰ clays and modified clays,²¹ Zn/Al hydrotalcite²² and Amberlyst-15²³ as polymeric catalyst.

Many of submitted methods for this type of reaction suffer from some disadvantages such as the use of strong Lewis acids, expensive reagents, toxic metals and also the in situ generation of highly toxic and explosive hydrazoic acid. Indeed, design of safe and environmentally friendly protocols for the synthesis of tetrazoles from simpler and more available precursors is still highly desirable.

In recent years, tendency to the heterogeneous catalysts have received much attention because of being recyclable and environmentally benign. Mesoporous materials have unique properties such as high surface area and acidic sites that have been applied as heterogeneous solid acid catalyst for many organic transformations.²⁴ Mesoporous silicas are the widest members of mesoporous materials that have been applied as heterogeneous catalyst and support in many organic processes. These materials have high surface area and uniform tubular channels with tunable pore diameters in the range of 2–10 nm.²⁵ These properties provide good transportation channels for reactants especially for the large molecules to access active centers and for products to move out. In particular, modified mesoporous materials based on SiO₂ containing various transition metals such as Fe,²⁶ Cu,²⁷ Co²⁸ and Pd²⁹ have emerged as a useful heterogeneous catalysts due to their versatile applications in synthesis and catalysis. Among them, copper-modified molecular sieves have shown excellent catalytic behavior that have been prepared in variety structures such as CuO/MCM-48,³⁰ Cu/MCM-41^{31, 32} and Cu/SBA-15.²⁷

Recently, Negarkar and co-workers have reported a new method for the synthesis of 5-substituted 1*H*-tetrazole by the reaction of organic oxime with sodium azide (NaN_3) in the presence of copper acetate ($\text{Cu}(\text{OAc})_2$) as catalyst.³³

Considering the importance of tetrazoles, we report another novel method for the synthesis of this nucleus by one-pot multi-component reaction of a wide variety of aldehydes, hydroxylamine and sodium azide into the corresponding tetrazoles in the presence of Cu-MCM-41 as reusable solid acid catalyst (Scheme 1). A simple procedure was also developed for the synthesis of Cu-MCM-41 as a novel method under mild condition to produce spherical nanoparticles.



Scheme 1 The reaction of aldehydes, hydroxylamine and sodium azide in the presence of Cu-MCM-41.

Experimental

Catalyst preparation

The synthesis of nano-sized Cu-MCM-41 was carried out by method of direct insertion of copper ion in sol-gel preparation step at room temperature using tetraethyl orthosilicate (TEOS) as the Si source, cetyltrimethylammonium bromide (CTAB) as the template, ammonia as the pH control agent and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the copper source with the gel composition (mole ratio) of SiO_2 : CTAB: NH_4OH : H_2O : $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ = 1.00:0.127:0.623:508:0.1, 0.05 and 0.033 for the preparation of Cu-MCM-41(0.100), Cu-MCM-41(0.050) and Cu-MCM-41(0.033) respectively.

Cetyltrimethylammonium bromide (1.04 g) was dissolved in deionized water (200 mL) under stirring, and temperature was adjusted to 60 °C for 15 min. To this solution, tetraethyl orthosilicate (5 mL) was added dropwise and then a solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (appropriate amount of copper precursor in 5 mL of deionized water) was added dropwise under vigorous

stirring. Then pH of the solution was adjusted to 10.5 by adding 25 wt% ammonia solution. The mixture was stirred for 12 h at r.t. The gel was recovered by centrifuging and washed with ethanol (3×5 mL) and deionized water (3×10 mL). The obtained solid was dried at 120 °C for 2 h and calcined in air at 550 °C for 4 h. The obtained samples with Cu/Si molar ratio of 0.100, 0.050 and 0.033 were denoted as Cu-MCM-41(0.100), Cu-MCM-41(0.050) and Cu-MCM-41(0.033) respectively.

General procedure for the synthesis of 5-substituted 1*H*-tetrazoles 4a-o

A mixture of aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol) sodium azide (1.5 mmol), catalyst (30 mg) and DMF (3 mL) was taken in a 5 mL round bottomed flask and heated at 140 °C. After completion of the reaction (observed on TLC; *n*-hexane:ethyl acetate, 7:3) the reaction mixture was cooled to r.t. and separated from the catalyst by centrifugation. The solvent was removed under reduced pressure and residue was dissolved in water (5 mL) and acidified with HCl (37%). The precipitate was filtered and crystallized in mixture of water and ethanol. Further purification with column chromatography was not necessary.

Catalyst characterization

XRD analysis was carried out on a BRUKER D8 ADVANCE using Cu- α (1.54056 Å) radiation and the diffractograms were recorded in 0–10 ° and 10–70 ° ranges of 2θ . ^1H and ^{13}C NMR were recorded in DMSO- d_6 on a BRUKER DRX-400 AVANCE spectrometer. Fourier transform infrared (FT-IR) spectra were recorded on a BRUKER EQUINOX 55 single beam spectrometer at ambient conditions using KBr disks, with a nominal resolution of 4 cm^{-1} . Scanning Electron Microscopy (SEM) was obtained using KYKY-EM3200 Instrument. Potentiometric data was collected using pH/mV meter, AZ model86502-pH/ORP. Atomic absorption spectroscopy analysis was performed by analytic jena nova 300 model 330 Germany.

Analytical Data for 5-(3,5-dimethoxyphenyl)-1*H*-tetrazole(4l)

^1H NMR (400 MHz, DMSO- d_6): δ (ppm) = 3.84 (s, 6 H), 6.72 (t, 1 H), 7.21 (d, 2 H), 16.86 (br s, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm) = 55.5, 103.0, 104.8, 125.7, 161.0. IR (KBr): ν =

645, 680, 753, 846, 931, 1019, 1070, 1166, 1208, 1259, 1285, 1405, 1478, 1559, 1605, 2498, 2635, 2770, 2939, 3101 cm^{-1} .

Results and discussion

In this research a new method was developed for the synthesis of 5-substituted 1*H*-tetrazoles by multi-component reaction of aldehydes, hydroxylamine and sodium azide in the presence of Cu-MCM-41 as reusable solid acid catalyst. Cu-MCM-41 with Cu/Si molar ratios of 0.100, 0.050 and 0.033 were prepared and their catalytic and textural properties were characterized by XRD, SEM, FT-IR, pyridine adsorption method and potentiometric titration.

Catalysts characterization

The low angle XRD patterns of Cu-MCM-41 samples with Cu/Si molar ratio of 0.100, 0.050 and 0.033 are shown in Fig. 1. The intensity of the main peak of Cu-MCM-41 samples was decreased and the width of the peak was increased with increasing in copper content of the catalysts. Due to the incorporation of copper into the framework of MCM-41, a decrease in the long-range order of the hexagonal meso-structure of MCM-41 was observed and this indicate that copper loading destroy the crystalline structure of MCM-41. It might be expected that with increasing in ion/Si molar ratio, the main peak shift to the lower 2θ , but a certain trend is not observed in the various literatures for other types of metal modified MCM-41 because of using various sol gel methods and different size of ions and preparation conditions.^{34, 35}

As shown in Fig. 1 high angle XRD pattern of Cu-MCM-41(0.100) shows slight extent of CuO in tenorite phase. A lower distinct tenorite phase is also appeared in the pattern of Cu-MCM-41(0.050). This fact show high dispersion of copper ions in the MCM-41 framework especially for Cu-MCM-41(0.050) relative to Cu-MCM-41(0.100).

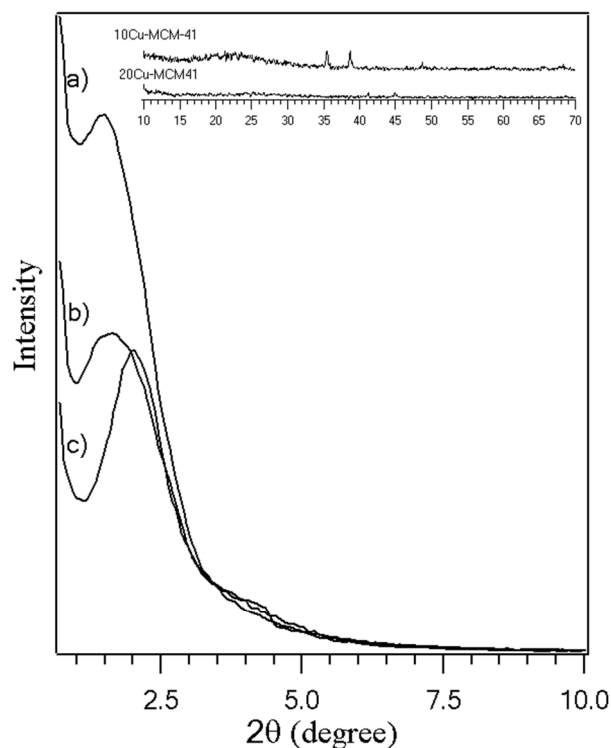


Fig. 1 The XRD patterns of a) Cu-MCM-41(0.033), b) Cu-MCM-41(0.050) and c) Cu-MCM-41(0.100)

Mesostructure of the Cu-MCM-41 was further studied by TEM. Porosity of the Cu-MCM-41 (0.050) is well observed in range of the mesoporous definition. Partial disordered mesoporous structure respect to hexagonal structure of nude MCM-41 and also non-uniform pore size distribution is related to the incorporation of Cu in to the MCM-41 framework that confirms by XRD data.

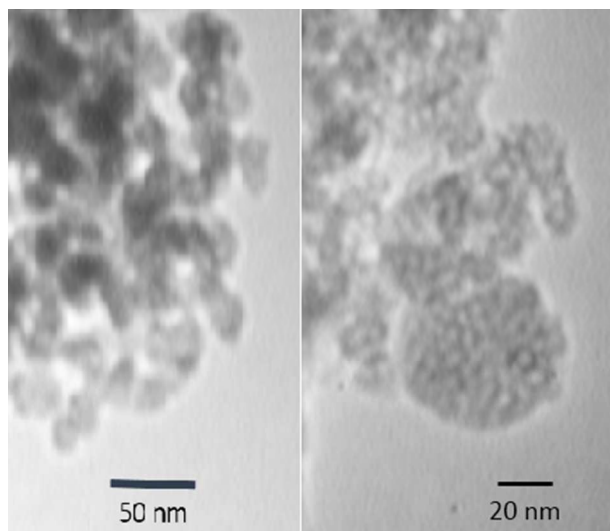


Fig. 2 TEM image of the Cu-MCM-41(0.050)

The FT-IR absorption spectra of pure silica MCM-41 and Cu-incorporated MCM-41 samples with different loading amounts of copper are shown in Fig. 3. In the range of 400–1600 cm^{-1} , MCM-41 shows three peaks at 460 cm^{-1} , 808 cm^{-1} , and 1089 cm^{-1} corresponding to the rocking, bending (or symmetric stretching), and asymmetric stretching of the inter-tetrahedral oxygen atoms in SiO_2 of Cu-MCM-41, respectively and also the peak at 966 cm^{-1} is assigned to the silanol group (Fig. 3a). A slight red shift to of the vibration absorption band at 1089 cm^{-1} , assigned to $\nu(\text{Si-O-Si})$, to the lower frequencies in the spectra of Cu-MCM-41 samples indicates the formation of Si-O-Cu bond and incorporation of Cu in the framework of MCM-41.

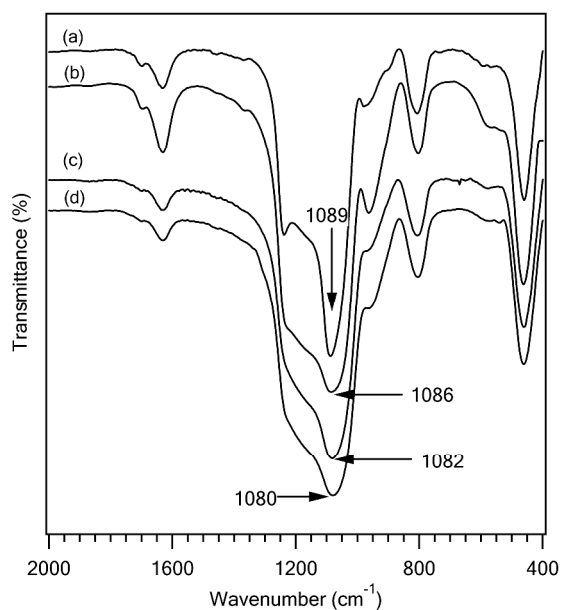


Fig. 3 FT-IR spectra of a) MCM-41, b) Cu-MCM-41(0.100), c) Cu-MCM-41(0.050) and d) Cu-MCM-41(0.033)

Fig. 4 represents the results of scanning electron microscopy (SEM) in order to investigate the particle size and morphology of the catalysts. The SEM of Cu-MCM-41 shows spherical nanoparticles with sizes of <100 nm.

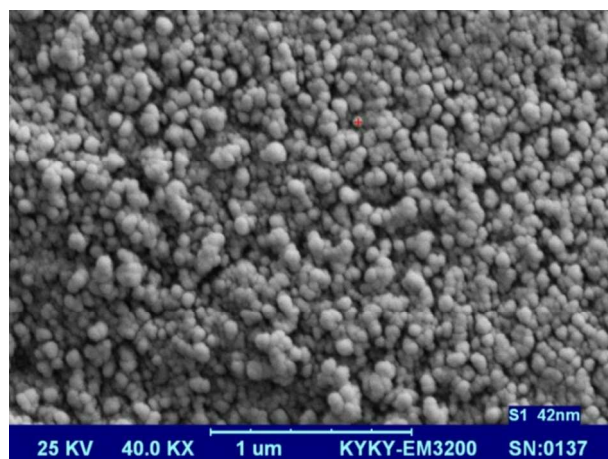


Fig. 4 SEM image of Cu-MCM-41(0.050)

In order to obtain a clear distinction between Lewis and Brønsted acid sites, FT-IR analysis of pyridine adsorbed on the catalyst surface were carried out and results are displayed in Fig. 5. The FT-IR spectrum of pyridine adsorbed Cu-MCM-41(0.050) before heat treatment (Fig. 5b) shows the contribution of pyridine adducts in the region of $1400\text{--}1650\text{ cm}^{-1}$. In this spectrum, the peaks at 1448 and 1598 cm^{-1} are attributed to pyridine bonded Lewis acid sites of the Cu-MCM-41(0.050). The weak peak at 1543 cm^{-1} , that so hard to find in current zoom, assigned to Brønsted acid sites (corresponds to protonation of pyridine on Brønsted acid sites). The weak peak at 1491 cm^{-1} is attributed to the combination mode. As shown in Fig 5c-g, with increasing in temperature, Lewis acidity characteristic peaks are still remained at 1448 and 1598 cm^{-1} . These results show that Lewis acidity of the catalyst is stronger than its Brønsted acidity.³⁶

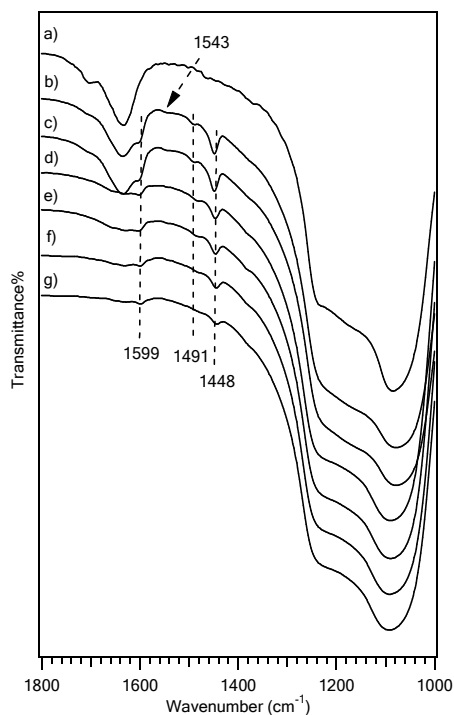


Fig. 5 FT-IR spectra of a) Cu-MCM-41(0.050), b) pyridine adsorbed Cu-MCM-41(0.050) at ambient temperature and pyridine adsorbed Cu-MCM-41(0.050) heated at c) 100 °C, d) 200 °C, e) 300 °C, f) 400 °C and g) 500 °C.

The catalyst acidity characters, including the acidic strength and the total number of acid sites were determined by potentiometric titration. According to this method, the initial electrode potential (E_i) indicates the maximum acid strength of the surface sites.³⁷ Therefore, a suspension of the catalyst in acetonitrile was potentiometrically titrated with a solution of 0.02 M *n*-butylamine in acetonitrile. As shown in Fig. 6, Cu-MCM-41(0.050) displays higher strength than the other samples.

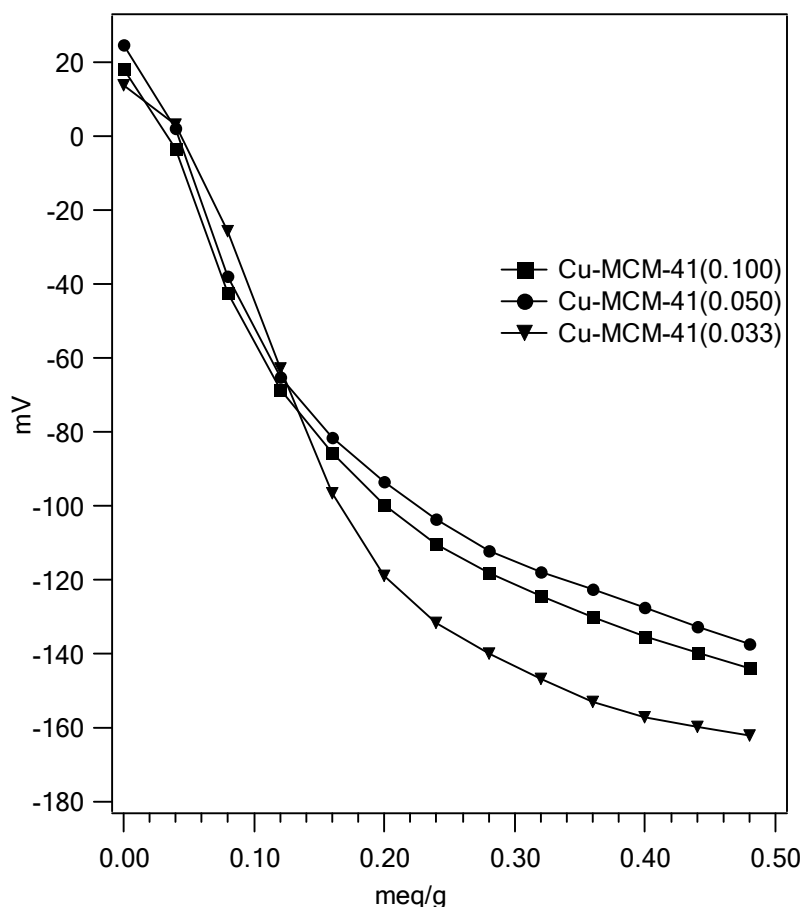


Fig. 6 Potentiometric titration of (■) Cu-MCM-41(0.100), (●) Cu-MCM-41(0.050) and (▼) Cu-MCM-41(0.033)

In order to determine effective Cu/Si molar ratios in the products, the prepared catalysts were analyzed by AAS and calculations show that CuO/SiO₂ molar ratios of the Cu-MCM-41(0.100), Cu-MCM-41(0.050) and Cu-MCM-41(0.033) are 0.093, 0.046 and 0.030 respectively. However, for simplicity, the sample names were presented by gel composition molar ratios.

Activity measurements

The catalytic activity was investigated in the synthesis of 5-substituted 1*H*-tetrazole through three-component reaction of aldehyde, hydroxylamine and sodium azide.

To optimize the reaction conditions, initially, the reaction of benzaldehyde, hydroxylamine and sodium azide was selected as model reaction. The reaction conditions and media have large effects on the yield and time due to the hard reaction conditions for the synthesis of tetrazoles. In this research, the solvent and temperature were found to play an important role in promoting of

the reaction. The reaction was optimized for various parameters such as temperature, solvent and catalyst loading. In the all of experiments the reactions were monitored by TLC based on the consumption of oxime because in the presented method oxime formation is faster than its reaction with azide for prudution of tetrazole. To investigate the effect of temperature, the reaction was performed at room temperature and the oxime (from the reaction of hydroxylamine and aldehyde) was formed rapidly but the corresponding product was not observed in this temperature. The reaction was also performed at 120, 130, 140 and 150 °C (Table 1, entries 1-3) and the best result was obtained at 140 °C. To optimize the catalyst amount, the model reaction was performed in the presence of various amounts of the catalyst and according to the obtained results (Table 1, entries 4-6) 30 mg of the catalyst was chosen as the best catalyst amount. The effect of solvent was also investigated by performing the model reaction in the presence of 30 mg catalyst in various solvents (Table 1, entries 11-13). Among them, DMF was found to be the best solvent (Table 1, entry 3) in terms of the time and yield of desired product. In a blank reaction, without the catalyst, moderate yield of the product was achieved after long time (Table 1, entry 8). Moderate yield was also obtained while MCM-41 and CuO were applied as the catalyst (Table 1, entries 9, 10). These result show that copper in MCM-41 lattice play important catalytic role in this reaction.

To investigate the catalytic activity of Cu-MCM-41(0.100) and Cu-MCM-41(0.033), the model reaction was performed in the presence of these samples in the optimized conditions and results (Table 1, entries 6, 7) show that these catalysts have considerable lower catalytic activity relative to Cu-MCM-41(0.050).

Table 1 Screening of the reaction parameters for the synthesis of 5-substituted *1H*-tetrazole^a

Entry	Reaction temp. (°C)	Cu/Si molar ratio	Catalyst amount (mg)	Solvent	Time ^b (h)	Yield ^c (%)
1	120	0.050	30	DMF	24	43
2	130	0.050	30	DMF	24	64
3	140	0.050	30	DMF	12	90
4	150	0.050	30	DMF	12	90
5	140	0.050	20	DMF	12	75

6	140	0.050	50	DMF	12	90
7	140	0.100	30	DMF	12	75
8	140	0.033	30	DMF	12	60
9	140	-	0	DMF	24	45 ^d
10	140	CuO ^e	8	DMF	24	40
11	140	MCM-41	30	DMF	24	35
12	140	0.050	30	DMSO	24	52
13	140	0.050	30	Ethanol	24	0
14	140	0.050	30	H ₂ O	24	0
15	140	0.050	30	-	24	0

^aReaction conditions: aldehyde (1 mmol), NaN₃ (1.5 mmol), hydroxylamine hydrochloride (1mmol).

^bReactions time is based on the consumption of oxime monitored by TLC.

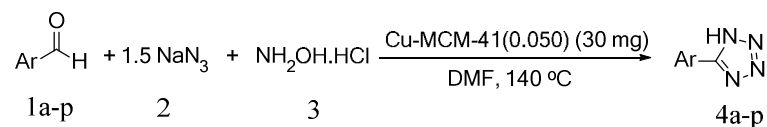
^cIsolated yield

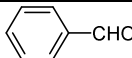
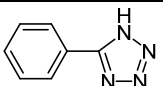
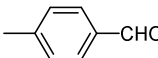
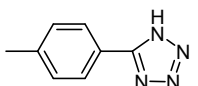
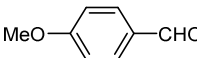
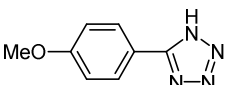
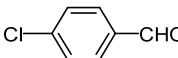
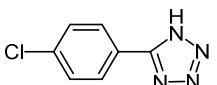
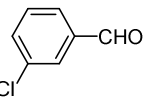
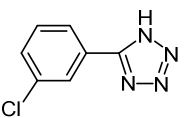
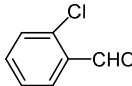
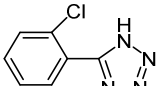
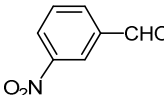
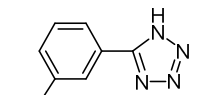
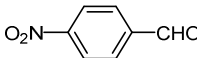
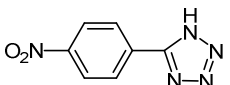
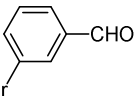
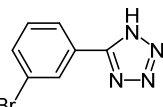
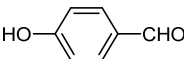
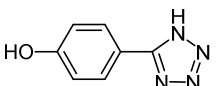
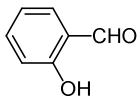
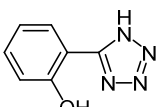
^dReaction performed without catalyst.

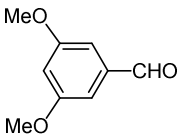
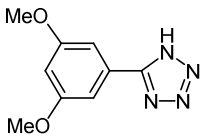
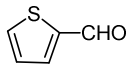
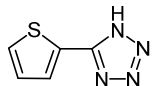
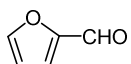
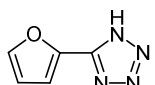
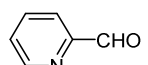
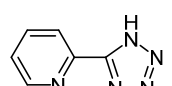
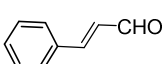
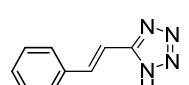
^eThe reaction was carried out in the presence of 10 mol% of CuO.

Thereafter, the above optimized reaction conditions were explored for the synthesis of 5-substituted 1*H*-tetrazole derivatives and the results are summarized in Table 2. As exemplified in Table 2, this protocol is rather general for a wide variety of electron-rich as well as electron-deficient aromatic aldehydes. The better results were observed for aldehydes containing electron-donating substituent. Steric hindrance of substrate is an important factor in yield and time of the reaction. For instance, time and yield of the reaction for 4-chloro benzaldehyde and 2-chloro benzaldehyde show this fact.

Table 2 Cu-MCM-41 catalyzed synthesis of 5-substituted 1*H*-tetrazole^a



Entry	Substrate 1	Product 4	Time ^b (h)	Yield ^c (%)	M.p. (°C) ^{ref}
a			12	90	218-219 ³⁸
b			12	91	251-252 ³⁹
c			12	85	231-232 ³⁹
d			9	92	252-253 ³⁹
e			11	80	137-139 ³⁹
f			18	80	180-182 ⁴⁰
g			10	88	154-156 ⁴¹
h			12	85	218-220 ¹⁹
i			10	94	154-155 ⁴⁰
j			14	87	234-235 ¹⁹
k			10	85	224-225 ⁴²

l			10	85	210-213 ³⁹
m			5	82	205-206 ⁴³
n			5	87	199-201 ⁴⁴
o			13	85	212-214 ³⁸
p			12	75	154-156 ³⁸

^aReaction conditions: aldehyde (1 mmol), NaN₃ (1.5 mmol), hydroxylamine hydrochloride (1 mmol), Cu-MCM-41(0.050) (30 mg) and temperature (140 °C).

^bReactions time is based on the consumption of oxime monitored by TLC.

^cIsolated yield

One of the most important features of our method is easy workup and purification of products. After completion of the reaction, the catalyst was separated and the solvent was evaporated. Thereafter, the residue was acidified and product crystallized in mixture of water and ethanol. Further purification with column chromatography was not necessary.

Regeneration and reusability of the catalyst

The most important benefit of the applied catalyst is reusability. Thus the recovery and reusability of the catalyst was investigated in the model reaction under the optimized reaction conditions. The catalyst was separated from the reaction mixture by centrifugation and reused three times with moderate loss of the catalytic activity (Table 3). Partial loss of the catalyst activity is probably due to the coke depositions and slight amount of copper leaching from the catalyst.

Table 3 Reusability of Cu-MCM-41(0.050) in the model reaction.

Entry	Fresh	Cycle 1	Cycle 2	Cycle 3
Yield (%)	90	85	80	78
Time(h)	12	12	12	12

Conclusion

We introduced a simple method for the synthesis of copper modified molecular sieves with MCM-41 structure at room temperature without using hydrothermal condition. Three different Cu-MCM-41 with Cu/Si molar ratios of 0.100, 0.050 and 0.033 was prepared and characterized by XRD, FT-IR, SEM, pyridine adsorption and potentiometric titration. The catalysts were applied in a novel method for the synthesis of 5-substituted 1*H*-tetrazoles through one-pot multi-component reaction of aldehyde, hydroxylamine and sodium azide with excellent to good yields. The results show that Cu-MCM-41(0.050) has the best catalytic activity in agreement with the characterization results. The simple experimental procedure, using aldehydes as simpler starting materials than the nitriles, easy workup, ease of the catalyst recovery and reusability make this method attractive for the synthesis of tetrazoles.

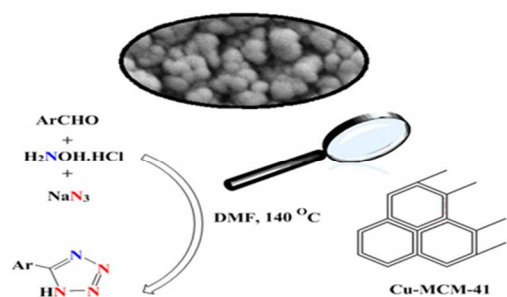
Acknowledgment

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A new method was developed for the synthesis of 5-substituted 1H-tetrazoles in the presence of copper modified MCM-41, as the heterogeneous and reusable nano structured catalyst .