Chemical Methodologies 6(2022) 639-648

Chemical Methodologies

Journal homepage: http://chemmethod.com

Original Research Article

Four-Component Synthesis of Polyhydroquinolines *via* Unsymmetrical Hantzsch Reaction Employing Cu-IRMOF-3 as a Robust Heterogeneous Catalyst

Reza Taghavi, Sadegh Rostamnia*

Organic and Nano Group (ONG), Department of Chemistry, Iran University of Science and Technology (IUST), PO Box 16846-13114, Tehran, Iran

ARTICLE INFO

Article history

Submitted: 2022-03-04
Revised: 2022-04-07
Accepted: 2022-05-12
Manuscript ID: CHEMM-2205-1511
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Behrouz Jamalvandi
Editor who approved publication:
Dr. Sobhan Rezayati

DOI:10.22034/CHEMM.2022.340599.1511

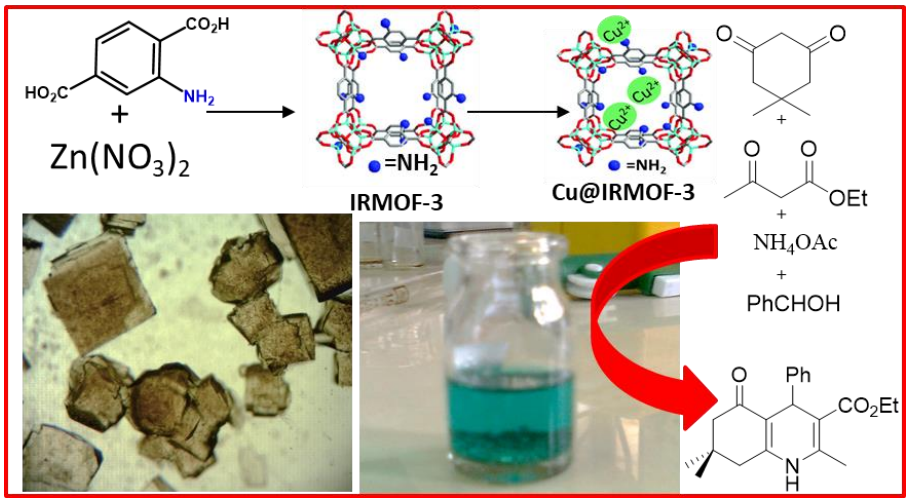
KEYWORDS

Metal-organic frameworks
Polyhydroquinoline
IRMOF-3
Unsymmetrical Hantzsch reaction

ABSTRACT

In this report, an IRMOF-3 was synthesized via a solvothermal method and then used as support for stabilizing Cu(II) ions. Characterization methods such as FT-IR, XRD, SEM, and BET were employed to analyze produced Cu@IRMOF-3, demonstrating that the suggested catalyst effectively conserved its structure throughout the synthesis processes. The FT-IR results indicate that the presence of the -NH_2 group in the structure of the MOF helped stabilize the Cu(II) ions. The manufactured catalyst was used to prepare polyhydroquinoline derivatives which showed superior results.

GRAPHICAL ABSTRACT



* Corresponding author: Sadegh Rostamnia
✉ E-mail: srostamnia@gmail.com

Introduction

Heterocyclic chemistry, the process of synthesizing aromatic rings with at least two distinct atoms in their primary ring, has long been acknowledged as one of the most important and appreciated disciplines of chemistry [1]. Most pharmacological chemicals, as well as catalytic and photocatalytically active organic molecules, possess heterocyclic rings [2]. In this regard, nitrogen-containing heterocyclic rings, known as quinolines, are of great interest due to their broad biological activities as antimalarial, antibacterial, antiasthmatic, antihypertensive, and anti-inflammatory [3]. Researchers sought green, practical, and cost-effective catalytic methods to manufacture polyhydroquinolines due to their widespread use in Alzheimer's, hypertension, and cardiovascular disease therapy [4]. Various catalytic systems have developed to promote the formation of polyhydroquinolines. Cooper (Cu)-based systems are particularly appealing owing to their availability, low cost, and the green and mild condition for the reaction's development in the presence of these catalysts [5].

In synthesizing natural and physiologically potent compounds, the Knoevenagel condensation process is routinely used as an essential step [6]. This reaction was first introduced to the scientific community by German scientist Emil Albert Knoevenagel. When an aldehyde or ketone reacts with activated methylene in the presence of a basic catalyst, such as primary and secondary ammonia (but not third-tier ammonia), their salts, and ammonia, the reaction is known as a Knoevengel condensation [7]. In particular, the amine may react with aldehyde or ketone to produce an iminium ion as an intermediate when utilized as a catalyst. The enolate simultaneously targets this iminium ion [8]. Various solid-phase nanoparticles, including graphene oxide, perovskites, carbon nanotube, metal-organic frameworks, etc., have been utilized as supports and catalysts for organic reactions [9].

In recent years, metal-organic frameworks (MOFs) have gained increasing attention due to their fascinating capability to be designed, modified, and form composites with other materials to show enhanced features toward a specific application [10]. High and permanent porosity, firm frameworks, tunable physical and chemical properties, and accessible compositions with other materials are just some of their unique properties, making them interesting to use as heterogeneous supports [11, 12]. IRMOF-3, as an isoreticular framework of MOF-5, demonstrates exceptional performance for various applications such as adsorption, separation, catalyst, photocatalyst, etc., due to its particular structure [13, 14]. The amine functionality of the organic linker increases its water stability compared with parent MOF-5 and improves its catalytic and photocatalytic performance. The amine pendant also provides the opportunity for post-synthesis modification of the MOF and helps to stabilize metal entities encapsulated by MOF [15].

Here, we managed to prepare an IRMOF-3 via a solvothermal method and use it to support the stabilization of Cu(II) ions. Characterizations showed that the amine functionality of the MOF helps the stabilization of the Cu(II) ions and boosts the catalytic performance of the proposed catalyst. The proposed catalyst was employed to promote the synthesis of polyhydroquinoline derivatives, which exhibited superior catalytic activity.

Materials and Methods

Chemicals and apparatus

Zinc(II) nitrate hexahydrate ($Zn(NO_3)_2$), amino-functionalized terephthalic acid (NH_2-BDC), cooper(II) acetate ($Cu(OAc)_2$), *N*,*N*-dimethyl formamide (DMF), Dimethyl sulfoxide DMSO, $CHCl_3$, and CH_2Cl_2 were purchased from Merck.

Synthesis of IRMOF-3

IRMOF-3 was prepared by dissolving 12.5 mmol of $Zn(NO_3)_2$ (2.36 g) and 4.1 mmol NH_2-BDC (0.075 g) in 100 mL dry DMF. After being agitated for 60 minutes at ambient temperature, the solution was sealed in a Teflon-lined autoclave and kept at 100 °C for 18 hours. IRMOF-3 was washed with DMF and $CHCl_3$ and then vacuum-dried at 60 °C.

Synthesis of Cu@IRMOF-3

Loading of Cu(II) ions to the pores of IRMOF-3 has been performed by adding 0.025 g of $Cu(OAc)_2$ to

a 5 mL DMSO solution containing 0.12 g synthesized IRMOF-3. This solution was agitated for two h at room temperature. Afterward, the catalyst was removed from the solution and dried at 60 °C in a vacuum for storage. According to atomic absorption data, the adsorption rate of copper ions was 8 wt%.

General procedure for the preparation of polyhydroquinolines

Preparation of the heterocyclic organic compounds was proceeded by adding 2 mmol of each of aldehyde, ketoester, dimedone, and ammonium acetate (NH_4OAc) to a round-bottom flask containing 0.01 g of Cu@IRMOF-3 as a catalyst in ethanol and stirred at 80 °C for an appropriate time. Progress of the reaction was monitored by the thin-layer chromatography (TLC) technique. At the end of the reaction, the desired product was separated from the mixture by adding CH_2Cl_2 and purified by column chromatography. In this regard, an *n*-Hexane/ethyl acetate (9:1) solution was used as an eluent solution.

Results and discussion

Figure 1**a** represents a schematic illustration of the preparation steps of IRMOF-3 and Cu@IRMOF-3. The synthesis steps included solvothermal preparation of IRMOF-3 in a DMF solution at 100 °C and then deposition of Cu(II) ions into the pores of MOF. Figure 1**b** shows the cubic structure of synthesized bare IRMOF-3, and Figure 1**c** shows an aqueous solution containing Cu(II) ions embedded in IRMOF-3.

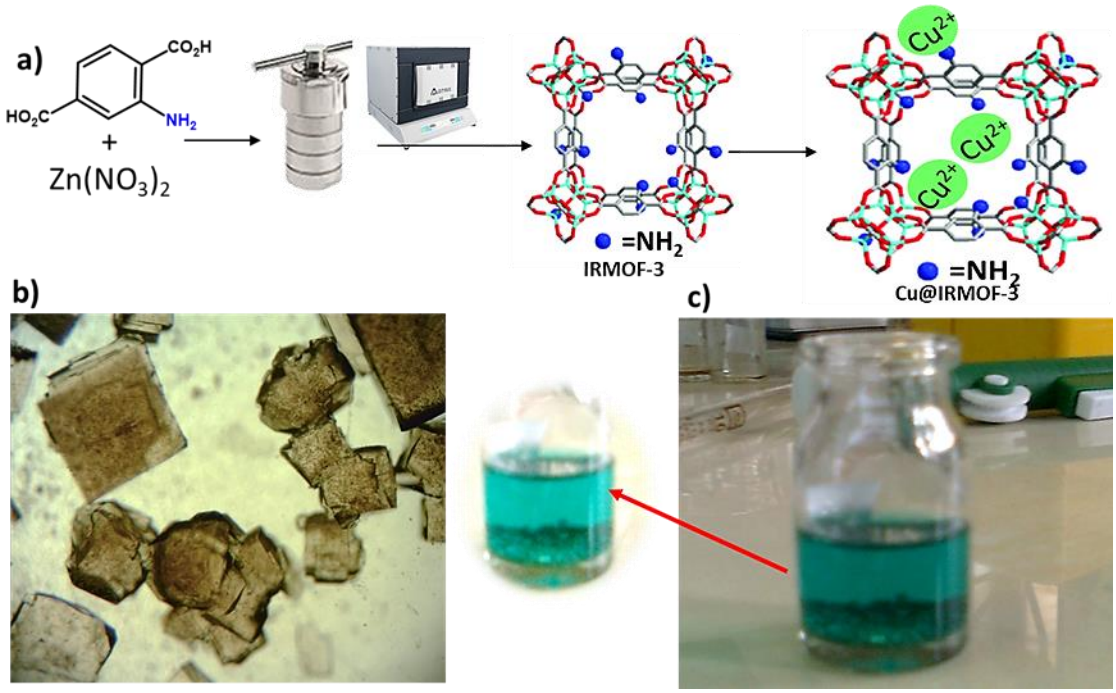


Figure 1: a) Schematic illustration of the preparation steps of IRMOF-3 and Cu@IRMOF-3. b) Optical photomicrograph [14] c) A solution containing Cu@IRMOF-3

The FT-IR spectra of IRMOF-3 and Cu@IRMOF-3 are presented in Figure 2, as mentioned in our previous report [13]. For the FT-IR spectra of IRMOF-3, the amino group of the organic linker is responsible for the peaks at 3359 and 3470 cm^{-1} in IRMOF-3. Carboxylic acid's C-O group is shown by the peaks at 1385 and 1575 cm^{-1}. The aromatic ring's C=C bonds are represented by the spectrum's three distinct peaks at 1421, 1496, and 1656 cm^{-1}. The aromatic ring-amino group C-N bond is responsible for the peak at 1257 cm^{-1}. In the case of Cu@IRMOF-3, there was a dramatic decrease in intensity of the $-NH_2$ peak, proving that the amino group of organic linker helped the stabilization of Cu(II) ions.

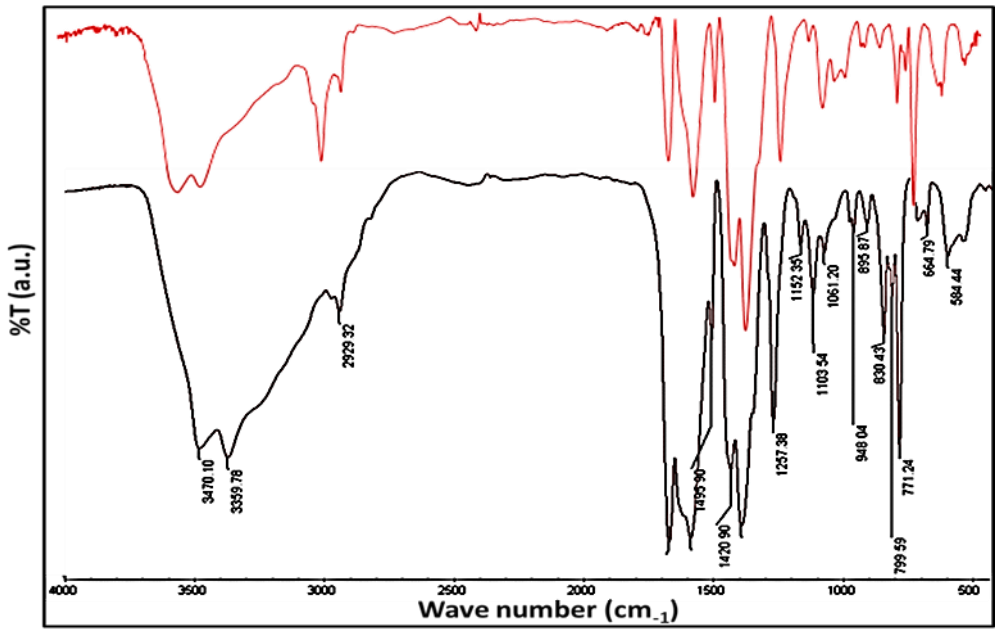


Figure 2: The FT-IR of black) IRMOF-3 and red) Cu@IRMOF-3

We further hired X-ray diffraction analysis (XRD) to examine the crystallinity and phase purity of the synthesized IRMOF-3 and Cu@IRMOF-3 (Figure 3**a**). As we mentioned in our previous report [13], the IRMOF-3 XRD pattern displays firm peaks, indicating that the MOF was crystalline. Furthermore, the peak positions are in close agreement with previously reported cases, showing the successful formation of the structure [16]. The XRD pattern of Cu@IRMOF-3 demonstrates that the crystallinity of IRMOF-3 was retained even after the encapsulation of Cu (II) ions. Compatible with the JCPDS-36-1451 data set, the ZnO lattice characteristics may be utilized to index a hexagonal wurtzite structure. As mentioned in our previous report [13], Figure 3b represents the Brunauer–Emmett–Teller (*BET*) of Cu@IRMOF-3. The BET plot is a type I, which proves its microporous structure. A hysteresis of type H4 is noticeable in the mentioned plot, which further emphasizes the microporous characteristics of the Cu@IRMOF-3. Hysteresis type H4 could further imply the blockage of the pores of the IRMOF-3, which proves the positioning of the Cu(II) ions into the pores of the MOF.

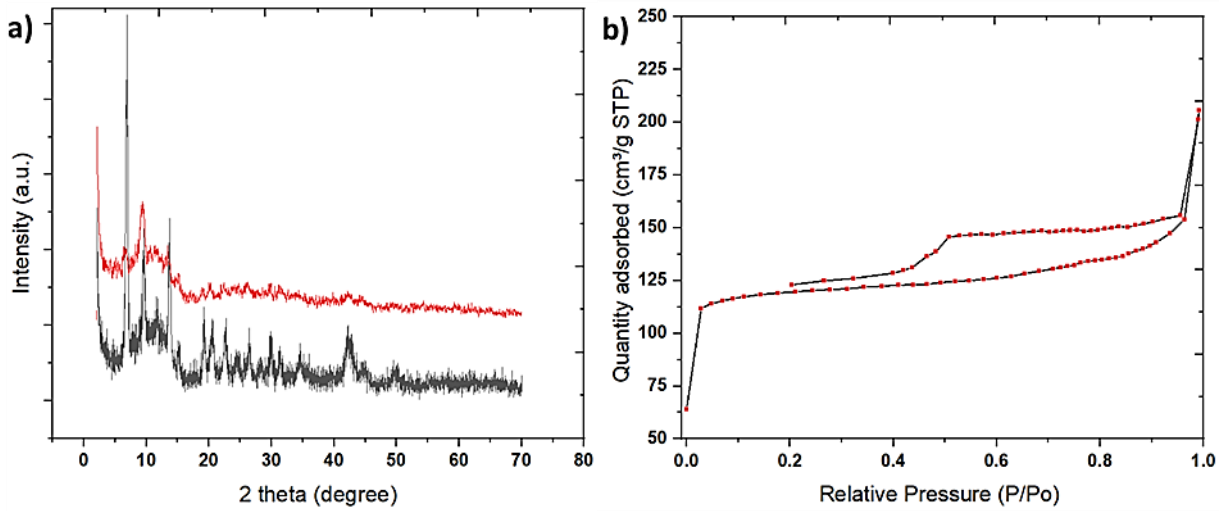


Figure 3: a) XRD patterns of IRMOF-3 (black) and Cu@IRMOF-3 (red). b) BET of Cu@IRMOF-3

Scanning electron microscope (SEM) images investigated the morphology of prepared Cu@IRMOF-3. Figure 4 exhibits the structural morphology of Cu@IRMOF-3. Noncovalent interactions between the Cu@IRMOF-3 layers, such as hydrogen bondings, π-π interactions, and aromatic-metal interactions, resulted in the aggregation of the MOF in this structure.

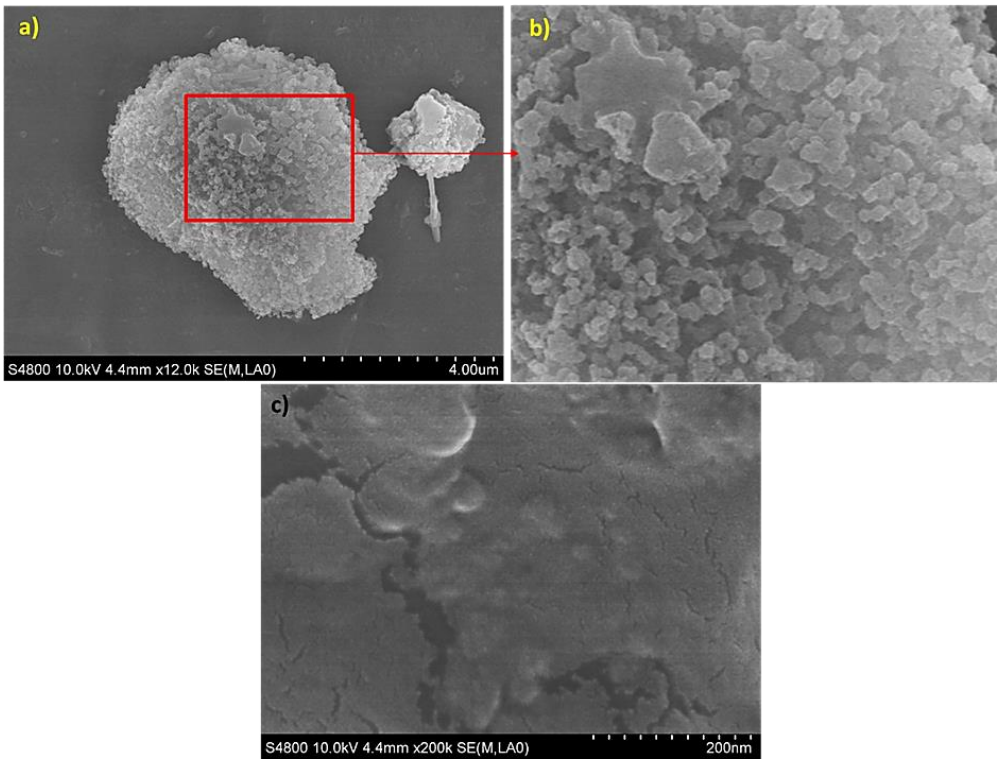
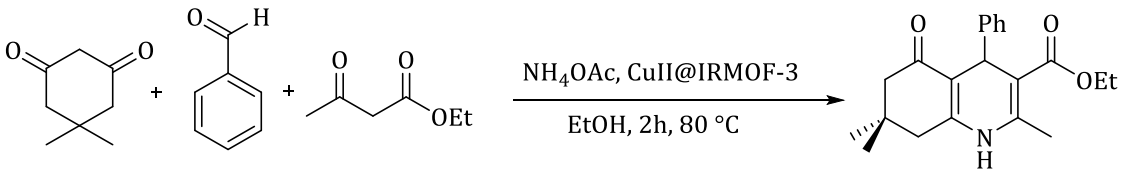


Figure 4: SEM image of Cu@IRMOF-3 in various scale bars [13]

Catalytic performances

In this report, according to our previous reports on multi-component reactions and porous materials [15, 17–21], a reaction between benzaldehyde, dimedone, ammonium acetate, and ethyl acetoacetate was chosen as the model reaction to test the efficiency of Cu@IRMOF-3 as a porous catalyst (Scheme 1). The substrates were stirred at 80 °C for 2 h in an ethanol solution in this proposed method. The TLC technique was employed to study the progress of the reaction. Finally, the products were extracted by CH_2Cl_2 and purified by column chromatography.



Scheme 1: The model reaction for preparation of polyhydroquinolines

The optimization of this reaction proceeded by investigating the effect of various parameters, including dosage of the catalyst, solvent, and temperature, on the progress of the reaction. First, to obtain the best solvent, we monitored the progress of the reaction in EtOH, MeOH, H_2O, CH_3CN, and DMF (Table 1). According to the findings of this investigation, protonic solvents are the best at promoting the progression of the reaction. Because of the higher yield of the reaction in EtOH and the environmentally friendly quality of this solvent, we selected ethanol as the

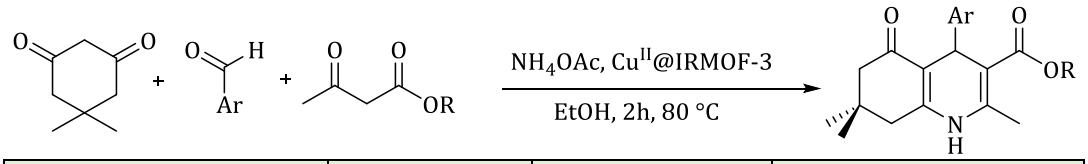
optimum solvent. Then, the progress of the reaction was investigated at various temperatures, including room temperature, 70, 80, and 100 °C, to obtain the best temperature. The reaction yield was almost 100% at 80 °C in ethanol, chosen as the optimum condition.

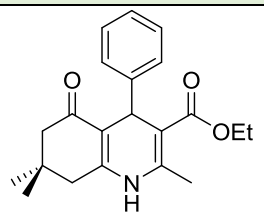
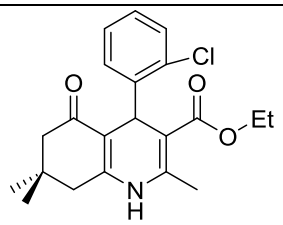
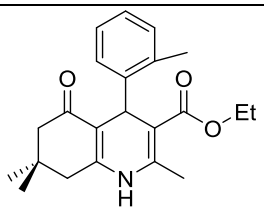
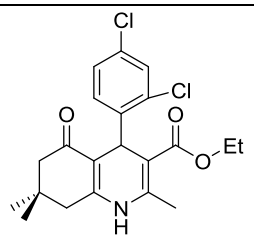
We investigated the generality of the proposed method by synthesizing a series of polyhydroquinolines. This study shows that using aromatic aldehydes with electron-donating groups in the para position of the aromatic ring as substrate results in more yield. However, the existence of an electron-donating or withdrawing group in the ortho position of the aromatic ring lowers the yield of the reaction due to the steric hindrance of such groups. Table 2 provides an overview of the structure and the yield of synthesized polyhydroquinolines

Table 1: Optimization of the condition for the heterocyclic synthesis of polyhydroquinolines

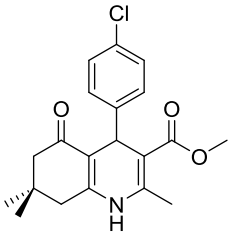
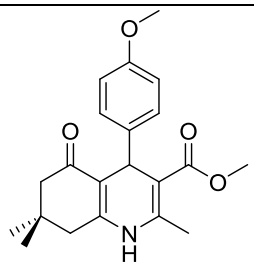
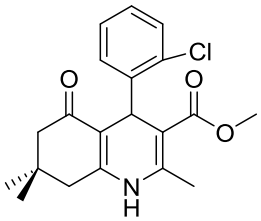
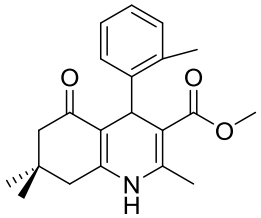
Solvent	Temperature (°C)	Time (h)	Yield %
H_2O	100	2	84
EtOH	r.t	4	90
EtOH	80	4	97
EtOH	80	2	97
MeOH	80	2	90
CH_2CN	70	2	80
DMF	100	2	75

Table 2: prepared polyhydroquinoline derivatives

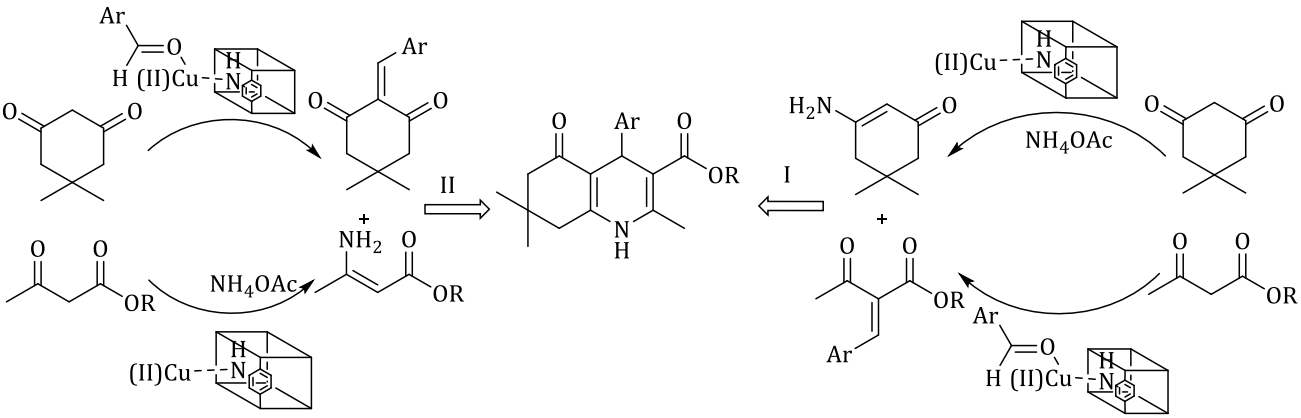


product	Yield (%)	MP.	Reported MP.
	97%	200-205	201-203 [22]
	92%	200-205	202-204 [23]
	89%	209-215	210-212 [23]
	88%	242-245	241-243 [23]

Continue of Table 2:

	93%	217-219	219-221 [23]
	91%	247-250	256-258 [23]
	90%	253-238	253-238 [23]
	89%	260-264	260-264 [23]

Scheme 2 exhibits the proposed mechanisms for preparing polyhydroquinolines in the presence of Cu@IRMOF-3 catalyst. The Knoevenagel reaction (the proposed reaction for the synthesis of polyhydroquinolines) involving ethyl acetoacetate, benzaldehyde, and ammonia, yields ester enamine. Dimedone may also be Knoevenagel condensed with ammonia and benzaldehyde to produce ester enamine and cyclic benzaldehyde derivatives of dimedone. The intermediates thus formed further undergo condensation to yield polyhydroquinolines.



Scheme 2: The proposed mechanism for preparing polyhydroquinolines using Cu@IRMOF-3 as the catalyst

Finally, to test the reusability of the proposed catalyst, ethanol and CH_2Cl_2 were used as eluents to recover the catalyst (Figure 5). The recovered catalyst was used for the synthesis of polyhydroquinolines derivatives several times. The results showed that even after five cycles, Cu@IRMOF-3 exhibited no significant loss in its catalytic performance. However, by the 6th cycle, the catalytic performance dropped dramatically due to the loss of crystallinity.

Table 3 provides the necessary information to compare the result of the model reaction in this work with previously reported outcomes. Based on the results, the Cu@IRMOF-3 shows superior catalytic performance compared with many others.

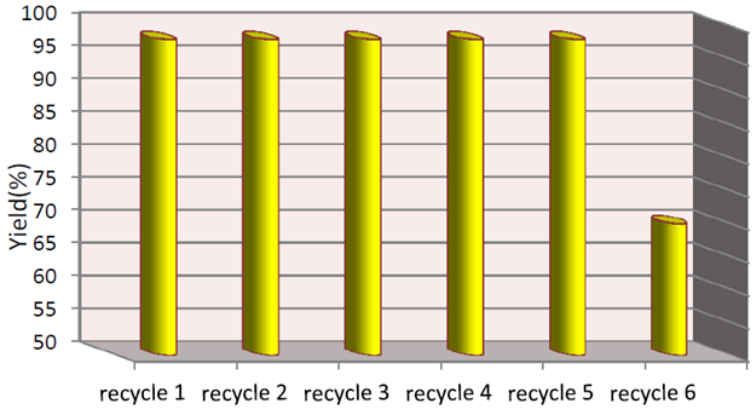


Figure 5: Recycling ability of the proposed catalyst

Table 3: Comparison of the catalytic performance of the proposed catalyst with some of the reported samples.

Entry	Catalyst	Conditions	Yield	References
1	BINOL-derived phosphoric acids	CH_3CN, 0 °C	77%	24
2	$Fe_{3-x}Ti_xO_4$-supported sulfamic acid	Solvent-free, 60 °C	58%	25
3	Cell-Pr-$NHSO_3H$	Ethanol, Reflux	90%	26
4	AgI NPs	H_2O, EtOH, Reflux	90%	27
5	Succinic acid	1:1 EtOH: water, 80 °C	92%	28
6	Ti@PMO-IL	Solvent free, 60 °C	96%	29
7	UiO-66-NH-$CH_2CH_2N(CH_2PO_2H_2)_2$	EtOH, 70 °C	95%	30
8	Cu@IRMOF-3	EtOH, 80 °C	97%	This work

Conclusion

We were able to construct an IRMOF-3 using a solvothermal approach and utilize it to aid in the stabilization of Cu(II) ions in this study. Characterizations revealed that the MOF's amine functionality aids in stabilizing Cu(II) ions and improves the catalytic performance of the proposed catalyst. The suggested catalyst was used to enhance the production of polyhydroquinoline derivatives, which showed high catalytic activity.

Funding

This research did not receive any specific grant from fundig agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

ORCID

Sadegh Rostamnia

https://www.orcid.org/0000-0001-6310-8754

References

[1]. Martins M.A., Frizzo C.P., Moreira D.N., Buriol L., Machado P., Solvent-free heterocyclic synthesis,

Chemical reviews, 2009, **109**:4140 [Crossref], [Google Scholar], [Publisher]

[2]. Erian A.W., Sherif S.M., Gaber H.M., The chemistry of α-haloketones and their utility in heterocyclic synthesis, *Molecules*, 2003, **8**:793 [Crossref], [Google Scholar], [Publisher]

[3]. Prajapati S.M., Patel K.D., Vekariya R.H., Panchal S.N., Patel H.D., Recent advances in the synthesis of quinolines: a review, *Rsc Advances*, 2014, **4**:24463 [Crossref], [Google Scholar], [Publisher]

[4]. Kazemi M., Mohammadi M., Magnetically recoverable catalysts: Catalysis in synthesis of polyhydroquinolines, *Applied Organometallic Chemistry*, 2020, **34**:e5400 [Crossref], [Google Scholar], [Publisher]

[5]. Taghavi Fardood S., Ramazani A., Golfar Z., Joo S.W., Green synthesis of Ni-Cu-Zn ferrite nanoparticles using tragacanth gum and their use as an efficient catalyst for the synthesis of polyhydroquinoline derivatives, *Applied Organometallic Chemistry.*, 2017, **31**:e3823 [Crossref], [Google Scholar], [Publisher]

[6]. Vekariya R.H., Patel H.D., Recent advances in the synthesis of coumarin derivatives via Knoevenagel condensation: A review, *Synthetic Communications*, 2014, **44**:2756 [Crossref], [Google Scholar], [Publisher]

[7]. Lee A., Michrowska A., Sulzer-Mosse S., List B., The catalytic asymmetric Knoevenagel condensation, *Angewandte Chemie International Edition*, 2011, **50**:1707 [Crossref], [Google Scholar], [Publisher]

[8]. Sarkar L., Nishad A.R., Novel Methods of Knoevenagel Condensation, *Journal of Scientific Research*, 2021, **65**:38 [Crossref], [Google Scholar], [Publisher]

[9]. Fazeli-Attar S.A., Mirjalili B.B.F., Synthesis of quinoxalines using Gum Arabic as a nontoxic metal-free biocatalyst at room temperature in aqueous media, *Environmental Chemistry Letters*, 2018, **16:**671 [Crossref], [Google Scholar], [Publisher]

[10]. Ramish S.M., Ghorbani-Choghamarani A., Mohammadi M., Microporous hierarchically Zn-MOF as an efficient catalyst for the Hantzsch synthesis of polyhydroquinolines, *Scientific Reports*, 2022, **12**:1 [Crossref], [Google Scholar], [Publisher]

[11]. Devarajan N., Suresh P., MIL-101-SO 3 H metal–organic framework as a Brønsted acid catalyst in Hantzsch reaction: an efficient and sustainable methodology for one-pot synthesis of 1, 4-dihydropyridine, *New Journal of Chemistry*, 2019, **43**:6806 [Crossref], [Google Scholar], [Publisher]

[12]. Rostamnia S., Xin H., Nouruzi N., Metal–organic frameworks as a very suitable reaction inductor for selective solvent-free multicomponent reaction: IRMOF-3 as a heterogeneous nanocatalyst for Kabachnik–Fields three-component reaction, *Microporous and Mesoporous Materials*, 2013, **179**:99. [Crossref], [Google Scholar], [Publisher]

[13]. Rostamnia S., Morsali A., Size-controlled crystalline basic nanoporous coordination polymers of Zn4O (H2N-TA) 3: catalytically study of IRMOF-3 as a suitable and green catalyst for selective synthesis of tetrahydro-chromenes, *Inorganica Chimica Acta*, 2014, **411**:113 [Crossref], [Google Scholar], [Publisher]

[14]. Rostamnia S., Morsali A., Basic isoreticular nanoporous metal–organic framework for Biginelli and Hantzsch coupling: IRMOF-3 as a green and recoverable heterogeneous catalyst in solvent-free conditions, *RSC Advances*, 2014, **4**:10514 [Crossref], [Google Scholar], [Publisher]

[15]. Rostamnia S., Xin H., Basic isoreticular metal–organic framework (IRMOF-3) porous nanomaterial as a suitable and green catalyst for selective unsymmetrical Hantzsch coupling reaction, *Applied Organometallic Chemistry*, 2014, **28**:359 [Crossref], [Google Scholar], [Publisher]

[16]. Nouri F., Rostamizadeh S., Azad M., Post-synthetic modification of IRMOF-3 with an iminopalladacycle complex and its application as an effective heterogeneous catalyst in Suzuki-Miyaura cross-coupling reaction in H_2O/EtOH media at room temperature, *Molecular Catalysis*, 2017, **443:**286 [Crossref], [Google Scholar], [Publisher]

[17]. Ahadi A., Alamgholiloo H., Rostamnia S., Liu X., Shokouhimehr M., Alonso D.A., Luque R., Layer-Wise Titania Growth Within Dimeric Organic Functional Group Viologen Periodic Mesoporous

Organosilica as Efficient Photocatalyst for Oxidative Formic Acid Decomposition, *ChemCatChem*, 2019, **11**:4803 [Crossref], [Google Scholar], [Publisher]

[18]. Hosseini H.G., Rostamnia S., Post-synthetically modified SBA-15 with NH 2-coordinately immobilized iron-oxine: SBA-15/NH 2-FeQ_3 as a Fenton-like hybrid catalyst for the selective oxidation of organic sulfides, *New Journal of Chemistry*, 2018, **42**:619 [Crossref], [Google Scholar], [Publisher]

[19]. Rostamnia S., Liu X., Zheng D., Ordered interface mesoporous immobilized Pd pre-catalyst: En/Pd complexes embedded inside the SBA-15 as an active, reusable and selective phosphine-free hybrid catalyst for the water medium Heck coupling process, *Journal of Colloid and Interface Science*, 2014, **432**:86 [Crossref], [Google Scholar], [Publisher]

[20]. Rostamnia S., Rahmani T., Ordered mesoporous SBA-15/$PrSO_3Pd$ and SBA-15/$PrSO_3PdNP$ as active, reusable and selective phosphine-free catalysts in C-X activation Heck coupling process, *Applied Organometallic Chemistry*, 2015, **29:**471 [Crossref], [Google Scholar], [Publisher]

[21]. Doustkhah E., Rostamnia S., Hossieni H.G., Luque R., Covalently Bonded PIDA on SBA-15 as Robust Pd Support: Water-Tolerant Designed Catalysts for Aqueous Suzuki Couplings, *ChemistrySelect*, 2017, **2:**329 [Crossref], [Google Scholar], [Publisher]

[22]. M. Mohammadi and A. Ghorbani-Choghamarani, *RSC Adv.*, 2022, **12:**2770 [Crossref], [Google Scholar], [Publisher]

[23]. Goli-Jolodar O., Shirini F., Seddighi M., Introduction of a novel nanosized *N*-sulfonated Brönsted acidic catalyst for the promotion of the synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions, *RSC Advances*, 2016, **6**:26026 [Crossref], [Google Scholar], [Publisher]

[24]. Quinonero O., Lemaitre C., Jean M., Vanthuyne N., Roussel C., Bonne D., Constantieux T., Bressy C., Bugaut X., Rodriguez J., *On the Enantioselective Phosphoric-Acid-Catalyzed Hantzsch Synthesis of Polyhydroquinolines, Organic Letters*, 2021, **23:**3394 [Crossref], [Google Scholar], [Publisher]

[25]. Azarifar D., Abbasi Y., Jaymand M., Zolfigol M.A., Ghaemi M., Badalkhani O., Fe3-xTixO4-supported sulfamic acid nanoparticles: New magnetic nanocatalyst for the synthesis of hexahydroquinolines, *Journal of Organometallic Chemistry*, 2019, **895**:55 [Crossref], [Google Scholar], [Publisher]

[26]. Karhale S., Bhenki C., Rashinkar G., Helavi V., Covalently anchored sulfamic acid on cellulose as heterogeneous solid acid catalyst for the synthesis of structurally symmetrical and unsymmetrical 1, 4-dihydropyridine derivatives, *New Journal of Chemistry*, 2017, **41:**5133 [Crossref], [Google Scholar], [Publisher]

[27]. Ghasemzadeh M.A., Safaei-Ghomi J., An efficient, one-pot synthesis of polyfunctionalised dihydropyridines catalysed by AgI nanoparticles, *Journal of Chemical Research*, 2014, **38:**313 [Crossref], [Google Scholar], [Publisher]

[28]. Patil S., Pawar P.B., Jadhav S.D., Deshmukh M.B., An efficient one-pot multicomponent synthesis of dihydropyridines by using succinic acid as mild organocatalyst, *Asian Journal of Chemistry*, 2013, **25**:9442 [Crossref], [Google Scholar], [Publisher]

[29]. Yari O., Elhamifar D., Shaker M., Self-assembled ionic liquid based organosilica-titania: A novel and efficient catalyst for green epoxidation of alkenes, *Journal of Organometallic Chemistry*, 2021, **940**:121787 [Crossref], [Google Scholar], [Publisher]

[30]. Askari S., Khodaei M.M., Jafarzadeh M., Heterogenized Phosphinic Acid on UiO-66-NH2: A Bifunctional Catalyst for the Synthesis of Polyhydroquinolines. *Catalysis Letters*,, 2022, **152**:1517 [Crossref], [Google Scholar], [Publisher]

HOW TO CITE THIS ARTICLE

Reza Taghavi, Sadegh Rostamnia. Four-Component Synthesis of Polyhydroquinolines *via* Unsymmetrical Hantzsch Reaction Employing Cu-IRMOF-3 as a Robust Heterogeneous Catalyst. *Chem. Methodol.*, 2022, 6(9) 639-648
https://doi.org/10.22034/CHEMM.2022.340599.1511
URL: http://www.chemmethod.com/article_151361.html