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Synthesis of Polyhydroquinoline Catalyzed by Cu nps/ Stilbite Zeolite

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Abstract:*In the present research article, a new method to synthesize polyhydroquinoline derivative is discussed. Polyhydroquinoline derivative synthesized using catalyst Cu nps/stilbite zeolite. The catalyst shows excellent catalytic activity in synthesis of polyhydroquinolines using aromatic aldehyde, dimedone, ethylaceto acetate and ammonium acetate in ethanol medium. The reaction procedure was very simple, easy to handle, excellent yields are the plus point of present method.*

Key Word*:Cu nps/stilbite zeolite, Polyhydroquinoline, catalyst*

Introduction

In recent years, heterogeneous catalysts of advanced material like nanoparticle deposited on various solid material are gaining much more importance due to environmental, economical and technological factors. The efficiency may be improved by increasing surface area of catalyst by using deposition of nano material on solid hetero substances.

Multi-component reaction (MCRs) have manifested as a powerful tool for the rapid introduction of molecular diversity in less time. Multi-component reactions contribute to the requirements of an green chemistry process by reducing the number of synthetic steps, less energy consumption and low waste production. One such reaction is the synthesis of polyhydroquinolines.

1,4-dihydropyridine (1,4-DHP) and its derivatives represent the most promising group of compounds having broad spectrum of biological activities such as vasodilator, bronchodilator, anti-atheroscerotic, anti-tumor, geroprotective, hepatoprotective and antidibetic agents [1]. Recent studies have revealed that 1,4-DHPs exhibits several medicinal applications which include neuroprotectant [2] and platelet anti-aggregatory activity [3]. Also they have been reported for their applications in treatment of Alzheimer's diseases [4] due to their cerebral antischematic activity and chemo-sensitizer in tumor-therapy [5]. These examples clearly demonstrate the remarkable potential of 1,4-DHPs as a source of valuable drug candidate. Realizing the importance of polyhydroquinoline derivatives, several synthesis methods are reported for its synthesis using different substituent and different methods. In 1882, Arthur Hantzsch reported multi-component reaction for the synthesis of substituted 1,4-dihydropyridines by condensation of ethylacetoacetate, aromatic aldehydes and ammonia. The reaction was conducted in acetic acid or at reflux in ethanol [6] for long periods resulting low to moderate yields. It is reported that such condensations can be accelerated by molecular iodine [7], $HClO_4$-SiO_2[8], TMSCl [9], ceric (IV) ammonium nitrate [10], L-proline [11], ionic liquids [12], silica sulphuric acid [13], Ni-nanoparticle [14], expensive metal triflate $Yb(OTf)_3$ [15], $Sc(OTf)_3$ [16], Bakers yeast [17], solid phase organic synthesis technique [18] and without catalyst [19]. Each reaction shows some advantage but drawback also, such as longer reaction times, expensive catalysts and consumable material, harsh reaction conditions, low product yields and the use of large quantity of volatile organic solvents. Effluent

pollution and use of expensive metal precursors as a catalyst that is harmful to the environment is also a large issue. The problems or drawback associated with the reported methods avoided by using green, efficient and safe catalyst. Therefore, introducing clean processes by utilizing ecofriendly conditions and green catalysts which can be simply recycled at the end of reactions, have been under permanent attention. The demand for environmentally benign procedure with heterogeneous and reusable catalyst promoted us to develop a safe alternative method for the synthesis of polyhydroquinoline derivatives.

The main objectives of this work are 1) to develop an ecofriendly method for the synthesis of polyhydroquinolines. 2) to utilize maximum principles of green chemistry while carrying out synthesis of polyhydroquinolines. 3) to find better pathway to understand synthesis of polyhydroquinolines. 4) to explore the scope of Cu nps/ stilbite zeolite catalyst.

Experimental Procedure for catalyst preparation:

Cu nano powders were prepared by Sol-Gel method. The aqueous solution of $CuCl_2.6H_2O$ (0.2 M) is prepared in cleaned round bottom flask. 1 ml of glacial acetic acid is added to above aqueous solution and heated to 100°C with constant stirring. 8 M NaOH is added to above heated solution till pH reaches to 7. The color of the solution turned from blue to black immediately and the large amount of black precipitate is formed immediately.

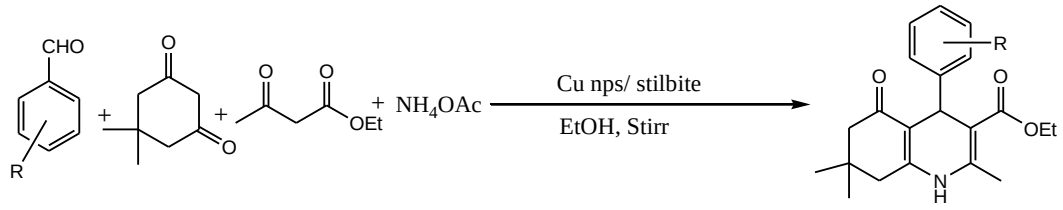
The above copper nanoparticle prepared were mixed with 2 gm of stilbite zeolite, stirred for 2 hrs, air dried and heated at 200°C in muffle furnace, cooled and named as Cu nps/ stilbite zeolite.

I. Material And Methods

Melting points of products were determined by using Metler instrument are uncorrected. The reactions were monitored by Thin Layer Chromatograph and visualized with UV light in chamber. IR spectra were recorded on a matrix of KBr with FTIR-4100 (Jasco, Japan) spectrometer. ^{1}H NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus (400 MHz) and the chemical shifts are given in ppm relative to TMS as an internal standard.

Procedure for synthesis of polyhydroquinolines:

A mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol), ehtylacetoacetate (1 mmol), ammonium acetate (1.5 mmol) and Cu nps/ stilbite zeolite (200 mg) were added in ethanol (5 ml). The reaction mixture was stirred at room temperature until the reaction was completed monitored by TLC. After completion of the reaction, the reaction mixture was dissolved by heating. The reaction mass filtered. The undissolved material, i.e. catalyst was washed by n- hexane (5 ml), dried at 80°C further used for next reaction. The filtrate was concentrated under reduced pressure and the obtained solid was recrystallized from ethanol to obtain pure product.



1 2 3 4 5

Scheme 1

Catalyst characterization:

X-ray diffraction:

The sample was characterized by XRD using model D8 Bruker AXS with monochromatic Cu-Kα radiation (40Kv and 30mA) at room temperature. The XRD spectra are shown in fig. 1. The XRD diffraction data are obtained in the 2Θ range of 05-80°. From XRD it is seen that, the powder sample shows intense reflection at 2Θ =8.2, 17, 22,24,29 and 37°. The nature is crystalline.

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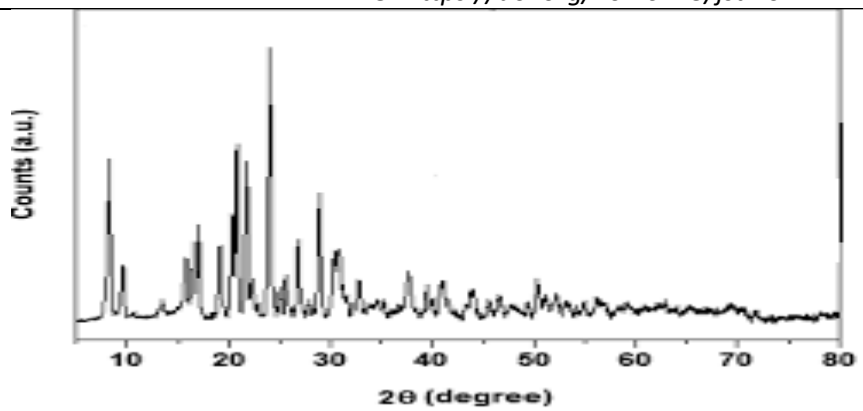


Fig.1. XRD of Cu nps/ stilbite zeolite.

FTIR spectroscopy:

FT-IR spectroscopy was performed on Perkin Elmer FTIR spectrometer. The samples were prepared with KBr and pressed into pellet. Spectra were collected in the mid- IR range of 650 to 4000 cm-1 with resolution of 1cm-1. The results of IR spectroscopy are shown in figure. Peak at 1045 cm-1 is due to Cu-O-Si bond. The peak at 912 cm-1 is assigned to Si-O-Si bond and peak at 3390 is due to Si-OH. The fig.14 shows the FTIR spectra of Cu nps/stilbite zeolite.

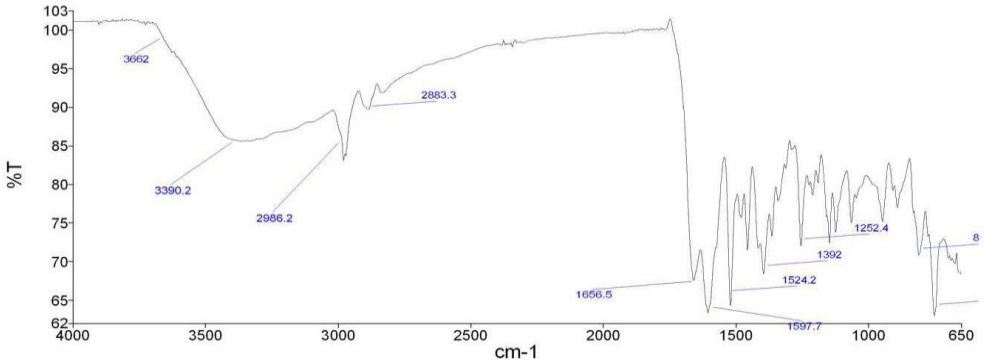


Fig. 2. FTIR of Cu nps/ stilbite zeolite.

II. Resultand Discussion

In order to achieve the best experimental conditions, we initially studied the effect of activity of Cu nps/ stilbite zeolite as a catalyst in condensation of benzaldehyde (1 mmol), dimedone (1 mmol), ethylacetoacetate (1 mmol), and ammonium acetate (1 mmol) in different solvents and the results are summarized in Table 1. After solvent screening studies reaction was optimized to find out suitable catalytic quantity and it was found that the quantitative yield of desired product was obtained in the presence of 200 mg of Cu nps/ stilbite zeolite in ethanol system is a very active catalytic system for this reaction, it is noteworthy that in the absence of catalyst, reaction does not form any product even after 2 hrs. The observed yield of polyhydroquinoline is maximum in ethanol as a solvent having dielectric constant 24.3. This is an important observation indicating that this transformation requires the protic solvents of medium dielectric constant for the enolisation of active methylene compounds.

The scope and efficiency of this approach was explored for the synthesis of wide variety of polyhydroquinolines by reacting a diverse range of aldehydes possessing electron donating as well as electron withdrawing groups with dimedone, ethylacetoacetate and ammonium acetate and results are summarized in Table 2. Therefore, it is clear that in all the cases irrespective of the presence of electron donating or electron withdrawing groups in an aldehyde moiety, the desired products were obtained in good yields.

This methodology avoids the use of hazardous solvents and requires only catalytic amount of the cu nps/ stilbite zeolite to promote the reaction.

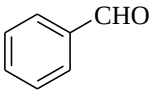
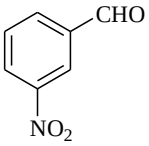
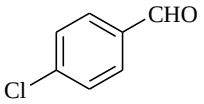
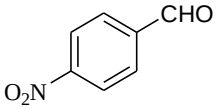
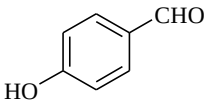
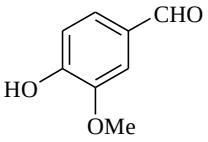
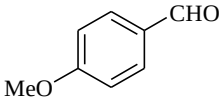
We have successfully used recovered Cu nps/ stilbite zeolite for the model reaction and the results of recycling experiments are shown in Table 3. These results clearly indicate that the recovered Cu nps/ stilbite zeolite can be recycled successfully without significant loss of activity.

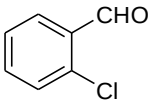
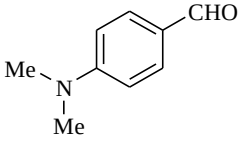
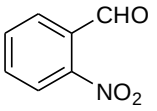
All the reactions run rapidly and were found to furnish good to excellent yields of polyhydroquinoline derivatives. And no other byproducts were formed during the course of the reaction.

Table 1. Optimization of reaction condition.

Solvent	**Wt. of catalyst (mg)**	**Reaction time**	**Yield (%)**
Water	200	2hr	27
Ethanol	200	45min	96
Acetonitrile	200	45min	79
Dichloromethane	200	1hr	63
Ethanol	150	45min	88
Ethanol	250	45min	96

Table 2. Synthesis of polyhydroquinoline derivatives using Cu nps/ stilbite zeolite in ethanol.

Compound	**Aldehyde**	**Time (min)**	**Yield (%)**[a,b]	**M.P. (°C)**
5a		40	96	252-253
5b		45	92	175-177
5c		35	95	247-248
5d		40	93	240-242
5e		45	93	247-248
5f		50	92	233-235
5g		35	95	246-248

5h		45	94	210-211
5i		35	96	262-263
5j		45	90	211-213

[a]Yield refers to isolated product. [b]-All products are known and spectral data matched with authentic sample.

Table 3. Reusability of the catalyst.

Entry	**Cycle**	**Yield (%)[a]**
1	Fresh	96
2	First	96
3	Second	95
4	Third	95

[a]Yield refers to isolated product.

III. Conclusion

In conclusion, we have developed a convenient and efficient protocol for one-pot synthesis of polyhydroquinolines by four-component coupling reactions of aromatic aldehydes, ethylacetoacetate, dimedone and ammonium acetate in the presence of Cu nps/ stilbite zeolite catalyst. The method is associated with several advantages such as simple experimental procedure, utilization of heterogeneous catalyst, mild reaction conditions, short reaction times, excellent yields and reusability of the catalyst. We feel the method will find important applications for the synthesis of polyhydroquinolines.

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