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Synthesis Of Polyhydroquinoline Derivatives Using Cu Nps/Clinoptilolite Zeolite as a Catalyst

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Abstract

A sustainable and efficient protocol has been developed for the synthesis of polyhydroquinoline derivatives via a one-pot four-component Hantzsch reaction using copper nanoparticle-supported clinoptilolite (Cu NPs/clinoptilolite) as a heterogeneous catalyst. The catalyst was prepared by immobilizing copper nanoparticles onto natural clinoptilolite zeolite, providing high surface area, excellent metal dispersion, and enhanced catalytic activity. Various substituted aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate underwent smooth condensation under optimized reaction conditions to afford the corresponding polyhydroquinoline derivatives in excellent yields with short reaction times. The Cu NPs/clinoptilolite catalyst exhibited remarkable stability, easy recovery, and reusability over successive reaction cycles without significant loss of activity. The enhanced performance is attributed to the synergistic effect between copper nanoparticles and the porous clinoptilolite framework, which facilitates efficient adsorption and activation of reactants. This environmentally benign catalytic system offers a simple, cost-effective, and green approach for the synthesis of biologically important polyhydroquinoline derivatives with potential pharmaceutical applications.

Keywords: Polyhydroquinoline Derivatives, Copper Nanoparticles, Clinoptilolite Zeolite, Heterogeneous Catalysis

INTRODUCTION

The history of polyhydroquinoline (PHQ) derivatives is closely associated with the development of the Hantzsch reaction, one of the oldest and most important multicomponent reactions in organic chemistry. In

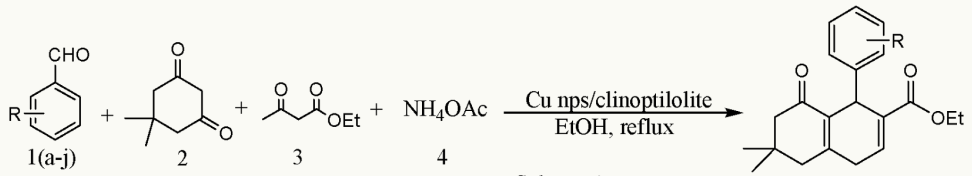
1881, Arthur Hantzsch reported the synthesis of 1,4-dihydropyridines (1,4-DHPs) through the one-pot condensation of an aldehyde, two equivalents of a β-ketoester, and ammonia [1]. This reaction became known as the Hantzsch reaction and remains a fundamental method for preparing nitrogen-containing heterocyclic compounds. In the 1970s and 1980s, interest in 1,4-dihydropyridines increased dramatically after the discovery that several derivatives exhibited potent calcium channel blocking activity [2]. Drugs such as nifedipine, amlodipine, and felodipine belong to this class and are widely used for the treatment of hypertension [3] and cardiovascular diseases [4]. This success stimulated extensive research into structurally related compounds, including polyhydroquinoline derivatives, which possess a fused cyclohexanone ring and often exhibit enhanced biological properties. Some of them have antitubercular [5], anticancer [6], neuropeptide YY1 receptor antagonist [7], neuroprotective [8], platelet anti-aggregation [9], and antidiabetic [10] activities.

On the other hand, because of the pharmacological uses of polyhydroquinoline derivatives, their synthesis has been extensively investigated in the presence of organic solvents and catalysts. Recently, the synthesis of polyhydroquinoline derivatives has been carried out using TMSCl [11], ionic liquids [12, 13], polymers [14, 15], Yb(OTf)3 [16], solar thermal energy [17] and Baker's yeast [18]. However, many of these methods suffer from harsh reaction conditions, long reaction times, the use of large quantities of volatile organic solvents, and generally low yields.

Clinoptilolite is one of the most abundant and commercially important naturally occurring zeolites. It belongs to the heulandite group of tectosilicate minerals and is characterized by a three-dimensional microporous framework composed of interconnected silica (SiO_4) and alumina (AlO_4) tetrahedra. The negatively charged framework is balanced by exchangeable cations such as Na^+, K^+, Ca^{2+}, and Mg^{2+}, which give clinoptilolite its exceptional ion-exchange and adsorption properties.

Copper (Cu)-doped clinoptilolite is generally a more effective catalyst than pure clinoptilolite because the incorporation of copper nanoparticles or copper ions introduces additional active catalytic sites while preserving the advantageous porous structure of the zeolite.

We herein report Cu nps/clinoptilolite natural zeolite [19] as an efficient catalyst for the synthesis of polyhydroquinolines in the condensation reaction of aromatic aldehydes, dimedone, ethylacetoacetate, and ammonium acetate in ethanol under reflux conditions.



1(a-j) 2 3 4 5(a-j)

Scheme 1

Experimental Section:

All chemicals were available commercially and used without purification. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Jasco instrument with KBr discs. ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d6 or CDCl3 on a BRUKER DRX-300 AVANCE spectrometer at 300 MHz.

General procedure for the synthesis of polyhydroquinoline derivatives:

A mixture of substituted benzaldehyde 1 (1 mmol), dimedone 2 (1 mmol), ethylacetoacetate 3 (1 mmol), ammonium acetate 4 (1.2 mmol), and Cu nps/clinoptilolite zeolite (0.02 g) was refluxed in ethanol for the

given time. The reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and then hot ethanol was added. The catalyst was insoluble in hot ethanol and it could therefore be recycled by a simple filtration. The crude product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give derivatives in high yields.

Spectral data of representative compounds

Ethyl-1,4,7,8-tetrahydro-2,7,7,4-(phenyl)-5-(6H)-oxoquinoline-3-carboxylate **(5a)**. Solid:IR (KBR): 3289, 3208, 3066, 1691, 1603, 1063, 691; 1H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (s, 3H, C-CH_3), 1.02 (s, 3H, C-CH_3), 1.21 (t, J = 6.99 Hz, 3H, CH_3-CH_2O), 2.04-2.08 (m, 4H, 2 x CH_2), 2.38 (s, 3H, =C-CH_3), 4.03 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 4.98 (s, 1H, Ar-CH), 6.39 (s, 5H, NH), 7.01-7.30 (m, 5H, Ar-H); MS: m/z = 340 $(M + H)^+$.

Ethyl-1,4,7,8-tetrahydro-2,7,7,4-(3-nitrophenyl)-5-(6H)-oxoquinoline-3-carboxylate **(5b)**. Solid: IR (KBR): 3296, 2961, 1682, 1609, 1163, 754; 1H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (s, 3H, C-CH_3), 1.04 (s, 3H, C-CH_3), 1.22 (t, J = 7.21 Hz, 3H, CH_3-CH_2O), 2.09-2.28 (m, 4H, 2 x CH_2), 2.37 (s, 3H, =C-CH_3), 4.05 (q, J = 6.7 Hz, 2H, OCH_2), 4.97 (s, 1H, Ar-CH), 6.36 (s, 1H, NH), 6.69 (d, J = 8.3 Hz, 1H, Ar-H), 7.01-7.16 (m, 2H, 2 x Ar-H), 7.36 (d, J = 8.3 Hz, 1H, Ar-H); MS: m/z = 385 $(M + H)^+$.

RESULTS AND DISCUSSION

The catalyst Cu nps/clinoptilolite natural zeolite was prepared by doping Cu nanoparticles into the clinoptilolite zeolite. The catalyst was used to synthesize polyhydroquinoline derivatives. At the outset, the synthesis of compound 5c was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by refluxing a mixture of 4-chlorobenzaldehyde, dimedone, ethylacetoacetate, and ammonium acetate in the presence of the catalyst in an ethanol medium. Firstly, we increased the amount of catalyst from 0.01, 0.015, 0.02, 0.025, 0.03 g and checked the yield of product obtained, and we saw that the efficiency of the reaction is affected mainly by the amount of catalyst. 0.03 g of catalyst was effective for the synthesis of compound 5c. The results are summarized in Table 1.

The same model reaction in the presence of 0.03 g of catalyst was carried out in different solvents to assess the effect of solvent on the reaction yield. As shown in Table 2, the yield of the reaction was higher in ethanol. Subsequently, all reactions were carried out using 0.03 g of catalyst and in ethanol. The results given in Table 3. All the products obtained by changing the aromatic aldehyde were of good to excellent yield.

To explore the recyclability of the catalyst, it was filtered off at the end of the reaction, washed with a mixture of hot ethanol and water, dried, and activated at 300 °C for 1 hr. The catalyst was reused as such for subsequent experiments (up to five cycles) under similar reaction conditions, and the change in its catalytic activity was studied with respect to time and percentage yield (Table 4).

Table 1. Effect of Catalyst amount on the model reaction.

Entry	Catalyst (g)	Time (Min)	Yield (%)
1	None	180	No reaction
2	0.01	45	67
3	0.015	45	78
4	0.02	40	86
5	0.025	40	91

6	0.03	30	95
7	0.035	30	95

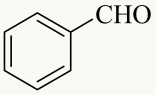
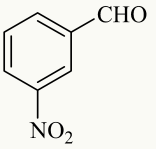
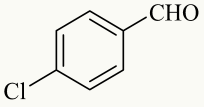
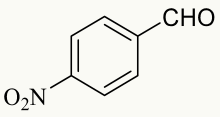
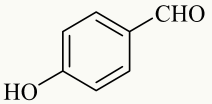
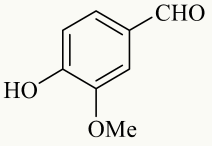
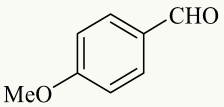
The yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product.

Table 2. Synthesis of compound 5a in the presence of 0.03 g Cu nps/clinoptilolite zeolite.

Entry	Solvent	Time (Min)	Yield (%)[a]
1	EtOH	30	95
2	MeOH	60	81
3	CH_3CN	45	73
4	CH_2Cl_2	45	85

The yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product.

Table3. Cu NPs/clinoptilolite zeolite-catalyzed synthesis of polyhydroquinoline derivative.

Compound	**Aromatic aldehyde**	**Time (min)**	**Yield (%)[a]**	**M.P. (°C)**
5a		40	94	252-253
5b		45	90	175-177
5c		30	95	248-249
5d		50	92	240-241
5e		55	91	248-249
5f		40	94	233-234
5g		35	92	245-246

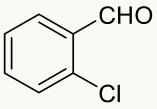
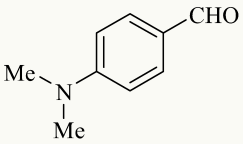
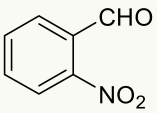
5h		40	93	210 -211
5i		35	96	261-262
5j		50	90	211-212

Table 4. Recyclability test of Catalyst on model reaction.

Entry	Yields (%)[a]
1	95
2	95
3	94
4	93
5	93

The yields were calculated based on 4-chlorobenzaldehyde and refer to the pure isolated product.

CONCLUSION:

Cu-doped clinoptilolite is superior to pure clinoptilolite because it combines the high surface area, ion-exchange capacity, porosity, and stability of the zeolite with the Lewis acidity, redox properties, and catalytic activity of copper species. This synergistic combination results in faster reactions, higher product yields, better selectivity, enhanced recyclability, and improved catalyst stability, making Cu Nps/clinoptilolite an excellent heterogeneous catalyst for organic transformations such as the synthesis of polyhydroquinoline derivatives.

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