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CuI Nanoparticles as a Reusable Heterogeneous Catalyst for the One-Pot Synthesis of N-Cyclohexyl-3-aryl-quinoxaline-2-amines Under Mild Conditions

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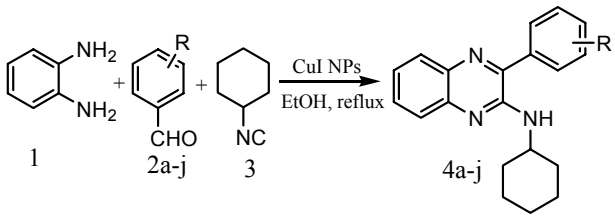
Abstract

CuI nanoparticles as an expedient and recyclable catalyst for the synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines in ethanol via a multi-component reaction are established. The products were separated from the catalyst simply by filtration. The catalyst could be recycled and reused for several times without noticeably decreasing the catalytic activity.

1. Introduction

Transition-metal catalyzed organic reactions are often considered to follow the principles of green chemistry; these catalyzed reactions consume a minimum of energy and reagents or auxiliaries and minimize waste. Nanocatalysts are considered to be a bridge between homogeneous and heterogeneous catalysis [1]. With the development of nanochemistry it has been possible to prepare soluble analogous of heterogeneous catalysts, materials that might have properties intermediate between those of bulk and single particles due to high surface areas and high densities of active sites [2]. Nanoparticles can be utilized as a suitable catalyst in organic reactions due to their high surface-to-volume ratio, which provides a larger number of active sites per unit area in comparison to their heterogeneous counterparts [3]. CuI nanoparticles indicated a significant level of performance as catalysts in

terms of reactivity, selectivity, and better yields of products [4-6]. Multicomponent reactions (MCRs) are highly important transformations due to their capacity to combine three or more substrates into a single target in one operation [7-11]. MCRs typically achieve a substantial increase in molecular complexity and offer chance for diversity-oriented synthesis. They have proven to be costly in drug discovery [12], as well as in the total synthesis of natural compounds [13-15]. This method is an alternative path to decrease drastic requirements for reactions, and also have efficient, facile and non-contaminating properties that reduce the use of expensive and toxic reagents [16]. The demand for environmentally benign procedure with heterogeneous reusable catalyst promoted us to develop a safe alternate method for the synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines using o-phenylenediamine, aromatic aldehydes, and cyclohexyl isocyanide in the presence of nano CuI (Scheme 1). In the view of recent interest in the use of heterogeneous nanocatalysts we have developed CuI NPs as heterogeneous, recyclable, eco-friendly and cheap catalyst which can be used in many organic reactions.



Scheme 1. Synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines using CuI nanoparticles under mild conditions.

2. Experimental

2.1 Materials and characterization

The products were isolated and characterized by physical and spectral data. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 MHz spectrometers in the presence of tetramethylsilane as internal standard. The IR spectra were recorded on FT-IR Magna 550 apparatus using with KBr plates. Melting points were determined on Electro thermal 9200, and are not corrected. CuI nanoparticles were obtained according to the method reported in the literature [17]. Microscopic morphology of products was visualized by SEM (LEO 1455VP). Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatized Cu Kα radiation (λ = 1.5406 Å).

2.2. Synthesis of CuI nanoparticles

The catalyst was prepared by ultrasonic irradiation approach. $CuSO_4$ was used as the Cu source. Firstly the copper substrate (1mmol) is ultrasonically cleaned for 20 sec in acetone and then in a 2M HCl solution, followed by repeated rinsing with distilled water. After drying, the substrate is dipped slowly into a solution of KI (2mmol) in 40 mL of distilled water and sonicated to react for 30 min. When the reaction was completed, gray precipitate was obtained. The solid was filtered and washed with distilled water, ethanol and dried at room temperature for 48 h.

The XRD pattern of the CuI nanoparticles is shown in Figure 1. All reflection peaks can be readily indexed to pure cubic crystal phase of Nano copper iodide as shown in figure 1.

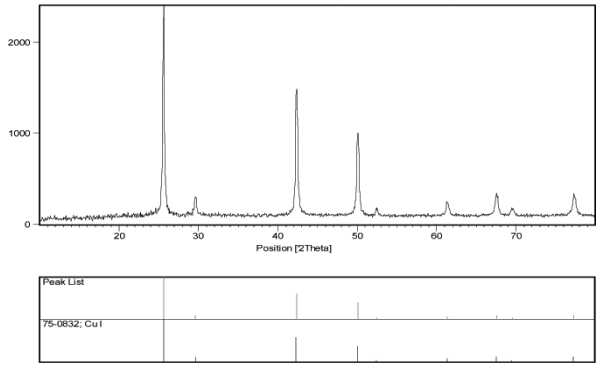


Fig. 1. The XRD pattern of copper iodide nanoparticles

Also no specific peaks due to any impurities were observed. The crystallite size diameter (D) of the CuI nanoparticles has been calculated by Debye–Scherrer equation ($D = K\lambda/\beta\cos\theta$), where β FWHM (full-width at half-maximum or half-width) is in radians and θ is the position of the maximum of diffraction peak, K is the so-called shape factor, which usually takes a value of about 0.9, and k is the X-ray wavelength (0.4723 Å for Cu Kα). Crystallite size of copper iodide has been found to be 20 nm.

In order to investigate the morphology and particle size of CuI nanoparticles, SEM image of CuI nanoparticles was presented in Figure 2. These results show that spherical CuI nanoparticles were obtained with an average diameter of 10-30 nm as confirmed by XRD analysis.

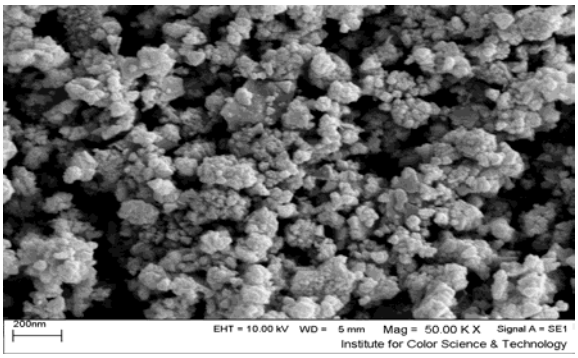


Fig. 2. SEM images of CuI nanoparticles**.**

2.3. General procedure for the preparation of N-cyclohexyl-3-aryl-quinoxaline-2-amines

A solution of o-phenylenediamine (2 mmol), aldehyde (2 mmol), cyclohexyl isocyanide and CuI NPs (5 mol %), in ethanol (3 mL) was stirring under reflux for appropriate times. During the procedure the reaction was monitored by TLC. After completion, the reaction mixture was filtrate until heterogeneous catalyst was recovered. The filtrate solution was evaporated and washed with cold chloroform to afford pure N-cyclohexyl-3-aryl-quinoxaline-2-amines.

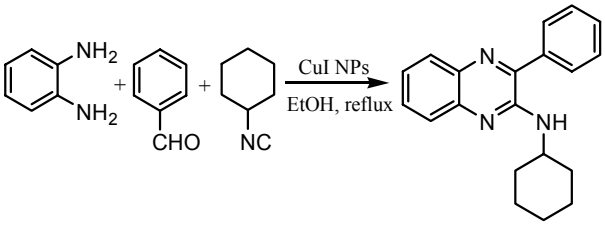
All of the products were characterized and identified with m.p., ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopy techniques. Spectral data of new compounds are given below:

N-Cyclohexyl-3-(4-fluorophenyl)-quinoxaline-2-amine (4e): Mp ^{o}C: 185-187. ^{1}H NMR (400 MHz, DMSO-d_6): δ: 1.15–2.18 (m, 10H), 3.51 (m, 1H), 4.47 (s, 1H, NH), 7.40–8.42 (m, 8H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6); δ: 23.34, 26.15, 33.71, 52.18, 127.32, 128.82, 128.55, 129.73, 130.15, 131.19, 132.67, 133.39, 134.51, 138.57, 141.22, 142.67, 148.87, 150.99; IR (KBr) *v*: 3155, 1629, 1620 cm^{-1}.

N-Cyclohexyl-3-(3-methylphenyl)-quinoxaline-2-amine (4i): Mp ^{o}C: 192-194. ^{1}H NMR (400 MHz, DMSO-d_6): δ: 1.18–2.37 (m, 10H), 2.66 (s, 3H), 3.38 (m, 1H), 4.41 (s, 1H, NH), 7.25–8.31 (m, 8H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6); δ: 24.13, 25.57, 30.17, 39.84, 52.51, 126.67, 128.51, 128.47, 129.97, 130.74, 131.27, 134.17, 138.56, 141.97, 141.09, 142.97, 150.93. IR (KBr) *v*: 3160, 1641, 1623 cm^{-1}.

3. Results and discussion

In our initial experiments, the standard reaction conditions were established based on the reactions of benzaldehyde, o-phenylenediamine, and cyclohexyl isocyanide was chosen as the model reaction for the synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amine derivatives (Scheme 2).



Scheme 2. The model reaction for the synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines in the presence of CuI NPs.

This reaction was carried out using the aprotic (Table 1, entries 1, 2) and protic solvents (Table 1, entries 3-5). The best result was obtained in ethanol (Table 1, entry 5).

Next, we studied the model reaction in ethanol at different temperatures (Table 1, entries 5,6). The maximum yield was obtained at reflux conditions (Table 1, entry 5) as the reaction rate increased by raising temperature**.**

The model reaction in ethanol at reflux was also studied using much type of catalysts (Table 1, entries 6-12). In absence of catalyst, the reaction did not progress at all (Table 1, entry 13). Notably, CuI NPs shows an activity higher than those of reported heterogeneous, we believe that nano copper iodide surface chemistry plays an important role in this reaction**.** The best results were obtained with 5 mol% of CuI NPs (Table 1, entry 11).

The study was then extended to the application of CuI NPs in synthesis of substituted N-cyclohexyl-3-aryl-quinoxaline-2-amines of various aldehydes with o-phenylenediamine, and cyclohexyl isocyanide. The best result was obtained in model reaction at reflux and at the presence of CuI NPs 5 % mol. The results are listed in Table 2.

Table 1. Optimization of the model reaction by using various catalysts and solvents.[a]

Entry	Solvent /condition	Catalyst (mol%)	Time (h)	Yield, (%)[b]
1	MeCN/reflux	CuI (10%)	3	66
2	CH_2Cl_2/reflux	CuI (10%)	3	53
3	H_2O/reflux	CuI (10%)	3	31
4	EtOH/reflux	CuI (10%)	3	67
5	EtOH /reflux	CuI (10%)	3	74
6	EtOH /rt	CuI (10%)	3	72
7	EtOH /reflux	ZnO (15%)	2.5	79
8	EtOH /reflux	I_2 (15%)	3	70
9	EtOH /reflux	$InCl_3$ (20%)	3	68
10	EtOH /reflux	CuI NPs (2%)	2	92
11	EtOH /reflux	CuI NPs (5%)	2	95
12	EtOH /reflux	CuI NPs (8%)	2	93
13	EtOH/reflux	none	4	trace

[a]benzaldehyde (2 mmol), o-phenylenediamine (2 mmol), and cyclohexyl isocyanide (2 mmol).
[b]Isolated yields.

Catalyst recovery

The recovered catalyst from the experiment was washed by acetone (3×5 mL). Then, it was dried and used in the synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines. Then the catalyst was recycled for four times. The separated catalyst was used several times with a slightly decreased activity.

Table 2. Synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines catalysed by copper iodide nanoparticles.

Product	R	Time (min)	Yield[a]	M.p (°C)
4a	H	120	95	185-187[18]
4b	4-Cl	115	94	190-192[18]
4c	4-Me	122	92	199-201[18]
4d	4-OMe	125	90	177-179[18]
4e	4-F	118	95	185-187
4f	4- NO_2	120	91	207-209[18]
4g	3-NO_2	130	87	193-195[18]
4h	4-OH	120	92	174-176[18]
4i	3-Me	125	86	192-194

[a] Isolated yields.

4. Conclusion

In summery we offer a simple and efficient protocol in one-pot procedures for the synthesis of N-cyclohexyl-3-aryl-quinoxaline-2-amines under reflux that was catalysed by 5% mol of CuI NPs. The catalyst was very mild, neutral, reusable and environmentally benign. Also it is very effective for the high surface- to-volume ratio. The products were also formed in excellent yields with short reaction times. This method have several advantages, such as omitting toxic catalysts, simple work-up and needs no chromatographic method for the purification of products.

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