http://dx.doi.org/10.5012/bkcs.2012.33.8.2679

# CuI Nanoparticles as New, Efficient and Reusable Catalyst for the One-pot Synthesis of 1,4-Dihydropyridines

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*Received May 5, 2012, Accepted May 16, 2012*

A simple one-pot synthesis of two derivatives of 1,4-dihydropyridines has been described under reflux conditions using copper iodide nanoparticles (CuI NPs) as a catalyst in high yields. This method demonstrated four-component coupling reactions of aldehydes and ammonium acetate *via* two pathways. In one route, the reaction was performed using 2 eq ethyl acetoacetate while in the other one 1 eq ethyl acetoacetate and 1 eq malononitrile were used. The CuI NPs was reused and recycled without any loss of activity and product yield. It is noteworthy to state that wide range of the 1,4-dihydropyridines have attracted large interest due to pharmacological and biological activities.

**Key Words :** 1,4-Dihydropyridines, Copper iodide nanoparticles, Multicomponent

## Introduction

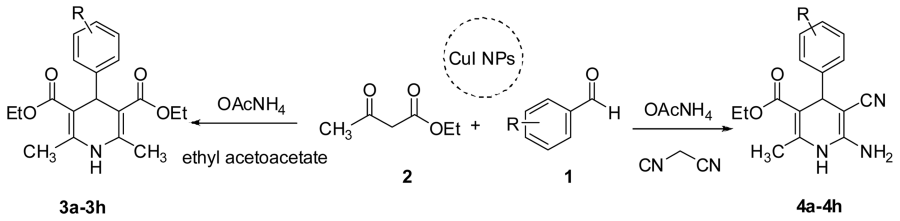
1,4-Dihydropyridines (1,4-DHPs), possess a range of biological activities such as a group of calcium modulators bronchodilator, vasodilator, antiatherosclerotic, geroprotective hepatoprotective, antitumor and antidiabetic agents.[1-4] The various activities of 1,4-DHPs derivatives frequently derives from the functional groups substituted on the 1,4-dihydropyridines moiety.[5] On the other hand, multicomponent reactions have become highly popular in the discovery of biologically active new compounds due to their quite simple experimentation, atom economy and high yields of the products.[6,7] The effective strategy offers considerable advantages over classical stepwise methods, allowing the formation of several bonds and the construction of complex molecules from simple precursors in a single synthetic procedure without the essential requirement for isolation of intermediates.[8] 1,4-DHPs are broadly synthesized using Hantzsch method,[9] that involves one-pot cyclocondensation of dicarbonyls, aldehydes and ammonium acetate/primary amine/ammonia either in reuxing with acetic acid or alcohol leading to low yields with longer reaction time.[10] In recent decades, numerous modified approaches have been developed.[11-17] All methods, however, are associated with some drawbacks such as longer time, unsatisfactory yields, difficulty in handling of reagents. Hence, the development of an efficient method seemed to be of prime importance. Consequently, we targeted to alter the reaction of Hantzsch 1,4-DHPs to make it more convenient and extremely efficient. 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.[18] CuI NPs indicated a significant level of performance as catalysts in terms of reactivity, selectivity, and better yields of products.[19-21]

Therefore, a well-organized and simple method for the synthesis of 1,4-DHP derivatives is reported by using CuI NPs as catalyst (Scheme 1).

## Results and Discussion

The synthesis involved in the Hantzsch condensation of 1,4-DHPs started from the reactions of diversely substituted aromatic and heteroaromatic aldehydes with β-ketoester and ammonium acetate in ethanol under reflux in the presence of CuI NPs as catalyst (Scheme 1). In order to broaden the scope of the present method, the replacement of 1 eq malononitrile with β-ketoester was examined. To find the best experimental conditions we started the investigations by performing this reaction at different conditions of solvents, temperature and catalysts.

These reactions were pursued with different groups of solvents such as aprotics and protics (Table 1, entry 1-5).




**Scheme 1**

**Table 1.** Optimization of reaction conditions for the synthesis of 1,4-DHPs

| Entry | Solvent/ condition | Catalyst (mol %) | Time (min) | Yield **3b/4b**[a] (%) |
|---|---|---|---|---|
| 1 | MeCN/reflux | CuI (10%) | 60 | 62/65 |
| 2 | $CH_2Cl_2$/reflux | CuI (10%) | 60 | 48/49 |
| 3 | $H_2O$/reflux | CuI (10%) | 60 | 26/31 |
| 4 | MeOH/reflux | CuI (10%) | 50 | 76/78 |
| 5 | EtOH/reflux | CuI (10%) | 40 | 80/83 |
| 6 | EtOH/rt | CuI (10%) | 120 | 40/40 |
| 7 | EtOH/reflux | $FeCl_3$ (15%) | 80 | 70/72 |
| 8 | EtOH/reflux | MgO (15%) | 80 | 73/75 |
| 9 | EtOH/reflux | $InCl_3$ (20%) | 80 | 70/71 |
| 10 | EtOH/reflux | CuI NPs (5%) | 20 | 92/94 |
| **11** | **EtOH/reflux** | **CuI NPs (2%)** | **15** | **94/96** |
| 12 | EtOH/reflux | CuI NPs (1%) | 25 | 84/88 |
| 13 | EtOH/reflux | none | 40 | trace |

[a]Isolated yield.

Obviously, the polar protic solvents such as ethanol were more suitable than nonpolar solvents (Table 1, entry 5). Also the reaction was investigated at different temperatures with ethanol as a suitable solvent in which the best yields were obtained at 80 °C (Table 1, entry 5, 6). The reaction was carried out in aforementioned optimized conditions by a variety of catalysts. The best result was obtained in the presence of 2% mol CuI NPs (Table 1, entry 11). It should be noted that the reaction did not proceed without any catalyst (Table 1, entry 13). The results show that heterogeneous nanoparticles have a considerable potential to be applied as catalysis in organic synthesis. In view of environmentally-friendly methodologies, reuse and recovery of the CuI NPs are highly desirable. The reusability of CuI nanoparticles was experienced under similar reaction conditions for 5 times and no significant loss of activity performance was observed (Figure 1).

The SEM image shows particles with diameters in the range of nanometers (Figure 2).

The study was then extended to the application of CuI NPs in synthesis of substituted 1,4-dihydropyridines of various aldehydes, ammonium acetate with ethyl acetoacetate or malononitrile and ethyl acetoacetate. The best result was obtained in model reaction at reflux and at the presence of

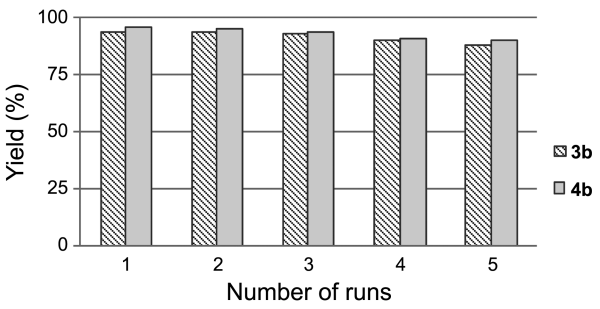



**Figure 1.** Reusability of CuI-nanoparticles catalyst for the preparation of **3b** and **4b**.

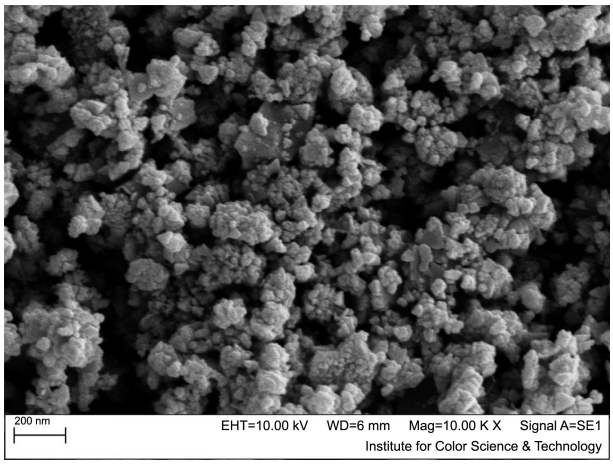
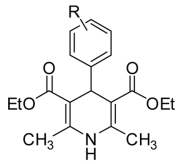
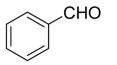
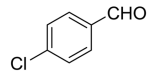
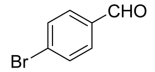
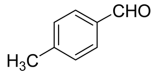
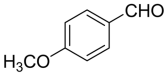
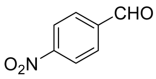
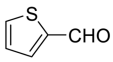
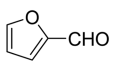



**Figure 2.** SEM image of the CuI NPs catalyst.

**Table 2.** CuI nano particles catalyzed four-component synthesis of substituted 1,4-dihydropyridines



**3a-3h**

| Product[a] | Aldehyde | Time (min) | Yield (%)[b] | mp (°C)[Ref] Found | Reported |
|---|---|---|---|---|---|
| **3a** |  | 18 | 88 | 158-160 | 156-158[22] |
| **3b** |  | 15 | 94 | 147-148 | 145-147[22] |
| **3c** |  | 17 | 92 | 146-148 | 148-150[22] |
| **3d** |  | 20 | 87 | 138-140 | 136-138[22] |
| **3e** |  | 16 | 90 | 160-162 | 158-160[22] |
| **3f** |  | 20 | 93 | 129-131 | 130-132[22] |
| **3g** |  | 20 | 90 | 170-172 | 172-174[22] |
| **3h** |  | 0 | 91 | 161-162 | 160-162[22] |

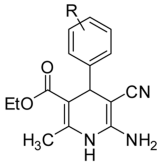
[a]All products were characterized from their melting points and spectroscopic ($^1$H NMR and $^{13}$C NMR) data and compared with authentic samples. [b]Isolated yield

CuI NPs 2% mol. These results obviously indicated in Table 2, 3.

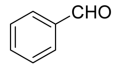
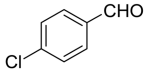
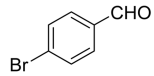
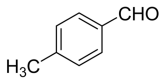
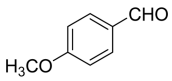
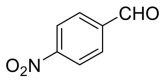
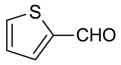
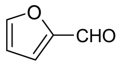
## Conclusions

In summary we offer a simple and efficient protocol in one-pot procedures for the synthesis of 1,4-DHPs under

**Table 3.** CuI nano particles catalyzed four-component synthesis of substituted 1,4-dihydropyridines



**4a-4h**

| Product[a] | Aldehyde | Time (min) | Yield (%)[b] | mp (°C)[Ref] Found | Reported |
|---|---|---|---|---|---|
| **4a** |  | 17 | 92 | 188-190 | 190-192[23] |
| **4b** |  | 15 | 96 | 188-200 | 202-204[24] |
| **4c** |  | 16 | 92 | 199-201 | 197-199[24] |
| **4d** |  | 18 | 88 | 221-223 | 220-222[24] |
| **4e** |  | 16 | 90 | 189-190 | 188-190[24] |
| **4f** |  | 18 | 91 | 173-175 | 175-176[23] |
| **4g** |  | 20 | 89 | 208-209 | 206-208[24] |
| **4h** |  | 20 | 88 | 203-204 | 204-205[23] |

[a]All products were characterized from their melting points and spectroscopic ($^1$H NMR and $^{13}$C NMR) data and compared with authentic samples. [b]Isolated yield

reflux that was catalyzed by 2% 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.

## Experimental Section

All reagents were purchased from Merck (Germany) and were used without further purification. Melting points were determined on Electro thermal 9200, and are not corrected. Infrared (IR) spectra were recorded using a FT-IR Magna 550 apparatus using with KBr plates. $^1$H NMR and $^{13}$C NMR spectra were recorded with a Bruker Avance-400 MHz respectively. NMR spectra were obtained in $CDCl_3$ and DMSO-$d_6$ solutions and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. Microscopic morphology of products was visualized by SEM (LEO 1455VP).

**Preparation of Copper Iodide Nanoparticle.** The catalyst was prepared by ultrasonic irradiation approach. $CuSO_4$ was used as the Cu source. Firstly the copper substrate (1 mmol) was ultrasonically cleaned for 20 sec in acetone and then in a 2 M HCl solution, followed by repeated rinsing with distilled water. After drying, the substrate is dipped slowly into a solution of KI (2 mmol) in 40 mL of distilled water and sonicated to react for 30 min. When the reaction was completed, a gray precipitate was obtained. The solid was filtered and washed with distilled water and dried.[25]

**General Procedure for the Preparation of 1,4 Dihydropyridine Derivatives (3a-3h).** 50 mL round bottomed flask was successively charged with aldehydes **1** (2 mmol), ethyl acetoacetate **2** (4 mmol), ammonium acetate (2 mmol), and CuI NPs (2 mol %) as catalyst, in ethanol (5 mL). The mixture was vigorously stirred at 80 °C. After completion of the reaction (monitored by TLC), the reaction mixture being cooled to room temperature was poured into cold water and extracted with ethyl acetate. The organic layer was washed with brine and water and dried over $Na_2SO_4$. Then solvent was evaporated, the crude products were puried by crystallization from ethanol to afford 1,4-dihydropyridines in 87-94% yields.

**General Procedure for the Preparation of 1,4 Dihydropyridine Derivatives (4a-4h).** 50 mL flask was charged with aldehydes **1** (2 mmol), ethyl acetoacetate **2** (2 mmol), malononitrile (2 mmol), and CuI NPs (2 mol %) as catalyst, in ethanol (5 mL). The mixture was vigorously stirred at 80 °C. After complecation of the reaction (monitored by TLC), the reaction mixture being cooled to room temperature was poured into cold water and extracted with ethyl acetate. The organic layer was washed with brine and water and dried over $Na_2SO_4$. Then solvent was evaporated, the crude yellow products were purified by crystallization from ethanol to afford 1,4-dihydropyridines in 88-96% yields.

**Acknowledgments.** The authors are grateful to University of Kashan for supporting this work by Grant NO: 159196/II.

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