Three-component reaction in 1,4-dihydropyridine synthesis catalyzed by Copper(I) Iodide nanoparticles

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Abstract. We have synthesized two 1,4-dihydropyridine derivatives via one-pot three-component reaction. The reactions were catalyzed by copper(I) iodide nanoparticles with crystallite size of 78.4 nm. Formations of cyclocondensation products were confirmed by Fourier Transform Infrared (FTIR), UV-Vis and Gas Chromatography-Mass Spectrometry (GC-MS) spectra.

Keywords: 1,4-dihydropyridine, multicomponent reaction, CuI.

1. Introduction

Nitrogen-containing six-membered heterocycles are valuable in the field of pharmaceutical and biological chemistry [1]. Specifically, 1,4-dihydropyridines (DHPs) are known to show various pharmacological activities such as calcium-channel blockers [2], antihypertensive [3], antianginal [4], antitumor [5], anticancer [6] and anti-inflammatory [7] activities. Other importances in medicinal chemistry are found to be reported such as antitubercular [8], analgesic [9], and platelet aggregation inhibitory [10] actions. Flashing back to more than one hundred years ago, the core structure of DHP was first synthesized by Hantzsch in 1882, which involves multicomponent cyclocondensation of aldehyde, ammonia and β-ketoester [11]. The Hantzsch method generally performed either in acetic acid or under reflux in alcohols for lengthy reaction times [11]. Due to the interesting and significant biological activities, considerable efforts have been developed to provide more efficient protocols for the synthesis of DHPs [12].

In the modern era of organic synthesis, there is an elevating awareness of clamant necessity to confine the use of harmful chemicals as well as harsh reaction protocols, also generation of by-products, which can decrease atom economy [13]. Multicomponent reactions (MCRs) are one-pot syntheses employing three or more reactants and incorporating all their skeletons or sub-skeletons to furnish products with interesting structural motifs [14,15]. They are powerful tools for efficient production of molecular diversity in a single reaction [16]. In the literature, many organic/ inorganic materials have been reported to catalyze MCRs in DHPs synthesis, such as various ionic liquids [17–20], CuSO4/chitosan [21], bismuth nitrate [22] and cellulose/sulfuric acid [23]. Although most of them showed appreciable performance, some reported methods still have one or more drawbacks like dangerous solvents, expensive reagents, tedious work-up after reaction, long time and high temperature [24]. Hence, the search of new method or catalyst that could be superior in this reaction is still highly required. In the present work, we report preparation of copper(I) iodide nanoparticles and its ability in synthesis of two DHP derivatives.

2. Materials and methods

2.1. Materials
Cinnamaldehyde, benzaldehyde, and other chemicals including solvents were analytical grade, used without further purification. TLC was performed on silica gel 60 F<sub>254</sub>. Catalyst morphology and crystallinity were studied using Scanning Electron Microscope-Energy Dispersive X-Ray Analysis (SEM-EDX) and X-ray Diffractometer (XRD), respectively. Presence of functional groups was analyzed on Shimadzu Prestige-21 Fourier Transform Infrared (FTIR) spectrophotometer. Beside FTIR, organic products were also identified by UV-Vis and Gas Chromatography and Mass Spectrometry (GC-MS) instruments.

2.2. Methods

2.2.1. Preparation of CuI nanocatalyst. The catalyst was prepared by ultrasonic irradiation approach. Copper(II) sulfate was used as precursor. First, copper(II) sulfate (1 mmol) was ultrasonically cleaned for 20 sec in acetone, then in 2M hydrochloric acid, followed by repeated rinsing with distilled water. After drying, precursor was added into potassium iodide solution (2 mmol in 40 mL distilled water). The mixture was sonicated for 30 min obtained grey precipitates were filtered, washed with distilled water and dried in vacuum between room temperature to 40 ºC [25].

2.2.2. Synthesis of 1,4-DHPs. In a 20 mL round-bottom flask integrated with cooling system, a mixture of benzaldehyde (2 mmol), ethyl acetoacetate (4 mmol), ammonium acetate (2 mmol) and 5 mL ethanol as solvent was stirred in the presence of various amount of CuI nanoparticles (varying from 0–10 mol%). The reaction mixture was cooled to room temperature then extracted with ethyl acetate. Organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. After evaporation, crude product was purified by recrystallization from hot ethanol to afford compound 1a, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate. Compound 1b, (E)-diethyl-2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate was synthesized by employing cinnamaldehyde instead of benzaldehyde, applying the best condition obtained from optimization of reaction conditions in synthesis of compound 1a.

3. Results and discussion

3.1. Characterization of CuI nanoparticles
Copper(II) sulfate and potassium iodide react in oxidation-reduction manner. Iodide acts as reducing agent, whereas Cu(II) as oxidizing agent. After mixing the precursors, grey to brown powder as product was expected to be the mixture of CuI, I<sub>2</sub> and potassium sulfate [26]. The solid was washed several times with distilled water and ethanol. Copper(I) iodide nanoparticles were first characterized by FTIR (figure 1). Two bands at 667 and 459 cm<sup>-1</sup> are characteristics of CuI samples. Broadband around 3600-3400 cm<sup>-1</sup> is attributed to intermolecular hydrogen bonding presents in residual water. These observations are in agreement with previous work by Humud et al. [27].
Characterization using SEM shows surface morphology of the CuI nanoparticles (figure 2a). It can be seen that most of them were found to have spherical shape. The particles are well dispersed and distributed equally in all directions. However, little agglomeration of the particles was also observed, resulting larger size irregular shape of some copper(I) iodide particles. EDX result in figure 2b shows elemental composition of the sample. Atom percentage of Cu and I was found to be 49.06 and 50.94 %, respectively. In the spectrum, it was found only peaks of Cu and I, absent of any other elements. This result signifies that copper(I) iodide nanoparticles was obtained in pure.

XRD pattern of CuI sample is depicted in figure 3. The crystal structure of the sample was determined by comparing its diffraction degree with literature (JCPDS Card No. 06-0246). The sample has diffraction peaks at 2θ of 25.7°, 29.7°, 42.4°, 50.2°, 52.5°, 61.4°, 67.6°, 69.6°, 77.6° and 83.0°. No other diffraction peaks arising in the XRD pattern, so it indicates the high phase purity of the sample [28]. The crystallite size diameter (D) of the sample was calculated by Debye-Scherrer equation (D = Kλ/βcosθ) and found to be 78.4 nm.

3.2. Synthesis of 1,4-DHPs
Benzaldehyde was chosen as model substrate for the optimization study and subjected for three-component reaction in the presence of different CuI nanoparticles amount. Initially, control reaction was conducted in the absence of catalyst, which provides product in 27% yield only (table 1). It is
Table 1. Optimization of reaction conditions in synthesis of compound 1a

| Entry | CuI catalyst (mol%) | Solvent     | Time (min) | Yield (%) |
|-------|---------------------|-------------|------------|-----------|
| 1     | None                | Ethanol     | 40         | 27        |
| 2     | 2                   | Ethanol     | 40         | 46        |
| 3     | 5                   | Ethanol     | 40         | 70        |
| 4     | 10                  | Ethanol     | 40         | 67        |
| 5     | 10                  | Water       | 40         | 67        |
| 6     | 10                  | Solvent-free| 40         | 27        |
| 7     | 10                  | Ethanol     | 80         | 49        |
| 8     | 10                  | Ethanol     | 120        | 85        |
| 9     | 10                  | Ethanol     | 180        | 73        |

- benzaldehyde (1 mmol), ethyl acetoacetate (4 mmol), NH$_4$OAc (2 mmol), solvent (5 mL)
- isolated yield

Figure 4. GC-MS spectra of compound 1a

noteworthy that the yield of compound 1a was increased up to 70% with higher catalyst amount (table 1, entry 2–4). Employing water as solvent instead of ethanol yielded 67% of product, slightly lower than that of ethanol. Unfortunately, the yield obtained only 27% when reaction was performed under solvent-less condition. Prolonging time up to 120 min gave the best result, product 1a was found to be 85% (table 1, entry 8). However, after 180 min reaction, the product was slightly decreased to 73%. It can be presumed that the product is slightly less stable under this condition. Having established the best condition, we further synthesized compound 1b under same condition. Yield of 1b was found to be 90%.

Organic products were first characterized by FTIR. Compound 1a has some important absorption. A sharp peak at 3342 cm$^{-1}$ indicating the presence of N-H vibration (secondary amine). Peaks at 1652 and 1213 cm$^{-1}$ are attributed to the C=O and C-O vibration, respectively. Compound 1b has maximum wavelength at 354 nm. GC-MS spectra of compound 1a are depicted in figure 4. It confirmed the formation of desired product with molecular cation value of 329.2. Meanwhile, like 1a, compound 1b shows N-H absorption band at 3337 cm$^{-1}$, C=O vibration at 1651 cm$^{-1}$ and C-O at 1223 cm$^{-1}$. Lambda maximum for 1b was found to be 353 nm. From GC-MS, molecular cation of 355.1 was observed, indicating the formation of desired product (figure 5). To test the reusability of catalyst, we have also performed reactions using recycled catalyst. For first run, 85% yield of product was obtained. After separation, copper(I) iodide nanocatalyst was washed with ethanol and dried under vacuum. Then, it is used for next three consecutive reactions under same condition. Yields were found to be 73, 61 and 49% for second, third and fourth run, respectively. The result indicated that the catalyst could be reused for 4 consecutive experiments with partial loss of catalytic activity.
4. Conclusions
We have successfully prepared copper(I) iodide nanoparticles by oxidation-reduction method with the help of ultrasonic irradiation. The material was successfully used to catalyze three-component reaction in synthesis of two derivatives of 1,4-DHPs.

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