

## Study of Fe<sub>2</sub>O<sub>3</sub>, CuO, ZnO as efficient catalysts for Hantzsch reaction under different conditions

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**Abstract:** 1,4-dihydropyridine derivatives one-pot synthesis under different condition was described. CuO nanoparticle as a catalyst in microwave irradiation (100w) gives product with excellent yields ( $\geq 87\%$ ) and short reaction time. No significant difference was observed between the obtained yield by using ZnO and Fe<sub>2</sub>O<sub>3</sub>.

**Keywords:** 1,4-Dihydropyridine, ultrasonic, Microwave irradiation, nanoparticle, catalyst.

### Introduction

Multicomponent reactions (MCRs) are one-pot processes that combine three or more substrates simultaneously<sup>1</sup>. The Hantzsch<sup>2</sup> reaction and their products 1,4-dihydropyridines (1,4-DHP) have attracted immense attention of synthetic chemists due to their pharmacological properties<sup>3</sup>. 1,4-Dihydropyridines (1,4-DHPs) heterocyclic rings are a common feature of various bioactive compounds such as vasodilator, bronchodilator, anti-atherosclerotic, anti-cancer and anti-diabetic agents<sup>4</sup>. They serve as key intermediates in biogenesis of indole alkaloids<sup>5</sup>. Additionally, 1,4-DHPs have several other medicinal applications which include neuroprotecting<sup>6</sup> and cerebral anti-ischemic properties<sup>7</sup>. Classical method for the synthesis of these compounds is one-pot condensation of aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol<sup>8</sup>. This method suffer from several disadvantages such as long reaction time, harsh refluxing condition, excessive use of volatile organic solvents and low yields. Due to the wide range of their applications other improved procedures have been subsequently reported include the condensation of aldehyde with  $\beta$ -dicarbonyl compounds and amines in the presence of different catalysts and solvents<sup>9</sup>.

Metal oxide based nanocatalyst have attracted much attention in the fields of catalysis, separation, optoelectronics, active adsorbents for gases, magnetism, and microelectronics owing to their unique physical and chemical properties<sup>10</sup>. Nanocatalysis is interesting area in organic synthesis as it provides not only an alternative to homogeneous catalysis but also has the advantage of highly porous, large surface area, minimum quantity requirement, recycling and mild reaction conditions<sup>11</sup>.

In recent years, several new efficient methods for 1,4-DHPs synthesis, have been developed including the use of metal triflates<sup>12</sup>, I<sub>2</sub><sup>13</sup>, CAN<sup>14</sup>, PPh<sub>3</sub><sup>15</sup>, L-proline<sup>16</sup>, PPA-SiO<sub>2</sub><sup>17</sup>, La<sub>2</sub>O<sub>3</sub><sup>18</sup>, and Nickel nanoparticle<sup>19</sup>. In the course of our studies for the metal catalyzed alkylation of 1,3-dicarbonyl compounds<sup>20,21</sup> and development of useful synthetic methodologies, we have designed and synthesized a series of 1,4-dihydropyridine derivatives by Hantzsch reaction in the presence of micro and nano-sized Fe<sub>2</sub>O<sub>3</sub>, CuO and ZnO as catalyst, under thermal, ultrasonic waves and MW irradiation (Scheme 1).

### Results and Discussion

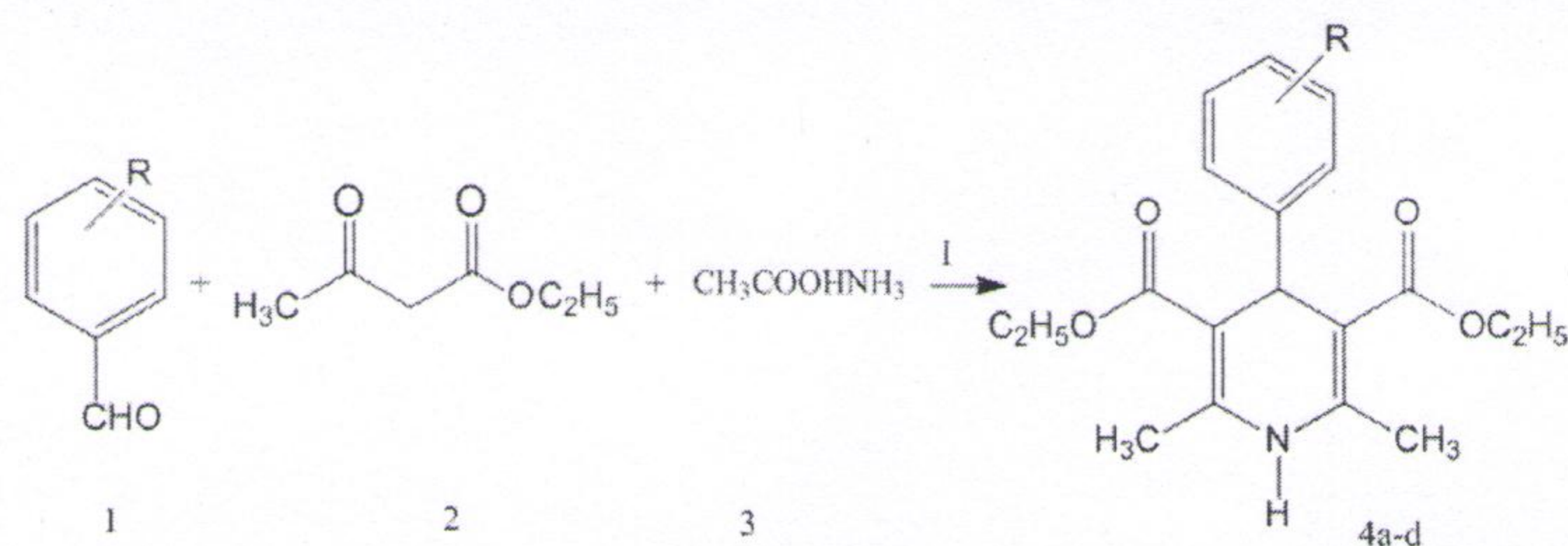
At first, the reaction of benzaldehyde (5 mmol), ethyl acetoacetat (10 mmol), amonium acetate (5 mmol) and 10 mL ethanol at reflux condition, is performed in presence of different catalyst and the appropriate amount of them was found, as 5 mol% Fe<sub>2</sub>O<sub>3</sub>, 2 mol% CuO and 2 mol% ZnO, as shown in Table 1.

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**Scheme 1.** Fe<sub>2</sub>O<sub>3</sub>, CuO and ZnO catalyzed Hantzsch reaction in different conditions  
I: reflux, 80°C, 2h, 10ml ethanol or ultrasonic, 1h, 10ml ethanol or MW, 100w, 3min, 10ml ethanol

**Table 1:** Reaction of benzaldehyde (5 mmol), ethyl acetoacetat (10 mmol), amonium acetate (5 mmol) and 10 mL ethanol at reflux condition, in presence of different catalyst

Entry	%mol Catalyst	Fe <sub>2</sub> O <sub>3</sub> yield <sup>a</sup> (%)	CuO yield <sup>a</sup> (%)	ZnO yield <sup>a</sup> (%)
1	No-catalyst	22	22	22
2	2	42	72	58
3	5	54	66	46
4	10	48	62	44

<sup>a</sup> Isolated yield.

In order to find out the most effective catalyst for the Hantzsch reaction, we performed this reaction with appropriate amounts of Fe<sub>2</sub>O<sub>3</sub>, CuO and ZnO powders, and corresponding nanoparticles, at reflux, ultrasonic and microwave irradiation conditions, as shown in Tables 2-4.

**Table 2:** Metal-catalyzed Hantzsch reaction at reflux condition (80°C) for 2h.<sup>a</sup>

Entry	Condition	Yield <sup>b</sup> (%)
1	no- catalyst	22
2	5%mol Fe <sub>2</sub> O <sub>3</sub>	54
3	5%mol nano-Fe <sub>3</sub> O <sub>4</sub>	55
4	2%mol CuO	72
5	2%mol nano-CuO	90
6	2%mol ZnO	56
7	2%mol nano-ZnO	56

<sup>a</sup> Reaction condition: benzaldehyde(5mmol), ethyl acetoacetat(10mmol), ammonium acetate(5mmol) in 10ml ethanol in presence of different catalyst. <sup>b</sup> Isolated yield.

The highest yield under reflux condition was obtained using CuO nanoparticles, as shown in Table 2. The use of ZnO and Fe<sub>2</sub>O<sub>3</sub> resulted in low yield. No significant difference was observed between the obtained yield by using ZnO and Fe<sub>2</sub>O<sub>3</sub>. Use of their nanoparticles led to increase in the reaction yield, however, effect of ZnO and Fe<sub>2</sub>O<sub>3</sub> nanoparticle on the reaction yield could not be considered significant.

**Table 3:** Metal-catalyzed Hantzsch reaction at ultrasonic condition for 1h.<sup>a</sup>

Entry	Condition	Yield <sup>b</sup> (%)
1	no-catalyst	16
2	5%mol Fe <sub>2</sub> O <sub>3</sub>	32
3	5%mol nano-Fe <sub>3</sub> O <sub>4</sub>	32
4	2%mol CuO	40
5	2%mol nano-CuO	52
6	2%mol ZnO	34
7	2%mol nano-ZnO	36

<sup>a</sup> Reaction condition: benzaldehyde(5mmol), ethyl acetoacetat(10mmol), ammonium acetate(5mmol) in 10ml ethanol in presence of different catalyst. <sup>b</sup> Isolated yield.

As could be seen from Table 3, synthesis of 1,4-DHPs under ultrasonic condition was not successful and the yields of reactions were low.



**Table 4:** Metal-catalyzed Hantzsch reaction at MW irradiation 100w for 3min.<sup>a</sup>

Entry	Condition	Yield <sup>b</sup> (%)
1	no-catalyst	44
2	5%mol Fe <sub>2</sub> O <sub>3</sub>	60
3	5%mol nano-Fe <sub>3</sub> O <sub>4</sub>	61
4	2%mol CuO	73
5	2%mol nano-CuO	94
6	2%mol ZnO	56
7	2%mol nano-ZnO	58

<sup>a</sup> Reaction condition: benzaldehyde(5mmol), ethyl acetoacetat(10mmol), ammonium acetate(5mmol) in 10ml ethanol in presence of different catalyst. <sup>b</sup> Isolated yield.

Microwave irradiations could increase both the rate and yield of the reaction. Preparation of 1,4-DHPs under microwave irradiation and in the presence of CuO nanoparticle proceeded rapidly with high yield, as shown in Table 4. Therefore, synthesis of 1,4-DHP derivatives was done under microwave irradiation and in the presence of CuO nanoparticle, as shown in Table 5. The products were characterized by IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy, and also by comparison with authentic samples<sup>19</sup>. This method offered marked improvement compared to previously reported ones. Its advantages included operational simplicity, low reaction time, and high yields of pure products.

**Table 5:** Synthesis of 1,4-dihydropyridines catalyzed by 2 mol% copper oxide nanoparticle under microwave irradiation (100w) in 10ml ethanol for 3 min.

Entry	R	product	Yeild <sup>a</sup> (%)	M.P. (°C)	
				Measured	Reported
1	H	4a	94	156-158	(156-158) [15]
2	4-OCH <sub>3</sub>	4b	93	156-159	(158-160) [15]
3	4-CH <sub>3</sub>	4c	87	134-136	(135-137) [15]
4	3-NO <sub>2</sub>	4d	90	160-162	(162-164) [15]

<sup>a</sup> Isolated yield.

### Conclusion

The presented method could be suggested for synthesis of 1,4-DHP derivatives because of low intensity of the used MW irradiation, familiar and inexpensive catalyst and short reaction time. Preparation of 1,4-DHPs by this new method is simple and efficient and could result in high reaction yield (87-94 %).

### Experimental Section

All starting materials were purchased from Merck and Aldrich companies. The IR spectra were recorded on a Perkin-Elmer RXI infrared spectrometer. <sup>1</sup>H NMR spectra were recorded with a 400 MHz Bruker FT-NMR spectrometer. TLC accomplished the purity of substrates and reactions monitored on silica gel polygram SIGL/UV254 plates. The reaction mixture was irradiated in Butane BC320N, 1200 w microwave oven.

#### 2.1. Materials and methods:

##### 2.1.1. Preparation of Nano-Fe<sub>3</sub>O<sub>4</sub><sup>22</sup>

Fe<sub>3</sub>O<sub>4</sub> nanoparticles were synthesized by electrooxidation of iron from an aqueous solution containing an electrostatic stabilizer (amine) using a chronoamperometry technique. (CH<sub>3</sub>)<sub>4</sub>NCl (Merck) solution was used as both supporting electrolyte and surfactant coating agent. Two purified Iron plates 1cm×1cm and 1cm×4cm (>99.9%) were purchased from Alfa Aesar and used as anode and cathode, respectively. Both electrodes were ultrasonically cleaned with DI water before electrooxidation. The cleaned electrodes were placed a distance of 1 cm apart from each other. After applying an appropriate potential between the electrodes, Fe<sub>3</sub>O<sub>4</sub> clusters begin to form in the solution. The reaction time was chosen as 1800 s for each case and the solution temperature was kept constant using a thermostatic water bath. During the reaction the solution color turns to yellow, brown-red, and subsequently to black indicating the formation of Fe<sub>3</sub>O<sub>4</sub>. The black precipitate was separated from the reaction medium with the aid of an external magnetic field, cleaned by three cycles of separation/washing/redispersion in DI water, and then dried at constant temperature.



### 2.1.2. Preparation of Nano-ZnO<sup>23</sup>

To prepare ZnO nanoparticles, two plates of zinc metal (purity of 99%) with a dimension of 1cm×2cm and 1cm×4cm were used as sacrificial anode and cathode, respectively. Initially, the electrodes were wiped out from possible contaminations by sonication and washing process with distilled water and ethanol. The cleaned electrodes were placed 1cm apart from each other. In this work, aqueous solution of (CH<sub>3</sub>)<sub>4</sub>NCl (Merck) salt was used as both supporting electrolyte and stabilizer. The pH of the solution was measured as 4.5. The process was progressed in thermostatic 60°C bath under stirring. In order to fabricate ZnO nanoparticles a cell voltage of 15V was applied for 20 minutes.

### 2.1.3. Preparation of Nano-CuO<sup>21</sup>

300mL of 0.02M Cu(NO<sub>3</sub>)<sub>2</sub> solution were prepared by dissolving Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O in deionized water. The solution was added into a round-bottom flask equipped with a refluxing device. The Cu(NO<sub>3</sub>)<sub>2</sub> solution were kept at 60 °C with vigorous stirring; then 0.50 g of solid NaOH (platelets) was rapidly added into the solution, where a large amount of blue or black precipitate was simultaneously produced and maintained at the crystallization temperature for 10 min. Next, the precipitate was heated at 100 °C for another 10 min. During this process, the initial blue color of the precipitate was gradually turned into black. After all reactions were completed, the resulting product were centrifuged, washed with water and ethanol for several times, and dried in air at room temperature.

### 2.2. General procedure

A mixture of aldehyde (5mmol), ethyl acetoacetate (10 mmol), ammonium acetate (10 mmol) and ethanol (10mL) at reflux conditions, ultrasonic waves and microwave irradiation was reacted in the presence appropriate amounts of micro and nano-sized catalysts from each of zinc oxide, copper oxide and iron oxide. The reaction was continued until TLC monitoring showed the completion of the reaction (for benzaldehyde in reflux condition, 2h; ultrasonic waves, 1h and microwave irradiation, 3 min.). Then the reaction mixtures have been cooled to room temperature and extract with ethyl acetate. Organic layer was washed with brine and water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation the solvent under vacuum, yellow products were purified by crystallization from ethanol. Selected spectral data for the products in Table 1 are given: Diethyl 4-(3-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (entry 4): FT-IR (KBr) cm<sup>-1</sup>: 3350, 3082, 1695, 1652, 1494, 1213, 1124, 779; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.25 (t, 6H, 2CH<sub>3</sub>), 2.29 (s, 6H, 2CH<sub>3</sub>), 4.10 (m, 4H, 2CH<sub>2</sub>), 4.96 (s, 1H, CH), 6.47 (s, 1H, NH), 7.16-7.33 (m, 4H, Ar); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): δ 14.5, 20.1, 39.8, 59.3, 104.4, 118.8, 131.0, 132.8, 144.1, 149.9, 167.6.

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