

Study of Fe₂O₃, 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 Fe₂O₃.

Keywords: 1,4-Dihydropyridine; ultrasonic; microwave irradiation ; nanoparticle; catalyst.

Introduction

Multicomponent reactions (MCRs) are one-pot processes that combine three or more substrates simultaneously¹. Due to their pharmacological properties, the Hantzsch² reaction and their products 1,4-dihydropyridines (1,4-DHP) have attracted the attention of synthetic chemists³. The heterocyclic rings of 1,4-DHPs are a common feature found in various bioactive compounds such as vasodilator, bronchodilator, anti-atherosclerotic, anti-cancer and anti-diabetic agents⁴. They serve as key intermediates in biogenesis of indole alkaloids⁵.

Moreover, 1,4-DHPs have several other medicinal applications such as neuroprotecting⁶ and cerebral anti-ischemic properties⁷.

These compounds are classically synthesized by one-pot condensation of aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol⁸. This method has several disadvantages such as long reaction time, harsh refluxing condition, excessive use of volatile organic solvents, and low yields. Because of their various applications other improved procedures have been subsequently suggested including the condensation of aldehyde with β -dicarbonyl compounds and amines in the presence of different catalysts and solvents⁹.

Owing to their unique physical and chemical properties, metal oxide based nanocatalysts have attracted widespread attention in catalysis, separation, optoelectronics, magnetism, microelectronics¹⁰ and as active adsorbents for gases. Nanocatalysis is an interesting field in organic synthesis that provides an alternative to homogeneous catalysis by using highly porous catalysts with large surface areas. The majority of these reactions occur under mild conditions, requiring minimum quantities of catalysts which are generally recyclable¹¹.

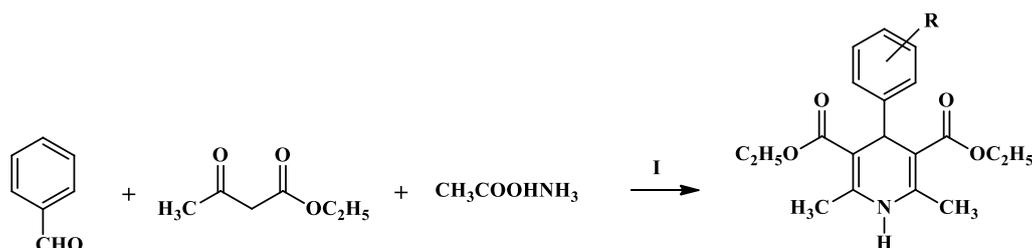
In recent years, several new efficient methods have been developed for 1,4-DHPs synthesis, including the use of metal triflates¹², I₂¹³, CAN¹⁴, PPh₃¹⁵, L-proline¹⁶, PPA-SiO₂¹⁷, La₂O₃¹⁸, and Nickel nanoparticles¹⁹.

In the course of our studies on the metal catalyzed alkylation of 1,3-dicarbonyl compounds^{20,21} and the 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 Fe₂O₃, CuO and ZnO as catalysts, under thermal, ultrasonic waves and MW irradiation (Scheme 1).

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Scheme 1. Fe₂O₃, CuO and ZnO catalyzed Hantzsch reaction in different conditions

I: reflux, 80°C, 2h, 10 ml ethanol or ultrasonic, 1h, 10 ml ethanol or MW, 100w, 3min, 10 ml ethanol

Results and Discussion

Initially, the reaction of benzaldehyde (5 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (5 mmol), and 10 mL ethanol at reflux condition, was performed in the presence of different catalysts at appropriate amounts, as shown in Table 1.

Table 1. Reaction of benzaldehyde, ethyl acetoacetate and ammonium acetate at reflux condition with diverse catalysts.

Entry	Mol% Catalyst	Fe ₂ O ₃ yield ^a (%)	CuO yield ^a (%)	ZnO yield ^a (%)
1	No-catalyst	22	22	22
2	2	42	72	58
3	5	54	66	46
4	10	48	62	44

^a Isolated yield.

In order to find out the most effective catalyst for the Hantzsch reaction, we performed this reaction with appropriate amounts of Fe₂O₃, CuO and ZnO powders, and their 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.^a

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

^a Reaction condition: benzaldehyde (5 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (5 mmol) in 10 ml ethanol in presence of different catalyst. ^b Isolated yield.

The highest yield under reflux condition was obtained using CuO nanoparticles, as shown in Table 2. No significant differences were observed between the use of ZnO and Fe₂O₃ even under their nanoparticle forms, all resulted in low yield of the obtained Hantzsch compounds.

Table 3. Metal-catalyzed Hantzsch reaction at ultrasonic condition for 1h.^a

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

^a Reaction condition: benzaldehyde (5 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (5 mmol) in 10 ml ethanol in presence of different catalyst. ^b Isolated yield.

As shown in 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.^a

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

^a Reaction condition: benzaldehyde (5 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (5 mmol) in 10 ml ethanol in presence of different catalyst.

^b Isolated yield.

Microwave irradiations increased both the rate and yield of the reaction. The preparation of 1,4-DHPs under microwave irradiation and in the presence of CuO nanoparticles proceeded rapidly with high yield (Table 4).

Therefore, the synthesis of 1,4-DHP derivatives was done under microwave irradiation and in the

presence of CuO nanoparticles (Table 5). The products were characterized by IR, ^1H NMR and ^{13}C NMR spectroscopy, and also by comparison with authentic samples¹⁹. This method offered marked improvement compared with previously reported ones. Its advantages included operational simplicity, low reaction time, and high yields of pure products (Table 5).

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

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

^a Isolated yield.

Conclusion

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

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Experimental Section

All starting materials were purchased from Merck and Aldrich companies. The IR spectra were recorded on a Perkin-Elmer RXI infrared spectrometer. ^1H 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.

Materials and methods

Preparation of Nano-Fe₃O₄²²

Fe₃O₄ nanoparticles were synthesized by electrooxidation of iron from an aqueous solution containing an electrostatic stabilizer (amine) using a chronoamperometry technique. (CH₃)₄NCl (Merck) solution was used both as 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 at a distance of 1 cm apart from each other. After applying an appropriate potential between the electrodes, Fe₃O₄ clusters are formed in the solution. The chosen reaction time was 1800 s for each case and the solution temperature was kept constant using a thermostatic water bath. During the reaction the solution color turns first to yellow, then brown-red, and subsequently to black indicating the formation of Fe₃O₄. 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.

Preparation of Nano-ZnO²³

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 (CH₃)₄NCl (Merck) salt was used as both supporting electrolyte and stabilizer. The pH of the solution was measured at 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.

Preparation of Nano-CuO²¹

300 mL of 0.02M Cu(NO₃)₂ solution were prepared by dissolving Cu(NO₃)₂·3H₂O in deionized water. The solution was added into a round-bottom flask equipped with a refluxing device. The Cu(NO₃)₂ 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.

General procedure

A mixture of aldehyde (5 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (10 mmol) and ethanol (10 mL) at reflux conditions, ultrasonic waves or microwave irradiation was reacted in the presence of 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 its completion (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 extracted with ethyl acetate. Organic layer was washed with brine and water and dried over anhydrous Na₂SO₄. After evaporation of the solvent under vacuum, the obtained yellow products were purified by crystallization from ethanol.

Selected spectral data for the product in Table 5 are given: Diethyl 4-(3-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (entry 4): FT-IR (KBr) cm⁻¹: 3350, 3082, 1695, 1652, 1494, 1213, 1124, 779; ¹H NMR (400 MHz, CDCl₃): δ 1.25 (t, 6H, 2CH₃), 2.29 (s, 6H, 2CH₃), 4.10 (m, 4H, 2CH₂), 4.96 (s, 1H, CH), 6.47 (s, 1H, NH), 7.16-7.33 (m, 4H, Ar); ¹³C NMR (62.9 MHz, CDCl₃): 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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