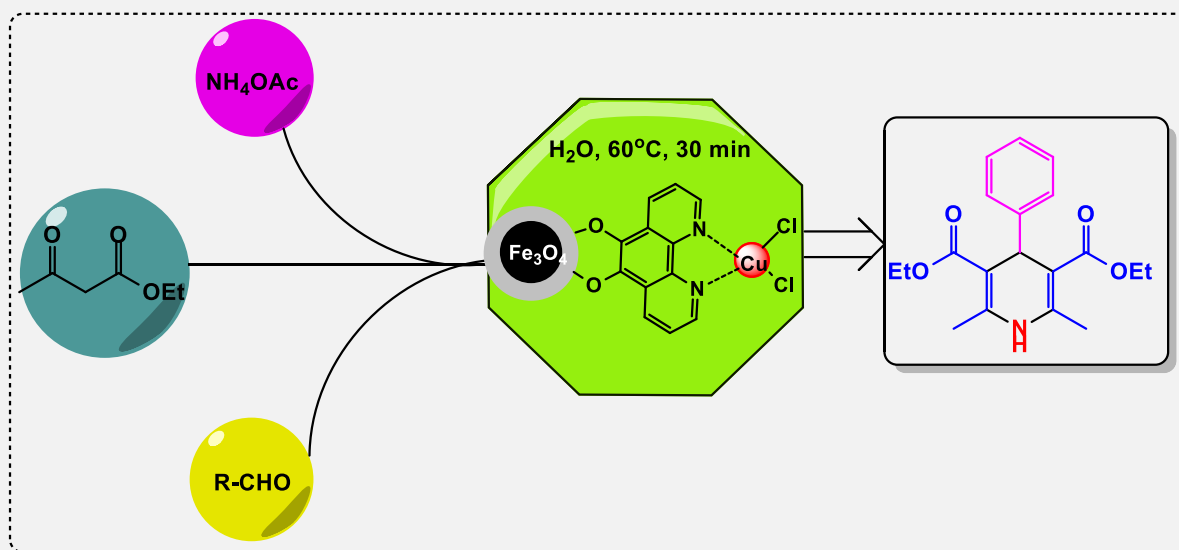


Eco-Friendly Synthesis of 1,4-dihydropyridines Derivatives Using Fe₃O₄@Phen@Cu Magnetic CatalystLin Willong^{1*}, Song Gangshin²¹ Department of Organic Chemistry, Fudan University.² Department of Organic Chemistry, Faculty of Chemistry, Peking University.

Mail corresponding-author: linwillong@gmail.com

ABSTRACT: Among the most well-known MCRs is the Hantzsch reaction, which can synthesis 1,4-dihydropyridines (1,4-DHPs) with important biological and medicinal properties. Organic transformations, including the Hantzsch 1,4-dihydropyridine cycle, have been successfully promoted by magnetic catalysts in recent years. With the use of magnetic catalysts in water solution and at low temperatures, the production of 1,4-DHP and aromatization of these compounds can be carried out successfully. The purpose of this review is to highlight recent developments in the synthesis and aromatization of Hantzsch 1,4-DHPs using Fe₃O₄@Phen@Cu as a green approach. An SEM and FT-IR analysis were conducted on the catalyst to identify it. Nanoparticles are between 20 and 60 nanometers in size, according to the results. An environmentally friendly catalyst that is easily separated from the test environment by a magnet, this catalyst can be reused five times.

**KEYWORDS:** Hantzsch, 1,4-dihydropyridines, Magnetic Catalysts Fe₃O₄@Phen@Cu.**Introduction**

Specific multicomponent reactions occur when raw materials are combined in a way that creates the desired product [1]. Strecker introduced the multi-reaction in 1850, combining the best tools and economic tools for synthesis [2]. There are a number of reasons why these reactions have high yields, short reaction times, few by-products, and no need for separation and purification of intermediates, as well as high selectivity[3]. In the field of increasing structural diversity and molecular complexity using a

Received: Nov, 30, 2023

Revised: Dec 9, 2023

Published: Dec 19, 2023

DOI: 10.22034/jsc.2023.431005.1060

J. Synth. Chem. 2023, 2, 252-264

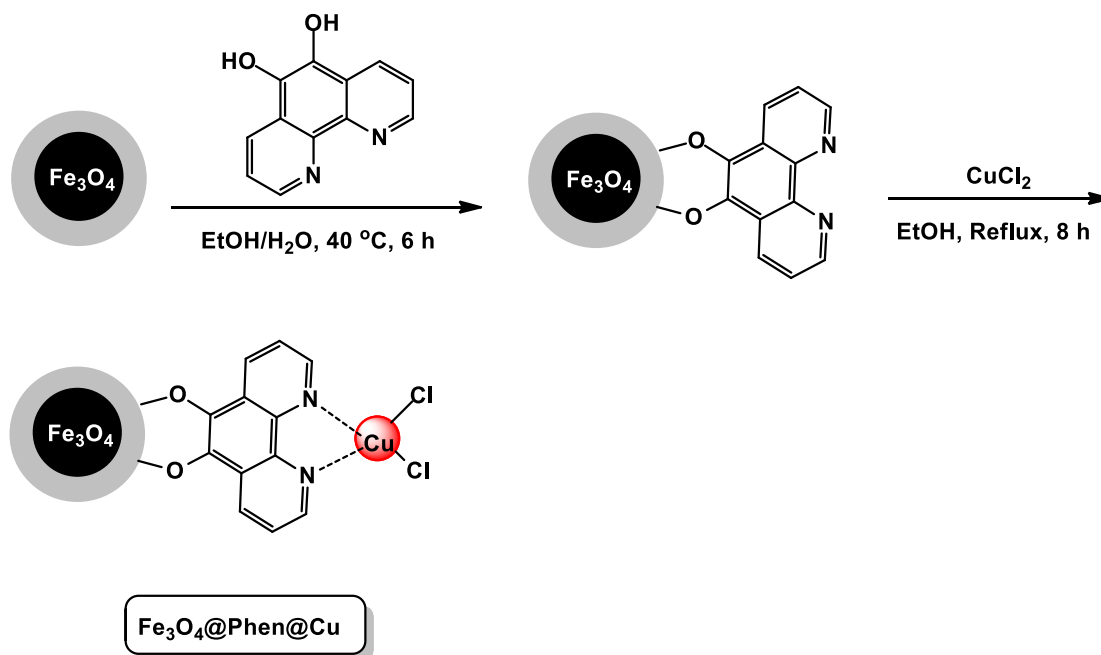
simple process, multicomponent reactions are one of the most successful methods [4]. Since this method is a developing method for the preparation of medicinal compounds, it allows a wide range of chemical compounds to be developed with a wider structural diversity; as a result, these reactions have altered the synthesis of all-natural products fundamentally; in recent decades, it has expanded rapidly [5]. Although a lot of new three- and four-component reactions have been developed, fewer studies have been conducted on "higher order" reactions with five or more components. In industries and universities, the investigation of the use of these reactions for the preparation of "pharmaceutical small molecules" has increased as the advantages of "biologically active molecules" have increased [6]. Compared to other methods, this method uses raw materials that are readily available, is low-cost, uses a simple work method, produces a wide range of products, contains a wide variety of steps, and is easy to automate. This review aims to describe the developments made in this field in recent years, to identify challenges, and to suggest ways for progress [7]. Pharmaceutical and biological applications of 1,4-Dihydropyridines have become increasingly important. Many natural products and drugs contain dihydropyridine derivatives, including 1,4-dihydropyridines. A six-membered ring containing a nitrogen atom at position 1 and a saturated atom at position 4 is called dihydropyridine [8]. Compounds like this act as calcium channel blockers or as anti-tumor agents [9]. This heterocyclic compound also has antihypertensive, anti-inflammatory, and analgesic properties [10]. Other biological activities of 1,4-dihydropyridine include anticonvulsant and cardiac depressant effects. 1,4-dihydropyridine has been found to have antiplatelet activity, as well as being used as a chemical agent to treat cancer and Alzheimer's disease in recent studies [11]. For the synthesis of 1,4-dihydropyridine, different methods have been proposed by different scientists [12]. By refluxing ethanol and aldehyde-acetoester with ammonia or ammonium salt, Hantzsch reported the synthesis of 4,1-dihydropyridine [13]. This was immediately followed by a one-pot synthesis of 1,4-dihydropyridine with three components (aldehyde, ethyl acetoacetate, and ammonia), which showed good results after refluxing with methanol [14].

Generally, this method produces a low yield of product and involves harsh reaction conditions. Hantzsch reaction has been improved with the help of alternative catalysts and greener methods by using a number of new and more efficient methods [15]. There are, however, a number of problems associated with these methods, including their slow reaction times, the use of toxic solvents, their low efficiency, their toxicity, and their inability to recycle or reuse their catalysts [16]. It is therefore imperative to find a catalyst that is cheaper, more reusable, easier to operate, more biocompatible, and more select in order to synthesize 1,4-dihydropyridine derivatives [17]. Environmentally friendly synthetic methods have been developed recently to make various desired molecules in one pot [18]. A green process uses efficient, cheap, biodegradable, and non-toxic catalysts, non-toxic agents, and non-toxic chemicals [19]. The ignition process is similar to water, ionic liquids, and solvent-free reactions [20]. Towards this goal, the use of polymeric catalysts has been highlighted for their low price, high efficiency, easy extraction, and recyclability [21].

Among these catalysts, phenanthroline attached to Fe_3O_4 NPs has been reported as a cheap, non-corrosive, non-volatile, and recyclable acid catalyst for the synthesis of some heterocycle molecules. Here, as part of the research program to develop efficient methods for the preparation of heterocyclic compounds, a green, easy and suitable one-pot method for the synthesis of 1,4-dihydropyridine derivatives through the reaction of ammonium acetate with various aromatic aldehydes and ethyl acetate in the presence $\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ has been reported as a biodegradable and efficient catalyst in water solvent.

Results and Discussion

In order to prepare 1,4-dihydropyridines, CuCl_2 was synthesized on Fe_3O_4 magnetic nanoparticles supported by 1,10-phenanthroline-5,6-diol. $\text{Fe}_3\text{O}_4@Phen@Cu$ nanocatalysts were fabricated through an experimental method, as depicted in **Scheme 1**. The $\text{Fe}_3\text{O}_4@Phen@Cu$ catalyst was formed by reacting phenanthroline with CuCl_2 after immobilization on magnetic nanoparticles. $\text{Fe}_3\text{O}_4@Phen@Cu$ nanocomposites were identified using SEM and FTIR techniques.



Scheme 1. Experimental details of the fabrication of $\text{Fe}_3\text{O}_4@Phen@Cu$ nanocatalyst.

FT-IR spectroscopy

As shown in **Figure 1**, the FT-IR spectroscopy of $\text{Fe}_3\text{O}_4@Phen@Cu$ nanocatalyst shows good agreement with the optical data. Based on the spectrum of $\text{Fe}_3\text{O}_4@Phen@Cu$ nanocatalyst, the stretching vibrations of Fe-O can be seen at 570 cm^{-1} , whereas the stretching vibrations of OH can be observed at 3400 cm^{-1} . It is clear that a complex with the Cu salt has formed at 1620 cm^{-1} as a result of the C-N stretching vibrations. Based on the FTIR spectrum, the magnetic iron nanoparticle is functionalized to a certain extent.

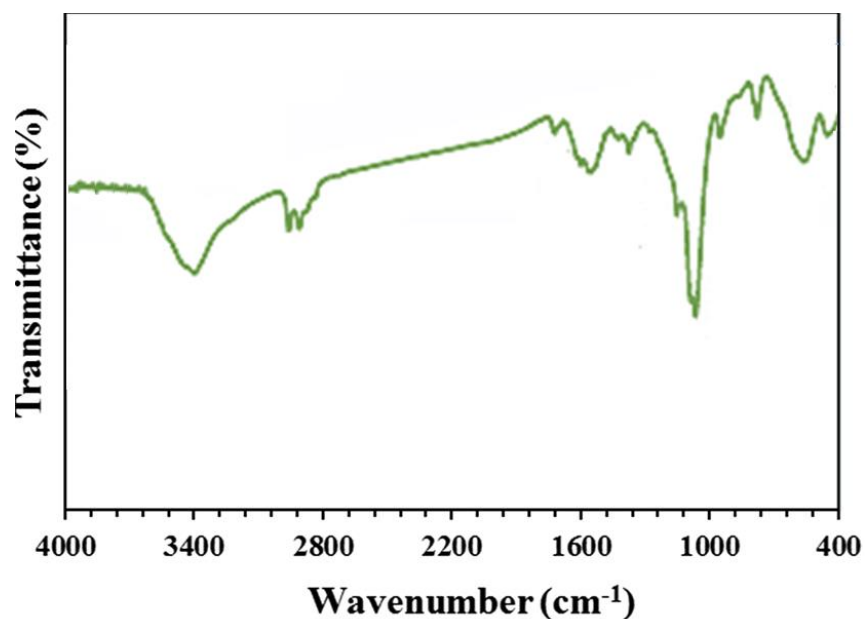


Figure 1. FT-IR spectroscopy of $\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ nanocatalyst.

SEM analysis

The morphological characteristics of the prepared materials were determined by FE-SEM observations. The SEM image of $\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ nanocatalyst is shown in **Figure 2**. Figure 2 shows that $\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ nanocatalyst have a spherical shape with an average particle size of 40 nm.

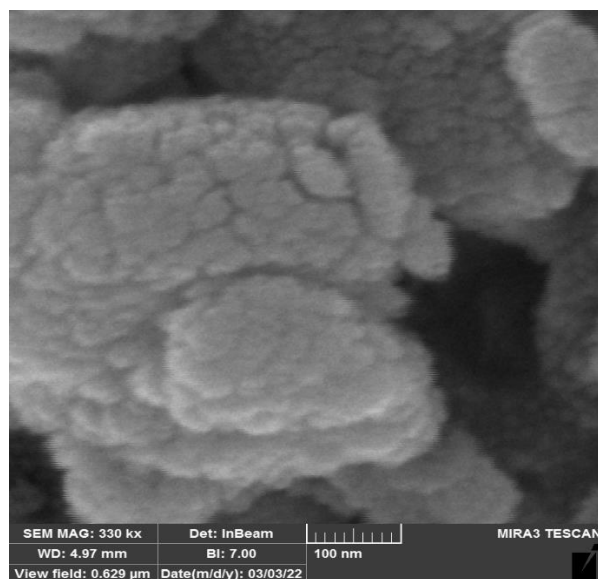
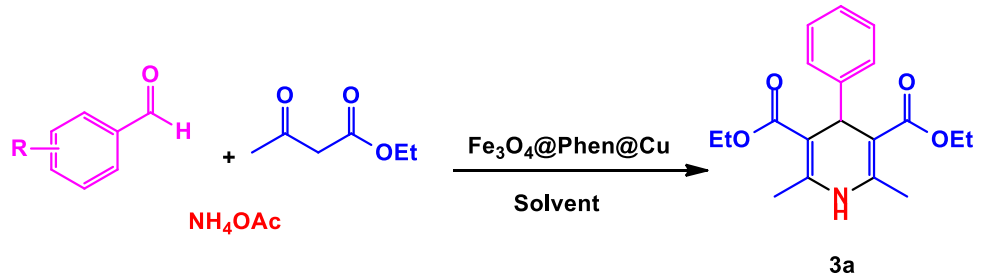


Figure 2. SEM image of $\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ nanocatalyst.

To investigate the Cu content, ICP analysis was used to evaluate the structure of the nanocatalyst; subsequently, Cu immobilized on Fe₃O₄ nanoparticles was found to be 17.20 × 10⁻⁵ mmol.g⁻¹.

At the beginning of the research, in order to evaluate the catalytic activity of Fe₃O₄@Phen@Cu and determine the optimal reaction conditions for the synthesis of 1,4-dihydropyridine derivatives, a one-pot reaction of benzaldehyde (1 mmol) with ethyl acetoacetate (2 mmol) and ammonium acetate (1.2 mmol) was carried out in the presence of a catalytic amount (10 mg) in PEG solvent at 60 °C. After 2 h, 44% of the desired product 3a was obtained (**Table 1, entry 1**). Then, the effect of the amount of catalyst on the reaction speed and also the efficiency of the products was investigated (**Table 1, entries 2-5**). It was observed that the amount of 25 mg Fe₃O₄@Phen@Cu is more effective for the reaction than other amounts. When the reaction was carried out in the absence of a catalyst, the results showed that the product 1,4-dihydropyridine 3a only with a yield of 21% after 24 hour was obtained (**Table 1, entry 6**). In order to achieve optimal conditions for the synthesis of compound 3a, the same reaction was investigated in different organic solvents under the same conditions. The results showed that the conditions in water solvent are superior and more efficient than other organic solvents, according to the desired 1,4-dihydropyridine production efficiency (**Table 1, entries 7-11**). In the next step, we investigated the effect of temperature on the reaction performance. The results showed that increasing the temperature above 60°C neither improves the performance nor reduces the reaction time. While the decrease in temperature will lead to a decrease in yield (**Table 1, entries 12-15**).

Table 1. Optimization parameters for the MCRs reaction in the presence of Fe₃O₄@Phen@Cu nanocatalyst

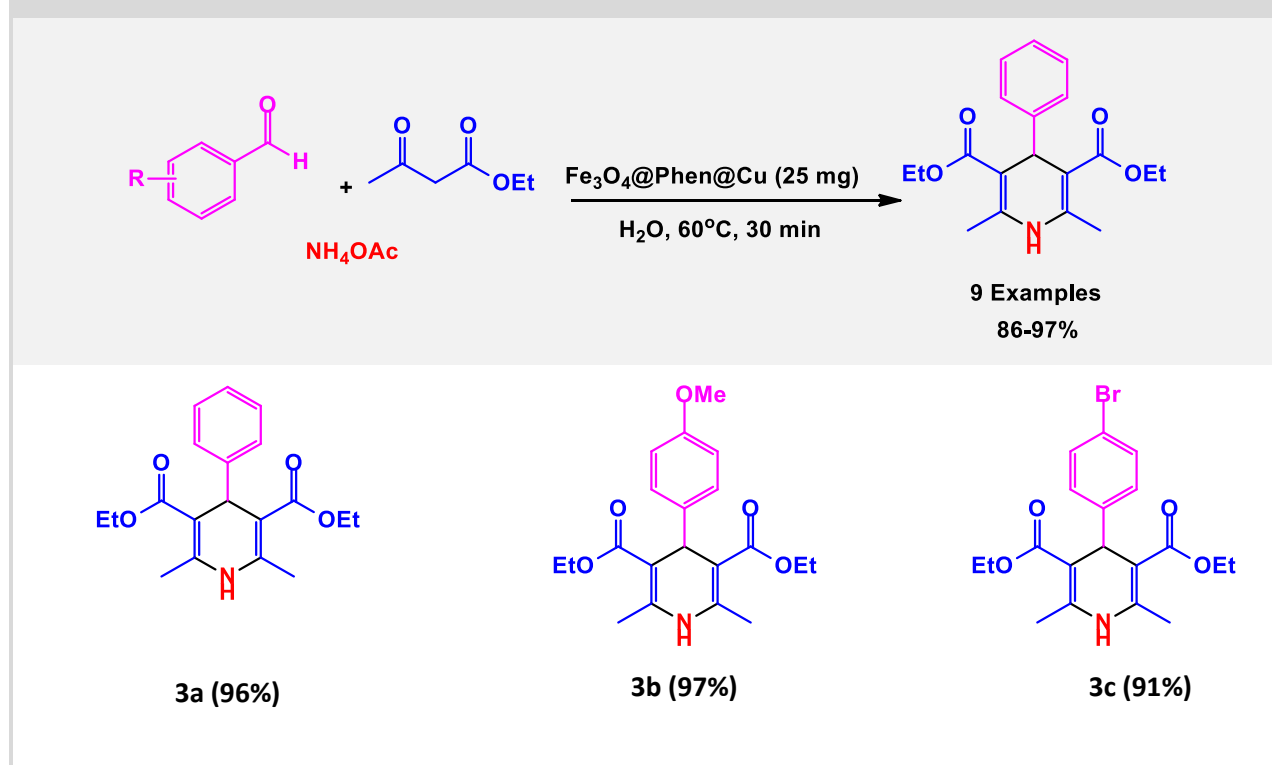


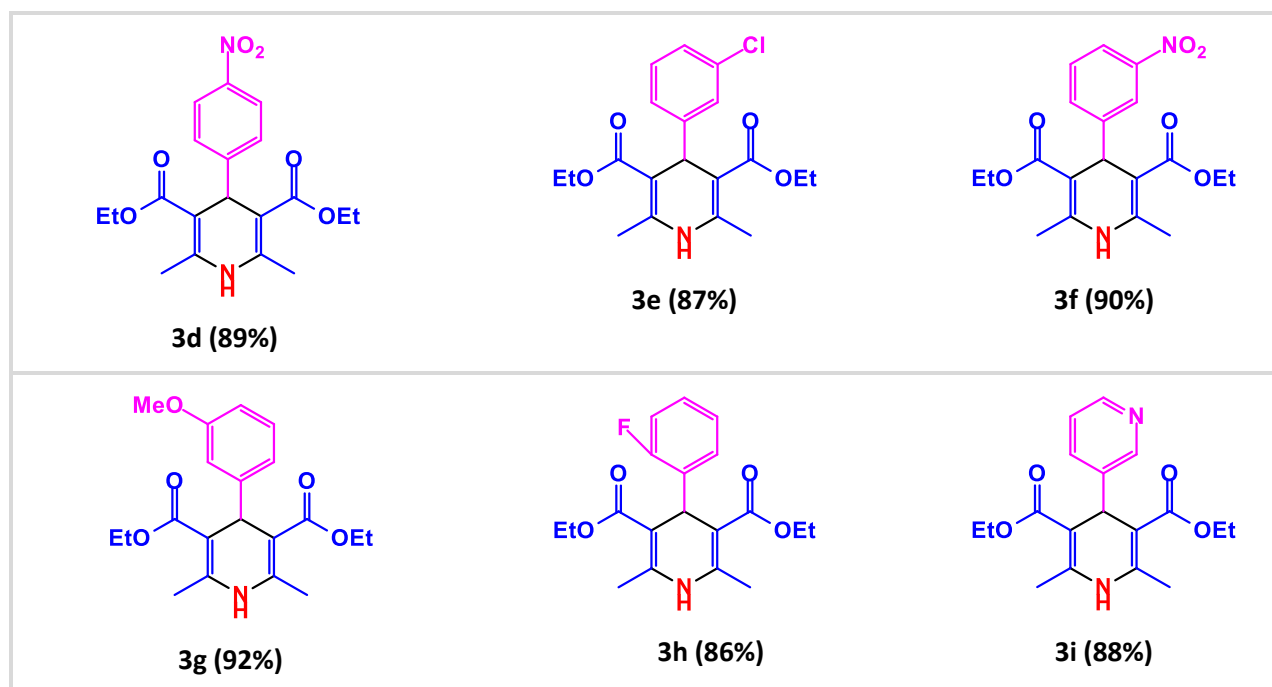
Entry	Catalyst (mg)	Temperature (°C)	Solvent (Tem °C)	Time (min)	Yield (%) ^a
1	10	60	PEG	180	44
2	15	60	H ₂ O	30	62
3	20	60	H ₂ O	30	85
4	20	60	PEG	30	69
5	25	60	PEG	30	90
6	--	60	H ₂ O	60	21
7	25	60	DMF	30	70
8	25	60	EtOH	30	62
9	25	60	DMSO	30	49
10	25	60	H₂O	30	98
11	25	rt	THF	30	56

12	25	40	H ₂ O	30	60
13	25	80	H ₂ O	30	75
14	25	100	H ₂ O	30	67
15	25	120	H ₂ O	30	81

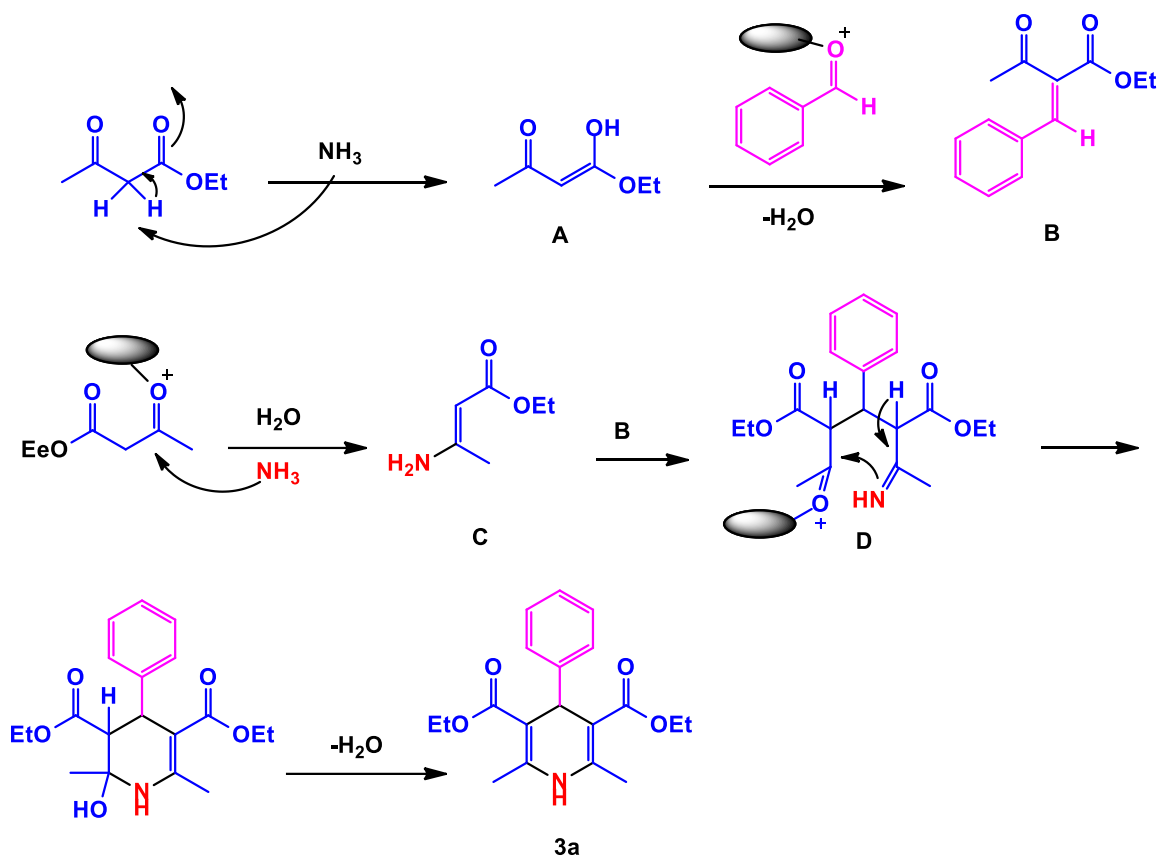
In summary, the optimal conditions for the Hantzsch reaction were a combination of 25 mg of Fe₃O₄@Phen@Cu, 1 mmol of benzaldehyde with 2 mmol of ethyl acetoacetate and 1.2 mmol of ammonium acetate in a water solvent at a temperature of 60 °C (**Table 1, entry 10**). After optimizing the reaction conditions, to prove reproducibility, this method was investigated using ethyl acetoacetate, various aromatic aldehydes, and ammonium acetate in the presence of Fe₃O₄@Phen@Cu. Under these conditions, various 1,4-dihydropyridine derivatives were synthesized under optimal reaction conditions (**Table 2**). As shown in **Table 2**, the reaction of various aromatic aldehydes with electron-donating or electron-withdrawing substitutions with β -ketostere and ammonium acetate in the presence of the amount of catalysis produced the corresponding products (86-97%) in a short time. This method is very simple and convenient, and it has the ability to tolerate a variety of other functional groups including halogens, methyl, nitro, and methoxy in the reaction conditions.

Table 2. Synthesis of 1,4-dihydropyridine derivatives using Fe₃O₄@Phen@Cu as a catalyst.





Scheme 2 shows the proposed mechanism for the formation of 1,4-dihydropyridine derivatives using catalyst $\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$. First, ammonium acetate is converted into ammonia and acetic acid. Then, ammonia as a base attacks ethyl acetoacetate and creates intermediate A, in the second step, the increase of nucleophilicity of intermediate A to the aromatic carbonyl aldehyde group, which is activated by the catalyst, is carried out and with the loss of a water molecule during the Knoevenagel reaction B is produced. Then, intermediate B together with intermediate C formed by the nucleophilic attack of ammonia on the second equivalent of ethyl acetoacetate activated by the catalyst, during Michael addition, causes the formation of intermediate D. Finally, the intramolecular cyclization of enamine D is formed by increasing the nucleophilicity of enamine to the carbonyl group activated by the catalyst, causing the ring to be closed and by removing the water produced by a3.



Scheme 2 .Proposed mechanism for the preparation of products 3a-i.

When choosing heterogeneous catalysts for industrial applications, it is important to consider their recyclability. To separate the catalyst from the reaction mixture, each cycle was followed by a measurement of product yield. Two times it was reused after being cleaned several times in ethanol and dried in an oven under vacuum. **Figure 3** shows that the catalyst could be reused for five successive catalytic cycles without significantly reducing its activity and yield. According to the obtained results, the catalyst will remain durable for a long period of time.

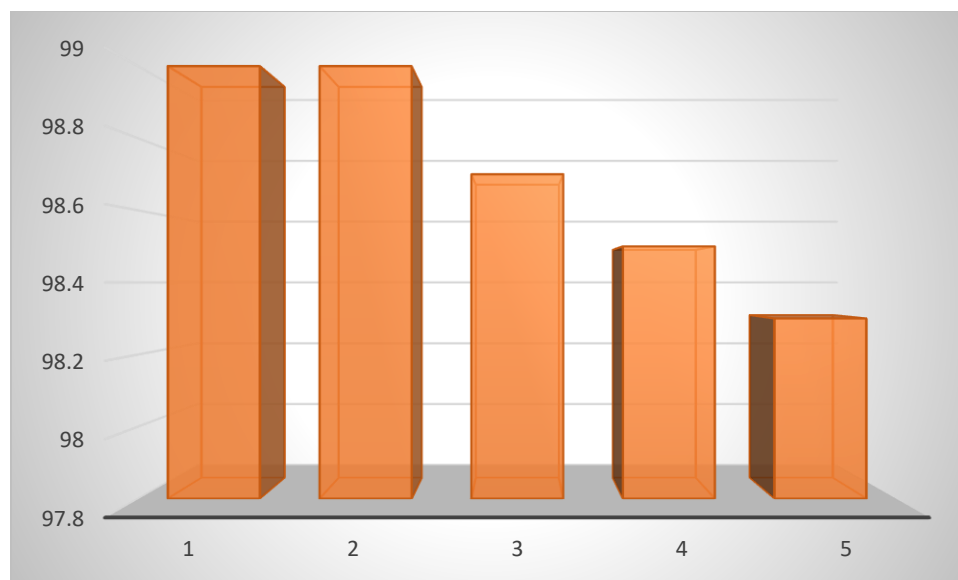


Figure 3. Reusability of $\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ catalyst in the synthesis of product 3a.

■ Conclusion

$\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ was successfully used as an environmentally friendly and efficient catalysis for the synthesis of 1,4-dihydropyridine derivatives by Hanch condensation reaction, and also using aqueous solvent in the reaction medium. The significant advantages of this method are high yield of products, short reaction time, economic efficiency of the catalyst, accessibility of the catalyst, simplicity of preparation of the catalyst and separation of the product. Also, preparation of 1,4-dihydropyridines in water solvent is an environmentally friendly method.

■ Experimental

The raw materials used for the reactions were purchased and used from Merck and Floka companies with high purity percentage. The melting temperature of the product was measured using the Electrothermal 9200 device in the capillary tube. All infrared spectra were recorded in a Shimadzu-470 spectrophotometer. Proton nuclear magnetic resonance spectra of the products were recorded by Bruker DRX-400 Advance in deuterium chloroform solvent. The products were identified by ^1H NMR spectral information, FT-IR, and their melting point and by comparing with the reported data.

General method of Synthesis of 1,4-dihydropyridine Derivatives

$\text{Fe}_3\text{O}_4@\text{Phen}@\text{Cu}$ catalyst (0.05 mmol, 25 mg) was added to a mixture of 1 mmol aldehyde, 2 mmol ethyl acetoacetate and 1.2 mmol ammonium acetate. The mixture was stirred at 60°C for the necessary time. After the end of the reaction, which was controlled by thin layer chromatography, the reaction mixture was cooled, then 20 ml of dilute sodium bicarbonate solution was added and the reaction mixture was extracted with ethyl acetate (5 x 3 ml). The obtained organic phase was dried with Na_2SO_4 . The obtained

solution was placed in a vacuum. After evaporation of the solvent, the nebulization method in ethanol was used to further purify the product.

Supporting Information

diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3d): Yield: 89%, M.P.:132-134°C. ¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 5.98 (s, 1H), 5.05 (s, 1H), 4.14 – 4.05 (m, 4H), 2.35 (s, 6H), 1.22 (t, J = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 167.1, 153.1, 144.7, 132.8, 128.9, 119.3, 109.6, 103.1, 59.9, 40.2, 19.5, 14.2.

diethyl 4-(2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3i): Yield: 88%, M.P.:150-152°C. ¹H NMR (400 MHz, CDCl₃): δ 7.40 (dd, J = 7.7, 1.7 Hz, 1H), 7.25 (d, J = 7.1, 1.2 Hz, 1H), 7.15 (td, J = 7.5, 1.3 Hz, 1H), 7.06 (td, J = 7.6, 1.7 Hz, 1H), 5.75 (s, 1H), 5.41 (s, 1H), 4.10 (qd, J = 7.1, 1.5 Hz, 4H), 2.32 (s, 6H), 1.22 (t, J = 7.1 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 167.7, 145.6, 143.9, 132.4, 131.6, 129.3, 127.3, 126.7, 103.8, 59.8, 37.5, 19.6, 14.3.

References

- [1] G.D. Brown, D. Batalla, C.L. Cavallaro, H.L. Perez, S.T. Wroblewski, T.C. Sherwood, A compact, practical photoreactor for multi-reaction arrays, *React. Chem. Eng.* 7 (2022) 1945–1953. <https://doi.org/10.1039/D2RE00062H>.
- [2] V. Balakotaiah, D. Luss, Global analysis of the multiplicity features of multi-reaction lumped-parameter systems, *Chem. Eng. Sci.* 39 (1984) 865–881. [https://doi.org/10.1016/0009-2509\(84\)85056-3](https://doi.org/10.1016/0009-2509(84)85056-3).
- [3] V. Nair, R.J. Offerman, G.A. Turner, A.N. Pryor, N.C. Baenzlger, Fluorescent 1,4-Dihydropyridines: The Malondaldehyde connection, *Tetrahedron*. 44 (1988) 2793–2803. [https://doi.org/10.1016/S0040-4020\(88\)90015-4](https://doi.org/10.1016/S0040-4020(88)90015-4).
- [4] A.F. Joslyn, E. Luchowski, D.J. Triggler, Dimeric 1,4-dihydropyridines as calcium channel antagonists, *J. Med. Chem.* 31 (1988) 1489–1492. <https://doi.org/10.1021/jm00403a002>.
- [5] S. Goldmann, L. Born, S. Kazda, B. Pittel, M. Schramm, Synthesis, pharmacological effects, and conformation of 4,4-disubstituted 1,4-dihydropyridines, *J. Med. Chem.* 33 (1990) 1413–1418. <https://doi.org/10.1021/jm00167a021>.
- [6] A. ASHIMORI, T. ONO, Y. INOUE, S. MORIMOTO, M. EDA, T. UCHIDA, Y. OHTAKI, Y. FUJINO, H. KIDO, Y. OGURA, C. FUKAYA, M. WATANABE, K. YOKOYAMA, Novel 1,4-dihydropyridine calcium antagonists. II. Synthesis and antihypertensive activity of 3-(4-(substituted amino)phenylalkyl)ester derivatives., *Chem. Pharm. Bull.* 39 (1991) 91–99. <https://doi.org/10.1248/cpb.39.91>.
- [7] C.A. Antonyraj, S. Kannan, Hantzsch pyridine synthesis using hydrotalcites or hydrotalcite-like materials as solid base catalysts, *Appl. Catal. A Gen.* 338 (2008) 121–129. <https://doi.org/10.1016/j.apcata.2007.12.028>.
- [8] E. Fasani, A. Albin, M. Mella, Photochemistry of Hantzsch 1,4-dihydropyridines and pyridines, *Tetrahedron*. 64 (2008) 3190–3196. <https://doi.org/10.1016/j.tet.2008.01.104>.
- [9] X. Li, Y. Meng, P. Yi, M. Stępień, P.J. Chmielewski, Pyridine-Fused Bis(Norcorrole) through Hantzsch-Type Cyclization: Enhancement of Antiaromaticity by an Aromatic Bridge, *Angew.*

- Chemie. 129 (2017) 10950–10954. <https://doi.org/10.1002/ange.201705715>.
- [10] L. Xue, G. Cheng, R. Zhu, X. Cui, Acid-promoted oxidative methylenation of 1,3-dicarbonyl compounds with DMSO: application to the three-component synthesis of Hantzsch-type pyridines, *RSC Adv.* 7 (2017) 44009–44012. <https://doi.org/10.1039/C7RA07442E>.
- [11] S. Farooq, M.A. Munawar, Z. Ngaini, Two Pot and One Pot Synthetic Methodologies of Hantzsch Pyridines, *Curr. Org. Chem.* 22 (2019) 2671–2680. <https://doi.org/10.2174/1385272822666181109124547>.
- [12] S. Penta, R.R. Vedula, Synthesis of 2,4,6-Tri-Substituted Pyridine Derivatives in Aqueous Medium via Hantzsch Multi-Component Reaction Catalyzed by Cerium (IV) Ammonium Nitrate, *J. Heterocycl. Chem.* 50 (2013) 859–862. <https://doi.org/10.1002/jhet.1589>.
- [13] No Title, (n.d.). <https://doi.org/https://doi.org/10.1016/B978-0-12-408100-0.00006-9>.
- [14] J. Yang, C. Jiang, J. Yang, C. Qian, D. Fang, A clean procedure for the synthesis of 1,4-dihydropyridines via Hantzsch reaction in water, *Green Chem. Lett. Rev.* 6 (2013) 262–267. <https://doi.org/10.1080/17518253.2013.781686>.
- [15] S. Ko, M.N.V. Sastry, C. Lin, C.-F. Yao, Molecular iodine-catalyzed one-pot synthesis of 4-substituted-1,4-dihydropyridine derivatives via Hantzsch reaction, *Tetrahedron Lett.* 46 (2005) 5771–5774. <https://doi.org/10.1016/j.tetlet.2005.05.148>.
- [16] M.A. Zolfigol, M. Safaiee, Synthesis of 1,4-Dihydropyridines under Solvent-free Conditions, *Synlett.* (2004) 0827–0828. <https://doi.org/10.1055/s-2004-820010>.
- [17] E. Rafiee, S. Eavani, S. Rashidzadeh, M. Joshaghani, Silica supported 12-tungstophosphoric acid catalysts for synthesis of 1,4-dihydropyridines under solvent-free conditions, *Inorganica Chim. Acta.* 362 (2009) 3555–3562. <https://doi.org/10.1016/j.ica.2009.03.049>.
- [18] J.H. Lee, Synthesis of Hantsch 1,4-dihydropyridines by fermenting bakers' yeast, *Tetrahedron Lett.* 46 (2005) 7329–7330. <https://doi.org/10.1016/j.tetlet.2005.08.137>.
- [19] J.-L. Wang, B.-K. Liu, C. Yin, Q. Wu, X.-F. Lin, *Candida antarctica* lipase B-catalyzed the unprecedented three-component Hantzsch-type reaction of aldehyde with acetamide and 1,3-dicarbonyl compounds in non-aqueous solvent, *Tetrahedron.* 67 (2011) 2689–2692. <https://doi.org/10.1016/j.tet.2011.01.045>.
- [20] S.M. Baghbanian, S. Khaksar, S.M. Vahdat, M. Farhang, M. Tajbakhsh, One-step, synthesis of Hantzsch esters and polyhydroquinoline derivatives using new organocatalyst, *Chinese Chem. Lett.* 21 (2010) 563–567. <https://doi.org/10.1016/j.ccllet.2009.12.011>.
- [21] K. Pajuste, A. Plotniece, K. Kore, L. Intenberga, B. Cekavicus, D. Kaldre, G. Duburs, A. Sobolev, Use of pyridinium ionic liquids as catalysts for the synthesis of 3,5-bis(dodecyloxycarbonyl)-1,4-dihydropyridine derivative, *Open Chem.* 9 (2011) 143–148. <https://doi.org/10.2478/s11532-010-0132-x>.

