

Synthesis of pyrroles, pyrazoles, imidazoles, pyridines, pyrimidines and pyrazines using nanocatalysts

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Abstract: Here, we outlined the synthesis of pyrroles, pyrazoles, imidazoles, pyridines, pyrimidines and pyrazines using nanocatalysts. For example, quinazolin-4(1H)-ones **49a-c** were produced by the multicomponent reaction between isatoic anhydride (**48**), various amines **3**, substituted aldehydes **7** in water using Fe₃O₄ nanoparticles. These N-heterocyclic compounds are essential in pharmaceutical fields. Using nanocatalysts in this synthesis is very important because these catalysts lie under the green synthesis or sustainable synthesis that most researchers headed in recent years, due to nanocatalysts have a large surface area compared with their volume making a larger chance of reaction between the reactants. In addition, they reduce side reactions, improve selectivity, enhance recycling rates, and enable cleaner, faster, and less expensive reactions. Furthermore, they show self-recovery and excellent product yield.

Keywords: Heterocyclic; pyrroles; pyrazoles; pyrazines; nanocatalysts; green chemistry. © 2025 ACG Publications. All rights reserved.

1. Introduction

Heterocycles are organic compounds that are very significant in industrial, chemical, and biological applications. Most of these heterocycles have biological activities such as anti-tumor, anti-bacterial, anti-inflammatory and antioxidant.¹⁻⁶ In addition, most of these compounds are synthesized by the multi-component reactions to produce novel compounds.⁷ These multi-component reactions are significant for the fast and eco-friendly syntheses of several N-heterocyclic compounds. “MCRs” are important for producing compounds with biological and pharmaceutical characteristics.⁸⁻¹¹ The “MCRs” show important advantages compared to the conventional methods.^{11,12} In the past decades, numerous methods have been developed to produce several compounds.^{13,14} But, most of these

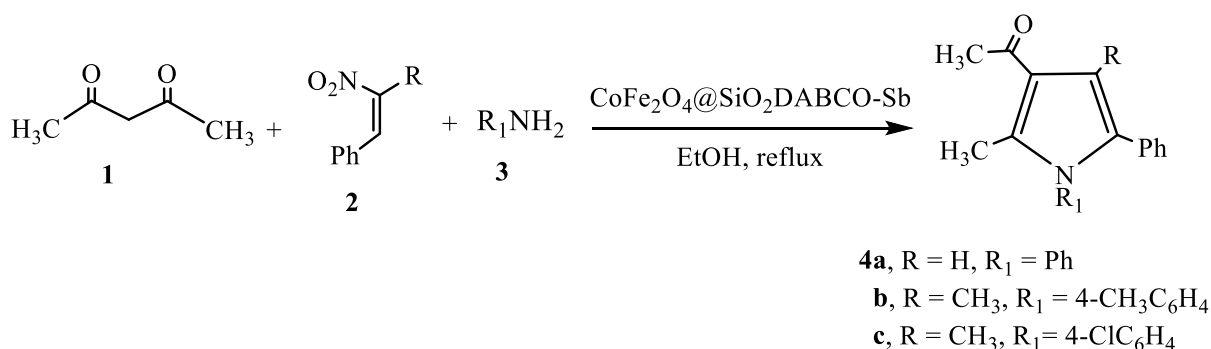
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methods have several disadvantages as the use of expensive materials, harsh conditions tedious multi-step procedures, excess toxic waste-generating reagents, low yields and large amounts of catalysts.¹⁵⁻¹⁹ Because of these disadvantages of traditional methods, researchers had to find effective, environmentally friendly, and fast methods with high yield for this synthesis.²⁰ Nanocatalysts have been used in the recent years. For example, Choudhary *et al.* reported that many researchers have synthesized various heterocyclic compounds using zirconia nanoparticles.²¹ Furthermore, Hussein *et al.* mentioned that there are many studies on the applications of nano magnesium ferrite as a nanocatalyst in the preparation of heterocyclic compounds.²² Nanocatalysts have improved selectivity and simplified procedures for this synthesis.^{12,23-28} Among them are *N*-heterocyclic compounds that show broad biological activity. Here, we highlighted on the production of pyrroles, pyrazoles, imidazoles, pyridines, pyrimidines and pyrazines using nanocatalysts.

2. Synthesis of Pyrroles, Pyrazoles, Imidazoles, Pyridines, Pyrimidines and Pyrazines Using Nanocatalysts

Li *et al.* published the synthesis of multisubstituted pyrroles **4a-c** by the reaction between 1,3-dicarbonyl **1**, nitroolefins **2** and amines **3** (Scheme 1) using $\text{CoFe}_2\text{O}_4@\text{SiO}_2\text{DABCO-Sb}$ magnetic nano-catalyst (Figure 1).^{29,30}



Scheme 1. Synthesis of pyrroles **4a-c**

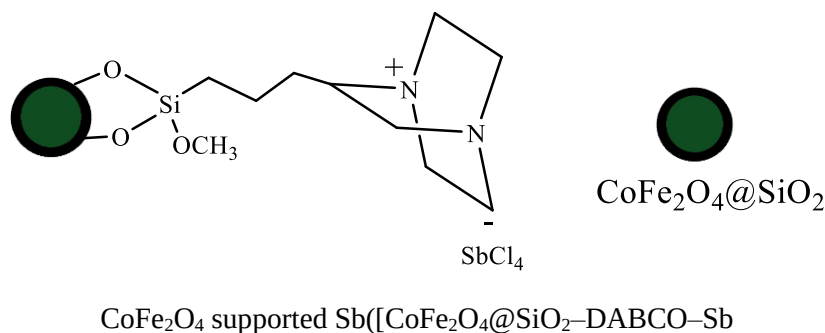
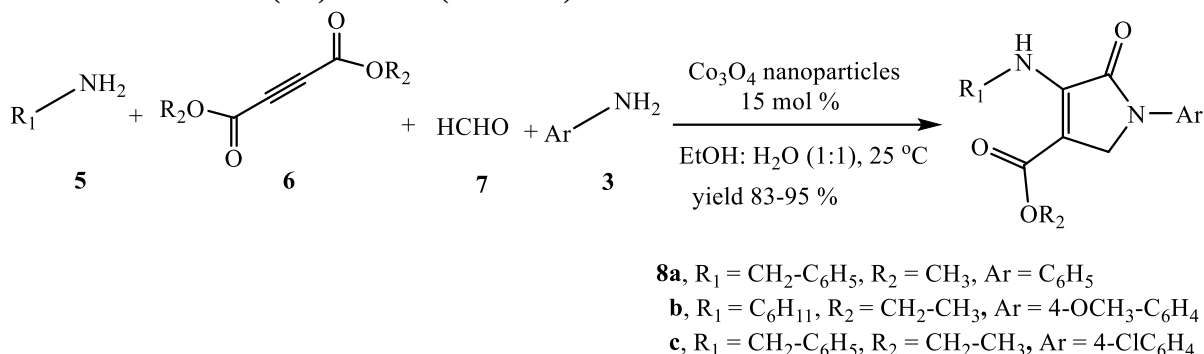


Figure 1. Structure of magnetic nano- CoFe_2O_4 supported $\text{Sb}([\text{CoFe}_2\text{O}_4@\text{SiO}_2\text{-DABCO-Sb})$

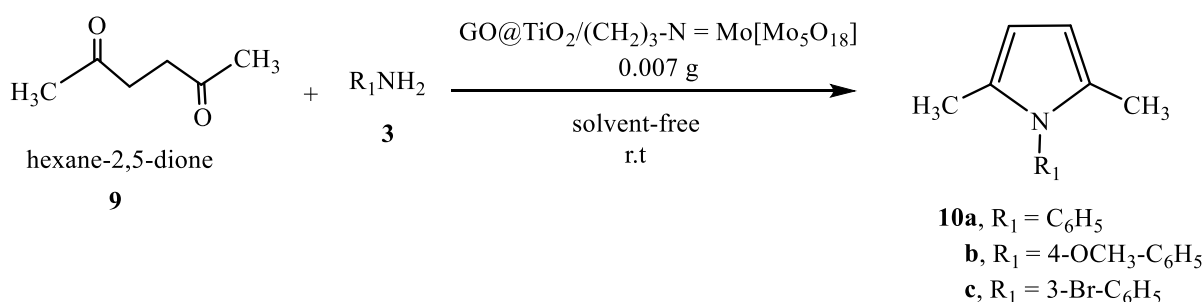
Almelibya *et al.* utilized Co_3O_4 nanoparticles to prepare two different components of nitrogen-containing heterocyclic compounds, achieving high synthesis efficiencies ranging from 83 % to 96 % at low temperatures and short reaction times. The Co_3O_4 nanoparticles were separated from the mixture using acetone and filtered with Whatman filter paper, allowing for their reuse six times without losing efficiency. Antioxidant and antimicrobial tests on the derivatives, utilizing the DPPH free radical method, were performed on Gram-positive and Gram-negative bacterial strains and fungal species. The pyrano [2,3-*c*]pyrazole derivatives were generally more effective against the studied species than the pyrrole derivatives. The interaction occurred to produce pyrrole derivatives through reactants cyclohexanamine or phenylmethanamine (**5**), dimethylbut-2-enedioate or diethylbut-2-

enedioate (**6**), an aromatic amine (**3**), and formaldehyde (**4**) with Co_3O_4 nanocatalysis in a water/ethanol mixture (1:1) at 25 °C (Scheme 2).³¹



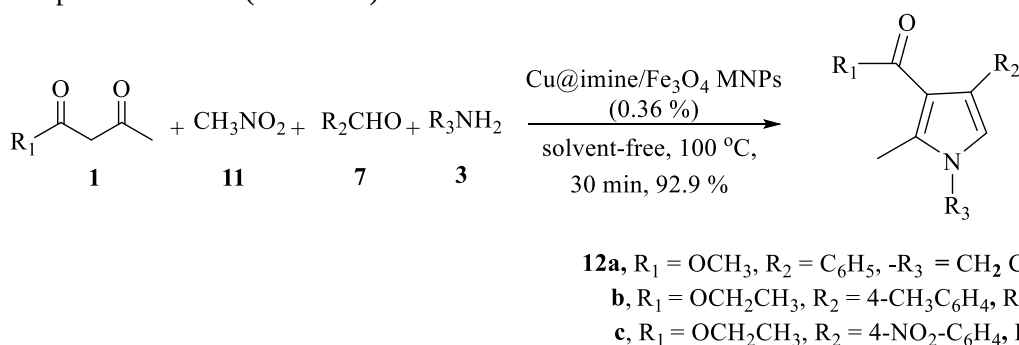
Scheme 2. Preparation of the pyrrole derivatives by using Co_3O_4 nanocatalyst

Keshavarz *et al.* prepared Pyrrole derivatives **10a-c** using an environmentally friendly heterogeneous solid nanocatalyst, $\text{GO@TiO}_2/(\text{CH}_2)_3\text{N}=\text{Mo}[\text{Mo}_5\text{O}_{18}]$, which exhibited exemplary performance and recyclability. This was accomplished by reacting the nanocatalyst with 2,5-hexadione (**9**) and amine (**3**) at 25 °C without solvent, conditions deemed optimal for the reaction, as reported by Keshavarz *et al.* (Scheme 3).³²



Scheme 3. Preparation of the pyrrole derivatives using $\text{GO@TiO}_2/(\text{CH}_2)_3\text{N} = \text{Mo}[\text{Mo}_5\text{O}_{18}]$ as the nanocatalyst

The method reported by Thwin *et al.* for the preparation of bioactive polysubstituted pyrroles derivatives **12a-c** through nanocatalysis using $\text{Cu@imine/Fe}_3\text{O}_4$ MNPs without solvent provides a practical approach for green and rapid synthesis, involving ethyl acetoacetate (**1**), nitromethane (**11**), benzaldehyde (**7**), and aniline (**3**) without solvent, utilizing a nanoparticle catalyst, in a four-component reaction (Scheme 4).^{33,34}

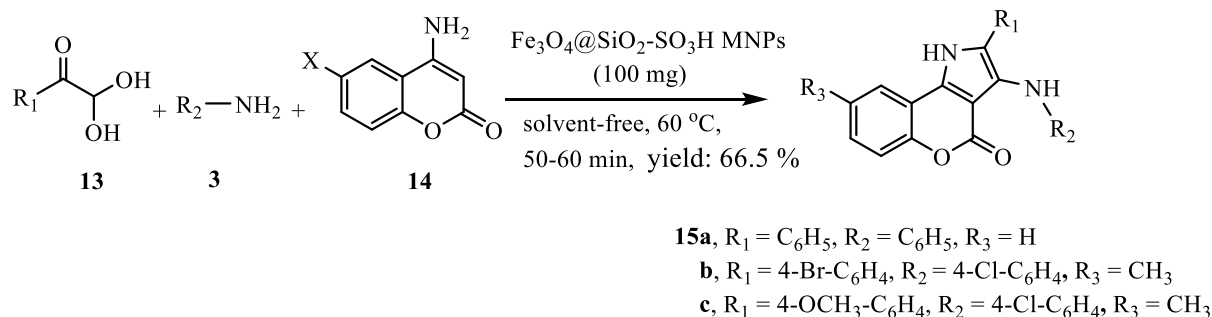


Scheme 4. $\text{Cu@imine/Fe}_3\text{O}_4$ MNP-catalysed for the synthesis of polysubstituted pyrrole derivatives

Utilizing a one-pot three-component domino condensation reaction, Mukherjee *et al.* prepared chromeno[4,3-b]pyrrol-4(1H)-one derivatives by the reaction between arylglyoxal monohydrates (**13**),

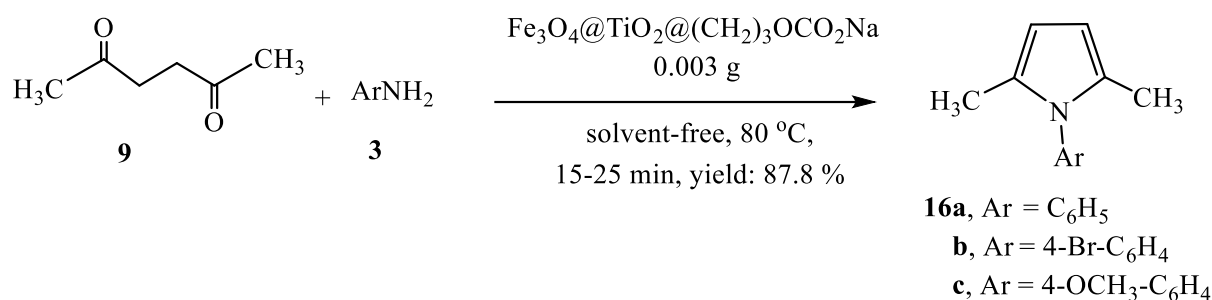
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arylamines (**3**), and 4-aminocoumarins (**14**), using $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-SO}_3\text{H}$ magnetic nanoparticles without solvent at 60 °C (Scheme 5). Mild reaction conditions, the elimination of risky solvents, and a high yield of products characterize the process.^{33,35}



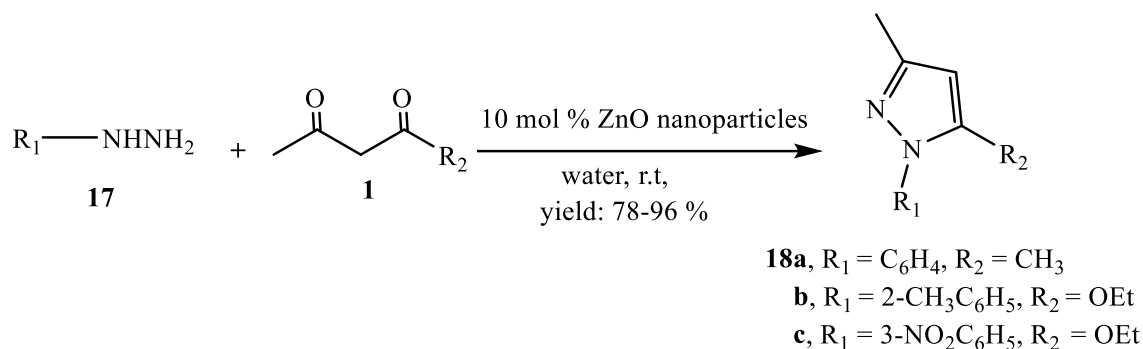
Scheme 5. Preparation of chromeno[4,3-b]pyrrol-4(1H)-one derivatives using $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-SO}_3\text{H}$ nanoparticles

According to Fattahi *et al.* the synthesis of pyrrole derivatives **16a-c** catalyzed by $\text{Fe}_3\text{O}_4@\text{TiO}_2$ -supported sodium carbonate ($\text{Fe}_3\text{O}_4@\text{TiO}_2@(\text{CH}_2)_3\text{OCO}_2\text{Na}$) through a novel Paal–Knorr reaction was reported. Additionally, it can be easily isolated using an external magnetic field and can be recycled without loss of activity. The interaction is taking place to produce pyrrole derivatives through reacting 2,5-hexadione (**9**) and amines (**2**) under green nanocatalysis with mild conditions (Scheme 6).^{33,36}



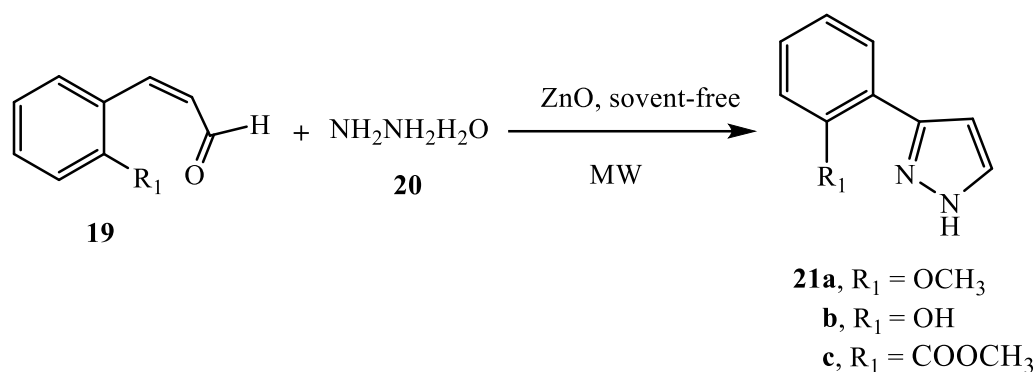
Scheme 6. Preparation of the pyrrole derivatives using $\text{Fe}_3\text{O}_4@\text{TiO}_2@(\text{CH}_2)_3\text{OCO}_2\text{Na}$

Girish *et al.* reported a high-yield synthesis of pyrazole derivatives **18a-c** using highly active zinc oxide (ZnO) nanoparticles. This reaction involves various structural variables phenyl hydrazines (**17**) with 1,3-diketones (**1**) in the presence of a zinc oxide (ZnO) nanocatalyst at room temperature and in H_2O . The characteristics of this method are that it is environmentally friendly and economical, and it also allows for easy product isolation (Scheme 7).³⁷



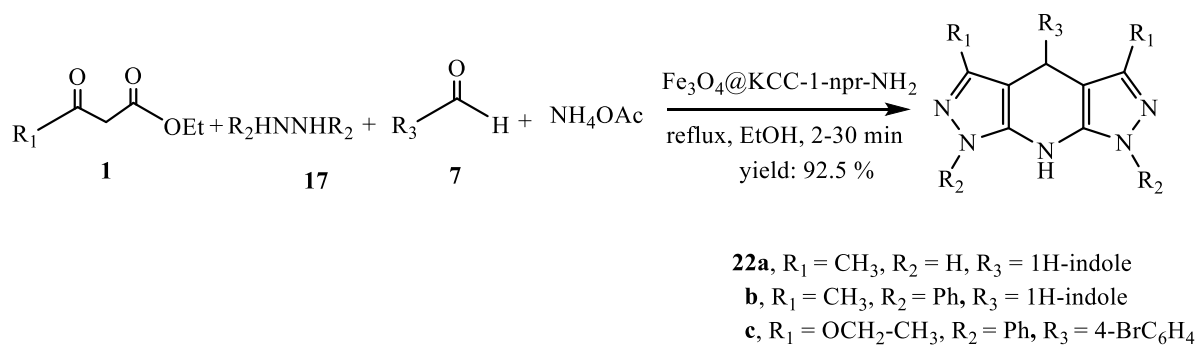
Scheme 7. Preparation of the pyrazole derivatives zinc oxide (ZnO) nanocatalyst

Yalapa *et al.* reported the synthesis of 2-substituted-3-phenyl-1H-pyrazoles **21a-c** by the reaction between cinnamaldehyde (**19**) and hydrazine hydrate (**20**) using two equivalents of the nanocatalyst ZnO without solvent under Microwave. The microwave method without solvent represented a simple reaction scheme, and the ZnO catalyst was proven to be environmentally benign (Scheme 8).³⁸



Scheme 8. Synthesis of different {3-(2-Substituted)-Phenyl}-1H-Pyrazoles

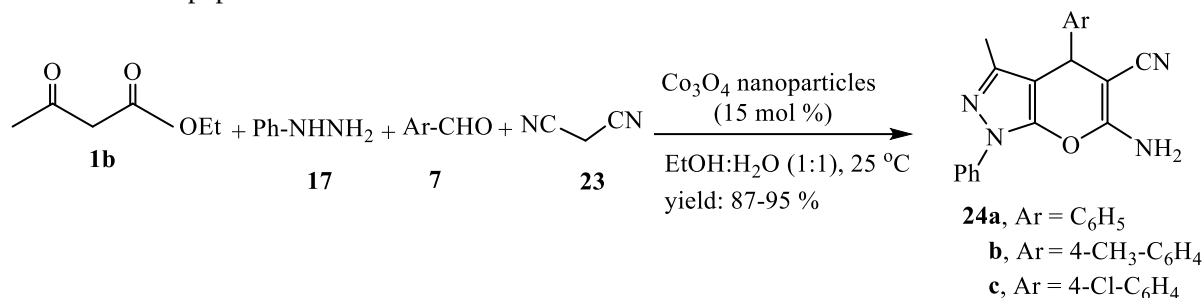
Azizi *et al.* demonstrated the synthesis of tetrahydrodipyrazolopyridines **22a-c** by the four-component reaction between ethyl acetoacetate (**1b**), hydrazine hydrate (**17**), aromatic aldehyde (**7**) and ammonium acetate using $\text{Fe}_3\text{O}_4@\text{KCC-1-npr-NH}_2$ catalyst at 25 °C in ethanol as a solvent under reflux conditions. The anticancer activity of the synthesized compounds was studied by MTT assay. These compounds demonstrated cytotoxic effects against specific types of cancer cells (Scheme 9).³⁹



Scheme 9. Preparation of the tetrahydrodipyrazolopyridines

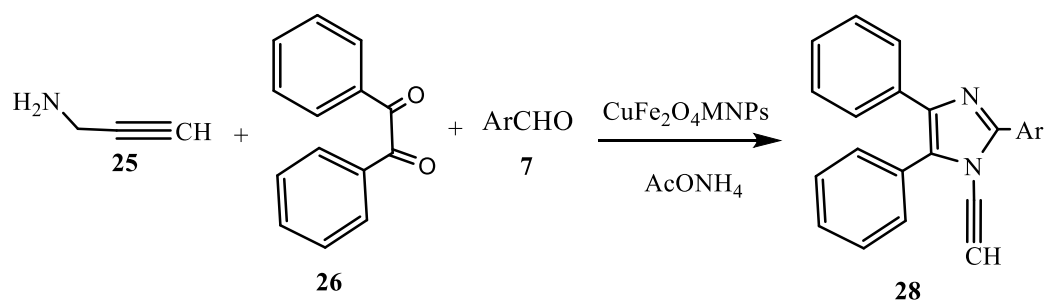
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The reaction of Co_3O_4 nanoparticles in synthesizing pyrano [2,3-*c*]pyrazole **24a-c** from ethyl acetoacetate (**1b**) and phenylhydrazine (**17**) was carried out in a water/ethanol mixture (1:1) and stirred at 50 °C. In the second step, after the reaction was completed, aldehyde (**7**) and malononitrile (**23**) were added and stirred at 50 °C to produce pyrano [2,3-*c*]pyrazole derivatives (Scheme 10).³¹ Following the completion of the reaction, which was monitored by TLC, the mixture was allowed to cool to room temperature before acetone was added, and Co_3O_4 nanoparticles were separated using Whatman filter paper.



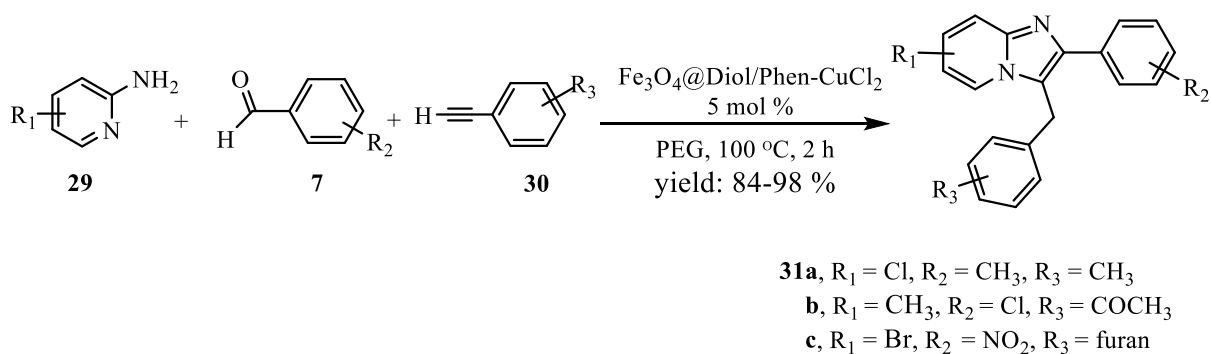
Scheme 10. Preparation of the pyrano [2,3-*c*]pyrazole derivatives by using Co_3O_4 nanocatalyst

Remaily *et al.* published the synthesis of tetrasubstituted imidazoles **28** by the reaction between propargylamine **25**, benzil **26**, aldehydes **7** and ammonium acetate using magnetic nano-catalyst CuFe_2O_4 (Scheme 11).^{40,41}



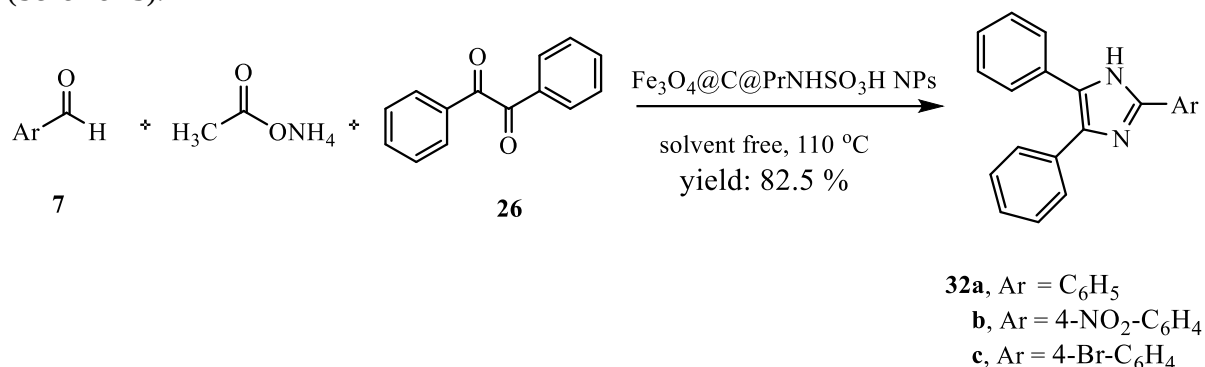
Scheme 11. Synthesis of 1,2,4,5-tetrasubstituted imidazoles **28** using magnetic nano-catalyst CuFe_2O_4

Through a one-pot three-component reaction, Jiang *et al.* used a significant amount of the environmentally friendly $\text{Fe}_3\text{O}_4@\text{Diol/Phen-CuCl}_2$ nanocatalyst to prepare imidazo[1,2-*a*]pyridine derivatives **31a-c** by reacting 2-aminopyridines (**29**), aldehydes (**7**), and terminal alkynes (**30**) with a nanocatalyst and solvent (PEG) at temperatures around 110 °C (Scheme 12).⁴²



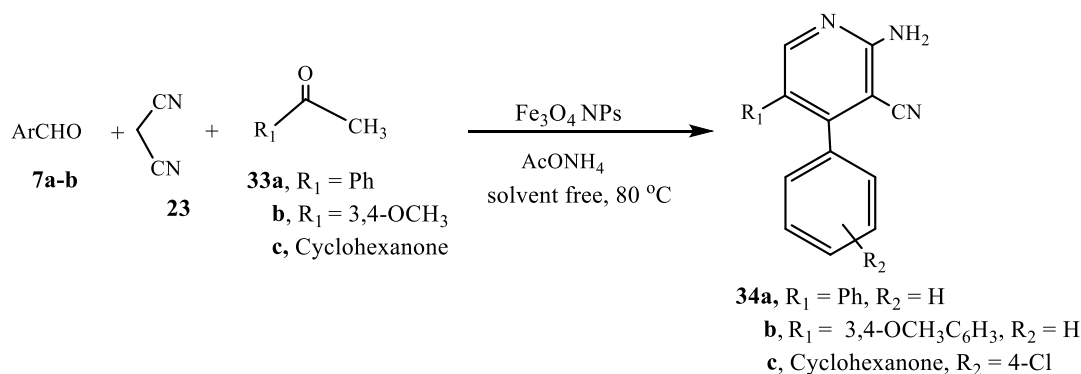
Scheme 12. Preparation of the imidazo[1,2-*a*]pyridines catalyzed using $\text{Fe}_3\text{O}_4@\text{Diol/Phen-CuCl}_2$

Nasehi *et al.* prepared the 4,5-diphenyl-1H-imidazole derivatives **32a-c** by using $\text{Fe}_3\text{O}_4@\text{C}@\text{PrNH}_3\text{SO}_3\text{H}$ NPs magnetic nanoparticles reacted with aldehyde derivatives **7**, ammonium acetate, and benzil (**26**) at 110 °C without solvent conditions in a one-pot three-component reaction (Scheme 13).⁴³



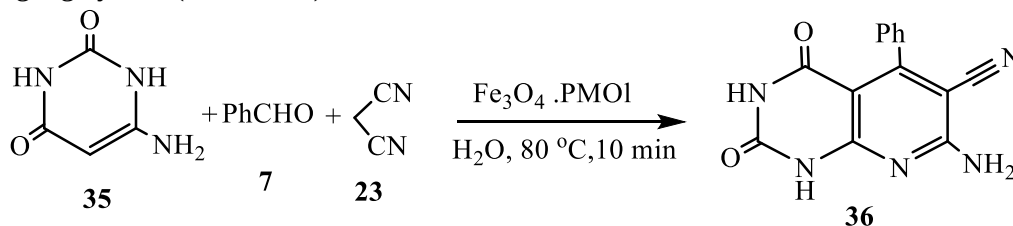
Scheme 13. Preparation of the 4,5-diphenyl-1H-imidazole derivatives with $\text{Fe}_3\text{O}_4@\text{C}@\text{PrNH}_3\text{SO}_3\text{H}$ NPs

Heravi, M. M., *et al.* reported the synthesis of 2-amino-3-cyanopyridine derivatives **34a-c** by the reaction between aldehydes **7a-b**, malononitrile (**23**), AcONH₄ and either of acetophenones **33a-b** or cyclohexanone **33c** using Fe_3O_4 magnetic nanoparticles (Scheme 14).⁴⁴



Scheme 14. Synthesis of 2-amino-3-cyanopyridine derivatives **34a-c**

Faroukian *et al.* studied the $\text{Fe}_3\text{O}_4\text{-ZnO-NH}_2\text{-PW}_{12}\text{O}_{40}$ nanoparticle for synthesizing pyrido[2,3-d]pyrimidines in water. This was accomplished by reacting the nanoparticles with equal amounts of 6-aminouracil (**35**), benzaldehyde (**7**), and malononitrile (**23**) in H₂O to produce pyrido[2,3-d]pyrimidines **36** in a short time and with good yields. Furthermore, the effects of varying solvent conditions and temperatures on the reaction were investigated. According to the results, the optimal conditions for this reaction involved using water at 80 °C with 20 mg of the nanocatalyst. This method features ease of operation and environmental benefits by preventing toxic solvents while producing high yields (Scheme 15).⁴⁵

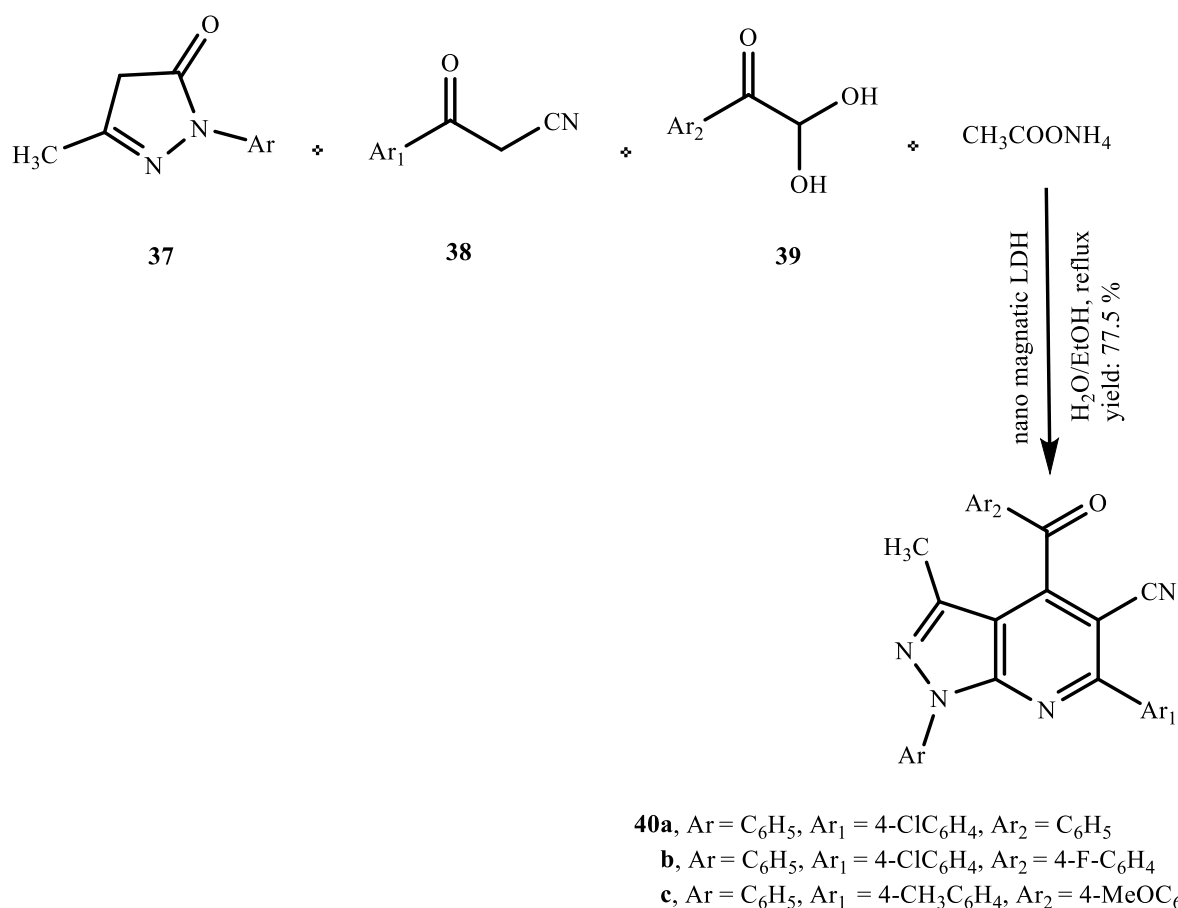


Scheme 15. Using nanoparticles $\text{Fe}_3\text{O}_4\text{-ZnO-NH}_2\text{-PW}_{12}\text{O}_{40}$ for the preparation of

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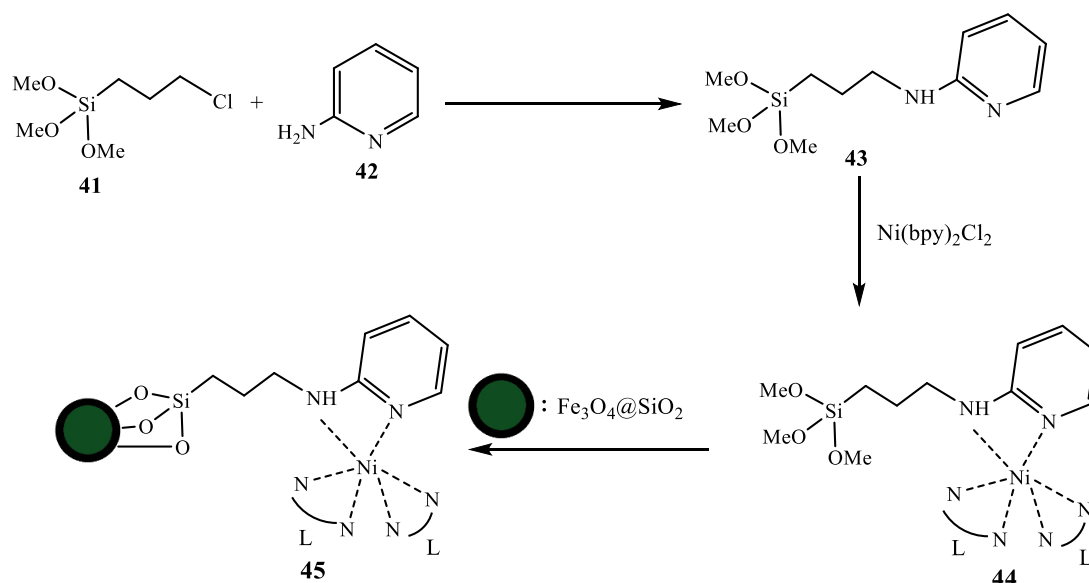
pyrido[2,3-d]pyrimidines

In a one-pot four-component reaction, Arlan and his co-workers synthesized a series of pyrazolopyridine derivatives **40a-c** using $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{Ni-Zn-Fe}$ LDH nanoparticles. The process involves 1-aryl-3-methyl-1H-pyrazol-5(4H) one (**37**), 3-aryl-3-oxopropanenitriles (**38**), various arylglyoxals (**39**), and ammonium acetate with a nanomagnetic catalyst under mild reaction conditions using EtOH/H₂O (1:1) at reflux to produce pyrazolopyridine derivatives (Scheme 16).⁴⁶

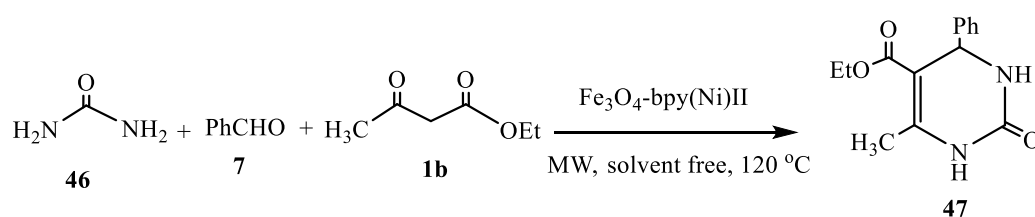


Scheme 16. Synthesis of pyrazolopyridine derivatives

Similarly, Girija *et al.* demonstrated the synthesis of dihydropyrimidin-one (**47**) using the nano- $\text{Fe}_3\text{O}_4\text{-bpy-Ni(II)}$ nanomaterial (Scheme 17) by the reaction between urea (**46**), benzaldehyde (**7**) and ethyl acetoacetate (**1b**) (Scheme 18).^{47,48}

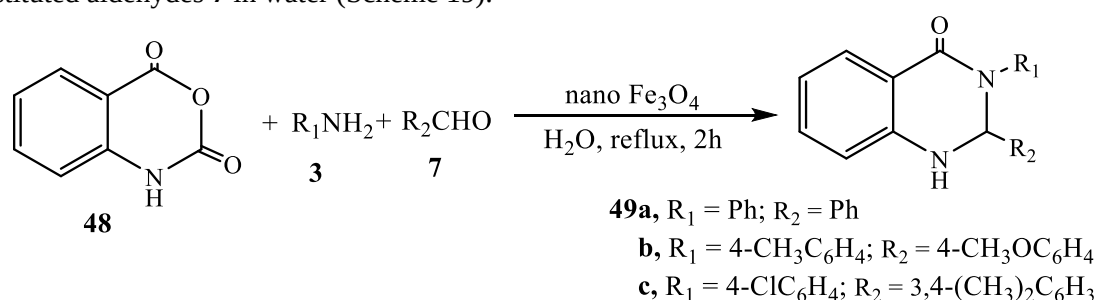


Scheme 17. Synthetic strategy for preparation of the nano- Fe_3O_4 -bpy-Ni(II) nanomaterial



Scheme 18. Microwave-assisted preparation of 3,4 dihydropyrimidinone 47 using nano- Fe_3O_4 -bpy-Ni(II) nanomaterial

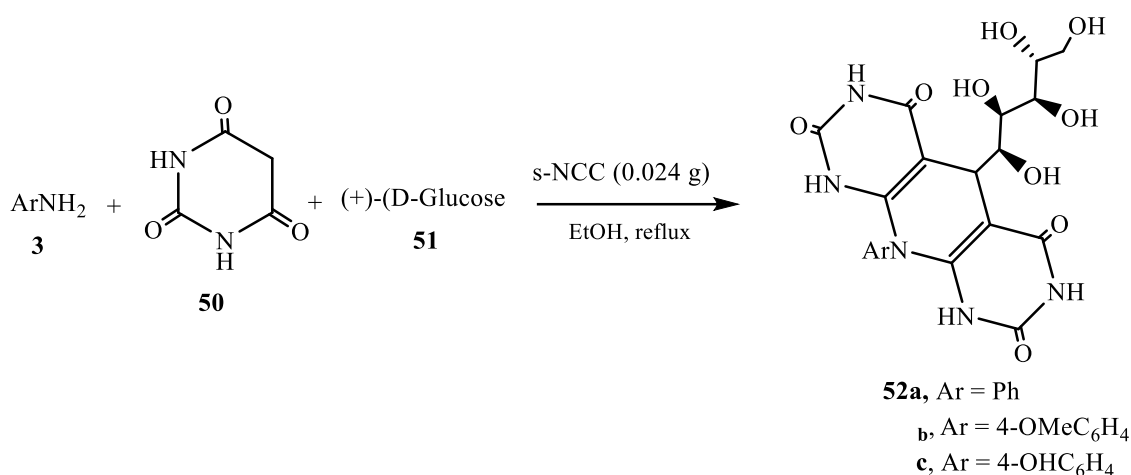
Zhang *et al.* reported the synthesis of quinazolin-4(1H)-ones 49 using Fe_3O_4 nanoparticles according to the multicomponent reactions between isatoic anhydride (48), various amines 3 and substituted aldehydes 7 in water (Scheme 19).^{49,50}



Scheme 19. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones 49a-c using Fe_3O_4 nanoparticles

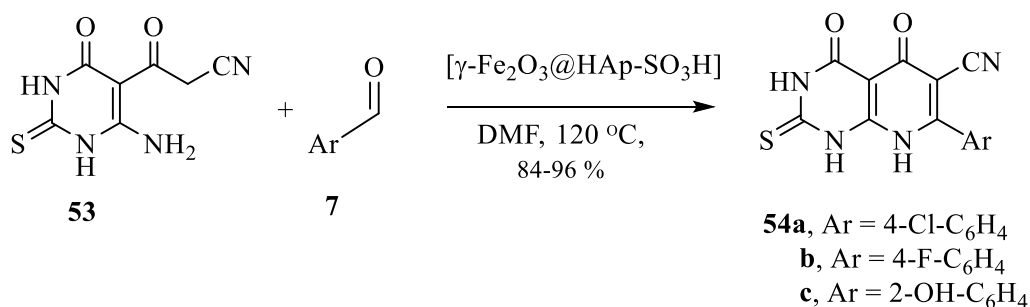
Nikoofar *et al.* demonstrated the synthesis of polyhydroxy pyrimidines 52 using a green nano-catalyst called crystalline cellulose sulfuric acid by the reaction between aromatic amines 3, barbituric acid (50) and carbohydrates 51 in ethanol under reflux (Scheme 20).⁵¹

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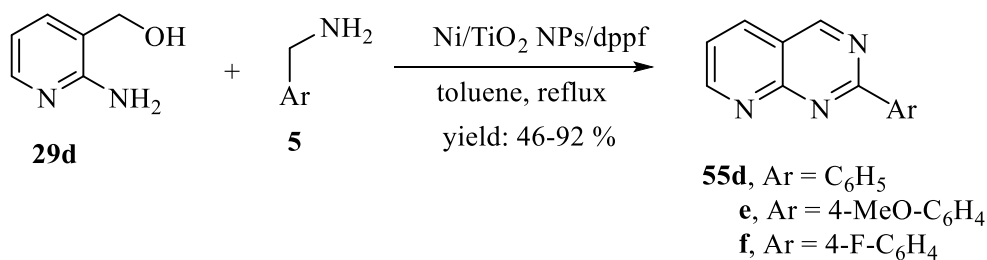
Scheme 20. Synthesis of polyhydroxy pyrimidine-fused heterocyclic compounds (PPFHs) **52a-c**

Mamaghani *et al.* used a [γ -Fe₂O₃@HAp-SO₃H] nanoparticle to synthesize pyrido[2,3-d]pyrimidines **54a-c**. The process involves reacting cyanoacetyl pyrimidinone (**53**) and aryl aldehydes (**7**) with nanocatalysis in solvent (DMF) at 120 °C through two-component reactions. Thanks to the nanocatalyst's role, high yields of 84–96 % were achieved (Scheme 21).^{52,53}



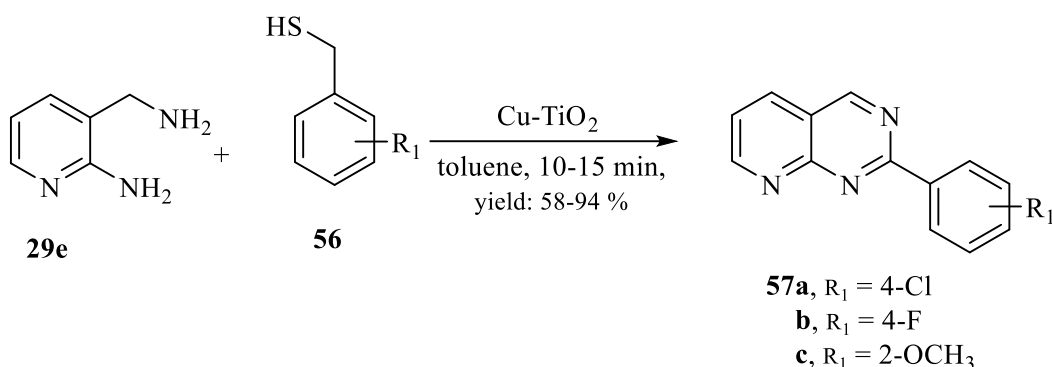
Scheme 21. Synthesis of hexahydropyridopyrimidines

Kaiba *et al.*⁵⁴ focused on using Ni-doped TiO₂ nanoparticles to synthesize 2-aryl-pyrido[2,3-d]pyrimidines. Nanoparticles of titanium dioxide are considered an efficient nanocatalyst, suitable for catalysis in the water gas shift,⁵⁵ hydrodesulfurization,⁵⁶ dehydrogenations^{57,58} and thermal decomposition.⁵⁹ The interaction involved (2-aminopyridin-3-yl)methanol (**29d**) and aryl methanamines (**5**) with a nanocatalyst of Ni-doped TiO₂ in toluene to synthesize pyridopyrimidine derivatives, occurring through two-component reactions (Scheme 22).⁵³



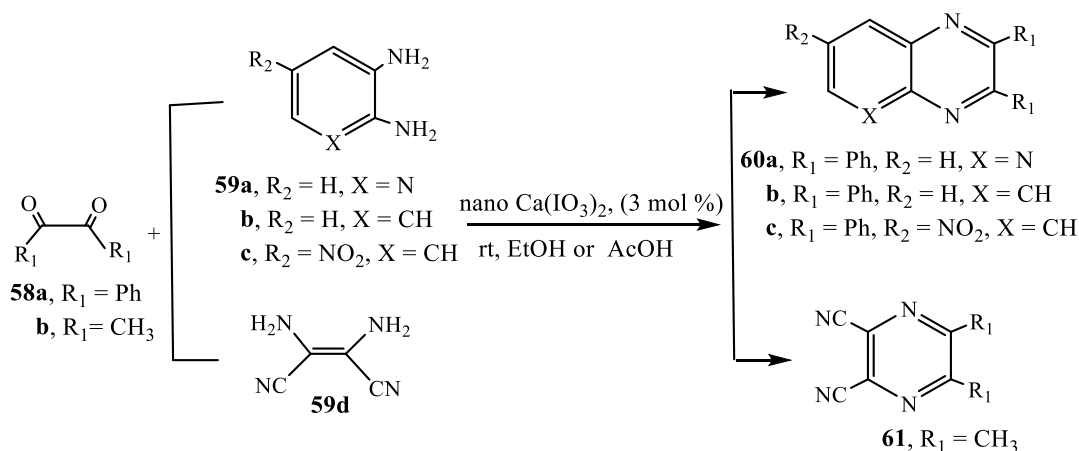
Scheme 22. Preparation of pyridopyrimidine derivatives by Ni/TiO₂ NPs/dppf

Geesi *et al.*⁶⁰ recently synthesized hexahydropyrido[2,3-d]pyrimidine derivatives with high yield rates, using Cu-doped TiO₂ nanoparticles as an efficient nanocatalyst. This was achieved through a cyclo-condensation reaction by reacting 3-(aminomethyl)pyridin-2-amine (**29e**) and aryl methanethiol (**56**) in toluene solvent at room temperature with the Cu-TiO₂ nanocatalyst. (Scheme 23).⁵³



Scheme 23. Preparation of the 2-aryl-pyrido[2,3-d]pyrimidines by Cu-TiO₂ nanocatalyst

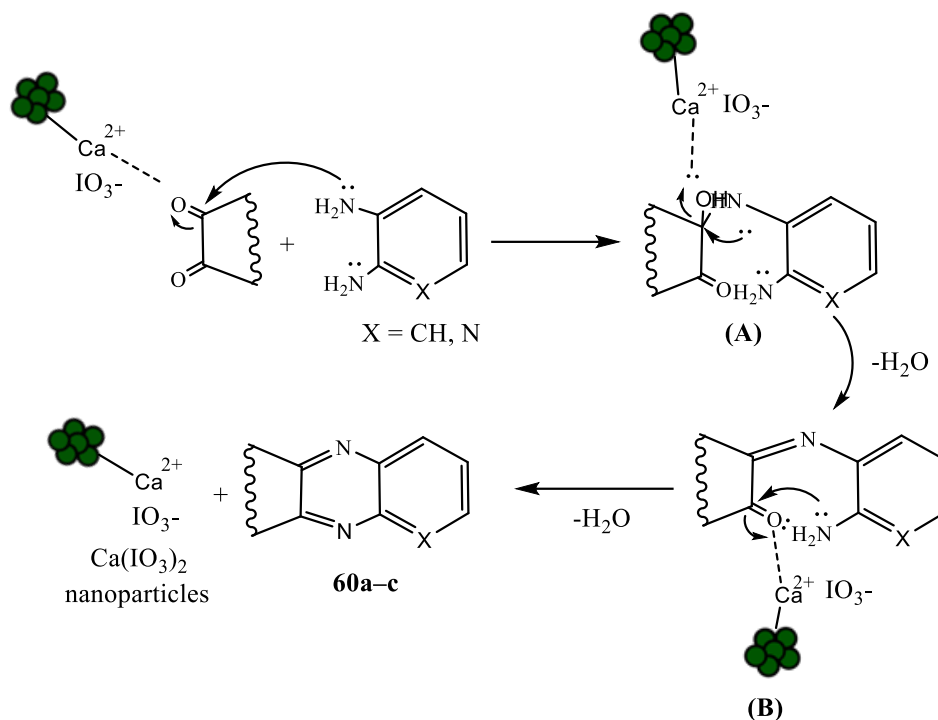
Kalhor *et al.* reported the synthesis of pyridopyrazines, quinoxalines and 2,3-dicyano pyrazines by the reaction between 1,2-diketones and either of aryl-1,2-diamines or 2,3-diaminomaleonitrile, respectively. The optimal reaction was in the presence of Ca(IO₃)₂ nanoparticles (3 mol %, 0.005 g) and ethanol as a solvent (Scheme 24).



Scheme 24. Synthesis of pyridopyrazines **60a**, quinoxalines **60b,c** and 2,3 dicyano pyrazines **61**

The carbonyl group was activated by calcium ion to give intermediate (**A**), followed by nucleophilic attack of the amine group and loss of water molecule to give the Schiff base intermediate through the catalytic oxidation. The same manner of nucleophilic attack of the other amine to the carbonyl of 1,2-diketone happened followed by intramolecular cyclization after the loss of water molecule to produce the pyrido-pyrazine, quinoxaline and dicyanopyrazine. Calcium ion is responsible for activating the diketone, increasing yield, and shortening the reaction time. It is a strong Lewis acid due to the higher oxidizing effect of iodate ions (Scheme 25).⁶¹

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Scheme 25. Proposed mechanism for the synthesis of compounds **60a-c**

3. Conclusion

In this review, we aimed to overview the synthesis of *N*-heterocyclic compounds using various of nanocatalysts, such as, $\text{CoFe}_2\text{O}_4@\text{SiO}_2\text{DABCO-Sb}$, Co_3O_4 , $\text{Cu@imine/Fe}_3\text{O}_4$ and $\gamma\text{-Fe}_2\text{O}_3@\text{HAp-SO}_3\text{H}$. Nanocatalysts are very important in heterocyclic synthesis, for many reasons. Firstly, using nanocatalysts is considered a type of green or sustainable synthesis that aims to synthesize compounds that are less hazardous to the environment. Secondly, nanocatalysts can be used several times up to six times, without losing their effectiveness. In addition, most of these nanocatalysts are cheap, economical and available. These nanocatalysts features facilitate the synthesis of these *N*-heterocyclic compounds which are important in the pharmaceutical field due to their broad biological importance.

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