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Magnetically recoverable nanocatalyst for the synthesis of pyranopyrazoles: $CoFe_2O_4$@SiO_2-$HClO_4$

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RESEARCH ARTICLE

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ABSTRACT

The multiheterocyclic ring system shows valuable pharmaceutical and biological activities. In the present study, a microwave-assisted three-component reaction between aryl aldehyde, malononitrile, and 5-methyl-2,4-dihydro-3*H*-pyrazole-3-one led to the synthesis of pyrano[2,3-c]pyrazoles has been described. The reaction was carried out under solvent-free conditions in the presence of a new magnetically recoverable nanocatalyst ($CoFe_2O_4$@SiO_2-$HClO_4$). The reported protocol offers several advantages such as being environmentally benign, being rapid, inexpensive, having high atom and step economy, and being facile. The simple method of catalyst preparation, easy magnetic recovery, and reusability of the catalyst for four runs are notable features of the nanocatalyst. Antibacterial activity of all synthesized compounds was tested against *Escherichia coli* and *Staphylococcus aureus*. All synthesized compounds showed promising biological activity and may be used as a potential antibacterial candidate in biological science.

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1. Introduction

Nowadays, heterocyclic scaffolds like pyranopyrazoles play a very important role because of their potential application in pharmaceutical and biological activities, such as anticancer [1], antimicrobial [2], anti-inflammatory [3], insecticidal, molluscicidal [4] and also, they are identified as a screening kit for Chk1 kinase [5]. In addition, Qvortrup *et al*. reported the synthesis of dihydropyrano-[2,3-c]pyrazoles as a new class of peroxisome proliferator-activated receptor gamma (PPARγ) partial agonists [6]. These compounds are found to be very good precursors in the field of medicinal chemistry [7,8]. Therefore, enormous efforts have been made to develop green and convenient routes for their high-yielding synthesis.

For the synthesis of such an important class of heterocyclic scaffolds, various synthetic procedures have been applied, such as single- or multi-step reactions, as well as two- or multi-component reactions [9]. Otto proposed the first reported method for the synthesis of dihydropyrano[2,3-c] pyrazoles in 1974, through base-catalyzed cyclization of 4-arylidene-5-pyrazolone [10]. In a further report, Otto and Schmelz showed that weak bases can also be used for a Michael-type cyclization [11]. The first multicomponent approach to the synthesis of the pyrano[2,3-d]pyrazole motif was based on the reaction between tetracyanoethylene and 3-methyl-1*H*-pyrazolin-5-one, which provide products in good yields. Subsequently, many synthetic routes for development substituted derivatives of pyrano[2,3-c]pyrazoles [12], spiro-pyrano[2,3-c]pyrazoles [13] and dihydropyrano[2,3-c]pyrazoles [14] were also reported. Recently, the most common and convenient approach to synthesize a library of various pyrano[2,3-c]pyrazoles was reported by catalyzed multicomponent reactions [15]. A catalyst is a substance that enhances the rate of reaction by lowering the activation energy. Some of the catalysts reported for pyranopyrazole synthesis were triethanolamine [16], urea [17], and earth clay bleaching [18]. Recently, environmentally compatible catalysts have been developed such as BF_3/MNP [19], $Fe_{3-x}TixO_4$@SO_3H [20], Nd-SM [21], ZnO_2 nanoparticles [22] sodium lactate [23] for the condensation of aldehyde, cyclic ketone, and malononitrile. In addition to the above, several strategies have been developed to synthesize pyrano[2,3-c] pyrazoles, such as microwave irradiation [24], electrocatalysis [25], ultrasonication [26] and reaction in different solvents, various temperature conditions and catalysts. Although the reported methods are quite satisfactory, some of them suffer from one or other drawbacks such as the absence of a green chemistry approach, the use of volatile and hazardous organic

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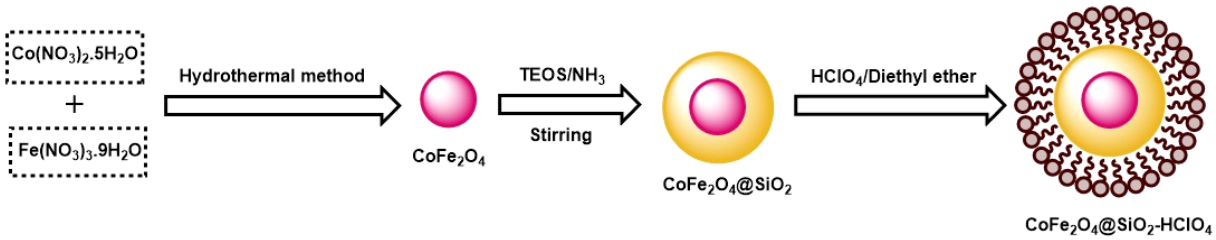


Scheme 1. Preparation of magnetic recoverable nanoparticles-$CoFe_2O_4$@SiO_2-$HClO_4$.

solvents, low yields, extended reaction time, high temperature, and a tedious procedure for the preparation of catalysts.

Therefore, we develop a new $CoFe_2O_4$@SiO_2-$HClO_4$ nanocatalyst that bridges the gap between homogeneous and heterogeneous catalysis. An easy method of preparation and magnetic recovery of nanoparticles follows the green chemistry principle. Previously developed and successfully characterized $CoFe_2O_4$@SiO_2-$HClO_4$ as magnetically recoverable nanoparticles exhibited its effectiveness against the microwave-assisted synthesis of 8-phenyl-7*H*-acenaphtho[1,2-d]imidazoles [27]. Furthermore, we explored the potential of $CoFe_2O_4$@SiO_2-$HClO_4$ magnetically recoverable nanoparticles against the synthesis of pyrano[2,3-c]pyrazoles via tandem reaction of aldehyde, malononitrile, and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one under solvent-free condition and microwave irradiation. The $CoFe_2O_4$@SiO_2-$HClO_4$ nanocatalyst brought notable organic transformations due to its ability to enhance the rate of organic reactions, high catalytic activity, higher yield of products, magnetic recovery, and reusability of the catalyst.

2. Experimental

2.1. Materials and instrumentations

All solvents and chemicals were of analytical grade and purchased from Sigma-Aldrich and used as received. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance spectrometer using DMSO-d_6 as solvent. A Fourier transform infrared spectrum was recorded on the Shimadzu FT-IR-8400 spectrometer. The microwave-assisted reaction was exhibited in a Scientific Ragatech microwave oven (2450 MHz). This system is fitted with a temperature and power feedback control switch and measures the temperature via a highly sensitive IR sensor.

2.2. Preparation of magnetically recoverable nanocatalyst-$CoFe_2O_4$@SiO_2-$HClO_4$

Previously developed and successfully characterized $CoFe_2O_4$@SiO_2-$HClO_4$ as magnetically recoverable nanoparticles used as nanocatalysts in the synthesis of pyranopyrazoles [27]. In the initial stage of preparation, $CoFe_2O_4$ nanoparticles were prepared by the known hydrothermal method by mixing stoichiometric proportions of $Co(NO_3)_2{\cdot}5H_2O$ (1 mmol) and $Fe(NO_3)_3{\cdot}9H_2O$ (2 mmol) and NaOH (1 mmol) dissolved in distilled water. To avoid agglomeration and to get chemical stability, the core nanoparticles of $CoFe_2O_4$ were wrapped with silica shells by slow addition of tetraethylorthosilicate (TEOS). The suspension of the formed $CoFe_2O_4$@SiO_2 nanoparticles was centrifuged on a centrifuge machine; the filtrate was discarded and the precipitate of the nanoparticles was first washed with water and then with ethanol. The obtained core-shell nanoparticles were dried in an oven overnight at 70 °C. The dried magnetic core-shell NPs were separated using an external magnet. In the next stage of preparation, the functionalization of the core-shell nanoparticles (NPs) was carried out by refluxing $CoFe_2O_4$@SiO_2 magnetic nanoparticles in diethyl ether and 0.03 mmol of $HClO_4$ of 70% aqueous solution under vacuum. The mixture was concentrated and the residue was heated for 72 h at 70 °C under vacuum to obtain functionalized $CoFe_2O_4$@SiO_2-$HClO_4$ magnetic nanoparticles. The surface-modified perchloric acid core-shell $CoFe_2O_4$@SiO_2 magnetic nanoparticles were characterized by XRD, SEM-EDX, TEM, VSM, BET, TG-DTA, and FT-IR analysis. Successfully synthesized and characterized magnetic nanoparticles (MNPs) employed in organic transformation as catalysts. This protocol is depicted in Scheme 1.

2.3. General procedure for the synthesis of pyranopyrazoles using magnetic recoverable nanocatalyst- $CoFe_2O_4$@SiO_2-$HClO_4$ (4a-4o)

A mixture of 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (1.0 mmol), aldehyde (1.0 mmol), malononitrile (1.0 mmol), and previously developed $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) was placed in 50 mL round bottom flask and the reaction mixture was irradiated in the microwave (560 W at 100 °C) for the desired time. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was diluted with dichloromethane: methanol mixture (1:1, v/v) (20 mL) and the catalyst was separated by an external magnet. The decanted solution was concentrated under reduced pressure to obtain a solid residue. The solid product was washed with water and recrystallized with DMF and water mixture (1:1, v/v). The recovered catalyst was washed with dichloromethane:methanol mixture (1:1, v/v) and dried at 70 °C and reused for the next cycle (Scheme 2). All purified products were characterized by IR, ^1H-NMR, ^{13}C-NMR, and MS and compared with the literature data.

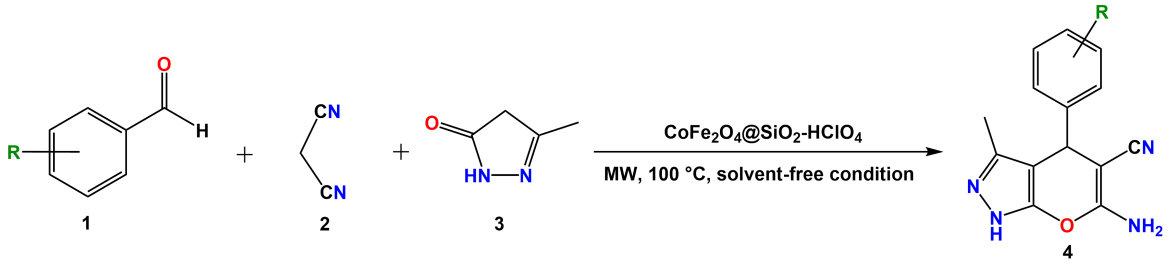
2.4. Antimicrobial activity

In the present protocol, we tested the bactericidal activity of the synthesized organic compounds using the disc diffusion method described by Kirby-Bauer [28,29]. Mueller-Hinton agar was used in the Kirby-Bauer method for rapid growth of aerobic organisms. The medium in the plates was sterilized and the depth of the medium was kept at about 4 mm. Pure culture was used as an inoculum. 3-4 similar colonies were selected and transferred to 5 mL of suitable broth such as tryptone soya broth. Incubation was kept at 35 °C for 2-8 hours until light to moderate turbidity developed. The turbidity was adjusted to yield a uniform suspension in the range of 1×10^5 and 1×10^6 cells/mL. A sterile non-toxic cotton swabbed dip into the standardized inoculum (turbidity adjusted to obtain confluent growth on the Petri plate), and rotated the soaked swab firmly against the upper wall of the tube to express excess fluid. We streaked the entire agar surface of the plate with the swab three times, turning the plate at 60 ° angles between each streaking. We allowed the inoculum to dry for 5-15 minutes with the lid in place. The sterilization of forceps was carried out by dipping them in alcohol and heating. A paper disc was taken using sterilized forceps and the disc was soaked in the chemical (2000 µg/mL antibacterial solution) to be tested.

Table 1. Effect of solvent on the synthesis of pyrano[2,3-d]pyrazole [a].

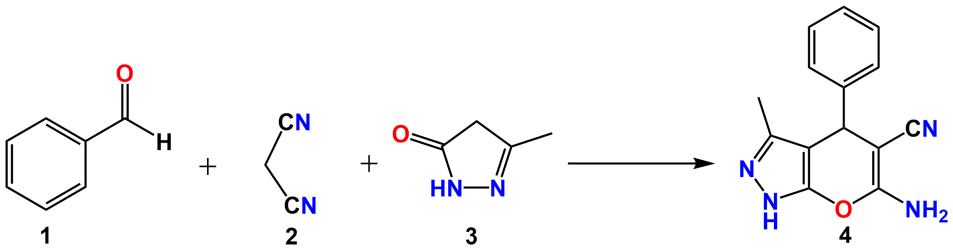
Entry	Solvent	Reaction condition	Time (min)	Yield (%) [b]
1	Methanol	Reflux	180	44
2	Ethanol	Reflux	180	62
3	THF	Reflux	180	56
4	Acetonitrile	Reflux	180	30
5	Water	Reflux	180	67
6	1,4-Dioxane	Reflux	180	64
7	Solvent-free	90 °C/MW	15	87

[a] Reaction conditions: 5-Methyl-2,4-dihydro-3*H*-pyrazol-3-one: benzaldehyde: malononitrile (1:1:1), $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt %).
[b] Isolated yield.



Compound 1/4	R	Compound 1/4	R
a	H	i	4-CH_3
b	3-NO_2	j	4-$(CH_3)_2CH$
c	4-Cl	k	4-$(CH_3)_2N$
d	4-OH	l	2-Furyl
e	3-OC_2H_5, 4-OH	m	2-Thiophene
f	4-OCH_3	n	3-Indolyl
g	3,4-OCH_3	o	Terephthalaldehyde
h	3,4,5-OCH_3		

Scheme 2. Synthesis of pyranopyrazoles using magnetic recoverable nanocatalyst-$CoFe_2O_4$@SiO_2-$HClO_4$ (**4a**-**4o**).



Scheme 3. Model reaction for the synthesis of pyrano[2,3-d]pyrazoles.

The excess chemical was drained by touching the disc on the sides of the tube. The disc was inserted into the center of the Petri dish in aseptic condition. After incubation of the Petri dish at 37 °C, the results were examined after 18-20 hours. Measurement of the zone showing complete inhibition was performed and data was recorded in diameter (mm).

3. Results and discussion

In continuation of our research, successfully synthesized and characterized nanoparticles were applied as a catalyst in multicomponent reactions to synthesize pyranopyrazoles and their derivatives. In the first stage of the investigation, we considered a three-component reaction of the 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) system as a model reaction. Various reaction parameters such as solvent, catalyst amount, temperature, and microwave irradiation frequency have been optimized for the model reaction (Scheme 3).

3.1. Effect of solvent

Initially, we carried out screening of solvents for pyropyazole synthesis. We tested the reaction in some protic and aprotic solvents such as ethanol, methanol, THF, 1,4-dioxane, water, and acetonitrile in the presence of $CoFe_2O_4$@SiO_2-$HClO_4$ nanocatalyst. It was observed that the reaction in the protic solvent had a satisfactory performance, but in the aprotic solvent (acetonitrile), the efficiency was poor, even after 24 h. Afterward, the reaction was carried out under solvent-free conditions. Because of solvent-free reaction conditions, the productivity of the reaction was better, and additionally, the reaction time also decreased. Related results are presented in Table 1. Therefore, in the next step of the investigation, we used solvent-free conditions for the synthesis of substituted pyranopyrazoles.

3.2. Effect of catalyst concentration

In the next stage of the investigation, we checked the best catalytic amount for the model reaction. The yield of products without or with different catalytic concentrations, under solvent-free conditions at 90 °C, is reported in Figure 1. The 10 Wt% of the catalyst shows good activity towards synthesis, afterward increasing the catalyst amount there were no remarkable changes observed in the yield of the product. Progress of the reaction was monitored with TLC after regular intervals. The resulting results are summarized in Figure 1.

Table 2. Optimization of temperature for the synthesis of pyrano[2,3-d]pyrazole [a].

Entry	Temperature (°C) / Condition	Time (min)	Yield (%) [b]
1	30 / Solvent free	180	-
2	80 / Solvent free	15	74
3	90 / Solvent free	12	87
4	100 / Solvent free	4	96
5	110 / Solvent free	4	96

[a] Reaction conditions: 5-Methyl-2,4-dihydro-3*H*-pyrazol-3-one: benzaldehyde: malononitrile (1:1:1) in microwave and $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) as catalyst.
[b] Isolated yield.

Table 3. Optimization of microwave irradiation for the synthesis of pyrano[2,3-d]pyrazole [a].

Entry	MW (watts)	Time (min)	Yield (%) [b]
1	140	4	15
2	240	4	34
3	350	4	67
4	450	4	86
5	560	4	96
6	700	4	95

[a] Reaction conditions: 5-Methyl-2,4-dihydro-3H-pyrazol-3-one: benzaldehyde: malononitrile (1:1:1) in microwave and $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) catalyst at 100 °C in solvent-free conditions.
[b] Isolated yield.

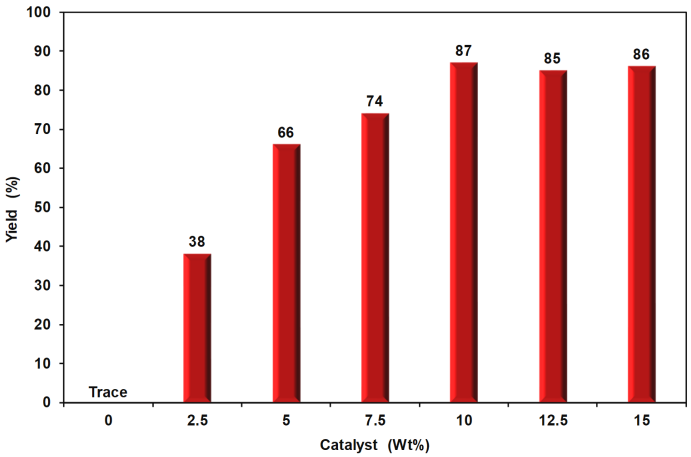


Figure 1. Optimization of the amount of catalyst for the synthesis of pyrano[2,3-d]pyrazole, reaction conditions: 5-Methyl-2,4-dihydro-3H-pyrazol-3-one: benzaldehyde: malononitrile (1:1:1) under microwave irradiation and solvent-free condition at 90 °C for 15 min, isolated yield.

3.3. Effect of temperature

In the next stage of the investigation, a test of the model reaction for temperature was carried out. It was observed that at room temperature 30 °C the reaction did not take place, even a trace amount of the product was not observed on TLC. Further increasing the temperature to 80°C and 90°C in a microwave reactor gives a yield of 74% and 87% of the desired product, respectively. The reaction was accelerated in the presence of $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) at 100 °C and the completion of the reaction occurred in just 4 min with a yield of 96% yield (Table 2, Entry 4). Furthermore, no increase in yield was observed when the reaction mixture was heated to 110°C in the microwave (Table 2, entry 5).

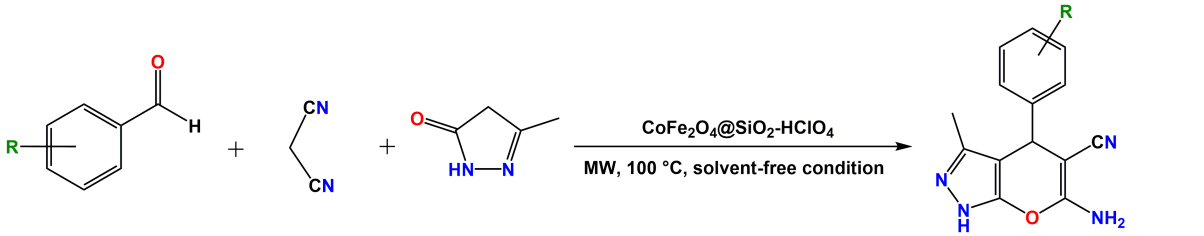
3.4. Effect of microwave irradiation

To optimize the reaction in microwave irradiation, we first exposed the reaction mixture below 350 W. At that condition, the reaction proceeded slowly and gives a relatively low yield. Although no significant improvement in product yield was observed above 560 W. All subsequent studies were carried out under solvent-free conditions with a 10% Wt catalyst at 100 °C for microwave irradiation (560 W) and the results are reported in Table 3.

3.5. Scope for substrate

With optimized reaction conditions, we started to synthesize derivatives of pyranopyrazoles in microwave under solvent-free conditions with $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) as a catalyst (Scheme 2). Next, the substrate scope was examined with various substituted aldehydes that afforded the corresponding pyranopyrazoles with different yields mentioned in Table 4. As evident in Table 4, all reactions preceded comfortably with good to excellent yield. The reaction was sensitive to steric hindrance on aromatic aldehydes, therefore yield of the product decreases in Table 4 (Entries 5 and 8). The structure of all synthesized products was confirmed using spectroscopic techniques that included ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectrometry. The structural variations in the aldehydes did not have a significant effect on the yields. Using aldehydes bearing functional groups such as Cl, OH, and OCH_3, the reaction proceeded smoothly to provide the corresponding products in good yields, Table 4 (Entries 3, 4, and 6). The catalyst also worked well even with heterocyclic aldehydes such as furfural, 2-thiophene, and 3-Indole without leading to the formation of any side products. It was observed that a group such as -NO_2, which has a strong electron-withdrawing nature as well as shows a mesomeric effect, gives an excellent yield of the desired product (Table 4, Entry 2). The electron-withdrawing group makes the carbonyl more vulnerable to nucleophilic attack. Terephthalaldehyde has also been used successfully to provide the corresponding bis nuclear pyrano [2,3-d]pyrazole in a good yield.

Table 4. Synthesis of substituted pyranopyrazoles using magnetically recoverable nanocatalyst-$CoFe_2O_4$@SiO_2-$HClO_4$ [a].



Entry	Product [b]	R	Time (min)	Yield (%) [c]	M.p. (°C)	
					Found	Reported [Reference]
1	4a	H	4	96	262-264	264-266 [30]
2	4b	3-NO_2	4	95	245-247	244-246 [30]
3	4c	4-Cl	6	82	244-245	245-247 [30]
4	4d	4-OH	5	90	222-225	218-220 [31]
5	4e	3-OC_2H_5, 4-OH	8	86	231-233	232-234 [32]
6	4f	4-OCH_3	5	92	212-215	210-212 [30]
7	4g	3,4-OCH_3	8	88	196-198	192-194 [33]
8	4h	3,4,5-OCH_3	12	84	211-212	209-211 [28]
9	4i	4-CH_3	5	92	205-207	206-208 [31]
10	4j	4-$(CH_3)_2CH$	7	90	188-190	181-182 [34]
11	4k	4-$(CH_3)_2N$	4	94	227-229	227-229 [30]
12	4l	2-Furyl	10	82	238-240	240-244 [32]
13	4m	2-Thiophene	10	86	245-246	246-248 [30]
14	4n	3-Indolyl	10	78	210-212	205-206 [34]
15	4o	Terephthalaldehyde [d]	8	87	261-263	258-260 [35]

[a] Reaction conditions: 5-Methyl-2,4-dihydro-3*H*-pyrazol-3-one (1 mmol): aldehyde (1 mmol): malononitrile (1 mmol) in the presence of $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) catalyst in microwave irradiation (560 W) at 100 °C under solvent-free conditions.
[b] All products are known and were identified by their melting point, IR, and ^1H and ^{13}C NMR spectra according to literature.
[c] Isolated yield.
[d] Reaction conditions: 5-Methyl-2,4-dihydro-3*H*-pyrazol-3-one (1 mmol); terephthalaldehyde (0.5 mmol); malononitrile (1 mmol) in the presence of $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) catalyst at 100 °C under solvent-free conditions.

Table 5. Comparative study with different catalysts.

Entry	Catalyst	Amount	Condition / Solvent	Time (min) / Yield (%) [a]	Reference
1	$[(CH_2)_4SO_3HMIM][HSO_4]$	75 Wt%	RT / Solvent-free	30 / 80	[37]
2	$H_4[W_{12}SiO_{40}]$	28 Wt%	60 °C / Solvent free	10 / 95	[38]
3	[bmim]OH	30 Wt%	60 °C / Solvent free	5 / 90	[39]
4	γ-Alumina	29 Wt%	Reflux / EtOH	50 / 80	[33]
5	ZrO_2	12 Wt%	RT / EtOH: H_2O	5 / 95	[40]
6	β-Cyclodextrin	36 Wt%	60 °C / EtOH: H_2O	35 / 87	[31]
7	CTACl	60 Wt%	90 °C / H_2O	240 / 81	[41]
8	Isonicotinic acid	12 Wt%	85 °C / Solvent free	10 / 90	[30]
9	$CoFe_2O_4$@SiO_2-$HClO_4$	10 Wt%	Microwave (100 °C) / Solvent-free	4 / 96	This work

3.6. Plausible mechanism

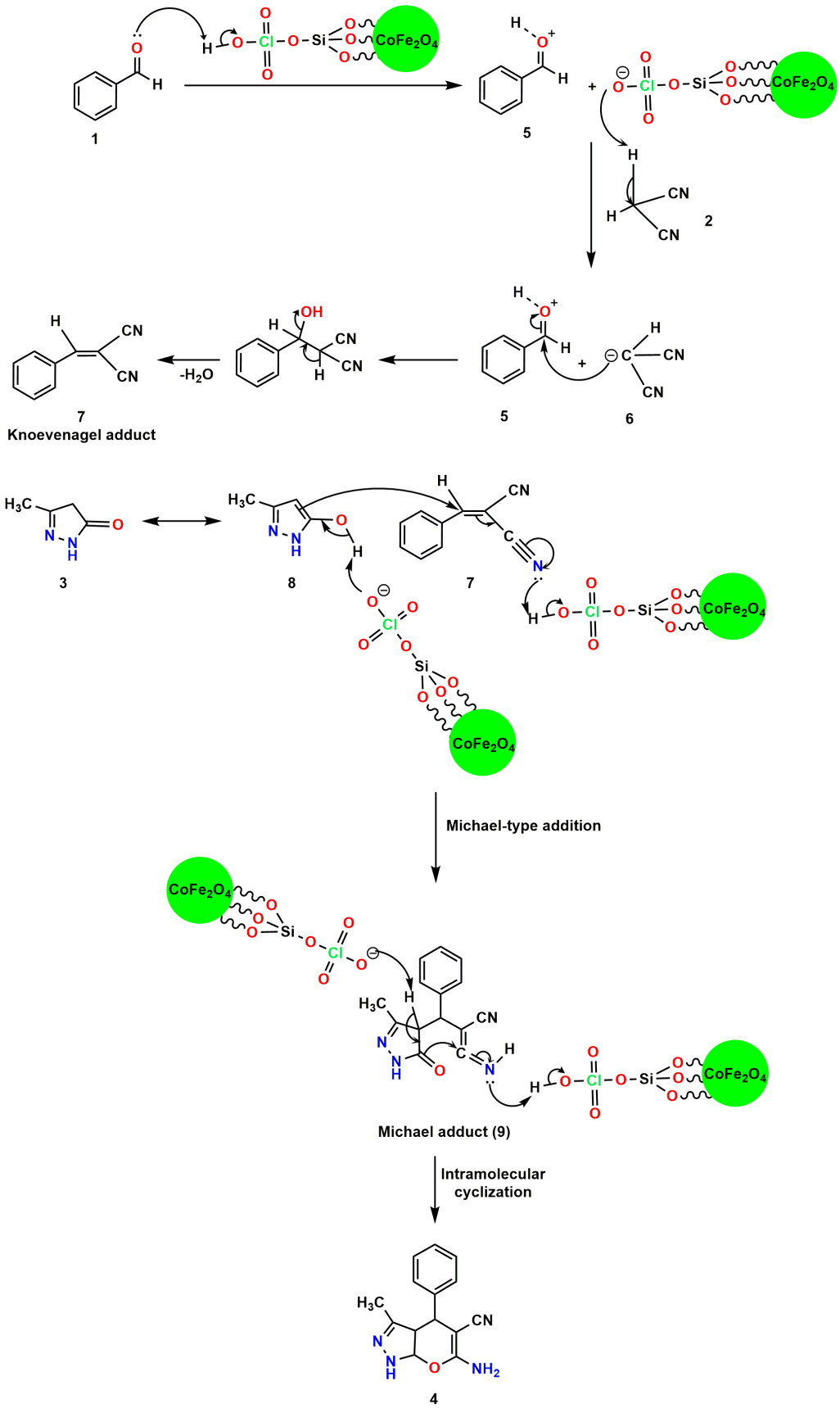
Based on the results presented above and previous studies [36], a plausible mechanism can reasonably be proposed for the synthesis of pyranopyrazole **4a** from 5-methyl-2,4-dihydro-3H-pyrazol-3-one (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol) in the presence of $CoFe_2O_4$@SiO_2-$HClO_4$ (10 Wt%) catalyst in microwave irradiation (560 W) at 100 °C in solvent-free conditions (Scheme 4). The presence of the $HClO_4$ group in the structure of $CoFe_2O_4$@SiO_2-$HClO_4$ catalyst plays an important role in its promotion activity for the formation of the Knoevenagel adduct (7) from the condensation of benzaldehyde and malononitrile. Initially, the catalyst can activate the carbonyl groups of aldehydes (1) by decreasing the energy of the transition state and abstracting an acidic proton from malononitrile (2). This results in the formation of the nitrile anion (6). Finally, the intermediate arylidene nitrile (Knoevenagel adduct-7) is formed by the Knoevenagel condensation reaction of the intermediate nitrile anion (6) with the transition state of aldehyde (5), 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one which undergoes tautomerism from an enolized compound. Subsequently, the enolizable compound condenses with the Knoevenagel adduct (7) followed by Michael addition, resulting in the formation of the intermediate in situ (Michael adduct-9). Finally, the intermediate (Michael adduct-9) underwent intramolecular cyclization by nucleophilic addition to provide the desired compound 4. Noticeably, $-H^+$ plays a significant synergic effect in the overall sequence of the mechanism. Therefore, by using this $CoFe_2O_4$@SiO_2-$HClO_4$ magnetically recoverable nanocatalyst, better catalytic activity can be achieved.

3.7. Catalyst comparison

The efficacy of $CoFe_2O_4$@SiO_2-$HClO_4$ nanocatalyst was evaluated and compared together with other solid catalysts for the preparation of pyrano[2,3-d]pyrazoles. Data of comparison are presented in Table 5. Among solid catalysts $[(CH_2)_4SO_3HMIM][HSO_4]$, $H_4[W_{12}SiO_{40}]$, [bmim]OH, γ-alumina, β-cyclodextrin, ZrO_2, CTACl, isonicotinic acid and $CoFe_2O_4$@SiO_2-$HClO_4$ was found to be superior in terms of catalyst amount as well as yield and reaction time.

3.8. Reusability of catalyst

The reusability of $CoFe_2O_4$@SiO_2-$HClO_4$ catalyst was studied by choosing the model reaction of benzaldehyde, 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one and malononitrile under solvent-free conditions. Upon completion of the reaction, the solid mixture was dissolved in a dichloromethane: methanol mixture (1:1, v/v) and the catalyst was easily separated and recovered from the reaction mixture by an external magnet, followed by decantation of the reaction solution. The remaining catalyst was washed with dichloromethane: methanol (1: 1, v/v) solvent mixture to remove the residual product and dried under vacuum and reused in a subsequent reaction.



Scheme 4. Plausible mechanism for the synthesis of pyranopyrazoles.

The recovered catalyst was reused for four cycles under the same reaction conditions for the preparation of products. The relationship between the number of reactions cycles and the catalytic activity in terms of product yields is presented in Figure 2.

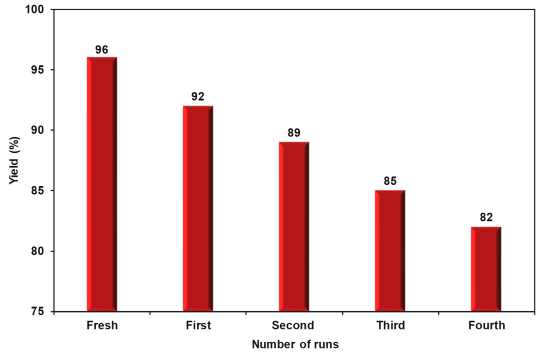


Figure 2. Recyclability of magnetically recoverable nanocatalyst-$CoFe_2O_4$@SiO_2-$HClO_4$.

3.9. Antimicrobial activity

All synthesized derivatives of pyrano[2,3-c]pyrazoles were tested for antimicrobial activities *in vitro* using the disc diffusion method. The antimicrobial activity of the synthesized compounds was monitored against *Escherichia coli* (Gram negative) (MTCC443) and *Staphylococcus aureus* (Gram positive) (MTCC96) bacterial strains using streptomycin as standard. The initial screening of the prepared products and standard drugs was carried out using 2000 µg/mL as a fixed concentration. The zone of inhibition was measured at the end of 24 h for bacteria at a temperature of 35 °C. The results of the screening are summarized in Figure 3 and the code of compounds mentioned in Table 4. From the above biological activities, it is found that compounds **4a** and **4c** is active against *E. coli*. Although compound **4c** is found to be fairly active against *S. aureus, it* may be due to the presence of a chlorine atom. The remaining compounds show moderate to very less activity against different strains.

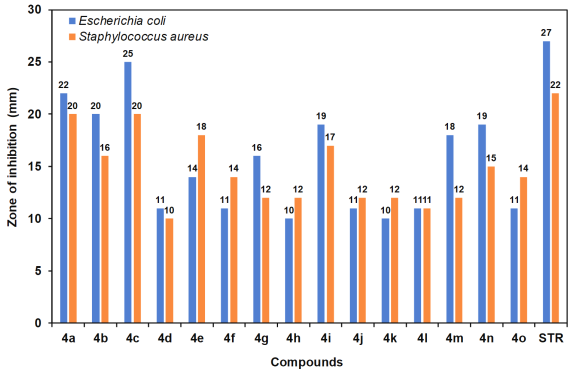


Figure 3. Antibacterial activity of pyrano[2,3-c]pyrazoles (4a-4o) compounds.

4. Conclusions

In this work, we have developed a new magnetically recoverable $CoFe_2O_4$@SiO_2-$HClO_4$ nanocatalyst via the simple known method. It has been proven that the catalyst manifests high catalytic performance during the synthesis of pyrano-pyrazoles and their derivatives under microwave irradiation conditions. The notable features of this protocol include mild reaction conditions, high activity, easy work-up, moderate to excellent yield, and reusability of a catalyst. Along with this, the synthesized compounds showed satisfactory antimicrobial activity. All these features of the present protocol make it a green alternative. Concerning the acceptable catalytic properties observed of $CoFe_2O_4$@SiO_2-$HClO_4$ nanocatalyst, we look further at its use in the investigation of other magnetically recoverable nanocatalysts.

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Disclosure statement

The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Anand Shankarrao Aswar; Methodology: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Software: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Validation: Anand Shankarrao Aswar; Formal Analysis: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Investigation: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Resources: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Data Curation: Anand Shankarrao Aswar; Writing - Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Writing - Review and Editing: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Visualization: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Funding acquisition: Nikita Vinod Thakare, Nilesh Govindrao Salunkhe; Supervision: Anand Shankarrao Aswar; Project Administration: Anand Shankarrao Aswar.

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