One-Pot MCR Of 3,4-Dihydropyrimidine-2-(1H)-One Derivatives By Silica Supported Cu-Zn Nanoparticle

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ABSTRACT

A rapid and environmentally sustainable one-pot MCR for the formation of 3,4-dihydropyrimidine-2-(1H)-one analogues, utilizing a silica-supported Cu-Zn nanocomposite as an efficient catalyst under 40 kHz ultrasound conditions with ethanol as the solvent. This one-pot multicomponent reaction, which integrates aromatic aldehydes, urea, and ethyl acetoacetate, yields remarkable results in a very short time, demonstrating high selectivity. The synthesized silica-supported nano catalyst was thoroughly characterized using SEM-EDX. Various spectroscopic techniques, including 1H NMR, 13C NMR, and mass spectrometry has been to confirm the structural information of formed molecules. This method additional advantages like as operational simplicity and environmentally viable, a nano-stable catalyst with excellent reusability (up to 8-10 cycles), rapid reaction times (<10 min), and the elimination of high-cost purification. Because of these attributes, the used method plays dual role sustainable and cost-effective.

Keywords: Green chemistry, Nano catalyst, Sonochemistry, Selective chemistry, High reusability of catalyst

1. INTRODUCTION

Formation of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) commonly known from Biginelli reaction is a topic in medicinal and organic chemistry. These compounds serve as key scaffolds for various biologically active molecules with properties such as Antiviral, Antibacterial, Antitumor, Anti-inflammatory, Antihypertensive [1]. Often acid-catalyzed (e.g., HCl)[2], but greener alternatives now include, Lewis acids (e.g., $FeCl_3$, $LaCl_3$, $BiCl_3$)[3,4,5],Ionic liquids, Microwave or ultrasound-assisted methods[6,7], Solvent-free or green solvents (like water or ethanol)[8,9],Recent developments aim to improve: Reaction efficiency (faster, higher yields),Environmental impact (greener solvents, catalysts), Product selectivity (toward desired isomers) Developing efficient and sustainable methods for synthesizing 3,4-dihydropyrimidine-2-(1H)-one derivatives is crucial for advancing medicinal chemistry and drug discovery. Given their broad spectrum of biological activities, these compounds serve as key scaffolds in the development of novel therapeutic agents. However, environmental impact and inefficiencies of traditional synthetic routes can hinder progress. Therefore, adopting greener approaches such as the use of recyclable nano-catalysts and energy-efficient techniques like sonochemistry not only enhances reaction performance but also aligns with the principles of green chemistry, supporting more responsible and scalable pharmaceutical development[10,11,12].

Here's a list summarizing previous studies and synthetic approaches for 3,4-dihydropyrimidine-2(1H)-ones (DHPMs), highlighting diversity MCRs and catalytic systems used in their synthesis

Lewis Acid Catalysis(eg:$FeCl_3$, $LaCl_3$, $Yb(OTf)_3$, $BiCl_3$, $Cu(OTf)_2$ Promote imine formation and cyclization, Advantage: Higher yields, milder conditions [13] , reviewed improved catalytic variants, Green Catalysis / Eco-Friendly Approaches Catalysts: Ionic liquids (e.g., $[bmim]BF_4$), Deep eutectic solvents, Bio-catalysts (e.g., enzyme-mediated reactions),Magnetically recoverable nanocatalysts(Reusability, non-toxic, solvent-free) [14].Solid Acid Catalysts Examples: Montmorillonite K10 clay,Amberlyst-15,Silica-supported acids,Benefit: Heterogeneous catalysis, easy separation[15].Ultrasound-Assisted Reactions Enhances molecular interactions via cavitation, Often combined with Lewis acids or green solvents[16].One-Pot Solvent-Free Synthesis No solvent, only grinding reactants in mortar and pestle or heating directly Catalysts: Acidic alumina, PPA-SiO_2 [17].Metal Nanoparticles as like Au, Ag, Cu, and Fe_3O_4 nanoparticles(High surface area, excellent recyclability)[18].

However, there is no research on the use of Silica supported Cu-Zn nanoparticles in sonochemical one-pot MCR reactions for these derivatives, Investigating the sonochemical synthesis using Silica supported Cu-Zn nanoparticles could offer a more eco-friendly and efficient approach,

This study aims to explore the sonochemical formation of 3,4-dihydropyrimidine-2-(1H)-one derivatives by silica supported Cu-Zn nanoparticles as sustainable catalyst system. By leveraging the synergistic effects of copper and zinc on a silica support, combined with the advantages of ultrasonic irradiation, the method seeks to achieve high yields under mild, eco-friendly conditions. This approach not only enhances reaction rates and selectivity but also aligns with green chemistry principles by reducing energy consumption, eliminating the need for toxic solvents, and enabling catalyst reuse offering a sustainable pathway for the synthesis of bioactive heterocyclic compounds.

2. EXPERIMENTAL METHODS

2.1. Chemicals and materials:

Copper nitrate ($Cu(NO_3)_2$),Zinc nitrate ($Zn(NO_3)_2$) ,Sodium hydroxide (NaOH),Ethanol (for washing and dispersion), Distilled water all material buy from local market.

2.2. Preparation and Characterization of the catalyst:

Copper nitrate and zinc nitrate were separately dissolved in distilled water to prepare their respective solutions, and zinc nitrate solution was slowly added to the copper nitrate solution under continuous stirring. This ensured the thorough mixing of the metal ions in the solution.

To initiate the precipitation of copper(II) nitrate ($Cu(NO_3)_2$) and zinc nitrate ($Zn(NO_3)_2$) in distilled water, each compound was dissolved in separate conical flasks to form clear solutions. These solutions were then mixed, and an aqueous solution of NaOH was added dropwise to adjust the pH to approximately 10.5. At this pH level, copper and zinc hydroxides precipitated out from the solution. The both hydroxide precipitate was thoroughly mixed and subjected to ultrasonic treatment at 40 kHz for 60 minutes. The resulting solid was filtered, washed with distilled water to remove impurities and excess ions, and subsequently dried in an oven at 90–100 °C. Alternatively, the dried precursor material was heated at temperatures ranging from approximately 300–350 °C to reduce it to nanoparticles.

Binding with silica: The Cu-Zn nanocomposite was dispersed in ethanol or another suitable solvent to form a stable dispersion. The porous silica in the Cu-Zn dispersion was sonicated for 2 hours (40kHz), during which the nanocomposite was adsorbed on surface of the silica particles. The mixture was periodically stirred to ensure uniform impregnation. To further enhance the stability and distribution of Cu-Zn nanoparticles on silica, the composite material was calcined at 500–600°C for 4 h. This step removes any residual organic solvent and ensures that nanocomposite is securely attached to silica.

After synthesis, the Cu-Zn/SiO_2 composite was characterized again using techniques such as SEM with EDX to confirm the successful incorporation of nanocomposite into silica support and to assess the morphology and surface properties

2.3 Synthesis of Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives:

An equimolar mixture comprising a substituted aldehyde (1 mmol), urea (1 mmol), ethyl acetoacetate (1 mmol) with 5% catalyst (w/w%) was subjected to stirring using an ultra-probe sonication at 60°C for a duration of five minutes to get product. The completion of the reaction was verified through thin-layer chromatography (TLC) employing solvent system make by n-hexane: ethyl acetate (7:3). The resultant solid product was soluble in ethanol, followed by filtration, catalyst subsequently collected, recrystallized, purified, dried, and prepared for reuse in the subsequent reaction cycle.

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2.3.1 Optimization of Reaction Parameters:

Table 1: Optimization of reaction
(Solvent, Temperature with Catalyst Quantity on Condensation Reaction of Benzaldehyde, Ethylacetoacetate, and Urea)

Sr Num	Solvent	Time (Min)	Temp.	Catalyst (%)(w/w)	Yield (%)
1	Nil	60	90	Nil	Not formed
2	Nil	60	90	2	Spot observed on TLC
3	Nil	60	90	5	48

4	Water	60	50	5	Not formed
5	Water	60	100	5	81
6	Ethanol	30	72	5	96
7	Methanol	30	62	5	82
8	DMC	30	65	5	76
9	Chloroform	30	RT	5	65
10	PEG-400	60	110	5	74
11	Glycerol	60	110	5	79

3 Progression reaction parameters was assessed catalyst-free conditions, both at ambient temperature with under reflux, employing solvent-free conditions. Results indicated ,it only trace amounts target compound, ethyl 6-methyl-4-(phenyl)-3,4-dihydropyrimidine-2(1H)-one-5-carboxylate (4a) was produced after60 minutes (Table 1, entries 1, 2). In subsequent experiments. catalytic efficacy various nanoparticles, with several green solvents such as water, ethanol, DMC, chloroform, PEG-400, and glycerol, was evaluated in the reaction at different reflux temperatures (Table 1, entries 3–8). The findings demonstrate notable potential ethanol as a solvent in reaction (Table 1, entry 6). Consequently, ethanol was used for reaction with a 5% (w/w) catalyst loading for another derivatives formation.

Table 2 Reaction optimization for the solvent ratio and Temperature optimization

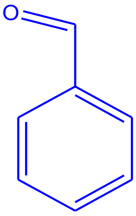
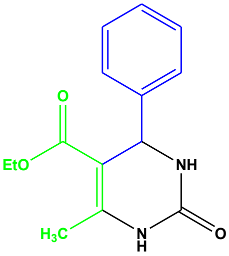
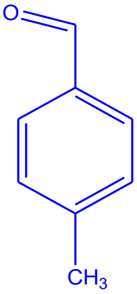
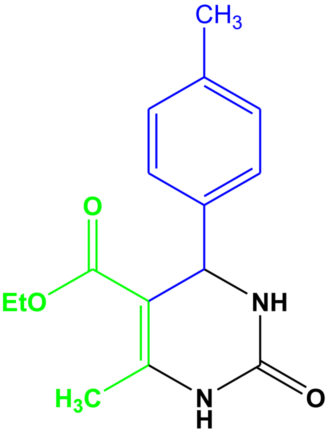
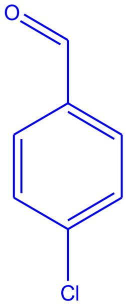
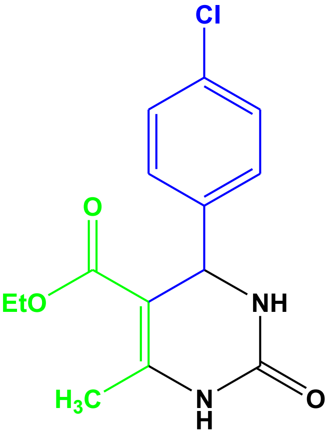
Sr Num	**Solvent Ethanol (Vol)**	**Time (Min)**	**Temp.**	**Catalyst (%) (w/w)**	**Yield (%)**
1	10	30	70	10	96
2	5	20	70	5	95
3	3	10	70	3	74
4	4	15	70	5	89
5	5	10	73-78	4	96
6	5	15	73-78	4	94

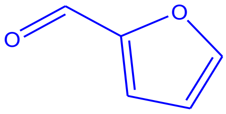
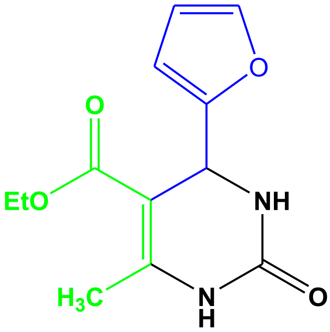
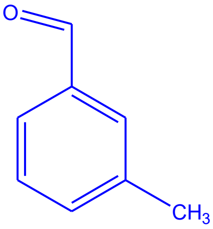
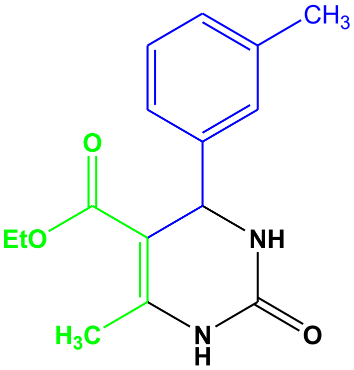
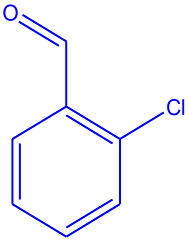
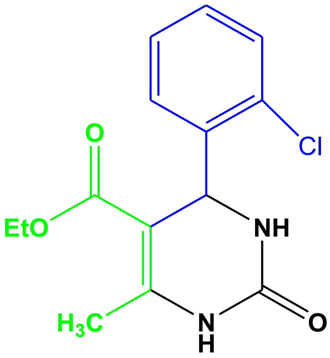
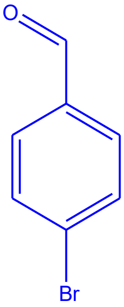
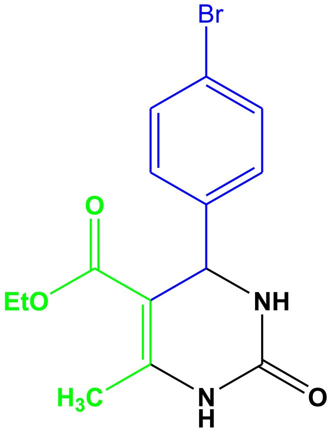
Therefore, the optimized conditions were 5%(w/w) loading of Cu-Zn Nps in an Ethanol under sonication condition. Check effectiveness, wide-ranging applicability of conditions, various DHPM derivatives were synthesized. Solvent, catalyst, and time optimization under 40 Hz ultrasound irritation conditions: The model reaction represents solvent optimization with advent time and temperature parameters. First initiate (entry1) ethanol solvent ratio, Temp and Time, all three parameters are set high for check the maximum efficiency of catalyst and solvent, Then step wise reduce the three parameters and check step wise (Entry 2-6),we find out optimum condition with 5 volume solvent for 10 min at 73-78 temp for 4% w/w catalyst loading got 96%yield (Entry-5).

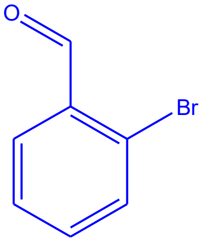
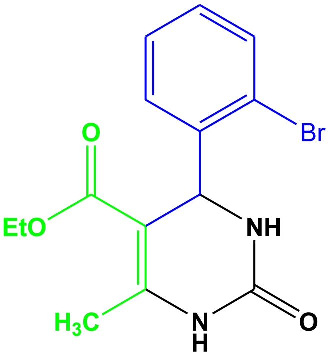
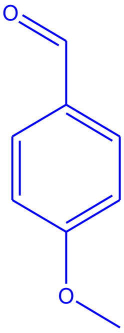
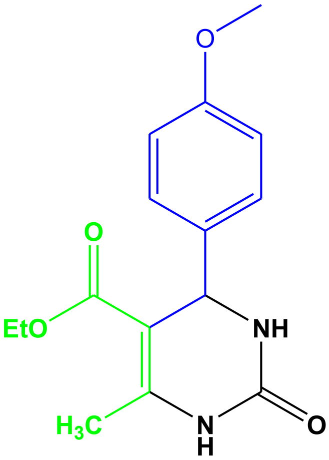
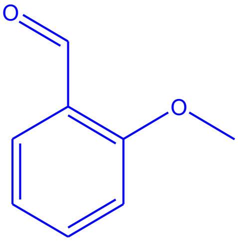
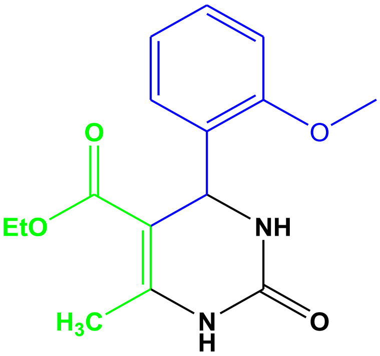
Table 3 provides a comprehensive assessment conducted by our team on this catalyst in conjunction with various aromatic aldehydes.

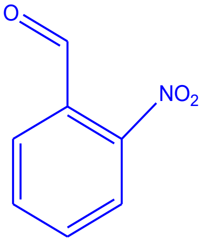
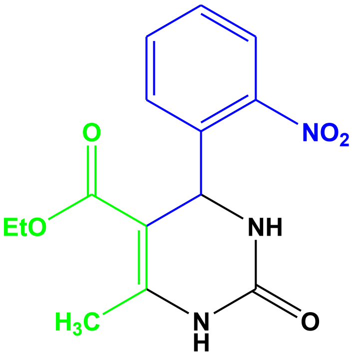
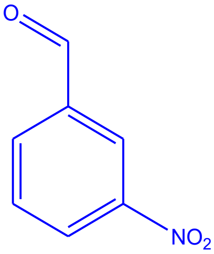
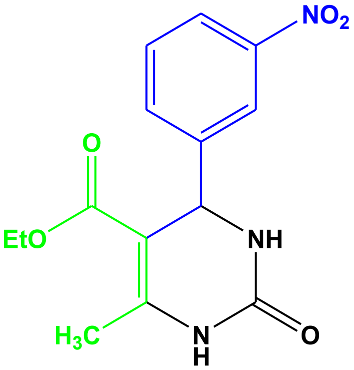
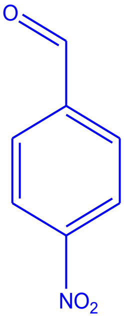
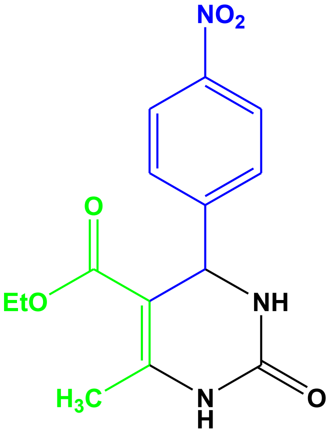
It was achieved via one-pot MCR involving various aromatic aldehydes 1-17 (1) ethyl acetoacetate (2) and urea (3) components. The results are listed in Table 3, all aldehydes DHPMs (Entry 1-8) in high to excellent yields. According to data presented in Table 3, This was achieved through a one-pot MCR reaction various aryl aldehydes 1-17 (1), ethyl acetoacetate (2), and urea (3) as reactants. Results are described in Table 3. It is noteworthy that all aldehydes examined, including the sensitive aldehydes DHPMs (Entry 1-8), was got to excellent yields. Data presented in Table 3 reveal that aromatic aldehydes with electron-withdrawing groups (–NO2, –Cl, –Br, O-CH3, CH3, and –OH) exhibited a more rapid formation of the desired products 1-6 and 8-16 compared to benzaldehyde and aromatic aldehydes have electron-donating groups (–OMe, –OH, –Me),It concept was impact to enhanced activity of aldehydes group with electron-withdrawing groups, It facilitated reaction with accelerates Yield improvement. In this reaction electron-rich heterocyclic aromatic aldehyde furfural (4) demonstrated more reaction time relative to benzaldehyde (1). Observation of higher electron density and reduced carbonyl activity compounds compared to aromatic carbocyclic aldehydes. Indeed, increased electron density in these five-membered heterocyclic aldehydes impedes the attack of both the enol forms of ethyl acetoacetate (2) and urea, as electrophiles, on their carbonyl groups. Consequently, slower product formation and lower yields were observed (Entry 10-12). These trends in reaction rates and yields are consistent with proposed reaction mechanism does suggests electrophilic attack on carbonyl group is rate-determining step.

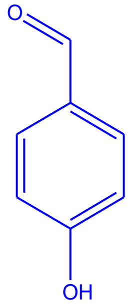
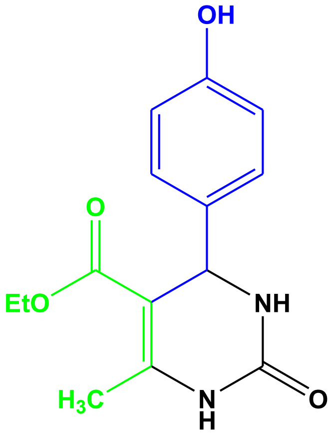
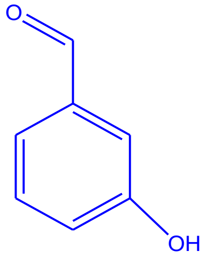
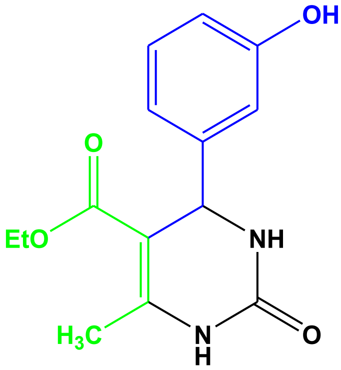
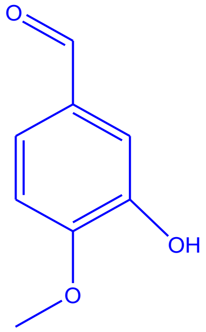
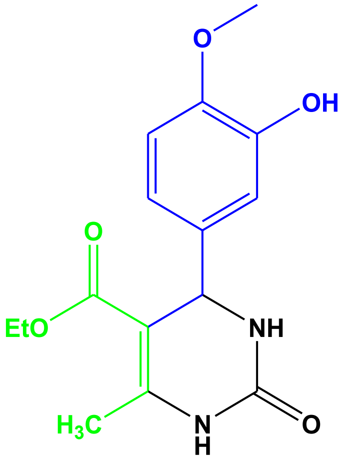
Table 3 three components condensation of ethyl acetoacetate, urea, and different aldehydes catalyzed by Silica supported Cu-Zn NPS via Ultrasound method

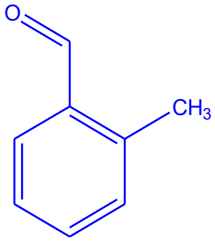
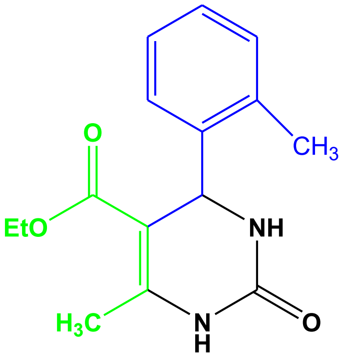
Sr Num	Aldehyde	Product	Yield (%)	Time (Min)
1			82	9
2			88	6
3			92	10

4			**78**	**10**
5			**81**	**5**
6			**90**	**9**
7			**76**	**5**

8			**55**	**5**
9			**87**	**9**
10			**79**	**10**

11			**79**	**10**
12			**90**	**10**
13			**95**	**5**

14			**79**	**10**
15			**72**	**10**
16			**74**	**7**

17			**69**	**5**

Evaluation of Recently Documented Protocols for the Synthesis of 4,3-Dihydropyrimidine-2(1H)-one:

Last 20 years highest cited paper of 4,3-Dihydropyrimidine-2(1H)-one derivatives

Entry	Catalyst	Solvent	Temperature (°C)	Time (min)	Yield (%)	References
1	5-Hf(OTf)4, 1.0 mol	-	80	20	95	20
2	Zwitterionic MSI and TRIP, 10 mol%	-	30	72	99	21
3	Niobium/Fe3O4	EtOH	Reflux conditions	720	99	22
4	Polyanilin-FeCl3, 200.0 mg	CH3CN	Reflux conditions	24	90	23
5	Bead-CDNS, 30.0 mg		Ultrasonic, 120 W	15	100	24
6	Zn coordination polymer	-	100	5	99	25
7	Silica supported Al	EtoH	Microwave-78	5	94	26
8	Fe3O4@Nb2O5, 0.1 mol%	Ethanol	80	12	99	27
9	Nb2O5/T, 5.0 mol%		130	1	94	28
10	BiFeO3 NPs	H2O:EtOH	Reflux conditions	10	93	29
11	5-Hf(OTf)$_4$, 1.0 mol	–	80	20	95	31
12	Zwitterionic MSI and TRIP, 10 mol%	Solvent-free	30	72	99	32
13	Niobium/Fe_3O_4, 1.5 mg	EtOH	Reflux conditions	720	99	33
14	Polyanilin-$FeCl_3$, 200.0 mg	CH_3CN	Reflux conditions	24	90	34
15	Bead-CDNS, 30.0 mg	H_2O	Ultrasonic, 120 W	15	100	35
16	Coconut husk ash twisted graphene, 100.0 mg	Solvent-free	130	14	94	36
17	IRMOF-3, 4.0 mol	Solvent-free	100	300	90	37
18	Zn coordination polymer, 5.0 mol%	Solvent-free	100	5	99	38
19	Wng Resin-Supported Sulfonic Acid, 30.0 mg	EtOH	100	30	96	39
20	Fe_3O_4@Nb_2O_5, 0.1 mol%	EtOH	80	12	99	40
21	Nb_2O_5/T, 5.0 mol%	Solvent-free	130	1	94	41
22	$BiFeO_3$ NPs, 4.0 mg	H_2O:EtOH	Reflux conditions	10	93	42
23	Silicasupported Cu-Zn Nps(5%w/w)	Ethanol	Sonochemistry	5-10	91-96	This work

Table 3 presents comparative analysis of synthesizing ethyl 6-methyl-4-(phenyl)-3,4-dihydropyrimidine-2(1H)-one-5-carboxylate (1) via silica supported Cu-Zn nanoparticles, focusing on yield and reaction time, in relation to recent methodologies.

In conclusion, the effectiveness of the silica supported Cu-Zn Nps catalyst comparison with previously documented methodologies. Illustrated in Table 3, the silica supported Cu-Zn Nps nano catalyst was developed for substantial efficiency for synthesis of DHPMs. A notable characteristic of Nps catalyst capacity to facilitate formation of DHPMs products under sustainable conditions, in accordance with the principles of green chemistry.

2.4 Characterization of Synthesized derivatives:

Spectral data of compounds:

1)Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate:
^{1}H NMR: δ : 1.09 (3H), 2.24 (3H), 3.99 (2H), 5.13 (1H), 7.21–7.34 (5H), 7.73 (1H), 9.19 (1H). 1^{13}C NMR: δ 14.4

(1C), 17.8 (1C), 54.1 (1C), 60.7 (1C), 99.3 (1C), 126.1 (2C), 127.4 (1C), 128.7 (2C), 144.0 (1C), 148.3 (1C), 152.1 (1C), 165.9 (1C).

2) Ethyl 6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:

^{1}H NMR: d (ppm): 1.12 (3H), 2.30(3H), 4.00 (2H), 5.11 (1H), 7.25 (4H), 7.70 (1H), 9.19 (1H). ^{13}C NMR: δ 14.1 (1C), 17.8 (1C), 21.4 (1C), 54.0 (1C), 60.0 (1C), 99.3 (1C), 127.7 (2C), 129.3 (2C), 136.9 (1C), 138.3 (1C), 148.3 (1C), 152.1 (1C), 165.9 (1C).

3) Ethyl 4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one-5-carboxylate;

^{1}H NMR:δ (ppm): 1.10 (3H), 2.22(3H), 3.96 (2H), 5.02 (1H), 6.64 (2H), 7.02 (2H), 7.57 (1H), 9.07 (1H). ^{13}C NMR: δ 14.1 (1C), 17.0 (1C), 54.0 (1C), 60.0 (1C), 99.3 (1C), 127.7 (2C), 128.9 (2C), 133.9 (1C), 138.8 (1C), 148.3 (1C), 152.1 (1C), 159.2 (1C).

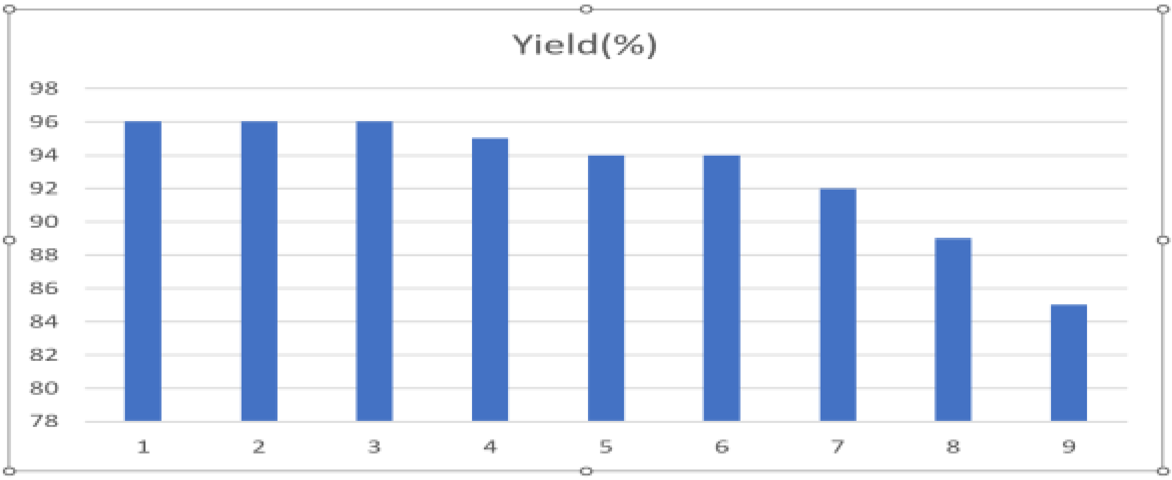
4)Ethyl6-methyl-4-(thiophen-2-yl)-3,4-dihydropyrimidine-2(1H)-one-5-carboxylate:

^{1}H NMR δ (ppm): 1.19 (3H), 2.53 (3H), 4.30(2H), 5.43(1H), 6.78 (1H), 6.98(1H),7.39 (1H), 7.92 (1H), 9.81 (1H). ^{13}C NMR: δ 14.1 (1C, s), 18.6 (1C, s), 60.0 (1C, s), 73.2 (1C, s), 99.5 (1C, s), 106.3 (1C, s), 110.5 (1C, s), 141.9 (1C, s), 145.8 (1C, s), 150.4 (1C, s), 156.3 (1C, s), 166.7 (1C, s).

2.4.1 Study of the recyclability and reusability of Cu-Zn Nps:

Catalysts are Sustainability and critical considerations in domain of green chemistry. Although heterogeneous catalysts compared to down than homogeneous counterparts, it was favored due to their ease of separation and reuse. A hot filtration was done to ascertain heterogeneity of the silica supported Cu-Zn Nps nano-catalyst. Approximately 5-10 minutes after the initiation of the reaction TLC was performed. If the reaction yielded a clear solution, it was filtered, allowing the solution to pass through filter paper while the catalyst was retained on the paper. The catalyst was then washed with ethanol, dried, and subsequently.it was utilized in next reaction cycle. Results, depicted in Figure , reveal catalyst's structure remain largely intact after multiple times reuse. These findings underscore promising potential of Cu-Zn NPS nanoparticles was Sustainable, stable, and efficient heterogeneous nano catalysts under suitable conditions.

Figure 3 Reusability cycle chart of catalyst



The nanoparticles demonstrated sustained catalytic activity over seven consecutive cycles (Figure 3). This prolonged effectiveness underscores the potential for its repeated use in catalytic processes. However, a decline in activity was noted after the seventh cycle, indicating a gradual reduction in catalytic efficiency over time. This behavior is characteristic of many catalytic systems, where factors such as particle agglomeration, surface contamination, and structural changes can lead to diminished performance with repeated use.

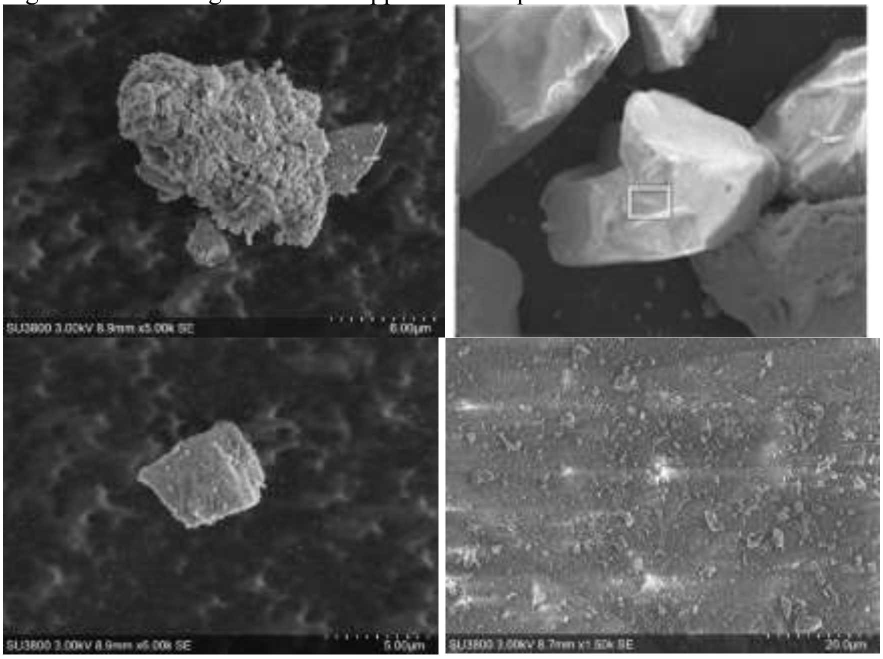
The performance of these nanoparticles signifies significant advancement in the field of catalysis. Traditional catalysts, including acids, bases, and metal-based systems, often pose challenges in terms of their recovery and reusability. It is difficult or impossible to recover many conventional catalysts post-reaction, resulting in increased costs and environmental concerns. Even when recovery is possible, these traditional catalysts frequently experience substantial activity loss, which limits their practical application in multiple reaction cycles. In contrast, the nanoparticle catalyst described herein offers improved recoverability and maintains its activity over several cycles, potentially providing a more sustainable and cost-effective alternative for various catalytic applications.

3. RESULTS AND DISCUSSION

3.1 Characterization of Silica supported Zn-Cu Catalyst:

Morphology study of catalysts by using SEM (Sanning Electron Microscope) . Figure 1 shows selected SEM images of the Cu-Zn-supported nano- catalyst. The successful functionalization of Cu-Zn over silica was indicated by the surface roughness in comparison with the silica binding.

Figure01:SEM images of Silica supported nano particles



The SEM image shows uniformly distributed spherical nanoparticles with an average diameter of ~8.9 mm, exhibiting minimal agglomeration. The EDX spectrum confirmed the presence of Cu, Zn, and Si, corresponding to Copper and Zinc nanoparticles supported on a silica matrix. The strong Cu and Zn peaks, along with consistent elemental mapping across the surface, confirmed the homogeneous dispersion and suggested successful synthesis of the nanocomposite.

SEM EDX image

The Energy Dispersive X-ray (EDX) spectrum, overlaid or presented adjacent to the SEM image, confirms the elemental composition of the analyzed region. The EDX analysis showed distinct peaks corresponding to Cu,Zn and Silica, indicating the presence of these elements within the scanned area. Minor chlorine peaks may suggest trace impurities in the synthesis method.

This we conclcude that the successful loading of Cu-Zn both nanoparticles on Silica.

4. CONCLUSION:

The research explored the use of silica-supported Cu-Zn nanoparticles (Nps) as heterogeneous acidic catalysts for formation of various derivatives of active 3,4-dihydropyrimidin-2(1H)-ones (DHPMs). It observed that catalytic efficiency of silica-supported Cu-Zn Nps was greatly affected by the solvent and temperature selected. DHPMs was produced by ethanol (EtOH), an environmentally friendly solvent, using a one-pot Biginelli approach. This technique provides several notable benefits, such as achieving high excellent yields of the targeted molecule, requiring minimal catalyst amounts, and shortening reaction times. Additionally, this method alternative of harmful organic solvents, streamlines the purification of the target products, simplifies the workup process, and enables the silica-supported Cu-Zn Nps catalyst to be recycled and reused for at least seven cycles without losing its effectiveness, whereas typical catalysts are effective for up to three cycles.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT:

Jaywant Patil: Writing-original draft, Conceptualization, review & editing Pushpendra Tiwari: Writing - original review & editing, Validation, Conceptualization, Pradip Patil: Writing-original draft, Conceptualization, Lalit Marathe: Methodology, Investigation, Validation

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