Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 15, Issue 6, 2025, 85
https://https://doi.org/10.33263/BRIAC156.085

Environmentally Benign Synthesis of Heterocyclic Compounds using Various Catalytic Approaches: A Comprehensive Review

Vasundhara Sawant [1,*], **Prerna Tamte** [1], **Ankita Khade** [1], **Akanksha Mankar** [1], **Pooja Sontakke** [1], **Saurabh Shelke** [1], **Minal Ghante** [1]

[1] Department of Pharmaceutical Chemistry, STES, Smt. Kashibai Navale College of Pharmacy, Kondhwa (Bk.), Savitribai Phule Pune University, Pune, Maharashtra-411 048, India; tamteprerna14@gmail.com (P.T.); ankitakhade1512@gmail.com (A.K.); akankshamankar2001@gmail.com (A.M.); poojasontakke888@gmail.com (P.S.); shelkesaurabh22@gmail.com (S.S.); minal.ghante@sinhgad.edu (M.G.);
* Correspondence: pr.vasundhara@gmail.com;

Received: 12.03.2025; Accepted: 3.08.2025; Published: 14.10.2025

Abstract: Heterocyclic compounds are essential building blocks in pharmaceutical agents. Conventional methods of synthesizing nitrogenous heterocycles rely on hazardous solvents and high energy requirements, which result in a significant amount of waste. In recent years, sustainable chemistry approaches have provided safer and more effective alternatives. This article highlights the eco-friendly methods employed over the last decade for the synthesis of various heterocyclic compounds. Catalytic systems, including metal nanoparticles, amino acids, organocatalysts, and biocatalysts, along with green reaction media such as water, solvent-free reactions, ionic liquids, and eutectic mixtures, were discussed in this study. Modern activation techniques, including microwave irradiation, ultrasound, photochemistry, and electrochemistry, facilitate chemical reactions with reduced reaction times and enhanced yields. In addition, a comparative study and critical analysis of various green synthetic conditions is provided, highlighting their relative efficiencies, limitations, and environmental impact. This study shall be helpful for future research in the development of sustainable methods for heterocyclic synthesis.

Keywords: thiazolidinone; pyrimidine; organocatalyst; nanocatalyst; solvent-free synthesis; green chemistry; sustainable methods.

1. Introduction

Nitrogen-containing heterocycles are a vital class of organic compounds widely used in the pharmaceutical and chemical industries [1]. These structural motifs form the core of numerous drugs and agrochemicals, driving extensive research into more efficient synthetic methodologies [2]. Traditional methods for synthesizing heterocycles often involve harsh reaction conditions, toxic solvents, and energy-intensive processes [3]. These approaches generate substantial waste and raise significant environmental and safety concerns [4]. As a result, the pharmaceutical industry is under increasing pressure to minimize its ecological footprint while maintaining high standards of production efficiency and quality [5,6].

Green chemistry principles provide a framework for developing more sustainable synthetic methods [7]. Sustainable chemistry emphasizes the use of safer reagents, renewable materials, and energy-efficient processes [8]. Useful green approaches are shown in Figure 1. This article reviews research from the past decade focused on eco-friendly methods for synthesizing heterocyclic scaffolds, particularly pyrimidine and thiazolidine derivatives. It highlights advances in nanocatalysis, organocatalysis, biocatalysis, solvent-free reactions, and techniques such as photochemical, microwave-assisted, and ultrasound-assisted synthesis. Representative reaction pathways of such reactions are also described [9]. The primary objective is to highlight current achievements in sustainable methods and identify opportunities for future development in this area of synthetic chemistry [10].

Incorporating green chemistry principles into the synthesis of nitrogen-containing heterocyclic compounds addresses environmental concerns and enhances reaction efficiency and selectivity [11]. By utilizing green catalysts in conjunction with sustainable reaction environments and renewable energy sources, research has made notable progress in terms of reaction time, yield, and ease of operation. This transition is particularly important in the large-scale production of pharmaceutical intermediates, where reducing harmful by-products is vital [12]. Additionally, green catalytic systems offer broad substrate compatibility, enabling the synthesis of structurally diverse heterocycles with potential therapeutic applications. As demand for environmentally sustainable chemical processes grows, the development of innovative green methods for synthesizing nitrogen-containing heterocycles remains a key focus in modern organic chemistry [13,14].

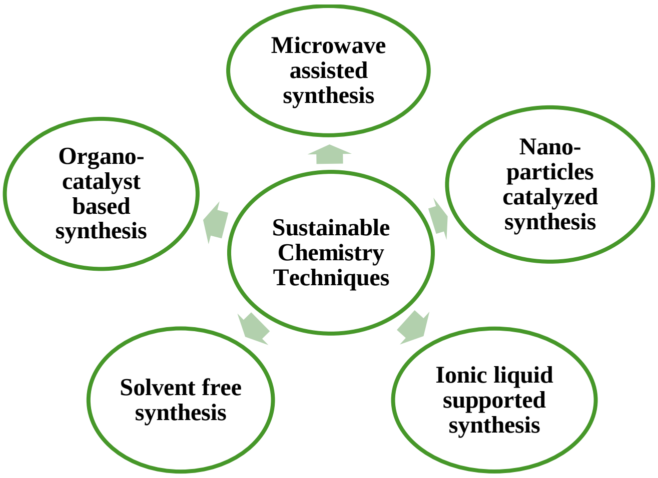


Figure 1. Sustainable chemistry techniques.

2. Ultrasonic Radiation Assisted

Sonochemistry provides a green and efficient route to organic pharmaceuticals by utilizing high-frequency sound waves [15]. It generates acoustic cavitation, which accelerates reaction rates and enhances selectivity. This process minimizes waste and energy consumption, while also improving yield [16]. Some ultrasound-assisted reactions are mentioned in Table 1, and their pros and cons are given in Table 2.

Table 1. Ultrasound-assisted synthesis.

Catalyst	Reaction conditions	Yield	Time	References
Alcoholic KOH	Ultrasonic/ room temperature (RT)	75-85	10-15 min	[17]
Ultrasonic irradiation	Biginelli reaction, sonification, 50°C	95%	90 min	[18]
NH_2SO_3H	Bignelli reaction under ultrasonic irradiation	98%	30 min	[19]

Catalyst	Reaction conditions	Yield	Time	References
Nano-$CdZr_4(PO_4)_6$ + ultrasound	60W ultrasonic irradiation	88%	25min	[20]

Ultrasonic irradiation enables the regioselective synthesis of 2-thio-5-hydroxy-5H-BPP **(1)** from thiourea and 3-formylchromone in alcoholic potassium hydroxide, as shown in Figure 2, achieving 75–85% yield within 10–15 min. Compared to the conventional way, ultrasound reduces reaction time, improves yield, and offers a greener, more efficient approach [17].

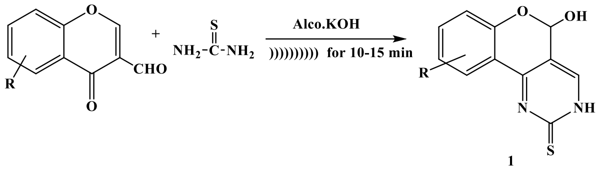


Figure 2. Synthesis of BPPs using ultrasound radiation.

One-pot method for the synthesis of 4, 6-diaryl DHPMs (Dihydropyrimidines) **(2)** was developed based on ultrasonic irradiation, and 95% product was achieved in 30 to 90 minutes, as shown in Figure 3 [18].

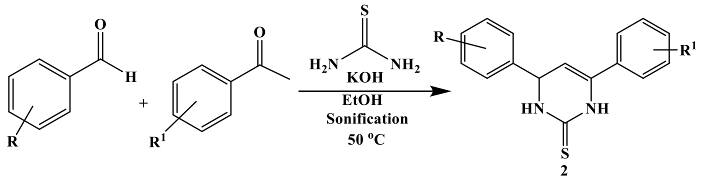


Figure 3. Ultrasound-assisted synthesis of 4, 6-diaryl DHPM.

The NH_2SO_3H catalysed condensation of aldehydes, urea and β-keto esters in ethanol, for the synthesis of DHPMs derivatives. This was noted as a quick and easy method for the synthesis of DHPMs **(3)** using NH_2SO_3H as a catalyst under ultrasonic radiation. For this process, a 98% yield was obtained within 30 min at 20°C to 25°C, as shown in Figure 4 [19].

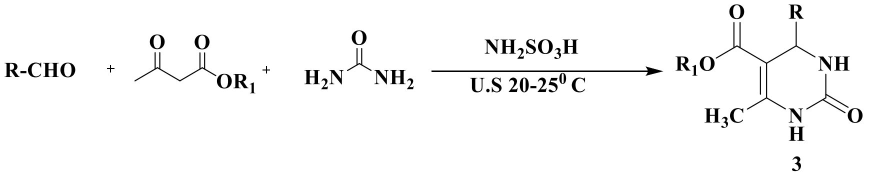


Figure 4. Synthesis of DHPMs using NH2SO3H.

Thiazolidinone **(4)** was prepared from aldehyde, TGA (Thioglycolic acid), and aniline with nano-$CdZr_4(PO_4)_6$ as a catalyst under 60W ultrasonic irradiation, as shown in Figure 5. This reaction was mediated through an imine intermediate, which further undergoes a sulphur attack and cyclization to give 1,3-thiazolidin-4-ones in 25 minutes with an 88% yield [20].

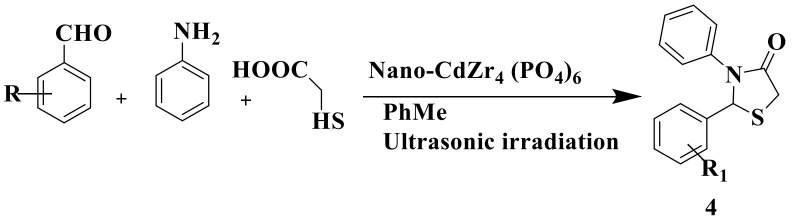


Figure 5. Synthesis of 1, 3-thiazolidin-4-ones by nano-CdZr4 (PO4)6.

Table 2. Pros and cons of ultrasound-assisted chemical reactions.

Aspects	Pros	Cons
Reaction rate	Drastically accelerates reaction kinetics via acoustic cavitation.	It can generate localized overheating, leading to thermal decomposition.

Aspects	Pros	Cons
Yield and selectivity	Improves yield and selectivity by enhanced micro mixing and radical formation.	High-intensity ultrasonic probes require substantial investment and high maintenance.
Energy and solvent efficiency	Enables solvent-free reactions, reducing the use of energy and hazardous waste.	Scaling sonochemical reactors is challenging; uniform cavitation distribution in larger volumes is difficult.
Catalyst and purification	Simplifies purification by minimizing side products.	Erosion can introduce metal contaminants and free radicals from tip corrosion.

3. Microwave Irradiation

Microwave-assisted synthesis is a green and efficient technique. It provides superheating, which results in reduced reaction times and energy consumption, often yielding higher yields with better selectivity. The method supports solvent-free and eco-friendly reactions [21]. Some reactions are mentioned in Table 3, and their pros and cons are listed in Table 4.

Table 3. Microwave-assisted synthesis.

Catalyst	Reaction conditions	Yield	Time	References
Apple juice	Biginelli reaction MW, < 180W	77%	9 Min	[22]
Pomegranate juice	Biginelli reaction (Microwave), 180W	72%	5 Min	[21]
HPA@HNTs-C (0.03 g)	Ultrasonic/ RT	80-95	4-22 Min	[23]

Apple juice, with a pH between 3.3 and 3.9, acts as a mild acidic catalyst in the reaction. Equimolar amounts of urea, ethyl acetoacetate, and an aromatic aldehyde are irradiated at 180 W, with reaction times varying from 9 to 14 minutes and yields ranging from 33% to 77%. For example, the synthesis of ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5**) achieved a 77% yield in 9 minutes and exhibited a melting point of 212°C –214°C (See Figure 6) [22].

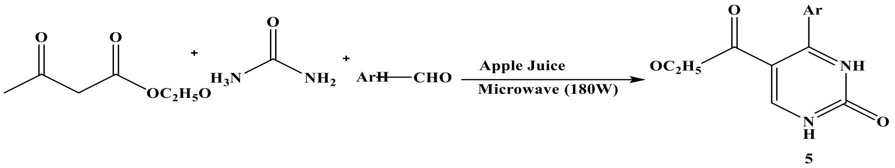


Figure 6. Green approach for synthesis of ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate.

Pomegranate juice serves as an eco-friendly catalyst for microwave-assisted Biginelli reactions with a mild pH of 2.93–3.2. Equimolar amounts of urea, ethyl acetoacetate, and substituted aromatic aldehydes were subjected to microwave irradiation at 180 W for 5 to 11 minutes, with yields ranging from 63% to 72%. (**Figure 7**). Remarkably, the synthesis of ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(6)** has achieved the 72% yield within 5 minutes [21].

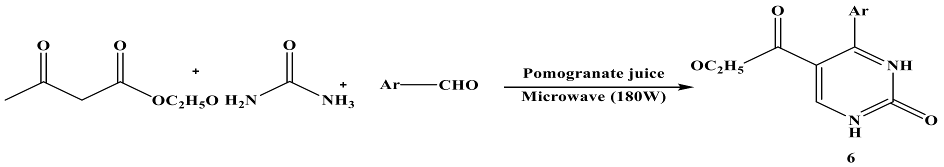
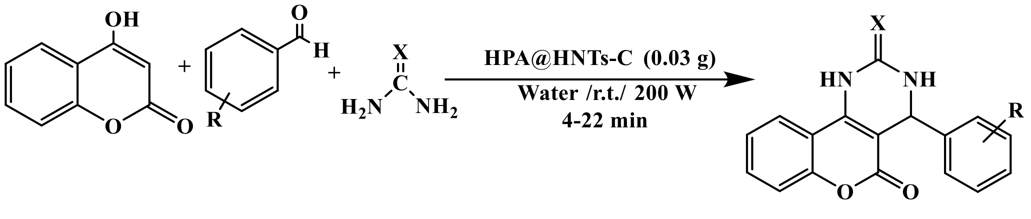


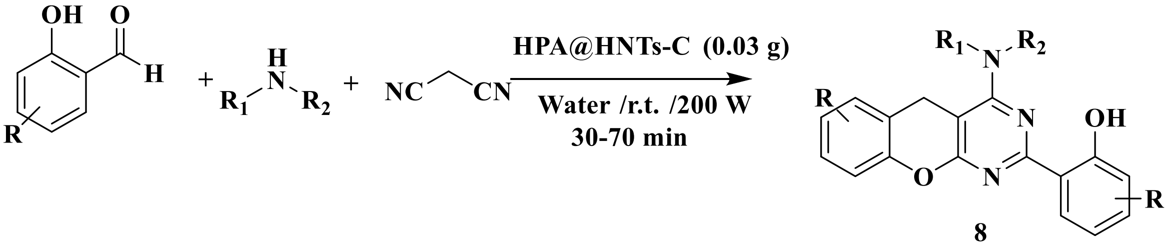
Figure 7. (ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate synthesis by using pomogranate juice.

A novel hybrid catalyst was designed by anchoring hetero-polyacid (HPA) on creatine-functionalized halloysite nanotubes (HNTs), the green one-pot ultrasonic-assisted synthesis of BPPs, i.e, products **(7)** and **(8)** in aqueous media. The catalyst enabled two pathways: (a) reactions of aldehydes, urea/thiourea, and 4-hydroxycoumarin, and (b) condensation of 2-hydroxybenzaldehydes, malononitrile, and amines, as shown in Figures 8 and 9. These reactions gave a higher yield of 75 to 95 % within 4 to 22 min, and the catalyst was recycled, avoiding HPA leaching [23].



7

Figure 8. Synthesis of BPP by using HPA@HNTs-C.



8

Figure 9. Synthesis of BPP using HPA@HNTs-C, water.

Table 4. Pros and cons of microwave-assisted reactions.

Aspect	Pros	Cons
Reaction time	Reduced due to rapid heating	Overheating risk in sensitive reactions
Energy efficiency	Lower energy consumption compared to conventional heating	Limited scalability for large-scale reactions
Solvent use	Enables solvent-free or aqueous-phase reactions	Not all reactions are compatible with microwave conditions
Yield and selectivity	Improves product yield and purity	Hot spots may affect uniformity in heterogeneous systems
Waste reduction	Minimizes by-products and chemical waste	Specialized equipment is costly
Safety	A controlled and enclosed system enhances safety	Pressurized systems require careful monitoring

4. Organocatalyst

Organocatalysts are small organic molecules that catalyze chemical reactions, typically non-toxic, biodegradable, and derived from renewable sources. Organocatalysis enables mild reaction conditions, reduces waste, and improves atom economy [24]. Some representative reactions are mentioned in Table 5 & their advantages and disadvantages are mentioned in Table 6.

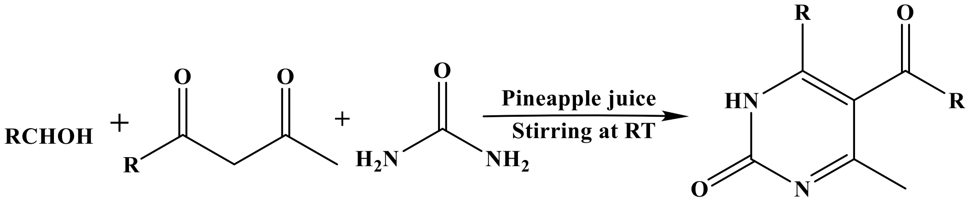
Table 5. An organocatalyst is employed in chemical reactions.

Catalyst	Reaction conditions	Yield	Time	References
Pineapple juice	Biginelli reaction Stirring at RT	82%	3.5Hr	[25]
Lime juice	Biginelli reaction, RT	80-95%	12Hr	[26]
Ver juice	Knoevenagel, RT	80-96%	5-10 Min	[27]

Catalyst	Reaction conditions	Yield	Time	References
Tamarind juice	Grinding H^+	80-95	30–40 Min	[28]
Lactic acid	Biginelli reaction, reflux (180°C)	86-92%	2.5–4 Hr	[29]
Dragon fruit	Biginelli reaction, 80˚C	72-92%	10-12Hr	[30]
Kelubi fruit	Biginelli reaction, 50˚ C	67.7%	180 Min	[31]
Coconut husk ash	Biginelli reaction	77-94%	14-36 Min	[32]
Mango fruit	Biginelli reaction, MW, 180W	60%	6-8 Min	[33]
Iron (III) fluoride	Biginelli reaction, Reflux 80°C	90%	1 Hr	[34]
Citric acid	25ºC	98%	15- 20 Min	[35]

4.1. Fruit juices.

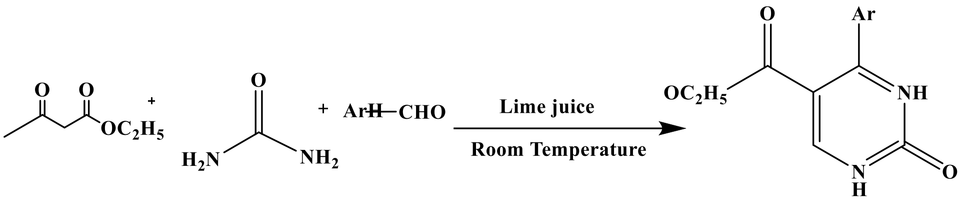
Pineapple juice is used as a catalyst in the single-step process of the DHPMs compound **(9)**. The reaction is solvent-free, yielding 93% within 3.5 Hr with agitation at room temperature, as shown in Figure 10. The solvent-free process is allowed to some extent and does not require hazardous chemicals [36]. In other words, it has been evaluated as an environmentally friendly approach for this cyclocondensation reaction [25].



9

Figure 10. Synthesis of 3, 4-Dihydropyrimidin-2(1H)-ones by using pineapple juice.

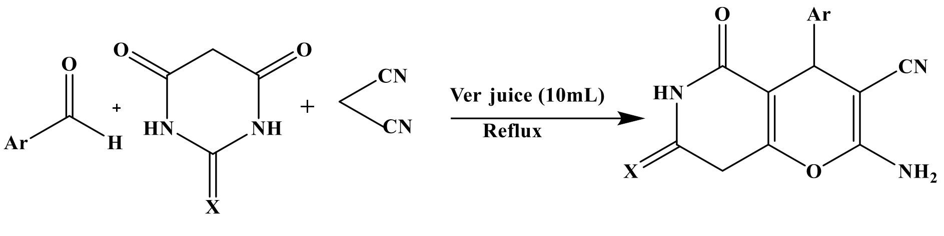
An eco-friendly, efficient, and green methodology for synthesizing various DHPM derivatives **(10),** including aromatic rings, at room temperature in a lime juice medium. It was noted that the Biginelli reaction involving electron-rich aromatic aldehyde needs a longer duration to complete than the reaction with electron-deficient aromatic aldehyde at room temperature for 12 Hrs in a lime juice medium, as shown in Figure 11. The yield of these reactions was recorded in the range of 80–95% [26].



10

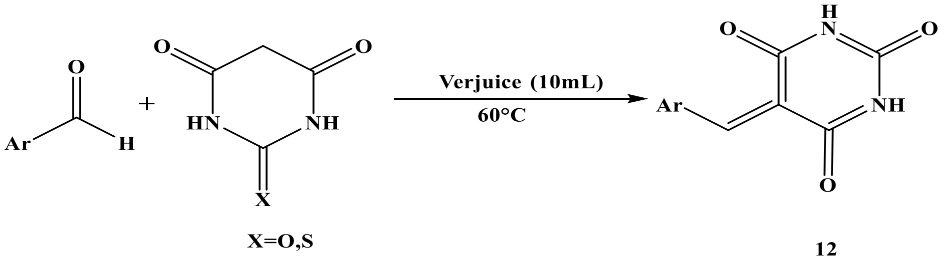
Figure 11. Lime juice-assisted synthesis of 3, 4-Dihydropyrimidin-2(1H)-ones.

Verjuice (fresh grape juice), a nature source of organic acids, was found to be an effective green catalyst in the synthesis of 5-arylmethylenepyrimidine-2,4,6-triones (11) (Figure 12), pyrimido[4,5-d]pyrimidinone derivatives (12) (Figure 13), and pyrano[2,3-d]pyrimidinone derivatives (13) (Figure 14) by Knoevenagel condensation of barbituric or thiobarbituric acid with aldehydes. This environmentally friendly method offers several advantages: simple procedures, short reaction times (5–15 minutes), high yield (80–95%), and a straightforward work-up. It eliminates the need for expensive reagents and avoids the use of hazardous organic solvents, while utilizing a natural, low-cost, biodegradable, and reusable catalyst [27].



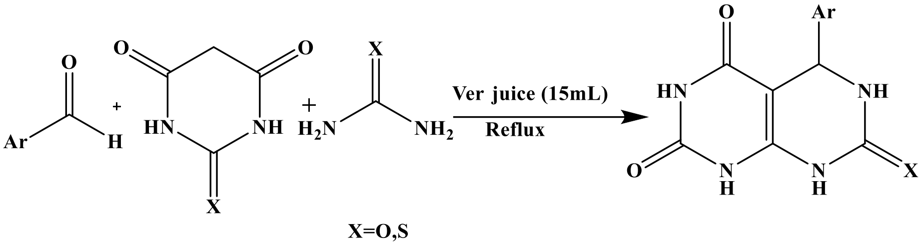
11

Figure 12. Synthesis of 5-arylmethylenepyrimidine-2,4,6-triones by using ver juice.



12

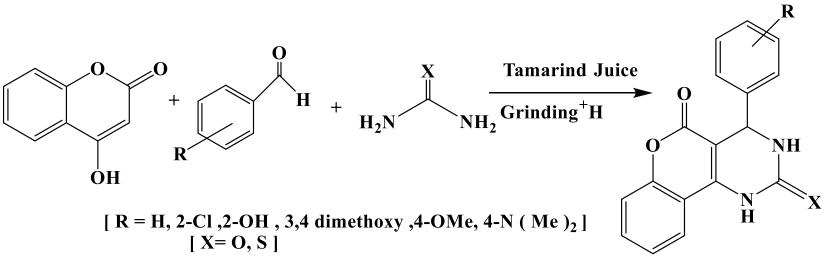
Figure 13. Synthesis of pyrimido [4,5-d]pyrimidinone derivatives by ver juice.



13

Figure 14. Pyrano[2,3-d]pyrimidinone derivatives synthesis using ver juice.

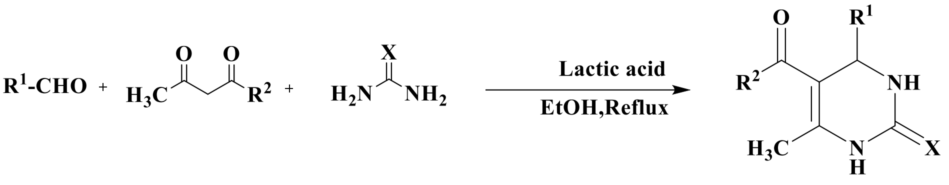
Tamarind (*Tamarindus indica*) juice was used as a natural catalyst to achieve BPPs (Biphenylpyrimidines) **(14)** in a green, one-pot synthesis. Under ambient grinding conditions, the reaction of 4-hydroxycoumarin, substituted benzaldehydes, and urea/thiourea, as shown in Figure 15, in water yielded BPPs **(14)** with 80–95% yield in 30–40 min, indicating an environmentally acceptable method [28].



14

Figure 15. BPPs synthesis using tamarind juice.

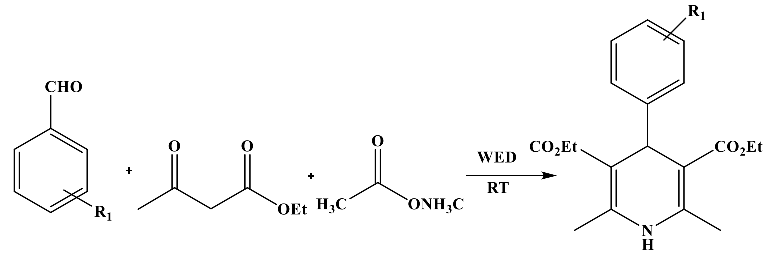
Recently, lactic acid was also used as an environmentally friendly organocatalyst for the synthesis of DHPMs **(15)**. Compared to the traditional process, which involves a longer reaction time, the reaction time is drastically decreased to 2.5–4 hours, yielding 86%-92% of the product, as shown in Figure 16. Acetonitrile and other low-boiling solvents are not used; the reaction condition is moderate [29].



15

Figure 16. Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones by using Lactic acid.

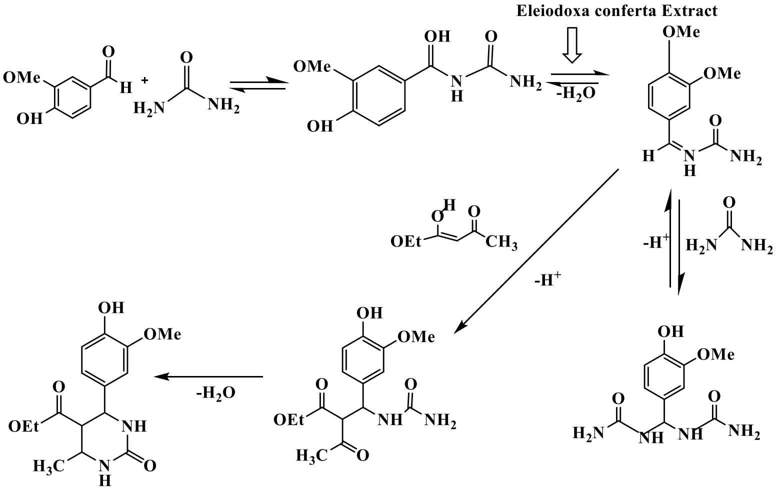
A recent strategy to synthesize DHPs (Dihydropyridine) uses dragon fruit water extract (WED). It promotes reactions, gives a yield of 92% within 10-12 hrs at a temperature of 80°C **(16)**. It encourages the synthesis of DHPM and its derivatives in solvent-free situations using this natural compound, shown in Figure 17 [30].



16

Figure 17. Synthesis of DHPM using dragon fruit water extract.

Recent studies highlight environmental concerns associated with synthetic Lewis acid catalysts derived from metals. This research presents an eco-friendly alternative using kelubi extract (Eleiodoxa conferta) as a natural catalyst for synthesizing DHPM derivatives (**17**), known for their medicinal and biochemical significance. The study focuses on developing a green catalytic method employing kelubi fruit extract to produce DHPM compounds sustainably [37]. The catalysts are prepared from aqueous extracts of kelubi fruit and added to an equimolar reaction mixture of benzaldehyde, urea, and ethyl acetoacetate for the synthesis of pyrimidine derivatives. Using hydrochloric acid as a benchmark acid catalyst at 50°C for 180 minutes, the process yielded the highest percentage of 67.7%, as shown in Figure 18 [31].



17

Figure 18. Kelubi fruit as a catalyst for the synthesis of 3,4-dihydropyrimidin-2 (1H)-ones.

4.2. Fruit ash

Coconut-husk ash (CHA), derived from waste coconut husks, provides a low-cost, green, and heterogeneous catalyst rich in alkaline oxides (e.g., K_2O), offering basic surface sites that facilitate multicomponent reactions. When combined with ball-milling to produce CHA–twisted graphene nanocomposites, the material exhibits enhanced catalytic properties, enabling solvent-free Biginelli reactions to deliver DHPMs in good to excellent yields. Notably, the reaction proceeds under mild, solvent-free conditions, affording 3,4-dihydropyrimidin-2-ones rapidly, with easy recovery and reuse of the catalyst and minimal toxicity (Figure 19). The catalysts generated show remarkable efficiency in the Biginelli reaction for producing DHPM **(18)** under solvent-free conditions [32].

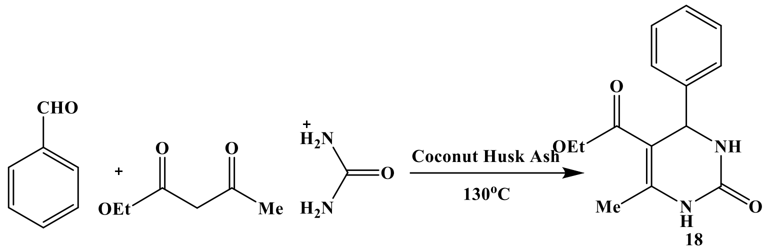


Figure 19. Coconut husk ash as a catalyst for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones.

4.3. Fruit peel

The WEMPA (Mango Fruit peels) has been successfully used for the synthesis of pyrazolophthalazine-5,10-dione (19) derivatives by employing aldehydes, malononitrile, and phthalhydrazide, and using microwave irradiation (180W) via condensation. This catalyst was obtained from agricultural waste, offering the advantages of being cost-efficient and readily available. Additionally, with reduced reaction time (6–8 min), excellent yield (83%–89%) was obtained at room temperature, as shown in Figure 20 [33].

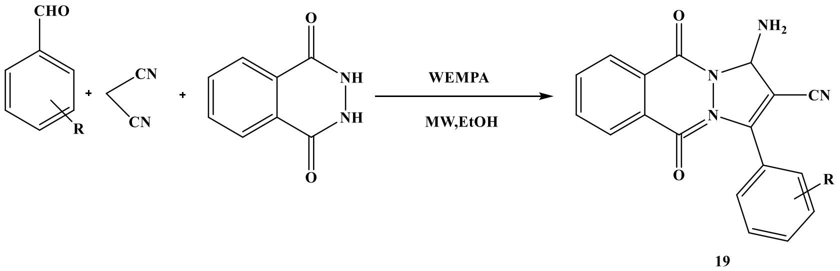


Figure 20. Synthesis of 1H-Pyrazolo [1, 2-b] phthalazine-5, 10-dione using mango fruit peels.

A simple and effective FeF_3-catalyzed process for the synthesis of DHPMs **(20)** derivatives was developed. The protocol was cost-effective and eco-friendly with catalyst reusability (Figure 21). The FeF_3 catalyst can be easily recycled and used up to five cycles [34].

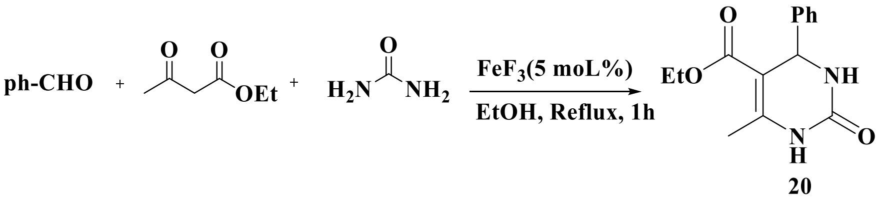
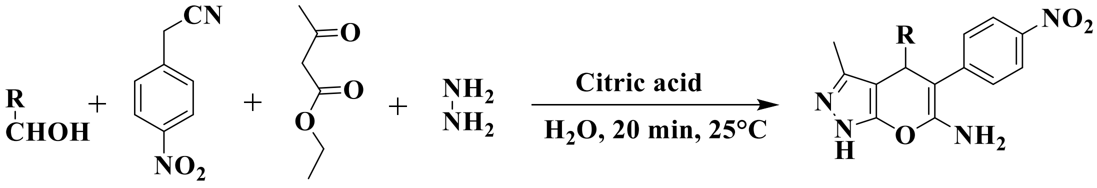


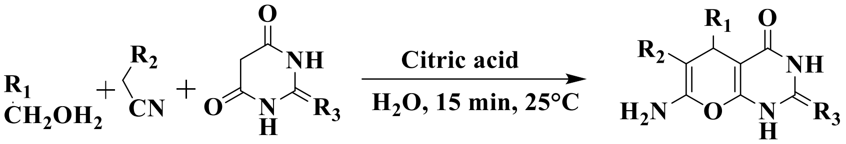
Figure 21. FeF_3-catalyzed reaction for synthesis of 3, 4-Dihydropyrimidin-2(1H)-ones.

For the synrhesis of Pyrano [2,3-e] pyrimidin amine citric acid has been employeed as a green catalyst. **(21)** and pyrano[2,3-d]pyrazol-amines **(22)**. The process is environmentally safe, eco-compatible, and successfully tolerates a broad variety of functional groups shown in Figures 22 and 23. Additionally, it does not require chromatographic purification of compounds. By demonstrating the advantages of citric acid as an effective, rapid, eco-friendly catalyst, the current method aligns with the tenets of green chemistry [35].



21

Figure 22. Pyrano [2, 3-d] pyrazol-amines synthesis using citric acid.



22

Figure 23. Pyrano [2, 3-e]pyrimidin-amine synthesis using citric acid.

Table 6. Pros and cons of organocatalysts.

Aspect	Pros	Cons
Metal-free catalysis	Avoids toxic and expensive transition metals	Limited catalytic activity compared to some metal catalysts
Toxicity and safety	Low toxicity; safer to handle and dispose	Some organocatalysts (Proline derivatives) require careful handling
Biodegradability	Often biodegradable and derived from natural products	Not all organocatalysts are fully environmentally benign
Reaction conditions	Operate under mild, solvent-free, or aqueous conditions	May require long reaction times or higher catalyst loadings
Selectivity	High stereo-, chemo-, and enantioselectivity in many reactions	Enantioselectivity can be substrate-specific
Environmental impact	Reduces heavy metal contamination and aligns with green chemistry principles	Large-scale applications still face limitations in cost and efficiency

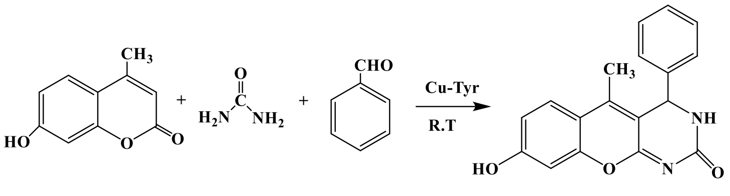
5. Biocatalyst

Biocatalysts such as enzymes are highly efficient and selective catalysts used in green chemistry. The catalyst operates under mild conditions, reducing energy consumption and harmful emissions. Biocatalysts are biodegradable and non-toxic. They enhance reaction specificity, minimize byproducts, and align with principles of sustainable chemistry [38,39]. Reactions are listed in Table 7; their advantages & disadvantages are outlined in Table 8.

Table 7. Biocatalyzed reactions.

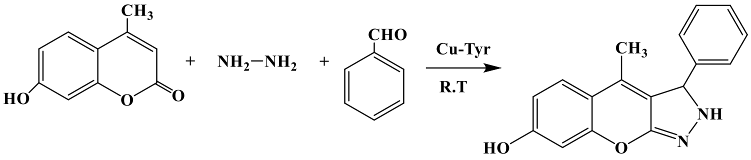
Catalyst	Reaction conditions	Yield	Time	References
Cu (II)-tyrosinase (0.5 g)	50 mM potassium phosphate buffer (pH 6.0)	82-98	2-4 min	[40]
β-Cyclodextrin-SO_3H	Reflux	95%	3-4Hr	[41]

Benzopyran-linked pyrimidine **(23)** and pyrazole derivatives **(24)** were effectively produced via a green Biginelli reaction employing pyrimidine derivatives, substituted aldehydes, urea, and Cu(II)-tyrosinase (0.5 g), as shown in Figures 24 and 25. This technique circumvented the drawbacks of conventional $CuCl_2{\cdot}2H_2O$ catalysis and hazardous additives like HCl to produce high yield (82–98%) in 2-4 min. A copper-based biocatalyst, specifically mushroom tyrosinase, has demonstrated environmental advantages and adaptability, rendering it a viable and efficient catalyst for the production of physiologically relevant heterocycles [40].



23

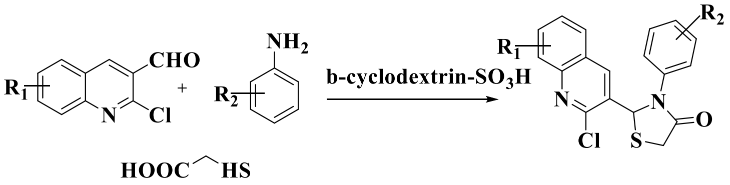
Figure 24. Synthesis of pyrimidine using mushroom tyrosinase.



24

Figure 25. Synthesis of pyrazole using mushroom tyrosinase.

One-pot, solvent-free synthesis of thiazolidinone derivatives **(25)** was performed using a biopolymer-based catalyst, β-cyclodextrin-SO$_3$H. The reaction mixture was refluxed for 3-4 hours, yielding 95% as shown in Figure 26 [41].



25

Figure 26. Synthesis of thiazolidinone derivatives using β-cyclodextrin-SO$_3$H.

Table 8. Pros and cons of biocatalysts.

Aspect	Pros	Cons
Environmental safety	Biocatalysts are biodegradable, non-toxic, and eco-friendly.	Sensitive to temperature, pH, and organic solvents.
Reaction conditions	Operate under mild conditions (ambient temperature, neutral pH, and aqueous media).	May require precise optimization of reaction conditions.
Selectivity	Exhibit high chemo-, regio-, and enantioselectivity, reducing side products.	Substrate scope can be narrow; it may not tolerate non-natural substrates.
Renewability	Derived from renewable biological sources (e.g., microbes, plants).	Production and purification of enzymes can be costly.
Waste reduction	Minimize need for hazardous reagents and solvents; generate less waste.	Limited shelf life and stability under industrial conditions.
Energy efficiency	Reduce energy input by functioning at low temperatures.	Slower reaction rates compared to some chemical catalysts.

6. Nano Catalysts

Catalysts with nanoscale dimensions offer a high surface-to-volume ratio, thereby enhancing catalytic activity and efficiency. Nanocatalyst facilitates faster reactions under mild conditions. These catalysts are highly selective and reusable [42, 43]. Some nanocatalyst reactions are listed below in Table 9. The pros and cons are presented in Table 10.

Table 9. Nano-catalyzed methods for the synthesis of heterocyclic compounds.

Catalyst	Reaction conditions	Yield	Time	References
Cu_2O@Mont/EAS-IL (25mg)	Reflux/60°C	60-98	15-100 min	[44]
ZrO_2 NPs (10 mol%)	Solvent-free/ 70°C	95%	60 min	[45]
Fe_3O_4\\SiO_2\\Salen\\Mn MNP	RT	82-96	50-70	[46]
Fe_3O_4@SiO_2@AE-SO_3H	H_2O/EtOH (1:1) 50°C	90	40-60min	[47]
CuI NPs (10 mol %)	Solvent-free, 70°C	90-94	46-60 min	[48]
Nano ZnO@PEG	EtOH, 25°C	96%	15 min	[49]
Nano CuO-Ag	DBU/ Ethanol/ CH_3COONH_4 / $HC(OEt)_3$	75-92%	20-30 min	[50]
Camphor Coated Ferrite	Biginelli reaction, solvent-free	92%	30 min	[50]
Nano-$CdZr_4(PO_4)_6$	0.6 mol% catalyst	86%	80-90min	[51,52]
Nano-$CoFe_2O_4$@SiO_2/$PrNH_2$	Solvent-free, RT	50-97%	30-60min	[51,52]

Cu_2O nanoparticles were immobilized on ionic liquid-functionalized Montmorillonite-K10 to produce a new Cu_2O@Mont/EAS-IL catalyst. With a 60–98% yield in 15–100 min at 60°C Figure 27, it effectively accelerated the mild one-pot synthesis of BPPs **(26)** in water. The catalyst provided a viable substitute for green synthesis due to its exceptional efficiency, recyclability (up to five cycles), and low copper leaching [44].

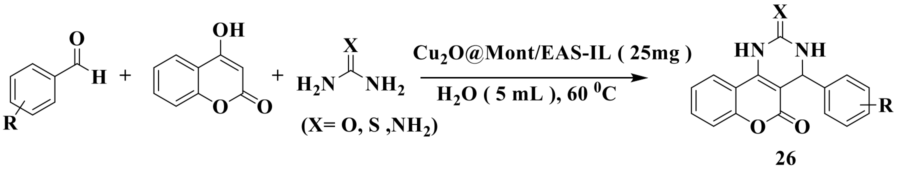
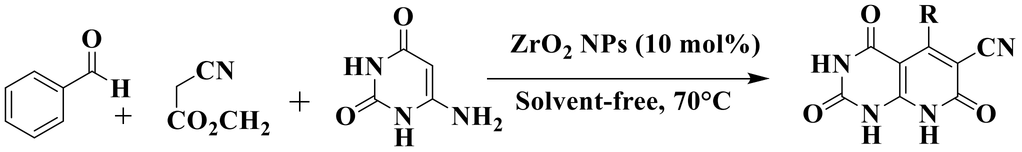


Figure 27. Synthesis of benzopyran-linked pyrimidine using Cu_2O@Mont/EAS-IL catalyst.

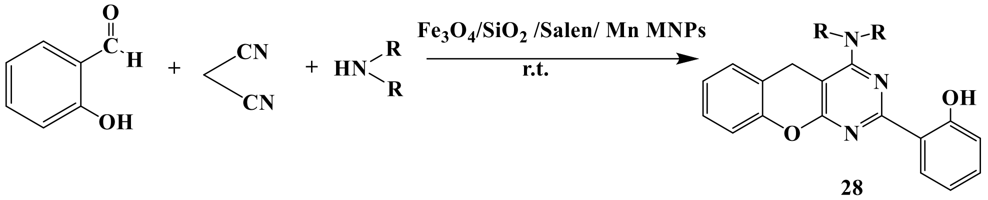
An efficient synthesis of [2,3-d] hexahydropyridotrione pyrimidine derivatives **(27)** is achieved by simultaneously adding 4-aminouracil, methyl cyanoacetate, and Knoevenagel-Michael of aromatic aldehydes as shown in Figure 28 in solvent-free conditions, while 10 mol% of ZrO_2NPs nanoparticles are present as a diverse catalyst. The technique is designed to produce high yield with a short response time and a friendly ecological specificity [45].



27

Figure 28. Synthesis of Pyrido [2,3-d] pyrimidine derivatives.

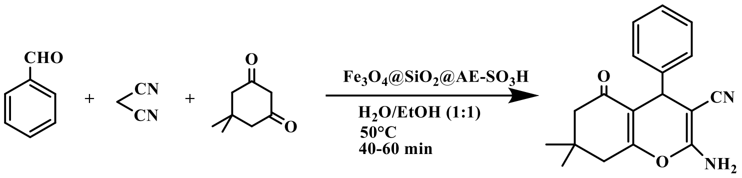
Fe_3O_4\\SiO_2\\Salen\\Mn, a magnetic nanoparticle-supported Mn salen complex, was created and employed as a catalyst for the solvent-free, room-temperature synthesis of benzopyran pyrimidines **(28)** from 2-hydroxybenzaldehyde, malononitrile, and amines given in Figure 29. In 50–70 min, a yield of 82–96% was obtained with a trace amount (0.8 mg) of catalyst. There was no significant reduction in catalytic efficiency after seven cycles [46].



28

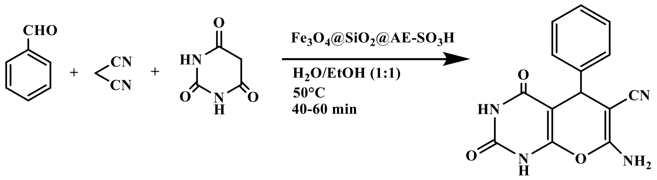
Figure 29. Synthesis of pyrimidines using magnetic nanoparticle-supported Mn.

Sulfonic acid groups on aminoethanol-functionalized silica-coated magnetic nanoparticles were immobilized to create a highly effective $Fe_3O_4@SiO_2@AE\text{-}SO_3H$ catalyst. In green aqueous conditions, the catalyst facilitated the one-pot synthesis of tetrahydrobenzo[b]pyran **(29)** and pyrano[2,3-d] pyrimidinone **(30)** derivatives, achieving 90% yield in 40–60 min at 50°C using ethanol-water as a solvent, as demonstrated in Figures 30 and 31. The catalyst demonstrated excellent reusability (96% recovery) over five cycles [47].



29

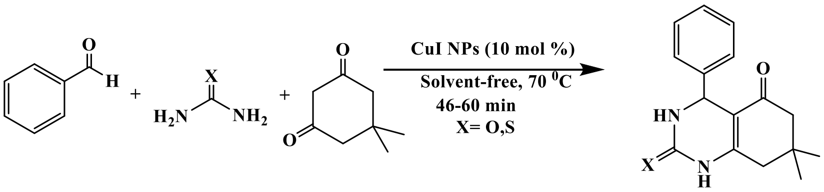
Figure 30. Synthesis of tetrahydrobenzo[b]pyran by using $Fe_3O_4@SiO_2@AE\text{-}SO_3H$.



30

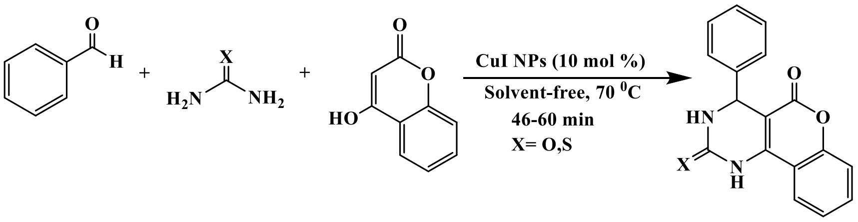
Figure 31. Synthesis of pyrano[2,3-d] pyrimidinone by using $Fe_3O_4@SiO_2@AE\text{-}SO_3H$.

Michael condensation and Knoevenagel reactions were used to create quinazolinones **(31)** and chromeno[*d*]pyrimidinones **(32)** without the need for solvents by employing reusable CuI nanoparticles (CuI NPs). In 45–60 min, a yield of 90–94% was obtained using 10 mol% CuI NPs at 70°C Figures 32 and 33. The procedure offers a simple, eco-friendly work-up under mild conditions [48].



31

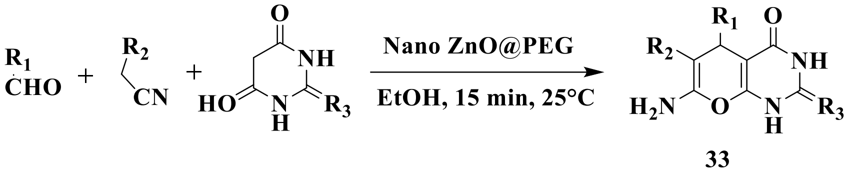
Figure 32. Synthesis of quinazolinones using reusable CuI nanoparticles.



32

Figure 33. Synthesis of chromeno[d]pyrimidinones using reusable CuI nanoparticles.

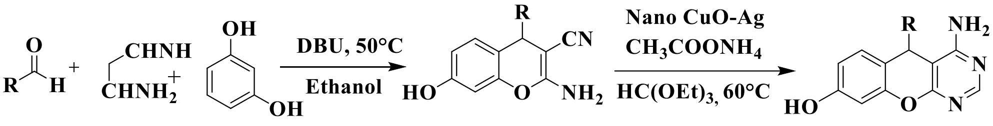
One-step synthesis with nano ZnO@PEG as a catalyst for producing pyrano[2,3-d] pyrimidine **(33)** derivatives by using substituted aldehydes, malononitrile/methyl cyanoacetate, and barbituric acid is given in Figure 34. This process is faster, generates improved yield (up to 93%), and the catalyst can be reused for five cycles with nearly identical catalytic activity. Overall, this technology represents a potential new approach to organic synthesis [49].



33

Figure 34. Synthesis of pyrano[2,3-d] pyrimidine using nano ZnO@PEG as a catalyst.

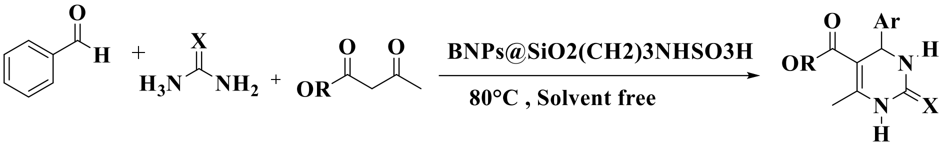
Synthesis of pyrimidine derivatives **(34)** consists of two steps and uses a catalyst nano CuO-Ag as demonstrated in Figure 35. It is initially synthesized by mixing substituted malanonitrile, aldehydes, and resorcinol in the presence of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) and ethanol at 50°C. In the next phase, pyran derivatives are converted into pyrano[2,3-d] pyrimidine derivatives using triethyl orthoformate, ammonium acetate, and 4 mol% nano CuO-Ag catalyst with a maximum yield of 92% [50,53].



34

Figure 35. Synthesis of pyrano[2,3-d] pyrimidine using nano CuO-Ag catalyst.

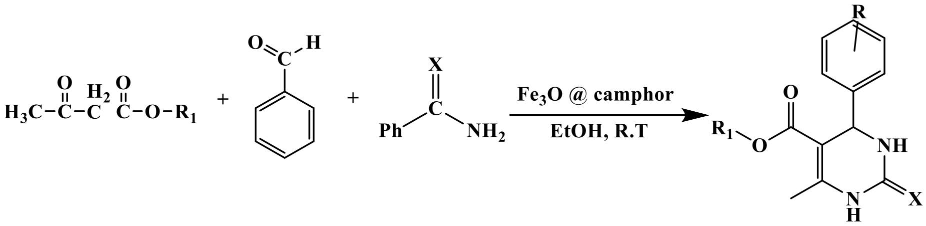
A novel derivative of DHPMs **(35)** has been synthesized successfully when boehmite nanoparticles functionalised with silylpropyl sulfamic acid (BNPs@SiO2(CH2)3NHSO3H) are used as an eco-friendly and metal-free catalyst. This protocol's advantages include rapid reaction time, easy catalyst separation, low cost, and the absence of a neutral environment. It gives up to 98% yield of derivatives and is accomplished within 30 min. There is only a 7% yield drop when the catalyst is recycled at least five times, as shown in Figure 36 [50].



35

Figure 36. BNPs@SiO2(CH2)3NHSO3H assisted synthesis of DHPM.

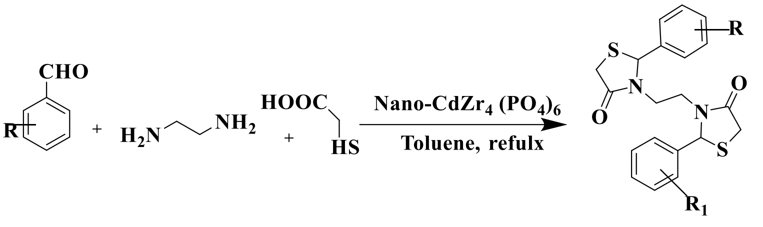
A Fe3O4@camphor as a novel heterogeneous magnetic nanocatalyst, used in a one-pot condensation of a β-ketoester, aldehyde, and urea or thiourea to synthesize DHPMs **(36)** derivatives. The percentage yield was 92%, and the reaction was completed within 30 minutes at room temperature, as shown in Figure 37 [51].



36

Figure 37. Synthesis of DHPMs by using Fe3O4@camphor.

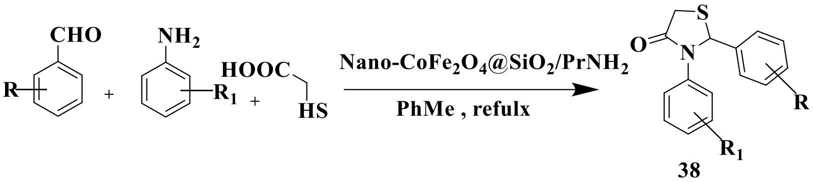
Bis-thiazolidinones **(37)** were prepared from substituted benzaldehyde, ethylenediamine, and TGA with nano-$CdZr_4(PO_4)_6$, a recyclable catalyst, as given in Figure 38. A 0.6 mol% catalyst loading provided high yield, with improved results for aromatic aldehydes with electron-withdrawing groups [52].



37

Figure 38. Synthesis of bis-thiazolidinones using nano-$CdZr_4(PO_4)_6$.

Nano-$CoFe_2O_4$ SiO_2/$PrNH_2$ is an eco-friendly and recyclable catalyst for the synthesis of 1,3-thiazolidin-4-one. It **(38)** was synthesized by refluxing $CoFe_2O_4$ SiO_2 with APTES (3-Aminopropyltriethoxysilane) in toluene, as shown in Figure 39. The catalyst was highly efficient and reusable in the MCR of aniline, chlorobenzaldehyde, and TGA in different solvents [54].



38

Figure 39. 1,3-thiazolidin-4-one synthesis by using Nano-$CoFe_2O_4$ SiO_2/$PrNH_2$.

Table 10. Pros and cons of nanocatalysts.

Aspect	Pros	Cons
Catalytic activity	High surface area improves reaction rates and conversion efficiency.	Aggregation of nanoparticles can reduce activity over time.
Reaction conditions	Enable reactions under mild temperature and pressure.	Often require careful control of synthesis and stabilization.
Selectivity	Surface modification allows high chemo- and regioselectivity.	Selectivity may be lost in complex and multicomponent systems.
Reusability	It can be easily recovered and reused, reducing waste.	Recovery methods (e.g., filtration or magnetic separation) can be energy intensive.
Scalability	Increasing use in industrial and pharmaceutical green processes.	The cost of synthesis and uniform scaling can be high.

7. Solvent Free

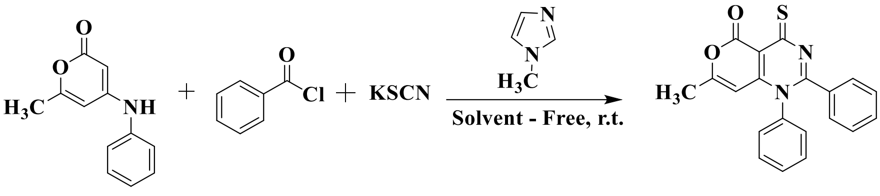
Solvent-free reactions help eliminate the use of toxic organic solvents, thereby reducing waste and pollution [55]. These reactions reduced purification steps and lowered environmental impacts (Table 11). Solvent-free processes enhance safety and sustainability by avoiding volatile organic compounds [56]. Its pros and cons are mentioned in Table 12.

Table 11. Solvent-free reactions.

Catalyst	Reaction conditions	Yield	Time	References
Methylimidazole	Solvent-free, RT	40-90%	50-90 min	[57]

Catalyst	Reaction conditions	Yield	Time	References
MTPPBr/ PHTH-DES	Solvent-free 70°C	85-90%	25-50 min	[58]
LED Bulb	CFL (22 W) irradiation	93%	20 min	[59]
N,N-diethyl-N-sulfoethanaminium	Biginelli reaction, solvent-free, 70°C	88%	40 min	[60]
Solvent- and catalyst-free	At room temperature	88%	5Hr	[61]
$FeNi_3$-IL magnetic nanoparticles (MNPs)	Solvent-free, 60°C	70-93%	40-80 min	[62]

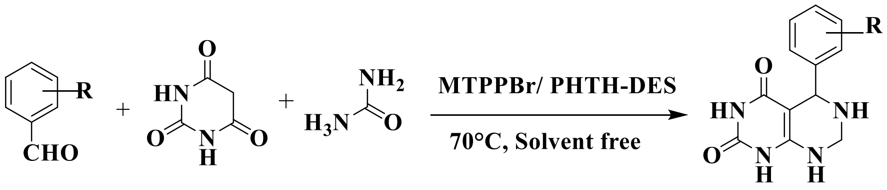
Synthesis of compound **(39)** can be made in a simple and efficient one-pot technique by reacting potassium thiocyanate with 6-methyl-4-phenylamino-pyran-2-one and aroyl chlorides when catalytic quantities of N-methylimidazole are present, as shown in Figure 40. No solvents are needed, high yield (40–90%), rapid reaction durations, simple work-up, mild reaction conditions, and the lack of hazardous solvents [57].



39

Figure 40. Synthesis of Pyrano[4,3-d] Pyrimidine-5-one using N-methylimidazole.

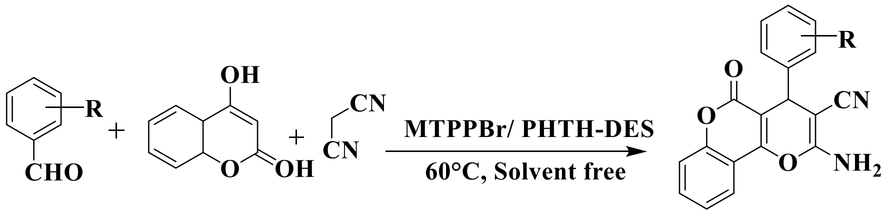
An eco-friendly method of synthesis of pyrimidines **(40)** by using urea, barbituric acid, and aldehydes was developed **(Figure 41)**. This technique makes use of MTPPBr-PHTH-DES, a novel kind of deep eutectic Solvent (DES). Methyltriphenyl-phosphonium bromide (MTPPBr) and phthalic acid (PHTH) are combined to create this DES. Due to its low temperatures, fast reaction periods, and high yield of 85–90%, the process is effective [58].



40

Figure 41. Synthesis of pyrimido[4,5-d] pyrimidines by deep eutectic solvent.

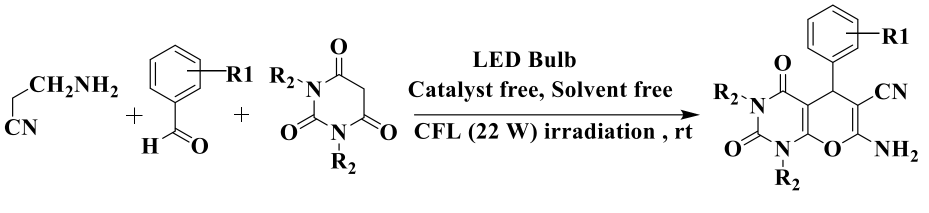
pyrano[3,2-c] chromes **(41)** are synthesized by a solvent-free approach using 4-hydroxycoumarin, malononitrile, and aldehydes. The deep eutectic solvent (DES) catalyst is easy to recycle and separate, making it a sustainable and practical method, as shown in Figure 42. It produces a high yield up to 85-97% [41,58].



41

Figure 42. Synthesis of pyrano[3,2-c] chromes using DES.

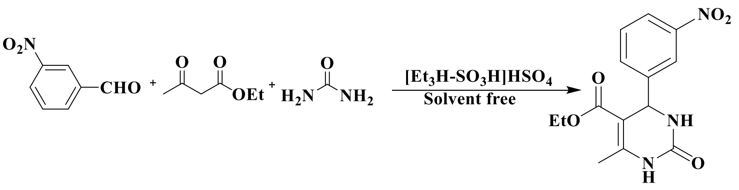
Novel approach for one-pot pyrano [2,3-d] pyrimidine **(42)** scaffold synthesis, in which visible light irradiation can be used as a green promoter without the need for a solvent or catalyst (Figure 43). Compact Fluorescent Lamp (CFL) irradiation is an inexpensive and eco-friendly medium, with high yield, non-hazardous reaction conditions, catalyst and solvent-free reactions, and time-saving features [59].



42

Figure 43. Catalyst and solvent-free synthesis of pyrano [2,3-d] pyrimidine.

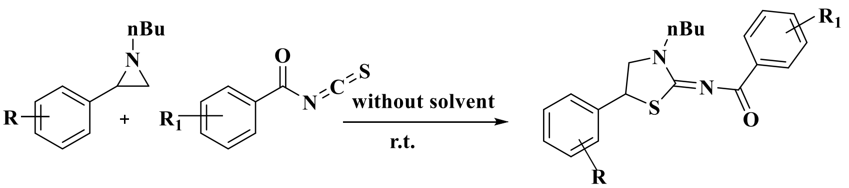
A N,N-diethyl-N-sulfoethanaminium hydrogen sulphate ($[Et_3N–SO_3H]HSO_4$) is a SO_3H-containing ionic liquid that has been synthesised. The Bronsted acidic ionic liquid's catalytic activity was investigated for the synthesis of DHPMs **(43)** through a solvent-free one-pot multicomponent reaction. The reaction was accomplished within 40 min with 88% yield Figure 44 [60].



43

Figure 44. $Et_3N–SO_3H]$ HSO_4 assisted synthesis for DHPMs.

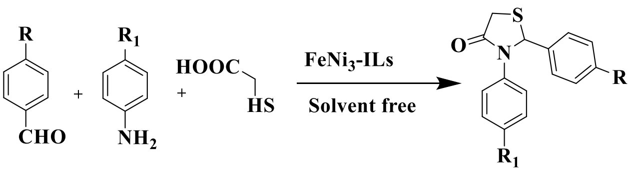
By using a catalyst-free and solvent-free Domino Ring Opening Cyclization (DROC) reaction, 2-iminothiazolidines **(44)** are prepared from aziridines and aroyl isothiocyanates through [3+2] cycloaddition reaction, given in Figure 45. It follows the SN_2 mechanism. Aroyl isothiocyanates act as both nucleophiles and electrophiles. Thus, the reaction provided a high yield with electron-donating aziridines and electron-withdrawing isothiocyanates [61].



44

Figure 45. Synthesis of 2-iminiothiazolidine using domino ring-opening cyclization.

Solvent-free, one-pot 1,3-thiazolidin-4-one **(45)** synthesis was performed with $FeNi_3$-IL MNPs as a catalyst at 60°C with 70-93% yield in 40-80 min, as given in Figure 46. The process was eco-friendly and facilitated easy recovery and reuse of the catalyst using an external magnet [62].



45

Figure 46. $FeNi_3$-IL MNPs catalysed the reaction for the synthesis of 1,3-thiazolidin-4-one.

Table 12. Pros and cons of a solvent-free catalyst.

Aspect	Pros	Cons
Cost efficiency	Cuts down on solvent cost and waste disposal expenses.	May require higher temperatures or energy input to compensate for the lack of solvent.
Energy efficiency	Often compatible with microwave or ultrasonic irradiation, enhancing energy savings.	Mechanical grinding or heating might consume more energy for certain substrates.
Scalability	Easy scale-up for industrial applications without solvent recovery systems.	Heat dissipation and uniform mixing become more difficult at a larger scale.
Catalyst performance	Compatible with solid recyclable catalysts (e.g., $FeNi_3$, MNPs, DES).	Some catalysts may lose activity in the absence of a liquid phase or require special conditions.

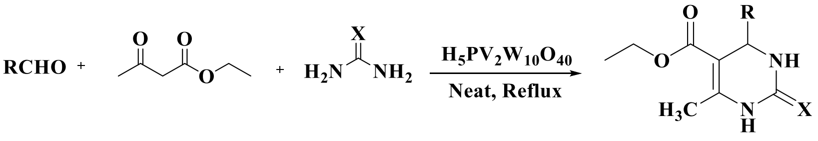
8. Recyclable Catalyst

Reusable catalysts are the catalysts that can be used multiple times in chemical reactions without losing their activity [63]. These catalysts favour eco-friendly reactions with high efficiency. After the reaction is completed, they can be easily separated and reused, which saves costs, time, and energy [64]. Some representative reactions are listed in Table 13; their advantages and disadvantages are outlined in Table 14.

Table 13. Reusable catalyst in organic reactions.

Catalyst	Reaction conditions	Yield	Time	References
Montmorillonite-KSF	Biginelli reaction, solvent-free reflux 80°C	98%	1 hr	[65]
Zn L-Proline	Biginelli reaction, MW, 180W	81-92%	5-10 min	[66]
L- Tyrosine	Biginelli reaction, grinding method, RT	87%	15 Min	[67]
$BF_3{\cdot}OEt_2$ + TBAHS	-30°C	97%	40min	[68]
Deep Eutectic Solvent	choline chloride: glycerol (1:2), 65°C	80%	90min	[69]

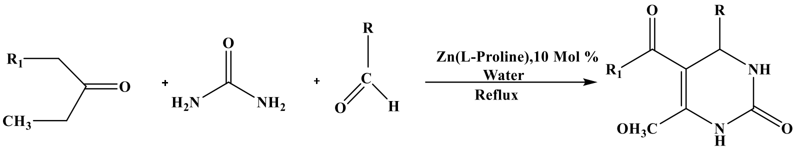
For the synthesis **(46)** of DHPMs, HPA-Montmorillonite-KSF was used as a reusable and heterogeneous catalyst. The catalytic efficiency was significantly improved up to 5 cycles. Key highlights of this process include easy work-up, excellent purity, and yield under mild reaction conditions [65] (Depicted in Figure 47).



46

Figure 47. HPA-Montmorillonite-KSF assisted synthesis of 3, 4-Dihydropyrimidin-2(1H)-ones.

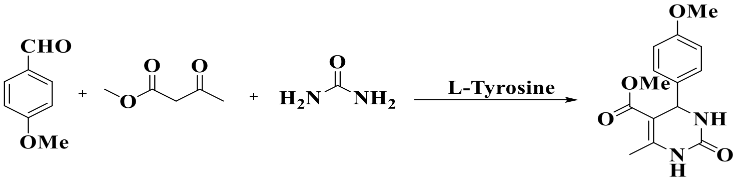
A new environment-friendly method was utilized for the synthesis of DHPM **(47)** derivatives employing bis[(L)prolina to-N, O]Zn as an affordable, effective, and mild Lewis acid catalyst in water. Utilizing this catalyst through the Biginelli reaction results in a yield of (81 to 92%) within 5-10 min, and it is active for up to five cycles, as shown in Figure 48 [66].



47

Figure 48. Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones.

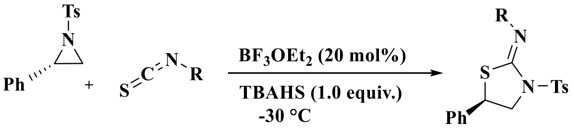
L-tyrosine is used as a catalyst to synthesize physiologically active 3, 4-dihydropyrimidin-2-(1H)-ones (DHPMs) **(48)** using a one-step grinding method at room temperature without the use of solvents. The reaction was accomplished within 15 min with 87% yield, as shown in Figure 49. The efficiency of L-tyrosine as a viable catalyst for the Biginelli reaction has been demonstrated by DFT calculations [67].



48

Figure 49. Green approach for the synthesis of DHPMs using L-tyrosine.

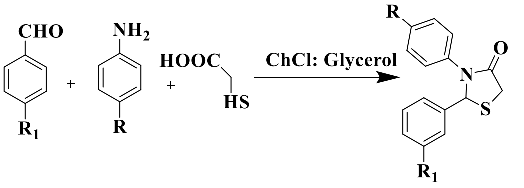
Stereoselective synthesis of 2-iminothiazolidines **(49)** was obtained with the use of Lewis Acid Catalyst $BF_3 \cdot OEt_2$ and tetrabutylammonium hydrogen sulphate (TBAHS) as catalyst at a temperature of -30°C, yielding 97% in 40 min as shown in Figure 50 [68].



49

Figure 50. Synthesis of 2-iminothiazolidine using Acid Catalyst $BF_3 \cdot OEt_2$ and tetrabutylammonium hydrogen sulphate (TBAHS).

Synthesis of 1,3-thiazolidin-4-ones **(50)** using aniline, benzaldehyde, and thioglycolic acid (TGA) in choline chloride: glycerol (1:2) as a DES. DES acted as a green, stable, and reusable catalyst, enabling imine formation, addition, and cyclization, as shown in Figure 51. It was recycled five times without losing efficiency, ensuring sustainability [69].



50

Figure 51. Synthesis of 1, 3-thiazolidine-4-one using deep Eutectic solvents.

Table 14. Pros and cons of a recyclable catalyst.

Aspect	Pros	Cons
Environmental impact	Minimize waste and pollution. Reduces catalyst disposal and environmental load.	Some catalysts require toxic reagents or solvents for regeneration.
Catalyst recovery	Easy separation from reaction medium (e.g., magnetic, heterogeneous catalysts).	Repeated recovery may reduce activity or selectivity over time.

Aspect	Pros	Cons
Product purity	Less contamination of the product due to the easy separation of the catalyst.	Leaching of metal or active species may still occur, affecting purity.
Stability and longevity	Can retain activity over multiple cycles (commonly 4–6 times).	Activity may degrade after several uses, requiring reactivation or replacement.

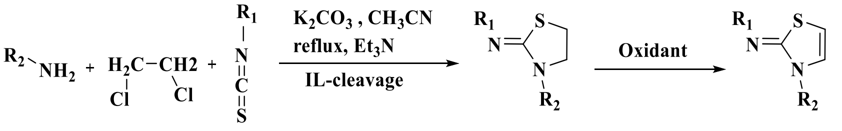
9. Ionic Liquid (IL) Catalysed Reactions

Ionic liquid catalysts are special salts that are liquid at room temperature. They are made of positive and negative ions and have unique properties such as high thermal stability and low vapour pressure [70]. These catalysts have the ability to dissolve many compounds and often work without toxic solvents. After the reactions, they can be reused up to several cycles without wasting activity, which makes them eco-friendly [71,72]. Representative reactions are given below (Table 15) its advantages and disadvantages are given in Table 16.

Table 15. Ionic liquid-catalyzed reactions.

Catalyst	Reaction conditions	Yield	Time	References
Ionic Liquids (ILs)	Reflux	90%	12 Hr	[73,74]
$[Et_3NH]$ $[HSO_4]$	One-pot, MCR, 80°C, 25 mol% catalyst	80%	1 Hr	[74]

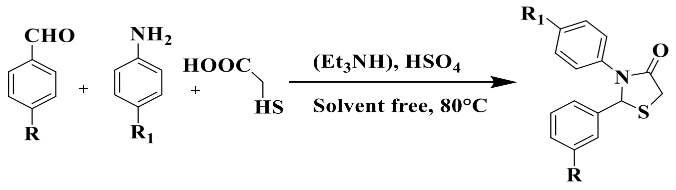
Isothiocyanate, 2-substituted-2-aminobenzimidazole, and triethylamine reacted together using ethylene dichloride as a solvent, producing 2-imino-1,3-thiazolidines **(51)** and 2-imino-1,3-thiazolines, as given in Figure 52. The reaction involved ionic liquid (IL) anchored 2-aminobenzimidazole, which first formed isothiourea and then reacted within and between molecules with 1,2-dichloroethene [73].



51

Figure 52. 2-imino-1,3-thiazolidines and 2-imino-1,3-thiazolinessynthesis using ionic liquid.

MCR was conducted using $[Et_3NH]$ $[HSO_4]$ as an ionic liquid-assisted catalyst at 80°C to synthesize 1, 3-thiazolidin-4-ones compound **(52),** given in Figure 53. It gives 80% yield in 1 hr and allows catalyst recyclability [73,74].



52

Figure 53. Sustainable synthesis of thiazolidinone derivative using $[Et_3NH]$ $[HSO_4]$ as an ionic liquid.

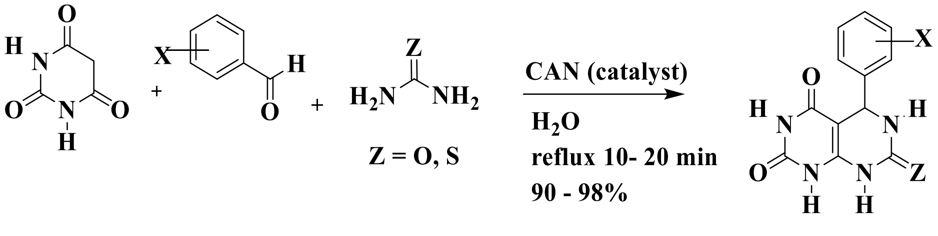
Table 16. Pros and cons of ionic liquid catalyst.

Aspect	Pros	Cons
Application in heterocycles	Effective in the synthesis of pyrimidines, thiazolidinones, pyrazoles, etc., under mild conditions.	Product isolation sometimes requires extra purification steps due to strong IL-product interaction.

Aspect	Pros	Cons
Catalytic efficiency	Promotes efficient multicomponent and one-pot reactions.	Reaction optimization is often needed; some ILs inhibit desired transformations.
Green chemistry compliance	Non-volatile, non-flammable, and low vapor pressure—reduces atmospheric pollution.	Some ILs are toxic or non-biodegradable, raising concerns about long-term environmental fate.
Thermal and chemical stability	Stable at high temperatures and under a wide pH range.	May degrade under very high thermal conditions or prolonged microwave exposure.

10. Miscellaneous

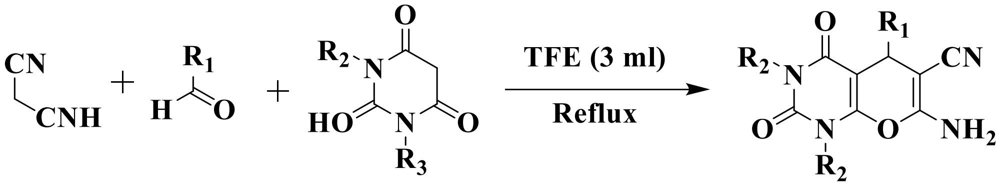
Synthesis of pyrimidinedione derivatives (**53**) using Ceric Ammonium Nitrate (CAN) catalyst involves barbituric acid, urea or thiourea, and substituted aldehyde (Figure 54). This method was considered cost-effective, environmentally friendly, and non-toxic, with an overall yield of approximately 90-98% [75]. Representative reactions are given **in Table 17.**



53

Figure 54. Synthesis of pyrimidinedione derivatives using Ammonium Nitrate (CAN).

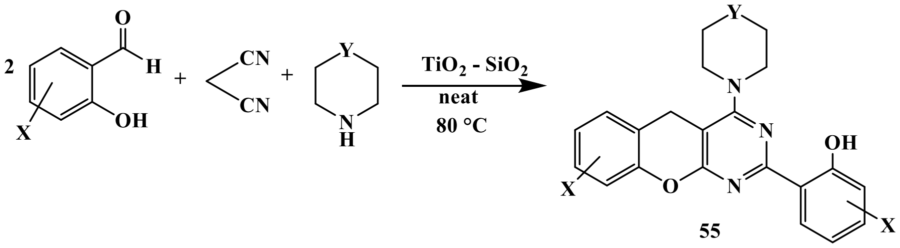
Pyrano[2,3-d] pyrimidine **(54)** scaffolds were synthesized using TFE as a catalyst from barbituric acid, malononitrile, 1,3-dimethylbarbituric acid, and aryl aldehydes, as shown in Figure 55. This process has utilized (2,2,2-trifluoroethanol) TFE, a polyfluorinated alcohol, as it is safe and reusable up to five times without requiring significant modifications [76,83].



54

Figure 55. Synthesis of Pyrano[2,3-d] pyrimidine using (2,2,2-trifluoroethanol) TFE.

One-pot synthesis of BPP derivatives **(55)** was carried out using 5% TiO_2-SiO_2 heterogeneous catalyst from substituted salicylaldehyde, malononitrile, and secondary amines at 80°C under solvent-free medium Figure 56. Under mild conditions, this process resulted in an improved yield (85–92%) within 15 minutes, and the catalyst was recyclable up to three cycles [77].



55

Figure 56. Synthesis of benzopyrano [2,3-d] pyrimidine using TiO_2-SiO_2.

Pyrimidine **(56)** and pyrimidine-5-yl-(2-hydroxyphenyl) methanone **(57)** derivatives were synthesized from guanylhydrazones and 3-formylchromone as shown in Figure 57 in the presence of ethanol [78].

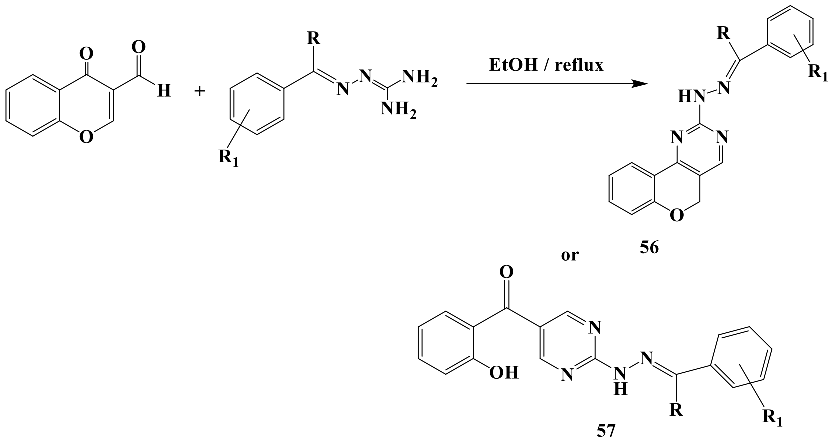


Figure 57. Synthesis of a pyrimidine derivative using ethanol.

Multicomponent condensation of hydrazine hydrate, ethyl acetoacetate, aromatic aldehydes, and barbituric/ thiobarbituric acid for the synthesis of pyranopyrimidines **(58)** in aqueous ethanol without the use of a catalyst is given in Figure 58. This is an eco-friendly reaction that achieved a good yield (79-93%) in a shorter reaction time [79].

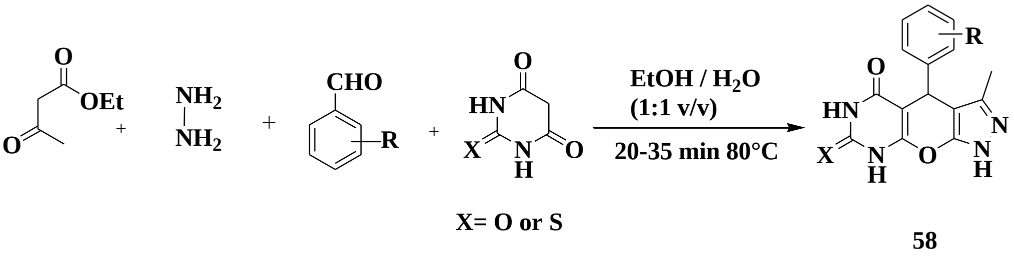


Figure 58. Pyrano[2,3-d] pyrimidines synthesis using ethanol and water.

Effective synthesis of thioxochromenopyrimidin-5-ones and chromenopyrimidine-2,5-diones **(59)** was achieved using recyclable, homogenous Keggin-type heteropoly acid catalyst, $H_5BW_{12}O_{40}$ (BWA), Figure 59. The multicomponent reaction of 4-hydroxycoumarin, urea/thiourea, and substituted benzaldehydes with a catalytic quantity of BWA (5 mg) under reflux yielded yields of 80-97% within 15-30 minutes. The BWA was readily recovered and reused three times with minimal activity loss [80].

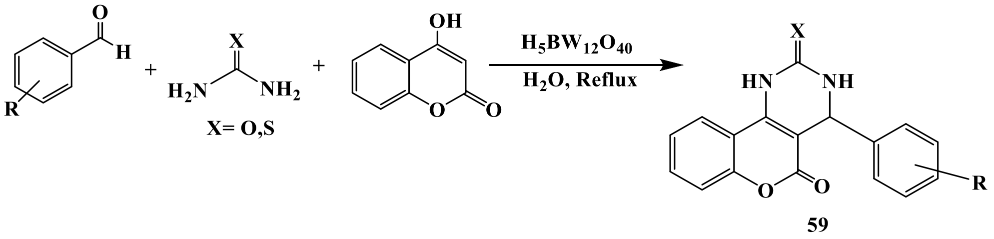
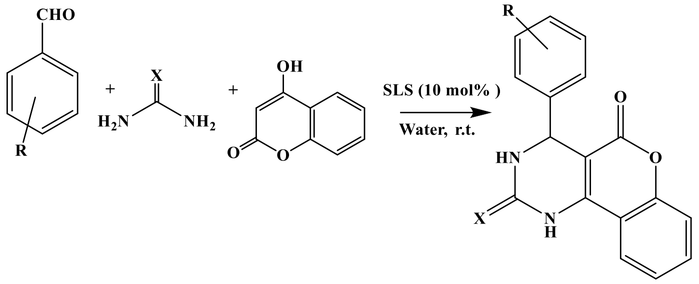


Figure 59. Synthesis of chromenopyrimidine-2, 5-diones using BWA.

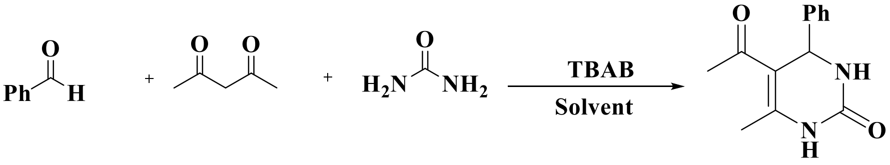
Biologically relevant fused pyrimidine-2,5-dione/thione (60) derivatives can be synthesized in an eco-friendly and effective manner at room temperature using water as a solvent in the presence of sodium lauryl sulfate (SLS). Synthesis of pyrimidine derivatives was achieved within 4-5 hrs from 4-hydroxycoumarin, aromatic aldehydes, and urea/thiourea. This yields up to 80–95% of fused pyrimidines using 10 mol% SLS Figure 60 [81].



60

Figure 60. Synthesis of pyrimidine-2, 5-dione/thione using SLS.

A novel synthesis technique for DHPMs **(61)** derivatives has been developed, utilizing tetrabutylammonium bromide (TBAB) as an eco-friendly, green catalyst. By replacing β-dicarbonyl with urea or thiourea and aromatic aldehydes at 80°C without the use of solvents and with the catalyst TBAB present, novel DHPM derivatives were synthesized. The reaction is accomplished within 30 minutes, yielding 95% of the product, as shown in Figure 61 [82].



61

Figure 61. Tetrabutylammonium bromide catalyzed the synthesis of DHPM.

Table 17. Reaction conditions for sustainable methods in organic synthesis.

Catalyst	Reaction conditions	Yield (%)	Time	References
Ceric ammonium nitrate (CAN)	Reflux	90-98	10- 20 min	[75]
Polyfluorinated alcohol (TFE)	Reflux	91	180 min	[76]
TiO_2 - SiO_2	Neat, 80°C	85-92	15 min	[77]
EtOH	Reflux / 60°C	11-94	3-8 Hr	[78]
Ethanol/H_2O (1:1 v/v)	80°C	96	20-30 min	[79]
$H_5BW_{12}O_{40}$	H_2O, Reflux	80-97	15-30 min	[80]
Sodium lauryl sulfate (SLS), 10 mol%	H_2O, RT	80-95	4.5 Hr	[81]
TBAB	Biginelli reaction, solvent-free, reflux 80°C	97	30 min	[82]

11. Discussion and Critical Analysis

Nitrogen-containing heterocycles are essential in pharmaceuticals and agrochemicals. Traditional synthesis involves toxic reagents, high temperature, and long reaction times, contributing to environmental harm. Green chemistry offers sustainable solutions through various approaches. Organocatalysts, such as fruit extract, fruit peel, and ash, enable metal-free synthesis under mild conditions; however, they often require high catalyst loading and have limited substrate scope. Biocatalysis enables enzymes to exhibit high selectivity in complex organic reactions. Nanocatalysts offer high efficiency and recyclability, although metal leaching and the high cost of metals pose significant challenges in their use. Solvent-free methods of synthesis reduce waste and increase the yield of reactions. Energy-efficient techniques, such as photochemistry, sonochemistry, and microwave, significantly reduce reaction times and improve selectivity. Additionally, green, non-toxic solvents, ionic liquids, deep eutectic mixtures, and biodegradable media facilitate the design of eco-friendly reaction schemes. Green methodologies have high potential, but they still face challenges such as high costs, scalability issues, and the need for comprehensive environmental safety studies.

12. Conclusion

This review highlights recent advancements in sustainable methods for the synthesis of nitrogen-containing heterocycles that reinforce a wide spectrum of therapeutic activities, including anticancer, antiviral, cardiovascular, and antibacterial effects. Conventional synthetic approaches often suffer from inherent limitations, including the use of hazardous reagents, toxic organic solvents, prolonged reaction times, and high energy demands, which collectively hinder eco-friendly drug development.

Over the past decade, the emergence of green synthetic strategies, encompassing solvent-free protocols, microwave- and ultrasound-assisted reactions, recyclable and heterogeneous catalytic systems, as well as bio-derived and safer solvents, has transformed heterocyclic chemistry. These eco-innovative methodologies not only minimize environmental burden but also offer significant improvements in reaction efficiency, yield, and product purity, thereby facilitating cost-effective and sustainable drug discovery. Continued exploration of environmentally benign synthetic routes is poised to play a pivotal role in advancing next-generation pharmaceutical agents. Adoption of such alternative, sustainable processes will form the cornerstone of a greener chemical industry, fostering innovation and long-term progress in medicinal chemistry. Hopefully, this article will serve as a valuable resource for researchers seeking to design efficient and environmentally friendly synthetic strategies for heterocyclic drug development.

13. Future Perspectives

Heterocyclic synthesis can be effectively accomplished using continuous-flow chemistry, biocatalysis, deep eutectic solvents (DES), nanocatalysts, organocatalysts, and solvent-free processes. Intricate nitrogenous heterocycles can be easily and selectively constructed with less energy and solvent if multicomponent and one-pot processes are developed. Currently, there is a need to develop even more economic methods for the synthesis of pharmaceutical agents using green principles. Future research can focus on improving yield and reducing the time required for multistep reactions. In the future, these methods will ensure a steady supply of bioactive nitrogenous heterocycles while reducing environmental impact. The utilization of recyclable catalysts, such as metal-free and biocatalysts, as well as various green solvents and ionic liquids, will also help drive sustainable synthesis processes.

Author Contributions

Conceptualization, V.N.S.; Methodology, A.K., P.T., A.M.; Software, S.S., P.S.; Validation, V.S., M.G.; Formal analysis, V.S.; Investigation, P.T., A.K., P.S.; Resources, A.K., A.M., S.S., P.S., P.T.; Data curation, V.S.; Writing—original draft preparation, P.T.; Writing—review and editing, V.S., P.T.; Visualization, V.S.; Supervision, V.S., M.G.; Project administration, V.S. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable.

Funding

This article received no external funding.

Acknowledgments

The authors sincerely thank Dr. Minal R Ghante, Principal, STES, Smt. Kashibai Navale College of Pharmacy, Kondhwa (Bk.), Pune, for continuous encouragement and support in the preparation of this review article. Their guidance and provision of necessary resources greatly facilitated the successful completion of this work.

Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	**Definition**
Hr	Hours
RT	Room Temperature
Min	Minutes
HPA	Hetero-Polyacid
HNTs	Halloysite Nanotubes
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
PHTH	Phthalic Acid
MTPPBr	Methyltriphenyl-Phosphonium Bromide
DES.	Deep Eutectic Solvent
CuI NPs	CuI Nanoparticles
Mn	Magnetic Nanoparticle
CAN	Ceric Ammonium Nitrate
TFE	Trifluoroethanol
BWA	$H_5BW_{12}O_{40}$
DHPMs	3,4-Dihydropyrimidin-2(1H)-ones
MCRs	Multicomponent Reactions
WED	Water Extract Dragon Fruit
WEMPA	Mango Fruit Peels
DFT	Density Functional Theory
TBAB	Tetrabutylammonium Bromide
TBAHS	Tetrabutylammonium Hydrogen Sulphate

Abbreviation	Definition
TGA	Thioglycolic Acid
IL	Ionic Liquid
DROC	Domino Ring Opening Cyclization
APTES	Aminopropyltriethoxysilane
BPP	Benzopyranopyrimidine

References

1. Vlocskó, R.B.; Xie, G.; Török, B. Green Synthesis of Aromatic Nitrogen-Containing Heterocycles by Catalytic and Non-Traditional Activation Methods. *Molecules* **2023**, *28*, 4153, https://doi.org/10.3390/molecules28104153.
2. Nishanth Rao, R.; Jena, S.; Mukherjee, M.; Maiti, B.; Chanda, K. Green synthesis of biologically active heterocycles of medicinal importance: a review. *Environ. Chem. Lett.* **2021**, *19*, 3315–3358, https://doi.org/10.1007/s10311-021-01232-9.
3. Becker, J.; Manske, C.; Randl, S. Green chemistry and sustainability metrics in the pharmaceutical manufacturing sector. *Curr. Opin. Green Sustain. Chem.* **2022**, *33*, 100562, http://dx.doi.org/10.1016/j.cogsc.2021.100562.
4. Bajwa, D.S.; Pourhashem, G.; Ullah, A.H.; Bajwa, S.G. A concise review of current lignin production, applications, products and their environmental impact. *Ind. Crops Prod.* **2019**, *139*, 111526, https://doi.org/10.1016/j.indcrop.2019.111526.
5. Campos, J.F.; Berteina-Raboin, S. Greener Synthesis of Nitrogen-Containing Heterocycles in Water, PEG, and Bio-Based Solvents. *Catalysts* **2020**, *10*, 429, https://doi.org/10.3390/catal10040429.
6. Ardila-Fierro, K.J.; Hernández, J.G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. *ChemSusChem* **2021**, *14*, 2145–2162, https://doi.org/10.1002/cssc.202100478.
7. Abdussalam-Mohammed, W.; Ali, A.Q.; Errayes, A.O. Green Chemistry: Principles, Applications, and Disadvantages. *Chem. Methodol.* **2020**, *4*, 408–423, https://doi.org/10.33945/sami/chemm.2020.4.4.
8. Zimmerman, J.B.; Anastas, P.T.; Erythropel, H.C.; Leitner, W. Designing for a green chemistry future. *Science* **2020**, *367*, 397-400, https://doi.org/10.1126/science.aay3060.
9. Fantoni, T.; Tolomelli, A.; Cabri, W. A translation of the twelve principles of green chemistry to guide the development of cross-coupling reactions. *Catal. Today* **2022**, *397-399*, 265-271, https://doi.org/10.1016/j.cattod.2021.09.022.
10. de Marco, B.A.; Rechelo, B.S.; Tótoli, E.G.; Kogawa, A.C.; Salgado, H.R.N. Evolution of green chemistry and its multidimensional impacts: A review. *Saudi Pharm. J.* **2019**, *27*, 1-8, https://doi.org/10.1016/j.jsps.2018.07.011.
11. Zanabe, J. Innovative Catalysts and Techniques in Eco-Friendly Heterocyclic Synthesis. *J. Chem. Pharm. Res.* **2024**, *16*, 11-12.
12. Majee, S.; Shilpa; Sarav, M.; Banik, B.K.; Ray, D. Recent Advances in the Green Synthesis of Active *N*-Heterocycles and Their Biological Activities. *Pharmaceuticals* **2023**, *16*, 873, https://doi.org/10.3390/ph16060873.
13. Li, H.; Guo, H.; Fang, Z.; Aida, T.M.; Smith, R.L. Cycloamination strategies for renewable N-heterocycles. *Green Chem.* **2020**, *22*, 582-611, https://doi.org/10.1039/c9gc03655e.
14. Hamidinasab, M.; Ahadi, N.; Bodaghifard, M.A.; Brahmachari, G. Sustainable and Bio-Based Catalysts for Multicomponent Organic Synthesis: An Overview. *Polycycl. Aromat. Compd.* **2023**, *43*, 5172-5226, https://doi.org/10.1080/10406638.2022.2097278.
15. Banerjee, B. Recent developments on ultrasound-assisted one-pot multicomponent synthesis of biologically relevant heterocycles. *Ultrason. Sonochem.* **2017**, *35*, 15–35, https://doi.org/10.1016/j.ultsonch.2016.10.010.
16. Borah, B.; Chowhan, L.R. Ultrasound-assisted transition-metal-free catalysis: a sustainable route towards the synthesis of bioactive heterocycles. *RSC Adv.* **2022**, *12*, 14022–14051, https://doi.org/10.1039/d2ra02063g.
17. Dhokale, N.T.; Kale, S.B.; Nagre, S.S.; Konda, S.G.; Dalvi, N.R. A convenient and efficient synthesis of 2-thio-5-hydroxy-5*H*-[1]benzopyrano[4,3-d] pyrimidines via ultrasonic irradiation compared with

conventional method. *Curr. Res. Green Sustain. Chem.* **2022**, *5*, 100282, https://doi.org/10.1016/j.crgsc.2022.100282.

18. Abbass, S.A.; Moustafa, G.A.I.; Hassan, H.A.; Abuo-Rahma, G.E.-D.A. Facile one-pot three-component synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones under ultrasonic irradiation. *Synth. Commun.* **2019**, *49*, 2995-3000, https://doi.org/10.1080/00397911.2019.1652759.
19. Abdolahi, S.; Soleiman-Beigi, M. Exploring the catalytic activity of –$NHSO_3H$ functionalized natural asphalt: a sustainable and efficient catalyst for condensation reactions in water. *RSC Adv.* **2025**, *15*, 9280–9294, https://doi.org/10.1039/d5ra00870k.
20. Safaei-Ghomi, J.; Navvab, M.; Shahbazi-Alavi, H. One-pot sonochemical synthesis of 1,3-thiazolidin-4-ones using nano-$CdZr_4(PO_4)_6$ as a robust heterogeneous catalyst. *Ultrason. Sonochem.* **2016**, *31*, 102–106, https://doi.org/10.1016/j.ultsonch.2015.12.008.
21. Chakraborty, A.; Giri, S.; Adhikari, T. Microwave assisted synthesis: An eco-friendly green chemistry approach of drug synthesis. *Int. J. Pharm. Pharm. Sci.* **2024**, *6*, 149–156, https://doi.org/10.33545/26647222.2024.v6.i2b.135.
22. Kale, A.A. Green Synthesis and Characterization of Dihydropyrimidinone Derivatives using Fruit Juice. *J. Curr. Pharma Res.* **2019**, *9*, 2854–2858.
23. Sadjadi, S.; Heravi, M.M.; Malmir, M. Heteropolyacid@creatin-halloysite clay: an environmentally friendly, reusable and heterogeneous catalyst for the synthesis of benzopyranopyrimidines. *Res. Chem. Intermed.* **2017**, *43*, 6701–6717, https://doi.org/10.1007/s11164-017-3016-2.
24. Flanigan, D.M.; Romanov-Michailidis, F.; White, N.A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307-9387, https://doi.org/10.1021/acs.chemrev.5b00060.
25. Gulati, S.; Singh, R.; Sindhu, J.; Sangwan, S. Eco-friendly Preparations of Heterocycles Using Fruit Juices as Catalysts: A Review. *Or Org. Prep. Proced. Int.* **2020**, *52*, 381–395, https://doi.org/10.1080/00304948.2020.1773158.
26. Pramanik, T.; Padan, S.K.; Gupta, R.; Bedi, P.; Singh, G. Comparative efficacy of microwave, visible light and ultrasound irradiation for green synthesis of dihydropyrimidinones in fruit juice medium. *AIP Conf. Proc.* **2017**, *1860*, 020059, https://doi.org/10.1063/1.4990358.
27. Safari, N.; Shirini, F.; Tajik, H. Verjuice as a green and bio-degradable solvent/catalyst for facile and eco-friendly synthesis of 5-arylmethylenepyrimidine-2,4,6-trione, pyrano[2,3-*d*]pyrimidinone and pyrimido[4,5-*d*]pyrimidinone derivatives. *J. Iran. Chem. Soc.* **2019**, *16*, 887–897, https://doi.org/10.1007/s13738-018-1565-y.
28. Shaikh, Y.I.; Shaikh, S.S.; Ahmed, K.; Nazeruddin, G.M.; Shaikh, V.S. A Facile and Efficient Tamarind Juice Catalyzed One-Pot Synthesis of Benzopyranopyrimidines in Aqueous Medium Just by Grinding: A Green Chemistry Approach. *Orient. J. Chem.* **2020**, *36*, 415-418, https://doi.org/10.13005/ojc/360308.
29. English, L.E.; Jones, M.D.; Liptrot, D.J. N-Heterocyclic Phosphines as Precatalysts for the Highly Selective Degradation of Poly(lactic acid). *ChemCatChem* **2022**, *14*, e202101904, https://doi.org/10.1002/cctc.202101904.
30. Saifan, A.A.A.; Al-horaibi, S.A. Water Extract of Dragon Fruit Peel Catalyzed Synthesis of Dihydropyridines By Hantzsch Condensation. *J. Chem. Nutr. Biochem.* **2021**, *2*, 46–54, https://doi.org/10.48185/jcnb.v2i1.205.
31. Sari, R.P.; Mahardika, R.G.M.G.; Nurhadini, N. Synthesis of dihydropyrimidinone derivatives using kelubi fruit (Eleiodoxa conferta) as a catalyst and its antibacterial activity. *Asian J. Health Appl. Sci.* **2022**, *1*, 1–6.
32. Narayanan, D.P.; Balasubramanyan, S.; Cherikkallinmel, S.K.; Vadery, V.; Sankaran, S.; Narayanan, B.N. A Green Approach for the Synthesis of Coconut Husk Ash –Twisted Graphene Nanocomposites: Novel Catalysts for Solvent-Free Biginelli Reaction. *ChemistrySelect* **2019**, *4*, 4785-47966, https://doi.org/10.1002/slct.201803352.
33. Hiremath, P.B.; Kamanna, K. Microwave-Accelerated Facile Synthesis of 1H-Pyrazolo[1,2-b]Phthalazine-5,10-Dione Derivatives Catalyzed by WEMPA. *Polycycl. Aromat. Compd.* **2022**, *42*, 2162–2178, https://doi.org/10.1080/10406638.2020.1830129.
34. Krishna, T.; Laxminarayana, E.; Kalita, D. FeF3 as a green catalyst for the synthesis of dihydropyrimidines via Biginelli reaction. *Eur. J. Chem.* **2020**, *11*, 206–212, https://doi.org/10.5155/eurjchem.11.3.206-212.1992.

35. Govindaraju, S.; Tabassum, S.; Pasha, M.A. Citric-Acid-Catalyzed Green and Sustainable Synthesis of Novel Functionalized Pyrano[2, 3-*e*]pyrimidin- and Pyrano[2, 3-*d*]pyrazol-amines in Water via One-Pot Multicomponent Approaches. *ChemistrySelect* **2018**, *3*, 3832–3838, https://doi.org/10.1002/slct.201703023.
36. Shaikh, Y.I.; Shaikh, V.S.; Nazeruddin, G.M.; Shekh, Z.; Gugale , G.S.; Prasad, N.R. A Green Chemistry Approach towards Synthesis of Biscoumarins Catalyzed by Different Biocatalysts such as Dragon Fruit Juice, Kiwi Fruit Juice, and Buttermilk Separately by Grind Stone Technique: A Comparative Study. *ES Food Agrofor.* **2022**, *7*, 25-29, https://doi.org/10.30919/esfaf641.
37. Leonte, D.; Bencze, L.C.; Paizs, C.; Irimie, F.D.; Zaharia, V. Heterocycles 38. Biocatalytic Synthesis of New Heterocyclic Mannich Bases and Derivatives. *Molecules* **2015**, *20*, 12300-12313, https://doi.org/10.3390/molecules200712300.
38. Yin, H.-N.; Wang, P.-C.; Liu, Z. Recent advances in biocatalytic C–N bond-forming reactions. *Bioorg. Chem.* **2024**, *144*, 107108, https://doi.org/10.1016/j.bioorg.2024.107108.
39. Abdel-Fattah Mostafa, A.; SathishKumar, C.; Al-Askar, A.A.; Sayed, S.R.M.; SurendraKumar, R.; Idhayadhulla, A. Synthesis of novel benzopyran-connected pyrimidine and pyrazole derivatives *via* a green method using Cu(ii)-tyrosinase enzyme catalyst as potential larvicidal, antifeedant activities. *RSC Adv.* **2019**, *9*, 25533-25543, https://doi.org/10.1039/c9ra04496e.
40. Chaudhari, M.A.; Gujar, J.B.; Kawade, D.S.; Shinde, P.V.; Shingare, M.S. β-Cyclodextrin-SO_3H-catalyzed facile and highly efficient synthesis of 4-thiazolidinones under solvent free conditions. *Res. Chem. Intermed.* **2015**, *41*, 10027-10035, https://doi.org/10.1007/s11164-015-2010-9.
41. Sultan Alwan, E. The applications of nanocatalysts in the synthesis of heterocyclic compounds. *Bull. Chem. Soc. Ethiop.* **2024**, *39*, 123–129, https://doi.org/10.4314/bcse.v39i1.10.
42. Das, R.; Roy, A.; Bahe, A.; Chanderıya, A.; Dangi, H.; Mishra, P.; Mishra, A. Synthesis of nitrogen and oxygen containing heterocyclic compounds using nano catalyst: A review. *J. Turk. Chem. Soc. A: Chem.* **2021**, *8*, 851-862, https://doi.org/10.18596/jotcsa.904246.
43. Besharati, Z.; Malmir, M.; Heravi, M.M. Cu_2O NPs immobilized on Montmorilonite-*K*10 decorated by acidic-ionic liquid: An environmentally friendly, heterogeneous and recyclable catalyst for the synthesis of benzopyranopyrimidines. *Inorg. Chem. Commun.* **2022**, *143*, 109813, https://doi.org/10.1016/j.inoche.2022.109813.
44. Bibi, S.; Zubair, M.; Riaz, R.; Kanwal, A.; Ali Shah, S.A. Recent advances in zirconium-based catalysis and its applications in organic synthesis: a review. *RSC Adv.* **2025**, *15*, 15417–15442, https://doi.org/10.1039/d5ra01808k.
45. Gebre, S.H. Recent developments in the fabrication of magnetic nanoparticles for the synthesis of trisubstituted pyridines and imidazoles: A green approach. *Synth. Commun.* **2021**, *51*, 1669-1699, https://doi.org/10.1080/00397911.2021.1900257.
46. Bodaghifard, M.A.; Allahbakhshi, H. Hybrid magnetic nanoparticles with sulfonic acid tags: an efficient catalyst for synthesis of benzopyrans and pyranopyrimidinones. *Org. Chem. Res.* **2024**, *10*, 20-27, https://doi.org/10.22036/org.chem.2024.466806.1345.
47. Abdolmohammadi, S.; Karimpour, S. Rapid and mild synthesis of quinazolinones and chromeno[*d*]pyrimidinones using nanocrystalline copper(I) iodide under solvent-free conditions. *Chin. Chem. Lett.* **2016**, *27*, 114–118, https://doi.org/10.1016/j.cclet.2015.08.014.
48. Tabassum, S.; Sunaja Devi, K.R.; Govindaraju, S. Nano ZnO@PEG catalyzed one-pot green synthesis of pyrano[2,3-*d*]pyrimidines in ethanol *via* one-pot multicomponent approach. *Mater. Today Proc.* **2021**, *45*, 3716–3721, https://doi.org/10.1016/j.matpr.2020.12.677.
49. Ni, Z.; Wan, M.; Tang, G.; Sun, L. Synthesis of CuO and PAA-Regulated Silver-Carried CuO Nanosheet Composites and Their Antibacterial Properties. *Polymers* **2022**, *14*, 5422, https://doi.org/10.3390/polym14245422.
50. Maleki, A.; Zand, P.; Mohseni, Z. Green Nanospheres Natural Camphor Coated Ferrite as a Highly Efficient Nanocatalyst for the Synthesis of Dihydropyrimidine Derivatives. *ChemistrySelect* **2017**, *2*, 2740–2744, https://doi.org/10.1002/slct.201700131.
51. Safaei-Ghomi, J.; Nazemzadeh, S.H.; Shahbazi-Alavi, H. Nano-$CdZr_4(PO_4)_6$ as a reusable and robust catalyst for the synthesis of bis-thiazolidinones by a multicomponent reaction of aldehydes, ethylenediamine and thioglycolic acid. *J. Sulfur Chem.* **2017**, *38*, 195–205, https://doi.org/10.1080/17415993.2016.1267176.

52. AbdEl-Azim, M.H.M.; Aziz, M.A.; Mouneir, S.M.; El-Farargy, A.F.; Shehab, W.S. Ecofriendly synthesis of pyrano[2,3-*d*]pyrimidine derivatives and related heterocycles with anti-inflammatory activities. *Arch. Pharm.* **2020**, *353*, 2000084, https://doi.org/10.1002/ardp.202000084.
53. Kazemi, M.; Ghobadi, M.; Mirzaie, A. Cobalt ferrite nanoparticles ($CoFe_2O_4$ MNPs) as catalyst and support: magnetically recoverable nanocatalysts in organic synthesis. *Nanotechnol. Rev.* **2018**, *7*, 43–68, https://doi.org/10.1515/ntrev-2017-0138.
54. Martins, M.A.P.; Frizzo, C.P.; Moreira, D.N.; Buriol, L.; Machado, P. Solvent-Free Heterocyclic Synthesis. *Chem. Rev.* **2009**, *109*, 4140–4182, https://doi.org/10.1021/cr9001098.
55. Rammohan, A.; Krinochkin, A.P.; Khasanov, A.F.; Kopchuk, D.S.; Zyryanov, G.V. Sustainable Solvent-Free Diels–Alder Approaches in the Development of Constructive Heterocycles and Functionalized Materials: A Review. *Top. Curr. Chem.* **2022**, *380*, 43, https://doi.org/10.1007/s41061-022-00398-2.
56. Abreshteh, M.; Ghazanfari, D.; Hassanabadi, A.; Rastakhiz, N. Synthesis of 2-Aryl-7-Methyl-1-Phenyl-4-Thioxo-1,4-Dihydro-Pyrano[4,3-d]Pyrimidin-5-One via a Three-Component Condensation. *Polycycl. Aromat. Compd.* **2024**, *44*, 555–561, https://doi.org/10.1080/10406638.2023.2179077.
57. Monem, A.; Habibi, D.; Alizadeh, A.; Goudarzi, H. The new phthalic acid-based deep eutectic solvent as a versatile catalyst for the synthesis of pyrimido[4,5-*d*]pyrimidines and pyrano[3,2-*c*]chromenes. *BMC Chem.* **2024**, *18*, 120, https://doi.org/10.1186/s13065-024-01227-x.
58. Mohamadpour, F. Visible light irradiation promoted catalyst-free and solvent-free synthesis of pyrano[2,3-*d*]pyrimidine scaffolds at room temperature. *J. Saudi Chem. Soc.* **2020**, *24*, 636–641, https://doi.org/10.1016/j.jscs.2020.06.006.
59. Zare, A.; Nasouri, Z. A green approach for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (and -thiones) using *N*,*N*-diethyl-N-sulfoethanaminium hydrogen sulfate. *J. Mol. Liq.* **2016**, *216*, 364–369, https://doi.org/10.1016/j.molliq.2016.01.056.
60. Dahiya, A.; Ali, W.; Patel, B.K. Catalyst and Solvent Free Domino Ring Opening Cyclization: A Greener and Atom Economic Route to 2-Iminothiazolidines. *ACS Sustain. Chem. Eng.* **2018**, *6*, 4272–4281, https://doi.org/10.1021/acssuschemeng.7b04723.
61. Sadeghzadeh, S.M.; Daneshfar, F. Ionic liquid immobilized on $FeNi_3$ as catalysts for efficient, green, and one-pot synthesis of 1,3-thiazolidin-4-one. *J. Mol. Liq.* **2014**, *199*, 440–444, https://doi.org/10.1016/j.molliq.2014.07.039.
62. Abbasi, M. β-Cyclodextrin as an Efficient and Recyclable Supramolecular Catalyst for the Synthesis of Heterocyclic Compounds. *J. Chin. Chem. Soc.* **2017**, *64*, 896–917, https://doi.org/10.1002/jccs.201600887.
63. El-Nassan, H.B. Amberlyst 15®: An Efficient Green Catalyst for the Synthesis of Heterocyclic Compounds. *Russ. J. Org. Chem.* **2021**, *57*, 1109–1134, https://doi.org/10.1134/s1070428021070125.
64. Farooq, S.; Alharthi, F.A.; Alsalme, A.; Hussain, A.; Dar, B.A.; Hamid, A.; Koul, S. Dihydropyrimidinones: efficient one-pot green synthesis using Montmorillonite-KSF and evaluation of their cytotoxic activity. *RSC Adv.* **2020**, *10*, 42221-42234, https://doi.org/10.1039/d0ra09072g.
65. Shamna, S.; Afsina, C.M.A.; Philip, R.M.; Anilkumar, G. Recent advances and prospects in the Zn-catalysed Mannich reaction. *RSC Adv.* **2021**, *11*, 9098–9111, https://doi.org/10.1039/d0ra10772g.
66. Khaskel, A.; Barman, P.; Jana, U. L-Tyrosine loaded nanoparticles: an efficient catalyst for the synthesis of dicoumarols and Hantzsch 1,4-dihydropyridines. *RSC Adv.* **2015**, *5*, 13366–13373, https://doi.org/10.1039/C4RA16627B.
67. Bhattacharyya, A.; Kavitha, C.V.; Ghorai, M.K. Stereospecific Synthesis of 2-Iminothiazolidines via Domino Ring-Opening Cyclization of Activated Aziridines with Aryl- and Alkyl Isothiocyanates. *J. Org. Chem.* **2016**, *81*, 6433–6443, https://doi.org/10.1021/acs.joc.6b01551.
68. Yedage, D.B.; Patil, D.V. Environmentally Benign Deep Eutectic Solvent for Synthesis of 1,3-Thiazolidin-4-ones. *ChemistrySelect* **2018**, *3*, 3611–3614, https://doi.org/10.1002/slct.201800157.
69. Steinrück, H.-P.; Wasserscheid, P. Ionic Liquids in Catalysis. *Catal. Lett.* **2015**, *145*, 380–397, https://doi.org/10.1007/s10562-014-1435-x.
70. Vafaeezadeh, M.; Alinezhad, H. Brønsted acidic ionic liquids: Green catalysts for essential organic reactions. *J. Mol. Liq.* **2016**, *218*, 95–105, https://doi.org/10.1016/j.molliq.2016.02.017.
71. Kaur, N. Ionic liquid assisted synthesis of S-heterocycles. *Phosphorus Sulfur Silicon Relat. Elem.* **2019**, *194*, 165–185, https://doi.org/10.1080/10426507.2018.1539492.
72. Chen, C.-Y.; Barve, I.J.; Sun, C.-M. One-Pot Three-Component Synthesis of 2-Imino-1,3-Thiazolines on Soluble Ionic Liquid Support. *ACS Comb. Sci.* **2016**, *18*, 638–643, https://doi.org/10.1021/acscombsci.6b00106.

73. Subhedar, D.D.; Shaikh, M.H.; Arkile, M.A.; Yeware, A.; Sarkar, D.; Shingate, B.B. Facile synthesis of 1,3-thiazolidin-4-ones as antitubercular agents. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1704-1708, https://doi.org/10.1016/j.bmcl.2016.02.056.
74. Ruggeri, M.P.; Luo, J.; Nova, I.; Tronconi, E.; Kamasamudram, K.; Yezerets, A. Novel method of ammonium nitrate quantification in SCR catalysts. *Catal. Today* **2018**, *307*, 48-54, https://doi.org/10.1016/j.cattod.2017.04.016.
75. Mohamadpour, F. 1,1,1,3,3,3-hexafluoro-2-propanol as a reusable media: Green and catalyst-free synthesis of pyrano[2,3-*d*]pyrimidine scaffolds. *J. Chem. Sci.* **2025**, *137*, 1, https://doi.org/10.1007/s12039-024-02334-x.
76. Kabeer, S.A.; Reddy, G.R.; Sreelakshmi, P.; Manidhar, D.M.; Reddy, C.S. TiO_2–SiO_2 Catalyzed Eco-friendly Synthesis and Antioxidant Activity of Benzopyrano[2,3-d]pyrimidine Derivatives. *J. Heterocycl. Chem.* **2017**, *54*, 2598-2604, https://doi.org/10.1002/jhet.2856.
77. Yavuz, S.Ç.; Akkoç, S.; Tüzün, B.; Şahin, O.; Saripinar, E. Efficient synthesis and molecular docking studies of new pyrimidine-chromeno hybrid derivatives as potential antiproliferative agents. *Synth. Commun.* **2021**, *51*, 2135–2159, https://doi.org/10.1080/00397911.2021.1922920.
78. Talaei, H.; Mosslemin, M.H.; Hassanabadi, A.; Mohebat, R. Synthesis of 2-Aryl-7-Methyl-1-Phenyl-4-Selenoxo-1,4-Dihydro-Pyrano[4,3-d]Pyrimidin-5-One via a Three-Component Condensation. *Polycycl. Aromat. Compd.* **2023**, *43*, 4299–4304, https://doi.org/10.1080/10406638.2022.2086890.
79. Heravi, M.M.; Hosseinnejad, T.; Tamimi, M.; Zadsirjan, V.; Mirzaei, M. 12-Tungstoboric acid ($H_5BW_{12}O_{40}$) as an efficient Lewis acid catalyst for the synthesis of chromenopyrimidine-2,5-diones and thioxochromenopyrimidin-5-ones: Joint experimental and computational study. *J. Mol. Struct.* **2020**, *1205*, 127598, https://doi.org/10.1016/j.molstruc.2019.127598.
80. Sahu, P.K.; Sahu, P.K.; Kaurav, M.S.; Messali, M.; Almutairi, S.M.; Sahu, P.L.; Agarwal, D.D. One-pot facile and mild construction of densely functionalized pyrimidines in water *via* consecutive C–C and C–S bonds formation. *RSC Adv.* **2018**, *8*, 33952-33959, https://doi.org/10.1039/c8ra04363a.
81. Zolfaghari, K.; Panahi, M.; Omidi, Z. Surfactant TBAB as a Catalyst for the Synthesis of 3, 4-Dihydropyrimidine Derivatives. *J. Synth. Chem.* **2024**, *3*, 49-60, https://doi.org/10.22034/jsc.2024.457661.1074.
82. Mohamadpour, F. Synthesis of pyrano[2,3-*d*]pyrimidine scaffolds promoted by polyfluorinated alcohol as a reusable solvent/catalyst. *Results Chem.* **2024**, *8*, 101563, https://doi.org/10.1016/j.rechem.2024.101563.

Publisher’s Note & Disclaimer