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Recent Review of One-Pot Synthesis of Heterocyclic Compounds Utilizing Green Catalysts

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The need for sustainable chemical reactions has spurred the adoption of green chemistry aimed at reducing waste and hazardous materials. One promising method is one-pot synthesis utilizing green catalysts, which simplifies lengthy chemical reactions by combining them in a single pot without extra reactants or intermediate isolation. This method has been applied to the synthesis of heterocyclic molecules. However, the literature on the efficiency of one-pot synthesis and green catalysts in catalytic reactions is limited. This underscores the need for a comprehensive review to better understand their impact on the selectivity of efficient synthetic pathways for producing heterocyclic compounds. This review explores the influence of green catalysts on the performance of one-pot synthesis. It discusses their role in promoting more environmentally friendly chemical reactions, emphasizing the importance of choosing one-pot synthesis and green catalysts to improve productivity in heterocyclic synthesis. Furthermore, it advocates for sustainable and environmentally friendly organocatalyst options in catalytic reactions for the synthesis of heterocyclic compounds. This review's significance lies in its effort to provide insights into one-pot synthesis and green catalysts, providing a reliable reference for future research in this area.

Keywords: One-pot synthesis; green catalysts; organocatalysts; heterocyclic compounds

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In the shift towards green chemistry, green catalysts have become essential in reducing costs, time, and environmental impact while increasing the efficiency of chemical reactions [1]. These catalysts are renowned for their reusability and recoverability from readily accessible sources, which promotes sustainability in line with the principles of green chemistry, even when used in small amounts [2, 3]. Green catalysts, including organic, biological, organometallic, and inorganic varieties, facilitate the transition from stoichiometric processes to both homogeneous and heterogeneous catalytic reactions.

This shift is particularly significant in the development of heterocyclic compounds, which are widely used in pharmaceuticals, agrochemicals, and materials science. However, within the framework of green chemistry, several challenges remain. A key concern is the need for recyclable catalyst systems, the use of renewable-based solvents, and the promotion of heterogeneous catalysis. Additionally, alternative methods that prioritize high atom efficiency and milder reaction conditions are essential, as traditional synthetic processes are often energy-intensive, involve multiple steps, and result in low productivity [4, 5]. Addressing these issues is essential for the efficient production of diverse, cost-effective, and scalable heterocyclic scaffolds for industrial applications.

Aromatic heterocyclic compounds associated with benzene offer great stability because of their fully conjugated pi-electron system. Some examples of heterocyclic analogous to benzene include pyrrole (**1**), benzodiazepine (**2**), benzopyran (**3**) and chromene (**4**) [5]. Generally, the classification of heterocyclic compounds could be easily assigned into monocyclic and polycyclic compounds. Heterocyclic consisting of only a single ring structure is characterized by monocyclic, which include furan (**5**), pyridine (**6**) and thiophene (**7**), while multiple fused rings are known as polycyclic heterocyclic compounds. Heterocyclic compounds are further categorized based on their ring size where larger rings comprising up to 5- or 6-membered rings are often considered more stable, with some possessing aromatic features, whereas smaller rings are more geometrically constrained and regarded as reactive intermediates [6, 7]. Heterocyclic categories could be extended to aromatic and non-aromatic, fused and unfused rings and the position of heteroatoms within the ring junction.

Over the past two decades, one-pot synthesis has gained significant attention in organic chemistry, with thousands of publications exploring cascade reactions [8], multi-component reactions (MCRs) [9], and one-pot stepwise synthesis (OPSS) [10]. The term

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"one-pot synthesis" refers to a technique where multiple chemical reactions are conducted in a single vessel without the need for isolating intermediates or adding extra reactants, reagents, or catalysts. This method also enables the sequential execution of consecutive chemical transformations, streamlining the reaction process. As long as the reactions are carried out in the same reactor, it qualifies as a one-pot synthesis, with the goal of achieving high mass efficiency, reducing the effort of intermediate isolation, minimizing energy consumption, and generating minimal waste [11].

This research review is significant for promoting green chemistry concepts by advocating for alternatives in organic synthesis, such as one-pot synthesis, to simplify intricate multi-step processes and enhance overall chemical production efficiency. It also emphasizes the use of environmentally friendly and sustainable catalysts, like organocatalysts, in the synthesis of heterocyclic compounds. Furthermore, the lack of comprehensive review papers on the application of one-pot synthesis in producing heterocyclic compounds has driven the need to conduct this study, providing a reliable reference for future research in this area.

METAL-BASED CATALYST

Bismuth derivatives are gaining significant interest among organic chemists. Bismuth(III) triflate, in particular, is recognized as an effective Lewis acid catalyst due to its strong catalytic activity, low toxicity, and high stability. Notably, bismuth triflate [Bi(OTf)$_3$] stands out as one of the most efficient catalysts, and it is especially appealing because it is either readily available commercially or can be easily synthesized from commercially accessible materials.

Bismuth(III)Triflate Catalyzed Reactions of One-pot Synthesis

In the study by Saglam and Turgut (2022) [12], pyrido [2,3-d] pyrimidines derivatives were synthesized through multi-component reactions (MCRs), specifically involving the condensation of three components which were 1,3-dimethyl-6-aminouracil, aryldehydes and malonitriles, with bismuth(III)triflate, Bi(OTf)$_3$ as catalyst. The reactions were repeated three times for each varying concentration of Bi(OTf)$_3$. The effect of different concentrations on the yield of pyrido[2,3-d]pyrimidine derivatives (**11**) was summarized in **Table 1**.

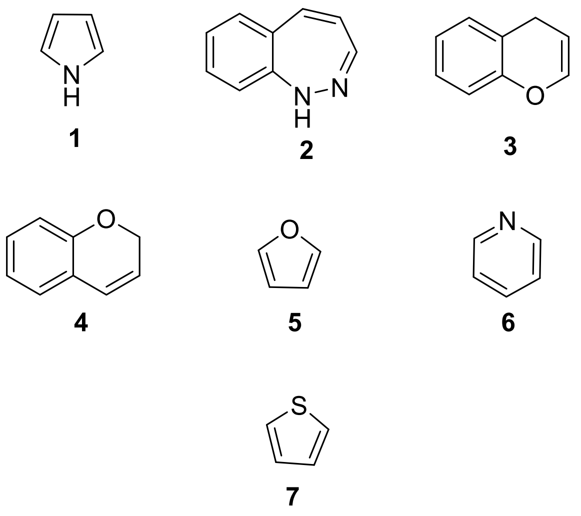


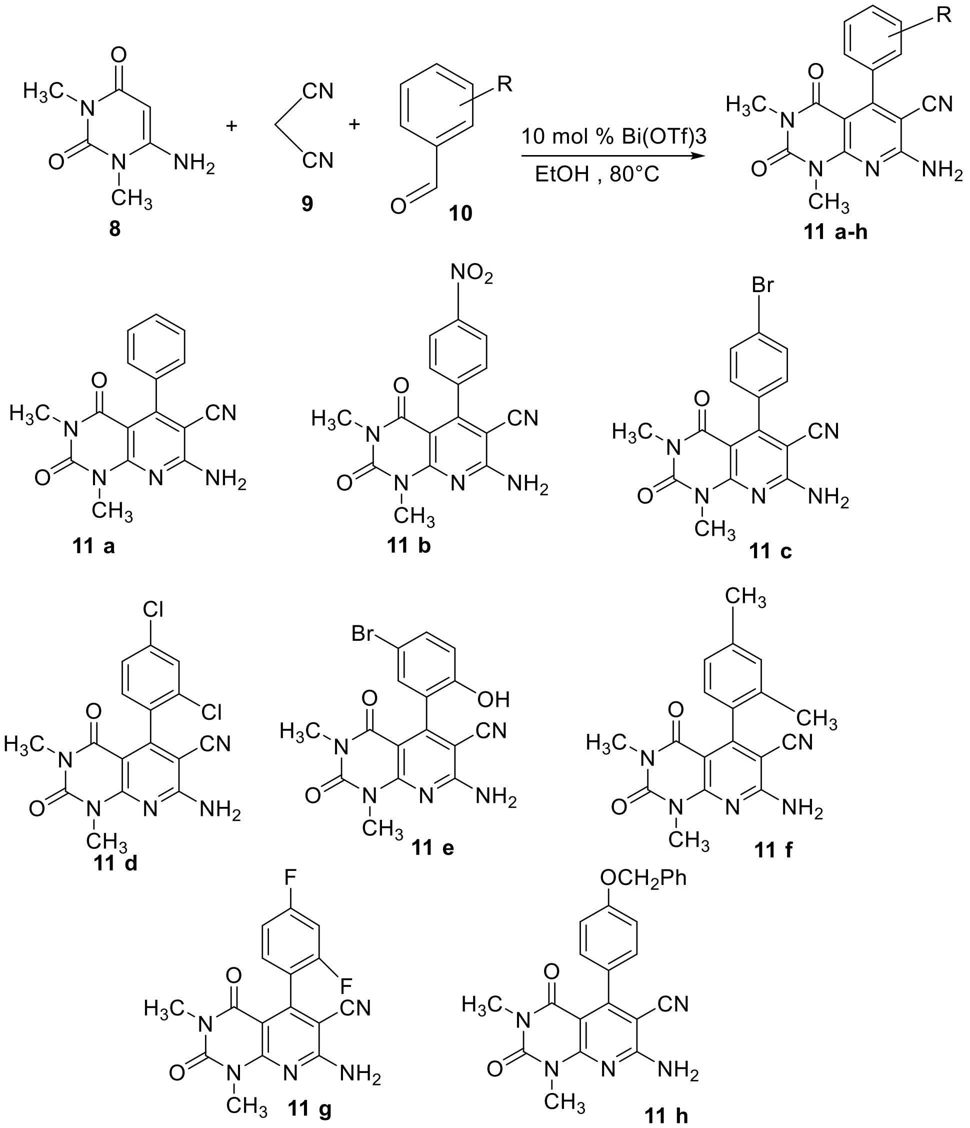
Figure 1. Some Examples of Common Heterocyclic Compounds.

Table 1. The effect of different amounts of Bi(OTf)$_3$ as catalyst in the % yield.

Entry	Catalyst, mol%	Solvent, mL	Temperature/time (°C/hr)	Reaction medium	%yield
1	Bi(OTf)$_3$, 10 mol%	EtOH, 5mL	80°C/1 hr	One-pot (MCR), reflux	86
2	Bi(OTf)$_3$, 20 mol%				84
3	Bi(OTf)$_3$, 30 mol%				85

Reaction conditions: 1 mmol of Benzaldehyde (**10**), 1 mmol of malonitrile (**9**) and 1 mmol of 6-amino-1,3-dimethyluracil (**8**).

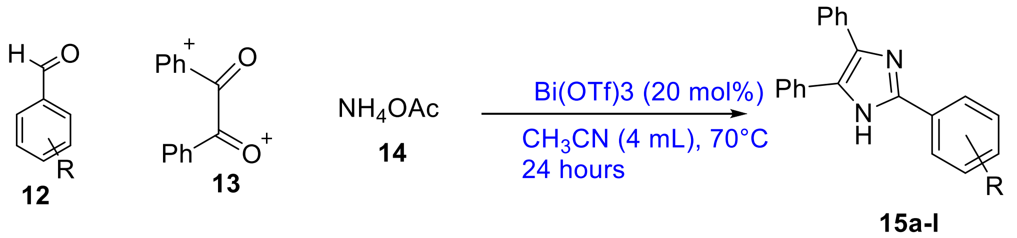
Scheme 1. Complete reactions yield a series of pyrido [2,3-d]pyrimidines derivatives (12 a-h).



Based on the results obtained, the optimum condition in synthesizing a series of these uracil derivatives would be by the use of 10 mol% $Bi(OTf)_3$ in 5 mL ethanol reflux at 80°C, involving a three-component reaction of 1,3-dimethyl-6-aminouracil (**8**), aromatic aldehyde (**10**) and malonitrile (**9**). Under this condition, the highest yield of 86% was achieved. This showed that with mild reaction conditions and a reusable catalyst, an ideal procedure to obtain these uracil derivatives, which may have many applications in pharmaceutical and biological activities such as antibacterial, antimicrobial, analgesic, and antifungal activities, also the ability to depict interesting luminescence properties. In this study, some [2,3-d]pyrimidines (**11e-h**) were synthesized for the first time, while compounds (**11a-d**) had already been reported in earlier studies by other researchers. Simple filtration was done for the isolation of these [2,3-d]pyrimidine compounds (**11 a-h**) as solids, where column chromatography was used to purify them.

Another $Bi(OTf)_3$ catalyzed MCR was also reported by Thorp and co-workers (2023) [13] to synthesize 2,4,5-trisubstituted imidazole (**15a-l**). Thorpe and his colleagues focused on the development of 2-substituted-4,5-diphenylimidazoles because of their anti-nociceptive and anti-inflammatory properties [14]. They successfully synthesized these compounds and their derivatives using a more efficient synthetic route compared to previous studies. This involved three-component reactions with different substituted aldehydes (**12a-l**), benzyl (**13**), and ammonium acetate (**14**). The method is proven to save time and reduce waste production. The $Bi(OTf)_3$ catalyzed MCR used CH_3CN as the ideal solvent to obtain the best result of 2,4,5-trisubstituted imidazole (**15a-l**) in the range of good to moderate yield between 64 to 91% after a few test with different Lewis acids as catalysts. The synthesis reactions are displayed in **Table 2**.

Table 2. Bi(OTf)$_3$ catalyzed MCR in the synthesis of 2,4,5-trisubstituted imidazole compounds.



Entry	Aldehyde	Yield (%)
a	PhCHO	82
b	*p*-OHC_6H_4CHO	70
c	*p*-$CH_3C_6H_4CHO$	87
d	*p*-$CH_3OC_6H_4CHO$	72
e	*p*-BrC_6H_4CHO	81
f	*p*-ClC_6H_4CHO	91
g	*p*-FC_6H_4CHO	67
h	2,4-$Cl_2C_6H_3CHO$	88
i	*m*-ClC_6H_4CHO	80
j	*m*-$CH_3OC_6H_4CHO$	87
k	*m*-$CH_3C_6H_4CHO$	81
l	*p*-$NO_2C_6H_4CHO$	64

ORGANOCATALYST

Organocatalysis involves chemical transformations catalyzed by a substoichiometric amount of a small, metal-free, purely organic molecule known as an organocatalyst. This process is prominent in most asymmetric catalysis reactions [15]. Organocatalysts typically comprise hydrocarbons with non-metallic elements such as sulfur, nitrogen, or oxygen. They are widely used in synthesizing heterocyclic compounds, which are cyclic organic compounds containing at least two different elements as ring members, commonly in the form of 5 or 6-membered rings. Notable heterocyclic compounds such as pyridine, pyrrole, and furan were discovered between the 1800s and 1900s [16].

In recent years, organocatalytic heterocyclic transformations have increasingly been conducted via one-pot synthesis, which involves combining reactants in a single vessel. This method streamlines chemical reactions, reducing reaction time and optimizing yields [17].

The history of organocatalytic transformation dates back to the 19th century. Justus von Liebig reported the first pure organocatalytic transformation in 1860, and the first asymmetric organocatalytic reaction was documented in 1912 by Bredig and Fiske. Despite significant advancements in the mid-20th century, the potential of small, metal-free organic molecules as catalysts were not fully recognized until the year 2000, marked by the influential studies of List, Lerner, Barbas, and MacMillan, which heralded the "Gold Rush" period of modern organocatalysis [15].

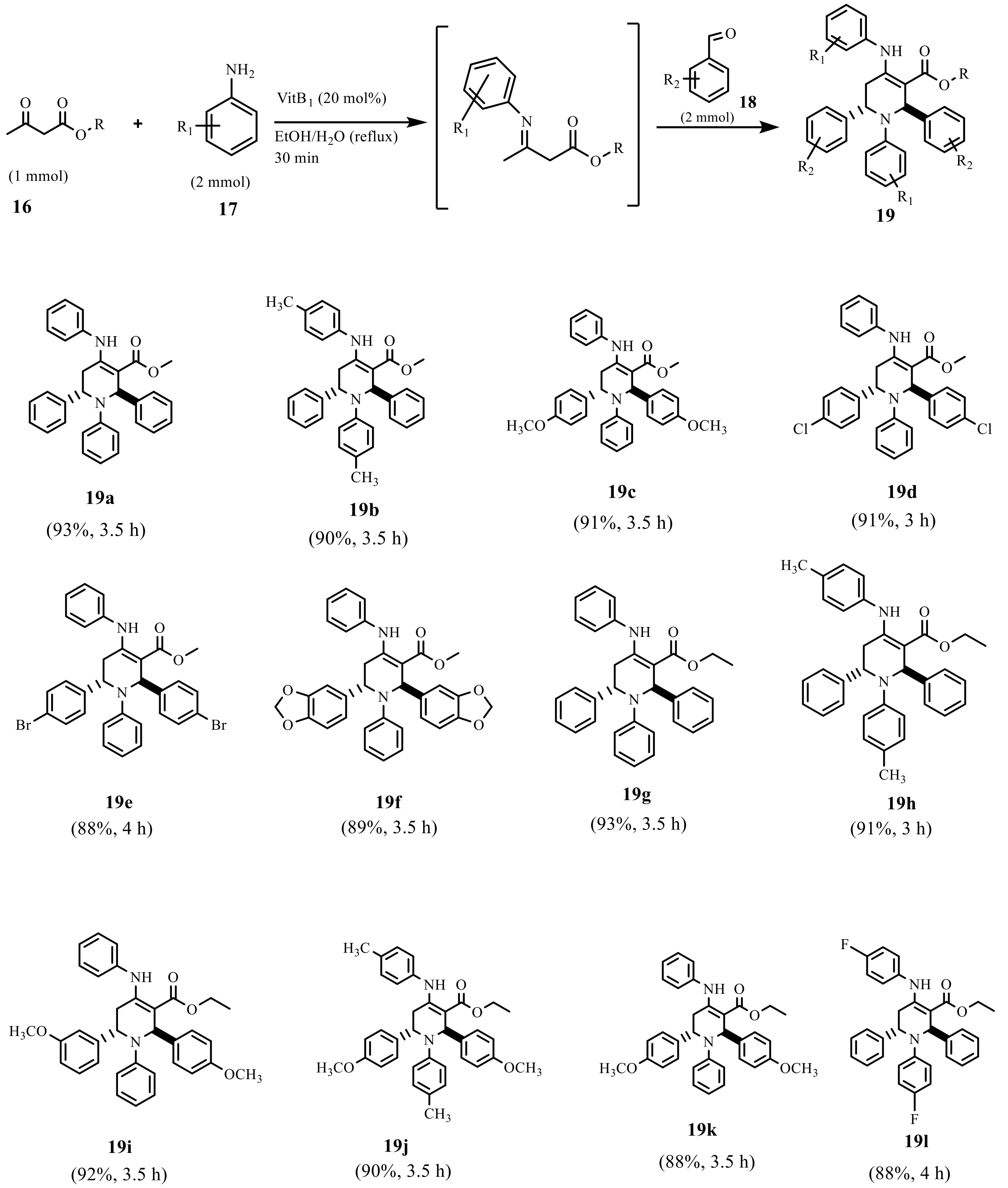
Organocatalysts offer substantial advantages in the chemical industry due to their sustainability, accessibility, and stability. They are less toxic and more cost-effective than heavy metal catalysts, which are expensive and complex to prepare. Organocatalysts can catalyze complex transformations with high enantioselectivity and have demonstrated superior efficiency in combination with other catalysis methods, such as photoredox catalysis [18].

Thiamine Hydrochloride Catalyzed Reactions of One-pot Synthesis

In a 2020 study by Singh, Gupta, and Kapoor [19], thiamine hydrochloride was highlighted as an effective catalyst for synthesizing heterocyclic compounds, specifically targeting tetrahydropyridines. The synthesis was achieved through a one-pot multi-component reaction (MCR) involving β-ketoesters, aromatic aldehydes, and anilines as reactants. Thiamine hydrochloride (VitB$_1$) was getting interest among chemical researchers, especially in the field of synthesizing heterocyclic compounds, due to its lower cost, availability as well as a green catalyst. Due to the wide range of biological features exhibited by tetrahydropyridines, such as analgesic, hyperglycemic, and anti-influenza effects, numerous methodologies were explored and devised for their synthesis. However, one-pot synthesis, specifically MCR, was the best method and most recognized for its efficiency and high yields of many heterocyclic scaffolds.

The MCR catalyzed by thiamine hydrochloride, involving a five-component reaction with β-ketoesters (methyl acetoacetate and ethyl acetoacetate), anilines, and various substituted aromatic aldehydes catalyzed by thiamine hydrochloride, successfully synthesized substituted tetrahydropyridines with significantly higher yields. The complete synthesis of the products is shown in **Scheme 2**.

Scheme 2. Complete Synthesis of substituted tetrahydropyridines (46a-r) in MCR catalyzed by thiamine hydrochloride (VitB$_1$).



16 **17** **18** **19**

19a (93%, 3.5 h)

19b (90%, 3.5 h)

19c (91%, 3.5 h)

19d (91%, 3 h)

19e (88%, 4 h)

19f (89%, 3.5 h)

19g (93%, 3.5 h)

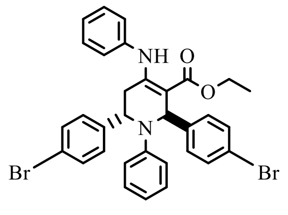
19h (91%, 3 h)

19i (92%, 3.5 h)

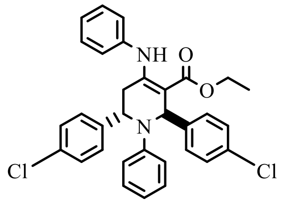
19j (90%, 3.5 h)

19k (88%, 3.5 h)

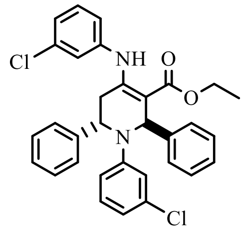
19l (88%, 4 h)



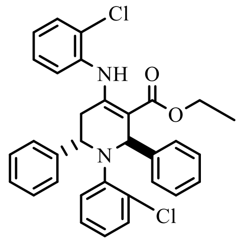
19m
(88%, 3 h)



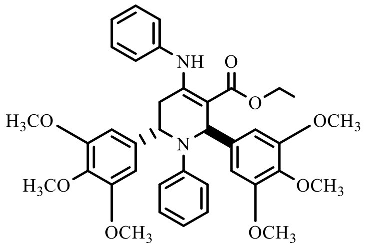
19n
(92%, 4 h)



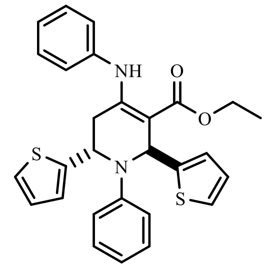
19o
(90%, 4 h)



19p
(89%, 4 h)



19q
(87%, 4 h)



19r
(88%, 4.5 h)

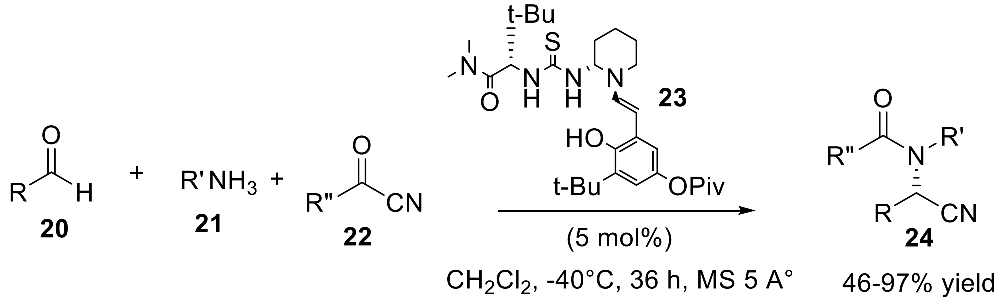
Thiourea-based Catalyzed the Synthesis of Heterocyclic compounds via Asymmetric MCR

Thiourea-based organocatalysts are recognized as an excellent alternative to metal-based catalysis, attracting considerable attention from researchers due to their unique characteristics and non-covalent catalytic mechanisms. These properties include their dual hydrogen-bonding capacity, enantioselective synthesis, green reaction conditions, atom efficiency and complexity, as well as their broad applicability in different fields of chemistry [20].

Through asymmetric acyl-Strecker reaction, the use of thiourea-based organocatalyst (**23**) was initially introduced in the three-components reaction of aldehyde (**20**), amine (**21**), and acetyl cyanide (**22**) to produce excellent yield of products (**24**) (**Scheme 3**). This modified reaction was first explored by List & Pan (2007) [19] to improve the acyl-Strecker reaction without the involvement of toxic HCN as one of the starting materials.

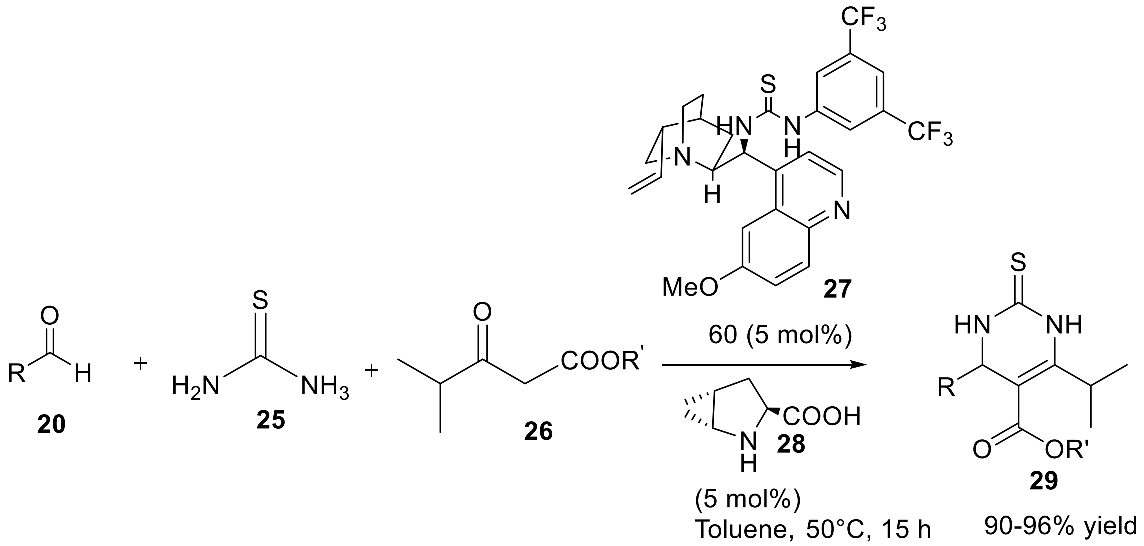
In another study, specifically the Biginelli reaction conducted by Hang et al. (2016) [21], the reaction involved three-component reactions of aldehyde (**20**), thiourea (**25**), and β-keto ester (**26**) in toluene under 50℃ for 15 hours long. This reaction successfully produced dihydropyrimidines (**29**) excellently (**Scheme 4**). The self-constructed thiourea-based organocatalysts, quinidine thiourea (**27**) and *trans*-4,5-methano-*L*-proline (**28**) were proven to be functioning greatly for a better result compared to the usually individualized precatalysts.

Scheme 3. Asymmetric acyl-Strecker thiourea-based reaction of three-component MCR.



R = Ph, 4-OMeC_6H_4, 4-ClC_6H_4, 2-naphthyl, PhCH=CH, iPr, tBu, nBu, tBuCH_2
R' = 4-OMe$C_6H_4CH_2$, 4-Cl$C_6H_4CH_2$, 1-naphCH_2, 2-furCH_2, allyl, nPent, Bn
R'' = Me, nHex

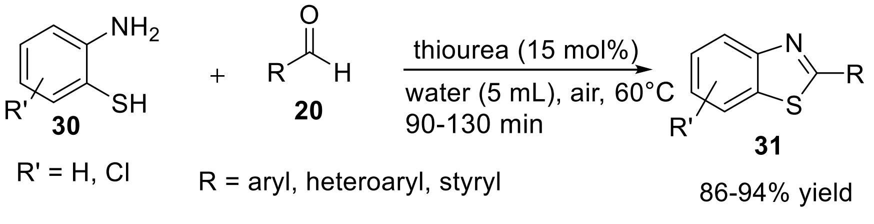
Scheme 4. Biginelli reaction of self-constructed thiourea-based organocatalysts in the synthesis of dihydropyrimidines.



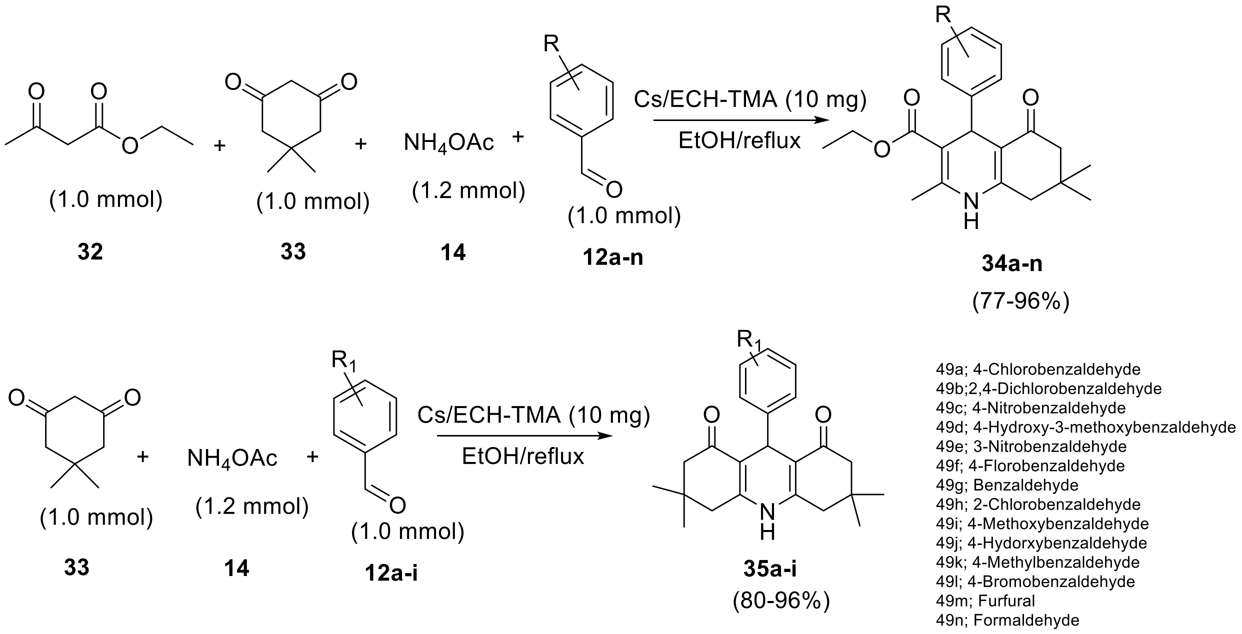
R = 4-FC_6H_4, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, Ph, 4-OHC_6H_4, 4-MeC_6H_5, 4-$OMeC_6H_4$, 4-$CH(CH_3)_2C_6H_4$, 2,4,6-$(CH_3)_3C_6H_2$, n-Pr; R' = Me, Et

Saini and his co-researchers (2024) [22] suggested that thiourea is capable as both bifunctional hydrogen bond donor as well as Bronsted base catalyst, which promotes the relevancy of using thiourea-based green catalysts in the synthesis of demanding compounds, such as heterocyclic compounds. The procedure involved the synthesis of benzothiazole derivatives (**31**) with various substituents comprising aryl, heteroaryl and styryl, a two-component reaction involving substituted aldehydes (**20**) and 2-amino thiophenols (**30**). The reaction took place in an aqueous medium under 60°C, and air acted as oxidant (**Scheme 5**). The one-pot strategy was ultrasound-irradiated, which enhanced the mobility of the movement towards greener chemistry procedures while still capable of effectively and efficiently offering excellent yields ranging between 86-94% of the targeted products. This research by Saini et al. was proven to be reliable advancements with the multiple twists of better innovation in the involvement of thiourea-based organocatalysts reactions compared to previous reports such as the prevention of excess acids or bases usage as well as the use of ultrasound irradiation to substitute the traditional heating procedure. This report is potentially to be referred for further advancements with all the advantages it can offer, including advanced one-pot strategy, effective reusability of catalyst, inexpensive yet productive yielding, and most importantly, simpler as well as mild conditions involved.

Scheme 5. Ultrasound-irradiated two-component MCR of benzothiazole derivatives synthesis.



Scheme 6. Synthesis of PHQ (13a-n) and PHA (14a-i) derivatives catalyzed by Cs/ECH-TMA solid acid catalyst under optimized conditions.



FUNCTIONALIZED BIOPOLYMER

Trisemic Acid-functionalized Chitosan Catalyzed Reactions of One-pot Synthesis

Beiranvand and Dekamin (2023) [23] reported the use of a trimesic acid-functionalized chitosan-based catalyst (Cs/ECH-TMA) to synthesize polyhydroquinoline (PHQ) and polyhydroacridinedione (PHA) compounds. This was achieved through a one-pot, four-component Hantzsch condensation reaction. The process involved using various aldehydes (**49a-n**), β-dicarbonyl compounds (**47** and **48**), and ammonium acetate (NH_4OAc, **15**) as reactants, with ethanol as the solvent under reflux conditions. The reaction resulted in high yields of the desired scaffolds, ranging from 80% to 96%, as illustrated in **Scheme 6**. The use of Cs/ECH-TMA as a reusable catalyst in multiple reactions facilitated various modifications in different trials of various factors and parameters to optimize the synthesis of PHQs (**50a-n**) and PHAs (**51a-i**). The synthesis of Cs/ECH-TMA was initially conducted using chitosan, epichlorohydrin, and trisemic acid. The study revealed the synergistic multifunctional nanocatalyst capabilities shown by the Cs/ECH-TMA material. Beiranvand and Dekamin demonstrated the efficiency of the Cs/ECH-TMA catalyst as an alternative for promoting green chemistry. Their research study showcased the impressive production of PHQs (**50a-n**) and PHAs (**51a-i**) in a short reaction time using Cs/ECH-TMA catalyst. The proposed use of Cs/ECH-TMA in the synthesis of heterocyclic compounds also provides another synthetic route in catalytic reactions to eliminate the commercial use of toxic transition metal-based catalysts and solvents.

CONCLUSION

Green chemistry has led to the development of one-pot synthesis, a method that simplifies lengthy chemical reactions without extra reactants or intermediate isolation. This review explores the influence of green catalysts, particularly organocatalysts, on the performance of one-pot synthesis and emphasizes the importance of choosing sustainable and environmentally friendly organocatalyst options in catalytic reactions for the synthesis of heterocyclic compounds. The review advocates for environmentally friendly and sustainable catalysts, like organocatalysts, in the synthesis of heterocyclic compounds. Several studies have demonstrated the efficiency and high yields of one-pot synthesis, such as synthesizing pyrido [2,3-d] pyrimidines derivatives through multi-component reactions (MCRs). The use of environmentally friendly and sustainable catalysts, such as organocatalysts, is essential for the efficient production of diverse, cost-effective, and scalable heterocyclic scaffolds for various industrial applications. The thiourea-based organocatalysts have gained attention as a greener alternative to metal-based catalysis due to their eccentric properties and non-covalent catalysis. They have been used in various fields of chemistry, such as the synthesis of heterocyclic compounds via asymmetric MCR. This review aims to promote the use of green catalysts in the synthesis of heterocyclic compounds.

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