

# Metal-free, acid-base, and organocatalyst-promoted semi-green protocols for the efficient construction of structurally diverse & highly functionalized pyrimidine derivatives: A long-term review (1876–2026)

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## Abstract

This review summarizes the 150-year development of pyrimidine synthesis from 1876 to 2026, highlighting progress in metal-free, acid-base-mediated, and organocatalytic methodologies for the construction of structurally diverse, highly functionalized pyrimidine derivatives. Emphasis is placed on the synthetic efficiency, practical applicability, and sustainability of these approaches, including classical condensation reactions and modern semi-green methodologies. This review aims to serve as a comprehensive reference for the development of efficient, sustainable, and metal-free strategies for the synthesis of complex pyrimidine scaffolds.

**Keywords:** pyrimidine synthesis, metal-free, organocatalysis, semi-green protocols, acid-base promotion.

## Protocolos semiverdes livres de metais, promovidos por ácido-base e organocatalisadores para a construção eficiente de derivados de pirimidina estruturalmente diversos e altamente funcionalizados: Uma revisão de longo prazo (1876–2026)

## Resumo

Este artigo de revisão resume o desenvolvimento de 150 anos da síntese de pirimidinas, de 1876 a 2026, destacando os avanços em metodologias livres de metais, mediadas por ácido-base e organocatalíticas para a construção de derivados de pirimidina estruturalmente diversos e altamente funcionalizados. Ênfase é dada à eficiência sintética, aplicabilidade prática e sustentabilidade dessas abordagens, incluindo reações clássicas de condensação e metodologias modernas semiverdes. Este trabalho de revisão tem como objetivo servir como uma referência abrangente para o desenvolvimento de estratégias eficientes, sustentáveis e livres de metais para a síntese de estruturas complexas de pirimidina.

**Palavras-chave:** síntese de pirimidinas, livre de metais, organocatálise, protocolos semiverdes, promoção ácido-base

## 1. Introduction

The construction of N-containing heterocycles, particularly the pyrimidine ring, has remained a focal point of organic synthesis for over a century. Since the late 19th century, starting with seminal works around 1876, the pyrimidine scaffold serves as the structural backbone for a vast array of applications in the pharmaceutical, veterinary, and agrochemical industries, as well as in cutting-edge biological and chemical research. Pyrimidine plays a crucial role as a fundamental constituent in various pharmaceutical and natural materials. Thus, the management and comprehension of the laboratory preparations of pyrimidine and its analogues have become areas of paramount importance in synthetic organic chemistry.

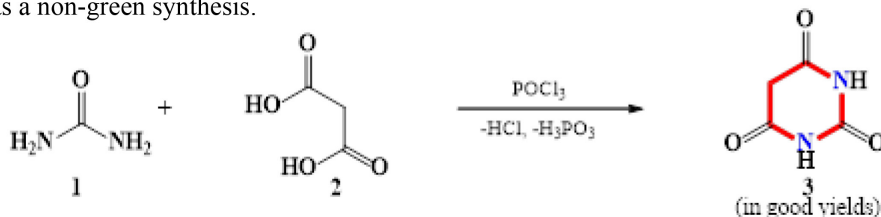
Historically, pyrimidine synthesis relied heavily on metal catalysts and harsh reagents, which often led to environmental concerns and purification challenges. However, the shift towards green chemistry has catalyzed a remarkable transformation in synthetic methodology. The quest for metal-free pathways has led to the emergence of acid-base and organocatalyst-promoted protocols, which offer superior selectivity and functional group tolerance. These semi-green protocols—defined by their use of non-toxic catalysts, mild reaction conditions, and reduced waste—have enabled the synthesis of structurally diverse pyrimidines, ranging from simple monocyclic rings to complex fused systems.

Furthermore, the ability to create highly functionalized derivatives has opened new doors in medicinal chemistry, allowing for the fine-tuning of molecular properties for targeted therapies (Adly et al., 2024; Albratty; Alhazmi, 2022; Brown, 1984; Bruce, 2007; Elderfield, 1957; Hantosh et al., 2023; Hassan; Mohaisen, 2025; Nekar, 2021; Tolba et al., 2022; Verma et al., 2020). This review systematically chronicles the evolution of pyrimidine synthesis from 1876 to 2026. This review presents key synthetic pathways, transitioning from the classical Pinner and Biginelli eras to the modern age of organocatalysis. A special emphasis is placed on how metal-free strategies have redefined the efficiency and sustainability of pyrimidine construction in the 21st century.

## 2. Metal-Free & Semi-Green Pyrimidine Synthesis

The landscape of pyrimidine synthesis, spanning from Pinner's seminal work in 1876 to the advancements of 2026, underscores the profound impact of acid-base and organocatalyst-promoted methodologies. Throughout this 150-year evolution, both classical foundations such as the Grimaux, Pinner Biginelli, and Knoevenagel reactions and modern multi-component strategies have frequently integrated metal-free and semi-green protocols, utilizing sustainable solvents like water or ethanol (Biginelli, 1893; Grimaux, 1876; Pinner, 18884).

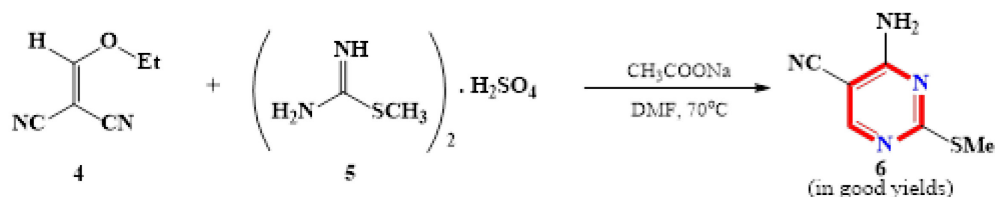
This long-standing commitment to accessible synthetic pathways has culminated in the 21st-century rise of highly efficient organocatalytic techniques. Today, these refined protocols stand as the most versatile and eco-friendly tools for the construction of structurally diverse and highly functionalized pyrimidine derivatives, bridging the gap between historical excellence and modern sustainability (Taylor et al., 1960). In the context of representing the foundational discovery in pyrimidine chemistry, the research team led by Grimaux described a classical acid-promoted condensation wherein urea **1** reacted with malonic acid **2** in the presence of  $\text{POCl}_3$  to yield barbituric acid **3** (Scheme 1) (Grimaux, 1876). This pioneering strategy is distinguished by its simplified starting materials and direct pyrimidine ring assembly; however, the use of corrosive  $\text{POCl}_3$  and mineral acids classifies it as a non-green synthesis.



Scheme 1. Reaction. Source: Authors, 2026.

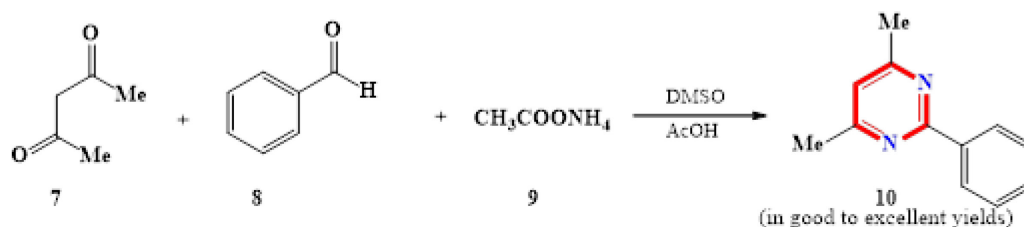
Building upon pioneering efforts in heterocyclic chemistry, Taylor et al. (1960) and later Drew et al. (1972) utilized a base-promoted cyclization between ethoxymethylene malononitrile **4** and S-methylisothiurea sulfate **5** in the presence of sodium acetate and DMF to afford the functionalized 4-amino-2-(methylthio)pyrimidine-5-carbonitrile **6** (Scheme 2) (Drew et al., 1972; Taylor et al., 1960). This practical, robust, and efficient protocol is notable for its operational simplicity and effective introduction of cyano and thio functionalities; however, the use of DMF and conventional thermal conditions renders the method

only partially green.



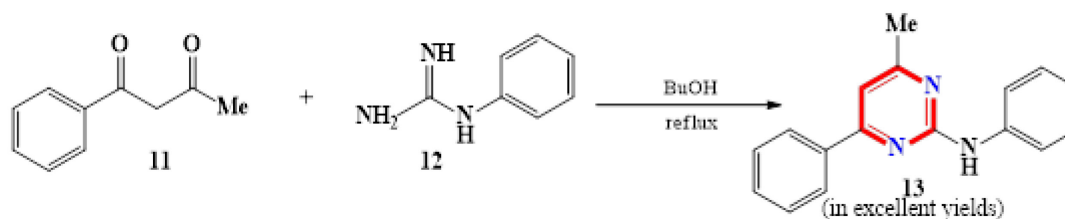
Scheme 2. Reaction. Source: Authors, 2026.

In a pursuit to expand the utility of multicomponent reactions, in 1981, Lewis's research group demonstrated an efficient three-component one-pot cyclocondensation strategy wherein acetylacetone **7**, benzaldehyde **8**, and ammonium acetate **9** reacted in a DMSO/AcOH medium to yield the 4,6-dimethyl-2-phenylpyrimidine derivative **10** (Scheme 3) (Lewis; Rosenbach, 1981). This approach features outstanding step economy and efficient bond formation; however, its dependence on DMSO and acetic acid as reaction media places it within the category of moderately green synthetic methodologies, despite its practical utility.



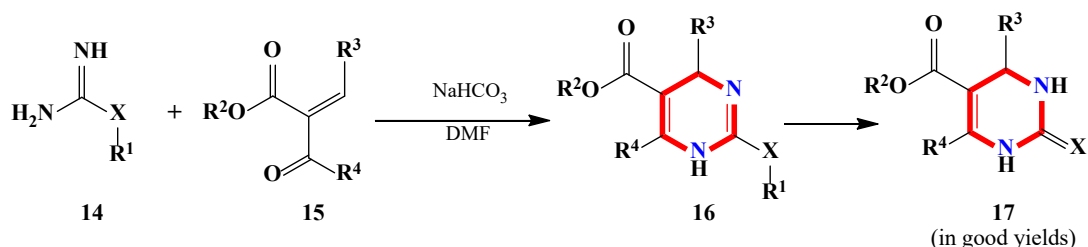
Scheme 3. Reaction. Source: Authors, 2026.

Focusing on the condensation of 1,3-dicarbonyl species, in 1983, Wendelin et al. (1983) reported an efficient base-promoted two-component cyclocondensation approach involving 1-phenylbutane-1,3-dione **11** and phenylguanidine **12** under reflux conditions in *n*-butanol, leading to the formation of a 2-aminopyrimidine derivative **13** (Scheme 4) (Wendelin et al., 1983). This synthetic transformation is valued for its ability to produce functionalized architectures with high regioselectivity and broad substrate scope; however, the requirement for high-boiling solvents like *n*-BuOH and reflux heating prevents the method from being considered a fully green process.



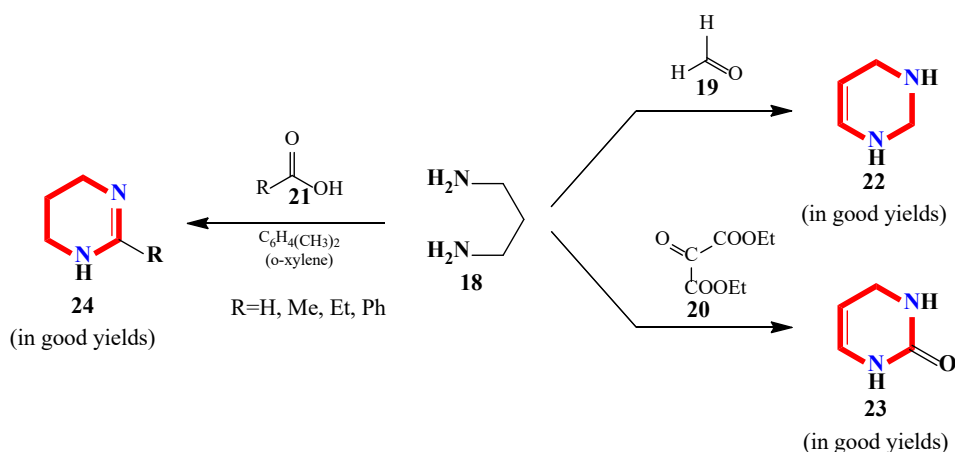
Scheme 4. Reaction. Source: Authors, 2026.

Facilitating the construction of highly substituted dihydropyrimidines, A base-promoted two-component cyclocondensation protocol was described by the research team led by Atwal (1987), wherein O-methylisourea or related amidines **14** reacted with  $\alpha,\beta$ -unsaturated 1,3-dicarbonyl compounds **15** in the presence of  $\text{NaHCO}_3$ -DMF to yield functionalized pyrimidine derivatives **17** (Scheme 5) (Atwal et al., 1987). Although the requirement of DMF as a solvent and traditional heating conditions restricts it to a partially green synthetic methodology, this developed procedure is notable for its regioselective transformation, mild basic conditions, and compatibility with various substituents.



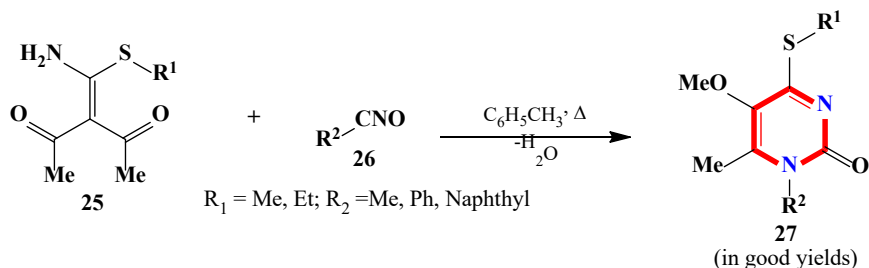
Scheme 5. Reaction. Source: Authors, 2026.

Building upon the foundational work on nitrogen heterocycles, Fischer et al. (1886) and later improved versions by Grath et al. (1988) established a versatile two-component cyclization strategy where 1,3-diaminopropane **18** reacted independently with formaldehyde **19**, diethyl carbonate **20**, or various carboxylic acids **21** to afford 1,2,3,4-tetrahydropyrimidine **22**, 3,4-dihydropyrimidin-2(1H)-one **23**, and 2-substituted-1,4,5,6-tetrahydropyrimidines **24**, respectively (Scheme 6). This highly efficient and versatile synthetic platform is distinguished by its operational simplicity and high atom economy; while the utilization of *o*-xylene and thermal reflux conditions places it under the category of semi-sustainable or conventionally-green synthesis.



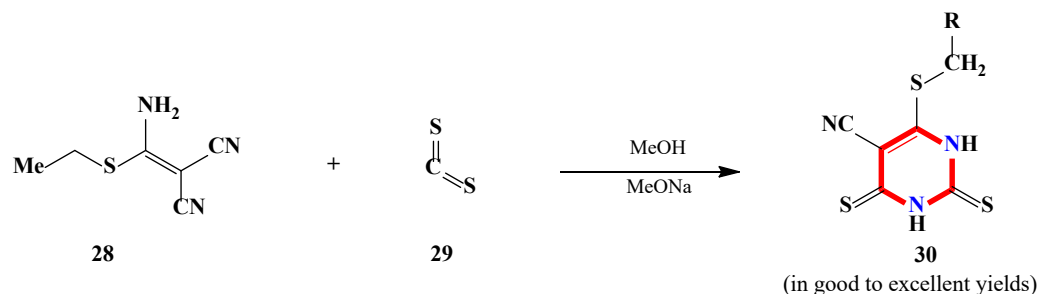
Scheme 6. Reaction. Source: Authors, 2026.

In a pursuit of sulfur-functionalized pyrimidine-2-ones, the research team led by Gordeev (1990) utilized an efficient two-component cyclization where thioether-based enaminones **25** reacted with isocyanates **26** in toluene to afford pyrimidine derivatives **27** (Scheme 7). Despite its classification as a partially green synthetic protocol due to the use of aromatic solvents and thermal heating, this approach enables regiospecific bond formation and the efficient transformation of a wide range of isocyanates.



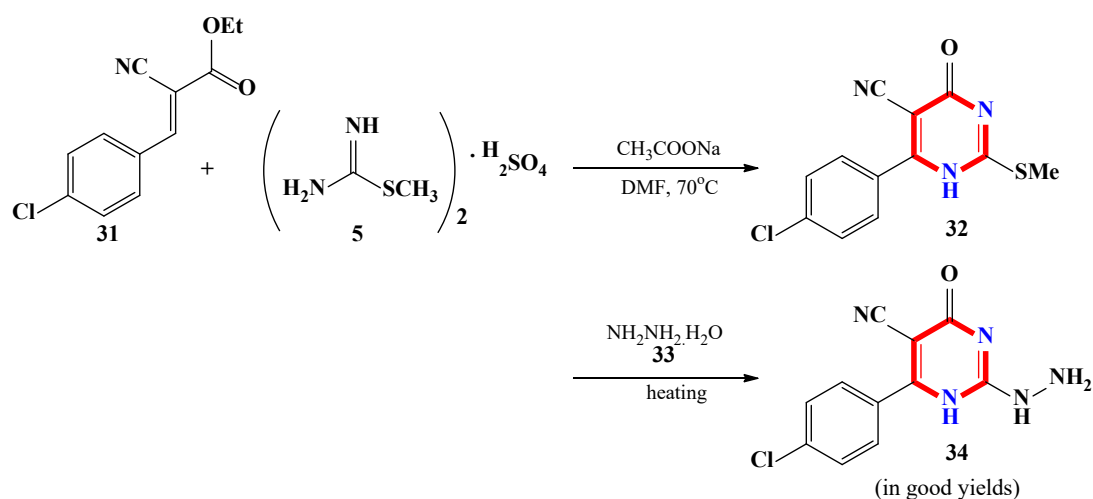
Scheme 7. Reaction. Source: Authors, 2026.

Advancing the synthesis of sulfur-rich pyrimidines, in 1994, a practical base-mediated two-component cyclization protocol was established by Holzer et al., wherein functionalized enaminonitriles **28** reacted with carbon disulfide **29** in MeOH-MeONa to deliver structurally diverse 4-(alkylsulfanyl)-6-thioxo-1,6-dihydropyrimidine-5-carbonitriles **30** with notable efficiency (Scheme 8) (Holzer et al., 1994). The use of toxic CS<sub>2</sub> and corrosive bases classifies it as a moderately sustainable approach due to environmental and safety concerns. Nevertheless, it remains an efficient and practical tool for the rapid assembly of sulfur-heterocycles with high regioselectivity and a broad substrate scope.



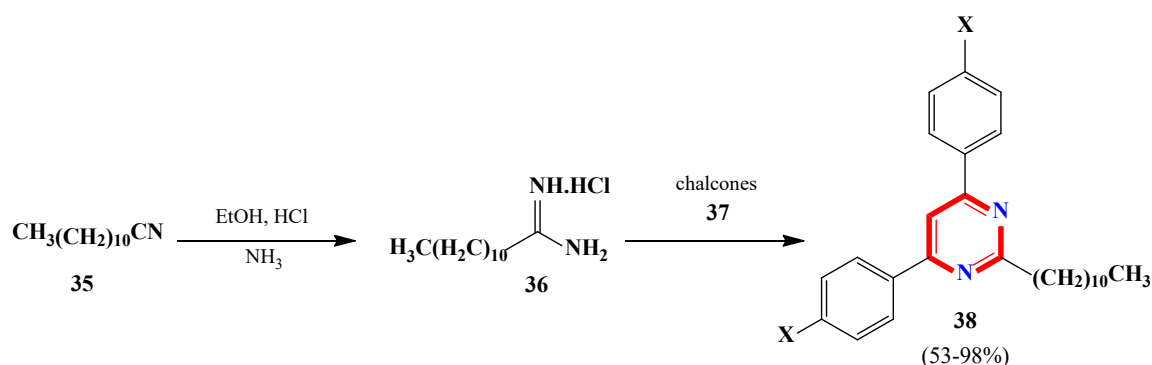
Scheme 8. Reaction. Source: Authors, 2026.

Expanding the accessibility of polyfunctionalized pyrimidines, the research team led by Nagahara (1994) and Masquelin (1998) demonstrated an efficient two-component cyclization between  $\alpha$ -cyano cinnamate derivatives **31** and *S*-methylisothiurea sulfate **5** in the presence of sodium acetate and DMF to afford 5-cyano-6-(4-chlorophenyl)-2-(methylthio)pyrimidin-4(3*H*)-one **32** (Scheme 9) (Masquelin et al., 1998). Although the use of DMF and conventional heating categorizes it as a partially eco-friendly synthesis, this protocol remains a highly effective and streamlined route, distinguished by its high regiospecificity and broad functional group tolerance.



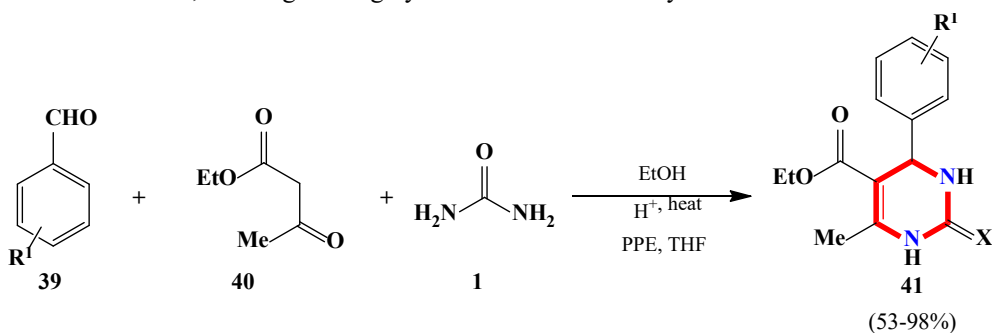
Scheme 9. Reaction. Source: Authors, 2026.

In a quest to develop long-chain lipid-like heterocycles, in 2000, an efficient acid-promoted two-step protocol was developed by Katritzky et al. (2000) wherein aliphatic nitriles **35** were transformed into amidine hydrochlorides **36**, which subsequently underwent cyclocondensation with chalcone derivatives **37** to furnish 2-substituted pyrimidines **38** (Scheme 10). High chemical efficiency, excellent regioselectivity, and a highly effective and robust synthetic route are the primary highlights of this methodology; however, the use of concentrated mineral acid and conventional heating renders it a partially green synthesis.



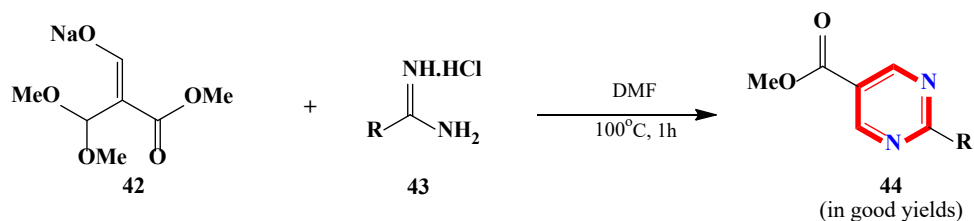
Scheme 10. Reaction. Source: Authors, 2026.

In a strategic effort to access functionalized dihydropyrimidines, one year later, the research team led by Falsone & Kappe (2001) synthesized pyrimidine-2-one/thiones via a one-pot three-component cyclocondensation of aromatic aldehydes **39**, ethyl acetoacetate **40**, and (thio)urea **1** in acidic conditions and the presence of polyphosphate ester in THF/EtOH (Scheme 11). Although the application of PPE and conventional solvents designates it as a somewhat green synthesis, this protocol is characterized by remarkable atom economy and versatile substrate tolerance, standing as a highly effective and reliable synthetic route.



Scheme 11. Reaction. Source: Authors, 2026.

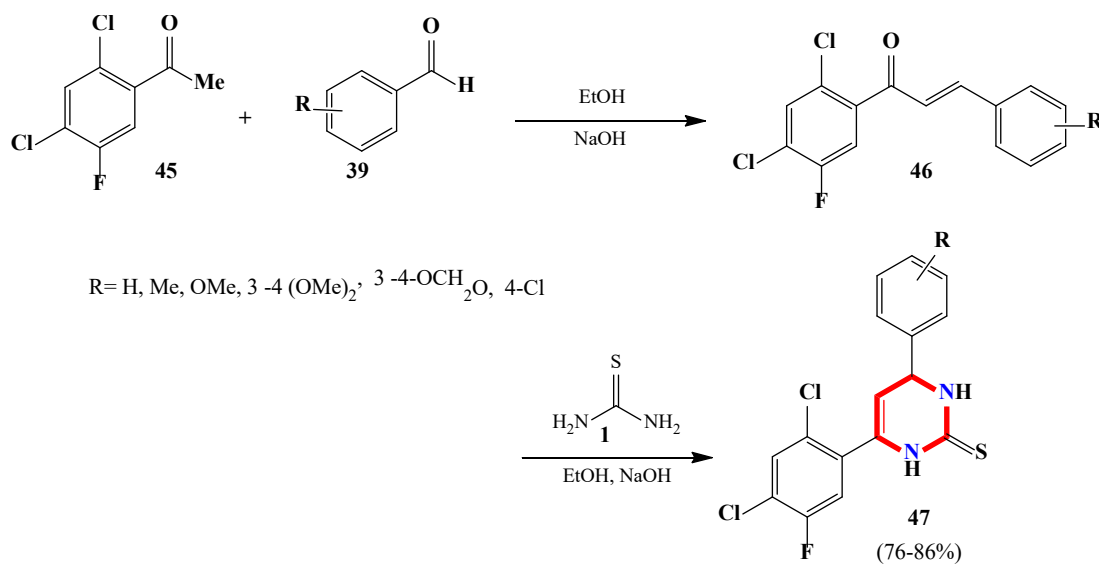
Offering a practical route to pyrimidine-5-carboxylate derivatives, in the following year, an efficient two-component cyclization was described by Zhichkin et al. (2002), wherein substituted enolate **42** reacted with amidine hydrochlorides **43** in DMF at  $100^\circ\text{C}$  for 1 h to yield aromatic pyrimidine core **44** (Scheme 12). This method is semi-sustainable due to the use of DMF at elevated temperatures; this strategy is highlighted by precise ring construction, ease of assembling the heterocyclic framework, and rapid reaction time, standing as a highly efficient and versatile synthetic pathway.



Scheme 12. Reaction. Source: Authors, 2026.

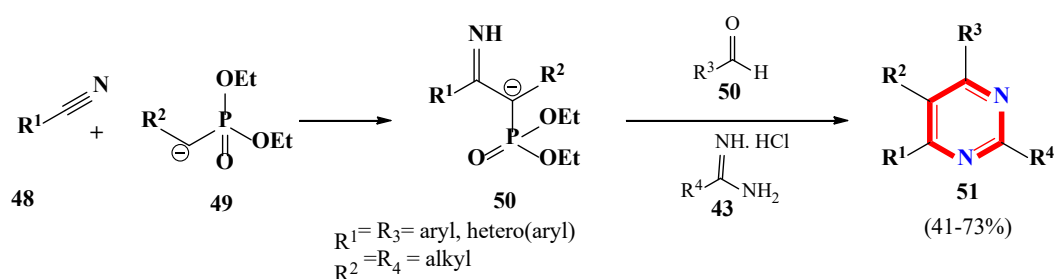
Expanding the diversity of sulfur-containing heterocycles, Dihydropyrimidine-2(1*H*)-thiones **47** were synthesized by Holla et al. (2004) via a three-component strategy involving chalcone intermediates, wherein substituted acetophenones **45** and benzaldehydes **39** reacted with (thio)urea **1** in  $\text{EtOH}$ - $\text{NaOH}$  (Scheme 13). Although

classified as a moderately sustainable methodology due to the use of a strong base and reflux, this approach is valued for its simplicity in assembling building blocks, efficient bond formation, and excellent yields, making it a highly productive and streamlined synthetic route.



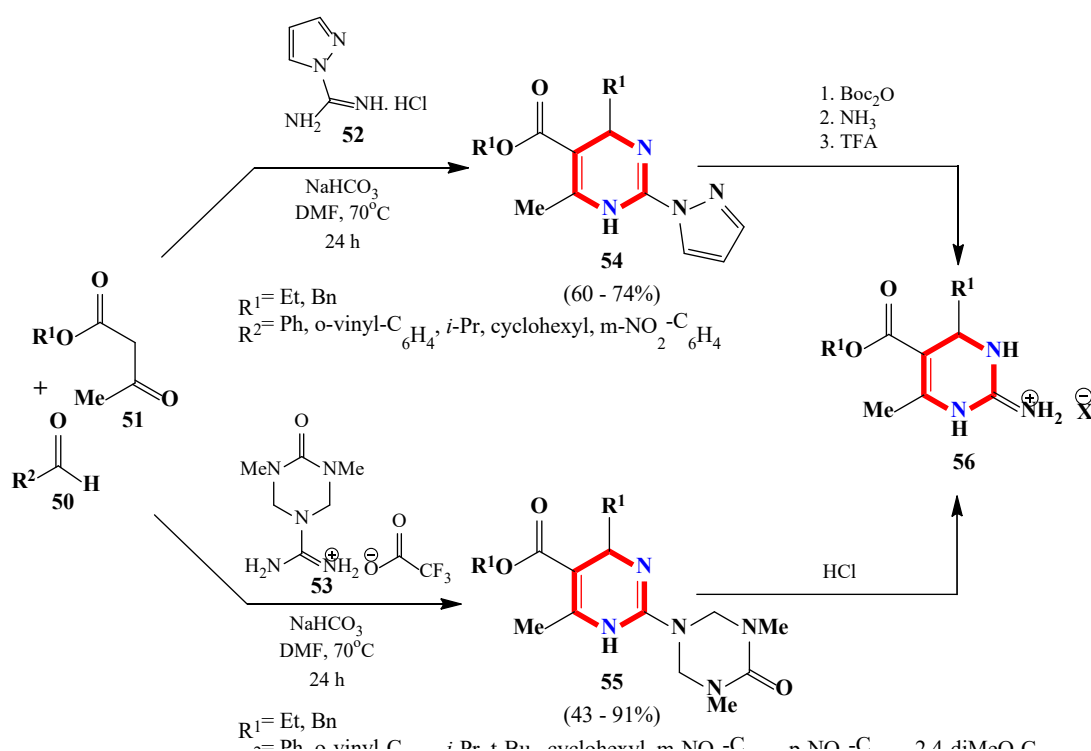
Scheme 13. Reaction. Source: Authors, 2026.

In a creative approach to scaffold construction, a base and acid-promoted four-component one-pot strategy was developed by the research team led by Alexander & Kiselyov (2005) for the sequential synthesis of tetra-substituted pyrimidines **51**, involving the coupling of nitriles **48**, lithiated alkylphosphonates **49**, aldehydes **50**, and amidine hydrochloride **43** (Scheme 14). Although classified as a moderately sustainable approach due to the multi-step sequence and reliance on specialized phosphorus reagents, which pose challenges in atom economy and purification, it remains a powerful and effective tool for quickly assembling functionalized pyrimidines.



Scheme 14. Reaction. Source: Authors, 2026.

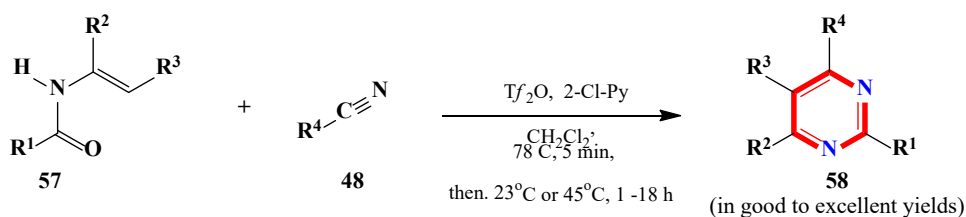
Facilitating the construction of diverse heterocyclic architectures, Nilsson et al. (2006) developed a base-promoted, one-pot, three-component cyclocondensation in which  $\beta$ -keto esters **51** and various aromatic or aliphatic aldehydes **50** reacted with pyrazole-1-carboxamide hydrochloride **52** or its cyclic urea-linked analog **52** in DMF at 70 °C, affording tetra-substituted pyrimidines **54** and **55**, which were subsequently converted into the corresponding salt **56** (Scheme 15).



Scheme 15. Reaction. Source: Authors, 2026.

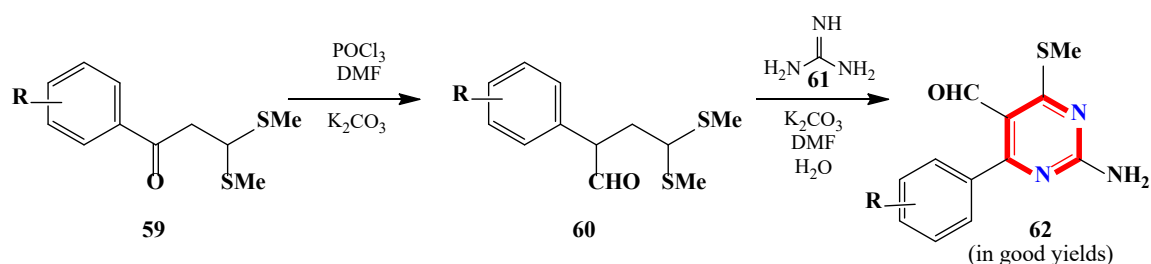
This protocol is distinguished by its high chemical efficiency and broad substrate scope; however, the reliance on high-boiling DMF and prolonged reaction time designates it as a semi-green protocol due to the energy intensity and solvent toxicity compared to ideal sustainable standards.

Establishing a highly versatile route to multi-substituted pyrimidine cores, in the same year, secondary enamides **1** and nitriles **2** underwent a one-pot, two-component cyclocondensation as reported by Movassaghi & Hill (2006), using triflic anhydride ( $\text{Tf}_2\text{O}$ ) and 2-chloropyridine in  $\text{CH}_2\text{Cl}_2$  (Scheme 16). High chemical efficiency and broad substrate scope, along with being an undeniably efficient and high-impact method, distinguish this synthetic approach; however, the use of chlorinated solvents and moisture-sensitive triflic anhydride makes it only partially green.



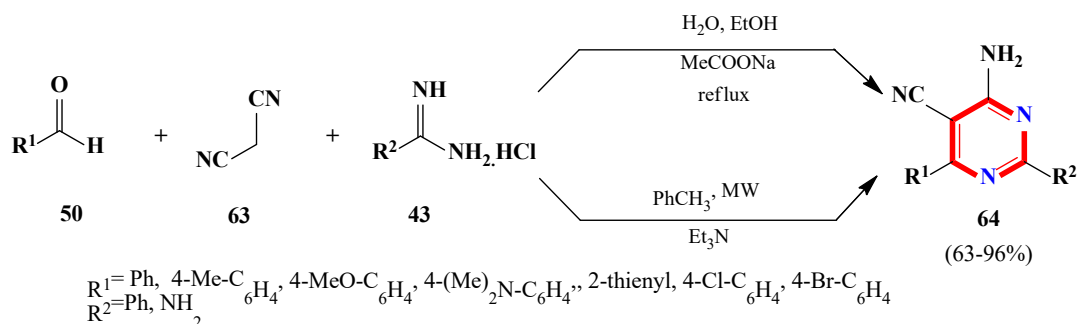
Scheme 16. Reaction. Source: Authors, 2026.

Developing a sophisticated route to multi-substituted pyrimidines, Mathews & Asokan (2007) successfully reported a series of tetra-substituted pyrimidine derivatives from ketene dithioacetal-functionalized ketone **59**. The ketone underwent Vilsmeier-Haack formylation ( $\text{POCl}_3$ , DMF,  $\text{K}_2\text{CO}_3$ ) to yield the  $\alpha$ -formyl intermediate **60**, which subsequently cyclocondensed with guanidine **61** under basic conditions to afford the substituted 2-amino-4-(methylthio)pyrimidine-5-carbaldehyde **62** in good yield. (Scheme 17). This synthetic pathway is undeniably efficient and high-impact and demonstrates high chemical efficiency; however, the initial use of corrosive  $\text{POCl}_3$  for formylation and the requirement of DMF as a solvent classify it as a semi-green protocol.



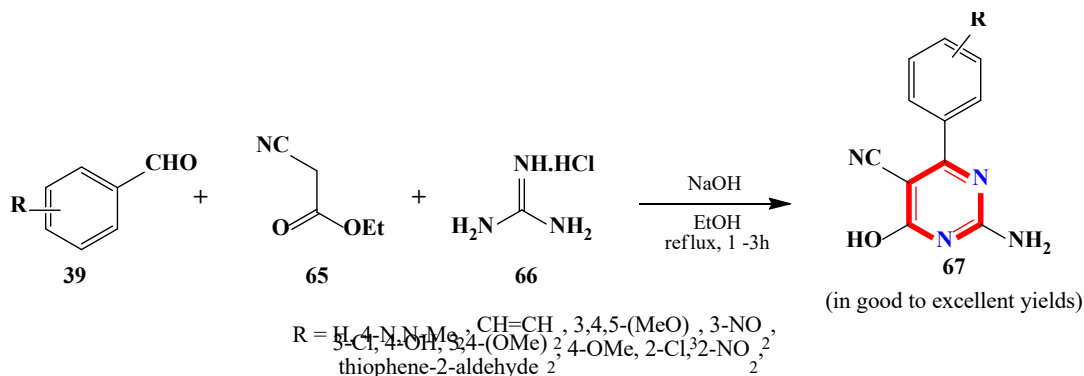
Scheme 17. Reaction. Source: Authors, 2026.

Offering a highly efficient approach to pyrimidines, in the following year (2008), synthesis of amino-substituted pyrimidines **64** was achieved by the research team of Sheibani et al. (2008) through a base-mediated, one-pot three-component cyclocondensation between aldehydes **50**, malononitrile **63**, and amidines **43**, employing sodium acetate in a water–ethanol reflux system or triethylamine in toluene under microwave irradiation (Scheme 18). This methodology is prized for its exceptional atom economy and the ability to produce high yields across a broad range of functional groups; however, the requirement for high-temperature reflux and the use of aromatic solvents like toluene in certain conditions designate it as a semi-green protocol.



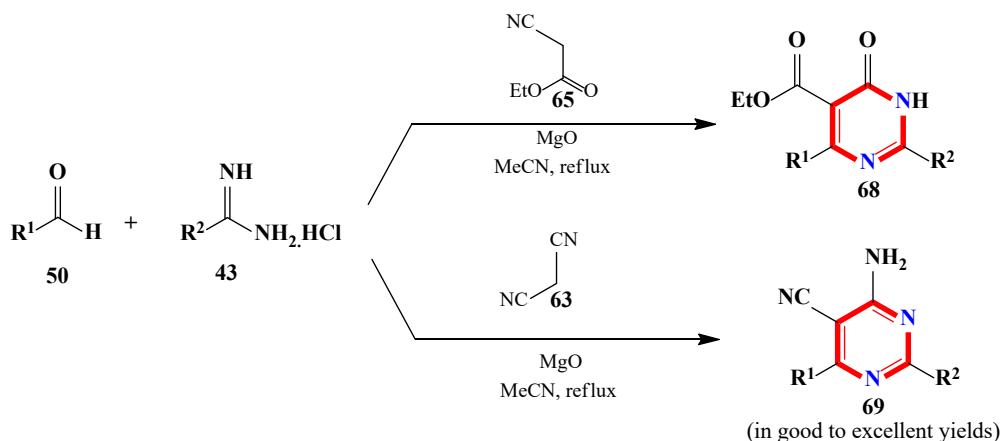
Scheme 18. Reaction. Source: Authors, 2026.

In a remarkable stride toward sustainable heterocyclic synthesis, in 2009 Deshmukh et al. (2009) developed a simple and straightforward one-pot, three-component method to synthesize highly functionalized pyrimidine derivatives **67** via the condensation of aromatic aldehydes **39**, ethyl cyanoacetate **65**, and guanidine hydrochloride **66** in the presence of sodium hydroxide (NaOH) under reflux conditions in ethanol (Scheme 19). This protocol uses a non-toxic base and safe solvent, offering high atom economy and a rapid, scalable route; though not fully green due to the corrosive base and reflux, it remains highly productive and efficient.



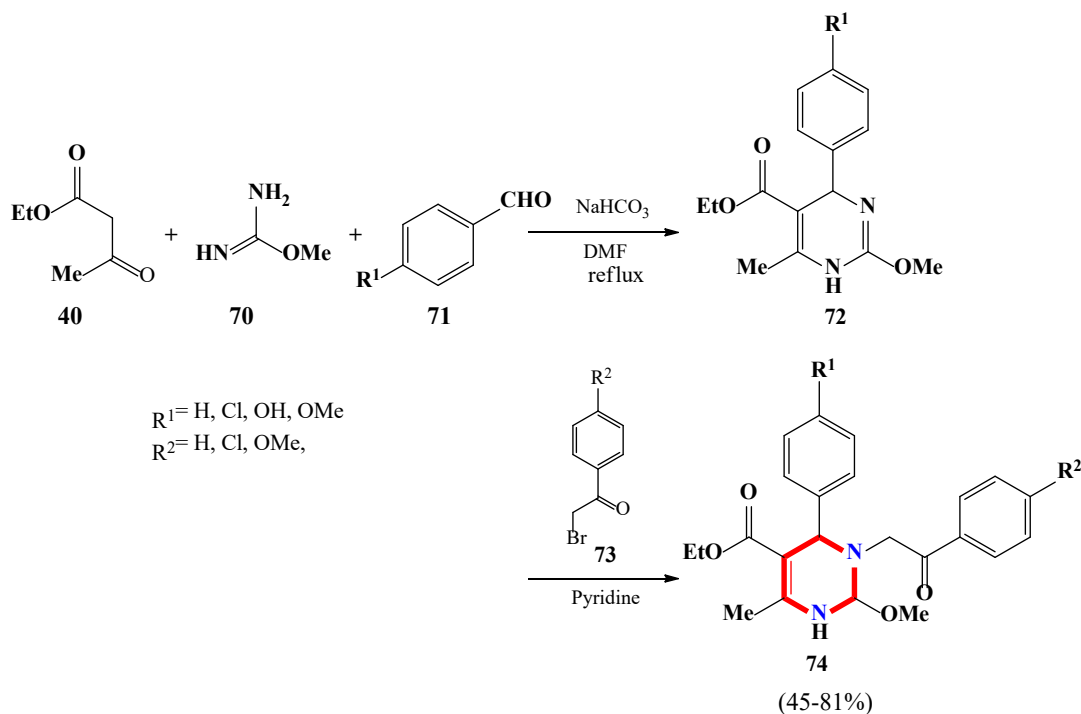
Scheme 19. Reaction. Source: Authors, 2026.

In accordance with green chemistry principles, within the same year, Sheibani et al. (2009) reported a magnesium oxide (MgO)-catalyzed three-component reaction of aldehydes **50**, amidines **43**, and ethyl cyanoacetate **63** or malononitrile **65**, affording pyrimidinone derivatives **68** and 4-amino-5-pyrimidine carbonitriles **69**, respectively (Scheme 20). Although magnesium oxide is used as an environmentally friendly catalyst, the use of methanol as a solvent and reflux conditions classifies this as a partially green protocol due to significant energy and safety requirements. Nevertheless, it remains a highly effective and productive method for the rapid construction of versatile bioactive scaffolds.



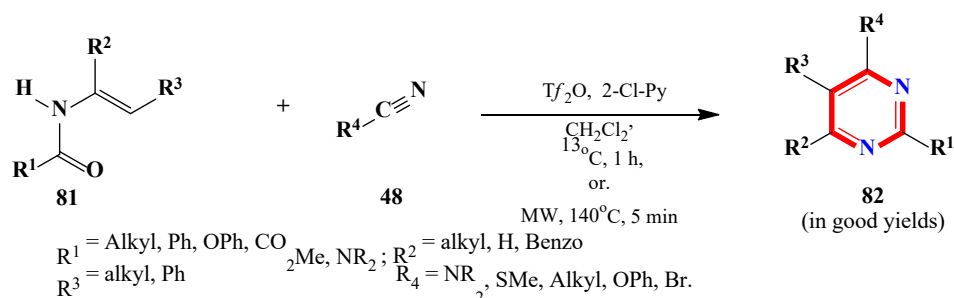
Scheme 20. Reaction. Source: Authors, 2026.

Establishing a versatile route to highly substituted dihydropyrimidines, a base-promoted, one-pot three-component cyclocondensation was developed by Chikhale et al. (2009), wherein ethyl acetoacetate **40**, *O*-methylisourea **70**, and aromatic aldehydes **71** reacted in refluxing DMF in the presence of NaHCO<sub>3</sub>, followed by a pyridine-mediated N-alkylation with phenacyl bromides **73** to afford tetra-substituted dihydropyrimidines **74** (Scheme 21).



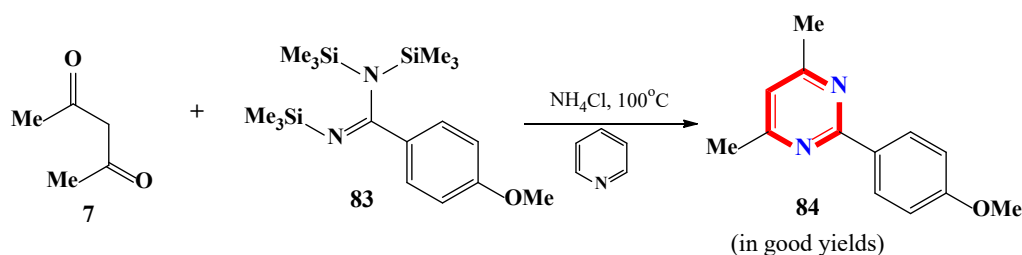
Scheme 21. Reaction. Source: Authors, 2026.





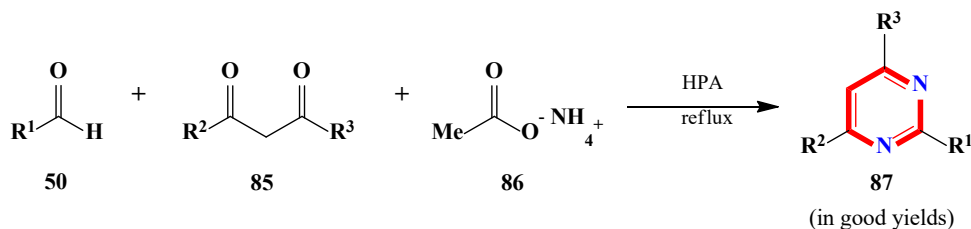
Scheme 24. Reaction. Source: Authors, 2026.

In the same year, as a streamlined approach for the synthesis of substituted pyrimidines, an  $\text{NH}_4\text{Cl}$ -promoted one-pot two-component cyclization was reported by the research team led by Ghosh & Katzenellenbogen (2009), wherein pentane-2,4-dione **7** and a silylated amidine derivative **83** reacted in pyridine at  $100^\circ\text{C}$  to yield the target molecules **84** (Scheme 25). The transformation exhibits high efficiency and good yields; however, the use of toxic pyridine and elevated temperature ( $100^\circ\text{C}$ ) makes it a semi-green protocol due to energy consumption and hazardous conditions, although the use of ammonium chloride as a low-cost, non-toxic catalyst offers a greener advantage over metal-based systems.



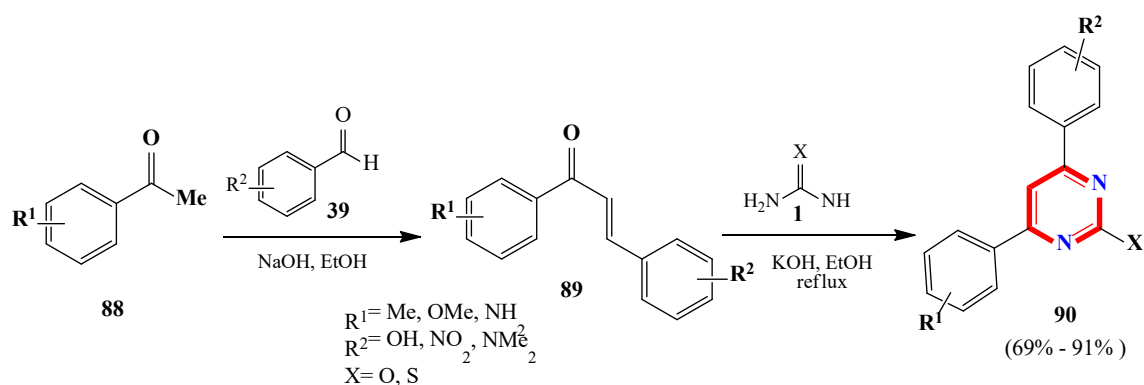
Scheme 25. Reaction. Source: Authors, 2026.

To establish a versatile route toward tri-substituted pyrimidines, Majid et al. (2009) reported an acid-promoted three-component cyclocondensation between aldehydes **50**, 1,3-diketones **85**, and ammonium acetate **86** under reflux conditions to yield the heterocyclic framework **87** in a one-pot sequence (Scheme 26). Although the necessity for reflux temperatures and the use of heteropoly acid (HPA) prevent this protocol from being categorized as a purely green reaction, it stands as a remarkably effective synthesis due to its operational simplicity and the ability to construct highly functionalized pyrimidine derivatives from readily available starting materials.



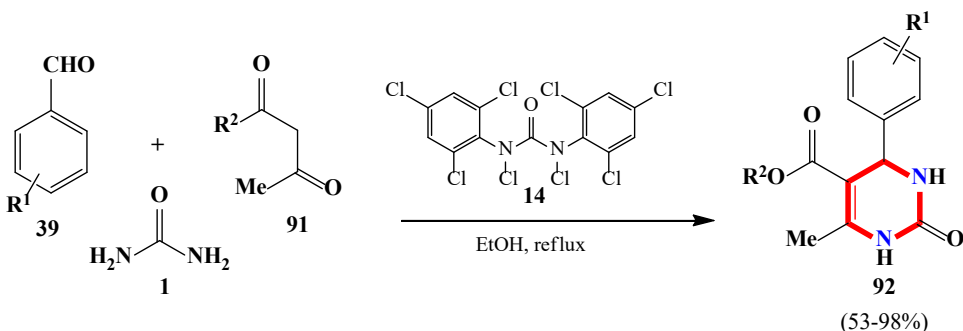
Scheme 26. Reaction. Source: Authors, 2026.

In the following year (2010), in an efficient two-step sequence for the synthesis of pyrimidines, the preparation of tetra-substituted pyrimidines was accomplished by the research team of Balaji et al. (2010) through a base-promoted three-component protocol, wherein acetophenones **88** and benzaldehydes **39** underwent Claisen–Schmidt condensation followed by a one-pot cyclization with various urea-type derivatives **1** in the presence of  $\text{KOH}/\text{EtOH}$  to afford the final scaffolds **13**. (Scheme 27). The dependence on strong bases and traditional reflux prevents this method from being fully green; nevertheless, it remains a highly productive synthesis with broad applicability and excellent yields.



Scheme 27. Reaction. Source: Authors, 2026.

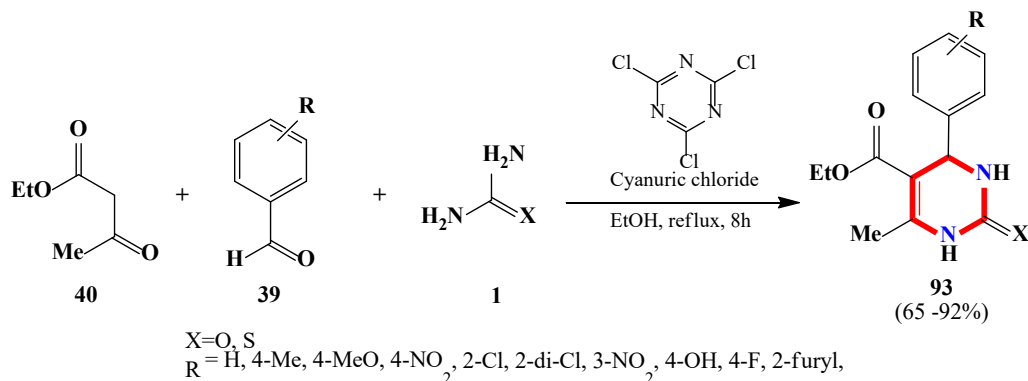
In a specialized application of multicomponent reactions, a year later, Rao et al. (2011) reported an organocatalyst-promoted three-component condensation between aromatic aldehydes **39**,  $\beta$ -keto esters **91**, and urea **1** using a bulky chlorinated urea derivative as a catalyst to yield dihydropyrimidinone **92** (Scheme 28).



Scheme 28. Reaction. Source: Authors, 2026.

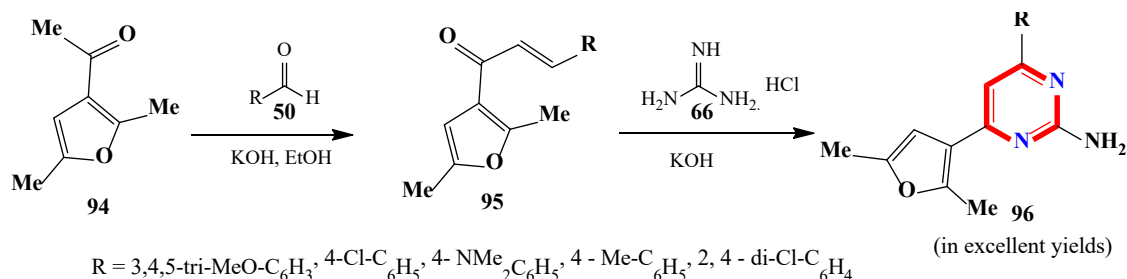
Although the requirement of ethanol reflux and the synthesis of a complex organocatalyst prevents this methodology from being strictly classified as green, it remains a highly effective synthesis due to its remarkable yield and the efficiency of the one-pot Biginelli-type transformation.

In the same year, facilitating the construction of highly substituted dihydropyrimidinones/thiones **93**, a cyanuric chloride-catalyzed, one-pot three-component Biginelli reaction was demonstrated by the research team of Jogula et al. (2011), involving ethyl acetoacetate **40**, aromatic aldehydes **39**, and (thio)urea **1** in refluxing ethanol (Scheme 29). Due to the use of toxic, moisture-sensitive cyanuric chloride and reflux conditions that generate hazardous byproducts, this synthetic approach is classified as quasi-green; nevertheless, it remains highly efficient and impactful for the rapid assembly of pyrimidine scaffolds.



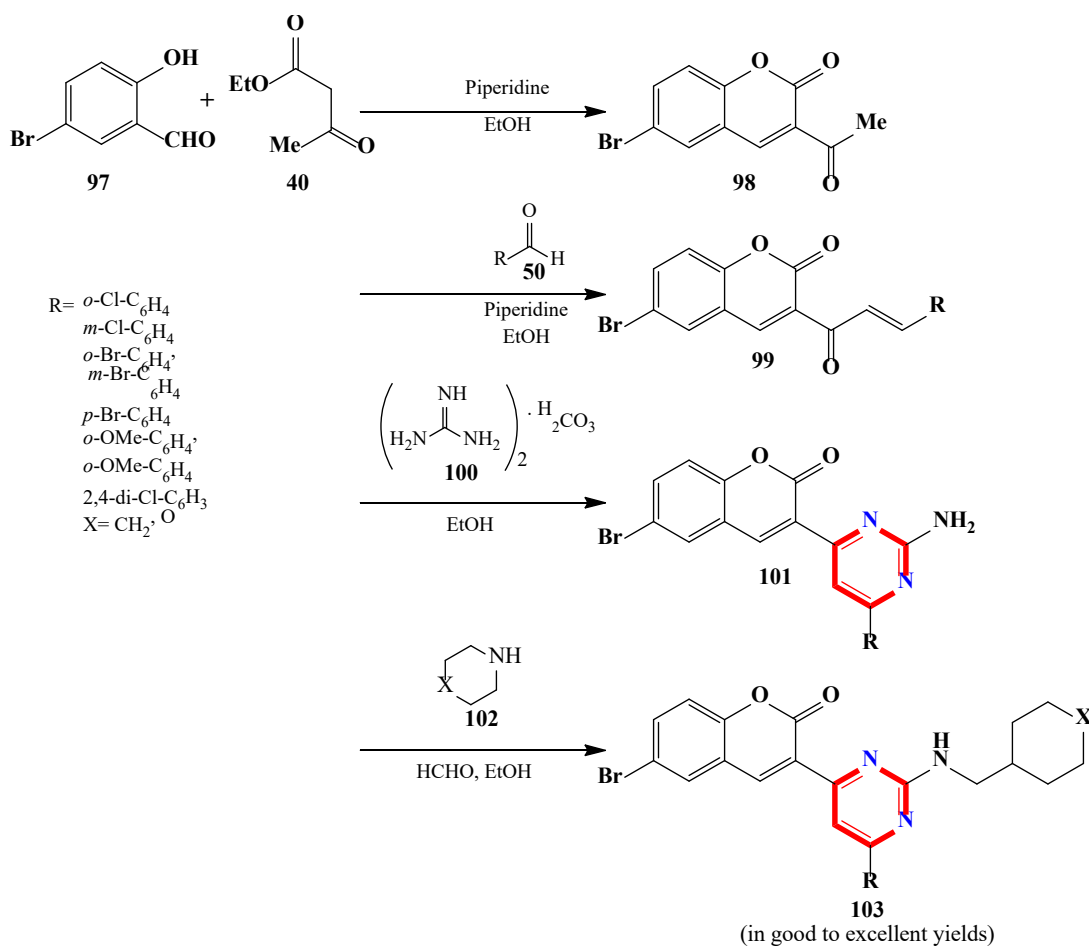
Scheme 29. Reaction. Source: Authors, 2026.

In a separate methodology aimed at heteroaryl pyrimidines, during the same year, Sridhar et al. (2011) introduced a base-promoted one-pot cyclo-condensation involving furan-based ketones **94** and aldehydes **50**, followed by reaction with guanidine hydrochloride **66** to afford compounds **96** in excellent yields (Scheme 30). While the reliance on strong bases (KOH) and ethanolic media excludes this process from pure green protocols, it is nonetheless a powerful and synthetically productive strategy for the assembly of furan-pyrimidine architectures.



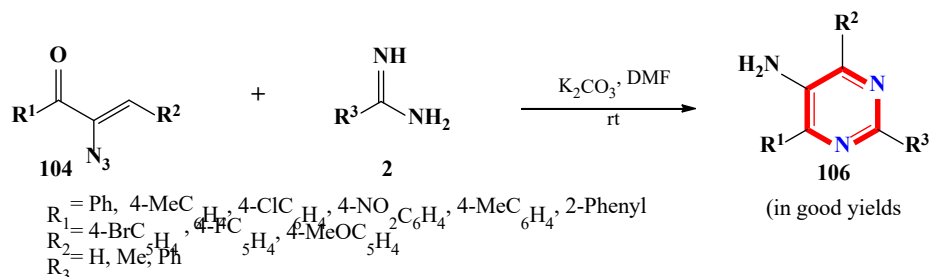
Scheme 30. Reaction. Source: Authors, 2026.

Transitioning to coumarin-fused pyrimidine derivatives, again in 2011, Chaudhary et al. (2011) established a consecutive multi-step base-promoted sequence starting from salicylaldehyde **97** and ethyl acetoacetate **40** to form 3-acetylcoumarin **99**, which eventually reacted with guanidine carbonate **100** and subsequent reagents to yield complex scaffolds **103** (Scheme 31). Although the multi-stage process and the use of piperidine with refluxing ethanol prevent this method from fully meeting green chemistry standards, the protocol remains an exceptionally powerful and effective strategy for producing coumarin-pyrimidine hybrids.



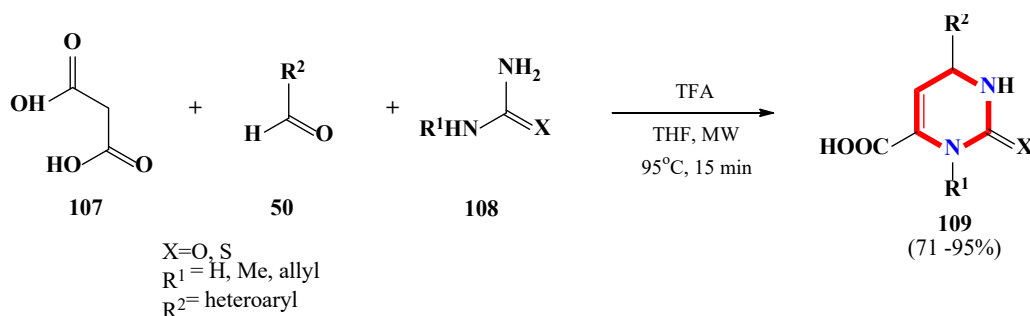
Scheme 31. Reaction. Source: Authors, 2026.

Focusing on the synthesis of amino-substituted pyrimidines, a series of polysubstituted 5-aminopyrimidines **106** were synthesized by Hu et al. (2011) via a base-promoted two-component condensation between  $\alpha$ -azido chalcones **104** and amidines **2** in the presence of  $K_2CO_3$  and DMF at room temperature (Scheme 32). Despite the use of DMF as a solvent, which limits its green chemistry credentials, the reaction is a remarkably effective method due to its mild operating conditions, its ability to generate high yields, and its streamlined one-pot access to diverse 4-aminopyrimidine derivatives.



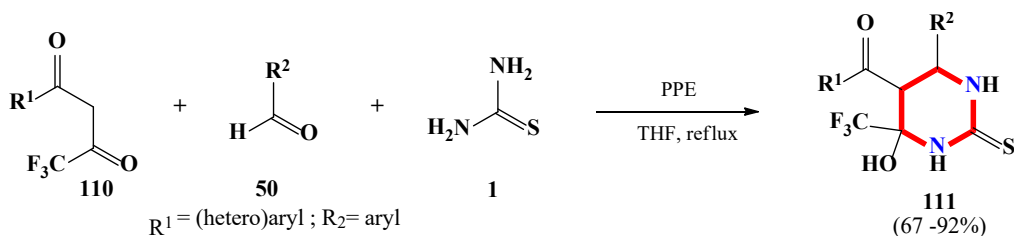
Scheme 32. Reaction. Source: Authors, 2026.

During that period, in an efficient multicomponent synthesis of high-yield carboxylic acid functionalized dihydropyrimidines, Fang et al. (2011) developed an acid-promoted three-component condensation between malonic acid **107**, heteroaryl aldehydes **50**, and (thio)urea derivatives **108** using Trifluoroacetic acid (TFA) as a catalyst under microwave irradiation (Scheme 33). The use of TFA and THF prevents this one-pot method from being strictly classified as green; nevertheless, it remains an exceptionally effective synthesis due to its rapid reaction time and high yields.



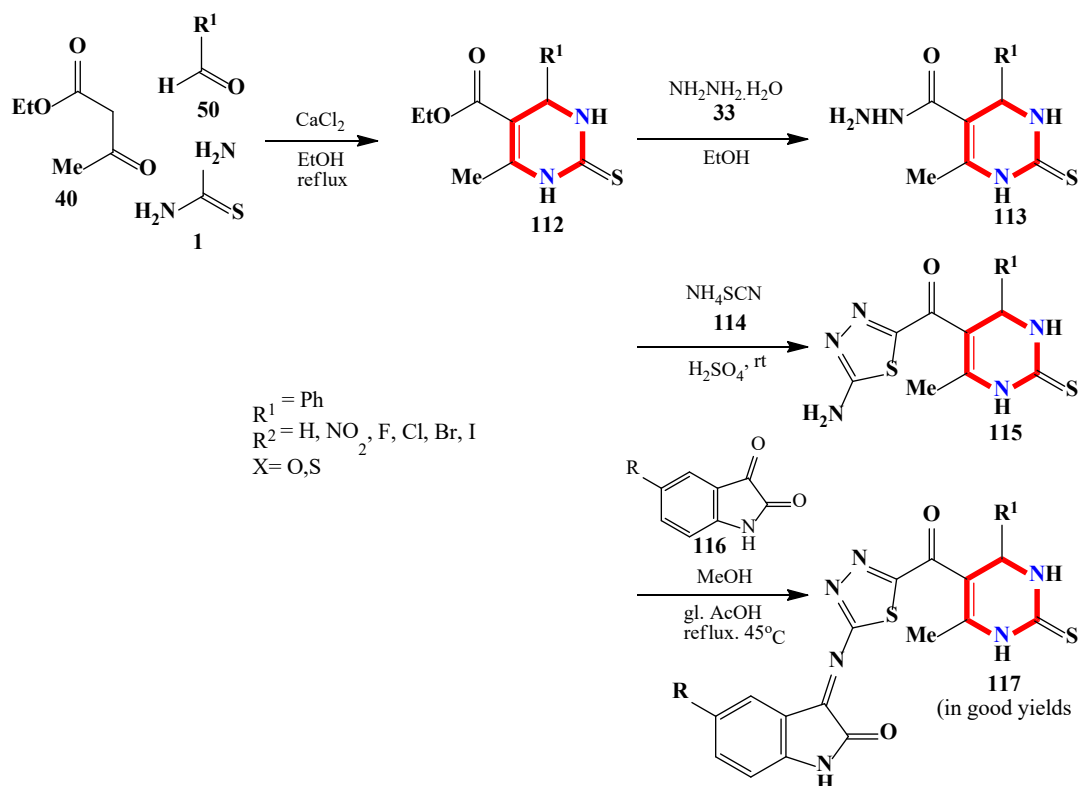
Scheme 33. Reaction. Source: Authors, 2026.

In an innovative Biginelli-type multicomponent condensation, in the same year, Agbaje et al. (2011) utilized an acid-promoted three-component coupling of fluorinated  $\beta$ -diketones **110**, aromatic aldehydes **50**, and (thio)urea **1** in the presence of Polyphosphate ester (PPE) to yield trifluoromethylated dihydropyrimidines **111** (Scheme 34). Although this protocol relies on PPE and refluxing THF, which categorizes it as moderately green, it remains a highly effective synthesis due to its ability to efficiently incorporate specific fluorine-containing groups and deliver excellent yields.



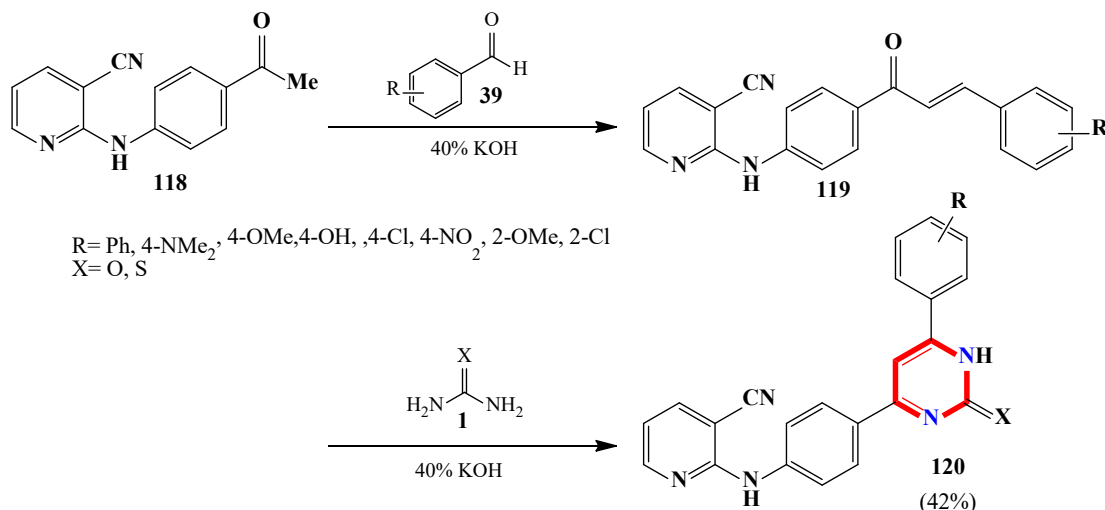
Scheme 34. Reaction. Source: Authors, 2026.

During that period, in an extensive multi-step synthetic strategy, a Lewis acid-promoted sequence was established by Akhaja & Raval (2011), beginning with a Biginelli-type three-component condensation of ethyl acetoacetate **40**, aromatic aldehyde **50**, and (thio)urea **1** using  $\text{CaCl}_2$  to form 2-thioxo-dihydropyrimidines **112**, which was followed by successive functional group transformations, including hydrazinolysis and cyclization, to ultimately append thiadiazole and indole moieties, yielding complex hybrid scaffolds **117** (Scheme 35). Despite this method proceeding in the presence of the safe Lewis acid  $\text{CaCl}_2$ , the reliance on concentrated  $\text{H}_2\text{SO}_4$ , glacial acetic acid, and multiple reflux steps classifies it as a partially green protocol; nevertheless, it remains an exceptionally effective and powerful synthetic approach for the construction of structurally diverse and complex pyrimidine-based conjugates.



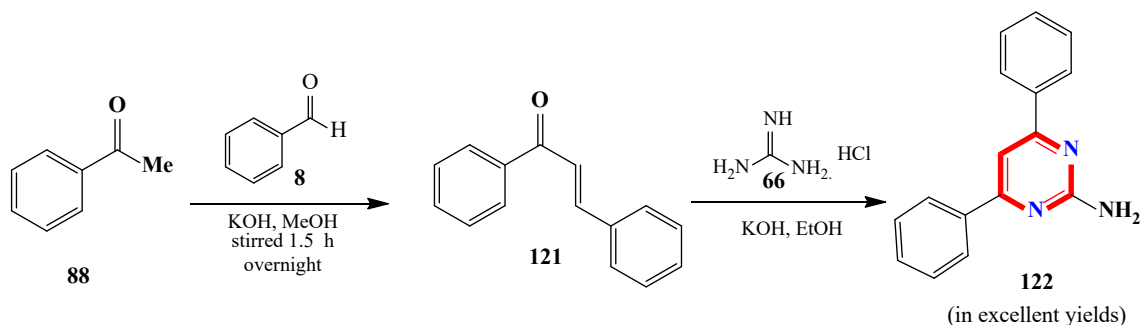
Scheme 35. Reaction. Source: Authors, 2026.

In the following year, building on the construction of more complex architectures, the synthesis of pyrimidine-2-one or pyrimidine-2-thiones **120** was demonstrated by Chintan et al. (2012), via a base-promoted two-step synthetic strategy; in the first stage, an acetyl-substituted anilinopyridine **118** underwent Claisen–Schmidt condensation with aromatic aldehydes **39** in the presence of 40%  $\text{KOH}$  to afford a chalcone intermediate **119**, which was subsequently cyclized with (thio)urea **1** under the same basic conditions (Scheme 36). While the use of strong caustic conditions and traditional reflux excludes this from being a purely green process, it is an exceptionally effective and powerful synthesis for generating highly functionalized heterocyclic hybrids containing both pyridine and pyrimidine motifs.



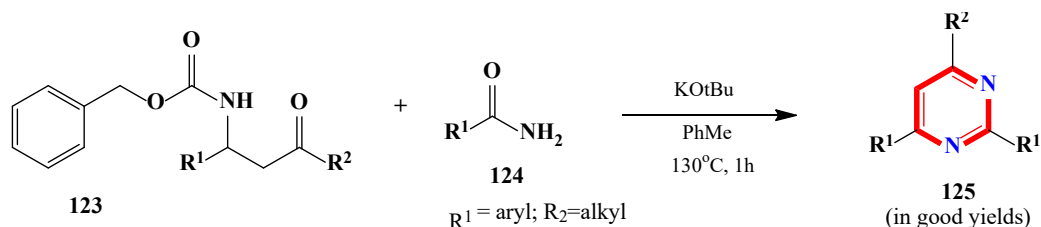
Scheme 37. Reaction. Source: Authors, 2026.

In a classic and streamlined two-step approach to amino-substituted pyrimidines, in the same year, a base-promoted synthetic sequence was utilized by the research group of Himaja et al. (2012), wherein acetophenone **88** and benzaldehyde **8** first underwent Claisen–Schmidt condensation to form chalcone intermediates **121**. These intermediates subsequently underwent a one-pot cyclization with guanidine hydrochloride **66** in the presence of KOH to afford 2-amino-4,6-diphenylpyrimidine **122** (Scheme 37). Exceptionally powerful and effective, this method is highly valued for its operational simplicity and ability to deliver the desired heterocyclic scaffold in excellent yields, although it relies on strong bases (KOH) and methanol/ethanol media, making it only relatively green.



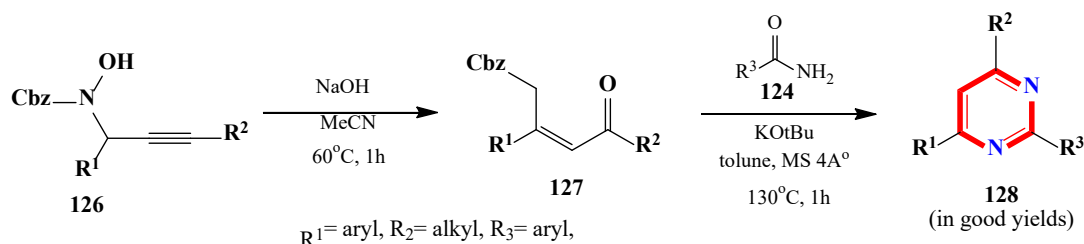
Scheme 37. Reaction. Source: Authors, 2026.

During that period, focusing on a base-promoted transformation, Gayon et al. (2012) reported the synthesis of 2,4,6-trisubstituted pyrimidines **135** via a base-promoted two-component cyclization of  $\beta$ -amido ketones **123** with benzamides **124** (Scheme 38). The use of KOtBu and high temperature (130 °C) categorizes this as a partially green reaction; nevertheless, it stands as a powerful synthetic tool for generating highly functionalized pyrimidine derivatives in good yields.



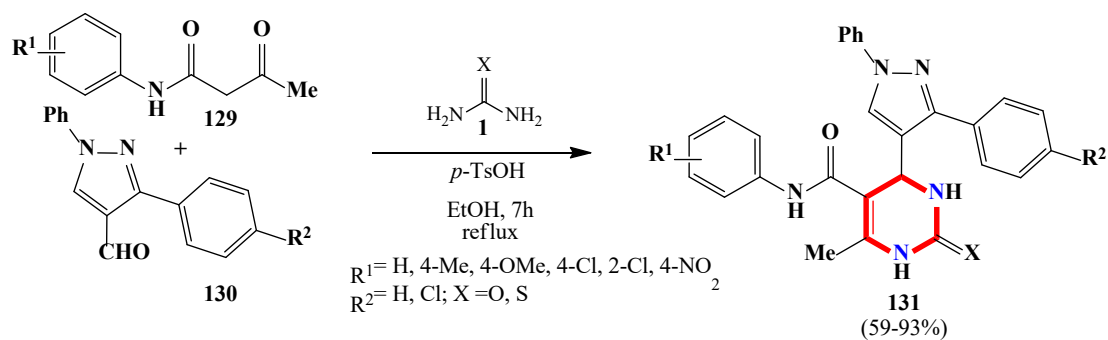
Scheme 38. Reaction. Source: Authors, 2026.

Transitioning to more complex heterocyclic precursors, the same research group further established a base-promoted, two-component, two-step protocol for the synthesis of trisubstituted pyrimidines **128**, involving the initial rearrangement of Cbz-protected propargylic hydroxylamines **126** to  $\beta$ -amino enones **127**, followed by cyclization with amides **124** in the presence of KOtBu at 130 °C (Scheme 39) (Gayon et al., 2012). While the high temperature and use of toluene exclude this process from pure green standards, it is an exceptionally powerful synthesis for accessing highly functionalized pyrimidine scaffolds with excellent structural control.



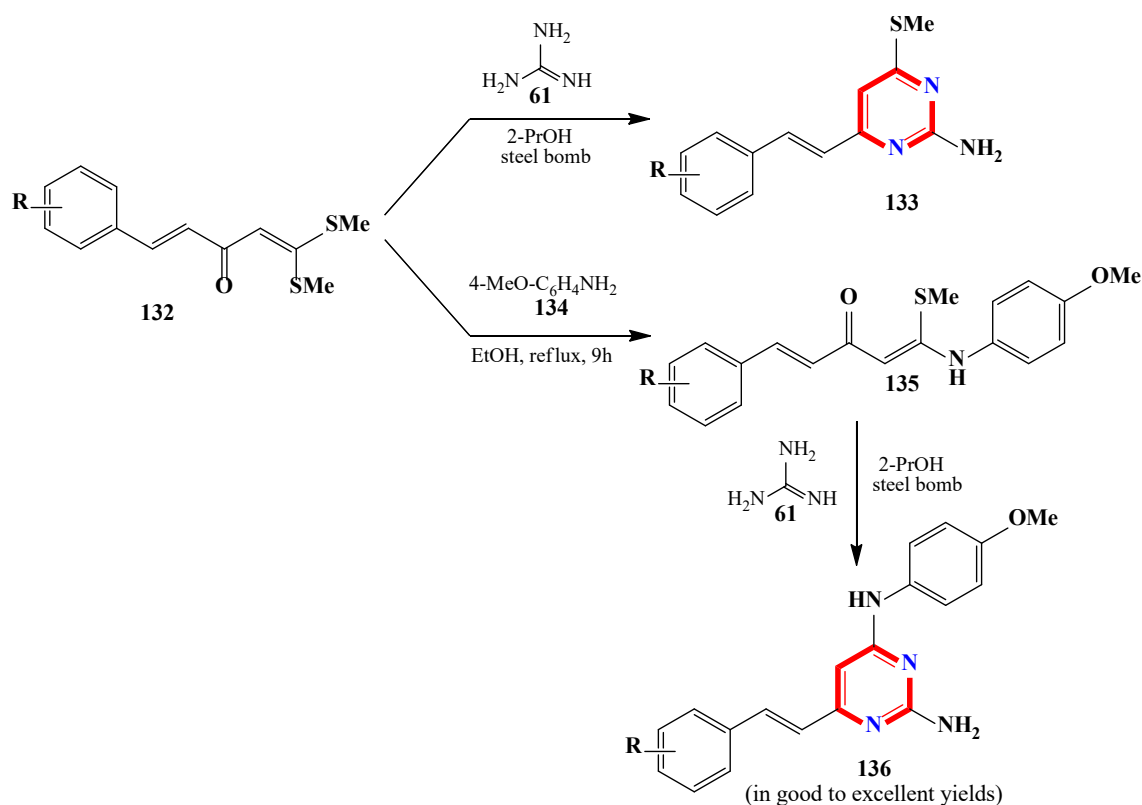
Scheme 39. Reaction. Source: Authors, 2026.

In a specialized approach to constructing pyrazolyl-pyrimidine hybrids, again, in 2012 the research team of Yadlapalli et al. (2012) reported an acid-promoted three-component one-pot condensation involving acetoacetanilide **129**, pyrazole-aldehyde **130**, and thio(urea) **1**. This reaction was carried out in the presence of *p*-TsOH (para-toluenesulfonic acid) as a catalyst in ethanol under reflux for 7 hours, affording the functionalized dihydropyrimidines **131**. (Scheme 40). Although the requirement for prolonged refluxing limits its classification as a strictly green protocol, the method remains a highly effective and synthetically reliable strategy for accessing specific bioactive heterocyclic scaffolds with high efficiency.



Scheme 40. Reaction. Source: Authors, 2026.

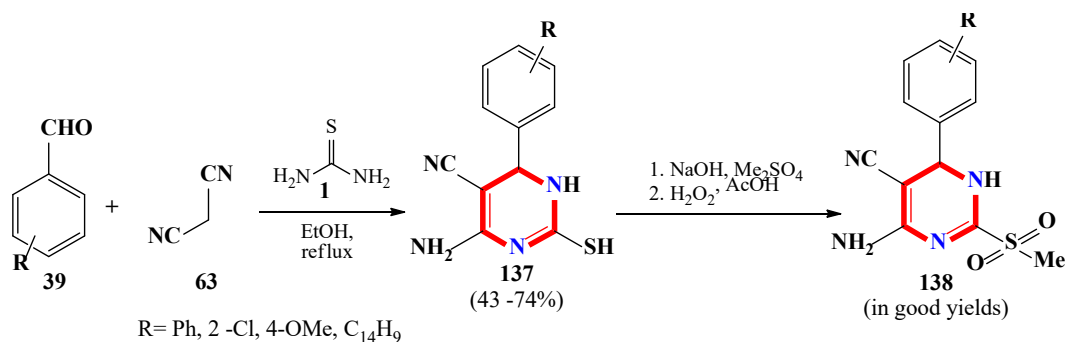
The year after, in a versatile approach to the synthesis of diverse pyrimidine derivatives, Suryawansh et al. (2013) established a strategy utilizing the  $\alpha,\beta$ -unsaturated ketone-based precursor **132** to access multiple pyrimidine architectures. In the first pathway, a base-promoted condensation with guanidine **61** was conducted in 2-propanol using steel bomb technology, yielding 2-amino-4-methylthio pyrimidines **133** with high efficiency. The second pathway involved an initial reaction with a primary aromatic amine in refluxing ethanol, followed by cyclization with guanidine **61** to produce 4-amino-aryl substituted pyrimidine scaffolds **136** (Scheme 41).



Scheme 41. Reaction. Source: Authors, 2026.

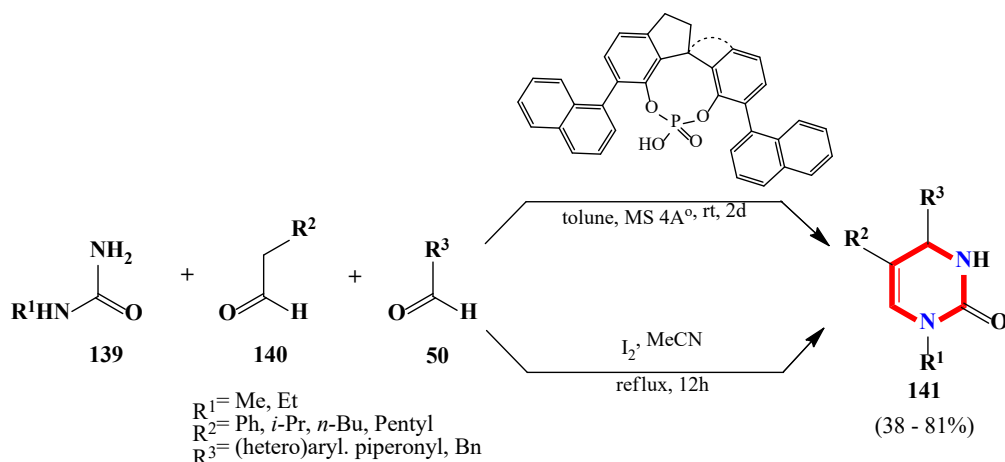
While the requirement for high temperature and pressure prevents this protocol from being strictly categorized as green, it remains an exceptionally powerful and effective synthesis for generating structural complexity and diversity from a single precursor.

In a strategic two-step protocol for constructing functionalized pyrimidines, in the same year, Ghodasara et al. (2013) systematically developed an efficient base-promoted three-component cyclization of aromatic aldehydes **39**, malononitrile **63**, and (thio)urea **1** in refluxing ethanol to form the thiol intermediate **137**. Subsequently, the synthesis involved *S*-alkylation with  $\text{Me}_2\text{SO}_4$  followed by an oxidation step using  $\text{H}_2\text{O}_2/\text{AcOH}$  to afford the corresponding methylsulfonyl pyrimidines **138** (Scheme 42). Although this sequence provides a powerful and effective route to access diverse sulfone-functionalized heterocycles with good yields, the use of NaOH,  $\text{Me}_2\text{SO}_4$ , AcOH, and reflux conditions prevents it from being strictly classified as a green chemistry protocol.



Scheme 42. Reaction. Source: Authors, 2026.

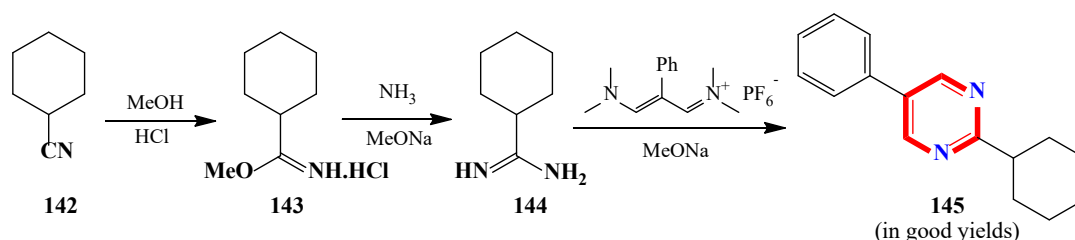
In a highly specialized advancement for constructing diverse pyrimidines, again, in 2013 the research team led by Qu reported an efficient three-component condensation between urea derivative **139**, aliphatic aldehydes **140**, and aromatic or heteroaromatic aldehydes **50** to afford substituted pyrimidines **141** (Scheme 43) (Qu et al., 2013).



Scheme 43. Reaction. Source: Authors, 2026.

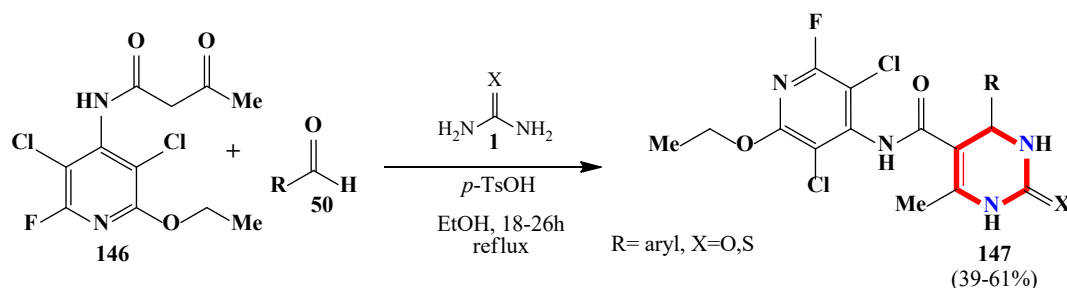
This was achieved under two distinct conditions: either using a bulky phosphoric acid catalyst in toluene at room temperature for 2 days, or utilizing iodine in acetonitrile under reflux for 12 h. This methodology is considered semi-green due to its metal-free catalysis despite requiring hazardous solvents and long reflux times; however, it remains an exceptionally powerful and effective tool due to its simple, one-pot execution.

During that period, in a regioselective multi-step strategy, Frutos et al. (2013) synthesized 2,5-disubstituted pyrimidines **145** starting from cyclohexanecarbonitrile **142** via imidate **143** and amidine **144** intermediates, followed by cyclization with a vinamidinium salt to afford the target products in good yields **145** (Scheme 44). Although the method avoids metal catalysts and uses relatively mild bases, it is considered semi-green due to its multi-step nature and use of corrosive HCl and specialized reagents; nevertheless, it remains highly effective for constructing diverse pyrimidine frameworks with excellent regioselectivity.



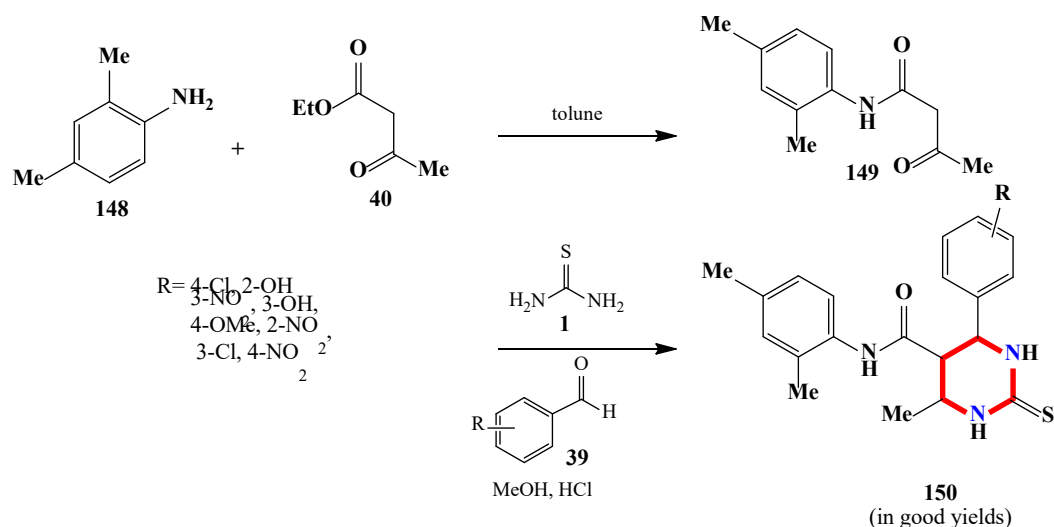
Scheme 44. Reaction. Source: Authors, 2026.

In a strategic construction of pyridine-functionalized scaffolds, Elumalai et al. (2013) reported a *p*-TsOH-mediated three-component condensation to yield dihydropyrimidines using  $\beta$ -ketoamide **146**, various aryl aldehydes **50**, and (thio)urea **1** (Scheme 45). Semi-green for its metal-free organic acid catalysis, this method requires extended reflux in volatile solvents but remains an exceptionally powerful and effective tool for assembling complex multi-ring bioactive architectures in a single step.



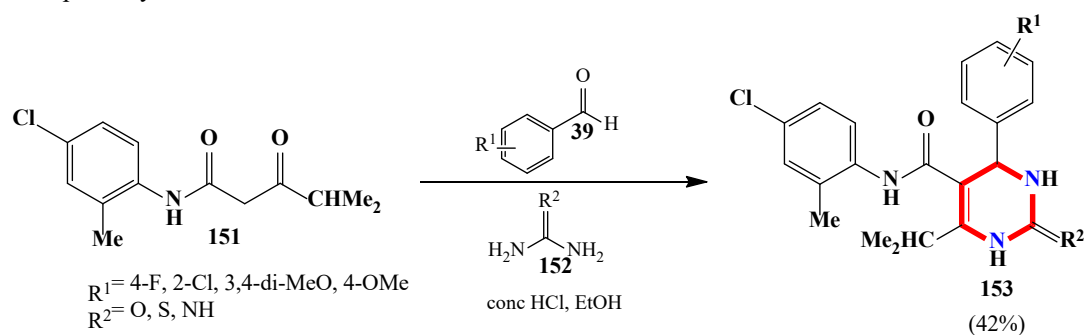
Scheme 45. Reaction. Source: Authors, 2026.

In 2014, utilizing a stepwise approach, an acid-promoted three-component cyclization was established by Godhani et al. (2014) for the construction of highly functionalized dihydropyrimidinethiones via a condensation of 2,4-dimethylaniline **148** with ethyl acetoacetate **40** in toluene to form the  $\beta$ -ketoamide intermediate **149**, which subsequently underwent cyclization with various aryl aldehydes **39** and (thio)urea **1** in MeOH/HCl to afford the target products. (Scheme 46). As an exceptionally powerful and effective tool, this methodology remains highly valued for its ability to regioselectively assemble complex bioactive architectures in good yields, although it is classified as moderately sustainable due to the use of corrosive HCl and volatile toluene.



Scheme 46. Reaction. Source: Authors, 2026.

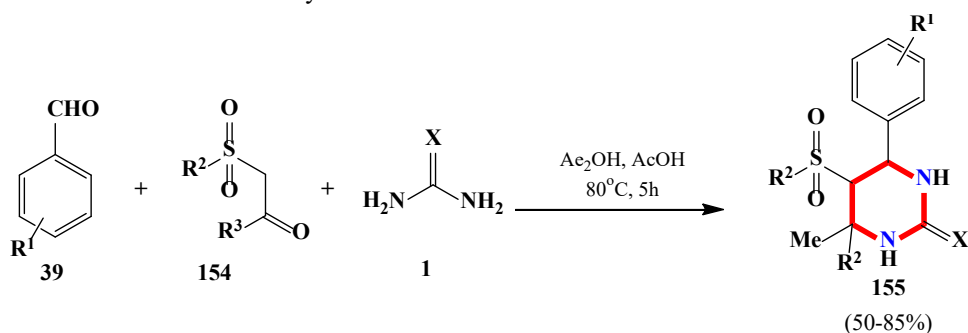
Within the same year, in a practical approach to Biginelli-type cyclocondensation, Hardik et al. (2015) established a route for the synthesis of highly substituted dihydropyrimidines **153** via a one-pot, three-component reaction using a chloro-substituted  $\beta$ -ketoamide **151**, various aromatic aldehydes **39**, and (thio)urea, or guanidine derivatives **152** in the presence of concentrated HCl and ethanol (Scheme 47). The use of corrosive mineral acid and volatile organic solvents prevents this methodology from fully meeting green standards, yet it remains a simple and powerful method for constructing pyrimidines from readily available precursors via a metal-free synthetic pathway.



Scheme 47. Reaction. Source: Authors, 2026.

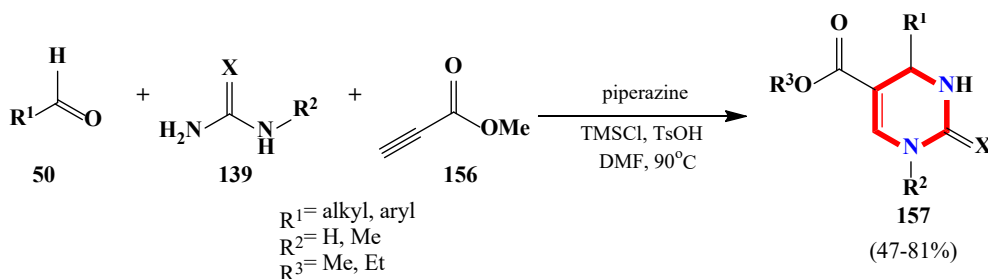
In a specialized application of multicomponent cyclization, in 2014, Timoshenko et al. (2014) developed a one-step three-component synthetic route to synthesize sulfone-substituted dihydropyrimidines **155** via the condensation of aromatic aldehydes **39**,  $\beta$ -ketosulfones **154**, and (thio)urea derivatives **1** in the presence of acetic anhydride (Ac<sub>2</sub>O) and acetic acid (AcOH) at 80 °C (Scheme 48). This methodology is regarded as somewhat green, as it avoids toxic metal catalysts, but falls short of ideal green criteria due to the use of corrosive acids and

prolonged heating. Nevertheless, it remains an effective approach for incorporating sulfonyl groups into bioactive heterocyclic scaffolds with consistent yields.



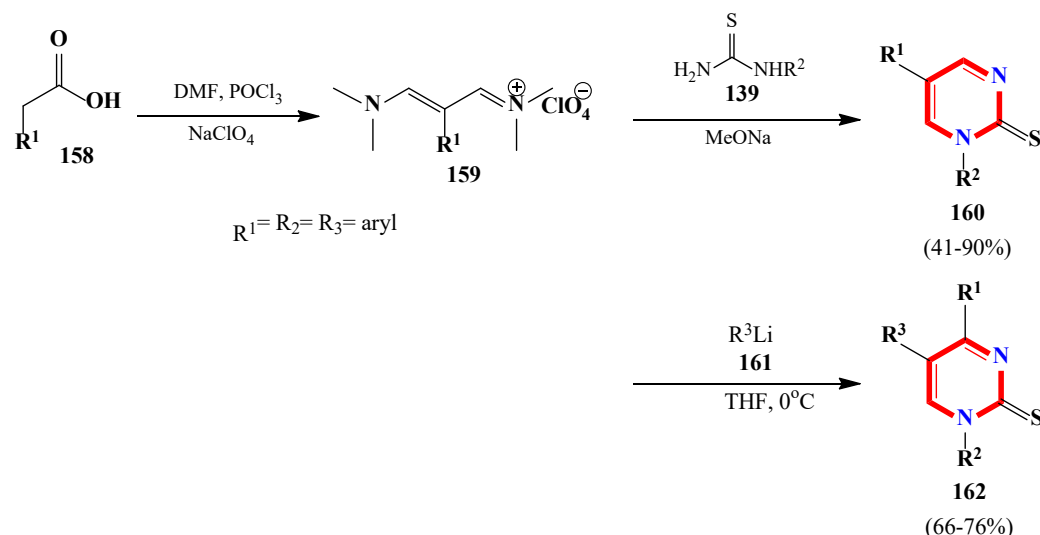
Scheme 48. Reaction. Source: Authors, 2026.

During the same year, in an innovative modification of the multi-component Biginelli-type cyclization, the research team of Wan et al. (2014) established a one-pot three-component approach to synthesize functionalized dihydropyrimidinones **157** using aldehydes **40**, (thio)urea derivatives **139**, and alkynoates **156** in the presence of piperazine, TMSCl, and TsOH in DMF at  $90^\circ C$  (Scheme 49). A powerful one-pot approach, this methodology remains highly effective for constructing structurally diverse pyrimidines, although it is considered semi-green due to the use of hazardous DMF and heating at  $90^\circ C$ , despite employing an organocatalytic base (piperazine) and metal-free acid promoters.



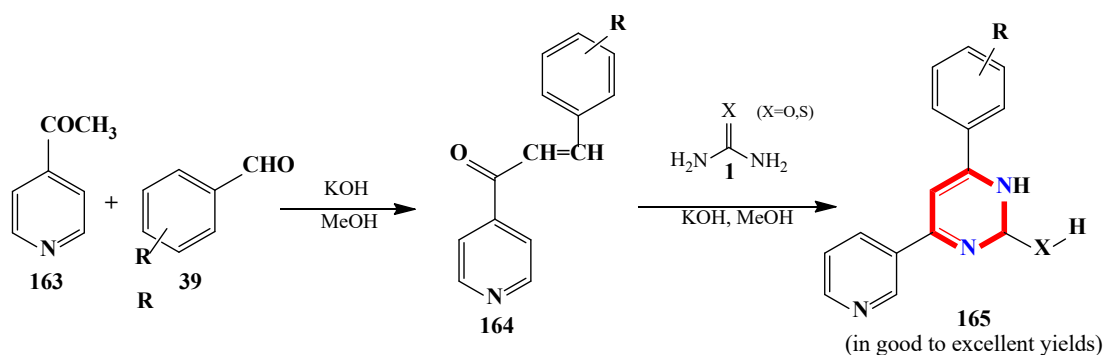
Scheme 49. Reaction. Source: Authors, 2026.

In a comprehensive multi-step strategy, Sośnicki et al. (2014) established an efficient route for the construction of trisubstituted pyrimidine-2-thiones **16** via a base-promoted two-component cyclization of vinamidinium salts **159** with (thio)urea derivatives **139**, followed by an organometallic-mediated addition using aryl lithium reagents **15** (Scheme 50). This transformation is considered partially sustainable for its metal-free cyclization step, despite the use of hazardous  $POCl_3$  and reactive alkyl lithium **161** in THF; however, it remains an exceptionally powerful and effective tool for constructing highly regioselective and complex pyrimidine scaffolds.



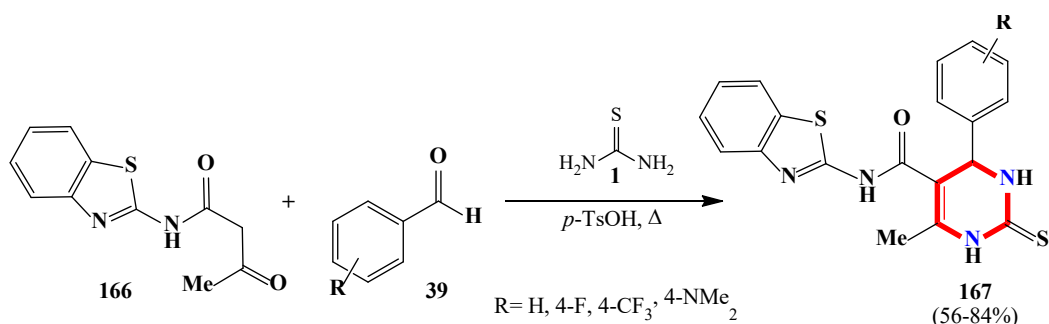
Scheme 50. Reaction. Source: Authors, 2026.

In a divergent synthetic approach, in the same year, the research team led by Kachroo et al. (2014) reported the construction of pyridine-substituted pyrimidines **165** via a base-promoted condensation to form chalcone **164**, followed by a base-promoted two-component cyclization with (thio)urea **1** (Scheme 51). Although considered semi-green for employing metal-free catalysis and methanol, this methodology deviates from ideal standards due to the use of strong KOH and multiple stages; nevertheless, it remains an exceptionally powerful and effective tool for the low-cost synthesis of pyrimidine scaffolds.



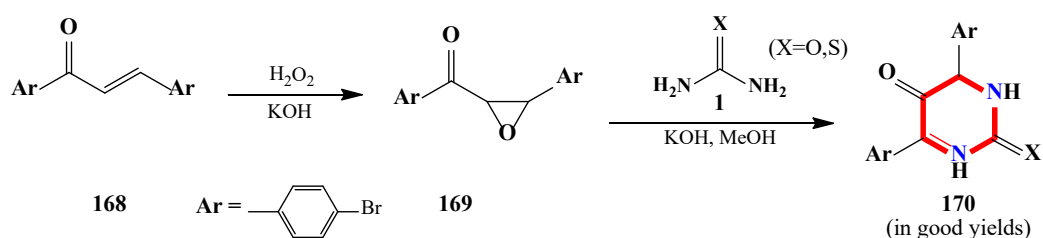
Scheme 51. Reaction. Source: Authors, 2026.

In a specialized three-component Biginelli-type cyclization, in 2015, the synthesis of novel benzothiazolyl pyrimidine-5-carboxamide derivatives **167** was described by the Chikhale et al. (2015) research group through a highly effective, structurally versatile, and robust acid-catalyzed one-pot multicomponent Biginelli-type reaction of benzothiazolyl oxobutanamide **166**, substituted aryl aldehydes **39**, and (thio)urea **1** (Scheme 52). As a highly efficient and robust one-pot strategy, this method uses organic acid catalysis but requires external heating and non-aqueous conditions, yet it remains excellent for assembling complex multi-heterocyclic bioactive frameworks.



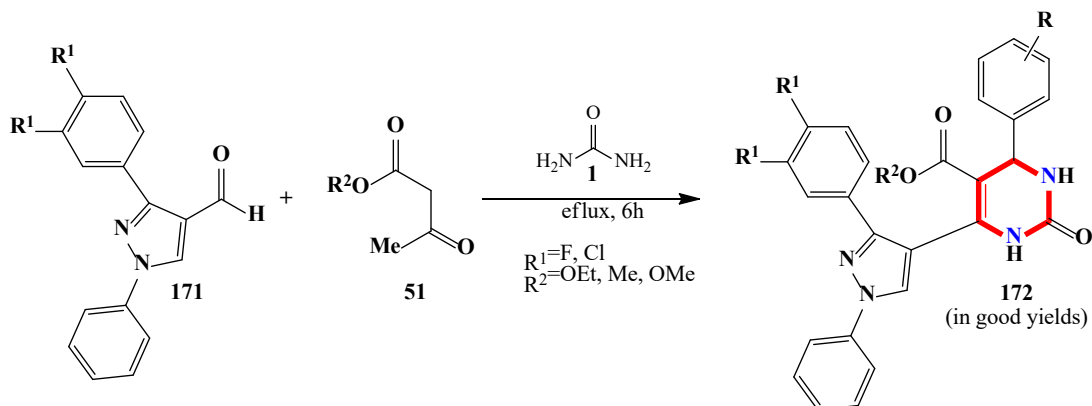
Scheme 52. Reaction. Source: Authors, 2026.

Within the same year, in a divergent synthetic route, El-Sayed et al. (2015) developed a strategy to construct aryl-substituted pyrimidines through an epoxide intermediate **169**. The process began with the  $H_2O_2/KOH$ -mediated epoxidation of chalcone-like precursors **168**, followed by a base-promoted two-component cyclization with (thio)urea **1** in  $MeOH-KOH$  (Scheme 53). This Multi-step oxidative sequence and the use of corrosive  $KOH$  limit this methodology from fully meeting green standards, yet it remains an exceptionally powerful and effective tool for synthesizing pyrimidines using metal-free catalysis and relatively benign solvents like methanol.



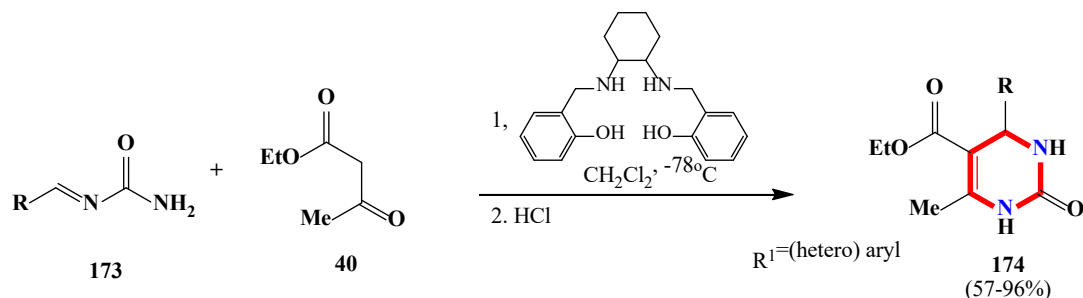
Scheme 53. Reaction. Source: Authors, 2026.

In a strategic assembly of multi-heterocyclic scaffolds **172**, Viveka et al. (2015) reported the synthesis of pyrazole-linked dihydropyrimidines **39** via a one-pot, three-component cyclocondensation between functionalized pyrazole-aldehydes **171**,  $\beta$ -keto esters **51**, and urea **1** under refluxing conditions for 6 hours (Scheme 54). While this metal-free protocol efficiently constructs complex motifs, it is only semi-green due to high energy requirements due to prolonged reflux and the use of volatile organic solvents. Nonetheless, its reliability and high yields make it a simple and powerful tool for structural diversity.



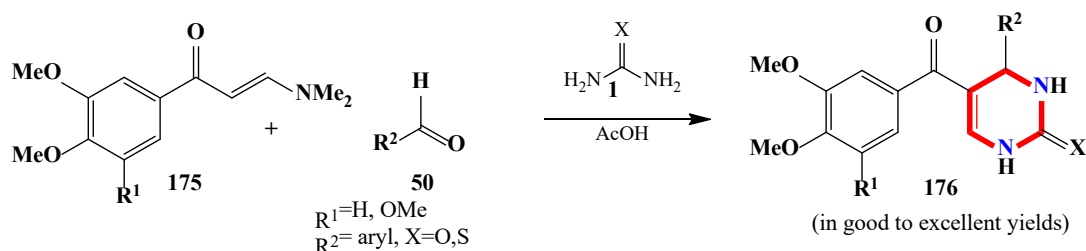
Scheme 54. Reaction. Source: Authors, 2026.

In 2016, applying advanced catalytic principles, Lillo et al. (2016) established an efficient route for the synthesis of functionalized dihydropyrimidinones **174** via a protocol promoted by both Lewis acid and organocatalyst-promoted condensation between *N*-acyliminium precursors **173** and ethyl acetoacetate **40** at -78 °C (Scheme 55). Although its metal-free approach and good atom economy make it semi-green, the need for sub-zero cooling and CH<sub>2</sub>Cl<sub>2</sub> use prevent it from being fully green. Still, the protocol is highly effective for synthesizing complex, enantiopure pyrimidines.



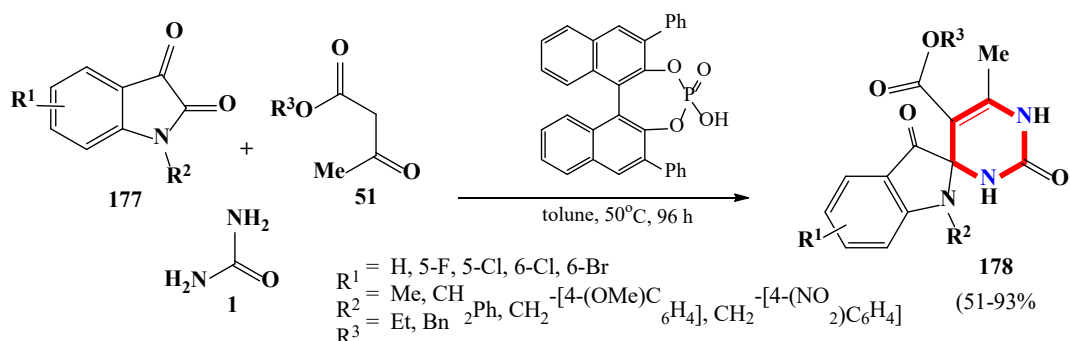
Scheme 55. Reaction. Source: Authors, 2026.

During that period, building on metal-free multicomponent strategies, Bhat et al. (2016) reported the synthesis of 6-unsubstituted DHPMs **176** via a one-pot Biginelli-type reaction using enaminones **175**, aromatic aldehydes **50**, and (thio)urea **1**. The reaction was promoted by acetic acid (AcOH), a simple, inexpensive, and relatively safe reagent, under reflux for 3 h, avoiding toxic heavy-metal catalysts and complex solvents (Scheme 56). As a result, this protocol is metal catalyst-free and exhibits several features of green chemistry.



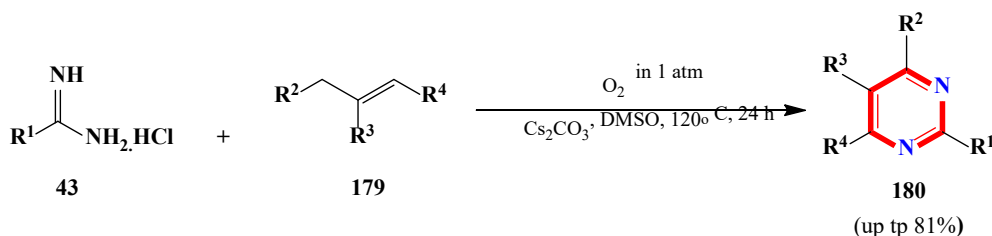
Scheme 56. Reaction. Source: Authors, 2026.

In a sophisticated enantioselective approach, an organocatalyst-promoted three-component condensation was reported by the research team of Stocchi et al. (2016) for the synthesis of complex spiro-oxindole dihydropyrimidinones **178**, using isatins **177**, urea **1**, and β-keto esters **51** in the presence of a chiral phosphoric acid in toluene at 50 °C (Scheme 57). This metal-free, semi-green protocol offers high enantioselectivity and atom economy, enabling precise construction of pyrimidine architectures, although it requires 96 h and hazardous solvents.



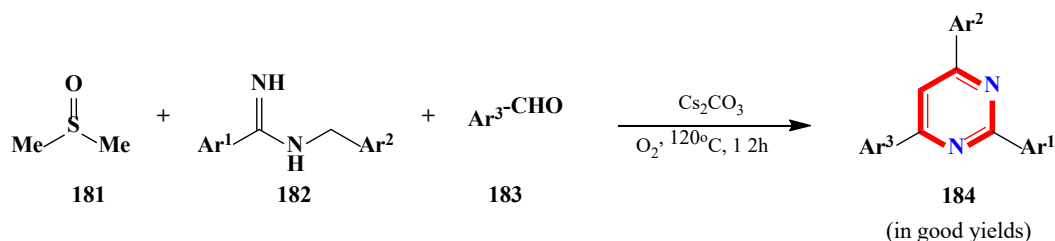
Scheme 57. Reaction. Source: Authors, 2026.

In the same year, under a distinct synthetic framework, Guo et al. (2016) reported a versatile protocol for the construction of multi-substituted pyrimidines **180** via a base-promoted two-component oxidative cyclization utilizing amidine hydrochlorides **43** and substituted alkenes **179** in the presence of  $\text{Cs}_2\text{CO}_3$  and DMF (Scheme 58). While using molecular oxygen as a clean oxidant, this method's high heat and polar aprotic solvent limit its green credentials, yet it effectively assembles diverse, fully aromatized pyrimidines from simple precursors



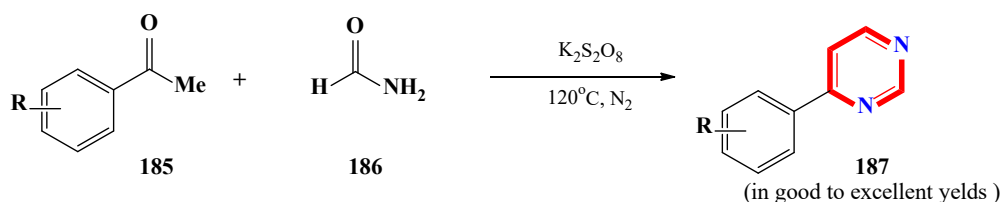
Scheme 58. Reaction. Source: Authors, 2026.

A year later, in a significant development for aerobic oxidative chemistry, Yuan et al. (2017) reported a base-promoted three-component cyclization to synthesize 2,4,6-trisubstituted pyrimidines **184** using DMSO **181**, amidines **182**, and aromatic aldehydes **183** in the presence of  $\text{Cs}_2\text{CO}_3$  at  $120^\circ\text{C}$  (Scheme 59). Avoiding heavy metal catalysts, this method uses molecular oxygen and DMSO, which, along with the high-temperature requirement, make it only moderately green; nevertheless, it remains a highly effective tool for building pyrimidine scaffolds from simple starting materials.



Scheme 59. Reaction. Source: Authors, 2026.

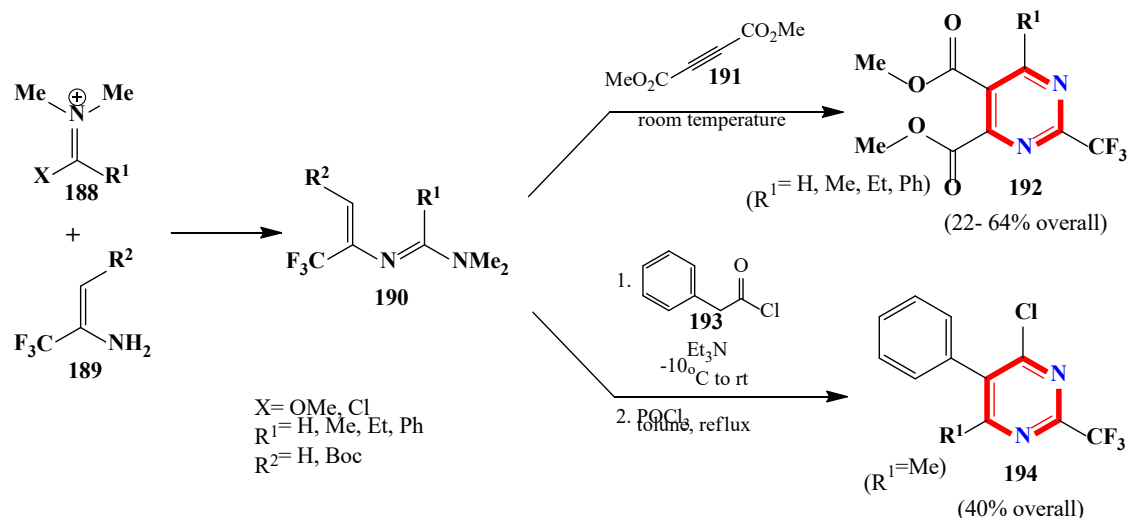
In the same year, shifting the focus toward innovative methine-source utilization, Jadah & Singh (2017) developed an oxidative annulation strategy to synthesize 4-arylpyrimidines **187** via the activation of acetophenone–formamide conjugates **185**, **186** (Scheme 60) in the presence of  $\text{K}_2\text{S}_2\text{O}_8$ . Non-green solvents like DMSO and prolonged reaction times render these reactions only partially green, despite using molecular nitrogen and  $\text{K}_2\text{S}_2\text{O}_8$  as oxidants instead of toxic metals and requiring high energy input. Nevertheless, they remain a remarkably efficient and high-impact strategy for the rapid assembly of mono-substituted pyrimidine scaffolds.



Scheme 60. Reaction. Source: Authors, 2026.

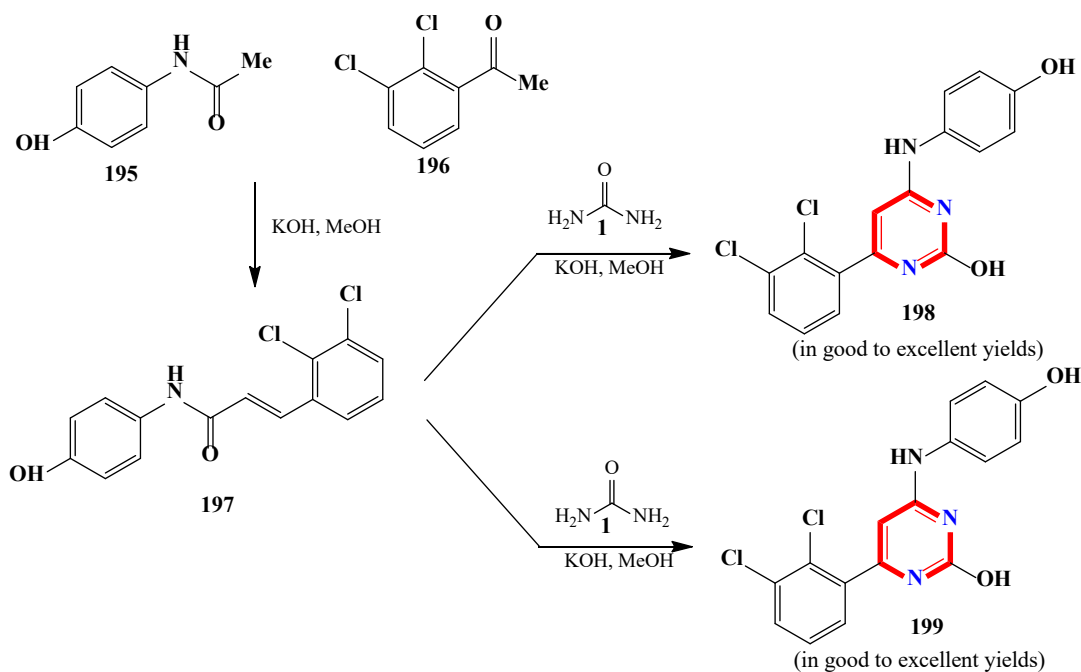
In 2018, for the synthesis of fluorinated heterocycles, the investigation by Medina-Mercado et al. (2018) focused on trifluoromethyl-substituted pyrimidines **192**, **194** using an intermediate **190** reacting with DMAD at room

temperature or via base-promoted condensation followed by reflux with POCl<sub>3</sub> in toluene (Scheme 61). This route is considered partially eco-friendly for its room-temperature stages; however, it deviates from ideal benchmarks due to the use of POCl<sub>3</sub> and toluene. It remains an exceptionally effective tool for accessing specialized fluorinated pyrimidine frameworks.



Scheme 61. Reaction. Source: Authors, 2026.

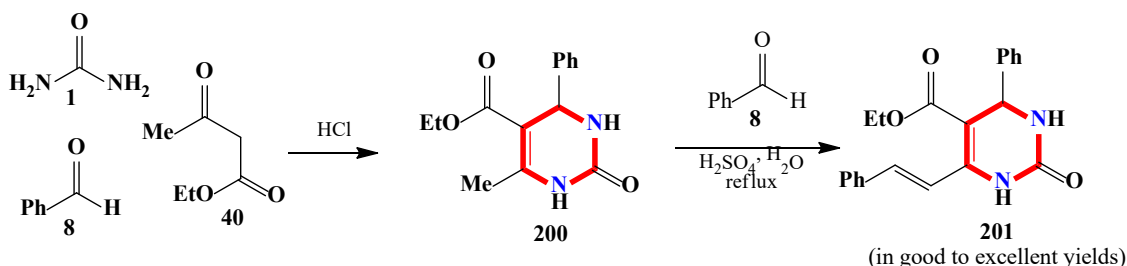
During the same year, a multi-step base-promoted three-component protocol for the synthesis of hydroxy-pyrimidine and thiol-substituted pyrimidine was reported by Zaied et al. (2018). Initially, a condensation reaction between compounds **195** and **196** was performed using KOH in MeOH to form the intermediate chalcone-like structure **197**. Subsequently, this intermediate was reacted separately with (thio)urea **1** under basic conditions (KOH-MeOH) to yield the final pyrimidine products **198**, **199** (Scheme 62).



Scheme 62. Reaction. Source: Authors, 2026.

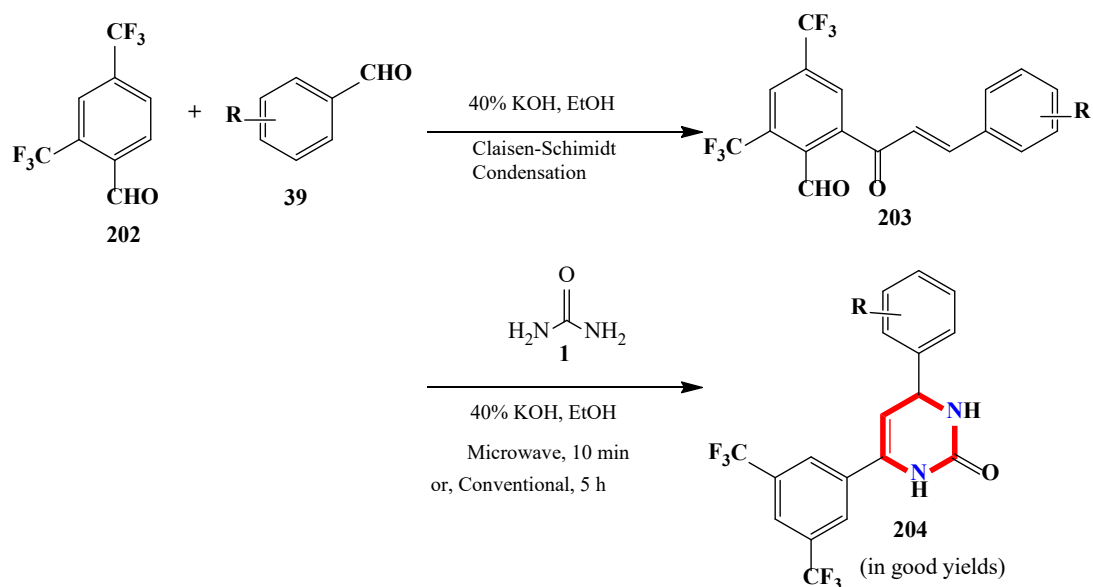
The use of strong KOH and multiple stages slightly limits the green profile of this eco-compatible protocol, which employs biodegradable solvents and avoids metal catalysts; nevertheless, it remains an effective tool for low-cost access to highly functionalized pyrimidine architectures.

The next year, in a systematic sequential protocol, Shehab et al. (2019) demonstrated an elegant route for the synthesis of styryl-substituted dihydropyrimidinones **201** via a two-step three-component acid-promoted Biginelli condensation involving urea **1**, benzaldehyde **8**, and ethyl acetoacetate **40** in the presence of HCl. In the subsequent stage, the resulting intermediate underwent a second condensation with an additional equivalent of benzaldehyde, mediated by H<sub>2</sub>SO<sub>4</sub> in water under reflux to yield the target styryl derivatives (Scheme 63). A highly efficient and robust strategy, this methodology avoids toxic heavy metals but relies on corrosive acids and high heat, yet effectively converts simple precursors into pyrimidine scaffolds.



Scheme 63. Reaction. Source: Authors, 2026.

Within the same year, in a sophisticated divergent approach, the research team led by Vora & Vyas (2019) reported the construction of trifluoromethylated pyrimidine-based scaffolds **204** via a base-promoted sequence that initiated with a two-component Claisen-Schmidt condensation between functionalized benzaldehydes **202** and aromatic aldehydes **39**, followed by a cyclization with urea **1** in EtOH (Scheme 64).

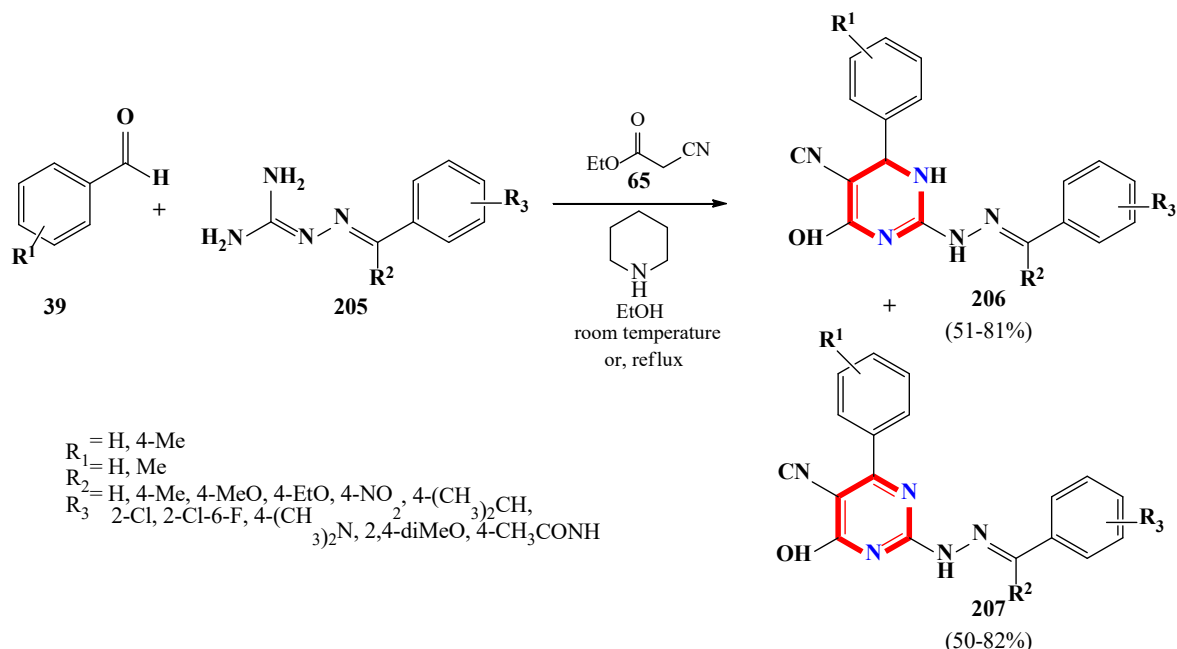


Scheme 64. Reaction. Source: Authors, 2026.

This multi-step protocol is considered partially green for offering a transition-metal-free pathway and utilizing efficient microwave-assisted heating; however, it deviates from ideal standards due to the use of concentrated 40% KOH and the prolonged 5-hour duration required for conventional heating.

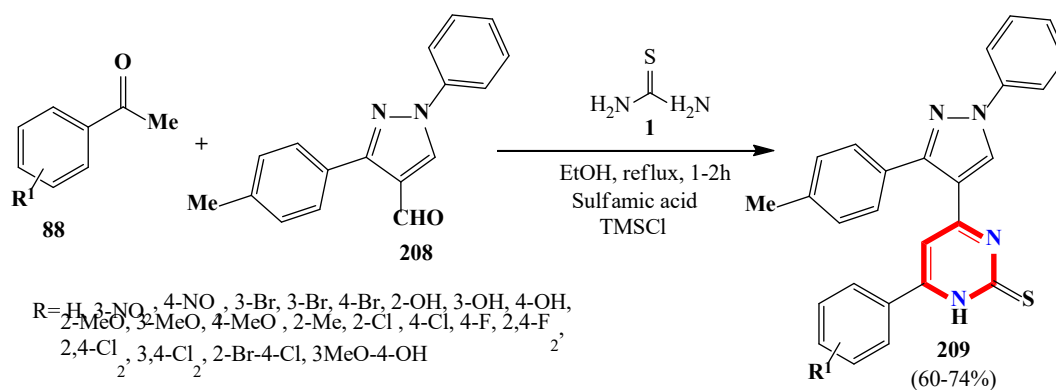
A year later, in a versatile multicomponent strategy, Yavuz et al. (2020) reported the construction of substituted pyrimidines **206** (51–81%) and **207** (50–82%) via a base-promoted three-component cyclization via aromatic aldehydes **39**, aminoguanidine derivatives **205**, and ethyl cyanoacetate **40** in the presence of piperidine within an ethanolic medium (Scheme 65). The protocol is moderately green, utilizing a bio-renewable solvent (EtOH) and

mild conditions, though limited by the use of organic bases and occasional heating or reflux. Nevertheless, it remains an efficient approach for rapidly generating diverse, highly functionalized heterocyclic architectures.



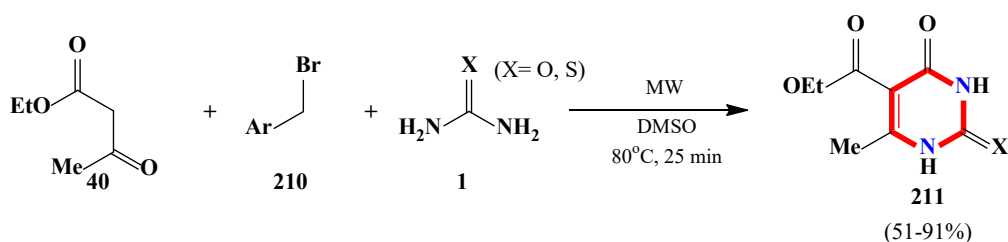
Scheme 65. Reaction. Source: Authors, 2026.

In an efficient three-component assembly, in the same year, Desai et al. (2020) reported the synthesis of pyrazole-linked dihydropyrimidinethiones **209** via an acid-promoted one-pot cyclocondensation of substituted acetophenones **88**, pyrazole-aldehydes **208**, and (thio)urea **1** using sulfamic acid and TMSCl in refluxing ethanol (Scheme 66). This protocol is considered moderately green for employing a reusable solid acid catalyst and biodegradable solvent, although it deviates from ideal standards due to the requirement for external thermal energy and the use of TMSCl. Nevertheless, it remains an effective tool for the rapid construction of diverse pyrimidines in a single operation.



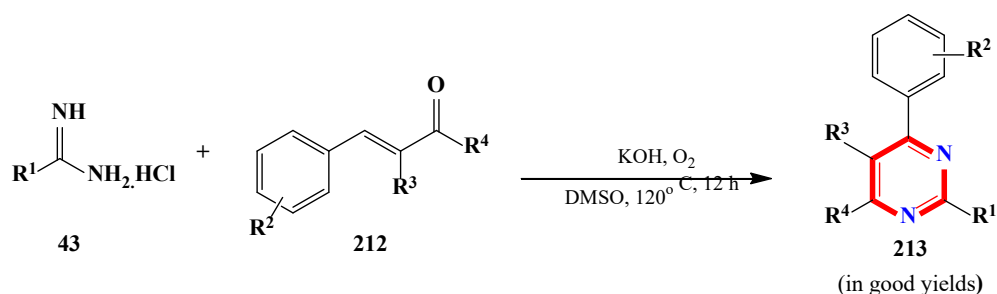
Scheme 66. Reaction. Source: Authors, 2026.

In a highly efficient three-component assembly, Malik et al. (2020) reported the construction of functionalized dihydropyrimidinones/thiones **73** via a base-promoted multicomponent reaction involving the cyclocondensation of ethyl acetoacetate **40**, aryl bromides **210**, and (thio)urea **1** in DMSO (Scheme 67). Due to the 80 °C thermal requirement and the use of aryl bromide precursors, this methodology is not fully green; nevertheless, it remains a highly efficient and practical approach for the rapid, energy-saving synthesis of pyrimidine scaffolds.



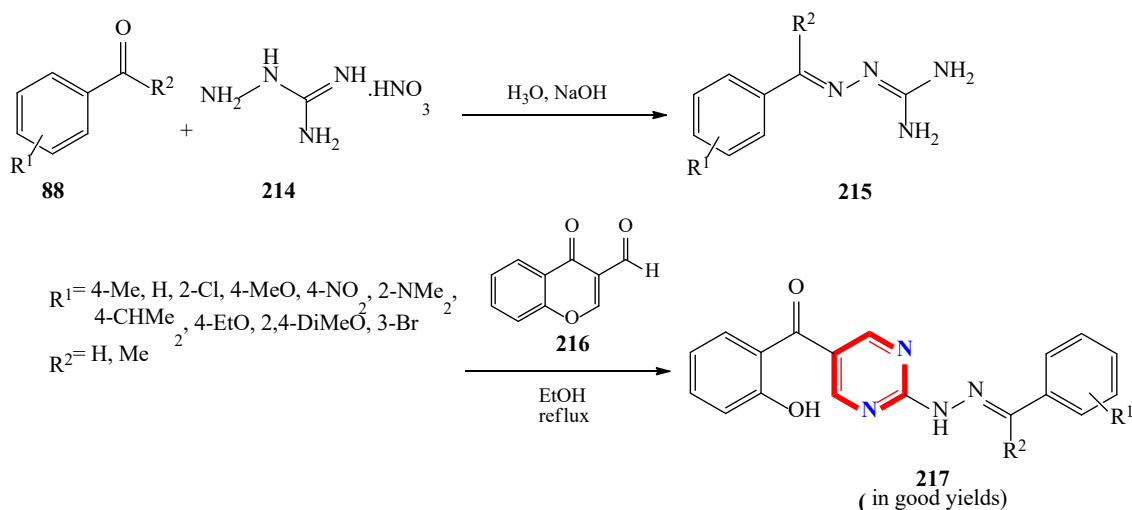
Scheme 67. Reaction. Source: Authors, 2026.

During that period, building upon previously reported oxidative cyclization strategies, the methodology established by Yu et al. (2020) describes a direct base-promoted two-component oxidative transformation of amidine hydrochlorides **43** and chalcones **212** to yield aryl-substituted pyrimidines **213** in good yields (Scheme 68). Classified as moderately green for using molecular oxygen as a clean oxidant, this protocol requires high temperature and KOH in DMSO, yet remains a highly efficient method for constructing pyrimidines.



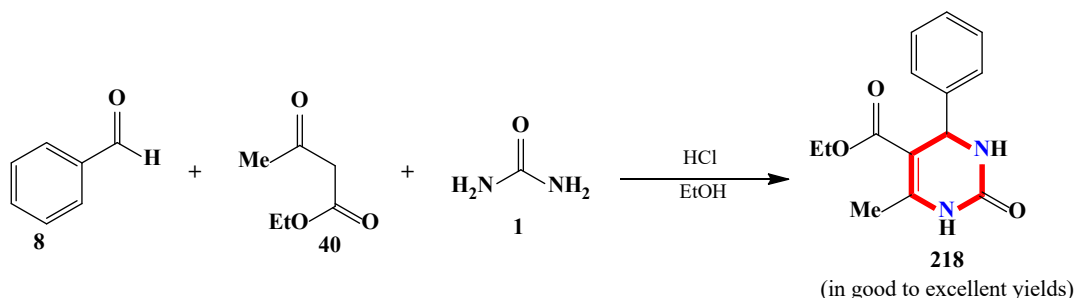
Scheme 68. Reaction. Source: Authors, 2026.

The next year, in continuation of efforts to design structurally diverse hybrid heterocycles, Yavuz et al. (2021) introduced a well-organized and efficient multi-step synthetic approach for the preparation of novel chromonyl-pyrimidine hybrids **217**. The strategy employs readily available and cost-effective starting materials, including substituted acetophenones **88** and aminoguanidine nitrate **214**, which initially reacted under basic conditions to form aminoguanidine hydrazone intermediates **215**. These intermediates subsequently underwent condensation with 3-formylchromone **216** in ethanol under reflux to afford the desired target compounds (Scheme 69). From a green chemistry perspective, the method can be considered partially sustainable due to the use of ethanol as an eco-friendly solvent and economically feasible reagents; however, the multi-step sequence and reliance on reflux conditions introduce certain environmental and energy-related limitations.



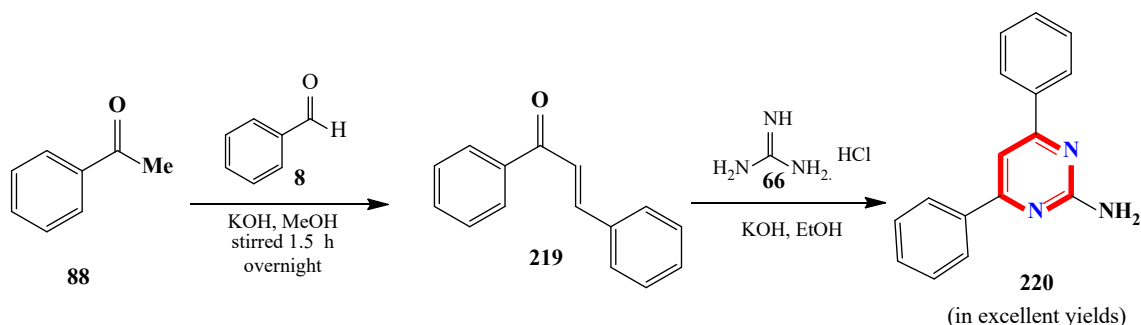
Scheme 69. Reaction. Source: Authors, 2026.

In a parallel advancement of pyrimidine synthesis, in the same year, Zarenezhad et al. (2021) reported a robust methodology for synthesizing dihydropyrimidinone derivatives **218** via a one-pot acid-promoted three-component Biginelli condensation of simple, cost-effective precursors, specifically benzaldehyde **8**, ethyl acetoacetate **40**, and urea **1** in an ethanol medium (Scheme 70). Utilizing a corrosive mineral acid catalyst limits its green credentials, yet this synthesis remains a highly efficient method for rapidly constructing pyrimidine scaffolds from simple, inexpensive precursors using a biodegradable solvent and multicomponent atom-economical approach.



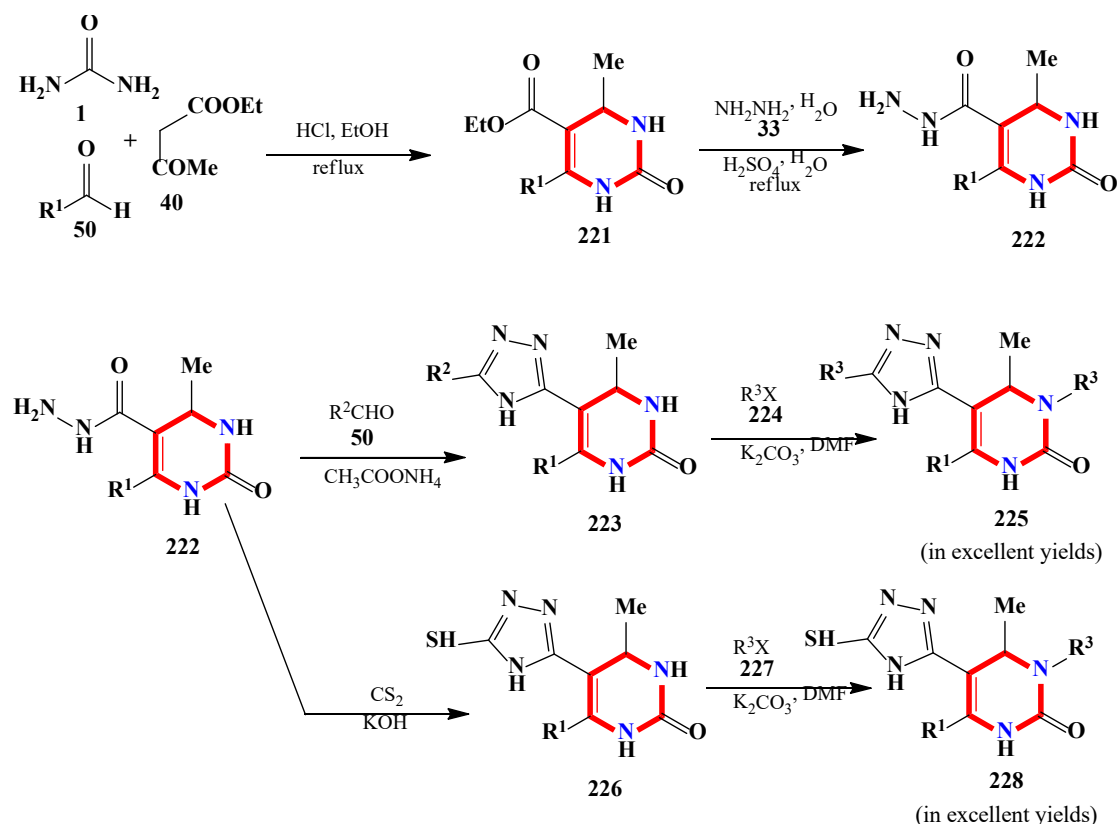
Scheme 70. Reaction. Source: Authors, 2026.

In pursuit of simplified pyrimidine architectures, again, in 2021, Bhargav et al. (2021) established a base-mediated, one-pot three-component strategy involving the initial formation of a chalcone intermediate **219** from acetophenones **88** and aldehydes **8** in MeOH/KOH, followed by cyclization with guanidine hydrochloride **66** in EtOH/KOH (Scheme 71). As a semi-eco-friendly synthesis, this route offers high atom economy and excellent yields of amino-substituted pyrimidines, but relies on strong bases and multiple alcoholic solvents, generating chemical waste and requiring energy-intensive reflux.



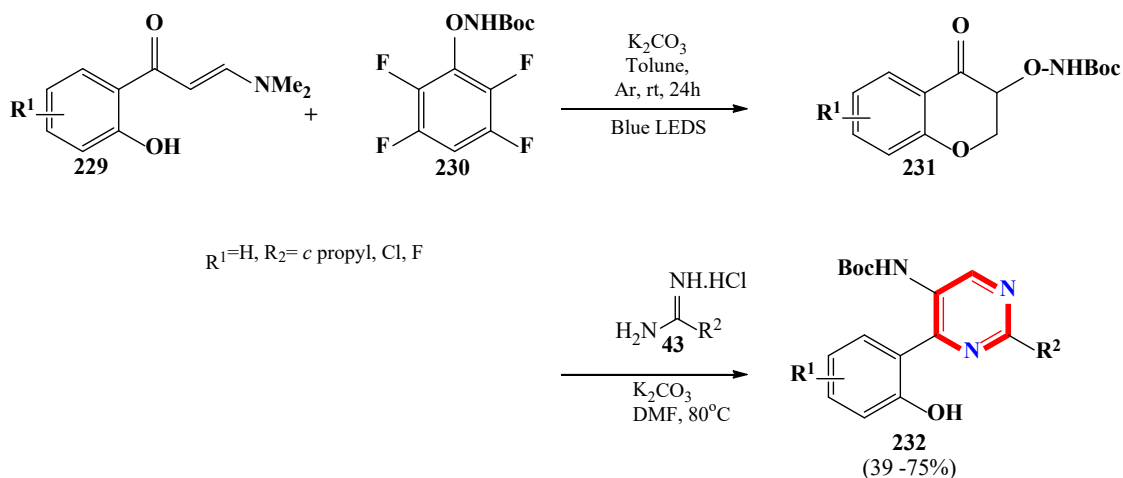
Scheme 71. Reaction. Source: Authors, 2026.

In 2022, serving as a versatile platform for triazole-linked pyrimidinones **225**, **228**, Tripathi's research group established an acid-promoted, one-pot three-component Biginelli reaction involving urea **1**, aldehydes **50**, and ethyl acetoacetate **40** in refluxing ethanol, followed by multi-step transformations including hydrazine-mediated hydrazide formation and CS<sub>2</sub>-KOH cyclization (Scheme 72) (Tripathi et al., 2022). The requirement for corrosive HCl and KOH, along with the use of toxic carbon disulfide and energy-intensive reflux, make this synthetic route only partially sustainable, despite its operational simplicity and excellent yields in generating complex scaffolds.



Scheme 72. Reaction. Source: Authors, 2026.

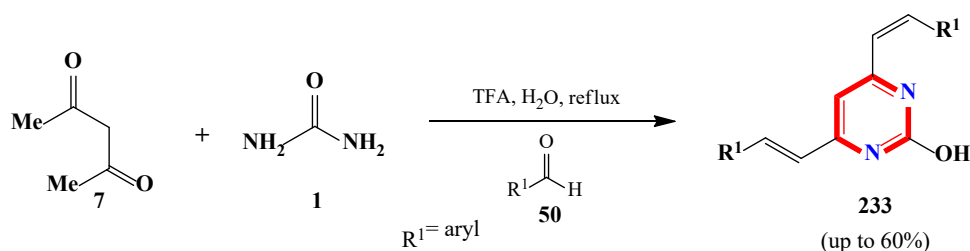
Within the same year, advancing the synthesis of Boc-protected aminopyrimidines, Wang et al. (2022) established a two-stage methodology starting with a Blue LED-mediated photochemical step in toluene, followed by a K<sub>2</sub>CO<sub>3</sub>-promoted cyclization with amidine hydrochlorides **43** in DMF at 80 °C (Scheme 73).



Scheme 73. Reaction. Source: Authors, 2026.

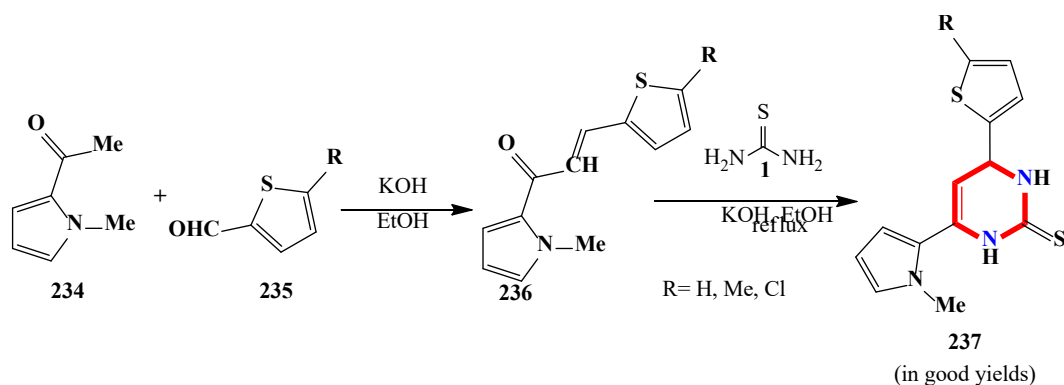
The strategy is highlighted by its moderate to good yields and the successful incorporation of specific protective groups; nevertheless, the utilization of DMF at elevated temperatures and the reliance on aromatic solvents like toluene classify this as a quasi-green methodology as it attempts to integrate modern light-driven steps with traditional energy-intensive heating cycles.

In the same year, providing an efficient route to styryl-substituted pyrimidines, Singh and collaborators reported an acid-catalyzed, one-pot 3-component cyclization where pentane-2,4-dione **7** reacted with urea **1** and aromatic aldehydes **50** in a refluxing mixture of trifluoroacetic acid (TFA) and water (Scheme-74) (Singh et al., 2022). As a highly efficient and practical strategy, this synthetic methodology enables the direct assembly of complex architectures with up to 60% yield, though refluxing conditions and corrosive trifluoroacetic acid make it only partially environmentally friendly.



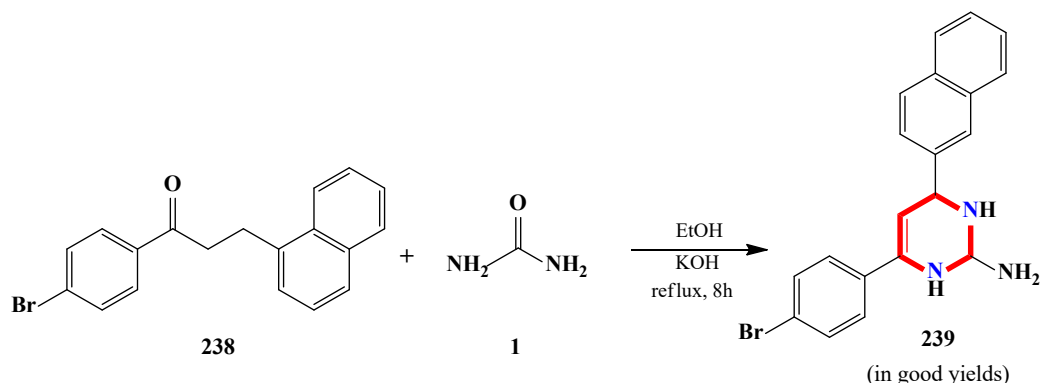
Scheme 74. Reaction. Source: Authors, 2026.

Again, in 2022, building on the principles of green and sustainable chemistry, Abdelrehim et al. (2022) documented an efficient two-step methodology for generating thiophene-substituted dihydropyrimidinethione derivatives **237**. The sequence initiated with a base-promoted Claisen–Schmidt condensation between 1-(1-methyl-1H-pyrrol-2-yl)ethan-1-one **234** and thiophene-2-carbaldehyde derivatives **235** in ethanol with KOH to produce chalcone intermediates. These intermediates then underwent cyclocondensation with (thio)urea **1** under reflux in a KOH/EtOH system to yield the final bioactive hybrids (Scheme 75). The use of strong base with continuous heating limits the green profile of this protocol; nevertheless, it remains an efficient and practical method due to its good reactivity and the use of sustainable solvents and inexpensive reagents.



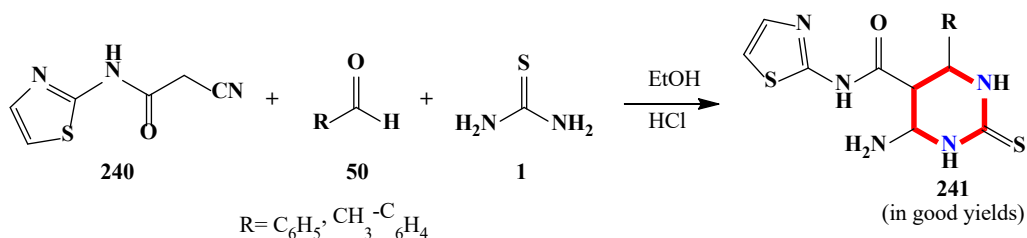
Scheme 75. Reaction. Source: Authors, 2026.

In 2023, building on the established efficiency of alkaline-mediated cyclization, Al-Hussein et al. (2023) described the successful synthesis of dihydropyrimidine derivative **239** via a base-catalyzed cyclocondensation between chalcone intermediate **238** and urea **1** in ethanol under reflux conditions for 8 hours (Scheme 76). The process is efficiently promoted by KOH, a readily available catalyst for constructing these bioactive scaffolds. While the use of sustainable solvents and a low-toxicity base makes it partially green, the 8-hour reflux and multi-step procedure limit its overall sustainability.



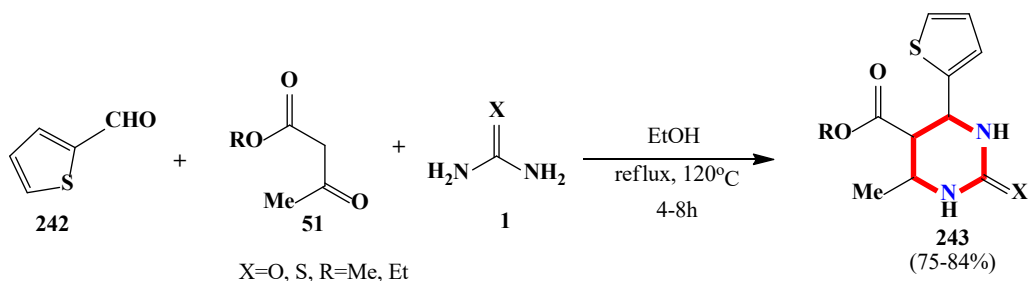
Scheme 76. Reaction. Source: Authors, 2026.

A year later, establishing a direct route to thiazole-linked dihydropyrimidine-2(1H)-thiones, Alamshany et al. (2024) developed an acid-catalyzed, one-pot three-component Biginelli reaction involving *N*-(thiazol-2-yl)-2-cyanoacetamide **240**, aromatic aldehydes **50**, and (thio)urea **1** in ethanol with HCl (Scheme 77). This methodology demonstrates high bond-forming efficiency and a broad substrate scope with good yields; however, the use of corrosive HCl and conventional heating renders it quasi-green. Nevertheless, it remains a robust and valuable strategy for the rapid assembly of multifunctional pyrimidine scaffolds.



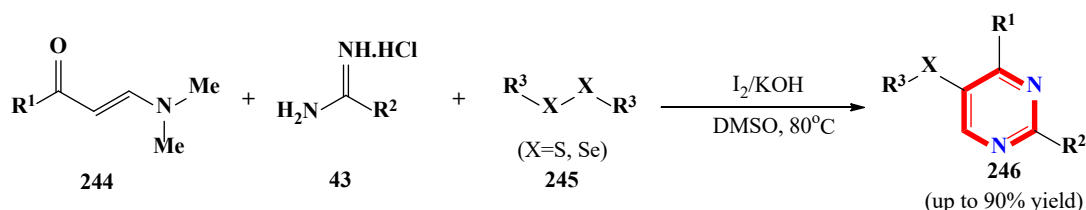
Scheme 77. Reaction. Source: Authors, 2026.

In the same vein, Nikama et al. (2024) utilized an acid-promoted three-component Biginelli reaction to synthesize thiophene-linked dihydropyrimidinones **243** by refluxing thiophene-2-carboxaldehyde **242**, β-keto esters **51**, and (thio)urea **1** in ethanol at 120 °C (Scheme 78). While this protocol is moderately green due to its high atom economy and the use of a biodegradable solvent, it is limited by high thermal energy requirements and prolonged reaction times. Nevertheless, it remains an exceptionally powerful and efficient approach for the rapid construction of sulfur-incorporated pyrimidines in a single step.



Scheme 78. Reaction. Source: Authors, 2026.

Most recently, providing a highly efficient route to chalcogen-functionalized pyrimidines, Ye et al. (2026) established an oxidative, one-pot three-component cyclocondensation between enaminones **244**, amidine hydrochlorides **43**, and dichalcogenides **245** in DMSO at 80 °C using an I<sub>2</sub>/KOH catalytic system (Scheme 79). As a remarkably efficient and high-impact strategy, this methodology delivers substituted pyrimidines in excellent yield with high chemical efficiency and atom economy; however, the use of a corrosive KOH, molecular iodine, and high-boiling DMSO renders it quasi-green.



Scheme 79. Reaction. Source: Authors, 2026.

## 5. Conclusions

In conclusion, the synthetic journey of pyrimidine derivatives from 1876 to 2026 reflects a remarkable shift from traditional, energy-intensive methods toward sustainable and metal-free protocols. Over the last 150 years, the transition from classical Pinner and Biginelli condensations to modern acid-base and organocatalyst-promoted strategies has enabled the efficient construction of structurally diverse and highly functionalized scaffolds. These semi-green protocols not only eliminate the need for toxic metal catalysts but also offer high atom economy and functional group tolerance, which are vital for drug discovery and material science. As we move further into the 21st century, these metal-free strategies continue to redefine the efficiency of heterocyclic synthesis, providing a robust foundation for the future development of next-generation pyrimidine-based therapeutics.

## 6. Acknowledgments

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## 7. Authors' Contributions

*Mohammad Mizanur Rahman*: writing original draft preparation. *A.F.G. Masud Reza*: reviewing and editing. *Mohammad Lokman Hossain*: reviewing and editing. *Abul Kalam Mohammad Lutfur Rahman*: reviewing and editing. *A.F.G. Masud Reza*: reviewing and editing. *Md. Rabiul Islam*: reviewing and editing.

## 8. Conflicts of Interest

No conflicts of interest.

## 9. Ethics Approval

Not applicable.

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