

Efficient synthesis of structurally diverse polysubstituted non-fused pyrimidines (NFPs) and their derivatives via four-component reaction (4-CRs) protocols

Mohammad Mizanur Rahman^{1,2}, Mohammad Lokman Hossain³, Abul Kalam Md. Lutfur Rahman³ & Abdul Fakhru'l Golam Masud Reza⁴

¹ Department of Textile & Fashion Management, Institute of Science Trade & Technology, Dhaka, Bangladesh

² S.Chem P. Dhaka, Bangladesh

³ Department of Chemistry, Jagannath University, Dhaka, Bangladesh

⁴ National University, Gazipur, Bangladesh

Correspondence: Mohammad Mizanur Rahman, Department of Textile & Fashion Management, Institute of Science Trade & Technology, Bangladesh. E-mail: drmizanchem1981@gmail.com

Submitted: May 07, 2026

DOI: 10.14295/bjs.v5i10.909

Accepted: June 26, 2026

URL: <https://doi.org/10.14295/bjs.v5i10.909>

Published: June 30, 2026

Abstract

Pyrimidine derivatives are vital nitrogen-containing heterocycles with significant biological and industrial importance. This review summarizes the advancements in their synthesis from 2005 to 2025, focusing on the shift from traditional multi-step methods to sustainable one-pot multicomponent reactions (MCRs). We highlight the efficacy of various transition metal catalysts and the emergence of metal-free, solvent-free, and microwave/ultrasound-assisted protocols. This compilation provides a strategic framework for developing atom-economical and eco-friendly pathways to access pyrimidine scaffolds.

Keywords: pyrimidines, multicomponent reactions, transition metal catalysis, one-pot synthesis, atom economy.

Síntese eficiente de pirimidinas não fundidas (NFPs) polissubstituídas estruturalmente diversas e seus derivados por meio de protocolos de reações de quatro componentes (4-CRs)

Resumo

Os derivados de pirimidina são heterociclos nitrogenados de grande importância biológica e industrial. Esta revisão resume os avanços na sua síntese entre 2005 e 2025, com foco na transição dos métodos tradicionais de múltiplas etapas para reações multicomponentes (MCRs) sustentáveis realizadas em uma única etapa (one-pot). Destaca-se a eficiência de diversos catalisadores à base de metais de transição, bem como o surgimento de protocolos livres de metais, livres de solventes e assistidos por micro-ondas ou ultrassom. Esta compilação fornece uma estrutura estratégica para o desenvolvimento de rotas sintéticas ambientalmente amigáveis, com elevada economia atômica, visando à obtenção de esqueletos de pirimidina.

Palavras-chave: pirimidinas, reações multicomponentes, catálise por metais de transição, síntese one-pot, economia atômica.

1. Introduction

The construction of complex heterocyclic architectures remains a key focus of modern synthetic organic chemistry, with the pyrimidine nucleus occupying a central position. Pyrimidines are fundamental components of nucleic acids, namely cytosine, thymine, and uracil, and thus represent essential building blocks of life while also possessing significant biological and clinical importance (Brown, 1984; Bruice, 2007; Elderfield, 1957).

Numerous pyrimidine derivatives have been reported to exhibit a wide range of biological activities, including antiviral, anticancer, antibacterial, antifungal (Dahabiyeh et al., 2023; Hekal et al., 2024; Padmashali et al., 2019; Pan et al., 2023; Venugopala et al., 2015; Venugopala et al., 2024a,b), anti-inflammatory, antidiabetic, antihypertensive, anticonvulsant, analgesic, antileishmanial, antitubercular (Bairagi et al., 2020; Bhole et al., 2023; Keshari et al., 2020; Kumar et al., 2023; Venugopala et al., 2020; Wu et al., 2022), antioxidant, insecticidal, larvicidal, and anthelmintic properties (Bairagi et al., 2018; DChitikina et al., 2020; uraisamy et al., 2023; Moharam et al., 2023; Venugopala et al., 2016; Venugopala et al., 2022).

In addition to their pharmacological significance, pyrimidine derivatives are also employed in diverse industrial and technological applications, such as dyes, organic semiconductors, agrochemicals, optoelectronic devices, corrosion inhibitors, electroluminescent materials, the petroleum industry, organic light-emitting diodes (OLEDs), fluorescent receptors exhibiting dual signaling mechanisms, photosensitizers, bioimaging, fluorescent pseudomonads, and photophysics and nonlinear optical materials (Abdel-Raheem et al., 2023; Achele et al., 2013; Al-Mosaiudi et al., 2015; Ganesan et al., 2017; Ghazoui et al., 2012; Haque et al., 2017; Irfan et al., 2017; Irfan et al., 2019; Park et al., 2017; Sayed et al., 2012; Upadhyay et al., 2010; Verbiskiy et al., 2014; West; Chu, 1986). Owing to these diverse biological, industrial, and technological applications, the development of efficient and innovative synthetic strategies for substituted pyrimidine derivatives continues to attract considerable research interest.

Historically, the synthesis of pyrimidine scaffolds relied heavily on classical methodologies, most notably the Pinner synthesis and the Biginelli reaction, which stand as the definitive examples of two-component (2-CRs) and three-component (3-CRs) reactions, respectively (Pinner, 1884, Alexander et al., 2005). While these foundational routes were instrumental in the development of heterocyclic chemistry, they were often plagued by multi-step sequences, prolonged reaction times, and the generation of substantial chemical waste. In response to these limitations and in strict adherence to the principles of Green Chemistry, the synthetic community has increasingly pivoted toward higher-order multicomponent reactions (MCRs).

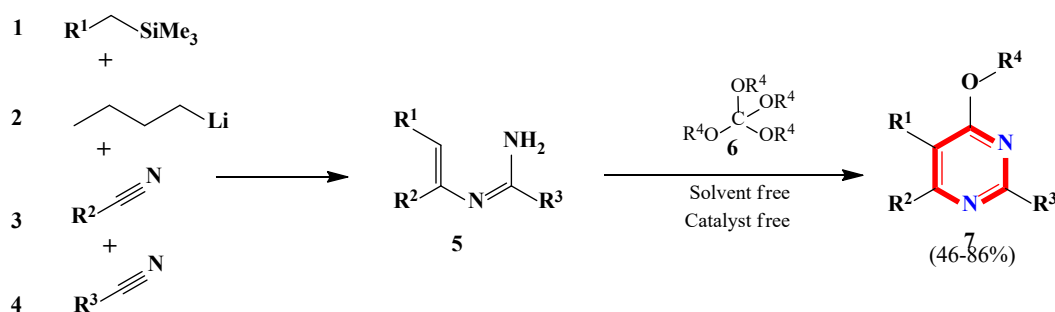
These advanced four-component reaction (4-CR) protocols facilitate the streamlined assembly of four distinct starting materials into a single, complex molecular architecture through a one-pot operation. Such a transition not only ensures superior cost-effectiveness and time efficiency but also achieves maximum atom economy. Recently, the integration of transition-metal catalysis and solvent-free protocols has further revolutionized this landscape, drastically minimizing the environmental footprint of chemical manufacturing while providing efficient access to structurally diverse, polysubstituted non-fused pyrimidines.

Therefore, this review aims to provide a comprehensive overview of recent advances (2005–2025) in the efficient synthesis of structurally diverse polysubstituted non-fused pyrimidines via four-component reactions (4-CRs), with particular emphasis on transition metal-catalyzed, metal-free, solvent-free, and energy-assisted synthetic strategies, highlighting their mechanistic aspects, substrate scope, catalytic efficiency, and potential contributions to sustainable heterocyclic synthesis.

2. Four-Component Synthesis of Pyrimidines

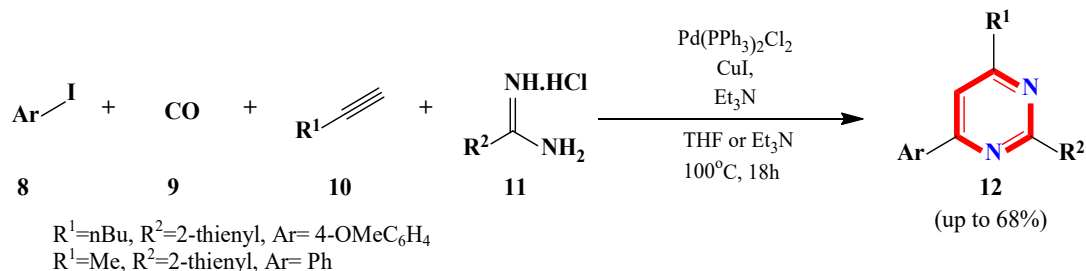
Four-component reactions (4CRs) are recognized as an exceptionally powerful strategy in heterocyclic chemistry, as they enable the organized assembly of four distinct starting molecules in a single step. Compared to traditional two- or three-component reactions, 4CRs offer superior structural diversity, allowing for the precise introduction of different functional groups at various positions (C-2, C-4, C-5, C-6) of the pyrimidine ring. Furthermore, this approach eliminates the need for intermediate isolation, thereby saving time and solvent, which makes the methodology environmentally sustainable. Over the past two decades, researchers have developed numerous protocols to synthesize functionalized pyrimidine frameworks. Among these, transition-metal catalysis and catalyst-free condensations have emerged as the two primary trends. The following synthetic methodologies demonstrate the capability and versatility of this multifaceted strategy:

Sakai et al. (2005) systematically described an efficient synthesis strategy for constructing versatile pyrimidine frameworks using readily available starting materials. In the first step, an α -silyl carbanion, generated from the reaction of commercially available silyl-substituted alkane **1** and *n*-butyllithium **2**, reacted sequentially with two nitrile molecules **3** and **4** to form a key intermediate, 3-amino-2-aza-1,3-diene **5**. In the second step, this intermediate underwent a cyclization reaction directly with tetraalkyl orthocarbonate in the absence of any external solvent or catalyst to afford 4-alkoxypyrimidine derivatives **7** (Scheme-1) (Sakai et al., 2005). This protocol represents a highly eco-friendly, concise, and straightforward synthetic route.



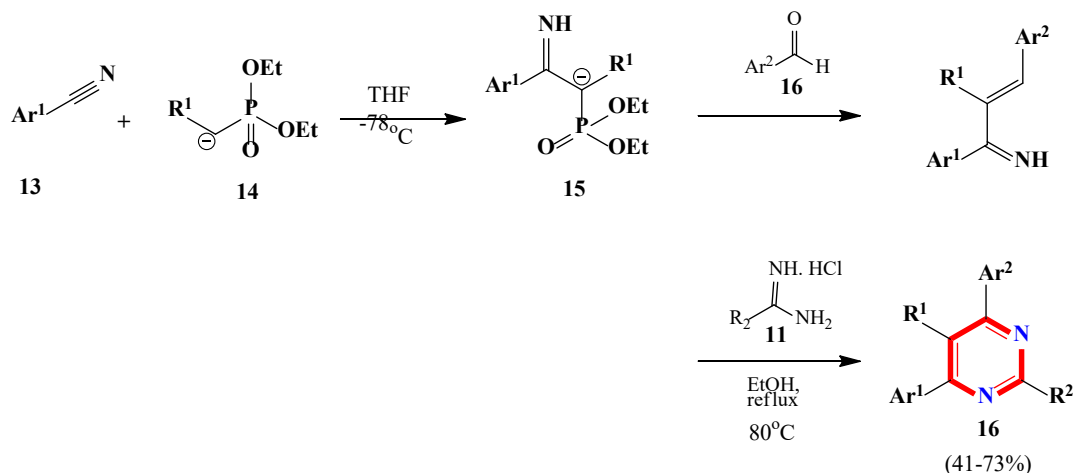
Scheme 1. Solvent and catalyst-free four-component synthesis of 2,5,6-Trisubstituted 4-alkoxypyrimidines **7** by Sakai et al. (2005).

In addition to solvent-free methods, transition-metal catalysis has also proven highly effective for pyrimidine synthesis. In the same year, Karpov et al. (2005) successfully introduced an alternative Pd-catalyzed one-pot multi-component protocol for the preparation of 2,4,6-trisubstituted pyrimidines **12**. This synthesis proceeded via the carbonylative coupling of aryl iodides **8**, terminal alkynes **9**, and CO **10** with amidinium salts **11**, which served as readily available and cost-effective starting materials. The transformation was mediated by the robust catalytic system of Pd(PPh₃)₂Cl₂ and CuI in the presence of triethylamine and THF, both inexpensive and easily accessible reagents, at 100 °C for 18 h (Scheme 2) (Karpov et al., 2005). Although this method is non-green due to the use of organic solvents and transition-metal catalysts, it remains remarkable for its ability to synthesize complex pyrimidines from simple, low-cost materials in a single step.



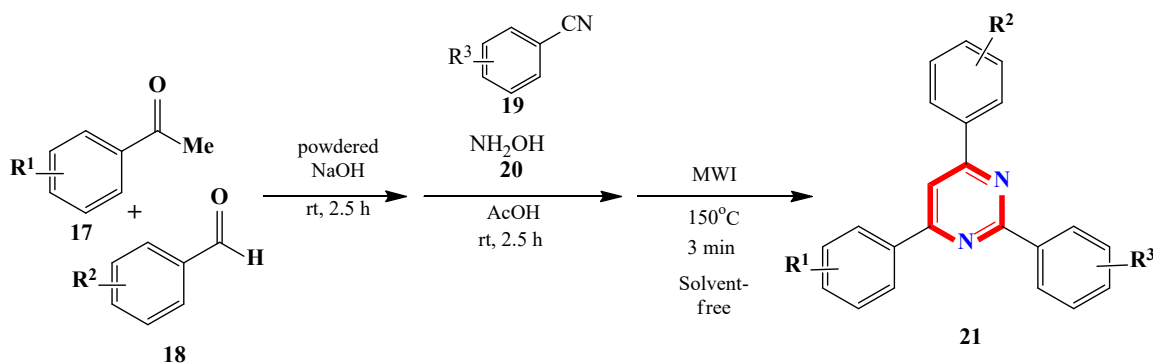
Scheme 2. Pd(PPh₃)Cl₂-CuI catalyzed synthesis of 2,4,6-trisubstituted pyrimidines **12** by Karpv et al. (2005).

Following the development of four-component reactions, within the same year, the research team of Alexander reported a convergent one-pot protocol for the synthesis of 2,4,5,6-tetrasubstituted pyrimidines **16**. The reaction began with the nucleophilic addition of a phosphonate-stabilized carbanion, generated from a readily available phosphonate ester **14**, to an aryl nitrile **13**, forming a resonance-stabilized imine-phosphonate intermediate **15**. This intermediate subsequently reacted with an aryl aldehyde **16** and an amidine hydrochloride **11**, likely proceeding through a tandem Knoevenagel condensation followed by cyclocondensation to afford the six-membered aromatic pyrimidine framework **16** (Scheme 3) (Kiselyov, 2005). This convergent one-pot protocol offers high atom economy and broad substrate scope with excellent functional group tolerance, utilizing readily available starting materials and catalysts in common solvents like THF and Ethanol (EtOH) through efficient microwave irradiation or reflux methods at temperatures ranging from -78 °C to 80 °C.



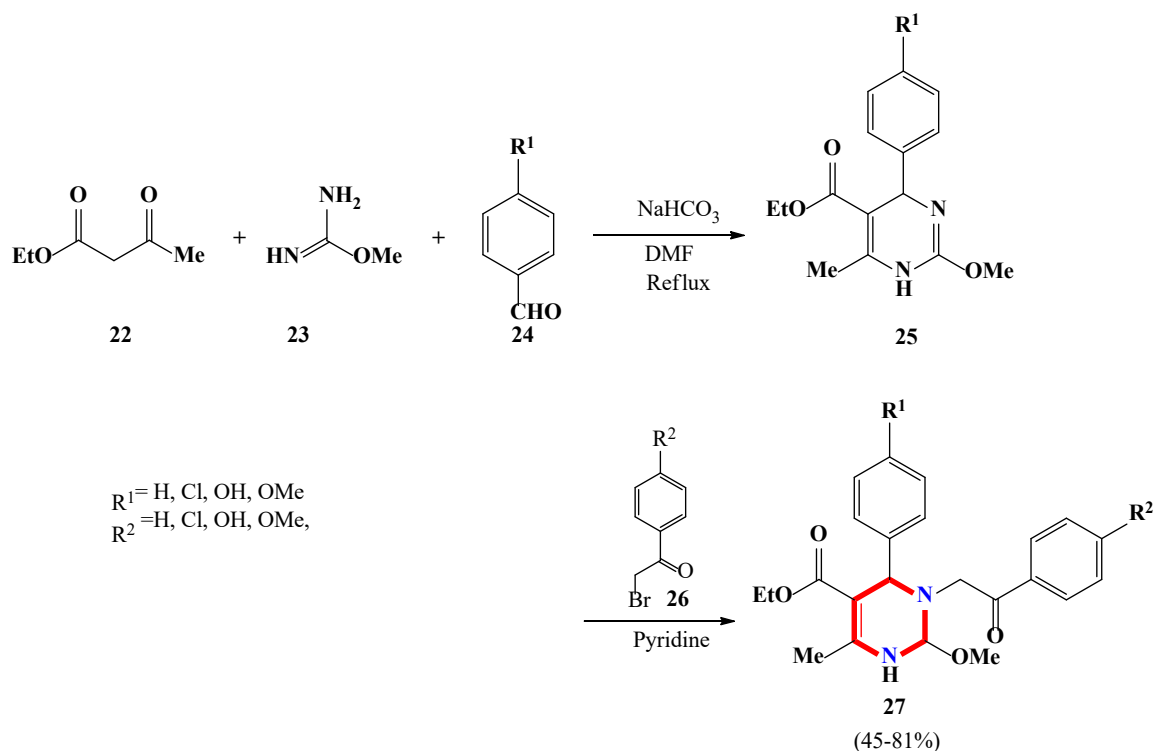
Scheme 3. Synthesis of 2,4,5,6-tetra-substituted pyrimidines **16** by Alexander et al. (2005).

Alongside metal, microwave-assisted, solvent-free protocols enable efficient access to symmetric and unsymmetric triarylpyrimidines. In the following year, 2,4,6-triarylpyrimidines **21** were synthesized via a one-pot, four-component $[2+2+1+1]$ annulation of aryl methyl ketones **17**, benzaldehydes **18**, aromatic nitriles **19**, and hydroxylamine **20** (Scheme 4) (Adib et al., 2006). The reaction was conducted at 150°C for only 3 min using powdered NaOH and AcOH under microwave irradiation (MWI), eliminating hazardous organic solvents. This green protocol ensures high atom economy and broad substrate scope by utilizing readily available starting materials under strictly solvent-free, microwave-assisted conditions at 150°C to synthesize triarylpyrimidines in very short reaction times.



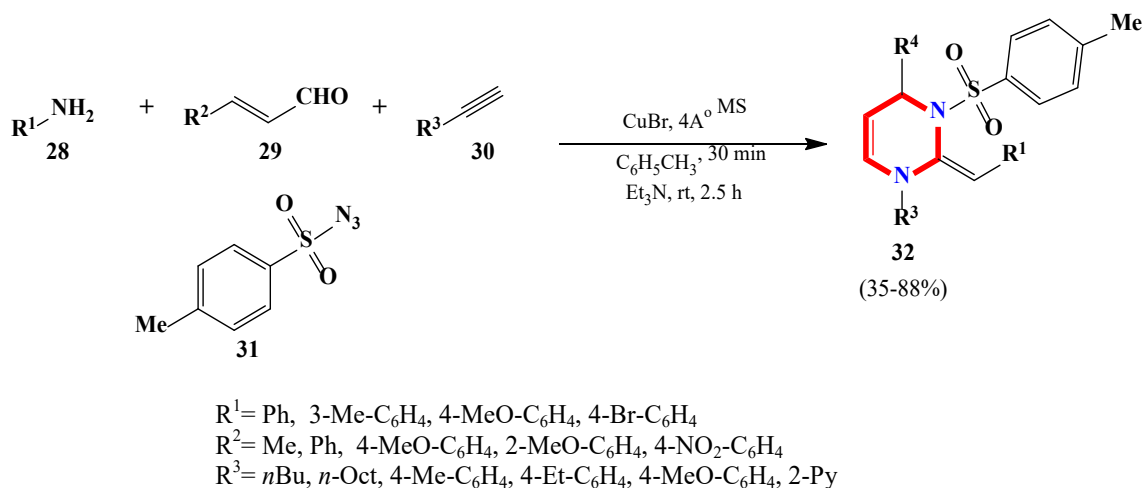
Scheme 4. Based on the promoted and microwave-assisted four-component synthesis of 2,4,6-triarylpyrimidines **21** by Adib et al. (2006).

In connection with multicomponent strategies, in 2009, Chikhale and collaborators reported an efficient and relatively green two-step approach for the synthesis of multisubstituted 3,4-dihydropyrimidin-2(1*H*)-ones/ethers **27** from readily available starting materials. Initially, a Biginelli-type cyclocondensation of ethyl acetoacetate **22**, *O*-methyl isourea **23**, and aromatic aldehydes **24** in the presence of NaHCO_3 in DMF under reflux, produced the intermediate **25**. Subsequently, the intermediate underwent regioselective *N*-alkylation with substituted phenacyl bromides **26** using pyridine as an inexpensive organic catalyst to furnish the final products (Scheme 5) (Chikhale et al., 2009). This efficient two-step approach ensures high atom economy and broad substrate scope using readily available materials, inexpensive organic catalysts (NaHCO_3 /Pyridine), and efficient reflux in DMF/Ethanol with excellent regioselectivity.



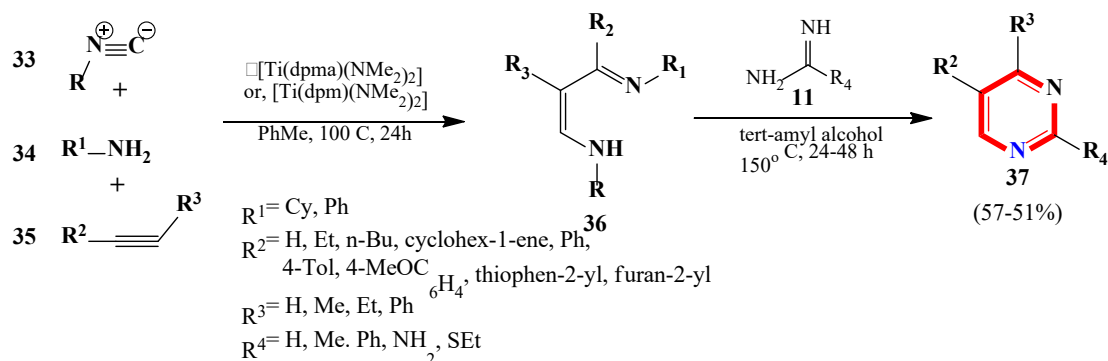
Scheme 5. Synthesis of 2,4,5,6-tetra substituted pyrimidines **27** by Chikhale et al. (2005).

Not only palladium, but copper catalysts have also proven highly effective in the four-component synthesis of pyrimidine frameworks. Following this trend, the research team of Lu et al. (2009) in the same year developed a robust multicomponent protocol for the construction of *N*-sulfonyl-1,2-dihydropyrimidines **32** using four cost-effective precursors, amine **28**, α,β -unsaturated aldehyde **29**, terminal alkyne **30**, and tosylazide **31**, mediated by a CuBr catalyst and 4Å molecular sieves in toluene under mild conditions (Scheme 6) (Lu et al., 2009). This robust four-component protocol offers high atom economy and broad substrate scope with excellent functional group tolerance, utilizing cost-effective precursors and CuBr catalyst in toluene under mild conditions with 4Å molecular sieves.



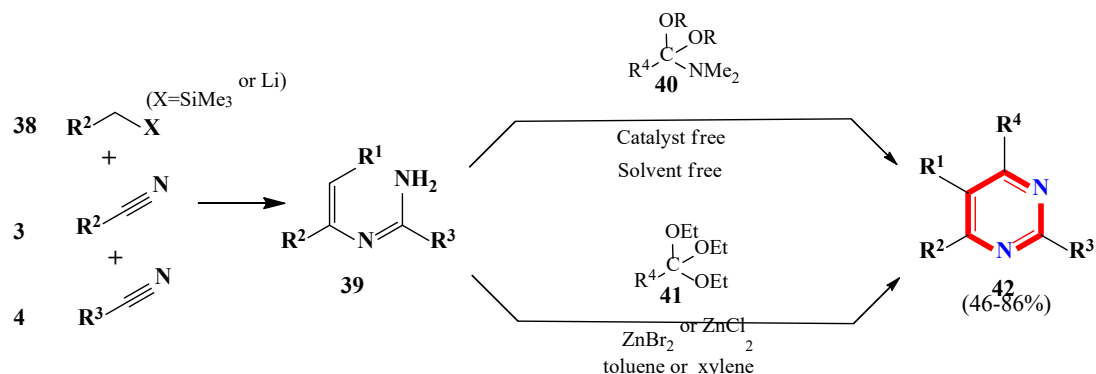
Scheme 6. CuBr mediated four-component synthesis of *N*-sulfonyl-1,2-dihydropyrimidines **32** by Lu et al. (2009).

Beyond palladium and copper, titanium catalysts have also been shown to play a highly effective and successful role in the four-component synthesis of pyrimidine frameworks. Progressing further, in 2010, Majumder & Odom reported a streamlined, two-step sequence for the synthesis of 2,4,5-trisubstituted pyrimidines **30**. The process began with a titanium-catalyzed three-component coupling of easily accessible isocyanides **27**, primary amines **23**, and alkynes **28**. In the initial step, efficient titanium catalysts, such as $\text{Ti}(\text{dpma})(\text{NMe}_2)_2$ or $\text{Ti}(\text{dpm})(\text{NMe}_2)_2$, were utilized in toluene at 100 °C to facilitate the formation of an α,β -unsaturated imine **29** intermediate. This intermediate subsequently reacted with an amidine derivative **11** in tert-amyl alcohol at 150 °C for 24–48 h to afford the target pyrimidine core **30** (Scheme 7) (Majumder; Odom, 2010). This streamlined two-step protocol ensures high atom economy and broad substrate scope using easily accessible materials and efficient titanium catalysts in toluene and tert-amyl alcohol at 100–150 °C.



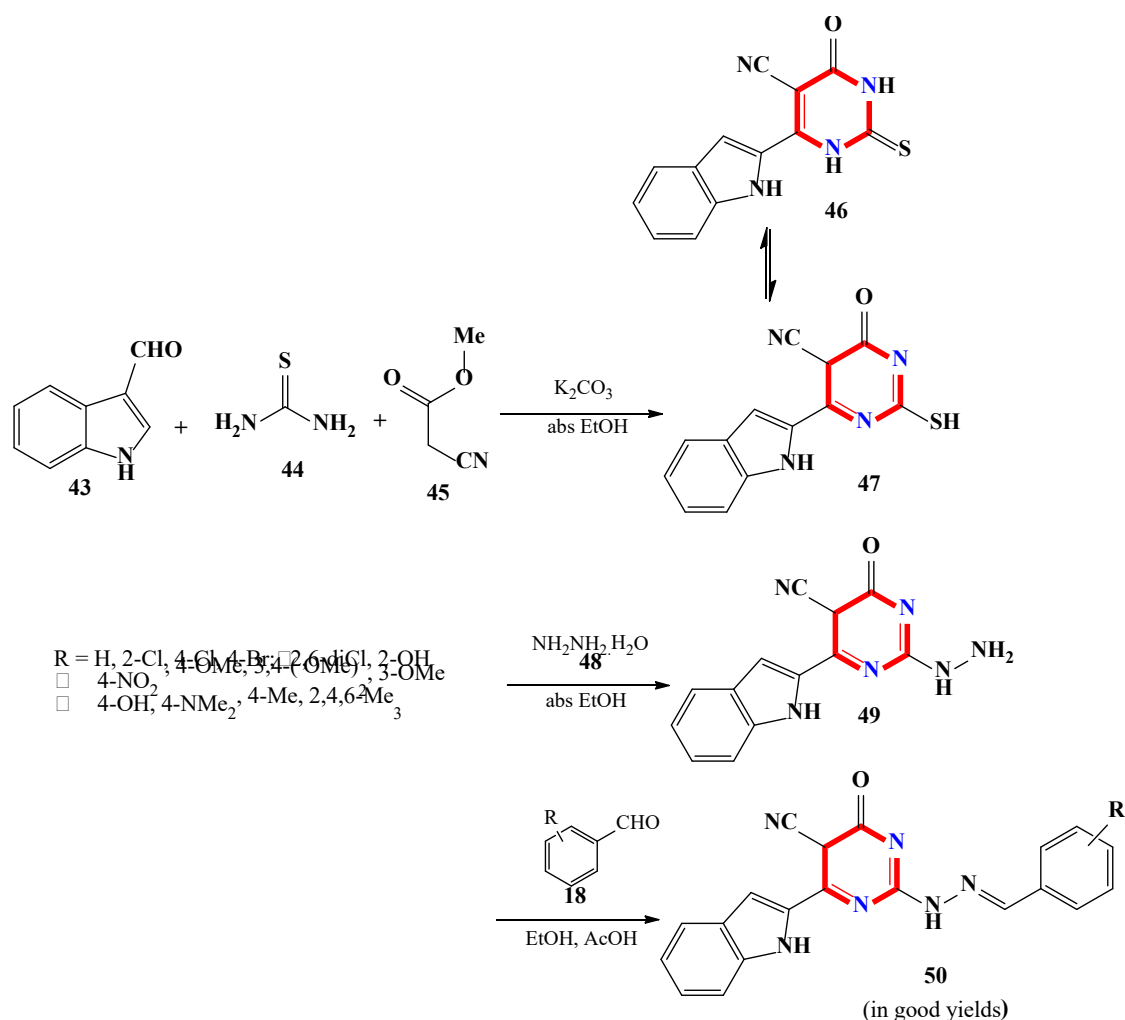
Scheme 7. Ti-mediated four-component synthetic approach of 2,4,5-trisubstituted pyrimidines **37** by Majumder & Odom (2010).

Alongside palladium, copper, and titanium, zinc catalysts have also emerged as highly effective and versatile tools in the multicomponent synthesis of pyrimidine derivatives. Following this trend, the same Sasada's research team in 2011 described another successful and attractive method for pyrimidine synthesis. In the reported process, an enamidine intermediate **39** was first generated from nitriles **3**, **4**, and lithiated or silylated precursors **38**. Subsequently, the reaction could proceed through two distinct pathways: a catalyst-free and solvent-free transformation into 2,4,5,6-tetrasubstituted pyrimidines **42** at high temperatures, or a more efficient pathway utilizing inexpensive and readily available ZnBr_2 or ZnCl_2 catalysts under mild conditions in toluene or xylene (Scheme 8) (Sasada et al., 2011).



Scheme 8. Both solvent and catalyst-free conditions or Zn-catalyzed four-component synthesis of 2,4,5,6-tetrasubstituted pyrimidines **42** by Sasada et al. (2011).

This versatile multicomponent protocol (Scheme 8) offers high atom economy and broad substrate scope using inexpensive $\text{ZnBr}_2/\text{ZnCl}_2$ catalysts in toluene or xylene, providing both a catalyst-free high-temperature route and a more efficient mild-condition pathway.

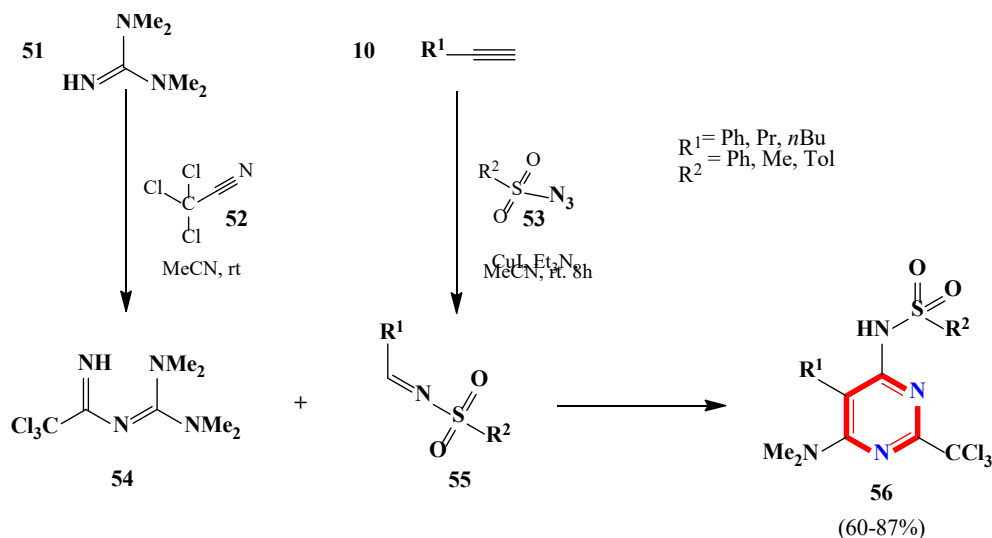


Scheme 9. Base-mediated consecutive four-component synthesis of Schiff base derivative of pyrimidines **50** by Alam et al. (2012).

In addition to the aforementioned transition-metal-catalyzed methods, research has also focused on multi-step strategies to construct Schiff base derivatives of pyrimidines under sustainable conditions. Following this trend, Alam et al. (2012) prepared a diverse series of indolyl-pyrimidine hydrazone derivatives **50** through a multistep synthetic strategy. The sequence initiated with a Biginelli-type cyclocondensation involving 1*H*-indole-3-carbaldehyde **43**, methyl 2-cyanoacetate **44**, and thiourea **45** to generate the core thiopyrimidine intermediate **47**. This intermediate subsequently underwent nucleophilic substitution with hydrazine hydrate **48** to afford another intermediate **49**, which was finally condensed with various aromatic aldehydes **18** to yield the target hydrazone derivatives (Scheme 9) (Alam et al., 2012). This sustainable multistep strategy offers a broad substrate scope and high functional group tolerance by utilizing readily available starting materials, employing inexpensive ethanol as a renewable solvent, and acetic acid as an efficient catalyst to yield diverse pyrimidine derivatives.

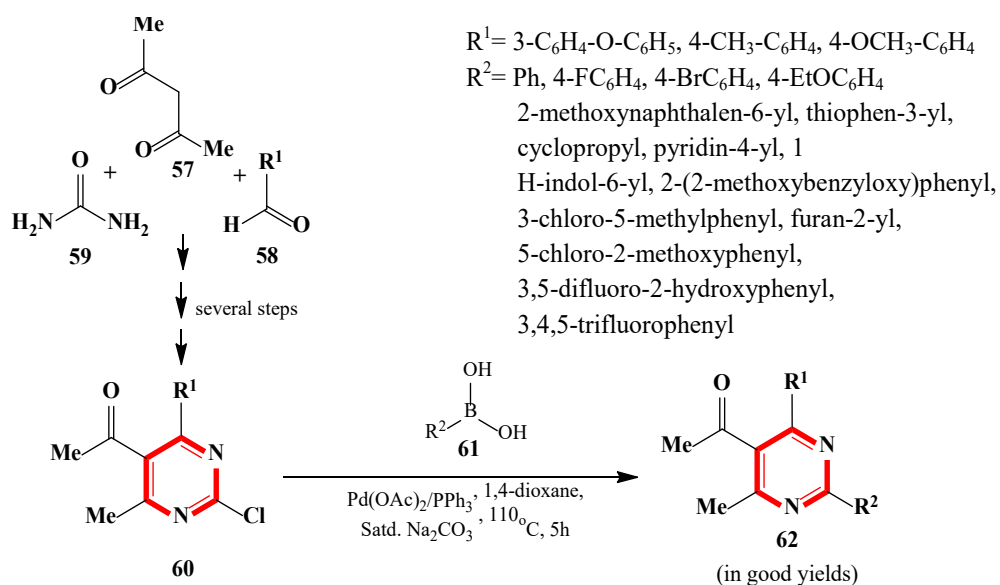
Further expanding the application of copper catalysis, in the next year, Yavari and co-workers developed a two-step synthesis for a series of 4-amino-sulfonyl-pyrimidine derivatives **56**. The protocol involved two parallel initial steps: first, the reaction of 1,1,3,3-tetramethylguanidine **51** with trichloroacetonitrile **52** in MeCN; and second, a CuI-catalyzed coupling of a terminal alkyne **10** with a sulfonyl azide **55** in the presence of Et_3N at room temperature (Scheme 10) (Yavari; Nematpour, 2013). Key findings of this methodology include the efficient use

of an inexpensive Cu(I) catalyst, mild reaction conditions at room temperature, and a broad substrate scope for constructing complex sulfonamide-linked pyrimidines.



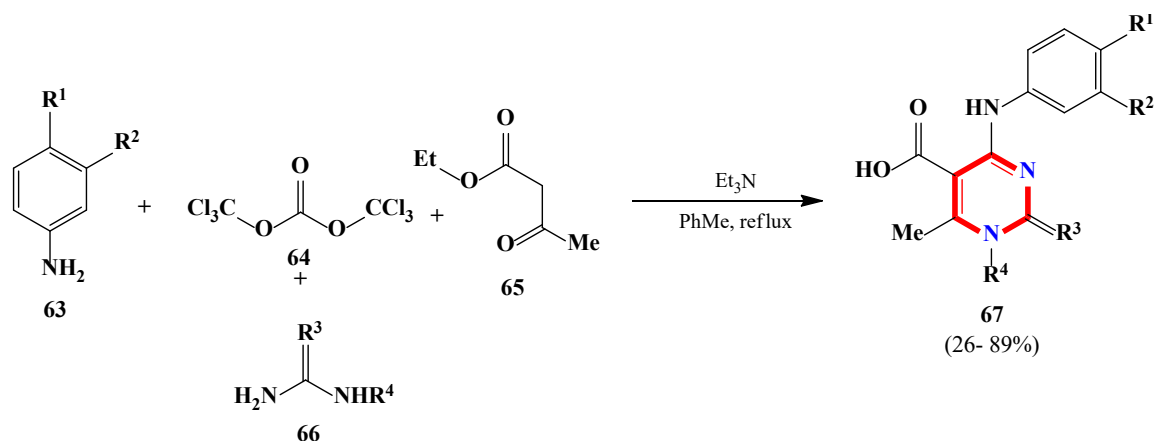
Scheme 10. Both catalyst-free conditions and CuI-mediated four-component synthesis of 4-amino-sulfonyl-pyrimidine derivative **56** by Yavari et al. (2013).

In addition to copper and titanium, palladium-catalyzed multi-step strategies have been refined to construct highly functionalized pyrimidine frameworks. Following this trend, the research team led by Faldu, in 2014, developed a two-stage approach to synthesize 5-acyl-tetrasubstituted pyrimidines **62**. The sequence initiated with a Biginelli-type transformation involving acetylacetone **57**, aldehyde **58**, and urea **59** to form a chlorinated pyrimidine intermediate **60**. This intermediate subsequently underwent a palladium-catalyzed Suzuki–Miyaura coupling with various boronic acids **61** to afford the final products (Scheme 11) (Faldu et al., 2014). This refined two-stage strategy ensures high atom economy and a broad substrate scope through a Biginelli-type transformation followed by an efficient palladium-catalyzed Suzuki–Miyaura coupling.



Scheme 11. Pd(OAc)₂/PPh₃ mediated synthesis of 5-acyl-tetrasubstituted pyrimidines **62** by Faldu et al. (2014).

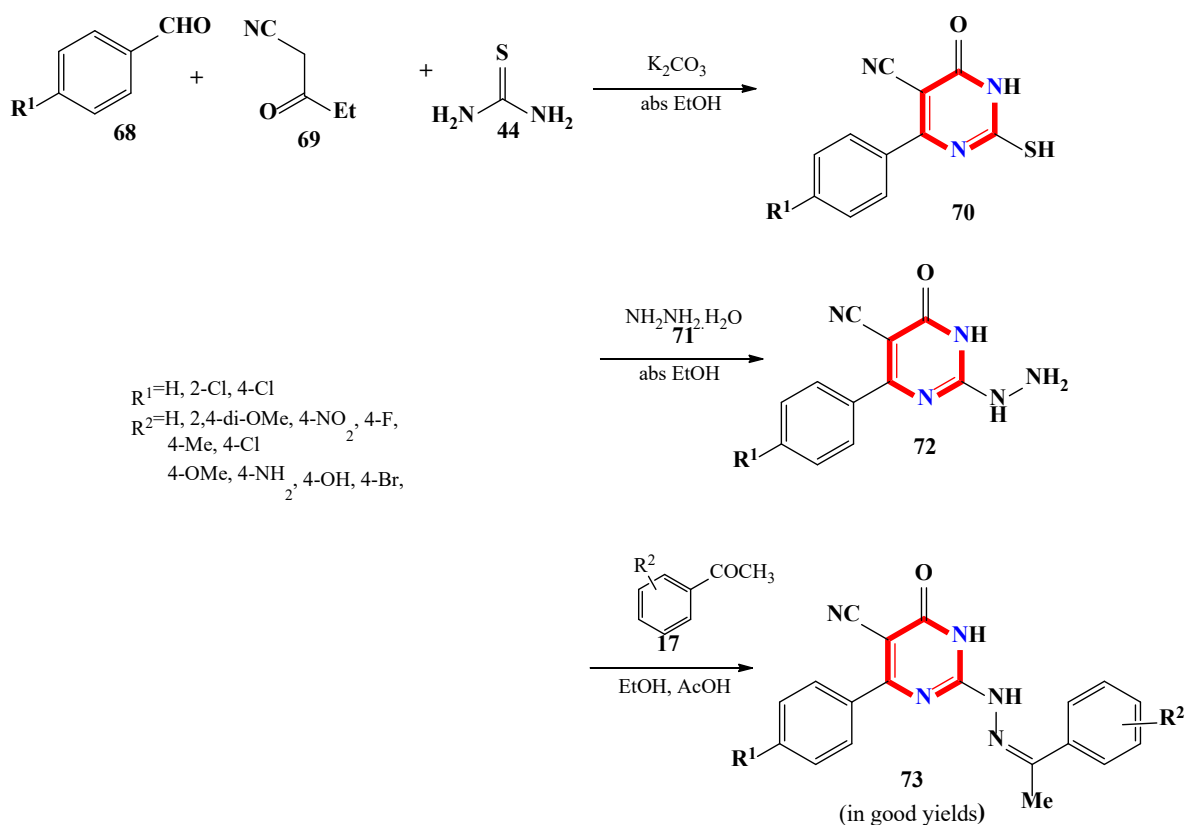
Further advancing the scope of metal-free four component strategies, during that period Liang's research team reported an operationally simple and one-pot three-step tandem method for synthesizing 4-arylamino-5-carboxyl pyrimidine derivatives **67** via a condensation of four reactive commercially available and low-cost starting materials like arylamine **63**, bis(trichloromethyl) carbonate **64**, ethyl acetoacetate **65**, and substituted ureas **66** using triethylamine as an efficient organic catalyst (Scheme 12) (Faldu et al., 2014). This unique protocol ensures high atom economy and yields with short reaction times, featuring a simple workup and non-chromatographic purification while safely avoiding the isolation of volatile, hazardous isocyanate intermediates.



Scheme 12. Metal-free four-component synthesis of 1,2-dihydro-4-arylamino-5-carboxyl pyrimidine derivatives **67** by Lianga et al. (2014).

Building upon the foundational principles of multicomponent condensations, a subsequent study in 2015 developed a systematic approach to synthesize indole-linked or aryl-substituted pyrimidine hydrazones. This involved a multi-component base-catalyzed Biginelli-type reaction using an aromatic aldehyde **68**, ethyl cyanoacetate **69**, and thiourea **44** in absolute ethanol to generate the 6-aryl-5-cyano-2-mercaptopyrimidin-4(3H)-one intermediate **70**.

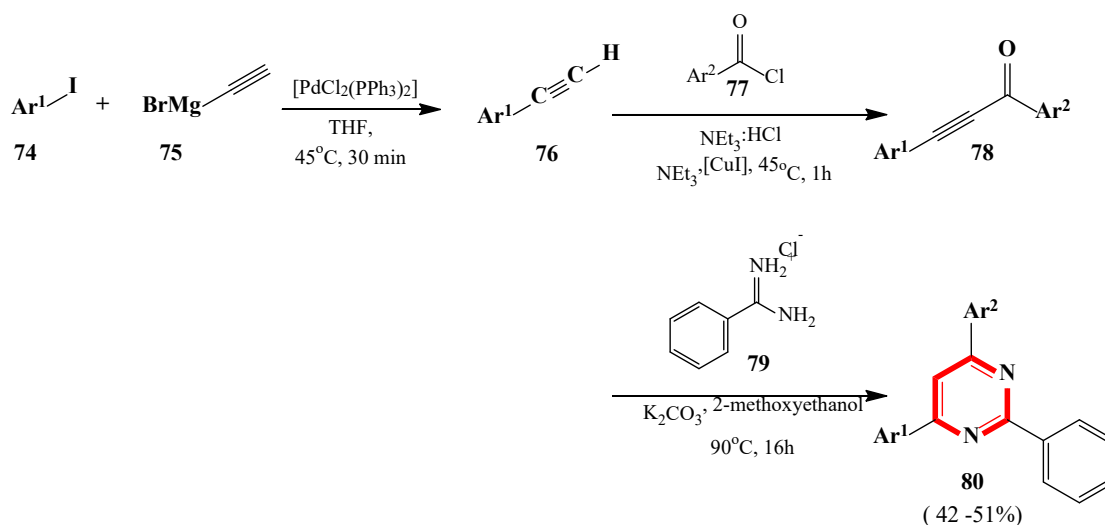
This core intermediate then underwent a nucleophilic displacement of the thiol group with hydrazine hydrate **71** to afford the 2-hydrazinyl derivative **72**. The final functionalization was achieved through a condensation reaction with various substituted acetophenones **17** in the presence of catalytic AcOH in ethanol, yielding the target 6-oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitrile derivatives **73** in good yields (Scheme 13) (Ali et al., 2015). This base-promoted strategy offers a broad substrate scope and high functional group tolerance by utilizing readily available starting materials, employing inexpensive K_2CO_3 as a base, ethanol as a renewable solvent, and acetic acid as an efficient catalyst to yield diverse pyrimidine derivatives under relatively mild conditions.



Scheme 13. Synthesis of 1,2-dihydro-4-arylamino-5-carboxyl pyrimidine derivatives **73** via multi-component base-catalyzed Biginelli-type reaction by Mohammad (2015).

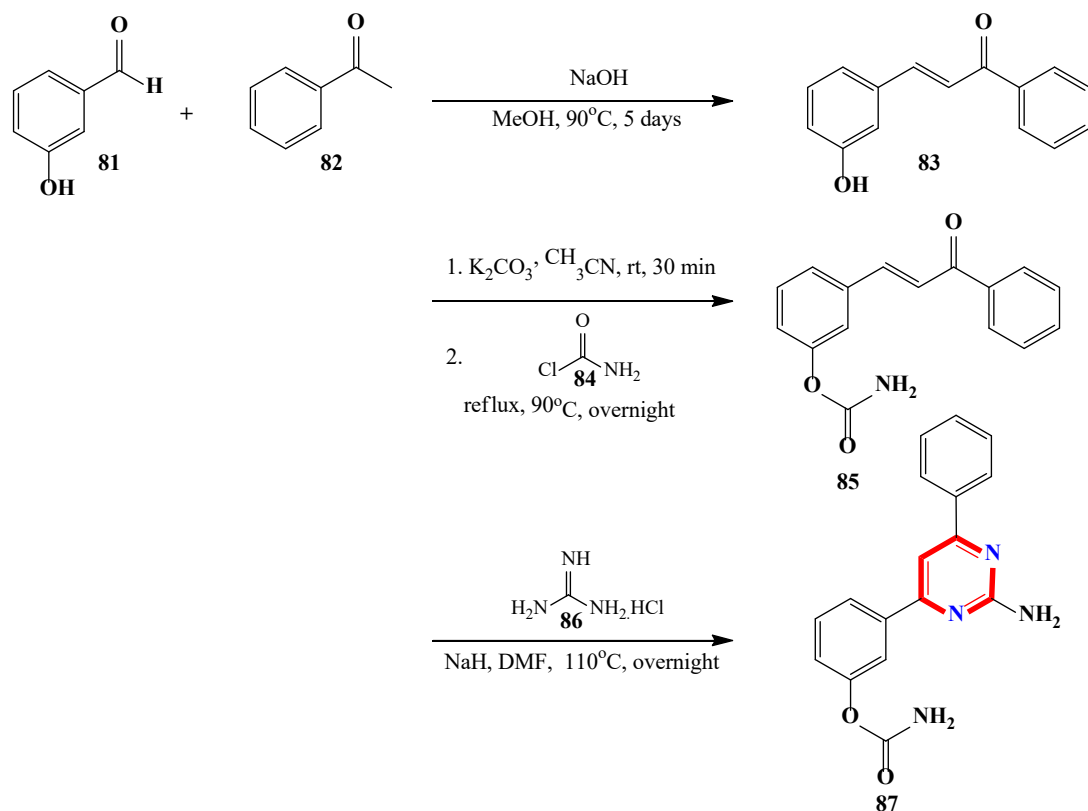
Further expanding the utility of 4d transition metals, palladium-catalyzed tandem strategies have proven essential for accessing highly substituted pyrimidine cores. Following this trend, in 2016, Götzinger and co-workers reported a versatile multi-step synthesis of 2,4,6-triarylpyrimidines **80** via consecutive four-component coupling–coupling–cyclocondensation. The sequence initiated with a palladium-catalyzed cross-coupling between aryl iodide **74** and ethynylmagnesium bromide **75** to produce the aryl-alkyne intermediate **76**, which was followed by a Pd-catalyzed coupling with an aryl acid chloride **77** to yield an aromatic alkynylketone **78**.

In the final stage, the ketone was treated with benzamidine hydrochloride **79** and K_2CO_3 in methoxyethanol at 90 °C to afford the target triarylpyrimidines **80** (Scheme 14) (Götzinger et al., 2016). This versatile tandem strategy ensures high atom economy and broad substrate scope by utilizing $PdCl_2(PPh_3)_2$ and CuI catalysts in solvents like THF and 2-methoxyethanol to achieve efficient coupling and cyclocondensation for 2,4,6-triarylpyrimidines.



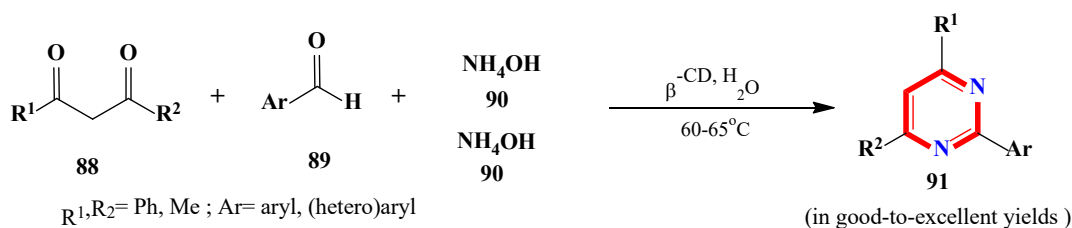
Scheme 14. Synthesis of 2,4,6-triarylpyrimidines **80** via consecutive four-component coupling-coupling-cyclocondensation by Götztzinger et al. (2016).

Further expanding the utility of chalcone intermediates in pyrimidine synthesis, a strategic multi-step protocol was developed to access carbamate-functionalized pyrimidines by Robinson and collaborators in the same year. As illustrated in Scheme 15, the sequence initiated with a base-catalyzed Claisen-Schmidt condensation between 3-hydroxybenzaldehyde **81** and acetophenone **82** in the presence of NaOH and MeOH at 90°C to afford the phenolic chalcone intermediate **83**, which was followed by the introduction of a carbamate moiety at the phenolic oxygen using chlorocarbonyl **84** in the presence of K_2CO_3 and CH_3CN . In the final stage, the functionalized chalcone **85** underwent a cyclocondensation reaction with guanidine hydrochloride **86** in the presence of NaH and DMF at 110°C to yield the target 2-amino-4,6-disubstituted pyrimidine derivative **87** (Robinson et al., 2016). This strategic protocol offers a broad substrate scope using readily available aldehydes and acetophenones, utilizing common solvents and simple bases to access functionalized pyrimidines with high efficiency.



Scheme 15. Base promoted four component synthesis of 3-(2-amino-6-phenylpyrimidin-4-yl)phenyl carbamate **87** by Robinson et al. (2016).

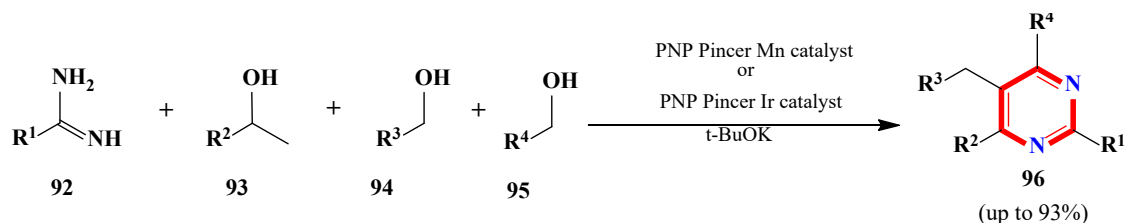
In line with the increasing demand for eco-friendly catalytic systems, within the same year, the use of a supramolecular host has emerged as a sustainable strategy for pyrimidine synthesis. Utilizing this approach, a series of substituted pyrimidines **91** were synthesized through a [3+1+2] multicomponent reaction involving 1,3-diketones **88**, aromatic or heteroaryl aldehydes **89**, and ammonium hydroxide **90** in the presence of an aqueous medium at 60–65 °C (Scheme 16) (Chowrasia et al., 2016). This eco-friendly protocol ensures high atom economy and broad substrate scope by utilizing readily available substrates in water as a sustainable solvent at 60–65 °C, mediated by inexpensive, biodegradable, recyclable, and readily available β -cyclodextrin (β -CD) with high efficiency.



Scheme 16. β -cyclodextrin (β -CD) mediated synthesis of 2,4,6-tri-substituted alkyl & arylpyrimidines **91** by Chowrasia et al. (2016).

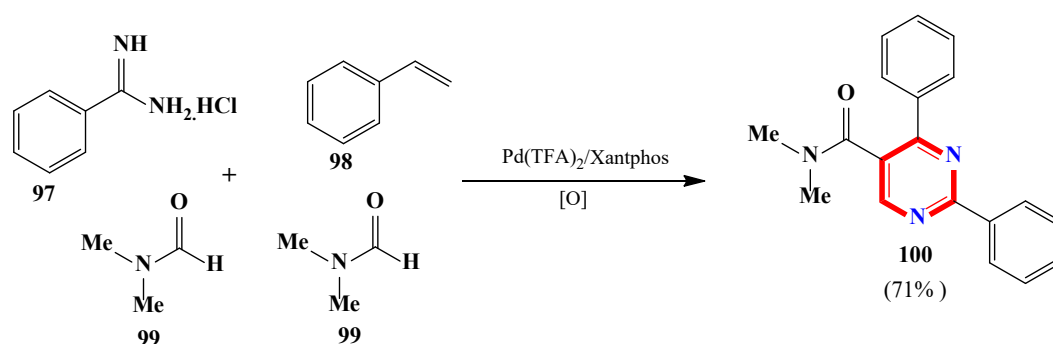
In the hierarchy of transition-metal catalysis, iridium (Ir)-catalyzed protocols are traditionally recognized for their exceptional efficiency and selectivity, particularly in hydrogen transfer and dehydrogenative coupling reactions. While these systems facilitate complex bond formations under moderate conditions, their large-scale viability is

often hindered by the high cost and scarcity of iridium. Seeking more sustainable alternatives within the 3d transition metal series, Deibi et al. (2017) reported an efficient and regioselective multicomponent synthesis of tetrasubstituted pyrimidines **96**, utilizing amidines **92** and three distinct alcohols **93**, **94**, **95** as cost-effective precursors. The reaction was mediated by an Ir(I) complex or Mn(I) featuring a sophisticated PNP pincer ligand in the presence of *t*-BuOK (Scheme 17) (Deibl; Kempe, 2017). This regioselective protocol ensures high atom economy and a broad substrate scope by utilizing cost-effective alcohols and amidines as precursors, mediated by sophisticated Ir(I) or sustainable Mn(I) pincer complexes in the presence of *t*-BuOK.



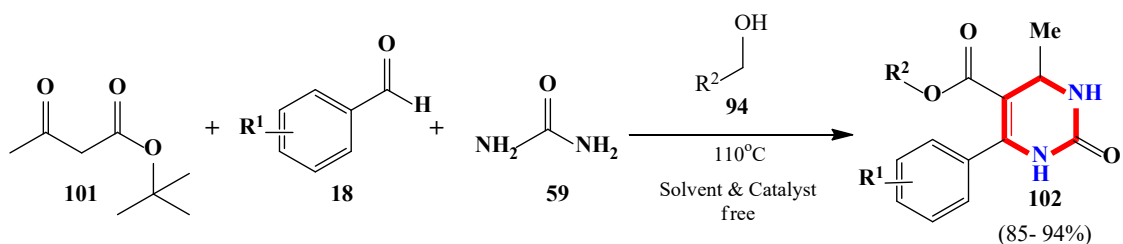
Scheme 17. Ir (I) or Mn (I) catalyzed synthesis of tetra-substituted alkyl or aryl pyrimidines **96** by Deibl et al., (2017).

In addition to the aforementioned transition-metal-catalyzed cyclizations, palladium-mediated oxidative coupling strategies have recently emerged as a sophisticated route for direct C–H functionalization. In this context, the research team of Guo (2017) reported an effective four-component strategy utilizing amidine hydrochloride **97**, styrene **98**, and *N,N*-dimethylformamide (DMF, **99**) (Scheme 18) (Guo et al., 2017) in the presence of Pd(TFA)₂/Xantphos as the catalytic system to afford *N,N*-dimethyl-2,4-diphenylpyrimidine-5-carboxamide **100**. A distinctive feature of this methodology is the versatile role of DMF as a dual synthon, providing both a one-carbon unit and the amide moiety. These roles were further confirmed through isotope-labeling experiments. This sophisticated strategy ensures high atom economy and a broad substrate scope by utilizing readily available amidines and styrene in common solvents, with DMF acting as a multifunctional reagent to achieve efficient direct C–H functionalization.



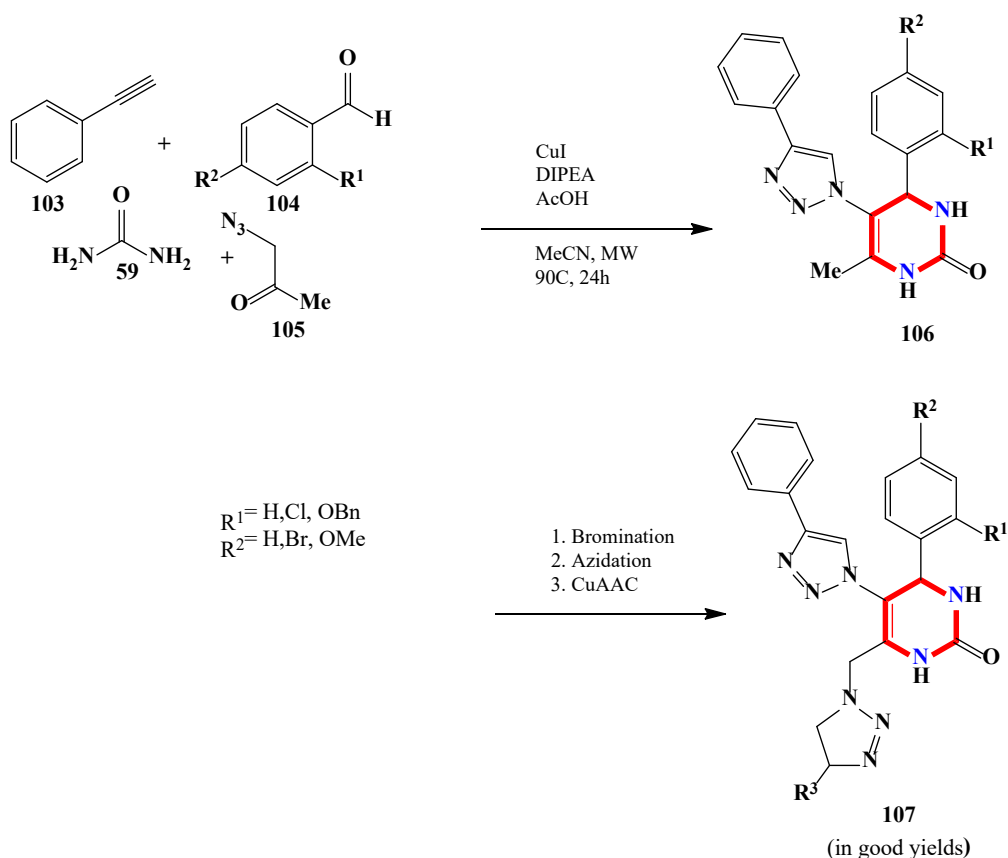
Scheme 18. Synthesis of *N,N*-dimethyl-2,4-diphenylpyrimidine-5-carboxamide **100** via Pd(TFA)₂/Xantphos catalysis by Guo et al. (2017).

In the pursuit of ultimate sustainability, researchers have focused on eliminating the need for both metal catalysts and organic solvents. In the following year, a prominent example of this eco-friendly approach is the multicomponent synthesis of functionalized dihydropyrimidinones **102**. In Scheme 19, the reaction involved the condensation of *tert*-butyl acetoacetate **101**, substituted benzaldehydes **18**, and urea **59**, using an alcohol **94** as a part of the reagent system. This transformation was conducted at 110 °C under strictly solvent-free and catalyst-free conditions, affording the target heterocycles in excellent yields (Tiwari et al., 2018). This ultimate sustainable protocol ensures high atom economy and a broad substrate scope by utilizing readily available aldehydes, urea, and acetoacetate under strictly solvent-free and catalyst-free conditions at 110 °C to achieve excellent yields.



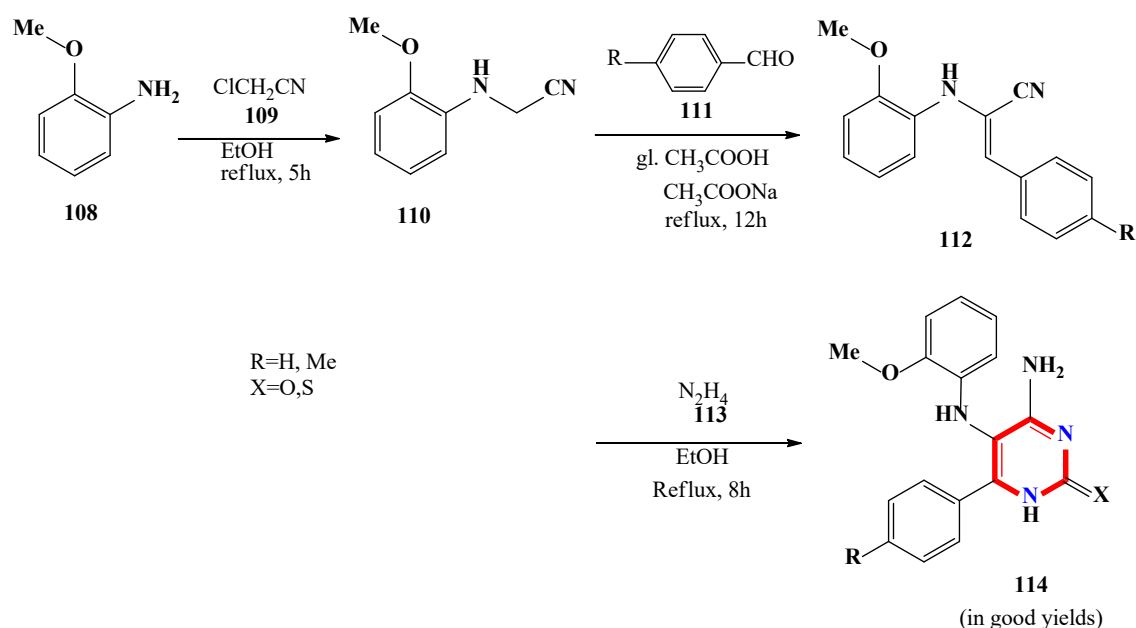
Scheme 19. Both solvent and catalyst-free four-component synthesis of poly-substituted dihydropyrimidinones **102** by Tiwari et al. (2018).

Further expanding the synergy between four-component reactions and click chemistry, a sophisticated protocol was developed for the synthesis of triazole-linked dihydropyrimidinones **107** in 2020. As depicted in Scheme 20, the initial phase involved a one-pot multicomponent coupling of phenylacetylene **103**, substituted benzaldehydes **104**, urea **59**, and an α -azido ketone **105** in the presence of CuI, DIPEA, and AcOH in acetonitrile. This transformation, assisted by MWI at 90 °C, yielded the 1,2,3-triazole-functionalized pyrimidinone core **105**. Subsequently, the methodology allows for further structural elaboration through a sequence of bromination, azidation, and a second Copper-catalyzed Azide-Alkyne Cycloaddition (CuAAC), leading to complex bis-triazole derivatives **107** in good yields (Carreiro et al., 2020). This sophisticated protocol ensures high atom economy and a broad substrate scope by combining a one-pot four-component coupling with MWI-assisted click chemistry using CuI-catalyst and readily available precursors in acetonitrile to yield complex bis-triazole derivatives.



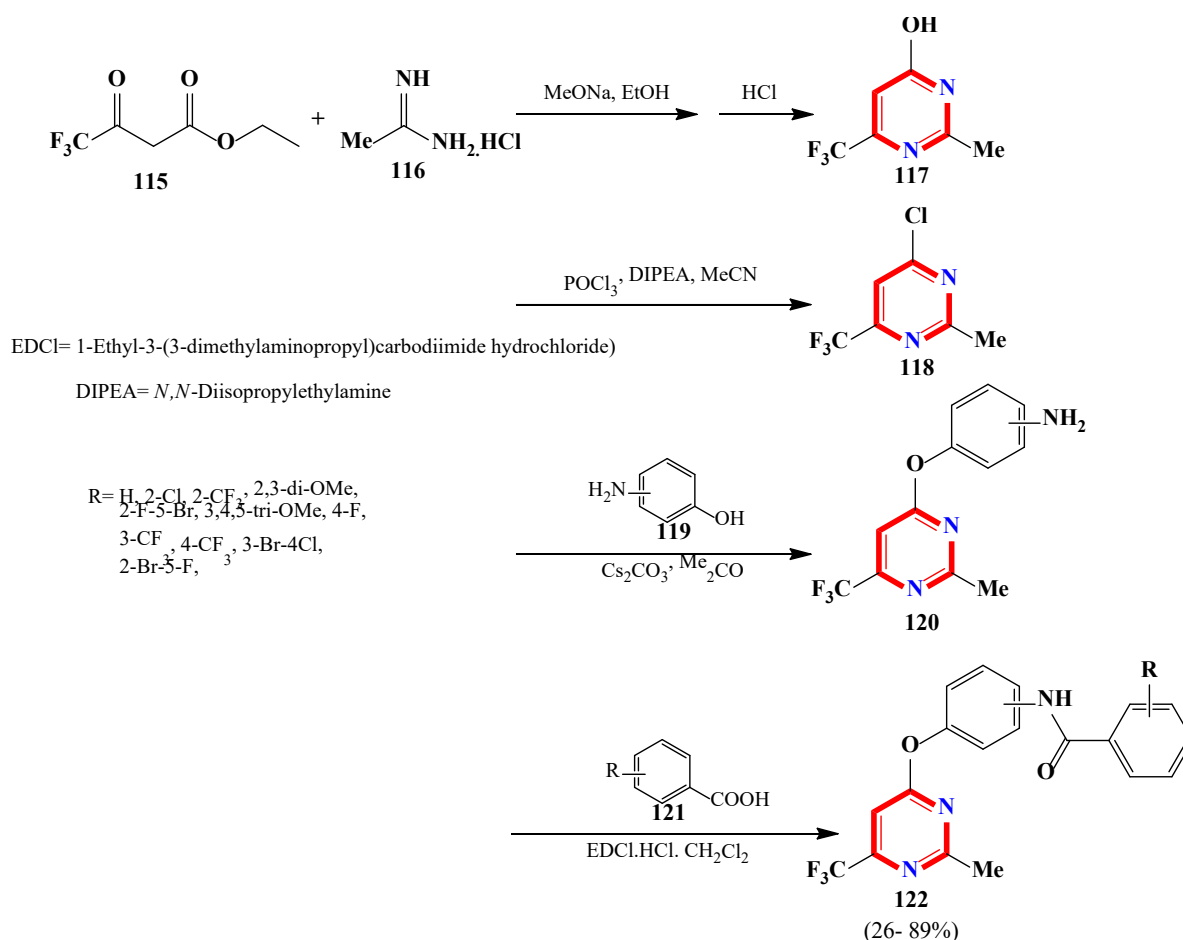
Scheme 20. CuI-catalyzed four-component synthesis of triazole-linked dihydropyrimidinones **107** by Carreiro et al. (2020).

In line with the development of diverse amino-functionalized heterocycles, during the year 2021, a systematic multi-step protocol was designed to access 4-amino-5-substituted pyrimidines by the *N*-alkylation of *o*-anisidine **108** using chloroacetonitrile **109** in refluxing ethanol to yield the corresponding nitrile intermediate **110**, which was followed by a Knoevenagel-type condensation with various aromatic aldehydes **111** in the presence of glacial acetic acid and sodium acetate to afford the α,β -unsaturated nitrile **112**. The final ring closure was achieved through a cyclocondensation reaction with hydrazine hydrate **113** in refluxing ethanol, providing the target 4-amino-pyrimidin-2(1*H*)-one/thione derivatives **114** (Scheme 21) (Othman et al., 2021). This systematic multistep protocol ensures high atom economy and broad substrate scope by utilizing readily available substrates in common solvents (EtOH, AcOH) to yield diverse functionalized pyrimidines with high efficiency.



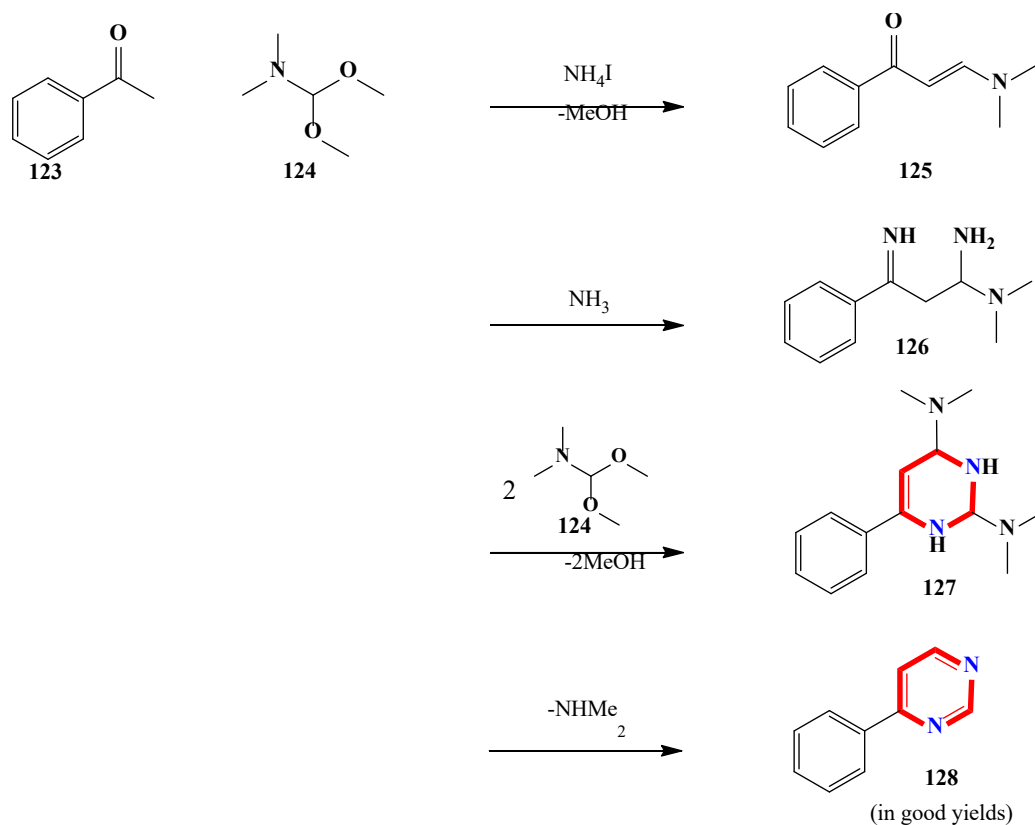
Scheme 21. Metal-free four-component synthesis 4-amino-pyrimidin-2(1*H*)-one/thione derivatives **114** by Othman et al. (2021).

Complementing the diverse array of synthetic protocols, recent advancements have highlighted the utility of multi-step transformations starting from fluorinated precursors to access highly functionalized pyrimidine scaffolds like trifluoromethyl-pyrimidinyl-oxy-benzamide derivatives **122** via a One-pot pseudo-four-component reaction within the same year. In this sequence, the synthesis began with the cyclocondensation of ethyl 4,4,4-trifluoro-3-oxobutanoate **115** with acetamidine hydrochloride **116** in the presence of MeONa-EtOH, followed by acidic workup to afford the 4-hydroxy-6-methyl-2-(trifluoromethyl)pyrimidine core **117**. Subsequently, chlorination with POCl₃ and DIPEA in acetonitrile yielded the 4-chloro intermediate **118**. This intermediate then underwent nucleophilic aromatic substitution with aminophenols **119** in the presence of Cs₂CO₃ to form the corresponding ether linkage. The final products were obtained through an amide coupling reaction with substituted benzoic acids **121** using EDCI·HCl as the coupling agent in CH₂Cl₂ (Scheme 22) (Wu et al., 2021). This sophisticated protocol ensures high atom economy and broad substrate scope by utilizing readily available fluorinated precursors in common solvents to synthesize functionalized pyrimidine derivatives with high efficiency.



Scheme 22. Base-promoted one-pot pseudo-four-component synthesis of trifluoromethyl-pyrimidinyl-oxy-benzamide derivatives **122** by Wu et al. (2021).

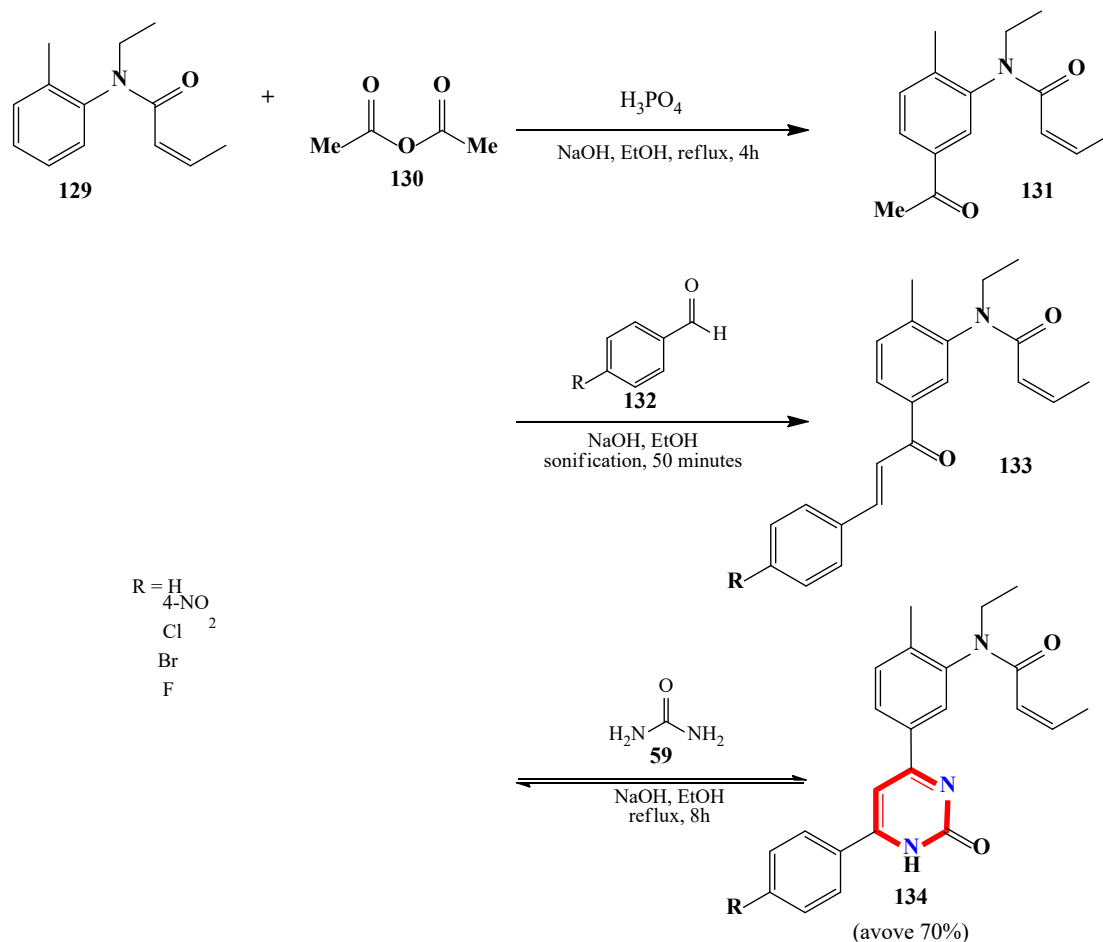
Further advancing the frontiers of sustainable pyrimidine synthesis, a facile and practical iodine-promoted approach has recently been developed for the preparation of substituted pyrimidines, such as 4-phenylpyrimidine **128**. This protocol utilized readily available ketones **123** and *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) **124** as starting materials. The NH₄I-promoted three-component tandem reaction operates under strictly metal- and solvent-free conditions, affording a broad range of substituted pyrimidines in acceptable yields (Scheme 23) (Fang et al., 2023). Key findings of this methodology include its exceptional environmental profile, a broad substrate scope with high functional group tolerance, and its demonstrated scalability through gram-scale synthesis, making it a highly attractive alternative to traditional transition-metal-catalyzed routes.



Scheme 23. NH_4I -promoted One-pot four-component synthesis of 4-phenylpyrimidine 128 by Fang et al. (2023).

Further expanding the synthetic methodologies for pyrimidine frameworks, most recently, a multistep synthetic strategy for the preparation of substituted pyrimidine-2-one derivatives 134 was reported by Mohaisen & Hassa (2005) employing aromatic amide 129 as the starting material. The initial step involved acetylation with acetic anhydride 130 in the presence of phosphoric acid and NaOH in ethanol under reflux for 4 h to obtain intermediate 131. This intermediate subsequently underwent ultrasonic-assisted condensation with a series of aromatic aldehydes 132 for 50 min, generating chalcone-type intermediates 133.

In the final step, these intermediates reacted with urea 59 in a basic NaOH/EtOH medium under reflux for 8 hours to yield the desired pyrimidine-2-one derivatives 134 (Scheme 24) (Mohaisen; Hassan, 2025). The key advantages of this protocol include ultrasonic-assisted condensation through a convenient sonication method, straightforward reaction conditions, the use of readily available reagents such as sodium hydroxide and ethanol, and the efficient construction of pyrimidine-2-one derivatives from easily accessible starting materials



Scheme 21. Both base & acid promoted the one-pot four-component synthesis of substituted pyrimidine-2-one derivatives **134** by Mohaisen & Hassan (2025).

5. Conclusions

The evolution of pyrimidine and its derivative synthesis clearly indicates a growing reliance on one-pot multicomponent reactions. Research conducted between 2005 and 2025 demonstrates that the utilization of transition metal catalysts (Pd, Cu, Ti, Zn, Mn) has not only simplified the construction of the pyrimidine core but also significantly expanded the substrate scope. The most promising development in this field is the successful application of solvent-free and catalyst-free protocols, which directly align with the goals of Green Chemistry. The synergy of these methods with modern technologies, such as microwave and ultrasound irradiation, has further accelerated these chemical processes. While metal catalysts remain indispensable in certain contexts, future research is expected to shift toward even more cost-effective and eco-friendly metal-free methodologies. The information compiled in this review serves as a robust foundation for researchers to innovate sustainable and advanced pyrimidine frameworks in the years to come.

6. Acknowledgments

The authors would like to express their deepest gratitude to Professor Dr. Fakir Rafiqul Alam, Dept of Chemistry, National University, Gazipur, Bangladesh for his cordial guidance and cooperation.

7. Authors' Contributions

Mohammad Mizanur Rahman: writing original draft preparation. *Mohammad Lokman Hossain*: reviewing and editing. *Abul Kalam Mohammad Lutfur Rahman*: reviewing and editing. *Abdul Fakhru'l Golam Masud Reza*: reviewing and editing.

8. Conflicts of Interest

No conflicts of interest.

9. Ethics Approval

Not applicable.

10. References

- Abdel-Raheem, S. A., Fouad, M. R., Gad, M. A., El-Dean, A. M. K., & Tolba, M. S. (2023). Environmentally green synthesis and characterization of some novel bioactive pyrimidines with excellent bioefficacy and safety profile towards soil organisms. *Journal of Environmental Chemical Engineering*, 11(5), 110839. <https://doi.org/10.1016/j.jece.2023.110839>
- Achelle, S., Malval, J. P., Aloïse, S., Barsella, A., Spangenberg, A., Mager, L., Akdas-Kilig, H., Fillaut, J. L., Caro, B., Robin-le Guen, F. (2013). Synthesis, photophysics and nonlinear optical properties of stilbenoid pyrimidine-based dyes bearing methylenepyran donor groups. *ChemPhysChem*, 14(12), 2725-2736. <https://doi.org/10.1002/cphc.201300419>
- Adib, M., Mahmoodi, N., Mahdavi, M., & Bijanzadeh, H. R. (2006). Microwave-assisted simple, one-pot, four-component synthesis of 2,4,6-triarylpyrimidines under solvent-free conditions. *Tetrahedron Letters*, 47(47), 9365-9368. <https://doi.org/10.1016/j.tetlet.2006.09.117>
- Al-Masoudi, N. A., Al-Salih, N. J., Marich, Y. A., Markus, T. (2015). Synthesis, and fluorescence properties of coumarin and benzocoumarin derivatives conjugated pyrimidine scaffolds for biological imaging applications. *Journal of Fluorescence*, 25, 1847-1854. <https://doi.org/10.1007/s10895-015-1677-z>
- Alam, M. M., Akhter, M., Husain, A., Marella, A., Tanwar, O. P., Ali, R., Hasan, S. M., Kumar, H., Haider, R., & Shaquiquzzaman, M. (2012). Anti-inflammatory and antimicrobial activity of 4,5-dihydropyrimidine-5-carbonitrile derivatives: Their synthesis and spectral elucidation. *Acta Poloniae Pharmaceutica*, 69(6), 1077-1085.
- Ali, M. R., Verma, G., Shaquiquzzaman, M., Akhter, M., & Alam, M. M. (2015). Synthesis and anticonvulsant activity of some newer dihydro-pyrimidine-5-carbonitrile derivatives: Part II. *Journal of Taibah University Medical Sciences*, 10(4), 437-443. <https://doi.org/10.1016/j.jtumed.2015.07.002>
- Bairagi, K. M., Younis, N. S., Emeka, P. M., Sangtani, E., Gonnade, R. G., Venugopala, K. N., Alwassil, O. I., Khalil, H. E., & Nayak, S. K. (2020). Antidiabetic activity of dihydropyrimidine scaffolds and structural insight by single crystal X-ray studies. *Medicinal Chemistry*, 16(7), 996-1003. <https://doi.org/10.2174/1573406416666191227123048>
- Bairagi, K. M., Venugopala, K. N., Mondal, P. K., Gleiser, R. M., Chopra, D., García, D., Odhav, B., & Nayak, S. K. (2018). Larvicidal study of tetrahydropyrimidine scaffolds against *Anopheles arabiensis* and structural insight by single crystal X-ray studies. *Chemical Biology & Drug Design*, 92(6), 1924-1932. <https://doi.org/10.1111/cbdd.13351>
- Bhole, R., Sarode, V., Kothapalli, L., Gurav, S., & Chikhale, R. (2023). Design, synthesis and pharmacological evaluation of some 2-methylsulfanyl-1,4-dihydropyrimidines derivatives as an analgesic agent. *Russian Journal of Bioorganic Chemistry*, 49, 897-904. <https://doi.org/10.1134/S1068162023040076>
- Biginelli, P. (1893). Synthesis of 3,4-dihydropyrimidin-2(1H)-ones. *Gazzeta Chimica Italiana*, 23, 360-416.
- Bruice, P. Y. (2007). Organic chemistry. 3rd edition. Singapore: Pearson Education.
- Brown, D. J. (1984). Comprehensive heterocyclic chemistry. Vol. 14. Katritzky, A. R., & Rees, C. W., editors. Oxford, UK: Pergamon Press.
- Carreiro, E. P., Sena, A. M., Puerta, A., Padrón, J. M., & Burke, A. J. (2020). Synthesis of novel 1,2,3-triazole-dihydropyrimidinone hybrids using multicomponent 1,3-dipolar cycloaddition (click)-Biginelli reactions: Anticancer activity. *Synlett*, 31(06), 615-621. doi: 10.1055/s-0039-1690781
- Chitikina, S. S., Buddiga, P., Deb, P. K., Mailavaram, R. P., Venugopala, K. N., Nair, A. B., Al-Jaidi, B., Kar, S. (2020). Synthesis and anthelmintic activity of some novel

- (E)-2-methylpropyl-4-(2-(substitutedbenzylidene)hydrazinyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidines. *Medicinal Chemistry Research*, 29, 1600-1610. <https://doi.org/10.1007/s00044-020-02586-5>
- Chikhale, R. V., Bhole, R. P., Khedekar, P. B., & Bhusari, K. P. (2009). Synthesis and pharmacological investigation of 3-(substituted-1-phenylethanone)-4-(substituted phenyl)-1, 2, 3,4-tetrahydropyrimidine-5-carboxylates. *European Journal of Medicinal Chemistry*, 44(9), 3645-3653. <https://doi.org/10.1016/j.ejmech.2009.02.021>
- Chowrasia, R., Katla, R., Darbem, M. P., Branquinho, T.A., de Oliveira, A. R., Manjari, P. S., & Domingues, N. L. C. (2016). Novel multicomponent syntheses of pyrimidines using β -CD in aqueous medium. *Tetrahedron Letters*, 57(14), 1656-1660. <https://doi.org/10.1016/j.tetlet.2016.03.003>
- Dahabiyeh, L. A., Hudaib, F., Hourani, W., Darwish, W., Abu-Irmaileh, B., Deb, P. K., Venugopala, K. N., Mohankall, V., Chandrashekharappa, S., & Abu-Dahab, R. (2023). Mass spectrometry-based metabolomics approach and *in vitro* assays revealed promising role of 2,3-dihydroquinazolin-4 (1H)-one derivatives against colorectal cancer cell lines. *European Journal of Pharmaceutical Sciences*, 182, 106378. <https://doi.org/10.1016/j.ejps.2023.106378>
- Deibl, N., & Kempe, R. (2017). Manganese-catalyzed multicomponent synthesis of pyrimidines from alcohols and amidines. *Angewandte Chemie International Edition*, 56(6), 1663-1666. <https://doi.org/10.1002/anie.201611318>
- Duraisamy, R., Al-Shar'i, N. A., Chandrashekharappa, S., Deb, P. K., Gleiser, R. M., Tratat, C., Chopra, D., Muthukurpalya Bhojgowd, M. R., Thirumalai, D., Morsy, M. A. (2023). Synthesis, biological evaluation, and computational investigation of ethyl 2,4,6-trisubstituted-1,4-dihydropyrimidine-5-carboxylates as potential larvicidal agents against *Anopheles arabiensis*. *Journal of Biomolecular Structure and Dynamics*, 42(8), 4016-4028. <https://doi.org/10.1080/07391102.2023.2217929>
- Elderfield, R. C. (1957). Heterocyclic compounds. Vol. 6. New York, NY, USA: John Wiley & Sons.
- Fang, F., Xia, J., Quan, S., Chen, S., & Deng, G. J. (2023). Metal- and solvent-free synthesis of substituted pyrimidines via an NH₄I-promoted three-component tandem reaction. *The Journal of Organic Chemistry*, 88(20), 14697-14707. <https://doi.org/10.1021/acs.joc.3c01700>
- Faldu, V. J., Talpara, P. K., & Shah, V. H. (2014). Efficient synthesis of diversely substituted pyrimidines by palladium catalyzed Suzuki-Miyaura coupling. *Tetrahedron Letters*, 55(8), 1456-1460. <https://doi.org/10.1016/j.tetlet.2014.01.042>
- Ganesan, P., Ranganathan, R., Chi, Y., Liu, X. K., Lee, C. S., Liu, S. H., Lee, G. H., Lin, T. C., Chen, Y. T., & Chou, P. T. (2017). Functional pyrimidine-based thermally activated delay fluorescence emitters: Photophysics, mechanochromism, and fabrication of organic light-emitting diodes. *Chemistry-A Europe Journal*, 23(12), 2858-2866. <https://doi.org/10.1002/chem.201604883>
- Ghazoui, A., Saddik, R., Benchat, N., Guenbour, M., Hammouti, B., Al-Deyab, S., & Zarrouk, A. (2012). Comparative study of pyridine and pyrimidine derivatives as corrosion inhibitors of C38 steel in molar HCl. *International Journal of Electrochemical Science*, 7(8), 7080-7097. [https://doi.org/10.1016/S1452-3981\(23\)15769-5](https://doi.org/10.1016/S1452-3981(23)15769-5)
- Götzinger, A. C., Theobald, J., Dreher-Helmer, L. M., Müller, T. J. J. (2016). One-pot coupling-coupling-cyclocondensation synthesis of fluorescent pyrazoles. *The Journal of Organic Chemistry*, 81(21), 10328-10338. <https://doi.org/10.1021/acs.joc.6b01326>
- Guo, W., Liao, J., Liu, D., Li, J., Ji, F., Wu, W., & Jiang, H. (2017). A four-component reaction strategy for pyrimidine carboxamide synthesis. *Angewandte Chemie International Edition*, 56(51), 1289-1293. <https://doi.org/10.1002/anie.201610486>
- Haque, J., Ansari, K., Srivastava, V., Quraishi, M., & Obot, I. (2017). Pyrimidine derivatives as novel acidizing corrosion inhibitors for N80 steel useful for petroleum industry: A combined experimental and theoretical approach. *Journal of Industrial and Engineering Chemistry*, 49, 176-188. <https://doi.org/10.1016/j.jiec.2017.01.025>
- Hekal, H. A., Hammad, O. M., El-Brollosy, N. R., Salem, M. M., & Allayeh, A. K. (2024). Design, synthesis, docking, and antiviral evaluation of some novel pyrimidinone-based α -aminophosphonates as potent H1N1 and HCoV-229E inhibitors. *Bioorganic Chemistry*, 147, 107353. <https://doi.org/10.1016/j.bioorg.2024.107353>

- Irfan, A., Al-Sehemi, A. G., Assiri, M. A., & Mumtaz, M. W. (2019). Exploring the electronic, optical and charge transfer properties of acene-based organic semiconductor materials. *Bulletin of Materials Science*, 42, 1-7. <https://doi.org/10.1007/s12034-019-1838-9>
- Irfan, A., Muhammad, S., Chaudhry, A. R., Al-Sehemi, A. G., & Jin, R. (2017). Tuning of optoelectronic and charge transport properties in star shaped anthracenothiophene-pyrimidine derivatives as multifunctional materials. *Optik*, 149, 321-331. <https://doi.org/10.1016/j.ijleo.2017.09.065>
- Karpov, A. S., Merkul, E., Rominger, F., & Müller, T. J. J. (2005). Concise syntheses of meridianins by carbonylative alkynylation and a four-component pyrimidine synthesis. *Angewandte Chemie International Edition*, 44(42), 6951-6956. <https://doi.org/10.1002/anie.200501703>
- Keshari, M., Khan, R. A., Khalilullah, H., Yusuf, M., & Ahmed, B. (2020). Pharmacophore modeling, design, and synthesis of potent antihypertensives, oxazolo/thiazolo-[3,2-a]-pyrimidin-3(2H)-one, and 1,5-dihydroimidazo-[1,2-a]-pyrimidin-3(2H)-one derivatives: A pilot trial. *Bioorganic & Medicinal Chemistry Letters*, 30(23), 127604. <https://doi.org/10.1016/j.bmcl.2020.127604>
- Kiselyov, A. S. (2005). One-pot synthesis of polysubstituted pyrimidines. *Tetrahedron Letters*, 46(10), 1663-1665. <https://doi.org/10.1016/j.tetlet.2005.01.068>
- Kumar, R., Singh, R., das Chagas Almeida, A., da Trindade Granato, J., de Oliveira Lemos, A. S., Kumar, K., Patil, M. T., da Silva, A. D., Rode, A. B., & Coimbra, E. S. (2023). Imidazo [1,2-a] pyrimidine as a new antileishmanial pharmacophore against *Leishmania amazonensis* promastigotes and amastigotes. *ACS Omega*, 8(43), 40613-40621. <https://doi.org/10.1021/acsomega.3c05441>
- Liang, C., Shi, C., Song, H., Jiang, H., Yao, Q. (2014). One-pot, four-component sequential synthesis of novel 4-arylamino-5-carboxyl pyrimidine derivatives. *Journal of Chemical and Pharmaceutical Research*, 6(4), 720-726.
- Lu, W., Song, W., Hong, D., Lu, P., & Wang, Y. (2009). Copper-catalyzed one-pot synthesis of 2-alkylidene-1,2,3,4-tetrahydropyrimidines. *Advanced Synthesis & Catalysis*, 351(11-12), 1768-1772. <https://doi.org/10.1002/adsc.200900260>
- Mohaisen, R. J., & Hassan, H. A. (2025). Design, synthesis and biological activity of pyrimidine derivatives of acetomido chalcone of crotamiton. *Advanced Journal of Chemistry, Section A*, 8(4), 1088-1105.
- Moharam, M. M., Saleh, E. A. M., Hassan, I., & Husain, K. (2023). Synthesis, Antifungal, and Antioxidant Evaluation of new class of thiazolo[3,2-a]pyrimidine and Pyrimido[5,4-d]thiazolo[3,2-a]pyrimidine derived from α , α -ketene dithioacetals as five and six-membered heterocycles analogues. *Russian Journal of Bioorganic Chemistry*, 49, 1119-1136. <https://doi.org/10.1134/S1068162023050199>
- Majumder, S., & Odom, A. L. (2010). Pyrimidine Titanium catalyzed one-pot multicomponent coupling reactions for direct access to substituted pyrimidines. *Tetrahedron*, 66(17), 3152-3158. <https://doi.org/10.1016/j.tet.2010.02.083>
- Othman, I. M., Alamshany, Z. M., Tashkandi, N. Y., Gad-Elkareem, M. A., Anwar, M. M., & Nossier, E. S. (2021). New pyrimidine and pyrazole-based compounds as potential EGFR inhibitors: Synthesis, anti-cancer, antimicrobial evaluation and computational studies. *Bioorganic Chemistry*, 114, 105078. <https://doi.org/10.1016/j.bioorg.2021.105078>
- Pan, N., Wu, R., Yan, C., Zhou, M., Fei, Q., Li, P., & Wu, W. (2023). Design, synthesis, antifungal activity, and molecular docking of novel trifluoromethyl pyrimidine derivatives containing 1,3,4-oxadiazole and thioether moieties as potential succinate dehydrogenase inhibitors. *Journal of Heterocyclic Chemistry*, 60(10), 1768-1777. <https://doi.org/10.1002/jhet.4719>
- Padmashali, B., Chidananda, B. N., Govindappa, B., Basavaraj, S. M., Chandrashekhara, S., & Venugopala K. N. (2019). Synthesis and characterization of novel 1, 6-dihydropyrimidine derivatives for their pharmacological properties. *Journal of Applied Pharmaceutical Science*, 9(5), 117-124. <https://dx.doi.org/10.7324/JAPS.2019.90517>
- Park, I. S., Komiyama, H., & Yasuda, T. (2017). Pyrimidine-based twisted donor-acceptor delayed fluorescence molecules: A new universal platform for highly efficient blue electroluminescence. *Chemical Science*, 8, 953-960. <https://doi.org/10.1039/C6SC03793C>
- Pinner, A. (1884). Ueber die einwirkung von acetessigäther auf die amidine. *Berichte der Deutschen Chemischen Gesellschaft*, 17(2), 2519-2526. <https://doi.org/10.1002/cber.188401702173>

- Robinson, S. J., Petzer, J. P., Rousseau, A. L., Terre'Blanche, G., Petzer, A., Lourens, A. C. U. (2016). Carbamate substituted 2-amino-4,6-diphenylpyrimidines as adenosine receptor antagonists. *Bioorganic & Medicinal Chemistry Letters*, 26(3), 734-738. <https://doi.org/10.1016/j.bmcl.2016.01.004>
- Sakai, N., Aoki, Y., Sasada, T., & Konakahara, T. (2005). New approach to the practical synthesis of tri- or tetrasubstituted pyrimidine derivatives: A four-component coupling reaction from a functionalized silane, two types of aromatic nitriles, and acetals. *Organic Letters*, 7(21), 4705-4708. <https://doi.org/10.1021/ol0519011>
- Sasada, T., Aoki, Y., Ikeda, R., Sakai, N., & Konakahara, T. (2011). Synthesis of tri- or tetrasubstituted pyrimidine derivatives through the [5+1] annulation of enamidines with either N,N-dimethylformamide dialkyl acetals or orthoesters. *Chemistry, Chemistry – A European Journal*, 17(34), 9385-9394. <https://doi.org/10.1002/chem.201100040>
- Sayed, A. Z., Aboul-Fetouh, M. S., & Nassar, H. S. (2012). Synthesis, biological activity and dyeing performance of some novel azo disperse dyes incorporating pyrazolo[1,5-a]pyrimidines for dyeing of polyester fabrics. *Journal of Molecular Structure*, 1010, 146-151. <https://doi.org/10.1016/j.molstruc.2011.11.046>
- Tiwari, S. V., Seijas, J. A., Vazquez-Tato, M. P., Sarkate, A. P., Karnik, K. S., & Nikalje, A. P. (2018). Ionic liquid-promoted synthesis of novel chromone-pyrimidine coupled derivatives, antimicrobial analysis, enzyme assay, docking study and toxicity study. *Molecules*, 23(2), 440. <https://doi.org/10.3390/molecules23020440>
- Upadhyay, K., & Kumar, A. (2010). Pyrimidine based highly sensitive fluorescent receptor for Al^{3+} showing dual signalling mechanism. *Organic & Biomolecular Chemistry*, 8, 4892-4897. <https://doi.org/10.1039/C0OB00171F>
- Venugopala, K. N., Deb, P. K., Kamat, V., Santosh, R., Poojary, B., Kugaji, M. S., Kumbar, V. M., Morsy, M. A., Aldhubiab, B., & Attimarad, M. (2024a). 5-(3-substituted phenyl)-pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione Derivatives as anticancer agents. U.S. Patent No. 11,932,649.
- Venugopala, K. N., Deb, P. K., Kamat, V., Santosh, R., Poojary, B., Kugaji, M. S., Kumbar, V. M., Morsy, M. A., Aldhubiab, B., & Attimarad, M. (2024b). 5-(substitutedphenyl)-7-imino-7,8-dihydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione Analogues as Anti-inflammatory Agents. U.S. Patent No. 11,884,677.
- Venugopala, K. N., Govender, R., Khedr, M. A., Venugopala, R., Aldhubiab, B. E., Harsha, S., & Odhav, B. (2015). Design, synthesis, and computational studies on dihydropyrimidine scaffolds as potential lipoxygenase inhibitors and cancer chemopreventive agents. *Drug Design, Development and Therapy*, 9, 911-921. <https://doi.org/10.2147/DDDT.S73890>
- Venugopala, K. N., Tratratt, C., Pillay, M., Chandrashekarappa, S., Al-Attraqchi, O. H. A., Aldhubiab, B. E., Attimarad, M., Alwassil, O. I., Nair, A. B., & Sreeharsha, N. (2020). *In silico* design and synthesis of tetrahydropyrimidinones and tetrahydropyrimidinethiones as potential thymidylate kinase inhibitors exerting anti-TB activity against *Mycobacterium tuberculosis*. *Drug Design, Development and Therapy*, 14, 1027-1039. <https://doi.org/10.2147/DDDT.S228381>
- Venugopala, K. N., Nayak, S. K., Gleiser, R. M., Sanchez-Borzone, M. E., Garcia, D. A., & Odhav, B. (2016). Synthesis, polymorphism, and insecticidal activity of methyl 4-(4-chlorophenyl)-8-iodo-2-methyl-6-oxo-1,6-dihydro-4h-pyrimido[2,1-b]quinazoline-3-carboxylate against *Anopheles arabiensis* mosquito. *Chemical Biology & Drug Design*, 88(1), 88-96. <https://doi.org/10.1111/cbdd.12736>
- Venugopala, K. N., Shinu, P., Tratratt, C., Deb, P. K., Gleiser, R. M., Chandrashekarappa, S., Chopra, D., Attimarad, M., Nair, A. B., & Sreeharsha, N. (2022). 1,2,3-triazolyl-tetrahydropyrimidine conjugates as potential sterol carrier protein-2 inhibitors: larvicidal activity against the malaria vector *Anopheles arabiensis* and *in silico* molecular docking study. *Molecules*, 27(9), 2676. <https://doi.org/10.3390/molecules27092676>
- Verbitskiy, E. V., Cheprakova, E. M., Subbotina, J. O., Schepochkin, A. V., Slepukhin, P. A., Rusinov, G. L., Charushin, V. N., Chupakhin, O. N., Makarova, N. I., & Metelitsa, A. V. (2014). Synthesis, spectral and electrochemical properties of pyrimidine-containing dyes as photosensitizers for dye-sensitized solar cells.

Dyes and Pigments, 100, 201-214. <https://doi.org/10.1016/j.dyepig.2013.09.006>

- Yavari, I., & Nematpour, M. (2013). Copper-catalyzed tandem synthesis of tetrasubstituted pyrimidines from alkynes, sulfonyl azides, trichloroacetonitrile, and tetramethylguanidine. *Synlett*, 24, 165-168. DOI: 10.1055/s-0032-1317664
- West, T. P., & Chu, C. P. (1986). Utilization of pyrimidines and pyrimidine analogues by fluorescent pseudomonads. *Microbios*, 47, 149-157.
- Wu, J., Hou, Z., Wang, Y., Chen, L., Lian, C., Meng, Q., Zhang, C., Li, X., Huang, L., & Yu, H. (2022). Discovery of 7-alkoxy-[1,2,4]triazolo[1,5-a]pyrimidine derivatives as selective positive modulators of GABAA1 and GABAA4 receptors with potent antiepileptic activity. *Bioorganic Chemistry*, 119, 105565. <https://doi.org/10.1016/j.bioorg.2021.105565>
- Wu, W., Lan, W., Wu, C., & Fei, Q. (2021). Synthesis and antifungal activity of pyrimidine derivatives containing an amide moiety. *Frontiers in Chemistry*, 9, 695628. <https://doi.org/10.3389/fchem.2021.695628>

Funding

Not applicable.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Copyrights

Copyright for this article is retained by the author(s), with first publication rights granted to the journal.

This is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/4.0/>).