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Recent green approaches for the synthesis of thienopyrimidine scaffolds: an overview (2007–2025)

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Thienopyrimidines are considered purine bioisosteres as they consist of a thiophene ring fused with pyrimidine. Thienopyrimidines are present in three isomeric forms: thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines, and thieno[3,4-*d*]pyrimidines. They are of interest in drug discovery owing to their extensive pharmacological and biological activities. Several drugs incorporating the thienopyrimidine scaffold are marketed commercially, while others are presently in the experimental and development stages. Green chemistry, also known as sustainable chemistry, aims to minimize the environmental impact of chemical products and processes. Thus, applying green techniques has become a necessity in organic chemistry. The current review discusses the different synthetic approaches to obtain thienopyrimidine scaffolds using various green techniques, including microwave-assisted synthesis, green solvents, one-pot reactions, solvent-less reactions, and catalysis, published between 2007 and 2025. Additionally, a brief overview of the conventional synthetic routes is provided. This review emphasizes how green chemistry is becoming increasingly important in promoting the synthesis of bioactive heterocycles such as thienopyrimidines.

1. Introduction

1.1. Green chemistry

Green chemistry is defined by the U.S. Environmental Protection Agency (EPA) as chemistry that prevents pollution of the environment through the design of chemical products and processes that are harmless to the environment.[1,2] Also, green chemistry is known as sustainable chemistry that aims to minimize the environmental impact of chemical products and processes. The 12 principles of green chemistry involve the use of renewable resources, the reduction of energy waste, the reduction of hazardous chemicals, and the use of safer solvents. One of the most prominent challenges in the synthesis of organic chemicals is avoiding costly and harmful reagents as well as reducing energy consumption.[3,4] As a result, one of the

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most prominent goals of green chemistry is the creation of environmentally safe chemical processes,[1] which produce chemical products that eventually break down after their application into components that are harmless and do not remain in the environment.[2] Recently, the industrial and chemical research fields have focused on developing eco-friendly green reactions.[5,6] In addition, both local and large companies are focused on enhancing synthetic techniques to produce a variety of heteroatom moieties with maximum yields.[7] While most other conventional methods are highly profitable, they are not eco-friendly because they produce a considerable amount of waste and by-products.[8] Therefore, green chemistry provides a promising approach for meeting the needs of the medical sector.[9] Various green techniques can be utilized in chemical processes, including microwave-assisted techniques, synthesis using green solvents, catalysis, solvent-less synthesis, and one-pot reactions.

1.1.1. Microwave-assisted technique. Recently, microwave-assisted organic synthesis (MAOS) has become an important technique in green chemistry. It is a highly valuable technique in new drug discovery research because of its efficiency and speed. Moreover, it is highly suitable for the automated parallel synthesis of diverse compound libraries.[10] In addition, microwave-assisted synthesis has gained popularity for the synthesis of organic and inorganic compounds, as it can synthesize porous substances such as metal–organic frameworks (MOFs) in minutes instead of days[11] and shorten the crystallization process required to form porous substances because nucleation occurs more rapidly in a microwave. Unlike traditional methods, MAOS avoids the use of harmful solvents. Eventually, MOFs synthesized by the microwave-assisted technique offer improved functionality and thus highlight the crucial role of this technique in future developments.[12]

1.1.2. Green solvents. Green solvents are non-toxic, environmentally friendly, and sustainable alternatives to conventional solvents, reducing the ecological impact of chemical processes. In organic synthesis, water is the optimal green solvent, being highly abundant, non-toxic, and allowing the reaction to proceed under mild conditions without producing hazardous waste. Likewise, ethanol is a prominent green solvent due to its biodegradability and renewability. In addition, dimethyl sulfoxide (DMSO) is utilized because of its high solvating power and ability to enable reactions at low temperatures, reduce energy consumption, and reduce harmful solvent use.[13] Ionic liquids are green solvents with different characteristics; they consist of cations and anions and exist in liquid state at room temperature. They have many advantages, such as low flammability, low vapor pressure, high thermal stability, high chemical stability, and recyclability. Thus, they are highly valuable alternatives to conventional volatile solvents.[13,14]

1.1.3. Catalysis. Catalysis plays a significant role in green chemistry as it reduces energy consumption, facilitates milder reactions, and enhances selectivity.[15] A catalyst is a substance that makes a reaction occur more rapidly without being consumed in the reaction. Since the catalyst is not consumed in the reaction, it can be utilized in multiple processes, and only a small amount is required compared to the substrate. There are various types of catalysts involving Lewis acids, protons (H^+), metals, and organometallic complexes.[16]

1.1.4. Solvent-less technique. The solvent-less reaction technique is a green chemistry approach used to decrease the production of waste materials or by-products because it avoids the use of traditional volatile solvents. Moreover, it produces high yields in a short time and provides easy separation and workup processes. Many solvent-less reactions can be performed using ultrasonication, microwave irradiation (MWI), infrared and UV-visible irradiation, milling, and grinding techniques. These technologies are added advantage, thereby making solvent-less reactions environmentally friendly and economical through decreasing waste production and energy consumption and shortening the reaction time.[17]

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1.1.5. One-pot technique. One-pot reactions, also known as multicomponent reactions (MCRs), are a powerful strategy in organic synthesis because they allow the combination of three or more reactants simultaneously in a single reaction pot. They enable the efficient preparation of the desired products through simple synthetic pathways, while maintaining the functional group integrity.[18,19] This technique is superior to the conventional methods as it shortens reaction times and avoids waste production that is common in conventional methods by utilizing protecting groups and sequential reactions.[20]

To quantitatively measure how much these green techniques make a synthesis method more efficient and eco-friendly, some indicators can be used for evaluating its greenness. These indicators are known as "green chemistry metrics". Green chemistry metrics include atom economy (AE) or atom efficiency, process mass intensity (PMI), real atom economy (RAE), environmental factor (*E*-factor), and reaction mass efficiency (RME). We will focus on AE, which is the ratio between the product formula weight to the formula weight of all reactants used. The higher the AE%, the greener the process (optimal value is 100%). Also, we focus on PMI, which is the ratio between the total mass of all utilized reactants to the mass of the product. The lower the PMI, the less waste produced (optimal value is 1). Additionally, we focus on the *E*-factor, which is the ratio between the mass of waste to the mass of the target product. The lower the *E*-factor, the less waste produced (optimal value is 0).[21]

Heterocyclic compounds, especially nitrogen-containing heterocycles, play an important role in organic research and therapeutic chemistry due to their diverse pharmacological and biological actions.[22–26] Thienopyrimidine is one of these nitrogen-containing heterocycles that has gained momentum. Thienopyrimidine scaffolds are of interest in drug discovery owing to their extensive pharmacological and biological activities.[27–32] Thienopyrimidine derivatives have been discovered to exhibit anti-cancer,[33–43] anti-infective,[44] antioxidant,[45] antimicrobial,[46–48] and anti-tuberculosis[49] activities. Furthermore, currently, different thienopyrimidine derivatives are undergoing clinical trials and are utilized in medical applications. For instance, relugolix (TAK-385) is in phase III and has been approved for the treatment of advanced hormone-sensitive prostate cancer in the European Union and for advanced prostate cancer in the USA.[50] Another example of a thienopyrimidine derivative undergoing

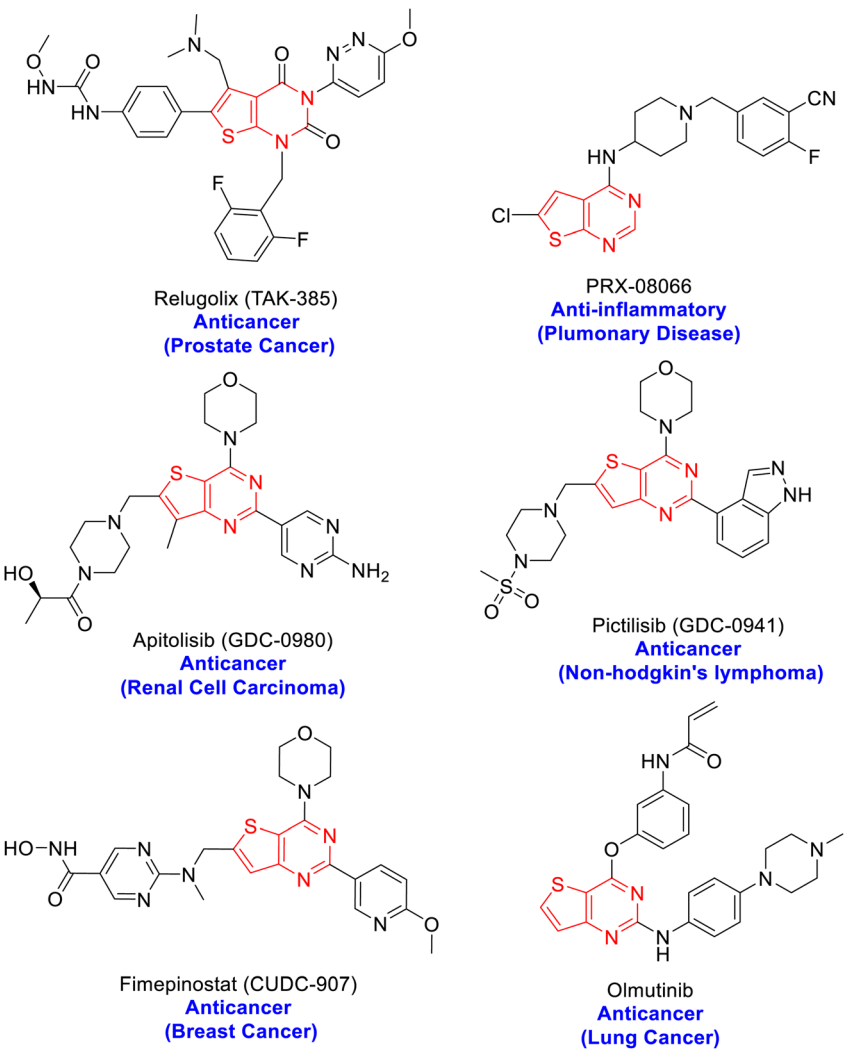


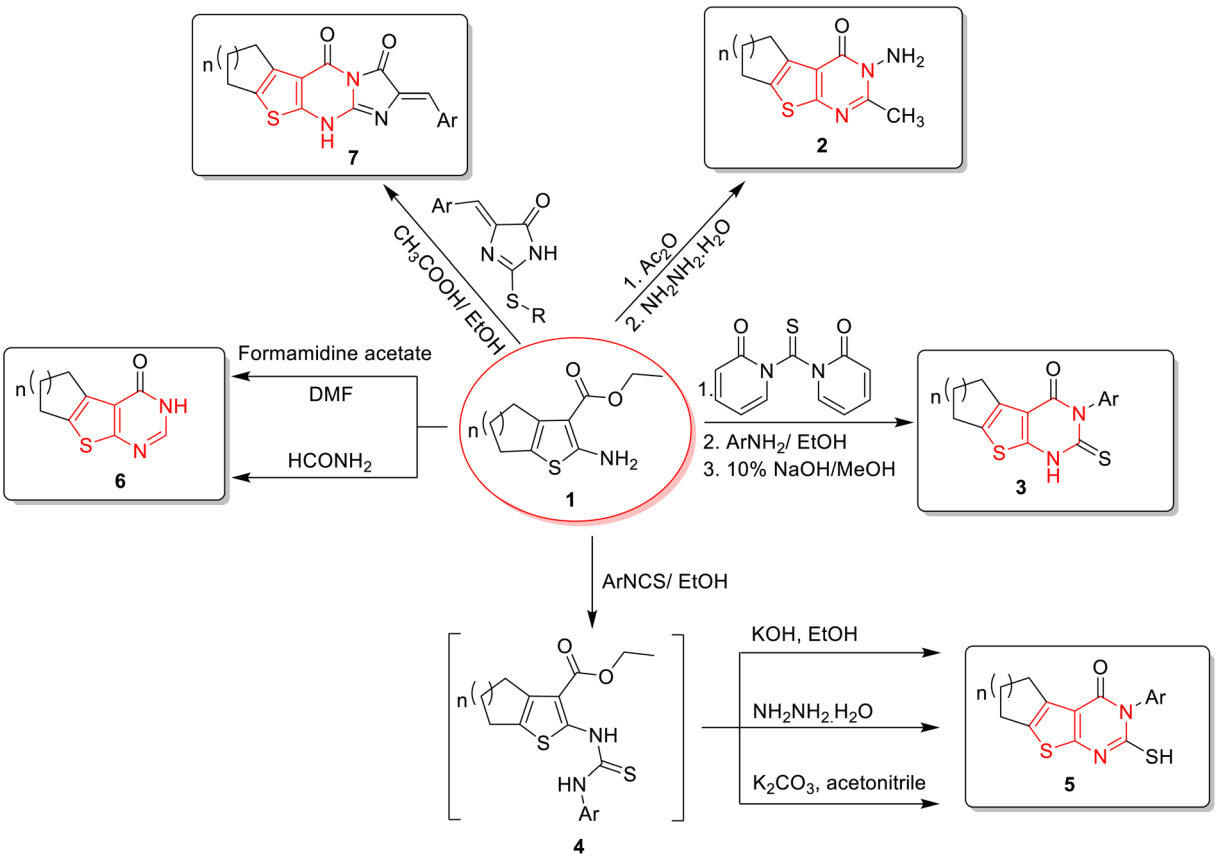
Fig. 1 Thienopyrimidine compounds in clinical trials and on the market.

phase a II trial is PRX-08066, which acts as a potent serotonin 5-HT subtype 2B receptor antagonist and is utilized for pulmonary diseases, particularly pulmonary arterial hypertension. Furthermore, it was revealed that it can prevent the activation of fibroblasts, making it a good candidate as an antitumor agent.[51,52] In addition, apitolisib (GDC-0980) showed a significant anti-tumor effect in PI3K hyperactivation or PTEN loss tumor models.[53,54] Similarly, pictilisib (GDC-0941) and fimepinostat (CUDC-907) are in phase II. Pictilisib is used for the treatment of non-Hodgkin's lymphoma, metastatic breast cancer, and advanced solid tumors.[53,55,56] Fimepinostat is used against breast cancer, multiple myeloma, and lymphoma.[57] Finally, olmutinib is a thienopyrimidine marketed as an EGFR tyrosine kinase inhibitor; it demonstrated high efficacy and showed controlled safety in patients with T790M-positive non-small cell lung cancer[58] (Fig. 1). Although several reviews discussed the synthesis and biological importance of thienopyrimidine derivatives,[36,44,59–65] this review focuses specifically on the green synthetic strategies reported over the last two decades.

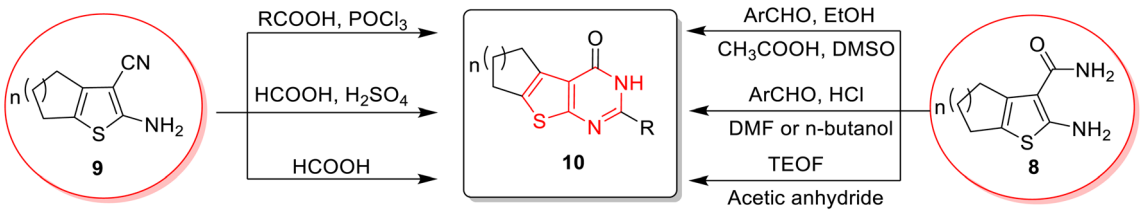
2. Synthesis of thienopyrimidine derivatives

2.1. Conventional synthesis

Thienopyrimidine can be synthesized through different synthetic pathways. The most prominent pathway is the Gewald reaction, which provides the key precursors for thienopyrimidine synthesis. The reaction usually starts from 2-aminothiophene-3-carboxylate **1**, 2-aminothiophene-3-carboxamide **8**, or 2-aminothiophene-3-carbonitrile **9**. Elmongy and colleagues[45] synthesized 3-amino-2-methyl thienopyrimidine derivatives **2** through the reaction of 2-aminothiophene-3-carboxylate **1** with acetic anhydride, followed by cyclization using hydrazine hydrate in ethanol. Kim and co-workers[66] reported the synthesis of thienopyrimidine derivatives **3** using 2-aminothiophene-3-carboxylate derivative **1** as a precursor, which reacted with 1,1′-thiocarbonylbis(pyridin-2(1*H*)-one) to convert the amino group into an isothiocyanate group. The isothiocyanate product reacted with substituted anilines to produce thiourea derivatives, which were then cyclized with the help of alcoholic sodium hydroxide. 2-Mercapto-thienopyrimidin-4-one **5** was afforded by reacting 2-aminothiophene-3-carboxylate with different isothiocyanates, giving rise to thiourea derivatives **4**, followed by cyclization with potassium hydroxide in ethanol;[67,68] likewise it was cyclized using hydrazine hydrate[69] or potassium carbonate in acetonitrile.[70] Another pathway for the synthesis of thienopyrimidinone from thiophene aminoester is through reaction with formamidine acetate in dimethyl formamide (DMF)[71–73] or with formamide.[74–76] Sheta *et al.*[77] prepared imidazothienopyrimidine **7** by reacting the starting material, substituted 2-aminothiophene-3-carboxylate **1**, with alkylated thioimidazolone in acetic acid and ethanol (Scheme 1).

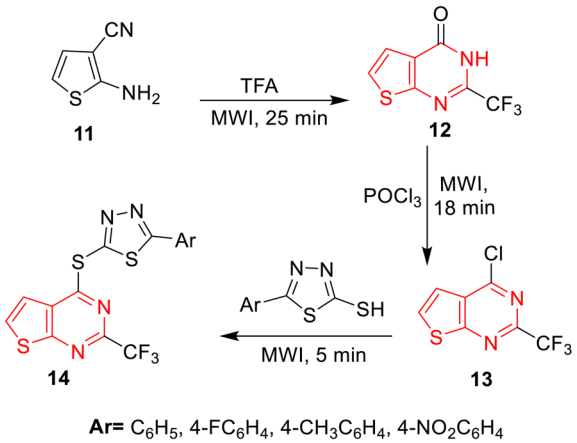


Scheme 1 Collective representation of the thienopyrimidine synthesis from thiophene aminoester.



Scheme 2 Different synthetic pathways for thienopyrimidinone.

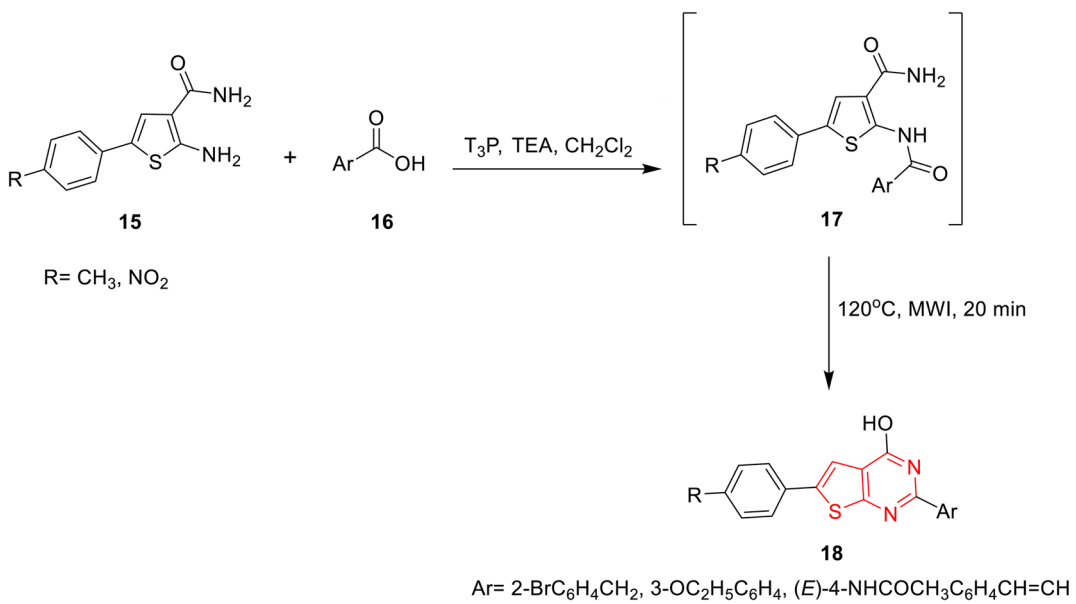
A different approach for thienopyrimidine synthesis was the reaction of 2-aminothiophene-3-carboxamide **8** with substituted benzaldehyde in glacial acetic acid and DMSO[78] or substituted benzaldehyde and HCl in DMF[79,80] or in n-butanol,[69] yielding thienopyrimidinone derivatives **10**.[81] Moreover, they can be obtained by reacting 2-aminothiophene-3-carboxamide **8** with triethyl orthoformate (TEOF) and acetic anhydride.[79] Furthermore, 2-aminothiophene-3-carbonitrile **9** provided thienopyrimidinone derivatives through a reaction with aliphatic acids and phosphorus oxychloride ($POCl_3$),[82] with formic acid and sulphuric acid,[83] or formic acid only[84–86] (Scheme 2). However, these conventional methods have a negative impact on the environment due to the use of harmful solvents, high energy consumption, and waste production. Thus, it has become necessary to replace these harmful conventional methods with more green ones that avoid the use of solvents or use greener solvents and the use of high temperatures, and involve multiple-step reactions. Therefore, applying green techniques is more eco-friendly, time-saving, and cost-saving.[87–89]



Scheme 3 Synthesis of 4-substituted-2-(trifluoromethyl)thieno[2,3-*d*]pyrimidines **14**.

2.2. Green synthesis

2.2.1. Using microwave technique. In 2012, Song and coworkers[90] prepared a new series of fluorinated thienopyrimidines *via* the microwave-assisted technique. 2-Aminothiophene-3-carboxynitrile (**11**) was cyclized using trifluoroacetic acid (TFA) under MWI for 25 min. The produced 2-trifluoromethyl thieno[2,3-*d*]pyrimidine-4(3*H*)-one (**12**) was chlorinated with $POCl_3$ under MWI for 18 min to yield 4-chloro-2-(trifluoromethyl)thieno[2,3-*d*]pyrimidine (**13**). Finally,



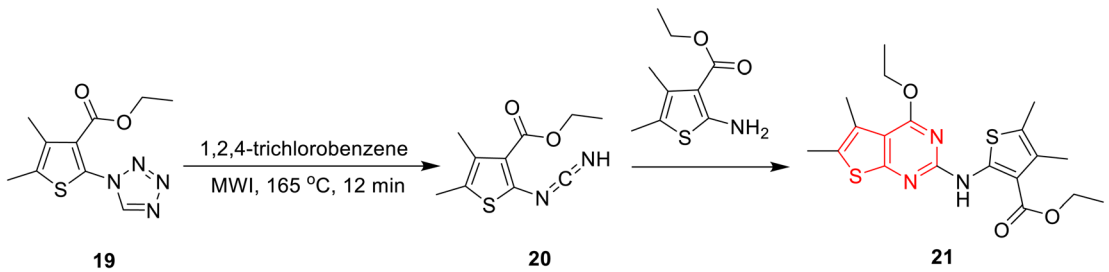
Scheme 4 Synthesis of 4-hydroxythieno[2,3-*d*]pyrimidine derivatives **18**.

nucleophilic substitution reactions took place with different 1,3,4-thiadiazole derivatives under MWI for 5 min to give compound **14** (Scheme 3). The use of MWI in all steps enhances the reaction efficiency and speed and provides a high yield of 82–91% and a high AE of 90.8%.

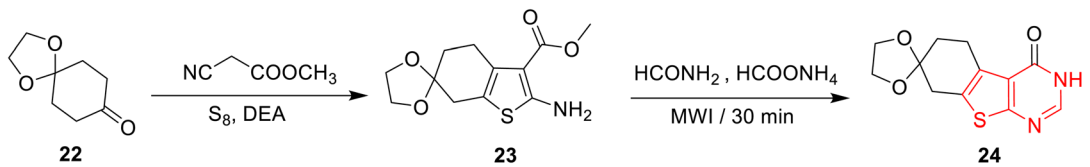
In the same year, Poojari and coworkers,[91] described an efficient microwave-assisted approach for synthesizing 4-hydroxythieno[2,3-*d*]pyrimidine compounds. This method utilized 2-aminothiophene-3-carboxamide derivatives **15** as precursors, which underwent a one-pot reaction with various acids **16** at 120 °C for 20 min in the presence of propylphosphonic anhydride (T_3P) and triethylamine (TEA), furnishing amide intermediate **17**, which was then cyclized to produce the target product **18** in a yield of up to 99% and an AE of 88.1% (Scheme 4). This method is highly efficient, rapid, and gentle, as the use of T_3P avoids the use of a strong acidic medium.

According to Soares *et al.*,[92] 4-ethoxythieno[2,3-*d*]pyrimidine **21** can be obtained through microwave-induced thermolysis of 4,5-dimethyl-2-(1*H*-tetrazol-1-yl)thiophene-3-carboxylate (**19**) (Scheme 5). This was explained by initial nitrogen elimination, followed by rearrangement into the respective carbodiimide and subsequent cyclization owing to the nucleophilic attack of the *in situ*-generated aminothiophene. Although the yield of this method is slightly low at 46%, the AE is very high (93.5%), with a PMI of 1.04 and *E*-factor of 0.04.

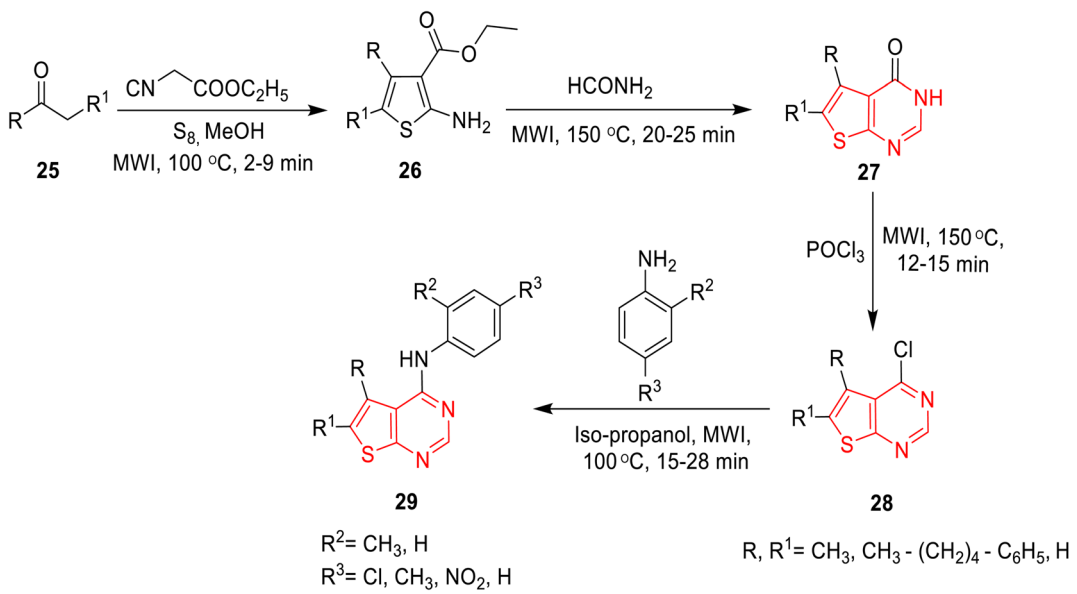
Di Fruscia and co-authors[93] reported the synthesis of thieno[2,3-*d*]pyrimidin-4-one scaffold through the Gewald condensation reaction, where ketone **22** reacted with methyl cyanoacetate



Scheme 5 Synthesis of 4-ethoxythieno[2,3-*d*]pyrimidine **21**.



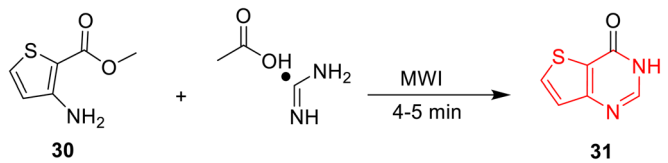
Scheme 6 Synthesis of substituted thieno[2,3-*d*]pyrimidin-4-one **24**.



Scheme 7 Synthesis of 4-chloro-5,6-disubstituted thieno[2,3-*d*]pyrimidines **29**.

and elemental sulfur in the presence of diethylamine (DEA) as a catalyst to produce compound **23**. Microwave-assisted cyclization is further performed in the presence of formamide and ammonium formate to afford the desired thienopyrimidone derivative **24**, which shows a neuroprotective effect in Parkinson's disease (Scheme 6).

Gill *et al.*[94] outlined the synthesis of 4-chloro-5,6-disubstituted-thieno[2,3-*d*]pyrimidine *via* the Gewald reaction under MWI for 2–9 min to yield 2-amino-3-carboethoxy thiophenes **26**. Subsequently, cyclization of newly formed thiophene derivatives **26** was conducted with formamide under neat conditions and MWI for 20–25 min to yield compounds **27**, followed by chlorination with $POCl_3$ under MWI for 12–15 min to produce 4-chloro-5,6-disubstituted thieno[2,3-*d*]pyrimidine **28**. Then, nucleophilic displacement of the chloride atom with substituted aniline afforded the desired product **29**, which has antibacterial activity (Scheme 7). Compared to traditional procedures, MWI enables the synthesis of target products with enhanced purity, yields, and reaction time.



30 **31**

Scheme 8 Synthesis of thieno[3,2-*d*]pyrimidine-4(3*H*)-one **31**.

32 **33**

R, R^1= CH_3, C_2H_5- $(CH_2)_3$- $(CH_2)_5$- $CH_2CH_2CH(CH_3)CH_2$- $(CH_2)_3CO$
R^2= H, CH_3, C_2H_5

Scheme 9 Synthesis of thieno[2,3-*d*]pyrimidine derivatives **33**.

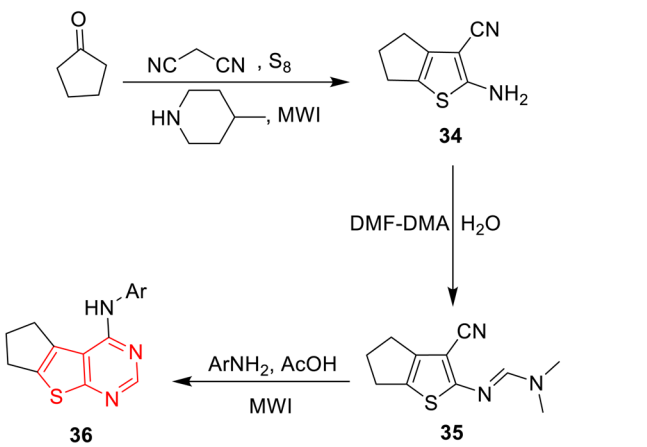
Meanwhile, Wang *et al.*[95] introduced microwave-assisted cyclization of methyl-3-aminothiophene-2-carboxylate (**30**) with formamidine acetate to give thieno[3,2-*d*]pyrimidine-4(3*H*)-one (**31**) (Scheme 8). This reaction provides a good yield of 76% and a shorter reaction time, but its PMI and *E*-factor are high at 2.4 and 1.4, respectively, indicating high loss of the reactants.

Accordingly, Sureja and collaborators[47] reported the reaction of 2-amino-4,5-substituted thiophene-3-carbonitrile **32** with different acids. The reaction was carried out in the presence of aluminium oxide and $POCl_3$ under MWI for 2–4 min, affording the antimicrobial 2,5,6-substituted thieno[2,3-*d*]pyrimidine-4(3*H*)-one derivatives **33** in yields ranging from 78% to 90%. This method is superior to the conventional method, which requires reflux for 1.5–2.5 h and gives yields of 70–83% (Scheme 9).

In 2018, a series of *N*-substituted thieno[2,3-*d*]pyrimidin-4-amines was synthesized starting with the typical Gewald reaction, but the reaction was upgraded with 4-methylpiperidine, which is an efficient and inexpensive catalyst; this led to a shorter reaction time and provided a higher yield of 2-aminothiophene-3-carbonitrile **34**. Eventually, polymerization, cyclization, and Dimroth rearrangement occurred under MWI, affording the desired product **36** in 71–95% yield (Scheme 10). This method is efficient as it is simple, shortens the reaction time, and produces higher yields compared to the conventional method, which requires a longer time of 0.5–5 h and gives yields of 64–90%.[96]

Two years later, Sun *et al.*[97] applied the same method to synthesize thiophene[2,3-*d*]pyrimidine derivatives **39** (Scheme 11). MWI was used in all steps of the synthesis, thereby minimizing the reaction time and providing a higher yield.

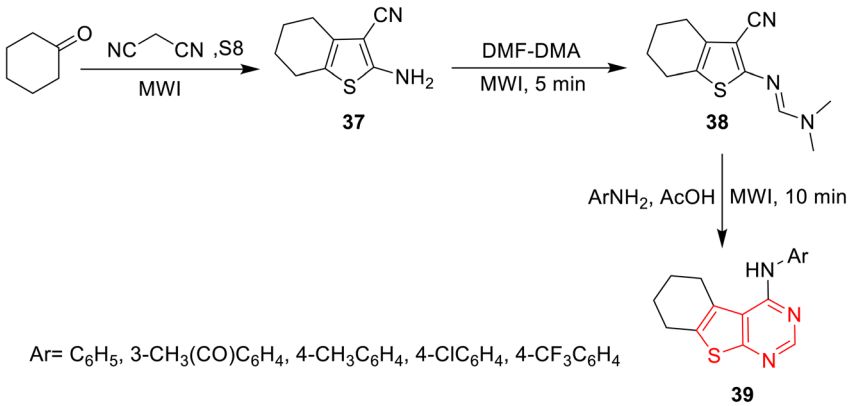
2.2.2. Using green solvents. In 2015, Han *et al.*[98] proposed a novel method for the synthesis of 5-substituted thieno[2,3-*d*]pyrimidin-4-ol **41** from 2-aminothiophene-3-carboxylate derivative **40**, where *N*-methylpyrrolidone (NMP) was used as a solvent under argon protection (Scheme 12). As a result, the



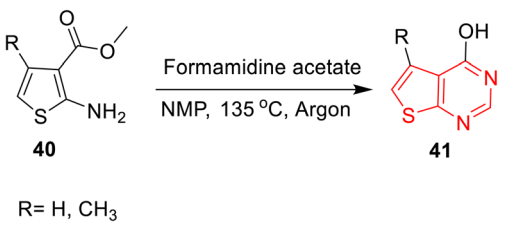
34 **35** **36**

Ar= C_6H_5, 2-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-FC_6H_4, 3,5-$Cl_2C_6H_3$, 3-Cl-4-F-C_6H_3

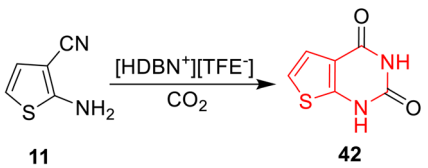
Scheme 10 Synthesis of *N*-substituted thieno[2,3-*d*]pyrimidin-4-amine derivatives **36**.



Scheme 11 Synthesis of *N*-aryl thieno[2,3-*d*]pyrimidin-4-amines **39**.



Scheme 12 Synthesis of 5-substituted thieno[2,3-*d*]pyrimidin-4-ol derivatives **41**.



Scheme 13 Synthesis of the thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivative **42**.

employed NMP solvent has several advantages, including high polarity, low viscosity and volatility, thermal and chemical stability, and high miscibility with water and many organic solvents. Also, the reaction conditions are mild and environmentally benign.

Li and coworkers developed a new method for the synthesis of a thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivative (**42**) using an ionic liquid, [HDBN$^+$][TFE$^-$], which is a simple and easily prepared solvent. The reaction occurs in the presence of CO_2, which is inexpensive, abundant, and renewable, and a green source of carbon atoms. This reaction is simple, effective, and produces a high yield of 94%, with the optimal AE (100%), PMI (1), and *E*-factor (0)[99] (Scheme 13).

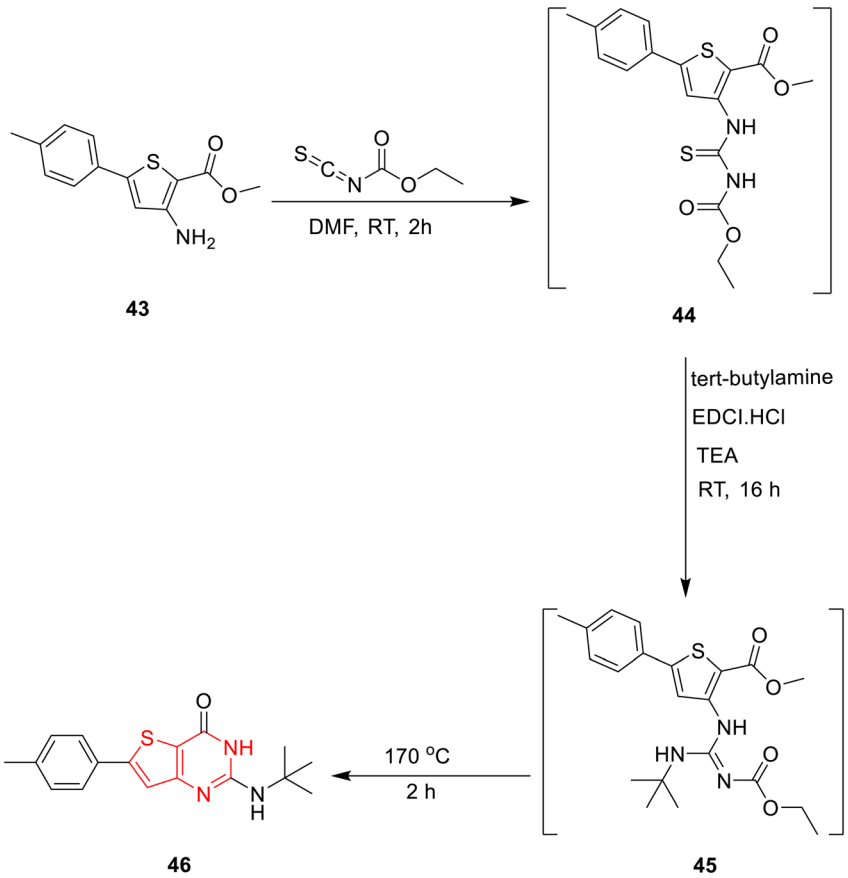
2.2.3. One-pot synthesis. A synthetic pathway to produce 2-(*tert*-butylamino)-6-(*p*-tolyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**46**) was suggested by Cohen *et al.*[100] Firstly, the precursor methyl 3-amino-5-(*p*-tolyl)thiophene-2-carboxylate (**43**) condensed with ethoxycarbonyl isothiocyanate in DMF to obtain thiourea carbamate intermediate **44**, which was not isolated. Thereafter, TEA, *tert*-butylamine, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) were added to the reaction mixture. The obtained guanidine intermediate **45** was cyclized at 170 °C to provide the desired product **46**, which has antimalarial activity (Scheme 14).

In 2017, Abaee *et al.*[101] developed a new approach for the synthesis of 2-phenylthieno[2,3-*d*]pyrimidine through a one-pot Gewald reaction. The reaction was performed by concurrently mixing the four reaction components: cyclohexanone, malononitrile, elemental sulfur, and benzonitrile simultaneously in the presence of NaOH as a base and *tert*-butanol as a solvent for 3 h at 50 °C. The targeted product 2-phenylthieno[2,3-*d*]pyrimidin-4-amine **47** was afforded in a very high yield of 95%, with an AE of 75.35%, a low PMI of 1.3, and an *E*-factor of 0.3 (Scheme 15).

Meanwhile, Wilding and colleagues[65] reported a one-pot method for the synthesis of 2-aminothiophene[2,3-*d*]pyrimidin-4-one (**50**). Initially, reacting 4-chloropyrimidine with sodium hydrosulfide provided mercaptopyrimidine derivative **49**, which was not separated from the reaction mixture. Hence, α-chloroacetaldehyde and K_2CO_3 as a catalyst were added to obtain the desired product **50**. Dimerization of the sulphydryl intermediate was prevented by carrying out the reaction under inert conditions (Scheme 16).

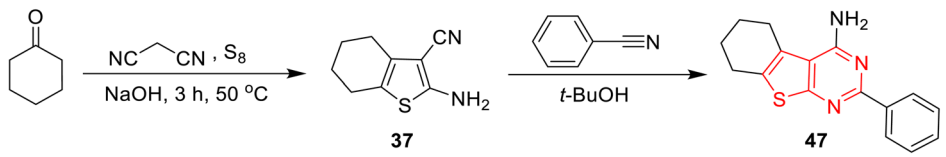
Shi and associates[102] reported a new strategy for the synthesis of 5-phenylthieno[2,3-*d*]pyrimidine-4(3*H*)-one (**51**) through a one-pot reaction without intermediate isolation, instead of the conventional method that involved three steps. The reaction comprises coupling all the reaction components, acetophenone, ethyl cyanoacetate, sulfur, and formamide, in one vessel at 170 °C for 6 h. In addition, the reaction was performed in the presence of DEA and L-proline as catalysts, affording AE of 73.5%, PMI of 2.5, and *E*-factor of 1.5 (Scheme 17).

Shi *et al.*[103] synthesized 5,6-substituted thieno[2,3-*d*]pyrimidin-4-amine derivatives **52** through a multicomponent reaction; hence, the reaction was rapid, efficient, provided a high yield reaching up to 96%, and shortened the reaction time immensely. The procedure involved incorporating ketone, malononitrile, sulfur, and formamide under catalysis with



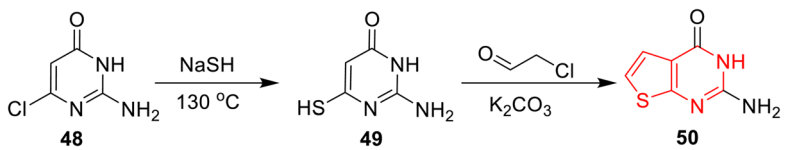
43 44 45 46

Scheme 14 Synthesis of 2-(*tert*-butylamino)-6-(*p*-tolyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**46**).



37 47

Scheme 15 One-pot synthesis of 2-phenylthieno[2,3-*d*]pyrimidin-4-amine **47**.



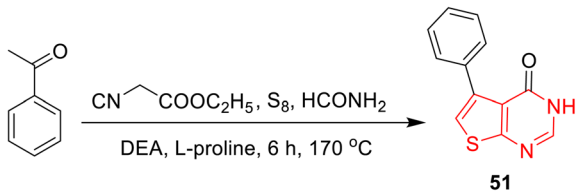
48 49 50

Scheme 16 Synthesis of 2-aminothieno[2,3-*d*]pyrimidine **50**.

Na_2HPO_4 and triphenylphosphine (PPh_3), which inhibits the dimerization of product **52** (Scheme 18). The product shows multi-targeted kinase inhibitory effect. The high AE (80.8%), low PMI (1.3), and low *E*-factor (0.3) indicate the effective incorporation of all the reactants in the reaction with minimal waste production.

A series of substituted pyrrolo[1,2-*α*]thieno[3,2-*e*]pyrimidine **55** was synthesized *via* a one-pot reaction. In this reaction, the three components, 2,4-dioxo-4-phenylbutanoic acid (**53**), malononitrile, and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**37**), were combined with dioxane as the solvent and *N*,*N*-diisopropylethylamine (DIPEA) as a catalyst. The reaction was refluxed at 80 °C for 2 h to obtain product **55** with a high AE (78.28%).[104] The obtained product shows antitumor activity (Scheme 19).

2.2.4. Catalyst-assisted synthesis. In 2007, Davoodnia and team[105] developed a novel catalytic method for the synthesis of thieno[2,3-*d*]pyrimidine-4(3*H*)-one **57**. The reaction was carried



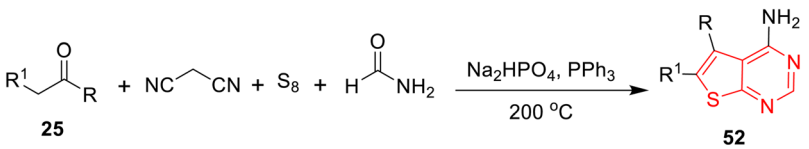
Scheme 17 Multicomponent approach to the synthesis of 5-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**51**).

out by heterocyclization of the starting materials 2-aminothiophene-3-carboxamide derivatives **56** and ortho esters and catalyzed by 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) in ethanol (Scheme 20). $H_3PW_{12}O_{40}$ has many advantages including high surface acidity, thermal stability, and low oxidation potential. This method is superior to the traditional method because the utilization of $H_3PW_{12}O_{40}$ shortened the reaction time from 130–170 min to 20–30 min and increased the yield from 56–68% to 69–82%.[106]

In their study, Bakavoli and collaborators[107] investigated an innovative and efficient method for the synthesis of 2-aryl-5,6-dimethylthieno[2,3-*d*]pyrimidine **60**, which has antibacterial activity. According to the Gewald reaction, butan-2-one, malononitrile, S_8, and DEA reacted to provide 2-amino-4,5-dimethylthiophene-3-formonitrile (**58**). Later, derivative **58** underwent acidic hydrolysis to produce **59**, which undergoes nucleophilic addition with a series of aromatic aldehydes in acetonitrile under the catalysis of iodine at room temperature for only 15–30 min and finally cyclization to obtain the target product **60** (Scheme 21). The reaction proceeded with a low PMI (1.1), good *E*-factor (0.1), and high AE (89.6%).

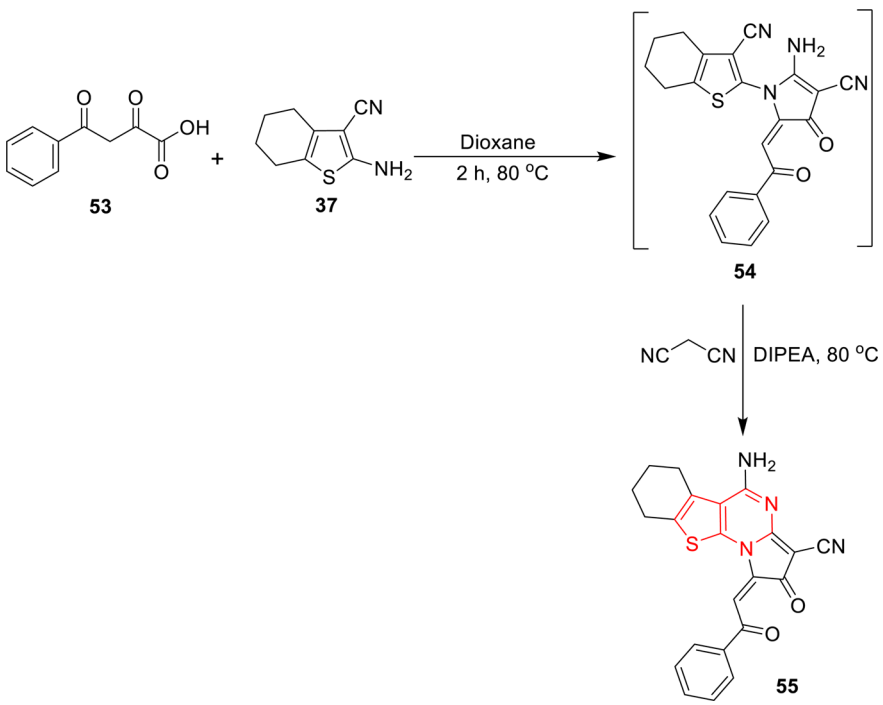
An organo-catalyzed method was investigated for the synthesis of 2-phenylbenzo[4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**62**). The reaction was conducted by aerobic cross-coupling of 2-amino-3-carboxamide derivative **61** with benzylamine using *ortho*-naphthoquinone (*o*-NQ1) catalyst and TFA as a co-catalyst.[108] The use of these catalysts helps to overcome the defects of the method reported by the Nguyen group involving closed systems, high temperatures, and metal catalysts, resulting in lower yields[109] (Scheme 22).

In a recent study, 2-phenylthieno[2,3-*d*]pyrimidin-4-one **65** could be prepared under catalysis by either the same method

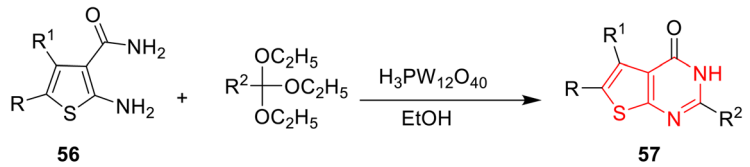


R, R^1= $(CH_2)_4$ - CH_3, C_6H_5 - C_6H_5, C_6H_5 - H, C_6H_5 - H, 4-$CH_3C_6H_4$ - H, 4-$OCH_3C_6H_4$ - H, 4-ClC_6H_4

Scheme 18 Synthesis of 5,6-substituted thieno[2,3-*d*]pyrimidin-4-amine **52** *via* a one-pot Na_2HPO_4-catalyzed reaction.



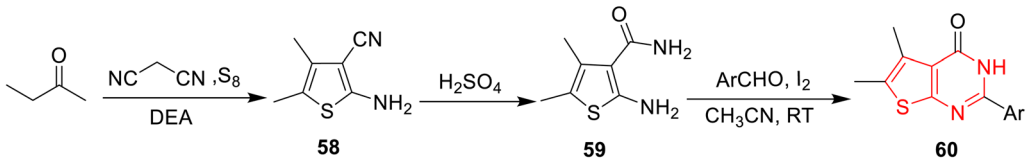
Scheme 19 Synthesis of the substituted pyrrolo[1,2-α]thieno[3,2-*e*]pyrimidine **55**.



56 57

R, R^1= CH_3, CH_3- $(CH_2)_4$
R^2= H, CH_3, C_2H_5

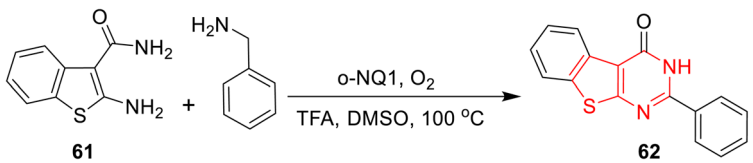
Scheme 20 Synthesis of thieno[2,3-*d*]pyrimidine-4(3*H*)-one **57** catalyzed by $H_3PW_{12}O_{40}$.



58 59 60

Ar= C_6H_5, 2-OHC_6H_4, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-$OCH_3C_6H_4$

Scheme 21 Iodine-catalyzed synthesis of 2-aryl-5,6-dimethylthieno[2,3-*d*]pyrimidines **60**.



61 62

Scheme 22 Synthesis of thieno[2,3-*d*]pyrimidine **62** catalyzed by *o*-NQ1.

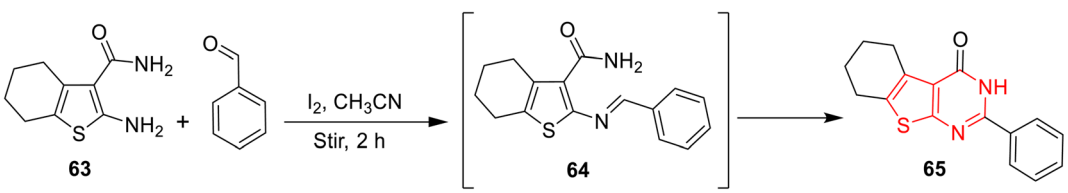
(Scheme 22) of using an *ortho*-naphthoquinone (*o*-NQ1) catalyst and TFA as a co-catalyst[108] or by cyclization with benzaldehyde, which was performed in acetonitrile and iodine was used as a catalyst. Consequently, as with all the catalyzed reactions, the conditions were substantially improved, as seen by the shorter reaction time and stirring at room temperature. In addition, this reaction showed greenness with a high AE (82.2%), low PMI (1.2), and good *E*-factor (0.2)[110] (Scheme 23).

2.2.5. Synthesis at room temperature. Room temperature reactions are more eco-friendly as they allow the use of greener solvents, less energy consumption, and less waste production. Thus, they align with the principles of green chemistry.[111]

In 2016, Narender *et al.*[112] investigated a new cyclization method for 2-substituted aminothieno[2,3-*c*]pyridine-3-carboxylate derivatives **66**. Cyclization occurs through stirring overnight with hydrazine hydrate and ethanol at room temperature. The reaction afforded the desired thieno[2,3-*d*] pyrimidine derivatives **67** in a good yield of about 65–71%. Later, **67** reacted with substituted aldehydes to give derivatives **68**, which have antimycobacterial activity (Scheme 24).

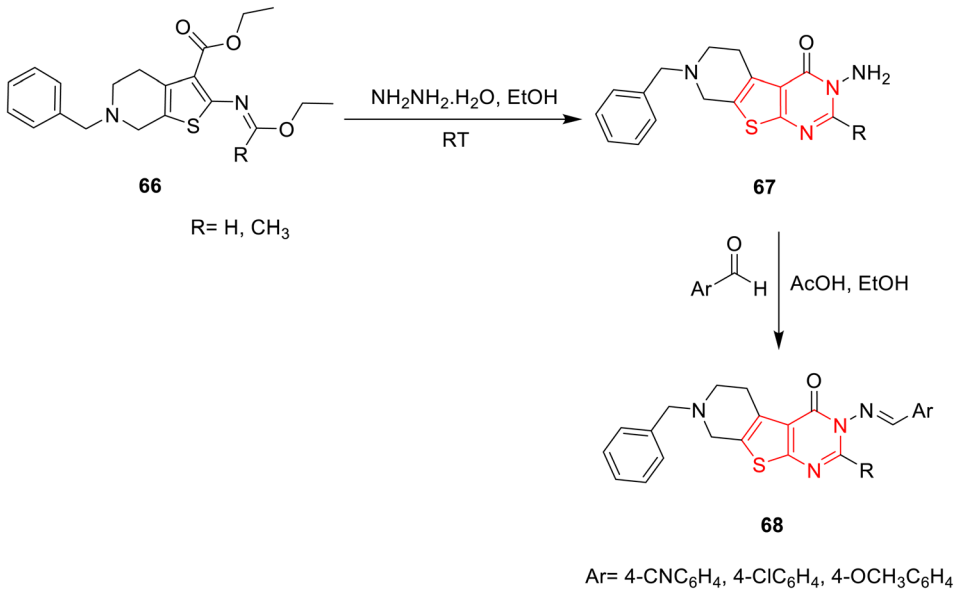
In 2019, a cyclization reaction between aminothiophene derivatives and formamide at room temperature was researched to provide the 7-substituted thieno[3,2-*d*]pyrimidin-4(3*H*)-one with a good yield of 60–65% and good AE of 75.2%. Additionally, it could be synthesized *via* acetylation of aminothiophene with acetic anhydride or by reacting aminothiophene with α-bromoketone in the presence of TEA and dichloromethane (DCM) under mild conditions. Product **70** was reacted with 30% NH_4OH to afford product **71** in high yields of 75–85% (ref. 113) (Scheme 25).

2.2.6. Synthesis through hybrid green techniques. Combining more than one green technique in the same reaction offers many advantages, such as less waste production, higher atom economy, shorter reaction time, and consequently, environmental impact minimization.



63 64 65

Scheme 23 Synthesis of 2-phenylthieno[2,3-*d*]pyrimidin-4-one **65**.



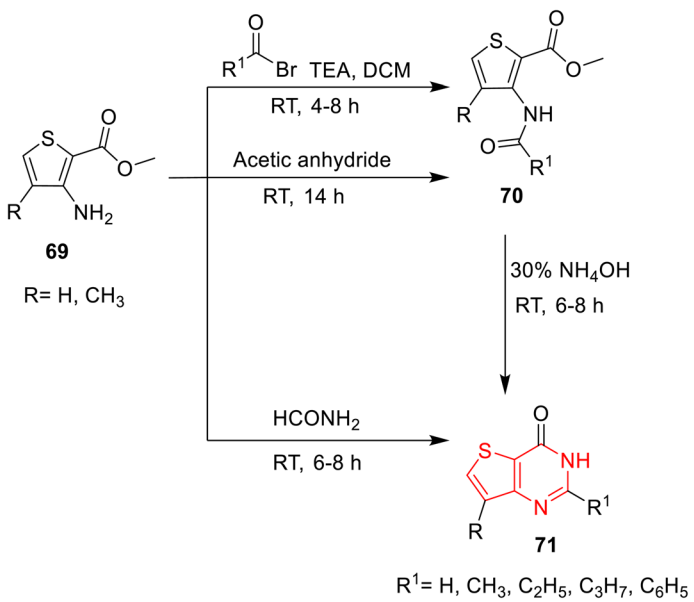
Scheme 24 Synthesis of 3-amino-7-benzyl-2-substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **68**.

Davoodnia and co-authors[114] investigated a one-pot, base-catalyzed cyclocondensation of 2-aminothiophene-3-carboxylate with aryl isocyanates to obtain a series of 3-arylthieno[2,3-*d*]pyrimidin-2,3(1*H*,3*H*)-diones **74** (Scheme 26).

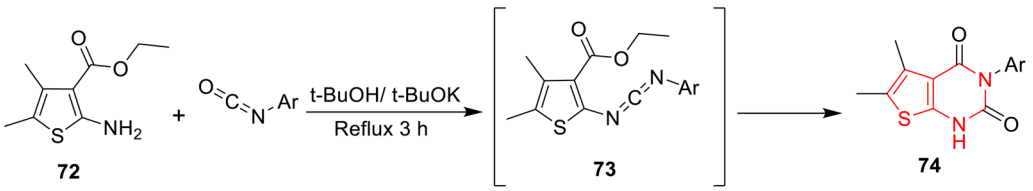
A new approach was established for the synthesis of thieno[2,3-*d*]pyrimidine derivatives **77** using various 2-aminothiophene-3-carboxylates with different arylamines **76** and TEOF. The reaction was performed under MWI and zinc acetate $Zn(OAc)_2$ catalysis. This approach reduced the reaction time to only 5 min and increased the yield to 72–95%[115] (Scheme 27).

Through the same previous method, 2,5-diaminothiophene-3,4-dicarboxylate **78** reacted with aniline to afford compound **79** in only 5 min, 88% yield, and 68.2% AE[115] (Scheme 28).

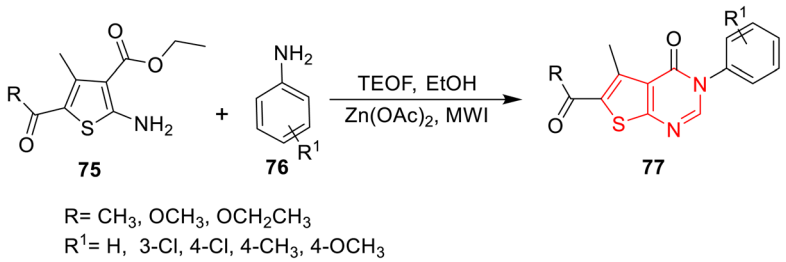
In 2017, 3-hydroxythieno[2,3-*d*]pyrimidine derivatives **81** were prepared through the Gewald reaction, in which 4-chloroacetophenone reacted with ethyl cyanoacetate in the presence of sulfur and morpholine as a base, but the reaction was enhanced by MWI. After that, the produced ortho amino ester intermediate **80** was cyclized under the catalysis of *p*-toluenesulfonic acid (*p*-TSA hydrate) in methanol at room temperature for 2–3 h (ref. 116) (Scheme 29). This reaction provides a very high AE (93.9%) and low PMI (1.06) and *E*-factor (0.06), which align with the greenness. Also, the prepared 3-hydroxythieno[2,3-*d*]pyrimidine derivatives **81** have considerable antiviral activity.



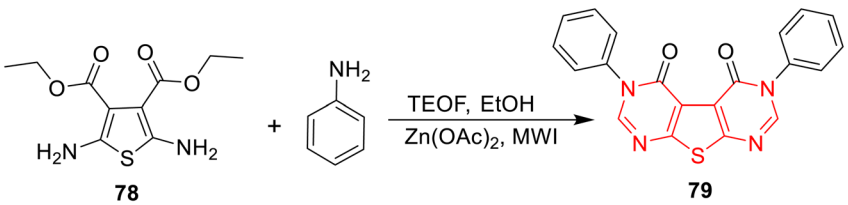
Scheme 25 Different synthetic routes for 7-substituted-thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **71**.



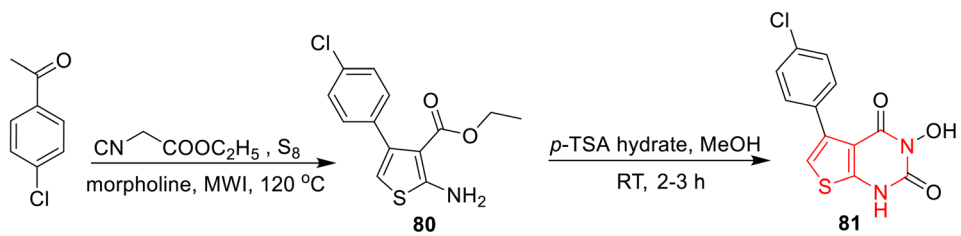
Scheme 26 One-pot synthesis of 3-arylthieno[2,3-*d*]pyrimidine derivatives **74**.



Scheme 27 $Zn(OAc)_2$ catalytic synthesis of thieno[2,3-*d*]pyrimidines **77**.



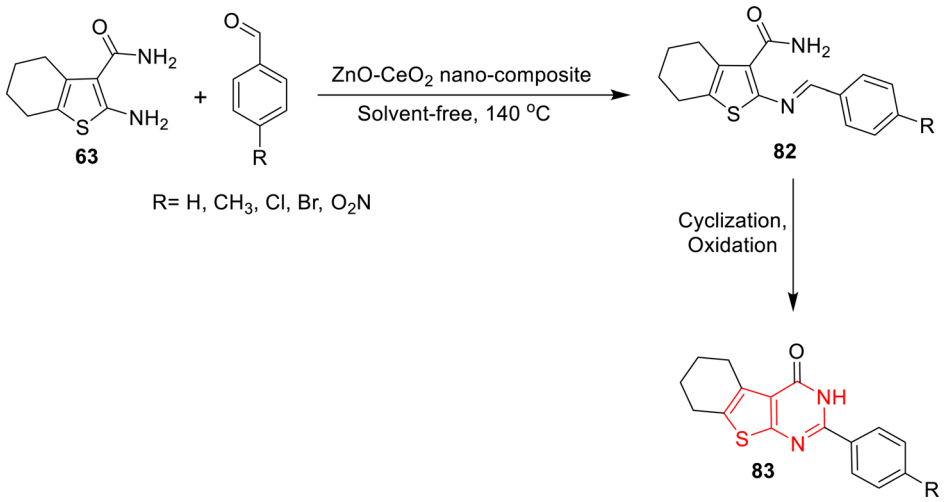
Scheme 28 Synthesis of 3,6-diphenylthieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5-dione **79**.



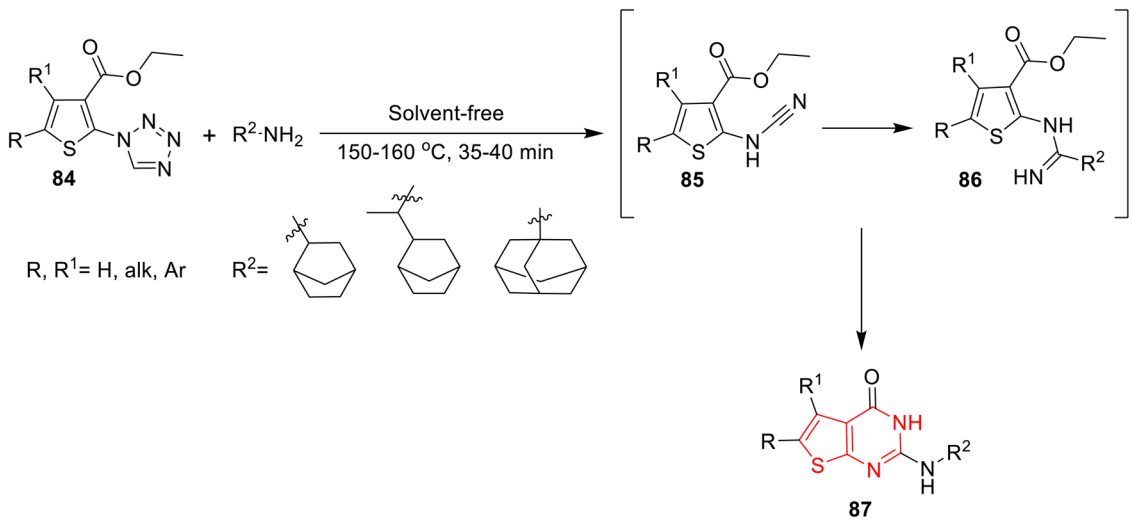
Scheme 29 Synthesis of 3-hydroxythieno[2,3-*d*]pyrimidine **81** catalyzed by *p*-TSA hydrate.

Ghayour and associates[117] developed a metal oxide nanocomposite-catalyzed synthetic route for 2-arylthieno[2,3-*d*] pyrimidine **83**. In this method, 2-aminothiophene-3-carboxamide condensed with a panel of aromatic aldehydes under zinc oxide–cerium oxide ($ZnO–CeO_2$) catalysis and neat conditions for 1.5 h. After that, cyclization and oxidation occur to produce the desired thieno[2,3-*d*]pyrimidine derivatives in a good yield of 95% (Scheme 30). Metal oxide nanocomposites are of great interest in catalysis because they are easily available, affordable, have a large surface area, and are reusable, meeting green chemistry requirements. The reaction conditions allow achieving a high AE (93.4%) and very low *E*-factor (0.07) and PMI (1.07), minimizing waste production.

Shyyka and collaborators[118] reported a thermally activated *trans*-annulation for 2-aminothieno[2,3-*d*]pyrimidine **87**. In this method, substituted-2-tetrazolylthiophene-3-carboxylate **84** was reacted with different cage-like amines in one-pot under solvent-free conditions at 150 °C-160 °C for 35–40 min, yielding the transannular thieno[2,3-*d*]pyrimidine with anticancer activity in a yield of 84–89%. This reaction involves three steps: cleavage of the tetrazole ring, nucleophilic addition, and finally cyclization (Scheme 31).



Scheme 30 ZnO–CeO_2 nanocomposite catalytic synthesis of 2-aryl thieno[2,3-*d*]pyrimidines **83**.



Scheme 31 Synthesis of 2-aminothieno[2,3-*d*]pyrimidines **89** through tetrazole ring *trans*-annulation.

3. Conclusion and future insights

Thienopyrimidine scaffolds represent distinctive lead compounds in drug discovery due to their various biological activities. Therefore, synthesizing new compounds containing thienopyrimidine is worthwhile. Developing eco-friendly synthetic pathways as alternatives to traditional ones helps to minimize waste production and reduce pollution. In this review, we have outlined different green principles and their applications in thienopyrimidine synthesis, for instance, microwave irradiation, green solvents, catalysis, and solvent-free and one-pot techniques. Despite the prominent progress achieved in designing eco-friendly approaches for the synthesis of thienopyrimidines, further progress is required to improve selectivity, efficiency, and scalability. Future research should focus on using renewable feedstock and biocatalysts that offer higher efficiency and selectivity. In addition, a combination of more than one green technique simultaneously can help in reducing the energy consumption, reaction time, and cost. We hope that this review helps medicinal chemists design novel thienopyrimidines for the treatment of many diseases through eco-friendly methods and avoiding the traditional polluting methods.

Conflicts of interest

The authors declare no competing financial or personal interests that could have influenced this work.

Data availability

No new data were generated or analyzed in support of this review article. All data discussed are from previously published studies and are properly cited within the manuscript.

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