Thienopyrimidine

Subjects: Chemistry, Organic

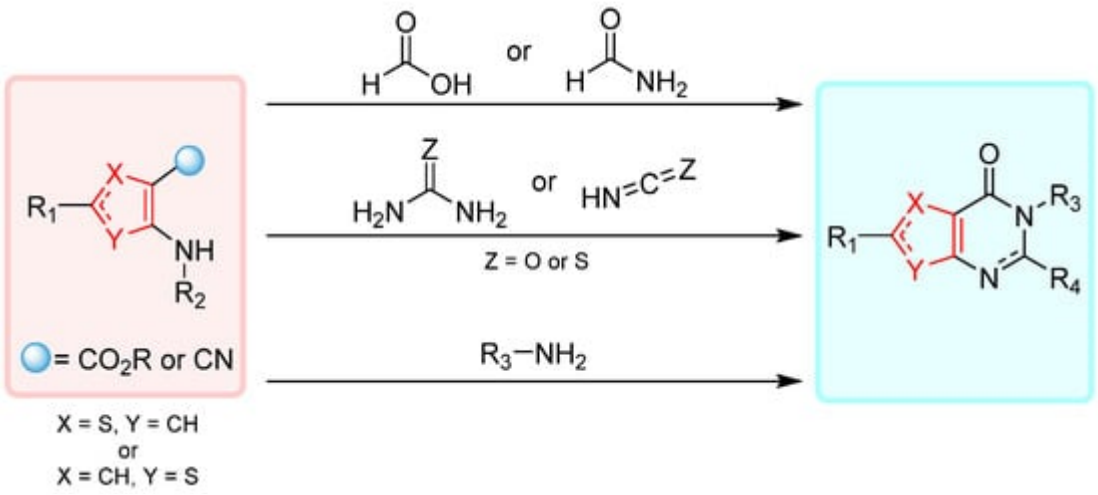
Contributor: Nicolas MASURIER

Thienopyrimidine emerges as an attractive scaffold in medicinal chemistry with a wide array of pharmacological properties, such as antibacterial, antifungal, antiparasitic and antiviral. Considering the fusion between pyrimidine and thiophene rings, three different thienopyrimidines can be obtained, namely thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines and thieno[3,4-*d*]pyrimidines. Different synthetic pathways involving the construction of the pyrimidine or the thiophene ring were reported in the literature to access polysubstituted thienopyrimidines. In these approaches, the synthetic strategies mostly involved the synthesis of a thienopyrimidin-4-one derivative, where position 4 could be modified via further functionalization.

thienopyrimidine heterocycle cyclization synthesis

1. Synthesis from Thiophene Derivatives

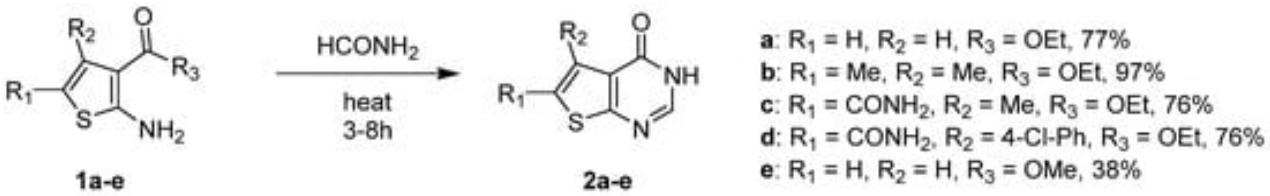
Due to the high diversity of supplies, the reaction between an aminothiophene derivative bearing an electrophilic center (ester or nitrile) and a carbonyl or an amine reactant is probably the easiest way for produce thienopyrimidin-4-one derivatives. The leading routes to afford thienopyrimidines from aminothiophene derivatives are described in Scheme 1.



Scheme 1. Main synthetic pathways to produce thienopyrimidin-4-ones from thiophene derivatives.

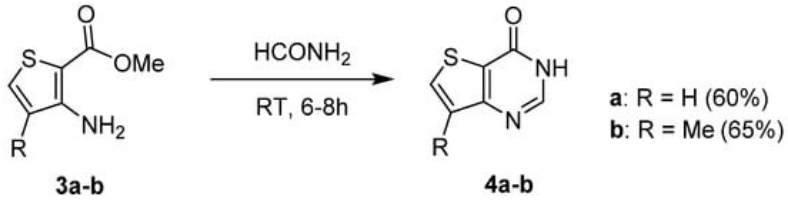
1.1. Cyclization with Carbonyl Reactants

The most efficient chemical approach to access 2- and 3-unsubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones involved a condensation reaction between an aminothiophene substrate and formamide. Thus, compounds **1a–e** treated with an excess of formamide at high temperature led to compounds **2a–e** with good yields (76 to 97%), except for compound **1e** for which the methoxy group in R_3 decreased the reaction yields compared to the ethoxy group (**1a**) (Scheme 2) [1][2][3][4][5].



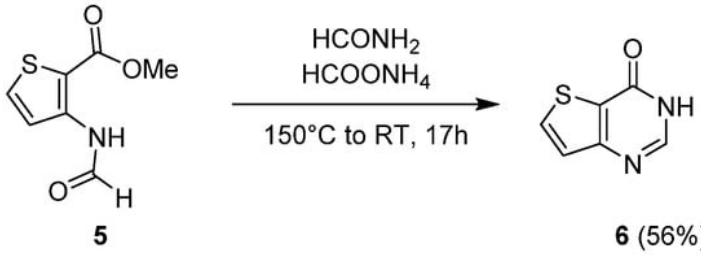
Scheme 2. Access to 2- and 3-unsubstituted thieno[2,3-*d*]pyrimidin-4-one derivatives (Me = methyl, Et = ethyl, and Ph = phenyl).

In contrast, mild conditions were sufficient to perform cyclization reaction with formamide to synthesize the thieno[3,2-*d*]pyrimidin-4(3*H*)-one isomers **4a–b** with good yields (60 to 65%, Scheme 3) [6].



Scheme 3. Synthesis of 3-unsubstituted thieno[3,2-*d*]pyrimidines **4a–b**.

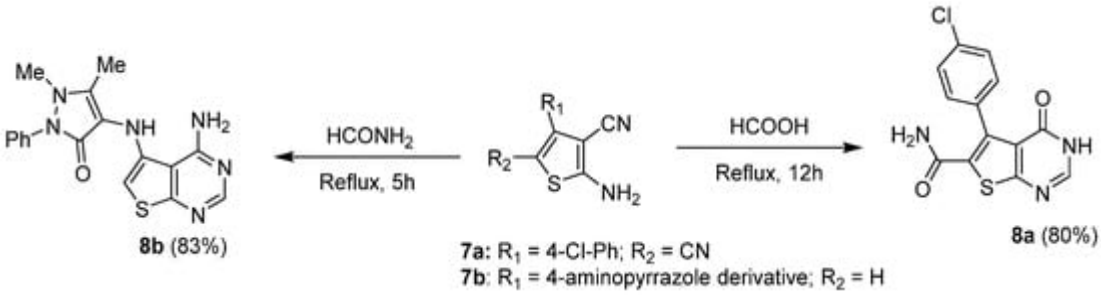
Woodring et al. presented a variant of this process that also involved formamide in combination with ammonium formate [5]. Cyclization of the thiophene intermediate **5** at 150 °C led to the unsubstituted thieno[3,2-*d*]pyrimidin-4-one **6** with a 56% yield (Scheme 4).



Scheme 4. Synthetic route to unsubstituted thieno[3,2-*d*]pyrimidin-4-one **6**.

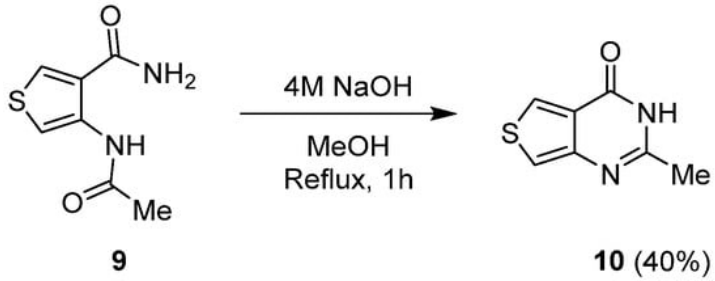
In addition, reaction of 2-amino-3-cyanothiophene derivatives with formic acid could also be considered to access 2- and 3-unsubstituted thieno[2,3-*d*]pyrimidin-4-ones [4]. In such approach, the cyano group is firstly converted into its corresponding primary amide, which could then be cyclized in the presence of formic acid. Kanawade et al. used such an approach to prepare thienopyrimidinone **8a** from 2-amino-3,5-dicyanothiophene **7a** (Scheme 5).

Replacing formic acid by formamide led to the formation of the 4-amino analogue, as reported by Aly et al. [7]. Thus, cyclocondensation involving **7b** and formamide occurred under reflux to afford the expected **8b** with a 83% yield (Scheme 5).



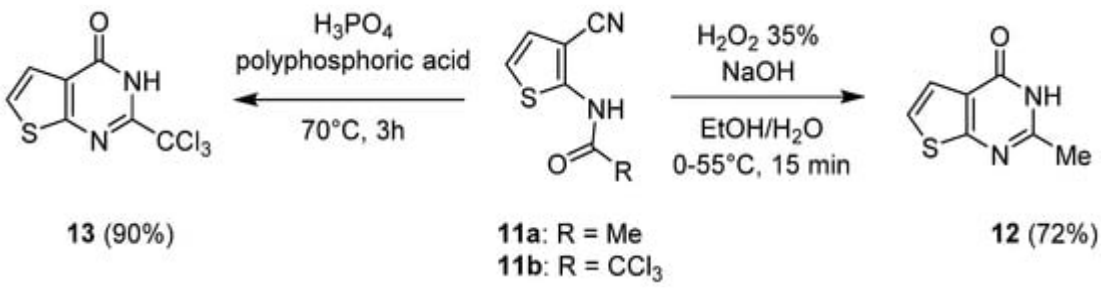
Scheme 5. Access to thieno[2,3-*d*]pyrimidine derivatives from 2-amino-3-cyanothiophene derivatives.

Cyclocondensation of thiophene carboxamide **9** in the presence of sodium hydroxide was used to synthesize thieno[3,4-*d*]pyrimidin-4(3*H*)-one **10** (Scheme 6). The expected molecule was isolated with a moderate yield (40%) after a 1 h reaction in refluxing methanol.



Scheme 6. Synthesis of 2-methyl-thieno[3,4-*d*]pyrimidin-4(3*H*)-one **10**.

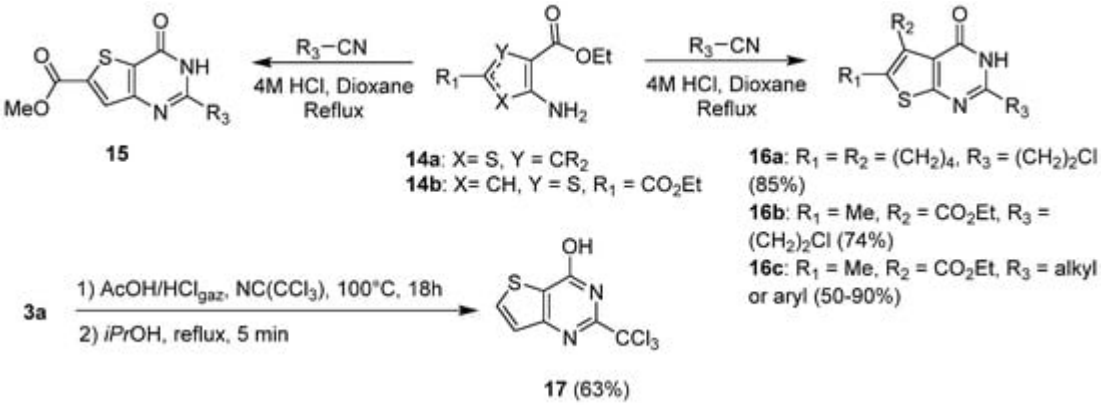
Using a similar approach, but with a nitrile group as the precursor of the primary amide, Desroches et al. synthesized 2-methyl- and 2-trichloromethyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **12** and **13**, respectively (Scheme 7) [8]. Thus, treatment of 3-cyanothiophene acetamide **11a** with hydrogen peroxide in alkaline medium (NaOH) afforded 2-methyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-one **12** with a 72% yield. Using 3-cyanothiophene trichloroacetamide as a substrate and phosphoric acid in polyphosphoric acid triggered the cyclocondensation reaction and the formation of the 2-trichloromethyl-thieno[2,3-*d*]pyrimidin-4(3*H*)-one **13** with good yields (90%).



Scheme 7. Synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones substituted in position 2.

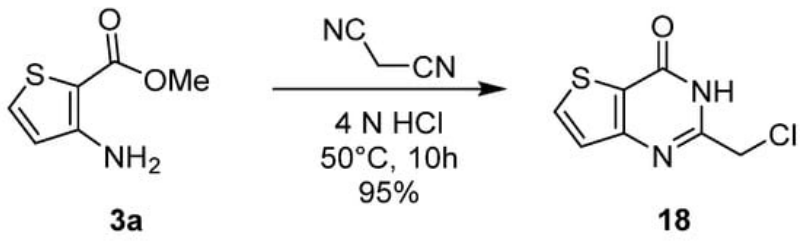
1.2. Cyclization with Nitrile Reactants

Various pathways exploiting nitrile condensation were reported in the literature to produce thieno-fused analogues. De Schutter et al. used a synthetic route involving a thiophene amino ester treated in strongly acidic conditions by a cyanoalkyl derivative at 90 °C (Scheme 8) [9]. Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **16c**, substituted in positions 2, 5, and 6 were then obtained in 1,4-dioxane in moderate to good yields (50 to 90%). In addition, Mavrora et al. used the same synthetic pathway and obtained chloroethyl derivatives **16a–b** with good yields (Scheme 8) after nitrile cyclocondensation at room temperature [10]. Likewise, thieno[3,2-*d*]pyrimidinones **15** substituted at position 2 were prepared from cyclization of the starting thiophene with the appropriate cyanoalkyl in acidic conditions at 90 °C in 1,4-dioxane (Scheme 8) [9]. To introduce a trichloromethyl group at position 2 of the thieno[3,2-*d*]pyrimidine core, Desroches et al. used trichloroacetonitrile in acetic acid, saturated with HCl gas, to afford 2-trichloromethyl-thieno[3,2-*d*]pyrimidine **17** with a 63% yield (Scheme 8) [8].



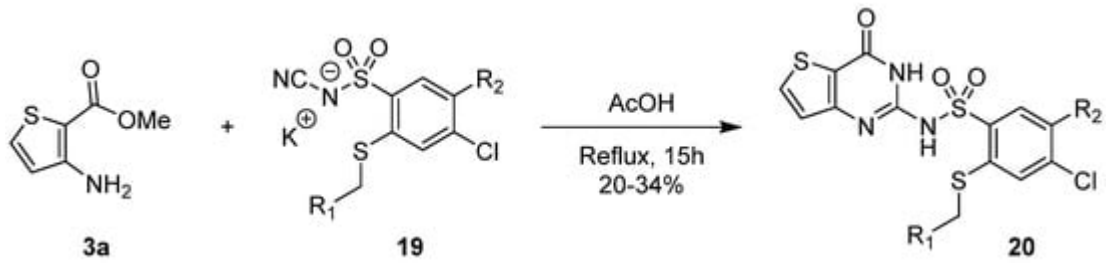
Scheme 8. Synthesis of 2-substituted thienopyrimidin-4-ones using nitrile reactants.

Using the same strategy, Kim et al. introduced a chloromethyl group at position 2 of thieno[3,2-*d*]pyrimidinones after slight modifications of the reaction conditions [11]. Formation of the thieno-fused core occurred with the cyclocondensation of malononitrile with 2-methyl-3-aminothiophene carboxylate under acidic conditions and mild heating to offer **18** with high yields (Scheme 9).



Scheme 9. Synthesis of 2-chloromethyl-thieno[3,2-*d*]pyrimidinone **18**.

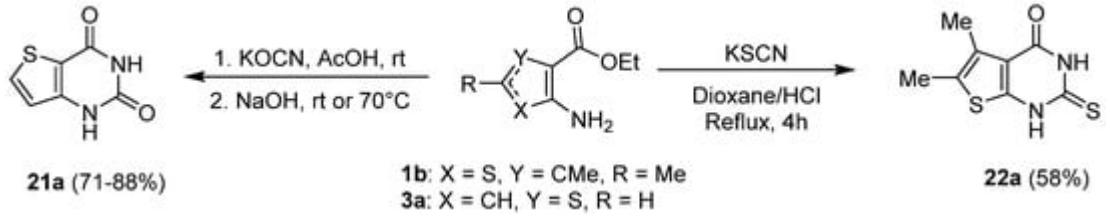
Slavinski et al. presented another synthetic pathway to introduce a sulfonamide group at position 2, using sulfonyl cyanamide potassium salts **19** [12]. Acidification of the reaction with boiling glacial acetic acid led to cyclization and afforded 2-sulfonamide-thieno[3,2-*d*]pyrimidinone derivatives **20** with low yields (20–34%, Scheme 10).



Scheme 10. Formation of 2-sulfonamide-thieno[3,2-*d*]pyrimidinones **20**.

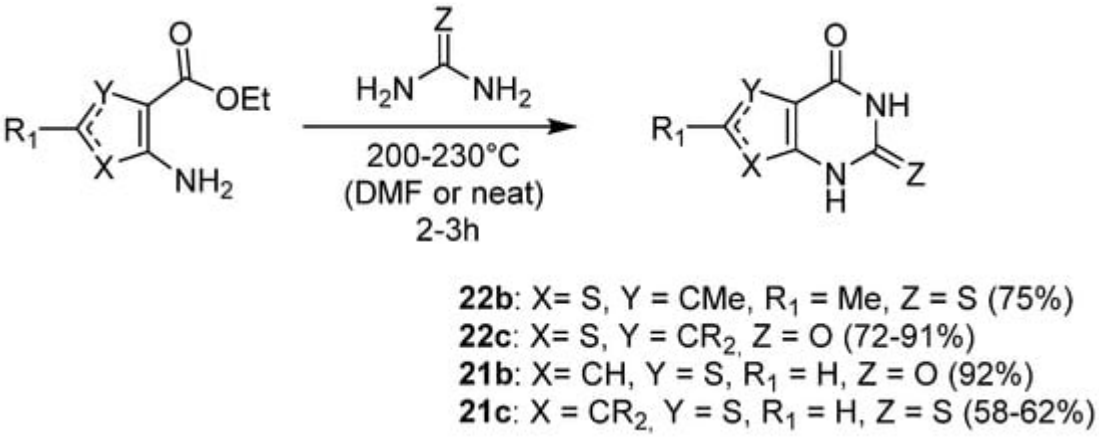
1.3. Synthesis from (Thio)urea Reagents, Iso(Thio)cyanate or (Thio)cyanate Derivatives

An easy way to access thienopyrimidin-2,4-dione or 2-thioxo-thienopyrimidin-4-one derivatives consisted of cyclocondensation of the appropriate ethyl aminothiophene-carboxylate with potassium (thio)cyanate in an acidic medium. Patel et al. obtained 2-thioxo-thieno[2,3-*d*]pyrimidin-4-one **22a** with a 58% yield, using hydrochloric acid in refluxing 1,4-dioxane (Scheme 11) [13], whereas Temburkinar et al. and other groups [14][15][16] used potassium cyanate in acetic acid to obtain thieno[3,2-*d*]pyrimidin-2,4-dione **21a** with 71 to a 88% yield.



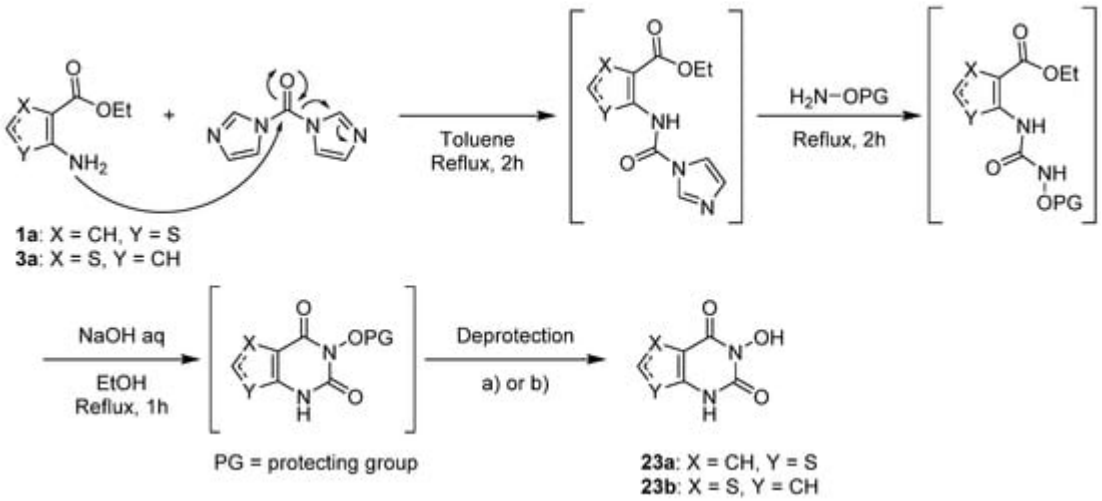
Scheme 11. Synthesis of 2-thioxo-thieno[2,3-*d*]pyrimidin-4-one **22a** and thieno[3,2-*d*]pyrimidin-2,4-dione **21a**.

Another way to access such compounds was to condensate the starting aminothiophene with urea or thiourea, followed by cyclization to afford thienopyrimidinone compounds **21** or **22**. Ortikov and Prabhakar teams used such conditions to synthesize 2-thioxo-thieno[2,3-*d*]pyrimidin-4-one **22b** and thieno[2,3-*d*]pyrimidine-2,4-diones **22c** (Scheme 12) with good yields (72–91%) [2][17][18]. Condensation and cyclization only occurred at very high temperatures after 2 or 3 h of heating without solvent. Thieno[3,2-*d*]pyrimidin-2,4-one **21b** could be synthesized under these conditions, whereas the synthesis of 2-thioxo-thieno[3,2-*d*]pyrimidin-4-ones **21c** required the use of *N*,*N*-dimethylformamide (DMF) as a solvent (Scheme 12) [19][20].



Scheme 12. Formation of 2-thioxo-thienopyrimidin-4-ones and thienopyrimidine-2,4-diones using (thio)urea.

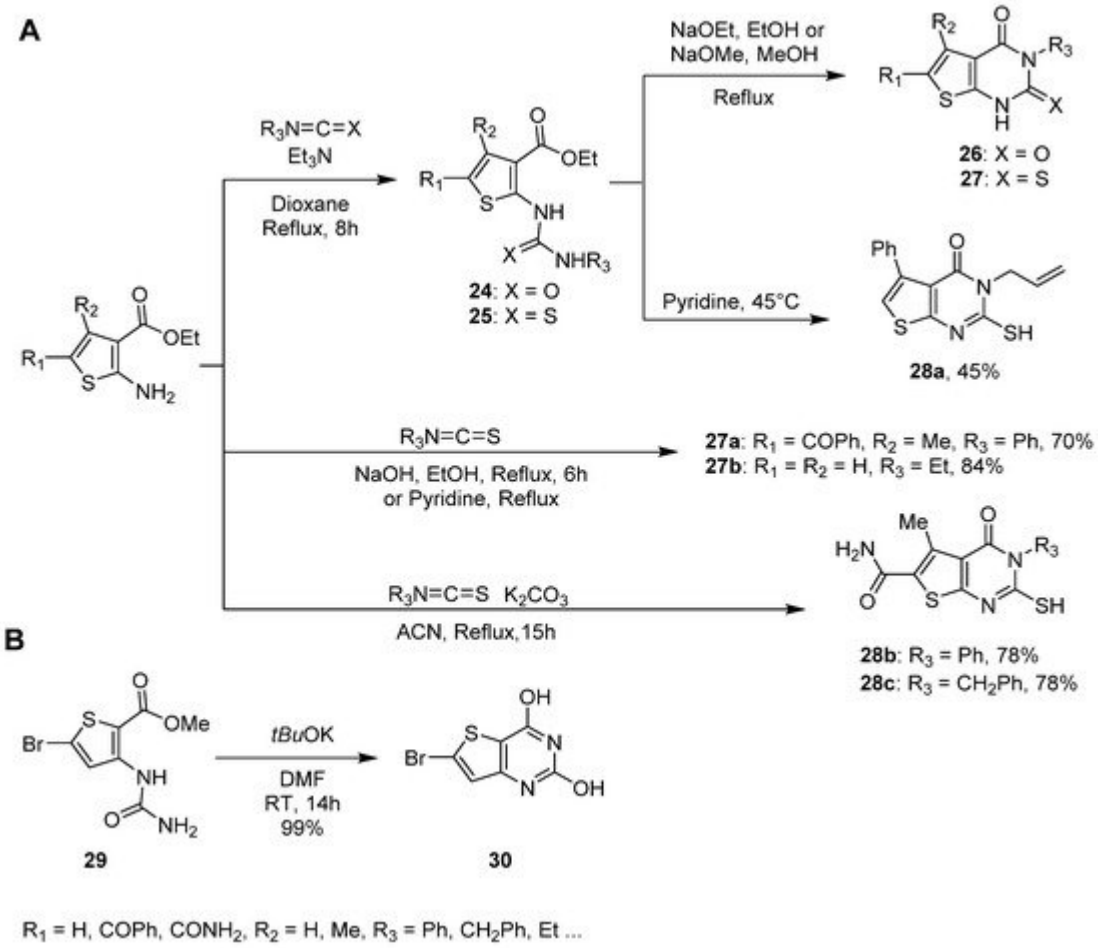
Kankanala et al. used a common synthetic pathway to access 3-hydroxythieno[2,3-*d*]pyrimidin-2,4-diones and thieno[3,2-*d*]pyrimidin-2,4-diones [21] bearing various groups in α and β positions of the sulfur atom. Firstly, the aminothiophene reacted with 1,1′-carbonyldiimidazole (CDI) to afford the imidazole-carboxamide intermediate after 2 h in refluxing toluene (Scheme 13). Secondly, the substitution of the imidazole group by protected hydroxylamine generated the hydroxyurea intermediate. Then, a basic treatment deprotonated hydroxyurea to allow cyclization. Afterward, deprotection of the hydroxyurea led to the final compounds **23** with correct to good yields (40–85%).



Scheme 13. Synthetic pathway to afford 3-hydroxythienopyrimidin-2,4-diones **23**.

To introduce more chemical diversity at position 3, a convenient synthetic route described by Abu-Hashem et al. involved nucleophilic attack of an aminothiophene derivative on an isocyanate or thioisocyanate in the presence of a catalytic amount of triethylamine in refluxing 1,4-dioxane (Scheme 14A) [22]. The (thio)ureidothiophene intermediate **24** or **25** was then isolated on average with good yields (60 and 70%). Thereafter, basic treatment of **24** or **25** with sodium ethoxide in refluxing ethanol led to thieno-fused derivatives **26** and **27** with good yields (70% and 75%) after 8 h. Dewal et al. obtained similar results using sodium methoxide under refluxing methanol to prepare trisubstituted thieno[2,3-*d*]pyrimidin-2,4-dione derivatives **26** with 88–90% yields [23]. In addition, Abu-

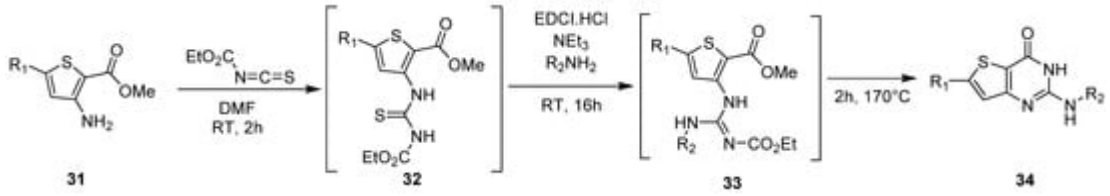
Hashem et al. reported a one-pot reaction with phenylisothiocyanate and sodium hydroxide as a base, in refluxing ethanol for 6 h [22]. Both the two-step procedure and the one-pot reaction offered **27a** with a 70% yield (Scheme 14A). Furthermore, the use of potassium carbonate in refluxing acetonitrile led to the 2-mercapto-thieno[2,3-*d*]pyrimidin-4-one analogues **28b–c** in even higher yields (78%) [3][24]. In a similar way, 3-ethyl-2-thioxo-thieno[3,2-*d*]pyrimidin-4-one **27b** was also accessible via the cyclization of 2-methyl-3-aminothiophene carboxylate with ethylisothiocyanate in refluxing pyridine [25]. In addition, 6-bromothieno[3,2-*d*]pyrimidin-2,4-diol **30** was synthesized in milder conditions with potassium *tert*-butoxide in DMF at room temperature and obtained it with a quantitative yield (Scheme 14B) [26]. It was then possible to introduce further chemical diversity in positions 2, 4, and 6, starting from this bicyclic product.



Scheme 14. (**A**). Synthesis of 3-substituted 2-thioxo-thienopyrimidin-4-ones or thienopyrimidine-2,4-diones **26**–**28**. (**B**). Synthesis of 6-bromothieno[3,2-*d*]pyrimidine-2,4-diol **30**.

Alternately, Cohen et al. suggested an original synthetic pathway to obtain thieno[3,2-*d*]pyrimidin-4(3*H*)-one derivatives **34**, substituted in position 2 by an amino group [27]. This one-pot procedure involved first the condensation of the starting material with ethoxycarbonyl isothiocyanate in DMF to generate the thiourea carbamate intermediate **32**, that was not isolated (Scheme 15). Afterward, a primary alkylamine reacted with this species, previously mixed with 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI.HCl) and triethylamine.

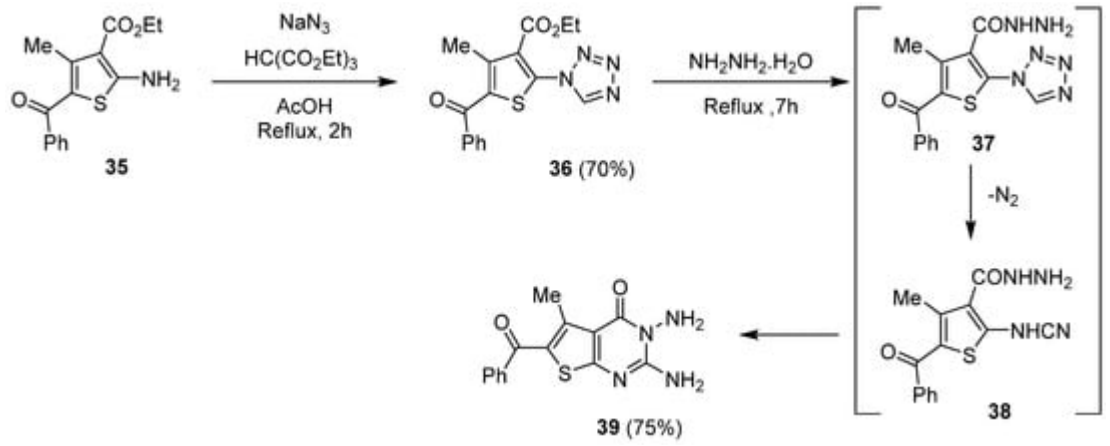
Guanidine intermediate **33** was observed but was not isolated. Then, this intermediate cyclized at 170 °C to afford thieno-fused derivatives **34** with 42 to 70% yields depending on the substituents.



Scheme 15. Synthetic pathway purposed by Cohen et al. [27].

1.4. Synthesis via a Tetrazole Intermediate

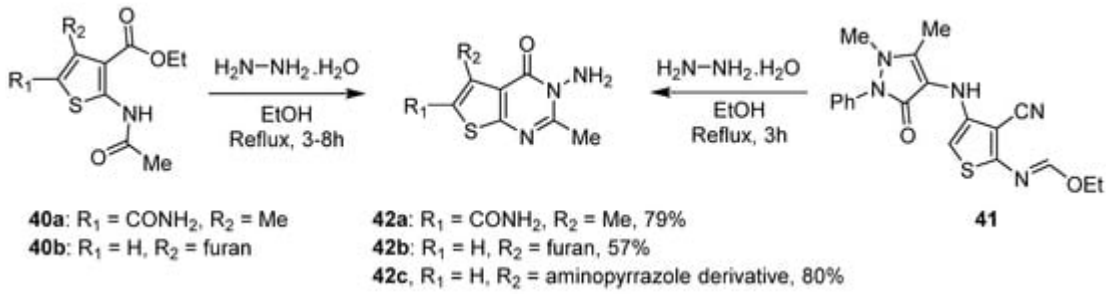
To generate thieno[2,3-*d*]pyrimidines substituted in positions 2 and 3 by an amino group, Abu-Hashem et al. purposed an access route via a tetrazole intermediate (Scheme 16) [22]. Firstly, the tetrazole ring was formed by treating **35** with triethyl orthoformate and sodium azide to generate **36** with good yields (70%). Then, refluxing **36** in the presence of a large excess of hydrazine hydrate led to two consecutive hydrazide intermediates **37** and **38**. Intramolecular cyclization of **38** afforded **39** with good yields (75%).



Scheme 16. Synthesis of 2,3-diaminothieno[2,3-*d*]pyrimidine **39**.

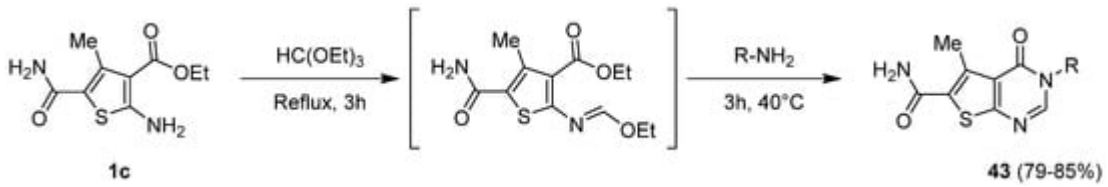
1.5. Cyclization with Amine/Hydrazine Derivatives

A more common way to access 3-amino-thieno[2,3-*d*]pyrimidin-4-ones consisted of the condensation and cyclization between a thiophene derivative and hydrazine monohydrate in refluxing ethanol. Using this strategy, several groups reported the synthesis of compounds **42a–b** with moderate to good yields (Scheme 17) [3][28]. Aly et al. employed the same reaction conditions to generate 3-amino-thieno[2,3-*d*]pyrimidin-4-one **42c**. Only the starting thiophene was different and achieved cyclocondensation with good yields (80%).



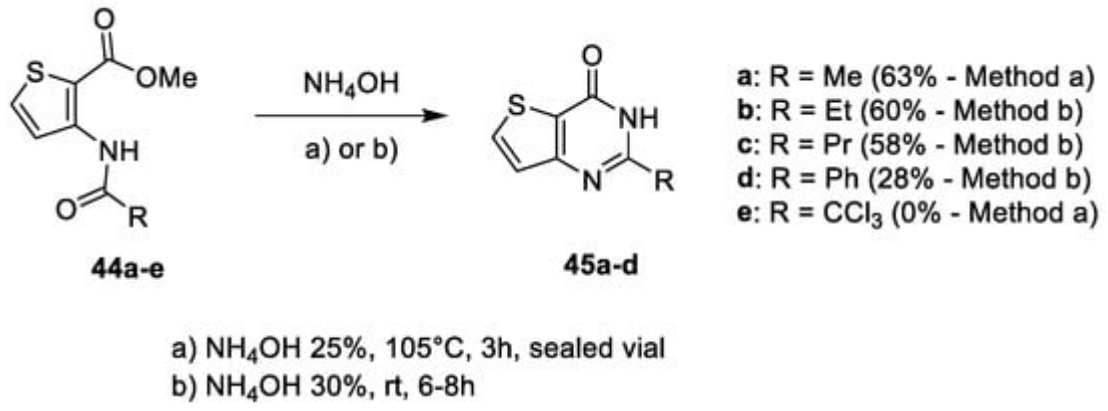
Scheme 17. Synthesis of 3-amino-thienopyrimidin-4-ones **42**.

To introduce chemical diversity at position 3, a similar route was followed by Habib et al. using various primary amines to synthesize a set of 3-substituted thieno[2,3-*d*]pyrimidinone derivatives **43** [3]. Firstly, the 2-aminothiophene **1c** reacted with triethyl orthoformate under reflux to prepare the imino intermediate, which was not isolated (Scheme 18). Then, the appropriate amine was added to allow cyclization and obtain 3-substituted thienopyrimidinone derivatives **43** with good yields (79–85%).



Scheme 18. Access route to synthesize 3-substituted thieno[2,3-*d*]pyrimidin-4-ones **43**.

Finally, condensation of ammonia with *N*-acylaminothiophenes **44** allowed access to 3-unsubstituted thieno[2,3-*d*]pyrimidin-4-ones **45** [6][8]. The first synthetic route involved 25% ammonia heated at 105 °C in a sealed vial to obtain thieno[3,2-*d*]pyrimidin-4-one **46a** after 3 h, with a 63% yield (Scheme 19). In contrast, using milder conditions with 30% ammonia at room temperature for 6 to 8 h led generally to lower yields (28–60%). Moreover, it has been observed by Desroches et al. that this method was not efficient when R = CCl_3 (compound **45e**) [8]. Indeed, with this substrate, cyclization in the presence of 25% ammonium hydroxide in a sealed vial failed.

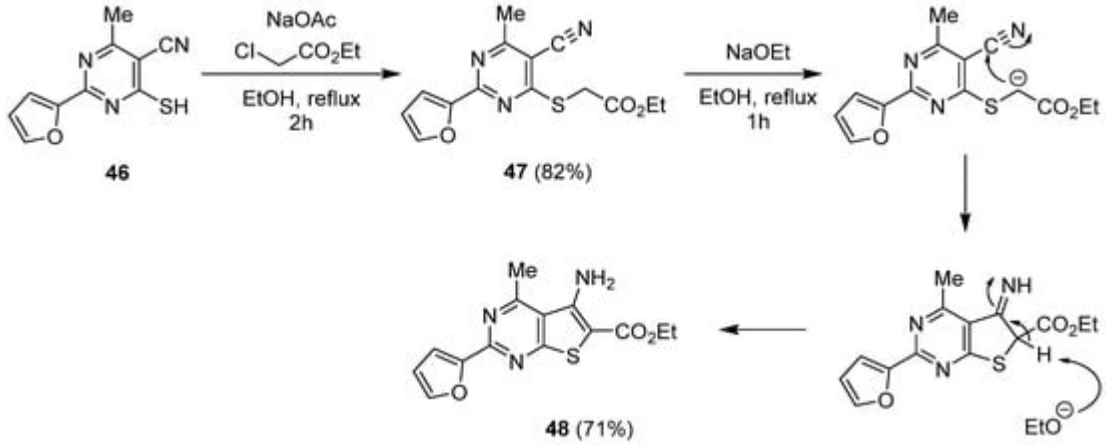


Scheme 19. Synthesis of 3-unsubstituted-thienopyrimidin-4-ones **45** (Pr = propyl).

2. Synthesis of Thienopyrimidines from Pyrimidine Derivatives

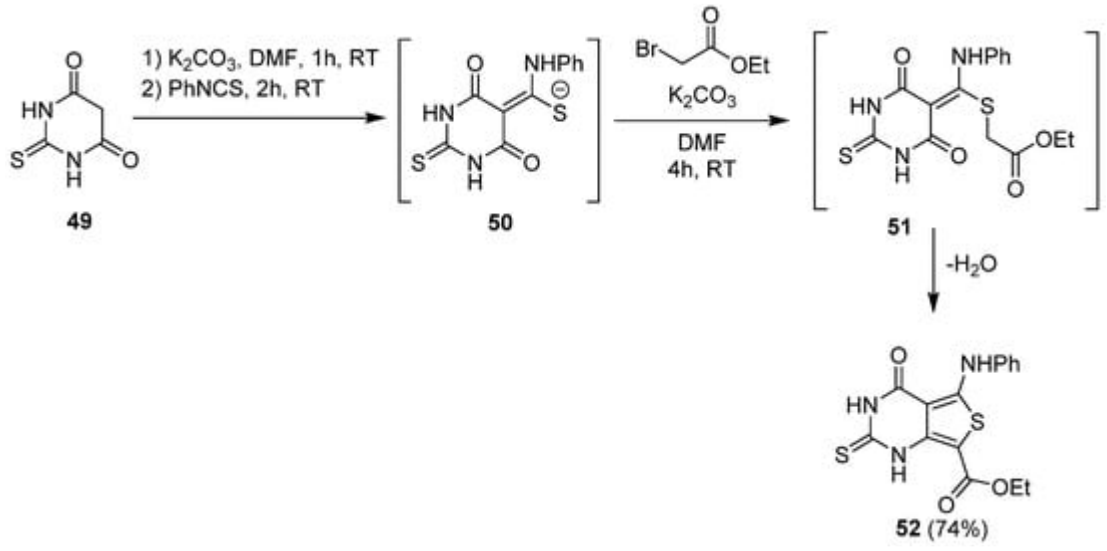
2.1. Synthesis from the Thorpe-Ziegler Reaction

One of the possibilities to shape the thieno-fused ring from pyrimidine derivatives is the Thorpe-Ziegler cyclization. A six-membered ring bearing a mercaptocarbonitrile group was the starting point to synthesize thienopyrimidines (Scheme 20). After substitution of alkyl chloroacetate by the sulfhydryl group (compound **47**), and subsequent deprotonation, cyclization can occur in basic conditions. In such a way, Abdel Hamid et al. reported the synthesis of compound **48** with a 71% yield [29].



Scheme 20. Synthesis of thienopyrimidin-4-one **48** via a Thorpe-Ziegler cyclization.

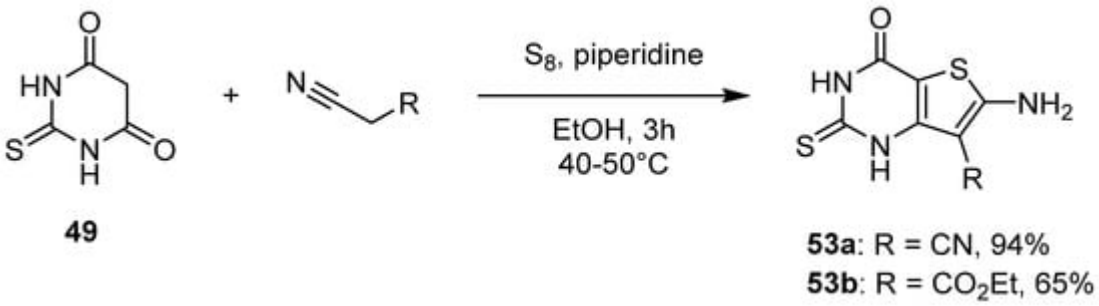
A variant of the previous approach was purposed by Ali and Saleh for the synthesis of 2-thioxo-1,2,3,4-tetrahydrothieno[3,4-*d*]pyrimidine **52** [30]. First, thiobarbituric acid **49** was deprotonated in α-position of the two carbonyl groups at room temperature (Scheme 21). Then, nucleophilic substitution on phenyl isothiocyanate led to the ketene aminothioacetal **50**. Thereafter, the addition of alkyl bromoacetate allowed cyclocondensation of **51** in basic conditions. The final product **52** was obtained with good yields (74%).



Scheme 21. Synthesis of 2-thioxo-1,2,3,4-tetrahydro thieno[3,4-*d*]pyrimidin-4-one **52**.

2.2. Synthesis from the Gewald Reaction

The Gewald reaction is a versatile reaction to access 2-aminothiophene derivatives involving one-pot cyclocondensation of ketones or aldehydes with activated nitrile derivatives and elemental sulfur. Using thiobarbituric acid **49** as the starting ketone, 2-thioxo-6-aminothieno[3,2-*d*]pyrimidin-4-one derivatives could be easily accessible. Treatment of **49** with piperidine in the presence of the appropriate alkyl cyanide led to the aminothieno-fused derivatives **53a** and **53b** with good yields (Scheme 22) [30].



Scheme 22. Synthesis of 2-thioxo-thieno[3,2-*d*]pyrimidines **53** by the Gewald reaction.

As shown in the previous examples, many access routes to these compounds are possible and allow to easily prepare a wide range of polysubstituted thienopyrimidines. Therefore, these compounds have been included in many biological studies. More particularly, their antiparasitic, antibacterial, antifungal and antiviral activities have been studied, and have been compiled in a entry. For more details, see P. Lagardère et al. [31]

References

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