Reviews

Thienopyrimidines: synthesis, properties, and biological activity*

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Data on the methods for the synthesis of isomeric thienopyrimidine derivatives, their chemical transformations, and biological activities are systematized and analyzed. Emphasis is given to studies published over the last 10—15 years.

Key rings: isomeric thienopyrimidines, synthesis, closure of the pyrimidine and thiophene rings, chemical transformations, biological activity.

1. Introduction

Fused pyrimidines continue to attract considerable attention of researchers in different countries because of their great practical usefulness, primarily, due to a very wide spectrum of their biological activities. This is evident, in particular, from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles, such as purines,[1—6] pteridines,[7] quinazolines,[8—10] pyridopyrimidines,[11—15] triazolopyrimidines,[16—21] pyrazolopyrimidines,[22] pyrimidoazepines,[23] furopyrimidines and pyrrolopyrimidines.[24]

Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annelated five-membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of the chemistry and biology of isomeric thienopyrimidines have been reviewed.[24—40]

The present review analyzes results of studies on the synthesis, chemical transformations, and biological activities of thienopyrimidines published primarily over the last 10—15 years.

2. Synthesis of thienopyrimidines

Synthetic approaches to the construction of thienopyrimidines are sufficiently well developed. Three possible types of annelation of thiophene to the pyrimidine ring and, correspondingly, three isomeric thienopyrimidines are known: thieno[2,3-*d*]pyrimidine (**1**), thieno[3,2-*d*]pyrimidine (**2**), and thieno[3,4-*d*]pyrimidine (**3**). The structures and the conventional numbering of these heterocyclic systems are shown below.

* The review is dedicated to the 70th anniversary of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, where studies of thienopyrimidines are carried out (at the Laboratory of Heterofunctional Compounds).

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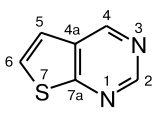

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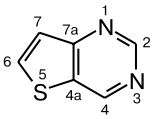

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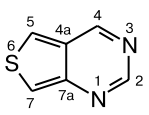


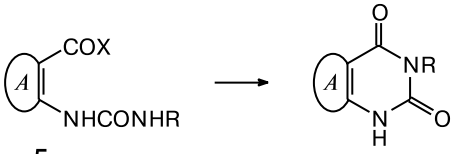
3

The known approaches to the synthesis of thienopyrimidines can be divided into two main groups: the construction of the pyrimidine ring by intramolecular cyclization of thiophene derivatives and the thiophene ring closure in pyrimidine derivatives.

2.1. Synthesis of thienopyrimidines by pyrimidine ring closure

Appropriately substituted aminothiophenes, which are accessible by various methods,[24,28,29,32] serve as the main starting compounds for the preparation of thienopyrimidines with the use of this approach. Syntheses involving the pyrimidine ring closure starting from both 2- and 3-aminothiophenes proceed under similar conditions and in virtually the same reaction sequences, due to which all three types of thienopyrimidines become accessible. Hence, it is reasonable to classify the reactions leading to these compounds according to the type of substitution in the pyrimidine rings formed.

One of the most popular approaches to the synthesis of thienopyrimidinediones **4** is based on the pyrimidine ring closure in thienylureas **5**.



5 **4**

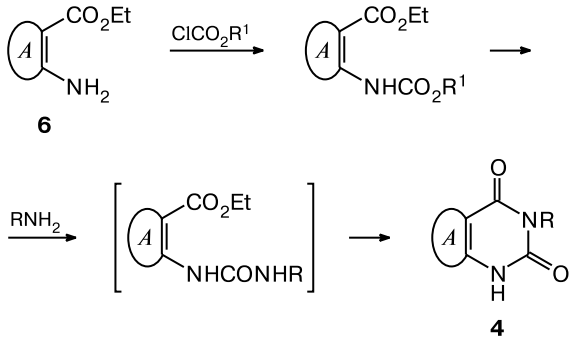
Hereinafter, *A* is the thiophene ring bearing substituents at positions 2 and 3 or 3 and 4; thienopyrimidine structure **4** is thiophene analogously annelated to the pyrimidine ring; the ester group is most widely used as the COX group.

The starting thienylureas are synthesized according to the known procedures based on reactions of aminothiophenes with isocyanates,[41–45] KOCN—HCl,[46] $ClSO_2NCO$,[47] and some other reagents. The substituent R in thienylureas can be replaced with other hydrocarbon groups using reactions with amines.[41]

Pyrimidine ring closure from thienylureas occurs easily upon treatment with bases (generally, with ethanolic or aqueous solutions of alkalis).[41–45,47,48] An example of the use of potassium *tert*-butoxide as a cyclizing agent was documented.[49] Cyclization of ureas with a $—CONH_2$ group in an acidic medium was also described.[46]

Thienopyrimidinediones containing the hydrogenated thiophene ring were synthesized starting from the corresponding tetrahydrothienylureas.[42,48,50,51]

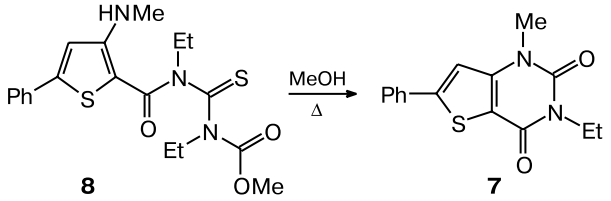
Thienopyrimidinediones **4** unsubstituted at the nitrogen atom (R = H) were prepared starting from aminothiophenes **6**, whose successive treatment with chloroformates (or phosgene) and primary amines[52–56] afforded the target products **4**.



6 **4**

Although intermediate thienylureas were not isolated, their transient formation is quite probable.[57,58]

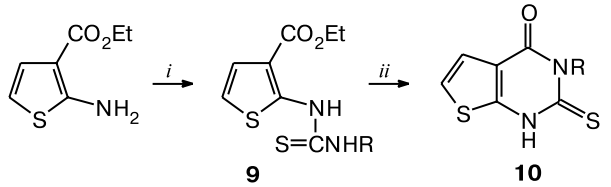
Substituted thienopyrimidinedione **7** was prepared in 91% yield by heating *N*,*N*′-diethyl-*N*-methoxycarbonyl-*N*′-(3-methylamino-5-phenyl-2-thenoyl)thiourea (**8**) in methanol.[59]



8 **7**

Salts of thieno[2,3-*d*]pyrimidine-2,4-dione with alkali metals were synthesized and their IR spectra were studied.[60]

Thienylthioureas **9** prepared by reactions of *vic*-amino(ethoxycarbonyl)thiophenes **6** with isothiocyanates[37,61–64] or by reactions of thiophenes **6** successively with thiophosgene and amines[63,64] undergo, like thienylureas **5**, the pyrimidine ring closure upon treatment with an ethanoholic solution of HCl [63] or ethanolic alkali followed by acidification of the reaction mixture with hydrochloric acid.[37,61–66] Earlier,[67,68] it has been demonstrated that for R = Acyl, the latter reactions resulted in hydrolysis to give unsubstituted thioxopyrimidinone **10** (R = H).



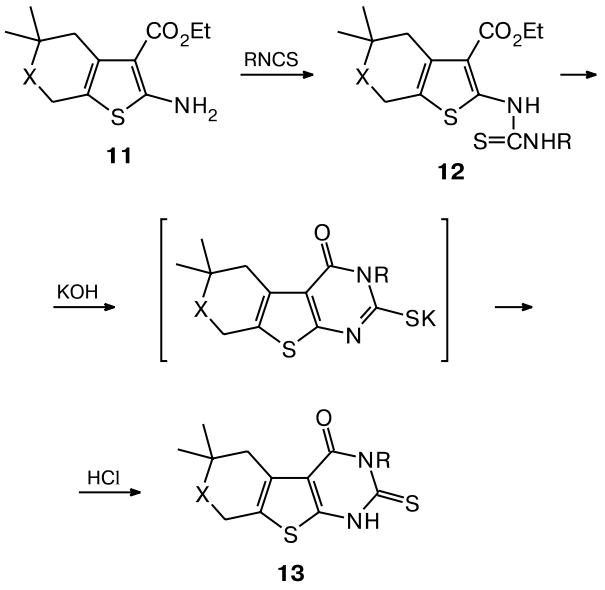
9 **10**

Reagents: *i*. RNCS or 1) $CSCl_2$, 2) RNH_2; *ii*. KOH—EtOH or HCl—EtOH.

As in the case of the corresponding ureas, thioureas **9** need not be isolated in the pure form. For example, treatment of esters **6** with isothiocyanates in the presence of bases directly afforded thioxopyrimidinones **10**,[37,69,70] the reactions of compounds bearing a $-CONH_2$ group proceeding in the absence of bases as well.[71] The reactions with *N*-arylthioureas are accompanied by elimination of the aniline molecule to form unsubstituted thioxopyrimidinone **10** (R = H),[57] which was also prepared by treating aminothiophene **6** with potassium thiocyanate in acetic acid or with formamide and elemental sulfur.[72]

Thiourea **9** can be prepared by the reactions of the corresponding isothiocyanates with an excess of primary amines[73,74] or hydrazine[75,76] as well as by the reactions of esters **6** with *N*-arylthiocarbamates.[77]

Fused 2-amino-3-ethoxycarbonylthiophenes **11** were successfully used in analogous reactions for the synthesis of tricyclic thioxothienopyrimidinones. For example, the reactions of compounds **11** with isothiocyanates gave rise to thioureido derivatives **12**, which underwent intramolecular cyclization under the action of ethanolic KOH to form 2-thioxodihydropyrano(thiopyrano)thienopyrimidine-4-ones **13** in yields higher than 95%.[78–82]

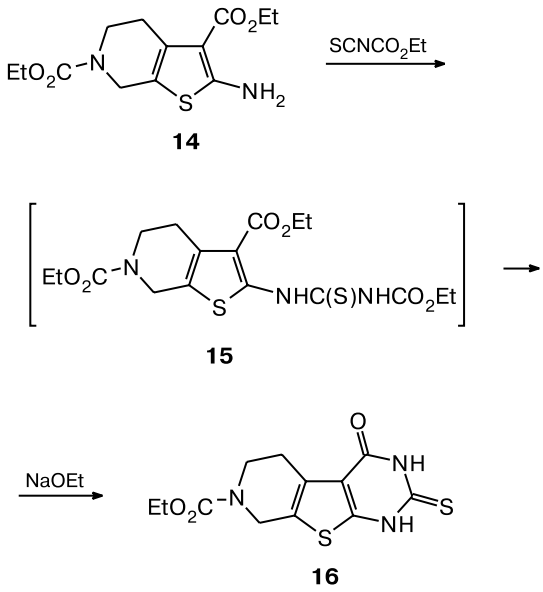


11 12 13

R = H, Me, $CH=CH_2$, Ph, Bn

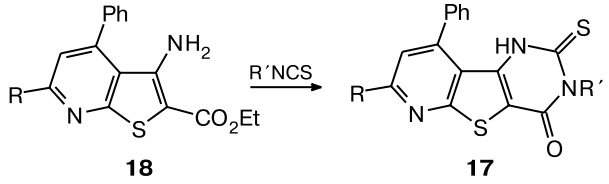
Condensation of diethyl 2-amino-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (**14**) with $SCNCO_2Et$ followed by treatment of intermediate **15** with NaOEt afforded ethyl 4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (**16**).[83]

2-Thioxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **17** isomeric to compound **16** were prepared by cyclocondensation of 2-ethoxycarbonyl-4-phenyl-6-substituted thieno[2,3-*b*]pyridines **18** with isothiocyanates



14 15 16

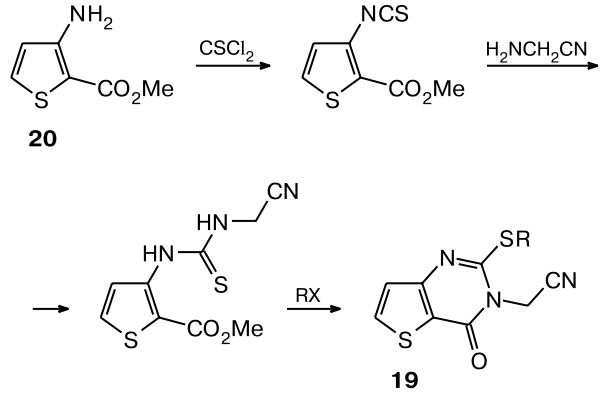
in the presence (or in the absence) of a phase-transfer catalyst.[84]



18 17

R = 4-MeC_6H_4, 4-$MeOC_6H_4$; R′ = Bu^n, Ph

A one-pot procedure was developed[85] for the synthesis of (2-alkylthio-4-oxothieno[3,2-*d*]pyrimidine-3-yl)acetonitriles (**19**) based on treatment of methyl 3-aminothiophene-2-carboxylate (**20**) successively with $CSCl_2$, NH_2CH_2CN, and alkyl halides.

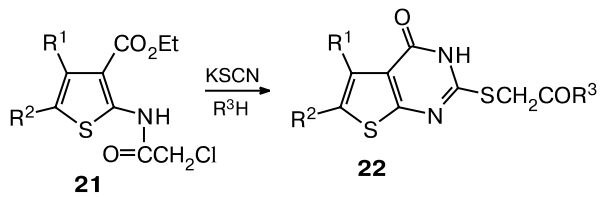


20 19

R = Me, Pr, Bn, $CH_2CO_2Bu^t$

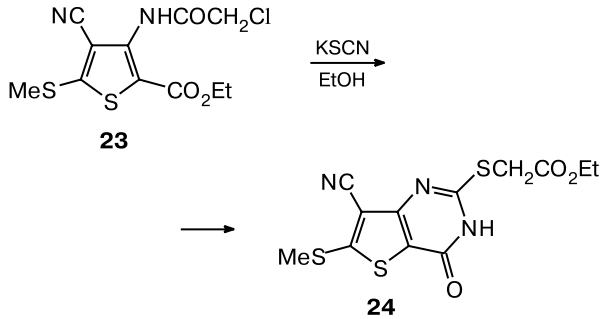
The reactions of aminocarbonyl derivatives of thiophene (**21**) with potassium thiocyanate afforded (4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-ylthio)acetic acid derivatives (**22**) in yields up to 51%. Analogously, the

isomeric aminocarbonyl derivative **23** gave ethyl (7-cyano-6-methylthio-4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-ylthio)acetate (**24**) in 85% yield.[86]



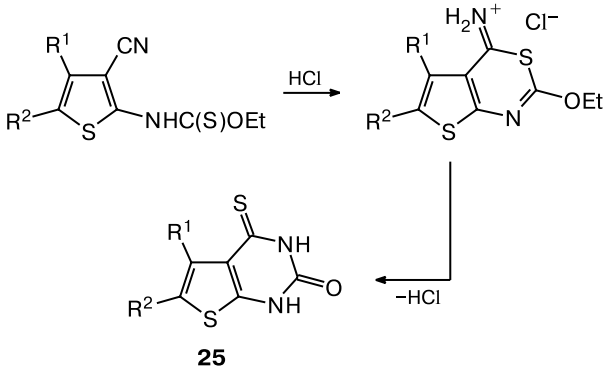
21 **22**

R^1 = Me, R^2 = Me, COEt; R^1, R^2 = $(CH_2)_4$;
R^3 = OEt, OH, $N(CH_2CH_2)_2$



23 **24**

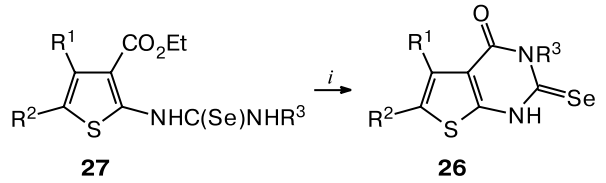
Thioxothienopyrimidinones **25** were prepared[87] by recyclization of thiazines in an acidic medium.



25

2-Thioxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones were synthesized by the reactions of 3-amino-2-ethoxycarbonylthieno[2,3-*b*]pyridines with isothiocyanates[84] or by the reactions of 3-amino-2-cyano(carbamoyl)thieno[2,3-*b*]pyridines with carbon disulfide.[88] An analogous reaction of 2-aminothiophene-3-carboxamide with carbon disulfide yielded thioxopyrimidinone **10**.[58,89]

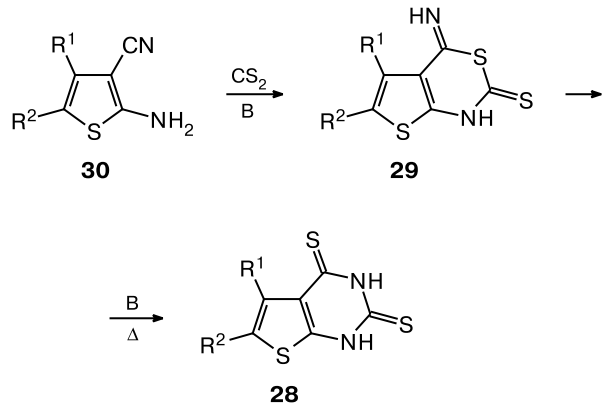
Selenium analogs of compounds **10**, *viz.*, selenoxothienopyrimidinones **26**, were prepared by intramolecular cyclization of selenoureas **27** in the presence of ethanolic KOH.[90]



27 **26**

i. KOH—EtOH.

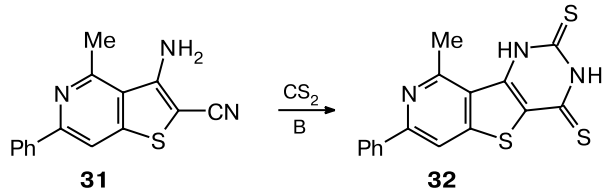
A procedure was developed[89,91–93] for the synthesis of thienopyrimidinedithiones **28** involving thermal recyclization of thiazines **29**, which, in turn, are prepared by the reactions of substituted 2-amino-3-cyanothiophenes **30** with carbon disulfide in the presence of bases.



30 **29** **28**

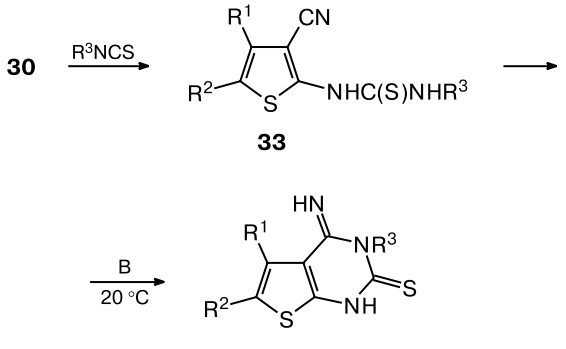
Hereinafter, B is a base.

The reaction of carbon disulfide with amino derivatives of thienopyridine **31** was used for the synthesis of pyridothienopyrimidinedithione **32**.[88]



31 **32**

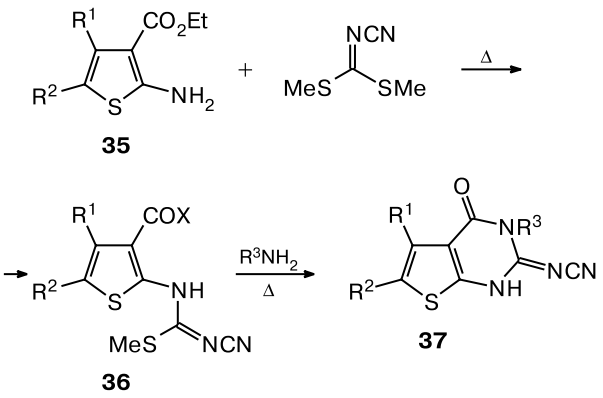
3-Cyano-2-thioureidothiophenes **33**, which are prepared by the reactions of aminocyanothiophenes **30** with isothiocyanates or by reactions successively with $CSCl_2$ and amines, undergo intramolecular cyclization in the presence of bases at room temperature to give 3-thioxothieno[2,3-*d*]pyrimidine-1-imines **34**.[94–96] The latter reaction requires a thorough control over the temperature to prevent the possible rearrangement (such as the Dimroth rearrangement) into aminothienopyrimidinethiones. At-



33 **34**

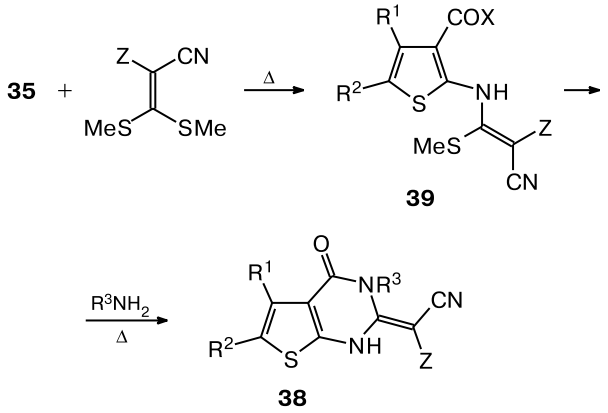
tempts to isolate the corresponding cyclization products of cyanourea failed due, apparently, to the rapid rearrangement into aminothienopyrimidinones.[96]

Aminothiophenes **35** react with *S*,*S*′-dimethyl *N*-cyanoiminocarbodithioate to give isothioureas **36**, which cyclize in the presence of amine (if X = OR) or by heating with a base (if X = NR_2) to yield compounds **37**.[97,98]



X = OR, NR_2

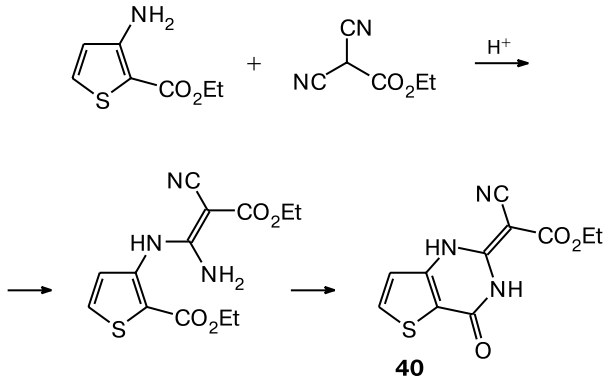
The dicyanomethylene substituent as well as its ester analog can cause a substantial shift of the tautomeric equilibrium in the pyrimidine moiety. Dicyanomethylene derivatives and their ester analogs **38** were prepared[99–101] by reactions of compounds **35** successively with (di)cyanoketene dithioacetal followed by cyclization of intermediate **39** in the presence of bases.



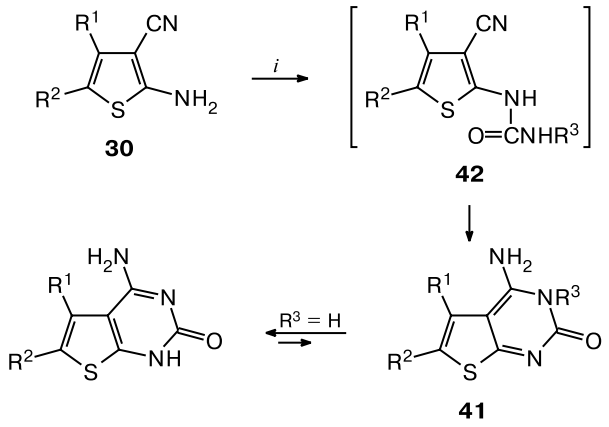
Z = CN, CO_2Me

Thienopyrimidinone **40** was prepared[102] by the reaction of 3-amino-2-ethoxycarbonylthiophene with ethyl dicyanoacetate.

Aminothienopyrimidinones **41** were synthesized by cyclization of *vic*-cyanothienylureas **42** generated *in situ* by the reaction of 2-amino-3-cyanothiophenes **30** with isothiocyanates[96] or urea.[103] Compound **41** with R^3 = H exists predominantly as the tautomeric 4-*NH* form. The

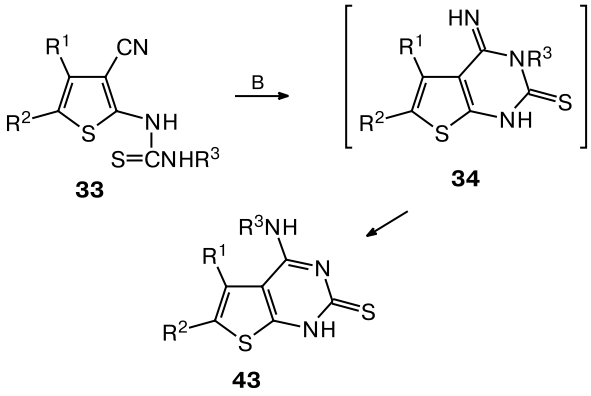


reactions with isothiocyanates are accompanied by dimerization as a side process.[92]

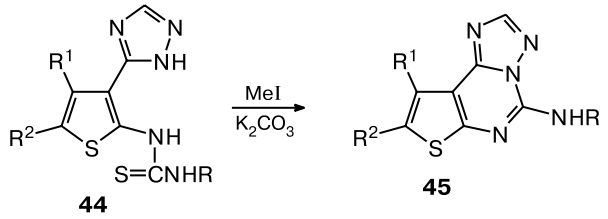


i. R^3NCO or $OC(NH_2)_2$, Δ.

1-Aminothieno[2,3-*d*]pyrimidine-3(4*H*)-thiones (**43**) were prepared by cyclization of *vic*-cyano(thioureido)thiophenes **33** followed by the Dimroth rearrangement of intermediates **34** under the action of bases[94,104–107] or by heating of 2-amino-3-cyanothiophenes **30** with thiourea.[103]

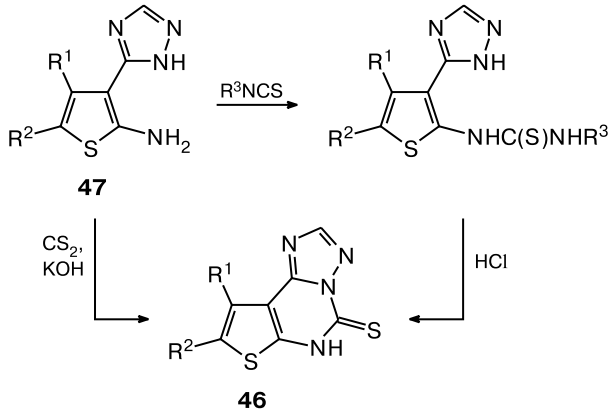


Thioureas **44** undergo cyclization to give annelated thienopyrimidines **45**.[108]



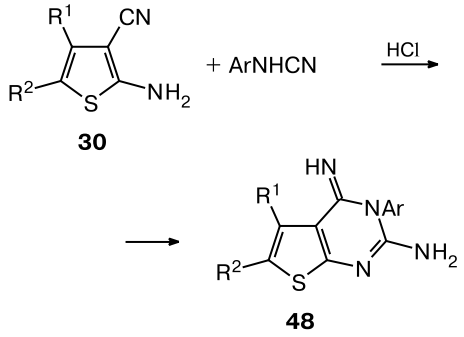
44 **45**

Angularly annelated thienopyrimidinethiones **46** were synthesized[108] by the reactions of 2-amino-3-thienyl-1,2,4-triazoles **47** with isothiocyanates or carbon disulfide.



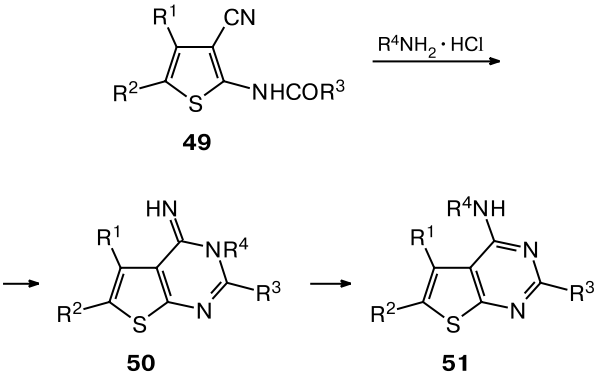
47 **46**

2-Aminothienopyrimidine-4-imines **48** were prepared[109] by the reaction of aminothiophenes **30** with cyanamides in an acidic medium.



30 **48**

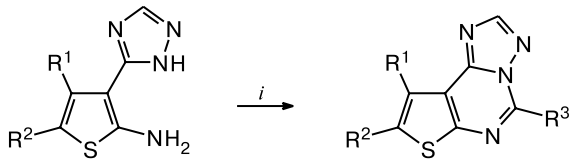
Treatment of 2-acylamino-3-cyanothiophenes **49** with amines afforded thienopyrimidineimines **50**, some of



49 **50** **51**

which are rather unstable and rearrange into aminothienopyrimidines **51** under the reaction conditions.[110–112]

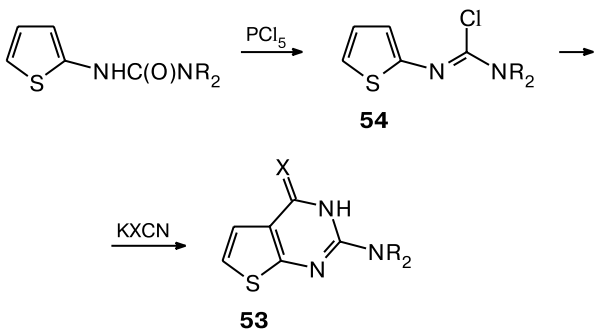
More stable compounds **52** in which the imino group is involved in the fused triazole ring were prepared[103,113] according to the following scheme:



52

i. R^3COCl or $R^3C(OEt)_3$, Δ; or R^3CN—HCl.

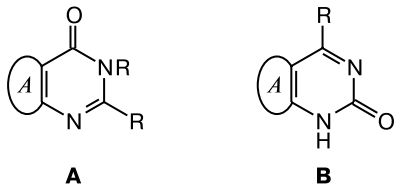
A general procedure for the synthesis[114] of aminothienopyrimidinones(thiones, selenones) **53** is based on the reaction of α-thienylchloroformamidines **54** with salts KXCN (X = O, S, or Se).



54 **53**

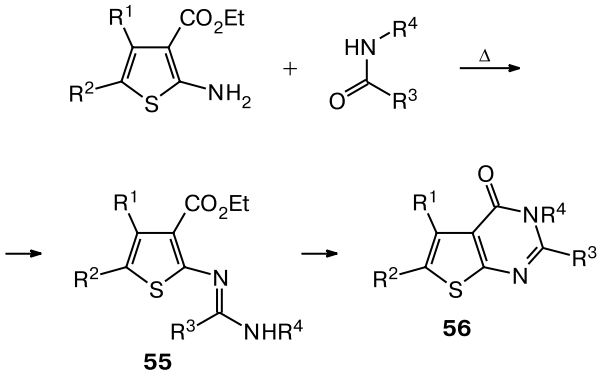
X = O, S, Se

In recent years, much more studies were devoted to the synthesis of thienopyrimidinones and their derivatives. There are two types of such structures depending on the position of the C=O group, *viz.*, the **A** structure containing the amide group and the **B** structure, which is a cyclic urea.



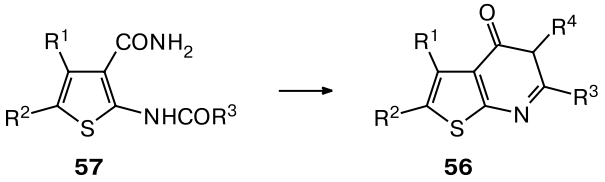
A **B**

As in earlier studies, three main procedures were used for the synthesis of thienopyrimidinones. One procedure involves intramolecular cyclization of *vic*-ethoxycarbonylthienylamidines **55**, which are formed in the reaction of 2-amino-3-ethoxycarbonylthiophenes of type **6** with amides, to give thienopyrimidinones **56**, cyclization being so rapid that it is impossible to isolate amidines **55**.[69,71,115–122] Secondary amides, including cyclic amides, react analogously.[115]



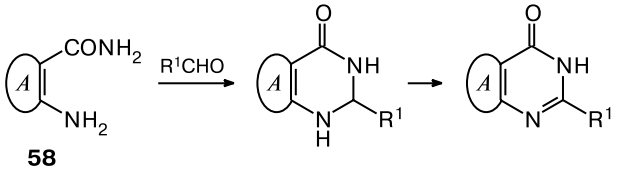
Amidines **55** can also be generated *in situ* by the reactions of thiophenes **6** with nitriles under acidic conditions.[122—134] In some cases, amidines **55** were prepared using milder (two-step) procedures, which involve treatment of thiophenes **6** successively with an orthoester and amine.[135—139]

An alternative procedure for the preparation of thienopyrimidinones **56** is based on the pyrimidine ring closure in *vic*-carbamoylacylaminothiophenes **57** by heating in an inert solvent[140—143] or under conditions of basic catalysis.[144—147]



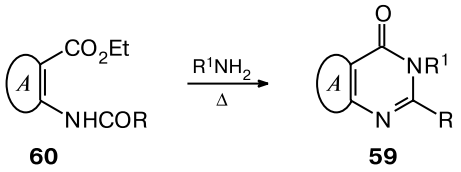
Diamides **57** need not be isolated from the reaction mixture. In these reactions, orthoesters,[71,148—150] acetic anhydride,[58,151,152] formic acid,[58,153] and diethyl oxalate[141,154—156] were used as reagents.

vic-Amino(carbamoyl)thiophenes **58** react with aromatic and heteroaromatic aldehydes to give hydrogenated thienopyrimidinones,[149,157—159] which are oxidized to the corresponding thienopyrimidinones on heating in an acidic medium.[158]

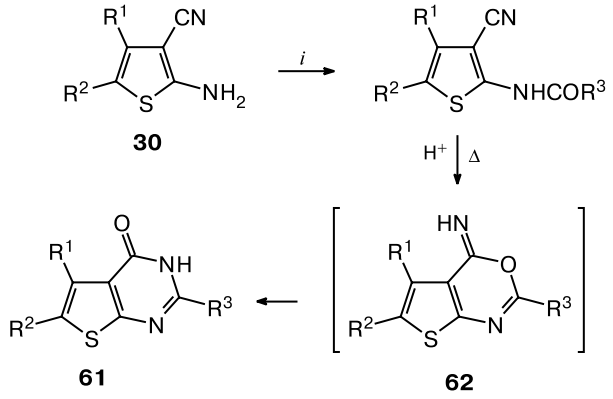


R = Ar, Het

Thienopyrimidinones **59** were prepared[128,160—164] by the reactions of thiophenes **60** containing the ethoxycarbonyl and amide groups with amines. It was postulated that these reactions proceed *via* intermediate diamides **57**.

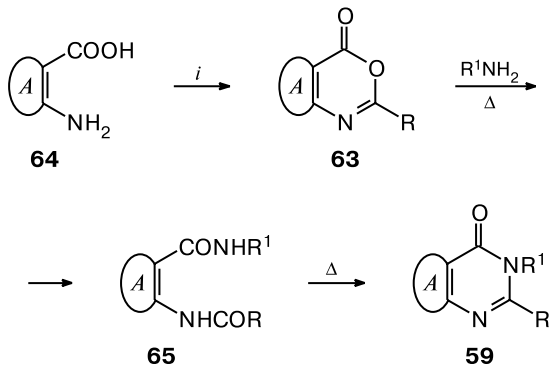


Heating of *vic*-aminocyanothiophenes **30** (following *N*-acylation) in the presence of acids affords thienopyrimidinones **61**. Apparently, the reaction proceeds *via* imines **62**, which undergo recyclization under the reaction conditions to form compounds **61**.[107,164—167]



i. R^3COCl or $(R^3CO)_2O$.

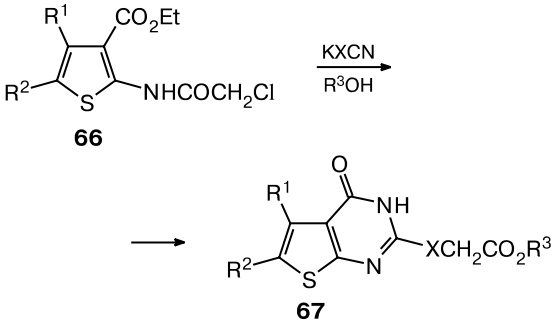
The third general procedure for the synthesis of thienopyrimidines **59** is based on recyclization of thienooxazinones **63**, which are generated by the reactions of aminocarboxylic acids **64** or esters **6** with acylating agents (Ac_2O, $HC(OEt)_3$, or PhCOCl) in the presence of bases, under the action of amines.[46,119,168—179] This recyclization proceeds through the intermediate formation of diamides **65**. The reactions with secondary amines give these diamides as the only reaction products.[178,180]



i. RCOCl or $RC(OEt)_3$.

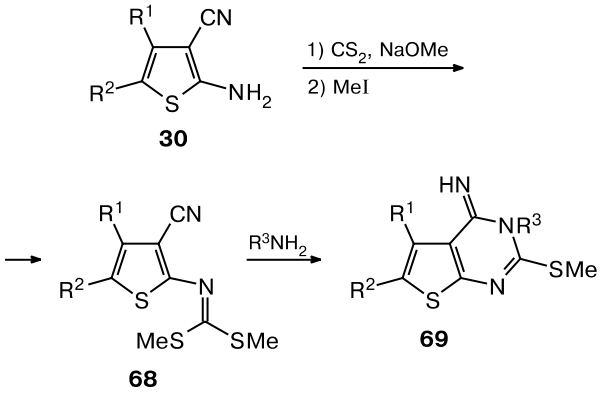
Other thienopyrimidinones bearing substituents in the pyrimidine fragment were successfully synthesized with the use of 2(3)-amino-3(2)-ethoxycarbonylthiophenes **6** and their annelated analogs.[123,124,181—189]

An unusual closure of the pyrimidine ring was observed in the reactions of 2-chloroacetylamino-3-ethoxycarbonylthiophenes **66** with salts KXCN (X = S or Se) giving rise to substituted thienopyrimidinones **67**.[190]

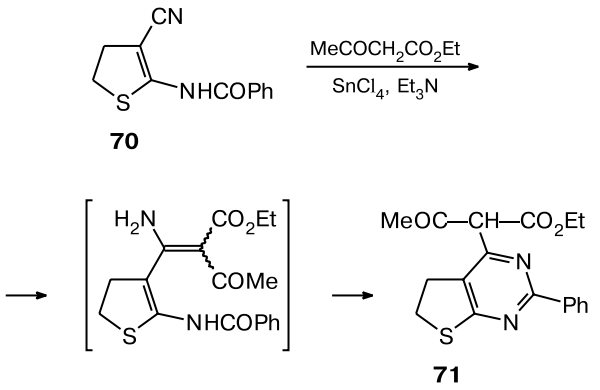


X = S, Se

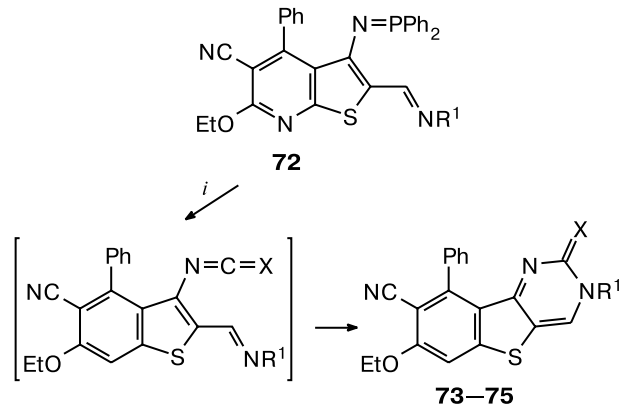
Successive treatment of 2-amino-3-cyanothiophenes **30** with carbon disulfide in the presence of sodium methoxide and then with methyl iodide gave rise to *vic*-bis(methylthio)methylideneamino(cyano)thiophenes **68**, which were transformed into alkylthiothienopyrimidineimines **69** under the action of amines.[93,191] It was emphasized that it is necessary to thoroughly control the reaction conditions to prevent the possible Dimroth rearrangement.



The reaction of 2-benzoylamino-4,5-dihydrothiophene-3-carbonitrile (**70**) with ethyl acetoacetate in the presence of tin(IV) chloride and triethylamine afforded ethyl 2-(5,6-dihydro-2-phenylthieno[2,3-*d*]pyrimidin-4-yl)-3-oxobutanoate (**71**).[192]



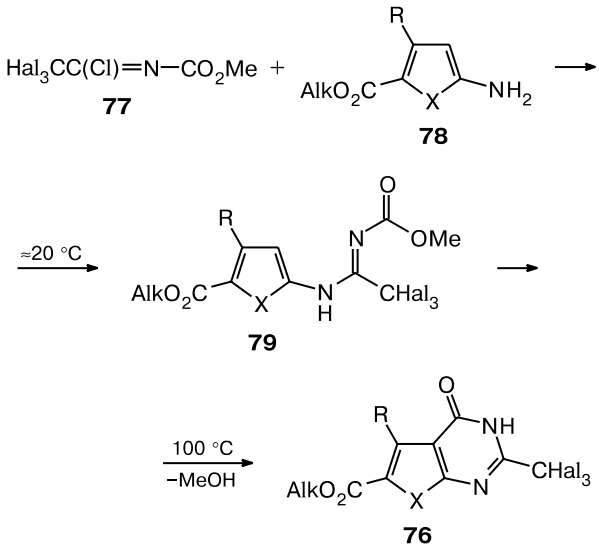
An efficient procedure was developed for the synthesis of pyridothienopyrimidines containing various substituents at position 2 of the pyrimidine fragment. For example, iminophosphoranes **72** react with isocyanates, CO_2, and CS_2 under mild conditions to give functionalized 2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidines **73—75**.[193]



R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2 = Et, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4;
X = NR^2 (**73**), O (**74**), S (**75**)

Reagents and conditions: *i*. R^2NCO, C_6H_5Me, Δ (for **73**); CO_2, C_6H_5Me, 120 °C (for **74**); CS_2, C_6H_5Me, 120 °C (for **75**).

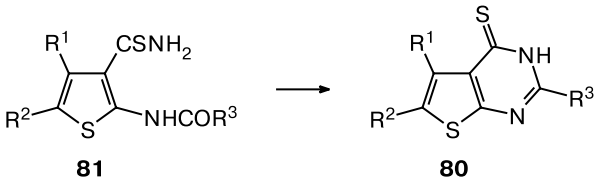
A new efficient approach to the synthesis of previously unknown trihalomethyl-substituted thienopyrimidinones **76** is based on the reaction of methyl *N*-(1-chloro-2,2,2-trihaloethylidene)carbamates **77** with thienylamines **78**.[194] Intermediate trihaloacetamidines **79** undergo intramolecular cyclization into thienopyrimidinones **76** on heating.



X = O, S

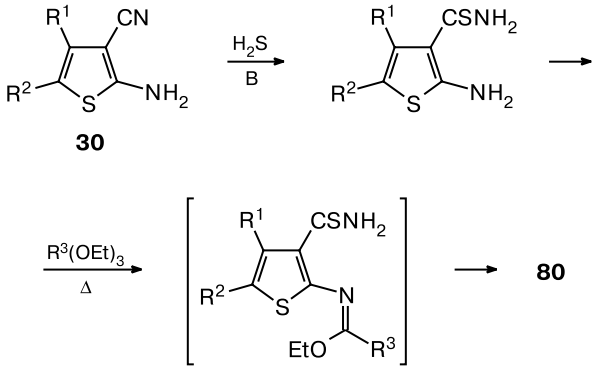
Several modifications of methods for the synthesis of thienopyrimidinones were documented.[159,182,195–199]

Two main procedures for the construction of thienopyrimidinethiones **80** containing a cyclic thioamide fragment are known. One of them is based on cyclization of *vic*-acylamino(thiocarbamoyl)thiophenes **81**.



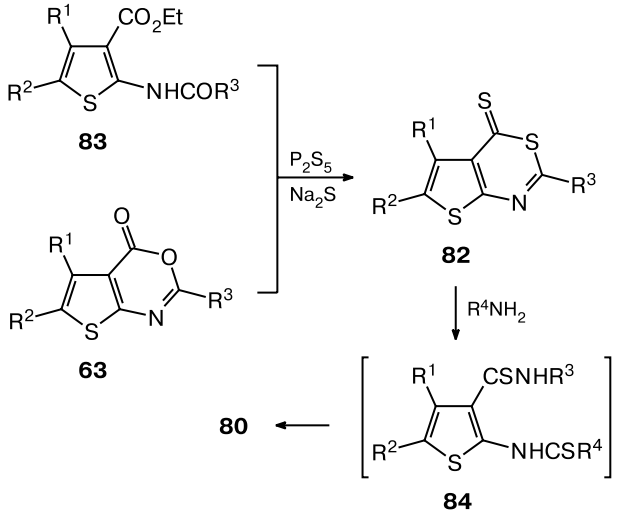
81 **80**

Thioamides required for this reaction are prepared from the corresponding nitriles **30**, which undergo cyclization to thienopyrimidinethiones **80** upon successive treatment with carbon disulfide in the presence of bases and then with orthoesters.[200] The reverse order of the reaction steps can also be used: an imidate or amide is initially formed from nitrile **30** and then these intermediates are transformed into compounds **80** upon treatment with NaSH.[91,200]



30

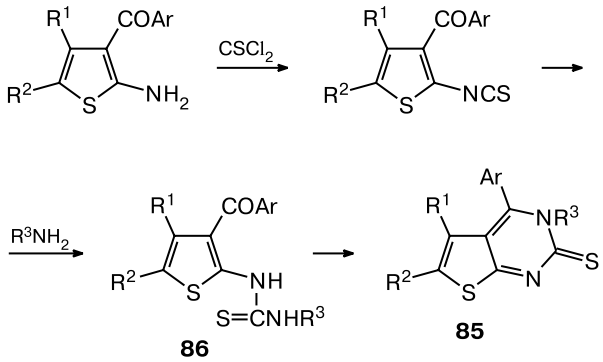
Another procedure for the synthesis of thiones **80** involves recyclization of thienothiazinethiones **82**, which



83 **82** **63** **84**

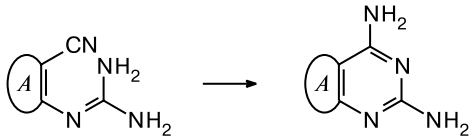
are prepared by the reactions of amides **83** or thienooxazinones **63** with P_2S_5 and Na_2S, under the action of amines.[201–202] These reactions proceed *via* intermediate bis-thioamides **84**. In the case of $R^4 = Bu^t$, the intermediates were isolated.[203] An excess of amine should not be used in recyclization because of the possible replacement of the thione group with the imino group.[205,206]

Thienopyrimidinethiones **85** isomeric to thiones **80** were synthesized by cyclization of thioureas **86** prepared from the corresponding amino(aroyl)thiophenes.[207]



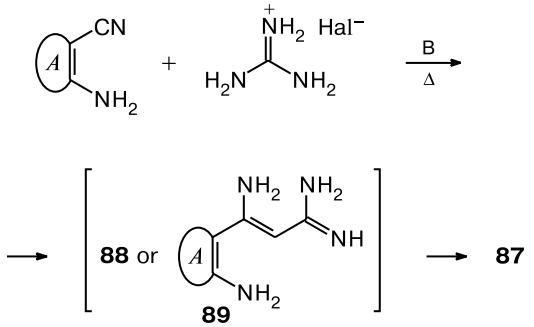
86 **85**

In recent years, the development of methods for the synthesis of thienopyrimidines containing two substituents in the pyrimidine moiety has also attracted attention. For example, a general procedure was devised for the synthesis of diaminothienopyrimidines **87**, which involves the pyrimidine ring closure in *vic*-cyano(guanidino)thiophenes **88**.



88 **87**

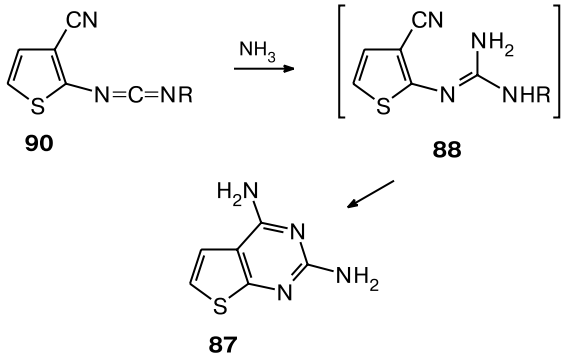
Compounds **87** are prepared *in situ* by the reaction of 2-amino-3-cyanothiophenes with chloroformamidine[208,209] or guanidine. The latter reaction proceeds *via* guanidines **88** or **89** as intermediates.[94,107,200,210]



89

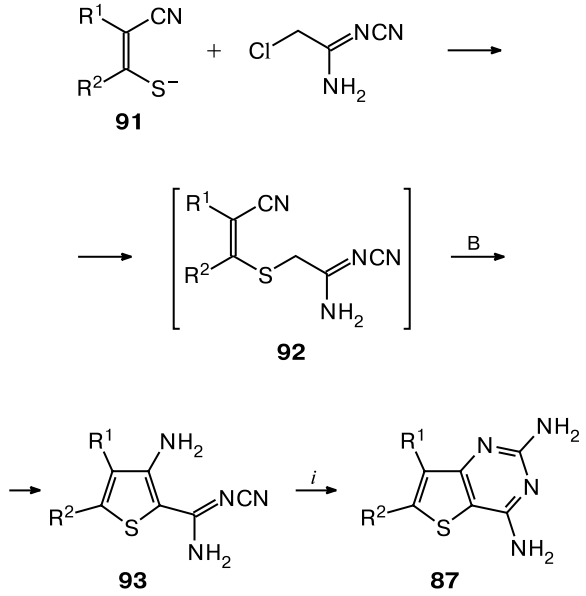
Diaminothienopyrimidines **87** were also synthesized by the reactions of thiophenes **30** with cyanamides in

acidic conditions[211] or by cyclization of guanidines **88** derived from the corresponding carbodiimides **90**.[212]



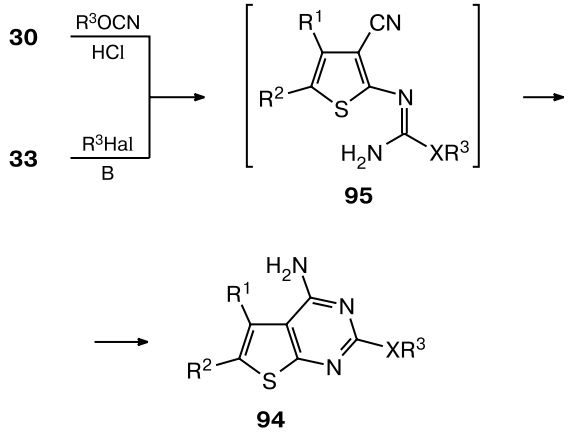
Diaminothienopyrimidines were also prepared[210] by treatment of thiophenes **30** successively with carbon disulfide and ammonia.

An original procedure was developed for the synthesis of thienopyrimidines **87** involving the simultaneous closure of the thiophene and pyrimidine rings.[39,213–215] For example, treatment of enethiolates **91** with *N*-cyanochloroacetamidine triggers a chain of successive reactions: alkylation at the sulfur atom to form compounds **92**, the Thorpe—Ziegler cyclization to give thiophenes **93**, and the pyrimidine ring closure. Intermediates need not be isolated from the reaction mixture and the target thienopyrimidine **87** can be synthesized by a one-pot procedure. The last step, *viz.*, the pyrimidine ring closure, can be performed both in basic and acidic media.



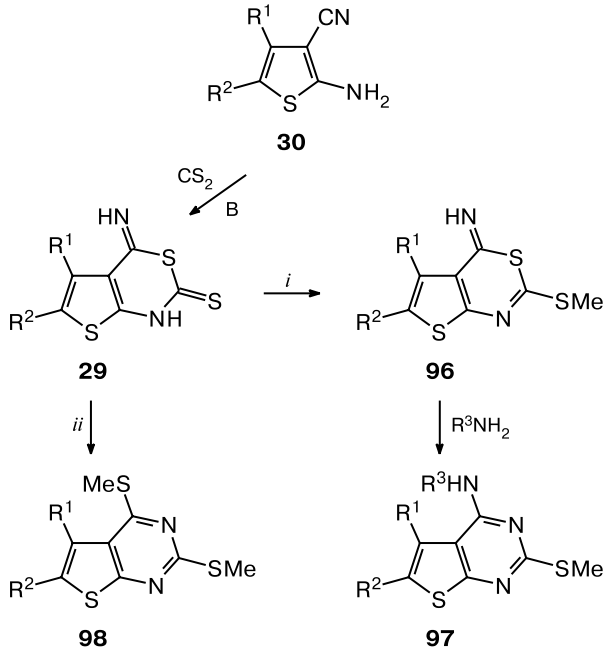
i. Base or H^+.

Alkoxy- and alkylthio-substituted aminothienopyrimidines **94** were prepared by cyclization of the corresponding isoureas and isothioureas **95**. Isoureas are generated *in situ* by the reactions of thiophenes **30** with cyanates in the presence of acids.[216] Isothioureas are produced by alkylation of thioureas **33**.[105]



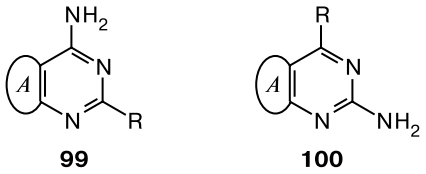
X = O, S

Another procedure for the synthesis of these compounds is based on the use of iminothienothiazinethiones **29** as the starting substrates. For example, their reactions with one equivalent of methyl iodide afforded compounds **96**, which underwent recyclization into thienopyrimidines **97** under the action of amines.[191] The reaction with two equivalents of methyl iodide gave rise to di(methylthio)thienopyrimidines **98**.[93]



Reagents: *i*. MeI (1 equiv.), Et_3N (1 equiv.); *ii*. MeI (2 equiv.), Et_3N (2 equiv.).

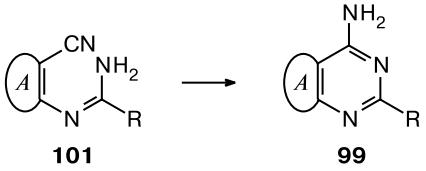
The two possible isomers of aminothienopyrimidines contain either the amidine (**99**) or guanidine (**100**) fragment.



99 **100**

R = H, Alk, Ar

Two general procedures for the direct synthesis of aminothienopyrimidines **99** are documented. One of these method involves cyclization of *vic*-amidino(cyano)thiophenes **101**.

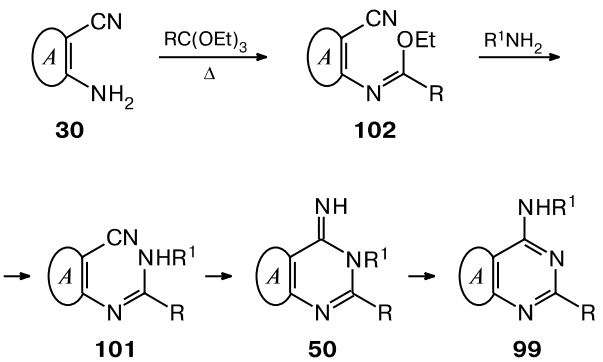


101 **99**

The most popular procedure for the preparation of the starting amidines **101** is based on the reaction of *vic*-amino(cyano)thiophenes **30** with formamide.[91,94,104,117,217,218] Under the reaction conditions, intermediate formamidine **101** cannot be isolated and it undergoes spontaneous cyclization to give aminothienopyrimidine **99**.

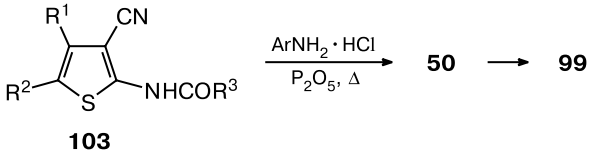
Imidates react with thiophenes **30** analogously. In the reactions of *N*-substituted imidates, the initially formed thienopyrimidineimines **50** undergo cyclization to give aminothienopyrimidines **51**.[219] Amidines **101** can also be prepared by the reactions of aminothiophenes **30** with nitriles in an acidic medium.[132,215,211,220,221] In this case, attempts to isolate amidines **101** also failed. The reaction is complicated by the side formation of chlorothienopyrimidine due, apparently, to the competitive attack of hydrogen chloride on the 3-CN group of thiophene **30**. The amount of chlorothienopyrimidine produced depends on the nature of the substituent R and the reaction conditions.[211,222]

A very mild procedure for the generation of amidines **101**, which allows their isolation, is based on aminolysis of imidates **102**, which are prepared by treatment of thiophenes **30** with orthoesters. The reaction with ammonia directly affords aminothienopyrimidine **99**,[200] whereas in the case of primary amines, recyclization of intermediate thienopyrimidineimine **50** takes place.[223,224] Thienopyrimidineimines **50**, like amidines **101**, can be isolated from the reaction mixture. It was demonstrated[223,224] that both these compounds give aminothienopyrimidines **99** on heating in the presence of a catalytic amount of bases.



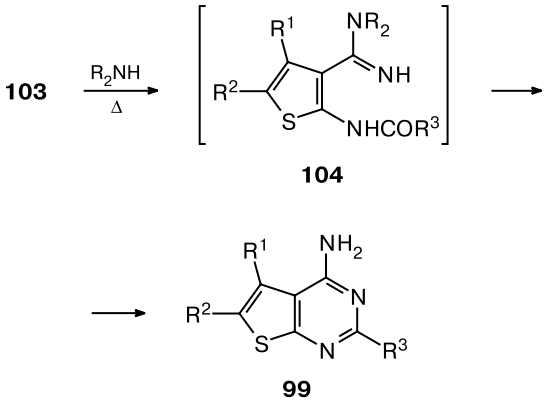
30 **102** **101** **50** **99**

Amidines **101** can also be generated by treatment of amides **103** with arylamine hydrochlorides in the presence of dehydrating agents, such as P_2O_5. In this case, attempts to isolate the corresponding amidines failed, but this procedure made it possible to prepare thienopyrimidines **99**.[110,111]



103

Another procedure for the synthesis of aminothienopyrimidines **99**, which is used much more rarely, is based on the pyrimidine ring closure in *vic*-acylaminothiophenecarbamidines **104** generated *in situ* from compounds **103** and amines.[163,225]



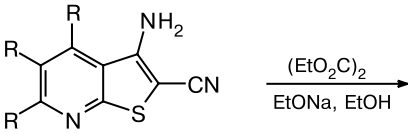
104 **99**

Aminothienopyrimidines **99** can also be prepared by substitution of an amine for the halogen atom in halothienopyrimidines synthesized from thienopyrimidinones of type **A**. An analogous synthesis based on thienopyrimidinones of type **B** provides the only approach to derivatives of isomeric aminothienopyrimidine **100**.[226]

Most compounds of this group are accessible only by an indirect route involving synthesis of thienopyrimidinones, preparation of chlorothienopyrimidines from these compounds, and the replacement of the chlorine atom with OR, SR, or other groups. However, procedures for the direct construction of the target pyrimidine ring were described for particular cases (for the preparation of specific compounds).

3-Amino-2-cyanothieno[2,3-*b*]pyridines **105** react with diethyl oxalate in the presence of sodium ethoxide to

give pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines **106**.[179] The reaction involves successive *N*-acylation, the formation of imidate **107**, and cyclization into pyrimidine **106**.



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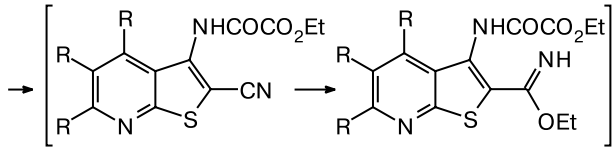

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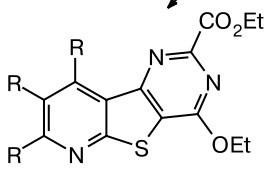
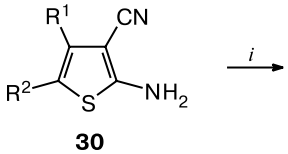


106

1-Chlorothieno[2,3-*d*]pyrimidines (**108**) are formed (sometimes as by-products) in the reactions of thiophenes **30** with nitriles in the presence of dry hydrogen chloride.[210,221] Apparently, the reactions involve the attack of HCl on the nitrile group in amidine **109** followed by the pyrimidine ring closure in imidoyl chloride **110** produced. Chlorothienopyrimidines **108** can selectively be prepared by the reaction of thiophenes **30** with the Vilsmeier reagent. In this case, the competitive reactions of the nitrile and amino groups are not observed.[227]



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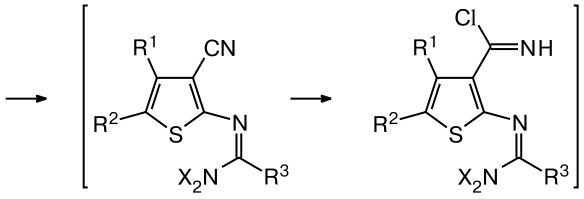
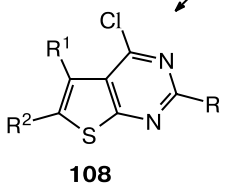


109 **110**



108

X = H, Me

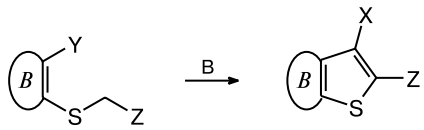
i. R^3CN, HCl or R^3COMe_2, $POCl_3$.

In recent years, procedures were devised for the synthesis of thienopyrimidines using recyclization of derivatives of thieno[2,3-*d*]oxazinones,[228,229] thieno[3,2-*d*]oxazines,[230] and pyrano[3,4-*d*]pyrimidines.[231]

2.2. Synthesis of thienopyrimidines by thiophene ring closure

As earlier, procedures for the synthesis of thienopyrimidines by the thiophene ring closure starting from the available pyrimidine system are used much more rarely than the pyrimidine ring closure. This is attributable to the fact that the starting appropriately substituted pyrimidines are less readily accessible. In this section, the data are systematized according to the types of reactions giving rise to the thiophene ring formation.

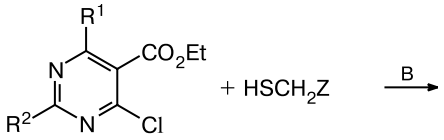
Generally, the synthesis of thienopyrimidines using the Claisen, Thorpe—Ziegler, and Friedläender condensations can be represented by the following scheme:



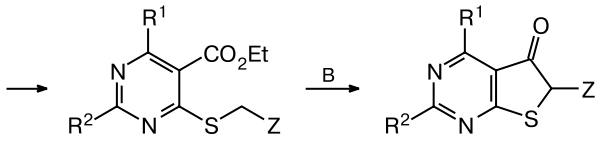
Y = CO_2Et, X = OH (=O); Y = CN, X = NH_2; Y = COR, X = R;

Z is an electron-withdrawing group, *B* is the pyrimidine ring

In the case of Y = CO_2Et, the reaction affords 5-hydroxythienopyrimidines, which exist predominantly as the oxo form (**111**). Pyrimidines **112** used as the starting compounds in this synthesis can be prepared by two methods. One of them involves substitution of the mercaptoacetic acid residue for the chlorine atom in 4-chloro-5-ethoxycarbonylpyrimidines **113**. Pyrimidines **112** are then subjected to cyclization in the presence of bases to give thieno[2,3-*d*]pyrimidin-5-ones **111**.[232,233]



113

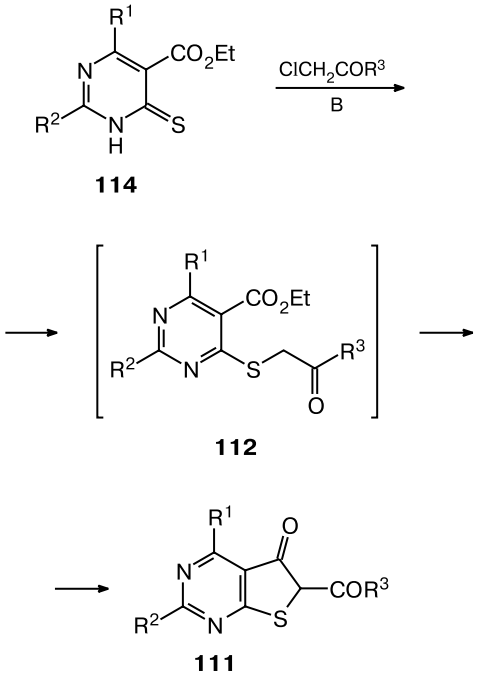


112 **111**

R^1 = H, Me, SMe; R^2 = Ph, Cl; Z = CO_2Alk, CONHAr, CN, NO_2

The sulfonyl group at position 4 of pyrimidine is replaced like the chlorine atom. The starting sulfonylpyrimidines were prepared[232] by oxidation of the corresponding allylthio compounds.

Another procedure for the synthesis of pyrimidines **112** involves alkylation of 5-ethoxycarbonylpyrimidine-4(3*H*)-thiones **114** with chloroacetic acid derivatives. In this case, thienopyrimidines **111** were prepared without isolation of intermediate pyrimidines **112**.[234—236]

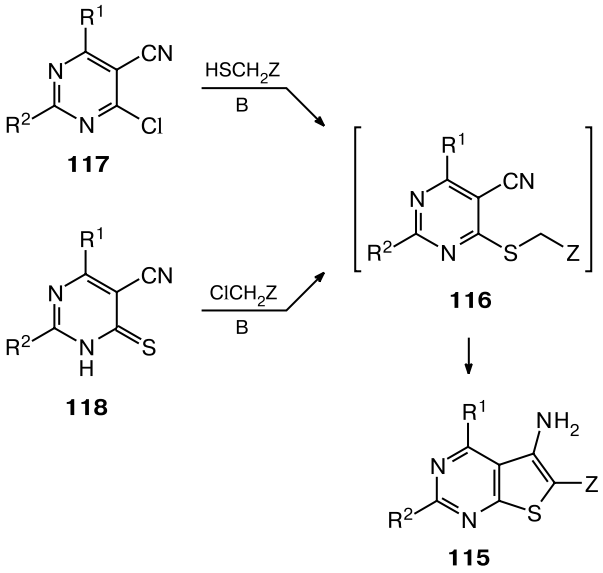


R^1 = Me, Ar; R^2 = Ar; R^3 = Me, OEt, NH_2NHAr

For Z = CN, the Thorpe—Ziegler reaction affords aminothienopyrimidines **115**. The starting pyrimidines **116**, like ester analogs **112**, are generated by the replacement of the chlorine atom in 4-chloro-5-cyanopyrimidines **117** with the corresponding thiols[118,232,233,237—241] or by alkylation of 5-cyanopyrimidinethiones **118** with chloroacetic acid derivatives.[242—247]

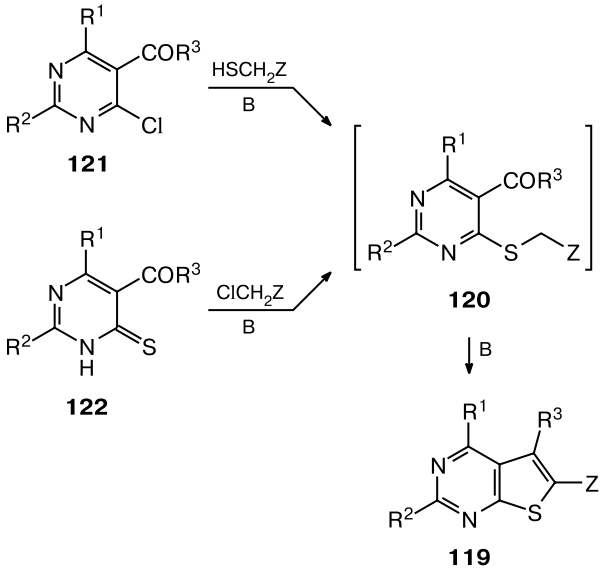
In some cases, pyrimidines **116** formed as intermediates in the *S*-alkylation of pyrimidinethiones **118** were isolated.[243,245] In the presence of a catalytic amount of bases, compounds **116** undergo cyclization to give the target products. In addition to compounds **115** containing the above-mentioned groups Z, 6-aryl-substituted derivatives can also be prepared, but cyclization of intermediates **116** is carried out with the use of metallic sodium or sodium hydride.[233]

In the case of Z = COR, the Claisen—Schmidt reaction affords thienopyrimidines **119**. The starting pyrimidines **120** are prepared by either substitution of the mercaptoacetic acid residue for the chlorine atom in 5-acyl-4-chloropyrimidines **121** [239,241,248—252] or alkylation of



R^1 = H, CO_2Et, SMe, Ar, OH (=O); R^2 = SMe, NR_2, Ph, Cl, OH (=O); Z = CO_2Alk, $CONR_2$, CN, COR, NO_2

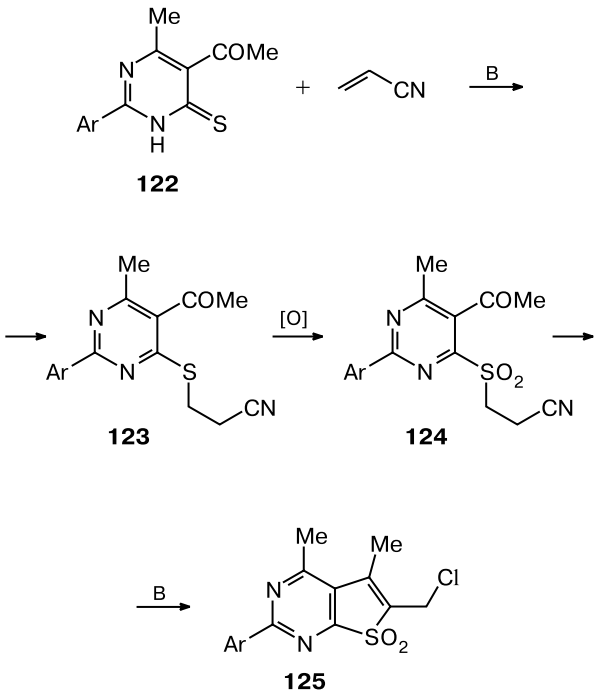
5-acylpyrimidinethiones **122** with α-halocarbonyl compounds.[241,253—260]



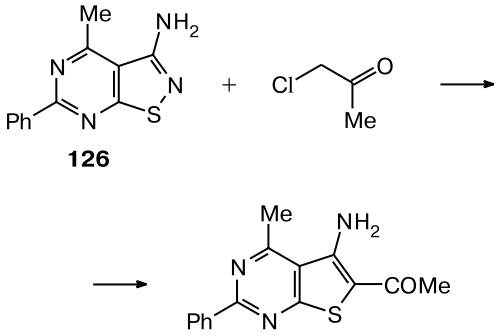
R^1 = H, Me; R^2 = Ar; R^3 = Me; Z = CO_2H, CO_2Et, CONHR, COR, CN

Both these procedures allow one to isolate intermediate pyrimidines **120**.[249,250,253]

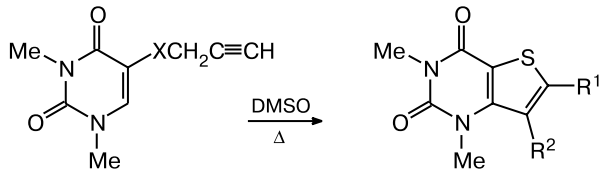
The Michael reaction of thione **122** with acrylonitrile affords pyrimidine **123**, which, however, does not undergo cyclization. After oxidation of pyrimidine **123** to sulfone **124**, the acidity of the methylene fragment becomes sufficiently high for cyclization of the latter to give thienopyrimidine **125**.[261,262]



Treatment of aminoisothiazolopyrimidine **126** with chloroacetone gave rise to an unexpected transformation. In this reaction, thienopyrimidine is formed, apparently, through the intermediate opening of the isothiazole ring and the formation of the corresponding nitrile.[263]

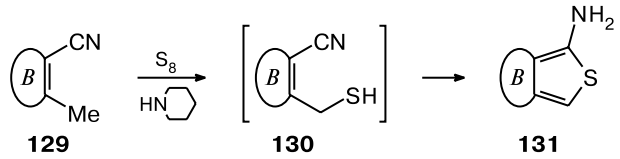


Alternative approaches to the synthesis of thienopyrimidines by the thiophene ring closure are also documented. For example, the thio-Claisen rearrangement of propargyl sulfide **127** (X = S) affords thienopyrimidinediones **128**; the rearrangement of sulfoxide **127** (X = SO) gives rise to the corresponding formyl derivative **128** (R^2 = CHO).[264]

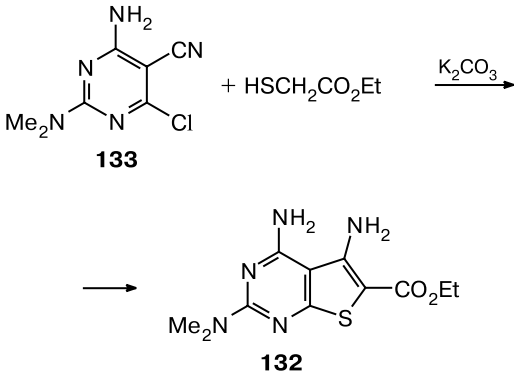


X = S, R^1 = Me, R^2 = H; X = SO, R^1 = H, R^2 = CHO

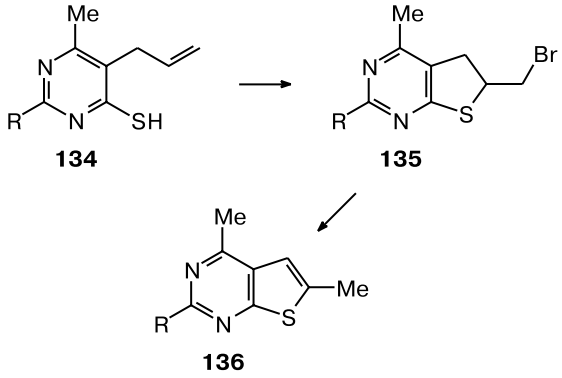
Another approach to the construction of the thiophene ring based on functionalized pyrimidines involves thiolation of the methyl group in *vic*-methylpyrimidinecarbonitriles **129** with elemental sulfur followed by cyclization of intermediate thiols **130** to give thienopyrimidines **131**. The reactions were carried out with pyrimidinethiones[265] and pyrimidinediones.[266,267]



Ethyl 4,5-diamino-2-(dimethylamino)thieno[2,3-*d*]pyrimidine-6-carboxylate (**132**) was prepared in 93% yield by the reaction of 4-amino-6-chloro-2-(dimethylamino)pyrimidine-5-carbonitrile (**133**) with ethyl 2-mercaptoacetate in refluxing EtOH—THF (5 : 1).[268]



Bromination of 5-allyl-6-methyl-2-methylthio(phenyl)pyrimidine-4-thiols (**134**) in chloroform afforded 6-bromomethyl-4-methyl-2-methylthio(phenyl)-5,6-dihydrothieno[2,3-*d*]pyrimidines **135**. The latter were transformed into 4,6-dimethyl-2-methylthio(phenyl)thieno[2,3-*d*]pyrimidines **136** by refluxing with ethanolic sodium ethoxide.[269]

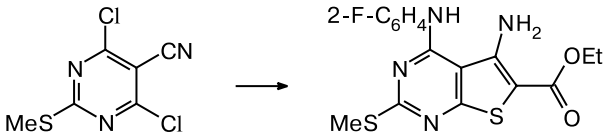


R = SMe, Ph

The thermal [3,3]-sigmatropic rearrangement of 1,3-dimethyl-5-(isopropylthio)uracils gave rise to

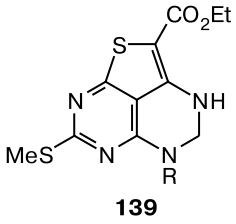
1,3,6-trialkylthieno[2,3-*d*]pyrimidines in yields of up to 82%.[270]

Ethyl ester **137** was synthesized by the reaction of 4,6-dichloro-2-(methylthio)pyrimidine-5-carbonitrile (**138**) with *o*-fluoroaniline followed by treatment of the intermediate fluoroanilino derivative with ethyl mercaptoacetate in the presence of NaOH.[271]



138 **137**

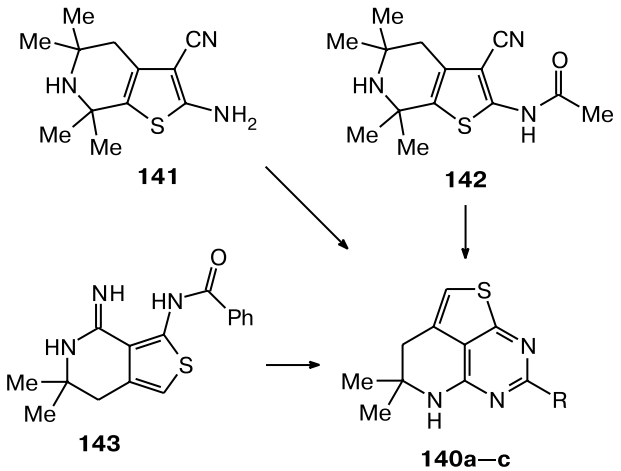
First representatives of the previously unknown tricyclic annelated system, *viz.*, ethyl 7-methylthio-4,5-dihydro-3*H*-thieno[2,3,4-*de*]pyrimido[4,5-*d*]pyrimidine-2-carboxylates **139**, were prepared by the three-step synthesis from 4,6-dichloro-2-methylthiopyrimidine-5-carbonitrile.[272]



139

R = H, 3-$F_3C_6H_4$

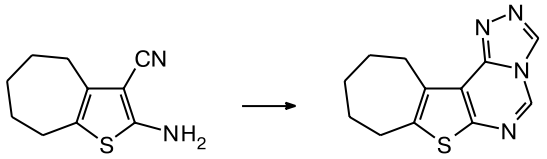
Other representatives of *ortho-peri*-fused thienopyrimidines, *viz.*, 4,4-dimethyl-4,5-dihydro-3*H*-thieno[2,3,4-*de*]pyrido[2,3-*d*]-pyrimidine (**140a**), 4,4,7-trimethyl-4,5-dihydro-3*H*-thieno[2,3,4-*de*]pyrido[2,3-*d*]pyrimidine (**140b**), and 4,4-dimethyl-7-phenyl-4,5-dihydro-3*H*-thieno[2,3,4-*de*]pyrido[2,3-*d*]pyrimidine (**140c**), were synthesized by a cascade heterocyclization of aminonitrile **141** with formamide, amide **142** with *N*-methylacetamide, or amide **143** with ammonium acetate, respectively.[273]



141 **142** **143** **140a—c**

R = H, Me, Ph

The previously unknown polyannelated heterocyclic system, *viz.*, tetrahydrocycloheptathieno-1,2,4-triazolopyrimidine (**144**), was constructed starting from 2-amino-3-cyanotetrahydrocycloheptathiophene (**145**) in four steps.[274]



145 **144**

3. Chemical properties of thienopyrimidines

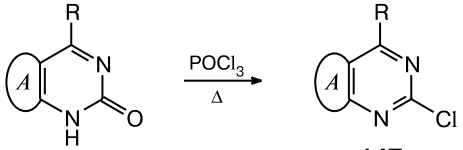
Knowledge of the behavior of heterocyclic systems under conditions of the principal reactions is required to perform the directed synthesis of practically important, particularly, of biologically active, compounds. As earlier, considerable recent attention has been given to investigations into modifications of substituents in the preformed thienopyrimidine structure. In addition, many studies were devoted to the use of various thienopyrimidine derivatives in the synthesis of linearly and angularly polyannelated, including previously unknown, heterocyclic systems.

3.1. Nucleophilic substitution

In the chemistry of thienopyrimidinones and thienopyrimidinediones, the replacement of the oxygen atom with the chlorine atom is used rather often. Earlier, it was found[275,276] that this reaction with thienopyrimidinediones **4** proceeds on heating with either $POCl_3$ (an excess of $POCl_3$, pyridine, or *N*,*N*-dimethylaniline is used as the solvent) or $SOCl_2$. The reaction is accompanied by the formation of the corresponding dichlorothienopyrimidines.

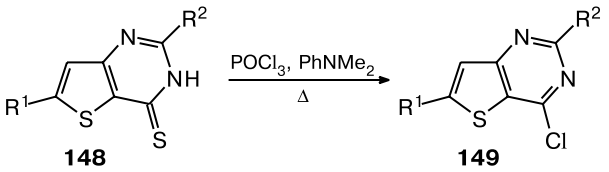
In recent years, such reactions in the series of thienopyrimidinones **59** were most often carried out with $POCl_3$ in pyridine or *N*,*N*-dimethylaniline to prepare chlorothienopyrimidines **108**.[56,122,144,149,158,179,277—285]

Thienopyrimidinones **146** react analogously to afford chlorothienopyrimidines **147**.[225,286]



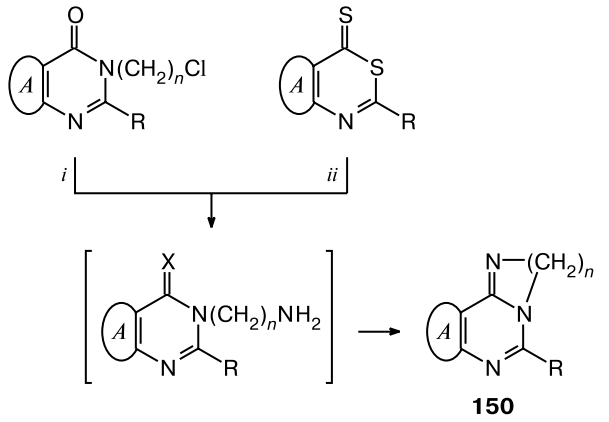
146 **147**

Compounds containing the thioxo group undergo the same transformations. Under the action of $POCl_3$, thienopyrimidinethiones **148** are converted into chlorothienopyrimidines **149**.[200]



148 **149**

Thienopyrimidinones and thienopyrimidinethiones undergo intramolecular condensation involving the primary amino group and the oxo- or thioxo group to form compounds **150** with a five- or six-membered ring.[143,163,204,205]



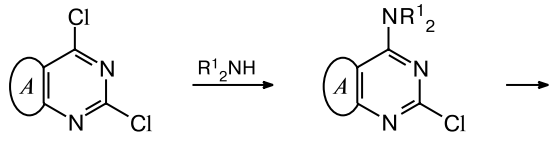
150

X = O, S

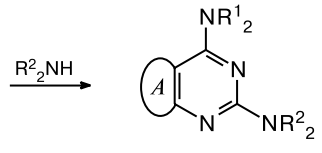
Reagents and conditions: *i*. NH_4OAc, Δ; *ii*. $NH_2(CH_2)_nNH_2$, Δ.

The nucleophilic substitution occurs particularly easily in chlorothienopyrimidines. The chlorine atom can be replaced with virtually any nucleophilic residue. In the last 10—15 years, the replacement of the chlorine (or bromine) atom in the pyrimidine fragment of thienopyrimidines with the amino group has been studied most extensively.

The nucleophilic substitution reactions of dichlorothienopyrimidines **151** with amines and hydrazines proceed stepwise. Initially, the chlorine atom involved in a fragment of cyclic imidoyl chloride is replaced to give aminochlorothienopyrimidines **152**, which can be isolated from the reaction mixtures in good yields. Compounds **152** are further transformed into diaminothienopyrimidines **153** in the presence of an excess of the amine or by treatment with another amine under more drastic conditions.[151,275,276,287—290]

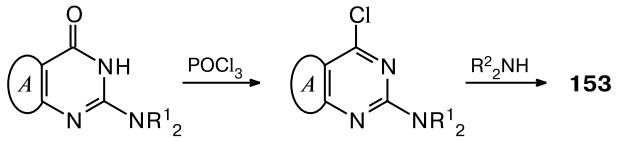


151 **152**



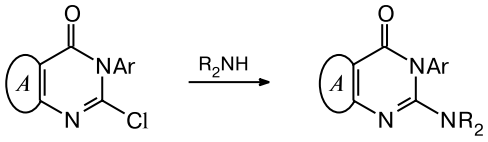
153

The chlorine atom in aminochlorothienopyrimidines **154**, which are readily derived from thienopyrimidinones **155** and $POCl_3$, is also replaced with the amino group to give compounds **153**.[291,292]



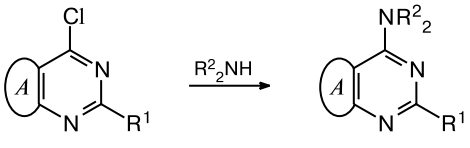
155 **154** **153**

The reactions of chlorothienopyrimidinones **156** with amines afford aminothienopyrimidinones **157**.[56,277]



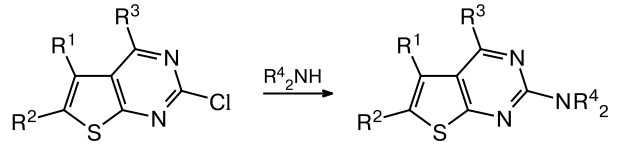
156 **157**

The replacement of the chlorine atom in chlorothienopyrimidines **108** with the amino group giving rise to aminothienopyrimidines **158** was studied in sufficient detail. This reaction was carried out with ammonia, primary and secondary amines, and hydrazine.[122,144,149,158,174,200,230,252,275,279—285,293—298]



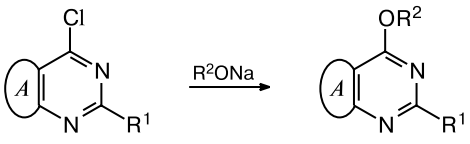
108 **158**

Chlorothienopyrimidines **159** isomeric to compounds **108** react with amines under more drastic conditions to give aminothienopyrimidines **160**.[225,299]



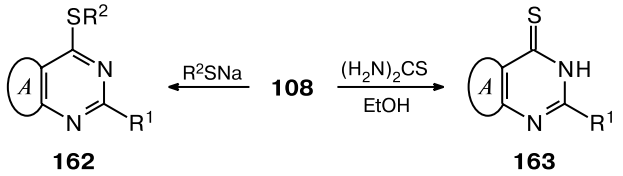
159 **160**

In turn, the chlorine atom in chlorothienopyrimidines **108** is readily replaced with the alkoxy group in the reactions with sodium alkoxides in alcohols to form alkoxy derivatives **161**.[149,174,252,275,276,278,287,288,300,301]



108 **161**

Procedures were also developed for the replacement of the chlorine atom in the pyrimidine fragment with the alkylthio group. For example, chlorothienopyrimidines **108** react with thiolates to form alkyl(aryl)thiothienopyrimidines **162**.[149,174–176,252,293,296,297]

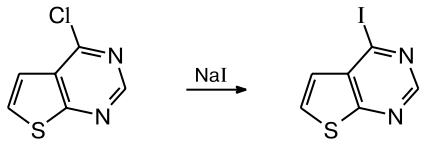


162 **163**

R^1 = H, Alk, Ar, Het, NH_2

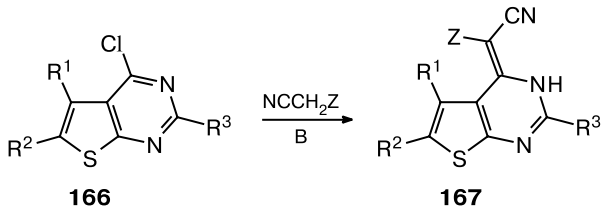
The reactions with thiourea produce the corresponding thiones **163**.[275] The replacement of the chlorine atom with the thiocyanate group is also documented.[296]

Earlier, it has been demonstrated[275] that the halogen atoms in these compounds can exchange with another halogen. For example, the reaction of 1-chlorothieno[2,3-*d*]pyrimidine (**164**) with NaI yielded the corresponding iodothienopyrimidine **165**.



164 **165**

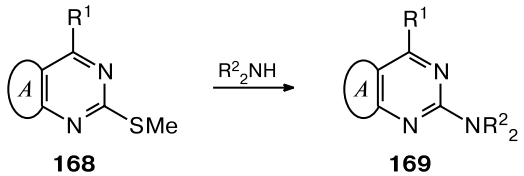
CH-Acids also substitute the chlorine atom in chlorothienopyrimidines **166** to give methylidenethienopyrimidines **167**.[297,302]



166 **167**

Z = CN, CO_2Et

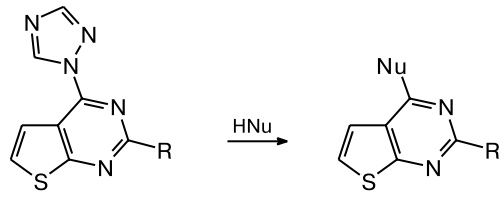
The replacement of the methylthio group in monothiomethylthienopyrimidines **168** with the amino group to form compounds **169** was studied.[242,303]



168 **169**

The alkylthio groups in thienopyrimidines are saponified with alkalis.[304,305]

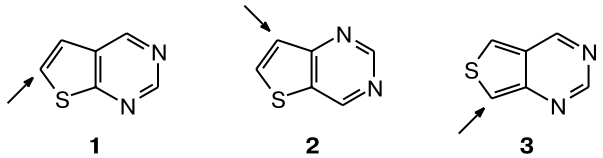
Yet another example of the nucleophilic substitution in the pyrimidine fragment of thienopyrimidines[306] is the replacement of the 1,2,4-triazolyl substituent with a nucleophile.



HNu = R^1_2NH, R^1SH

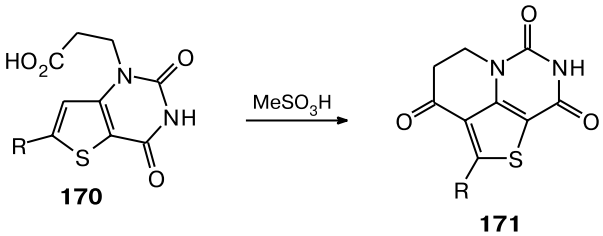
3.2. Electrophilic substitution

Both in earlier[24,30,35,37,38] and more recent[149,208,239,241,307] studies on chlorination, bromination, Vilsmeier formylation, and nitration demonstrated that the electrophilic substitution in thieno[2,3-*d*]pyrimidines **1** and thieno[3,4-*d*]pyrimidine **3** involves position 6 and equivalent position 7, respectively (in the presence of an excess of an electrophilic reagent, the latter reaction leads to disubstitution at positions 5 and 7), which is typical of thiophene itself and suggests a weak influence of annelation with the pyrimidine ring. A different situation is observed for the electrophilic substitution in thieno[3,2-*d*]pyrimidine **2**, where the influence of annelation of the pyrimidine ring is stronger than the effect of orientation of the sulfur atom in the thiophene ring and, concequently, the attack occurs at position 7.



1 **2** **3**

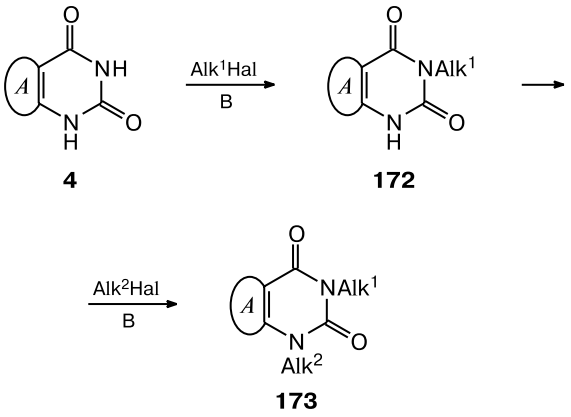
Intramolecular acylation of thieno[3,2-*d*]pyrimidine derivative **170** afforded tricyclic system **171**.[307]



170 **171**

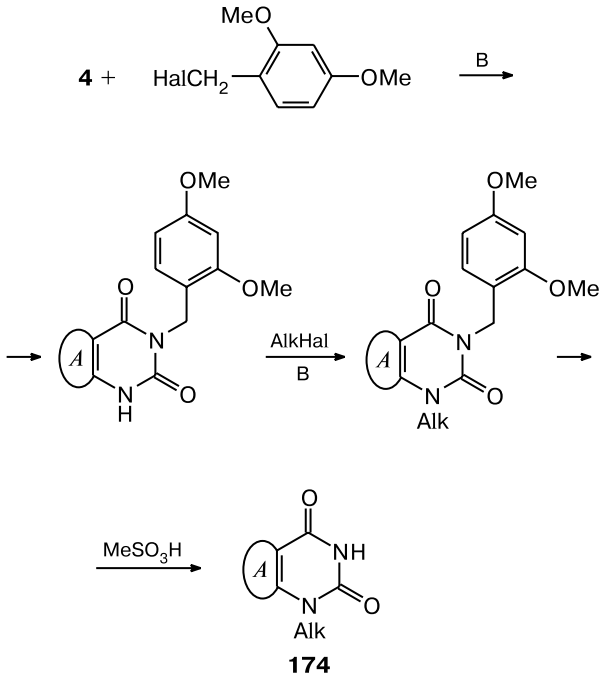
N-Alkylation of thienopyrimidinediones and thienopyrimidinones is often used in the series of thienopyrimidines. It was demonstrated[309–312] that thienopyrimidinediones **4** (R = H) are alkylated with alkyl halides in the presence of bases to give *N*-alkylthienopyrimidinediones **172**. The reactions were carried out with the use of

NaH or K_2CO_3 as the base or under conditions of phase-transfer catalysis.



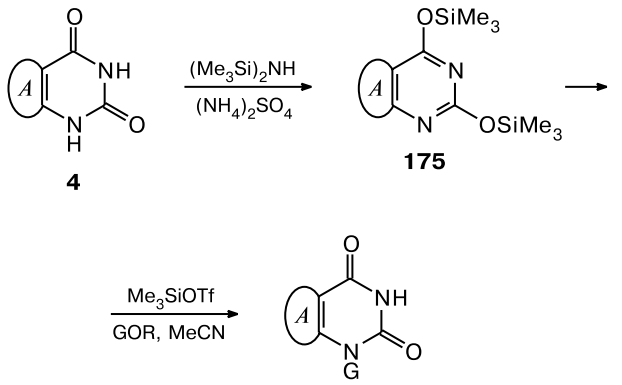
4 **172** **173**

Compounds **172** can be isolated from the reaction mixture in good yields. The reactions with an excess of an alkylating agent or alkylation of mono-*N*-alkylthienopyrimidinone **172** produce *N,N´*-dialkyl derivatives **173**.[53,55,306,309,311,313,314] A procedure proposed for the synthesis of 4-alkylthienopyrimidinediones **174** involves the protection of the nitrogen atom at position 2 with the dimethoxybenzyl group.[311]



174

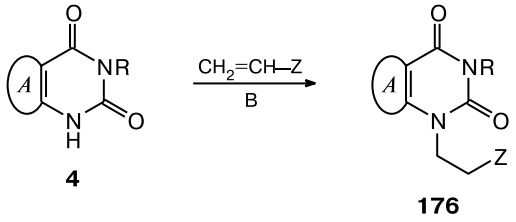
A method was developed for selective glycosylation of thienopyrimidines at position 4. Initially, dione **4** is transformed into disilyl derivative **175**, which is alkylated with sugar derivatives in the presence of Lewis acids (most often, of trimethylsilyl triflate). Glycosylation was carried out with the use of 1-OH[315–317] and 1-OAc derivatives[318] and methyl glycosides.[319,320]



4 **175**

G is the sugar residue; R = H, Ac, Me

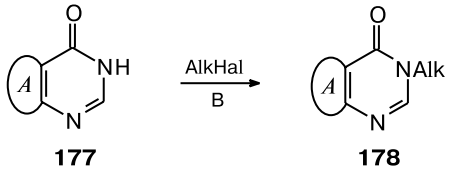
The Michael reaction of thienopyrimidinediones **4** bearing a substituent at position 2 with ethyl acrylate and acrylonitrile affords thienopyrimidinediones **176**.[54,307]



4 **176**

Z = CN, CO_2Et

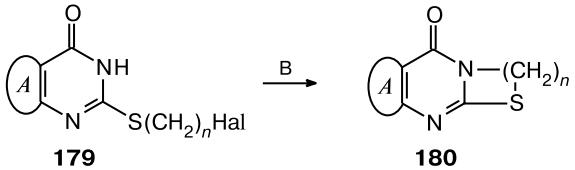
Thienopyrimidinones **177** are smoothly alkylated with alkyl halides in the presence of bases at the amide nitrogen atom to form 2-*N*-alkyl derivatives **178**.[275,276,309,310,312,321–325]



177 **178**

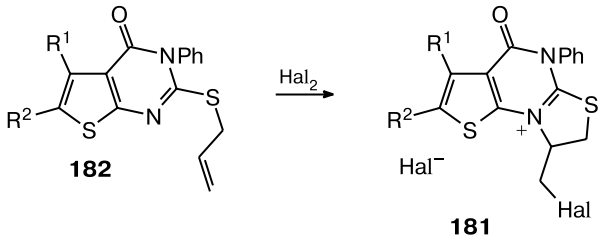
These reactions can be carried out with the use of alkoxides, aqueous alkalis, or NaH as a base.

An intramolecular alkylation of thienopyrimidinones **179** giving rise to tricyclic compounds **180** is also documented.[181,326]

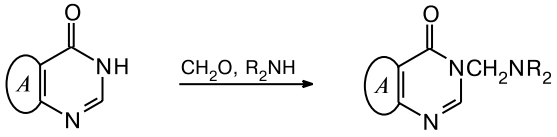


179 **180**

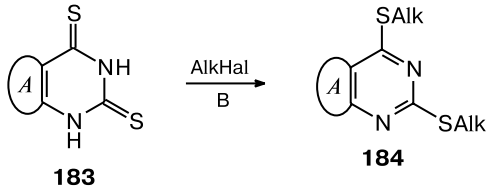
If the nitrogen atom at position 2 bears a substituent, alkylation proceeds at the nitrogen atom in position 4 of the thienopyrimidine system, as exemplified[305,327] by the formation of thiazolothienopyrimidinium salts **181** from *S*-allyl derivatives **182**.



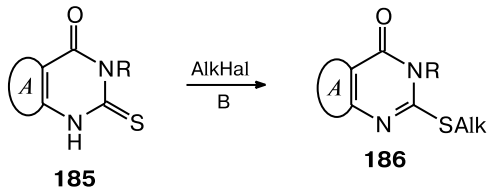
Under the conditions of the Mannich reaction, thienopyrimidinones underwent 2-*N*-aminomethylation.[130,328]



Thienopyrimidinethiones react with alkyl halides and alkyl sulfonates at the sulfur atom to give alkylthiothienopyrimidines. In thienopyrimidinedithiones **183**, the distinction between two sulfur atoms is insufficient for the reaction to proceed selectively. Therefore, the reactions are conducted to afford di(alkylthio)thienopyrimidines **184**.[89]

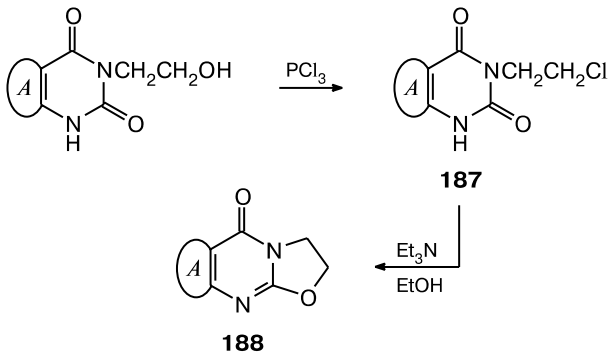


Alkylation of readily accessible thioxothienopyrimidinones **185** has received wide acceptance. The reaction proceeds selectively at the sulfur atom to give *S*-alkyl-substituted thienopyrimidinones **186** in high yields.[61,63,70,72,329–333]

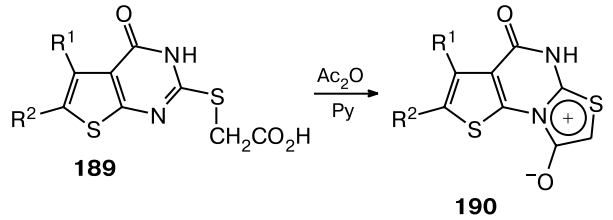


Examples of *O*-alkylation of thienopyrimidinones are scarce. However, such an alkylation can be carried out intramolecularly. For example, treatment of 2-(2-chloroethyl)thienopyrimidine-1,3-dione (**187**), which was prepared from the corresponding hydroxy compound and PCl_3, with a base led to the closure of the oxazolidine ring giving rise to tricyclic compound **188**.[334–336]

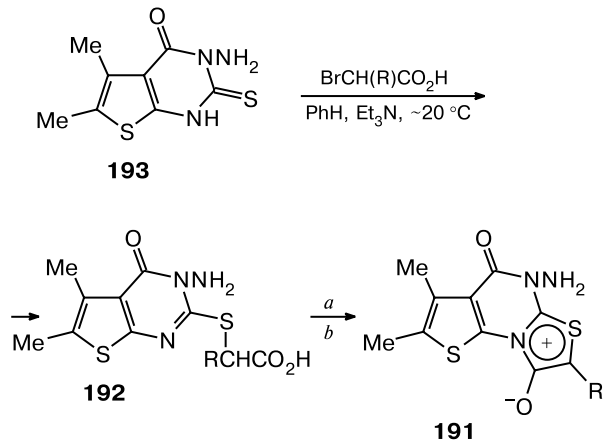
Analogous reactions of 4-(2-chloroethyl)thienopyrimidine-1,3-diones were also described.[337] In both cases, alkylation proceeds at the oxygen atom involved in the fragment of a cyclic urea. This fact can be attributable to the higher basicity of this oxygen atom compared to the oxygen atom at position 1.



2-(Carboxymethylthio)thieno[2,3-*d*]pyrimidin-4-ones (**189**) react with acetic anhydride in the presence of pyridine to form mesoionic heterocycles **190**.[338]



Mesoionic heterocycles **191** were synthesized by the reaction of aminothienopyrimidinones **192**, which were prepared in the reaction of 2-thioxothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**193**) with 2-bromopropionic or α-bromophenylacetic acid, with acetic anhydride and triethylamine (1 : 1) (method *a*), or with *N*,*N*′-dicyclohexylcarbodiimide (DDC) in ethanol (method *b*).[339]

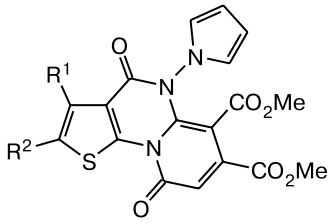


R = Me, Ph

Method *a*. PhH, Ac_2O, Et_3N, ~20 °C. Method *b*. EtOH, DDC, ~20 °C.

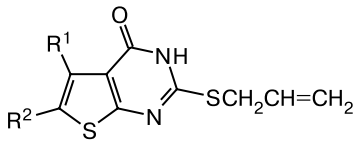
A new approach to 4,5-dihydro-9*H*-pyrido[1,2-*a*]thieno[3,2-*e*]pyrimidine-4,9-diones **194** is based on 1,3-di-

polar cycloaddition of the above-mentioned mesoionic compounds with dimethyl acetylenedicarboxylate.[340]

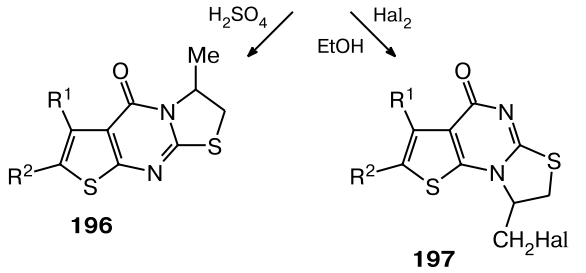


194

Intramolecular cyclization of allylthio derivatives of thienopyrimidines **195** under the action of concentrated sulfuric acid and halogens (Br or I) was studied.[265,341–345] It was demonstrated that treatment with sulfuric acid afforded linearly annelated thiazolothienopyrimidines **196**, whereas the reactions with halogens as cyclizing agents gave rise to angular isomers **197**.

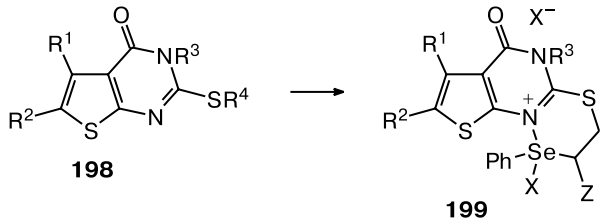


195



196 **197**

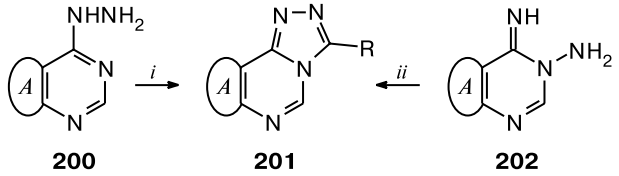
Heterocyclization of 2-(allylthio, propargylthio)thieno[2,3-*d*]pyrimidin-4-ones **198** with phenylselenenyl halides yielded thieno[3′,2′:5,6]pyrimido[2,1-*b*][1,4,3]thiaselenazinium halides **199**.[346,347]



198 **199**

R^4 = $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$; Z = CH_2X; X = Cl, Br

The reactions described for hydrazinothienopyrimidines can also be assigned to electrophilic substitution reactions. For example, treatment of 1-hydrazinothienopyrimidines **200** with formic acid,[275,276,348] acetic acid,[276] or orthoesters[349] led to the closure of the *s*-triazole ring to form compounds **201**.[348]

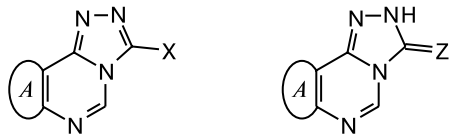


200 **201** **202**

Reagents: *i*. RCO_2H or $RC(OEt)_3$; *ii*. $RC(OEt)_3$.

Compounds **201** were prepared also by the reactions of unstable aminothienopyrimidineimines **202** with orthoesters.[350] These reactions can also be performed with acetylacetone, which undergoes acid cleavage under the reaction conditions.[351]

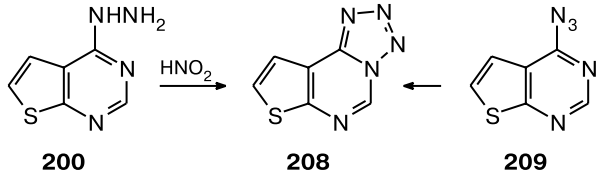
Analogous transformations occur with other acylating agents, such as diethyl oxalate,[201] diethyl malonate,[201] chloroformates,[285] guanidine,[352] and carbon disulfide,[285,351–353] to give compounds **203—207**.



203—205 **206, 207**

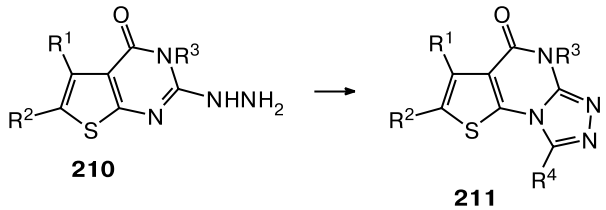
X = CO_2Et (**203**), CH_2CO_2Et (**204**), NH_2 (**205**);
Z = O (**206**), S (**207**)

Nitrosation of 4-hydrazinothieno[2,3-*d*]pyrimidine (**200**) led to the tetrazole ring closure giving rise to tetrazolothienopyrimidine **208**.[275,276,285,351] The same compound can be prepared by cyclization of 4-azidothienopyrimidine **209**.[349]



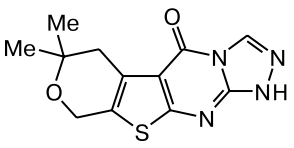
200 **208** **209**

2-Hydrazinothieno[2,3-*d*]pyrimidines **210** undergo cyclization to the corresponding triazolothienopyrimidines **211** under the action of aliphatic acids.[354–356]



210 **211**

In the synthesis of tetracyclic systems **212—214**, hydrazino derivatives of pyrano- and tetrahydropyridothienopyrimidines were used as the starting compounds.[357–359]



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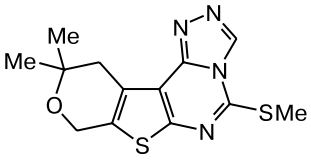

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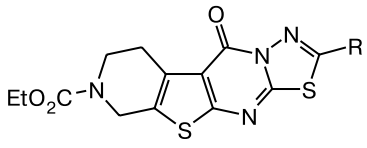

214

Syntheses of other annelated thienopyrimidines, *viz.*, benzothieno[2,3-*d*]pyrimidines,[360,361] pyrido[4′,3′:4,5]thieno[3,2-*d*]pyrimidines,[362] pyrrolothieno[2,3-*d*]pyrimidines and pyrrolo[1″,2″:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-*d*]pyrimidines,[363] triazolothieno[2,3-*d*]pyrimidines,[364] isoxazolo[5′,4′:4,5]thiazolo[3,2-*a*]thieno[2,3-*d*]pyrimidines,[365] imidazo[1,2-*a*]thiopyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidines,[366] and quinoxalinothienopyrimidines,[367] are also documented.

Aroylation of thieno[2,3-*d*]pyrimidines[368] and complex formation of 2,6-dimethylthieno[2,3-*d*]pyrimidine-2,4-dione with Cu^{II}, Mn^{II}, and V^{IV} ions[369] were investigated. 2-(Arylideneamino)thieno[2,3-*d*]pyrimidin-4-ones were studied by mass spectrometry.[370]

4. Biological activity and some aspects of practical use of thienopyrimidines

From the standpoint of biological activity, fused heteroaromatic systems are often of much greater interest than the constituent monocyclic compounds. The appearance of qualitatively new properties of an annelated molecule, enlargement of the possibility of varying pharmacophore groups in different positions of the molecule, and the ability of the latter to interact with a wider spectrum of receptors adopting various conformations are apparently of crucial importance. In addition, the structure of the molecule can be varied due to annelation at different positions of individual heterocyclic fragments.

Biological activities of thienopyrimidines have been partially reviewed.[25,38] The structure—activity relationships for certain types of derivatives have been discussed.[371—373] Thienopyrimidine derivatives are characterized by a very broad spectrum of biological activities, which includes several dozens of activities. To analyze this problem in more detail, it is worthwhile to survey both recent studies, including patents, and, in part, some earlier investigations. Since the detailed analysis of biological activities of this class of compounds is beyond the scope of the present review, only various activities and the corresponding references are mentioned below.

Certain thienopyrimidine derivatives exhibit antiallergic,[135,374—379] antiatherosclerotic,[194,380,381] antibacterial,[169,247,382—392] antiviral,[278,393] antihypertensive,[36,41,321,394—397] antidepressant,[299,398] depressant,[196,351,399] antidiabetic,[400,401] antihistaminic,[402,403] antimicrobial,[245,404—409] spasmolytic,[195] analgetic, and antiinflammatory[62,76,128,168,277,351,373,400,410—428] activities.

Many thieno[2,3-*d*]pyrimidine derivatives were covered by patents as phosphodiesterase inhibitors[377,429—440] and various receptor antagonists[441—459] (see also Refs. 208 and 460—467). Various thieno[2,3-*d*]pyrimidine and thieno[3,2-*d*]pyrimidine derivatives show pronounced antitumor[454,468—474] and radioprotective[475,476] activities. Based on thieno[2,3-*d*]pyrimidine derivatives, immunomodulators[477—481] and compounds used for prophylaxis and therapy of cerebral ischemia,[482,483] malaria,[391,484—488] tuberculosis,[115] Altzheimer's disease,[489] Parkinson's disease,[447] and other diseases were designed.[292,306,376,381,490—496]

Problems of biological activity of isomeric thienopyrimidines were also touched on in patents[497—523] and publications.[84,159,189,360,391,524—536]

In addition, promising pesticides (fungicides,[537—544] herbicides,[42,69,293,545] and insecticides[546,547]) were found among these derivatives.

Of other aspects, practical use of 4-[4-(arylazo)phenoxy]-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines as disperse dyes[548] and 2,4-dimethylthio-6-phenylthieno[3,2-*d*]pyrimidine as a material for nonlinear optics[549] is documented.

5. Conclusions

Analysis of the data on the chemistry of isomeric thienopyrimidines published over the last 10—15 years shows that this class of heteroaromatic compounds, which are structural analogs of natural compounds of the purine class, attract increasing interest of chemists and biochemists.

In the first half of the 21th century, new approaches to the synthesis of derivatives of these fused heterocyclic systems will be, undoubtedly, extensively developed. These derivatives are not only of theoretical interest but also possess a broad spectrum of practical use, primarily, due to various biological activities. Of approaches to their synthesis, multicomponent cascade heterocyclization, which allows one to construct various functionalized thienopyrimidines and their fused analogs in one technologically and ecologically safe step, holds the most promise.

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