Journal of Pharmaceutical and Applied Chemistry

ISSN: 2357-0210 VOLUME 2, ISSUES 3, 2016 www.egyptfuture.org/ojs/

Chemistry of Thienopyrimidines and Their Biological Applications

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Received: 5 Jan. 2016, Revised: 2 Jun. 2016, Accepted: 6 Jun. 2016.
Published online: 1 Sep. 2016.

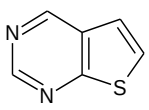
Abstract: The recent studies on the synthesis, reactions and biological applications of isomeric thienopyrimidine derivatives have been reported in this review

Keywords: Thienopyrimidines, synthesis, reactions, biological applications.

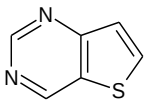
1 Introduction

Thiophene containing compounds are well known to exhibit various biological effects. Heterocycles containing the thienopyrimidine moiety are of interest because of their interesting pharmacological and biological activities [1–3]. They bear structural analogy and isoelectronic relation to purine and several substitutedthieno[2,3-*d*]pyrimidine derivatives shown to exhibit prominent and versatile biological activities [4,5]. Over the last two decades, many thienopyrimidines have been found to exhibit a variety of pronounced activities. Many of their derivatives have been synthesized as potential anticancer [6], analgesic [7], antimicrobial [8-9] and antiviral agents [10].

Recently, we reported some reviews on pyrimidinethiones [11] and condensed pyrimidines, namely pyrazolo-pyrimidines [12] and furopyrimidines [13]. The work deals with the study of the synthesis, reactions and biological applications of thienopyrimidines in view of their great importance. In the last decade, thienopyrimidines were reviewed [14]. The three fundamental thienopyrimidine systems are thieno[2,3-*d*]pyrimidine (I), thieno[3,2-*d*] pyrimidine (II) and thieno[3,4-*d*]pyrimidine (III). This article aimed to show the recent novel precursors to synthesize thienopyrimidine derivatives and reported their application in pharmaceutical and biological evaluations in the last decade.



(I)



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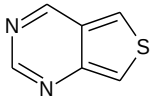


(III)

2 Synthesis Of Thienopyrimidines

The building of thienopyrimidine moiety has been achieved either by annulations of pyrimidine nucleus on the parent thiophene ring or annulations of thiophene nucleus on the parent pyrimidine ring. Also, they obtained from acyclic compounds.

2.1 Annulations of pyrimidine on thiophene ring

The simple approach to the formation of a new pyrimidine ring involves introducing a one-carbon fragment between two suitable and vicinal functional groups in thiophene ring.

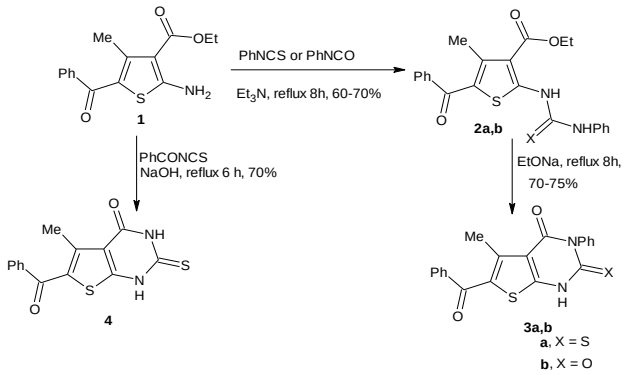
2.2- Using thiophene having vicinal amino ester groups

Thiophene derivatives having vicinal amino ester groups is considered a suitable synthon for the synthesis of thienopyrimidines *via* its interaction with various suitable reagents.

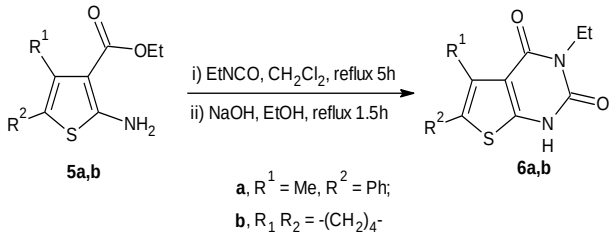
2.2.1- With isocyanate and isothiocyanate derivatives

Reaction of ethyl 2-amino-5-benzoyl-4-methylthiophene-3-carboxylate (**1**) [15] with phenyl isothiocyanate and/or phenyl isocyanate in presence of a catalytic amount of triethylamine afforded the corresponding thioureidothiophene and/or ureidothiophene **2a,b**, which underwent cyclization in etnanolic sodium ethoxide to yield thieno[2,3-*d*]pyrimidinone derivatives **3a**,**b**, respectively.

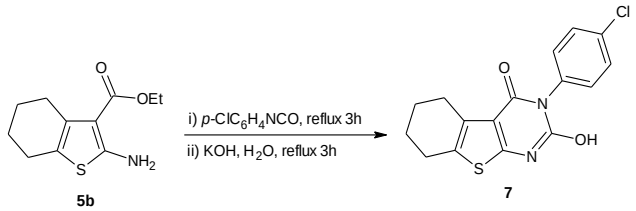
Moreover, treatment of compound **1** with benzoyl isothiocyanate in ethanolic sodium hydroxide gave 6-benzoyl-2-thioxothieno[2,3-*d*]pyrimidine derivative **4** [16].



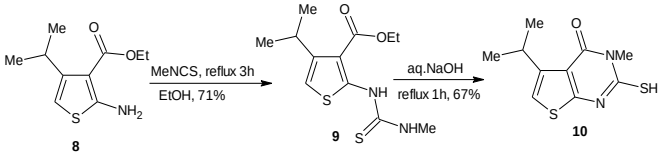
2-Aminothiophene-3-carboxylates **5a,b** [14] were used for synthesis of 3-ethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **6a,b** *via* conversion with *N*-ethylisocyanate followed by the cyclization using ethanolic sodium hydroxide [17].



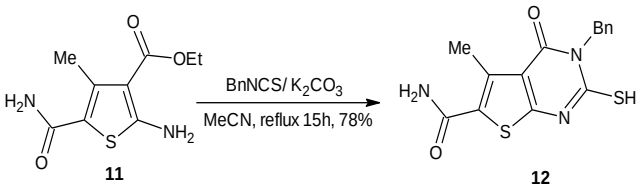
Also, 3-(4-chlorophenyl)-2-hydroxy-5,6,7,8-tetrahydro-benzo[*b*]thieno[2,3-*d*]pyrimidin-4-one (**7**) was synthesized from treatment of compound **5b** with *p*-chlorophenyl-isocyanate at 120˚C and followed by cyclization by aqueous potassium hydroxide solution [18].



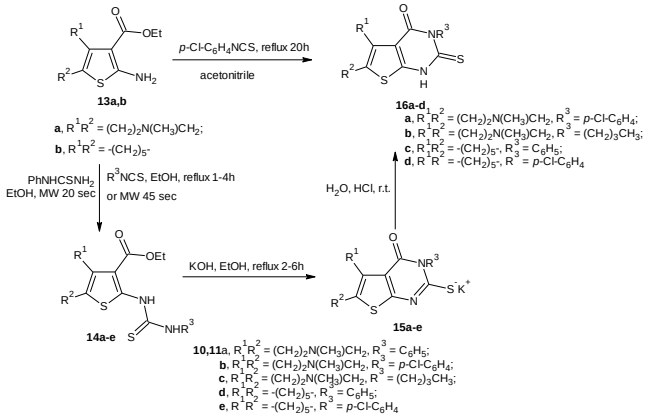
Further, addition of methyl isothiocyanate to ethyl 2-amino-4-isopropylthiophene-3-carboxylate (**8**) gave ethyl 4-isopropyl-2(3-methylthiourenyl)thiophene-3-carboxylate (**9**) followed by cyclization in aqueous sodium hydroxide to yield 5-isopropyl-2-mercapto-3-methylthieno[2,3-*d*] pyrimidin-4-one (**10**) [19].



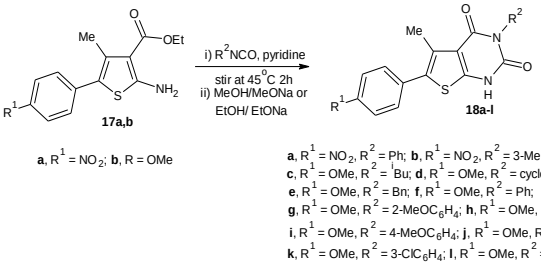
In the same way, cyclocondensation of ethyl 2-amino-5-carbamoyl-4-methylthiophene-3-carboxylate (**11**) [20] with benzyl isothiocyanate in presence of anhydrous potassium carbonate gave sulfanylthieno[2,3-*d*]pyrimidine derivative **12** [21].



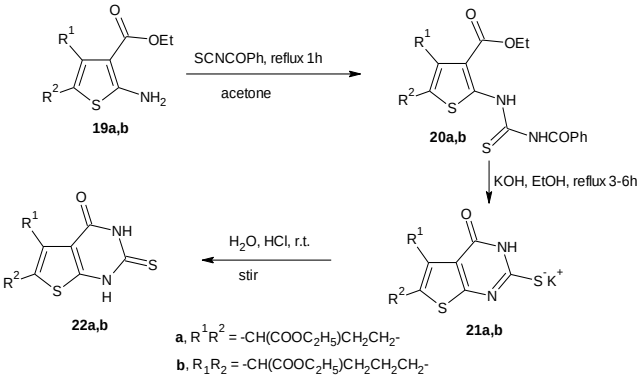
In addition to, thienylthiourea derivatives **14a-e** were prepared by addition of 2-amino-3-ethoxycarbonyl-4,5-disubstitutedthiophenes **13a,b** [15,22] to alkyl or aryl isothiocyanates, either by heating at reflux or under microwave irradiation [23-25]; the latter method afforded higher yields of the desired products in shorter time. Compound **14a** was also prepared by condensation of amino ester **13a** with phenyl thiourea under microwave irradiation. Furthermore, cyclization of compound **14a-e** using alcoholic potassium hydroxide gave the mono-potassium salts of the corresponding 3-substituted-2-thioxo-4,5-disubstitutedthieno[2,3-*d*]pyrimidin-4-ones **15a-e**. 2-Thioxo derivatives **16a-d** were prepared either from the appropriate potassium salts **15** by acidification or from the amino ester derivatives **13a,b** *via* cyclocondensation with aryl isothiocyanates [26,27].



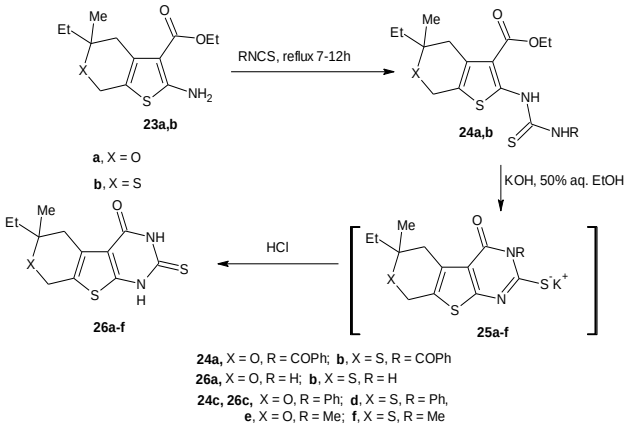
Reaction of ethyl 2-amino-4-methyl-5-(4-nitro/methoxy-phenyl)thiophene-3-carboxylate **17a,b** with a variety of isocyanates gave the corresponding ureas, which were cyclized under basic conditions to afford thieno[2,3-*d*] pyrimidine derivatives **18a-l** [28].



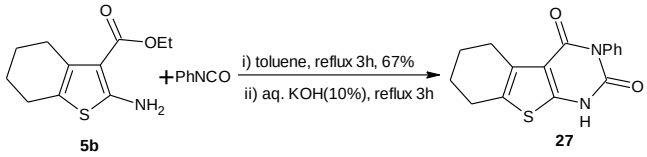
On the other hand, thiophene-3,4-dicarboxylates **20a**,**b** were obtained by refluxing the corresponding β-amino esters of thiophenes **19a,b** with benzoyl isothiocyanate in acetone [29]. Refluxing of compound **20a,b** in ethanolic potassium hydroxide solution, it gave the respective monopotassium salts **21a,b**, which on acidification with concentrated hydrochloric acid afforded the corresponding thieno[2,3-*d*]pyrimidine-5-carboxylates **22a**,**b**, respectively [30].



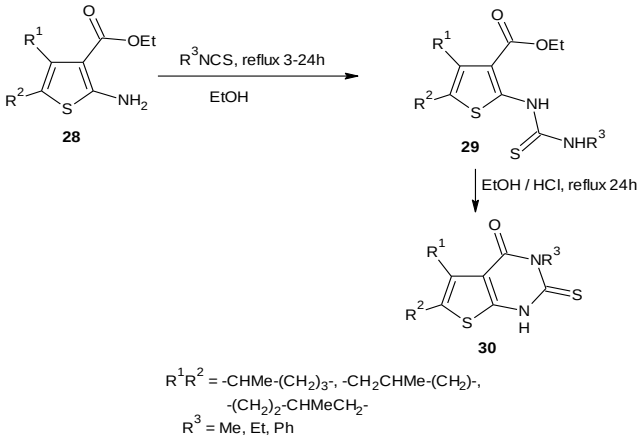
Also, treatment of 2-amino-5-ethyl-5-methyl-3-ethoxy-carbonyl-4,5-dihydro-7*H*-thieno[2,3-*c*]pyran(thiopyran) (**23a,b**) with various isothiocyanates gave the corresponding 2-*N*-thioureides of the thiophenes **24a-f**. This reaction belongs to the general class of nucleophilic addition reactions. Treatment of compound **24a-f** with aqueous alcoholic potassium hydroxide caused intramolecular cyclization with formation of the potassium salts of 4-oxo-2-thioxothieno[2,3-*d*]pyrimidines **25a-f**. 2-Thioxothienopyrimidines **26a-f** were isolated by acidification of aqueous solutions of **25a-f** [31].



Also, treatment of compound **5b** with phenyl isocyanate in dry toluene afforded 3-phenyl-5,6,7,8-tetrahydrobenzo[*b*] thieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione (**27**) [32].

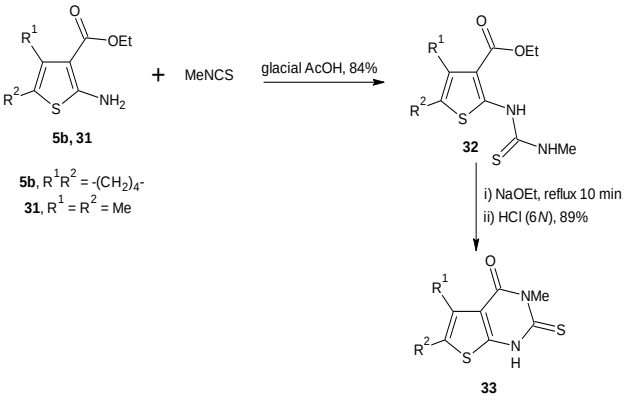


Addition of appropriate isothiocyanate to amino ester derivatives of thiophenes **28** [33] under reflux conditions yielded thienylthioureas **29**, which on refluxing in ethanol and hydrochloric acid gave the corresponding thieno[2,3-*d*] pyrimidine-2(1*H*)-thione derivatives **30** [34].



Furthermore, treatment of compounds **5b** or ethyl 2-amino-4,5-dimethyl-thiophene-3-carboxylate (**31**) [14] with methyl isothiocyanate in refluxing glacial acetic acid furnished the corresponding thiourea derivatives **32**, which were cyclized to the corresponding thiones **33** by refluxing in sodium ethoxide then cooled and acidified with 6 *N* HCl

[35].



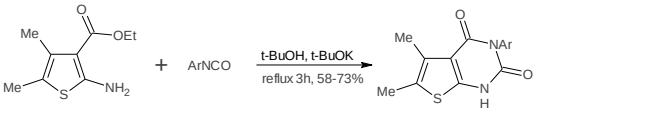
5b, 31

5b, R^1R^2 = -$(CH_2)_4$-
31, R^1 = R^2 = Me

32

33

Moreover, cyclocondensation of compound **31** with aryl isocyanates in the presence of potassium *t*-butaoxide yielded 3-aryl-5,6-dimethylthieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **34a-e** [36].

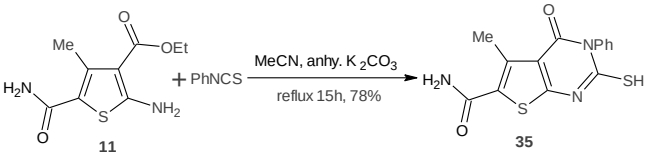


31

34a-e

a, Ar = Ph; **b**, Ar = 4-MeC_6H_4; **c**, Ar = 3-MeC_6H_4;
d, Ar = 3-ClC_6H_4; **e**, Ar = 3,4-Cl_2-C_6H_3

While, reaction of compound **11** with phenyl isothiocyanate in acetonitrile in the presence of anhydrous potassium carbonate yielded 2-mercapto-5-methyl-4-oxo-3-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxamide (**35**) [37].



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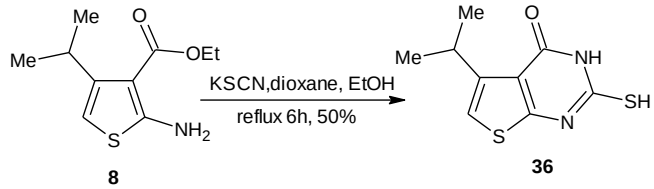
35

On the other hand, treatment of compound **8** with excess of potassium thiocyanate in dioxane afforded 5-isopropyl-2-mercaptothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**36**) [19].

When thiophene derivatives **31** and/or **37** were allowed to react with the substituted aryl isothiocyanate, they gave *N*-aryl-*N*`-(3-carboethoxythien-2-yl)-thioureas **38a-i**, which reacted with hydrazine hydrate to give 3-amino-3,4-dihydro-2-substitutedphenylaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **39a-i** [38].



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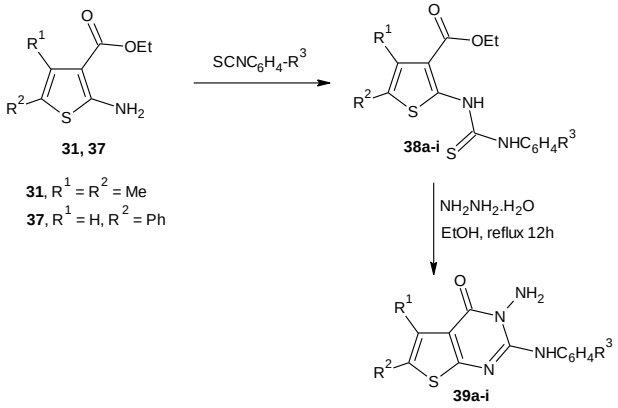
36



31, 37

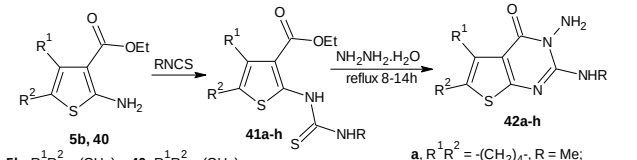
31, R^1 = R^2 = Me
37, R^1 = H, R^2 = Ph

38a-i

39a-i

a-e, R^1 = H, R^2 = Ph, R^3 = H, Me, OMe, Cl(*p*), Cl(*o*)
f-i, R^1 = R^2 = Me, R^3 = H, Me, Cl(*p*), Cl(*o*)

Also, treatment of amino ester **5b, 40** with the appropriate isocyanates gave *N*-(3-carbethoxy-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)-*N*`-substitutedthioureas **41a-h** [39,40], which on hydrazinolysis frunished 3-amino-2-susbstitutedamino-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **42a-h** [41,42].



5b, 40

5b, R^1R^2 = $(CH_2)_4$; **40,** R^1R^2 = $(CH_2)_3$

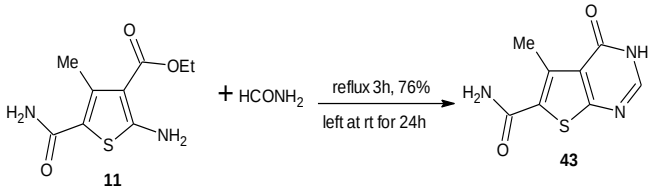
41a-h

42a-h

a, R^1R^2 = -$(CH_2)_4$-, R = Me;
b, R^1R^2 = -$(CH_2)_4$-, R = Et;
c, R^1R^2 = -$(CH_2)_4$-, R = Ph;
d, R^1R^2 = -$(CH_2)_4$-, R = 4-MeC_6H_4;
e, R^1R^2 = -$(CH_2)_4$-, R = Bn;
f, R^1R^2 = -$(CH_2)_4$-, R = 4-ClC_6H_4;
g, R^1R^2 = -$(CH_2)_3$-, R = Ph;
h, R^1R^2 = -$(CH_2)_3$-, R = 4-ClC_6H_4;

2.2.2 With formamide

5-Methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidin-6-carboxamide (**43**) was prepared *via* reaction of compound **11** with formamide [37].



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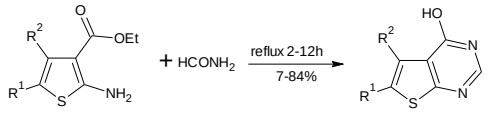
43

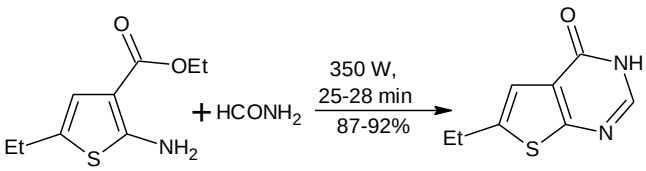
Also, treatment of ethyl 2-aminothiophene-3-carboxylate derivatives **44, 5b, 45a-f. 13b** and **46** with formamide gave 4-hydroxythieno[2,3-*d*]pryimidine derivatives **47-51** in good yield [43-50].



44, $R^1 = R^2 = H$
5b, $R^1R^2 = -(CH_2)_4-$
45a, $R^1 = Et$, $R^2 = H$; **45b**, $R^1 = Me$, $R^2 = H$;
45c, $R^1 = i\text{-}Pr$, $R^2 = H$; **45d**, $R^1 = t\text{-}Bu$, $R^2 = H$;
45e, $R^1 = Bn$, $R^2 = H$; **45f**, $R^1 = Me$, $R^2 = Et$
13b, $R^1R^2 = -(CH_2)_5-$
46, $R^1 = COOEt$, $R^2 = Me$

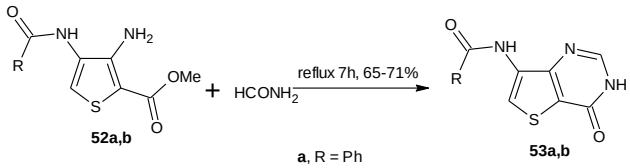
47, $R^1 = R^2 = H$
48, $R^1R^2 = -(CH_2)_4-$
49a, $R^1 = Et$, $R^2 = H$; **49b**, $R^1 = Me$, $R^2 = H$;
49c, $R^1 = i\text{-}Pr$, $R^2 = H$; **49d**, $R^1 = t\text{-}Bu$, $R^2 = H$;
49e, $R^1 = Bn$, $R^2 = H$; **49f**, $R^1 = Me$, $R^2 = Et$
50, $R^1R^2 = -(CH_2)_5-$
51, $R^1 = COOEt$, $R^2 = Me$

Moreover, cyclization of ethyl 2-amino-5-ethylthiophene-3-carboxylate (**45a**) with formamide under microwave irradiation at 350W for 25-28 minute gave thieno[2,3-*d*] pyrimidine derivative **49a** in good yield [51]. hydrogen chloride gas through a solution of compound **5b** or **46** with 3-chloropropanonitrile through intermediate **56** [55].



45a **49a**

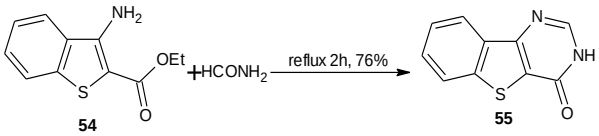
Also, treatment of methyl 4-acylamino-3-aminothiophene-2-carboxylates **52a,b** with formamide gave 7-acylamino-3,4-dihydrothieno[3,2-*d*]pyrimidin-4-ones **53a,b** [52].



52a,b **53a,b**

a, R = Ph
b, R = 4-MeC_6H_4

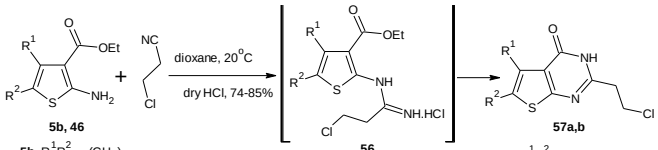
Similarly, ethyl 3-aminobenzothiophene-2-carboxylate (**54**) [53] reacted with formamide under reflux conditions to afford benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (**55**) [54].



54 **55**

2.2.3 With nitrile compounds

2-(2-Chloroethyl)-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **57a,b** were prepared *via* passing of a stream of dry hydrogen chloride gas through a solution of compound **5b** or **46** with 3-chloropropanonitrile through intermediate **56** [55].

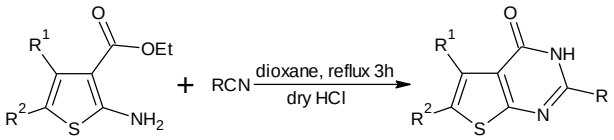


5b, 46
5b, $R^1R^2 = -(CH_2)_4-$
46, $R^1 = Me$, $R^2 = COOEt$

56

57a,b
a, $R^1R^2 = -(CH_2)_4-$
b, $R^1 = Me$, $R^2 = COOEt$

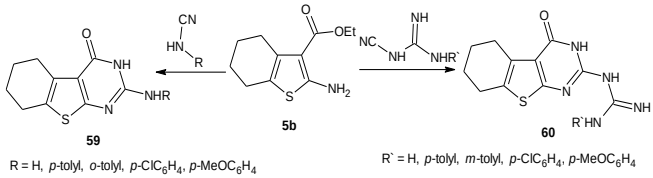
Also, treatment of compound **31** or **40** with alkyl/aryl nitrile in dioxane using dry hydrochloric acid afforded the corresponding 2-alkyl/arylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **58** [56].



31, 40
31, $R^1 = R^2 = Me$
40, $R^1R^2 = -(CH_2)_3-$

58
R = Me, Ph, Et, n-Pr, Bn, C_5H_4N

On the other hand, reaction of compound **5b** with cyanamide and 1-arylcyanamides gave 2-aminothieno [2,3-*d*]pyrimidin-4(3*H*)-ones **59**. A similar reaction of cyanoguanidine derivatives with compound **5b** afforded 2-guanidinothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **60** [57].

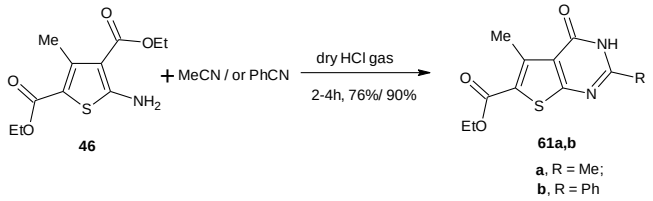


59
R = H, *p*-tolyl, *o*-tolyl, *p*-ClC_6H_4, *p*-$MeOC_6H_4$

5b

60
R` = H, *p*-tolyl, *m*-tolyl, *p*-ClC_6H_4, *p*-$MeOC_6H_4$

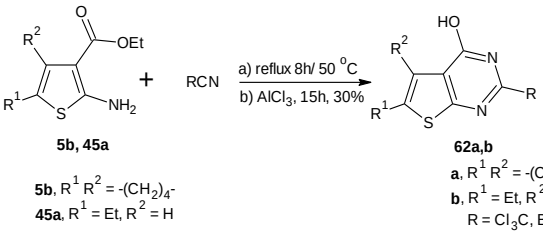
Also, treatment of compound **46** with acetonitrile or benzonitrile yielded the corresponding 2-(methyl/phenyl)-thieno[2,3-*d*]pyrimidines **61a**,**b** [50].



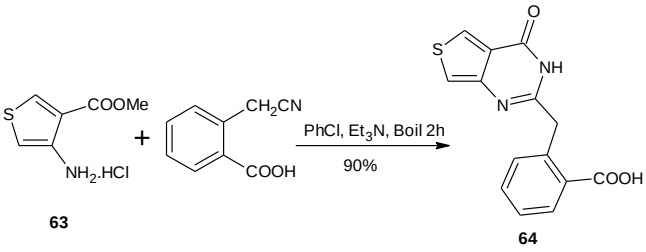
46

61a,b
a, R = Me;
b, R = Ph

By the same manner, reaction of compounds **5b** and/or **45a** with different nitrile compounds afforded 4-hydroxy-thieno[2,3-*d*]pyrimidine derivatives **62a,b** [58].

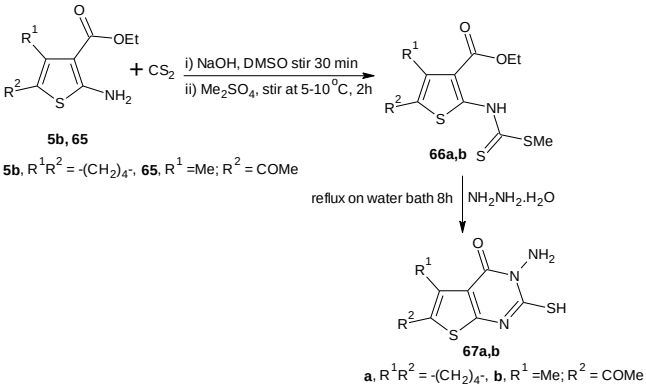


Reaction of methyl 3-aminothiophenehydrochloride-4-carboxylate (**63**) [58] with 2-cyanomethylbenzoic acid in presence of triethylamine gave 2-(4-oxo-3,4-dihydrothieno [3,4-*d*]pyrimidin-2-yl)methylbenzoic acid (**64**) in good yield [60].

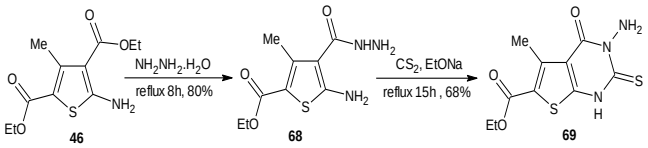


2.2.4 With carbon disulfide

Effect of carbon disulfide on vicinal amino ester was observed. Treating of thiophenes **5b, 65** [14] with carbon disulfide in aqueous sodium hydroxide followed by addition of dimethyl sulphate yielded sulfanylthiocarbonyl-aminothiophene derivatives **66a,b**, which on hydrazinolysis gave 3-amino-2-mercaptothieno[2,3-*d*]pyrimidin-4-ones **67a,b** [61,62].

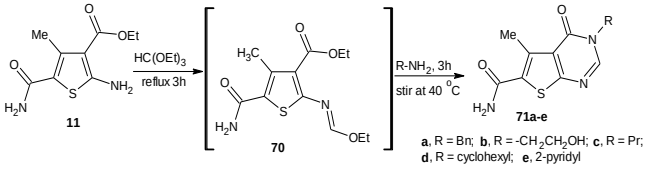


The acid hydrazide **68** obtained by refluxing of ethyl thiophene-3-carboxylate **46** with hydrazine hydrate underwent cyclocondensation on treatment with carbon disulfide to give 3-amino-6-carboxyethyl-5-methyl-2-thioxothieno[2,3-*d*]pyrimidin-4-one (**69**) [63].

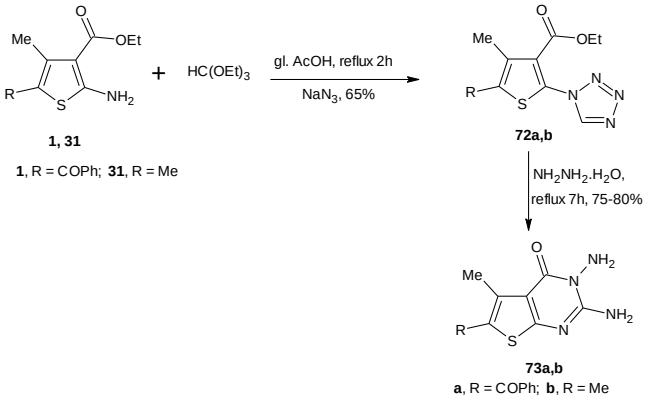


2.2.5 With triethyl orthoformate

Treatment of amino ester **11** with triethyl orthoformate and benzyl amine furnished 3-benzyl-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxamide (**71a**) in 83% yield accordance with the previously reported reaction conditions [64]. Accordingly, compounds **71b-e** were synthesized *via* the one pot reaction condition by reaction of amino ester **11** with triethyl orthoformate and appropriate amine in 79-85% [37].

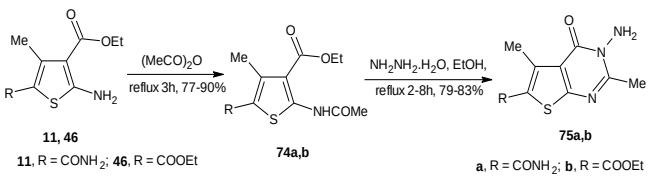


Also, reaction of amino ester **1, 31** with triethyl orthoformate and sodium azide afforded 2-(1*H*-tetrazol-1-yl)thiophenes **72a,b**, which cyclized to 2,3-diamino-thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives **73a,b** on refluxing with hyrazine hydrate [65,66].

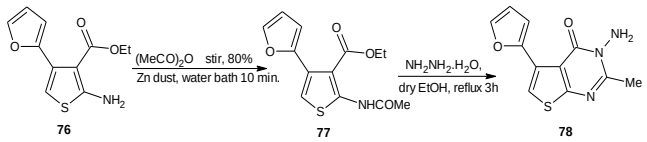


2.2.6 With acetic anhydride

Acylation of the amino ester **11** and/or **46** with acetic anhydride gave *N*-acetylated derivatives **74a,b**, which cyclized on treatment with hydrazine hydrate in ethanol to yield 3-aminothieno[2,3-*d*]pyrimidine derivatives **75a,b** in good yield [37,63].

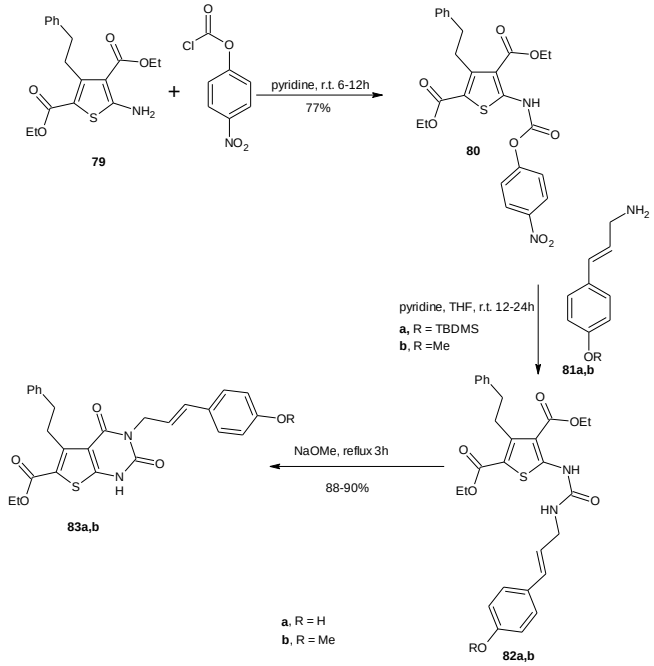


On the other hand, ethyl 2-amino-4-(2-furanyl)-thiophene-3-carboxylate (**76**) [14] was converted into ethyl 2-acetylamino-4-(2-furanyl)-thiophene-3-carboxylate (**77**) by nucleophilic acylation of amino group with acetic anhydride according to modified literature method [33]. Zinc dust was added in catalytic amount to improve the overall yield of compound **77**. Hydrazinolysis of compound **77** afforded 3-amino-5-(2-furanyl)-2-methyl-3*H*-thieno [2,3-*d*]pyrimidin-4-one (**78**) [67].

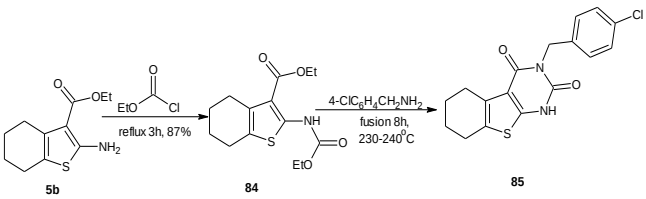


2.2.7 With chloroformate derivatives

Treatment of thiophene derivative **79** with *p*-nitro-phenyl chloroformate in basic medium gave carbonylamino-thiophene **80**, which reacted with (*E*)-3-(4-(*tert*-butyldimethylsilyloxy) phenyl)-prop-2-en-1-amine (**81a**) or (*E*)-3-(4-methoxyphenyl)-prop-2-en-1-amine (**81b**) in presence of pyridine gave ureidothiophene derivatives **82a,b**. Refluxing of compounds **82a,b** in sodium methoxide yielded thieno[2,3-*d*]pyrimidines **83a,b**[68].

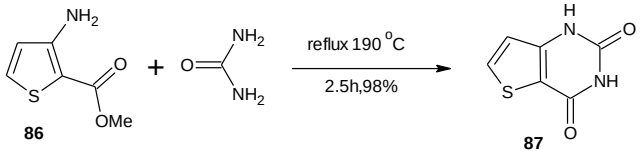


Also, condensation of compound **5b** with ethyl chloroformate gave 2-ethoxycarbonylaminothiophene **84**, which was fused with *p*-chlorobenzylamine to afford 3-(4-chlorobenzyl)-5,6,7,8-tetrahydro-1*H*-benzo[4,5]thieno [2,3-*d*]pyrimidin-2,4-dione (**85**) [49,69].

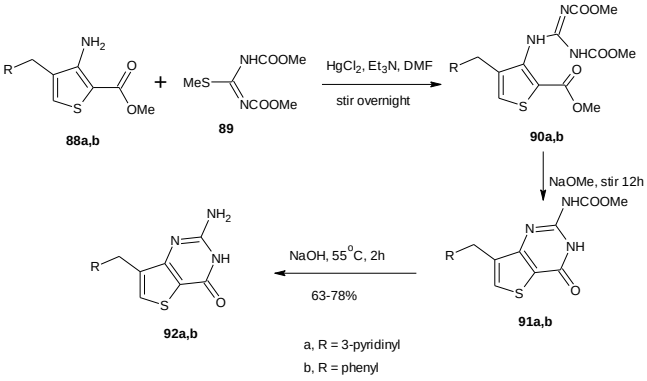


2.2.8 With urea and their derivatives

Methyl 3-aminothiophene-2-carboxylate (**86**) was condensed with urea at 190°C to yield thieno[3,2-*d*] pyrimidin-2,4(1*H*,3*H*)-dione (**87**) in high yield [70].



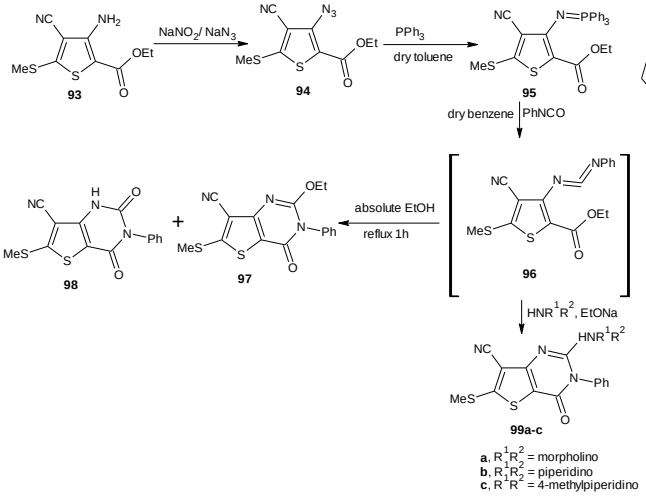
Also, 4-substitutedthiophenes **88a**,**b** were condensed with 1,3-dicarbmethoxy-2-methyl-2-thiopseudourea (**89**) [71] to give the guanidine adducts **90**, which was found to be more convenient to add an excess of sodium methoxide, whereupon cyclization occured with concomitant loss of a carbamate group to give pyrimidinone derivatives **91a,b**. The remaining carbamate group underwent hydrolysis and decarboxlation on treatment with aqueous sodium hydroxide to yield thieno[3,2-*d*]pyrimidin-4-ones **92a**,**b** [72].



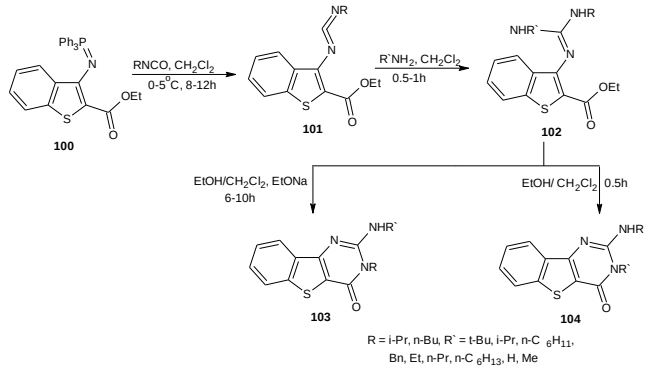
2.2.9 With other reagents

Azidothiophene ester **94** was prepared by reacting of aminothiophene derivative **93** [73] with sodium nitrite and sodium azide. Refluxing of compound **94** with one equivalent of triphenylphosphine yielded 3-triphenyl-phosphiniminothiophene **95**, which underwent aza-Wittig type reaction with phenylisocyanate to give highly reactive carbodiimide intermediate **96**, which was reacted with absolute ethanol under refluxing conditions to give 2-ethoxy-thieno[3,2-*d*]pyrimidine **97** and 2,4-dioxothieno [3,2-*d*]pyrimidine **98**. Also, compound **96** was reacted with

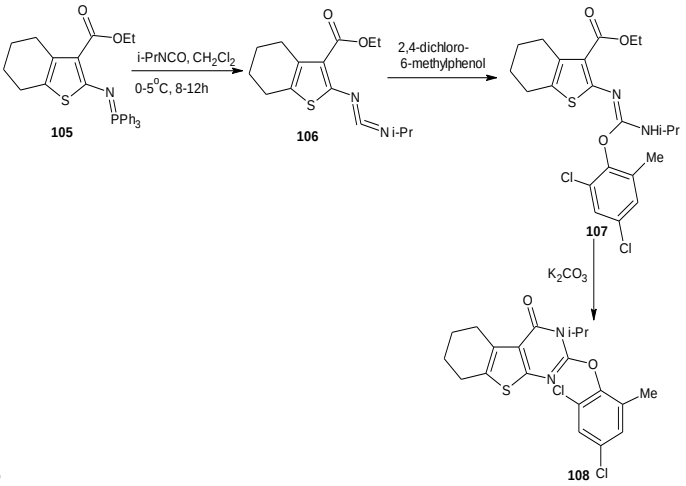
secondary amines in sodium ethoxide to afford the corresponding thieno[3,2-*d*]pyrimidines **99a-c**[74].



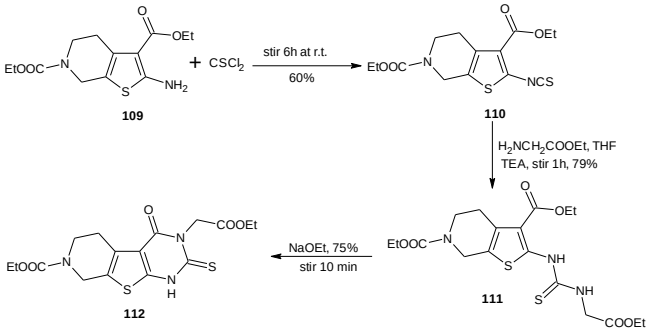
By the same way, treatment of iminophosphorane **100** [75] with aromatic isocyanates gave carbodiimide **101**, which were allowed to react with primary amines to provide guanidine intermediate **102**. Even in refluxing toluene, compound **102** did not cyclize, however, in the presence of catalytic amount of sodium ethoxide, compound **102** was converted easily to 2-alkylaminobenzo[*b*]thieno[3,2-*d*] pyrimidin-4(3*H*)-ones **103** and **104** in satisfactory yields at room temperature [76].



Also, condensation of iminophosphorane **105** with isopropyl isocyanate in anhydrous dichloromethane yielded carbodiimide **106**, which was allowed to dissolve in acetonitrile then reacted with 2,4-dichloro-6-methylphenol to give 2-iminothiophene **107**, which treated with excess potassium carbonate to afford thieno[2,3-*d*]pyrimidine derivative **108** [77].



Diethyl 2-amino-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (**109**) [78] was reacted with thiophosgene to afford 2-isothiocyanatothieno[2,3-*c*]pyridine **110**, which treated with ethyl glycinate to yield thieno[2,3-*c*]pyridine **111**. Moreover, compound **111** underwent intracyclo-addition in presence of sodium ethoxide to give thieno [2,3-*d*]pyrimidine derivative **112** [79].

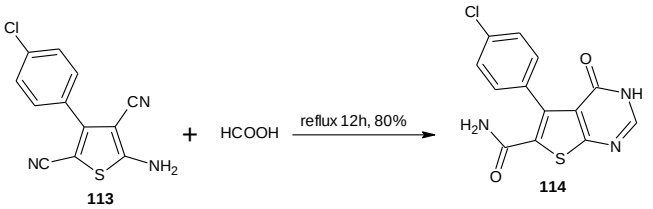


2.3 Using thiophene having vicinal cyanoamino groups

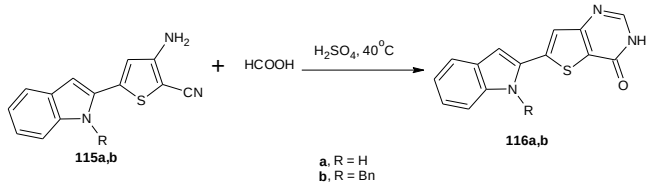
Also, thiophene derivatives having vicinal cyanoamino groups is considered a suitable reagent for the synthesis of thienopyrimidines *via* its interaction with various suitable reagents.

2.3.1 With formic acid

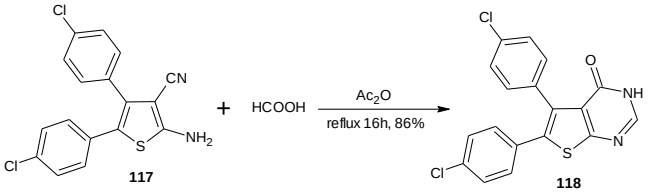
Formic acid was reacted with 5-amino-3-(4-chloro-phenyl)thiophene-2,4-dicarbonitrile (**113**) to give 5-(4-chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-*d*]pyrimidine-6-carboxamide (**114**) in good yield [80].



In similar manner, thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **116a,b** were synthesized by treatment of 3-amino-2-cyano-5-indol-3-ylthiophenes **115a,b** with formic acid in the presence of catalytic amount of sulfuric acid in 84% and 88% yield, respectively [81].

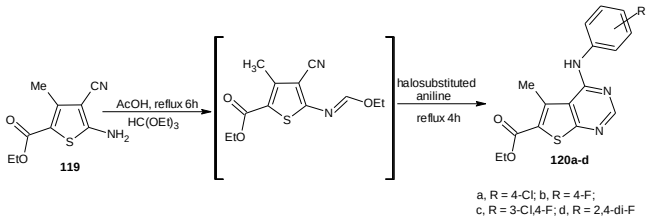


Also, cyclocondensation of 2-amino-4,5-bis(4-chlorophenyl)-thiophene-3-carbonitrile (**117**) with formic acid and acetic anhydride led to formation of 5,6-bis(4-chlorophenyl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**118**) [82].

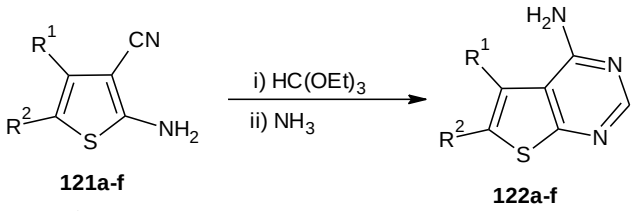


2.3.2 With triethyl orthoformate

Cyclocondensation of ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (**119**) with triethylorthoformate in the presence of few drops of acetic acid as a catalyst and appropriate susbtitutedaniline afforded ethyl thieno[2,3-*d*]pyrimidine-6-carboxalyte derivatives **120a-d** [83].



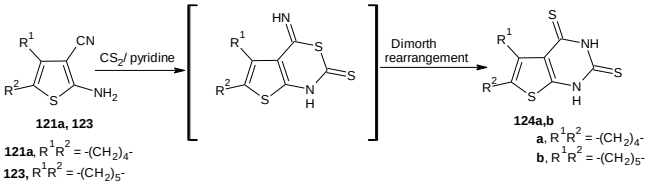
Similarly, 4-aminothieno[2,3-*d*]pyrimidine derivatives **122a-f** can be obtained by reaction of 2-amino-3-cyanothiophene derivatives **121a-f** with triethylorthoformate followed by treatment with ammonia at 0°C [84].



a, R^1R^2 = -$(CH_2)_4$-;
b, R^1R^2 = 7-methoxytetrahydrobenzo;
c, R^1 = Me, R^2 = H;
d, R^1R^2 = 3,4-dihydronaphtho[1,2];
e, R^1R^2 = naphtho[1,2];
f, R^1R^2 = 4-aminopyrimido[4,5]

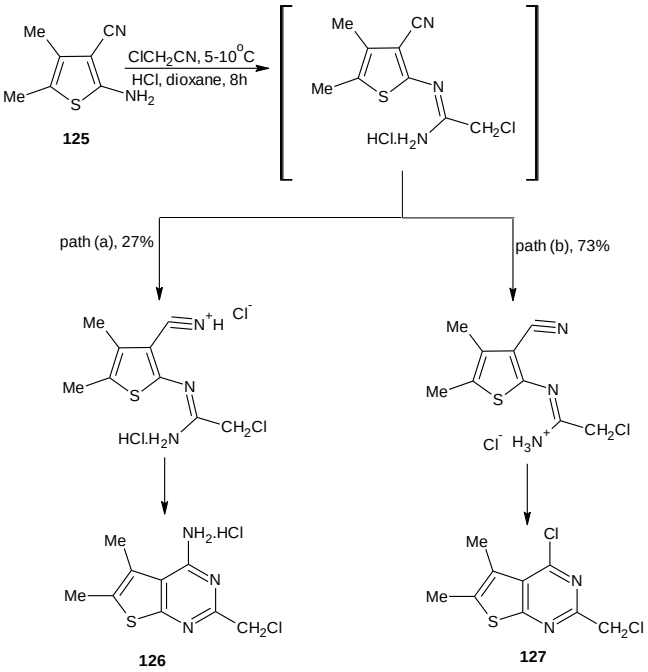
2.3.3 With carbon disulfide

Action of carbon disulfide on 2-amino-4,5,6,7-tetrahydro-benzo- and/or 4,5,6,7,8-pentahydrocyclohepta-thiophene-3-carbo-nitrile **121a**, **123** [14] in dry pyridine gave the corresponding susbtitutedthieno[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dithiones **124a,b** [85].

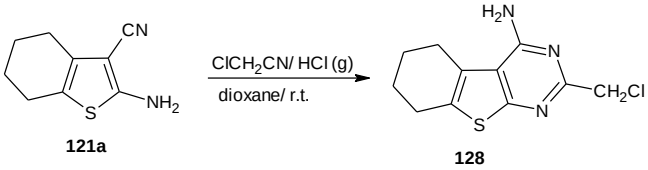


2.3.4 With nitrile compounds

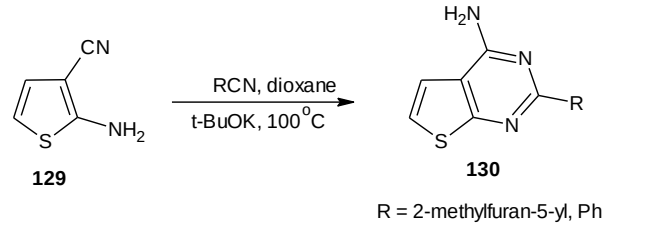
Nitriles reacted with vicinal aminocyanothiophene to yield the target thienopyrimidines. Thus, interaction of 2-amino-4,5-dimethylthiophene-3-carbonitrile (**125**)[14] with chloroacetonitrile in the presence of hydrogen chloride gas gave two possible thieno[2,3-*d*]pyrimidine derivatives **126** and **127** according to the following scheme [86].



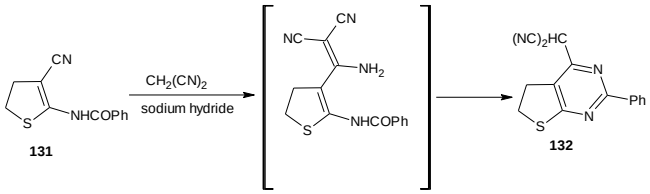
Similarly, chloroacetonitrile was reacted with thiophenes **121a** in presence of hydrogen chloride gas to yield 2-chloromethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*] pyrimidin-4-yl amine (**128**) [87].



Moreover, treatment of 2-aminothiophene-3-carbonitrile (**129**) with aryl and heteroaryl nitriles in presence of a catalytic amount of *t*-BuOK gave the corresponding 4-aminothieno[2,3-*d*]pyrimidine derivatives **130** [88].

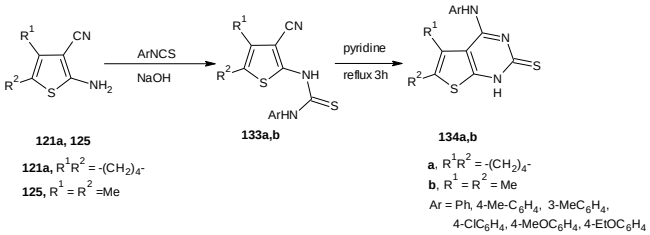


On the other hand, addition of the cyano group of 2-benzamido-4,5-dihydrothiophene-3-carbonitrile (**131**) [88] to malononitrile afforded the intermediate β-enaminonitrile, which underwent cyclization to give malnonitrile derivative **132** [90].

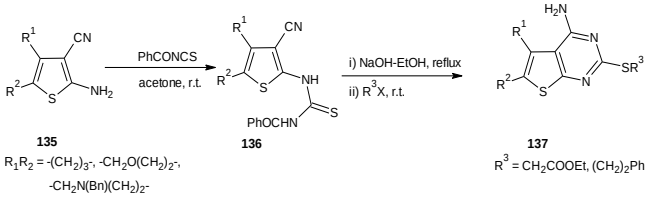


2.3.5 With isothiocyanates

Addition of aryl isothiocyanate to compounds **121a** and **125** in basic medium afforded 2-(*N*-arylthioureido)-3-cyanothiophenes **133a**,**b** which converted into 4-arylamino-2-thioxothieno[2,3-*d*]pyrimidines **134a**,**b** on refluxing with pyridine [91].

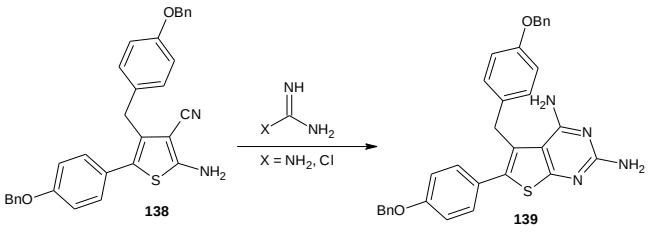


Also, addition of benzoyl isothiocyanate to cyanoamino thiophene derivatives **135** gave benzoylthioureas **136**. Thermal ring closure of these intermediates in aqueous sodium hydroxide solution was followed by the reaction with alkyl halides giving rise to the corresponding 4-aminothieno[2,3-*d*]pyrimidine derivatives **137** [92].



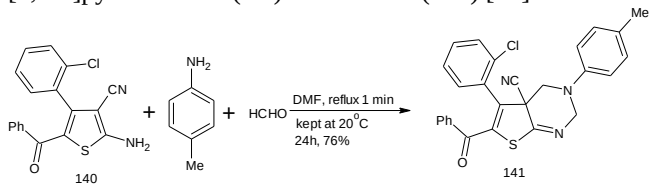
2.3.6 With amidine derivatives

Treatment of 2-aminothiophene-3-carbonitrile **138** with different cyclizing agents like guanidine carbonate and/or chloroformamidine hydrochloride gave 2,4-diaminothieno[2,3-*d*]pyrimidine derivative **139** [93].



2.3.7 By Mannich reaction

The three components condensation of 2-amino-3-cyano-4,5-dihydrothiophene **140** with *p*-toluidine and formaldehyde led to the formation of 6-benzoyl-5-(2-chlorophenyl)-3-(4-methylphenyl-3,4,5,6-tetrahydrothioeno [2,3-*d*]pyrimidine-4a(2*H*)-carbonitrile (**141**) [94].

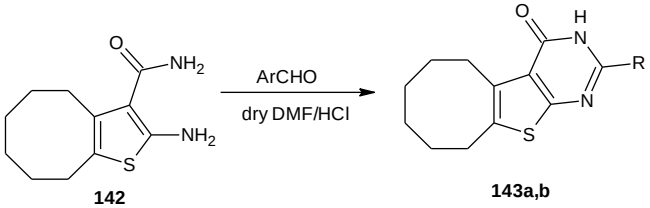


140 141

2.4 Using thiophene having Vicinal amino carboxamido groups

2.4.1 With aldehydes

Cyclocondensation of 2-amino-4,5,6,7,8,9-hexahydrocycloocta[4,5]thiophene-3-carbox-amide (**142**) with the appropriate pyridine carboxaldehyde in the presence of concentrated hydrochloric acid resulted in dry DMF in 2-(2-and/or 4-pyridyl)-5,6,7,8,9,10-hexahydro-cycloocta[4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one **143a,b** [95].

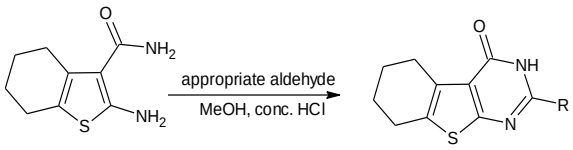


142

143a,b

a, R = 2-pyridinyl
b, R = 4-pyridinyl

In the same manner, treatment of 3-carbxamidothiophene derivative **144** with 3,4,5-trimethoxybenzaldehyde or cinnamaldehyde afforded the corresponding thieno[2,3-*d*] pyrimidin-4(3*H*)-ones **145a,b** [96,97]. Likewise, compound **144** was reacted with 2-nitrocinnamaldehyde or 2-methylcinnamaldehyde in the presence of catalytic amount of hydrochloric acid to give 2-substitutedthieno[2,3-*d*] pyrimidin-4(3*H*)-ones **145c,d** [98].

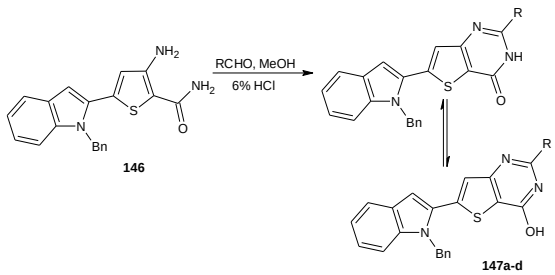


144

145a-d

a, R = 3,4,5-trimethoxyphenyl;
b, R = styryl;
c, R = 2-aminostyryl;
d, R = 1-phenylprop-1-en-2-yl

Also, condensation of 3-amino-5-(1-benzyl-1*H*-indol-3-yl)-2-thiophene-carboxamide (**146**) with heptaldehyde, *p*-anisaldehyde, 3,4,5-trimethoxybenzaldehyde and *p*-chloro-benzaldehyde in methanol containing 6% concentrated hydrochloric acid afforded 6-(1-benzyl-1*H*-indol-3-yl)-2-substituted thieno[2,3-*d*]pyrimidin-4-ol derivatives **147a-d** [99].

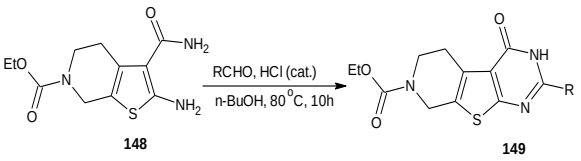


146

147a-d

a, R = n-hexyl; **b**, R = 4-MeOC$_6$H$_4$;
c, R = 3,4,5-(MeO)$_3$C$_6$H$_2$, **d**, R = 4-ClC$_6$H$_4$

Moreover, treatment of 2-amino-3-thiophenecarboxamide derivative **148** with different aromatic aldehydes in normal butanol and hydrochloric acid gave the corresponding thieno[2,3-*d*]pyrimidinone derivatives **149** [100].



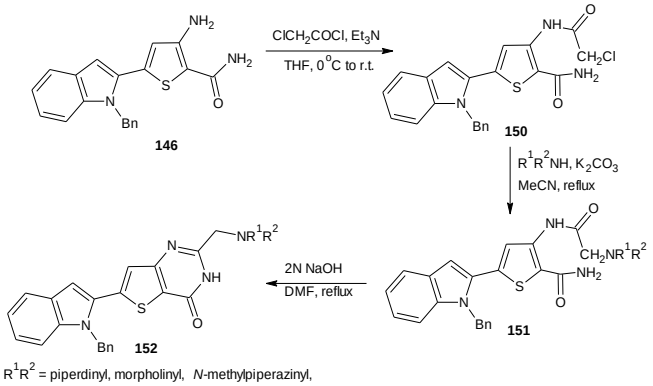
148

149

R = 2,3-dihydrobenzo[1,4]dioxin-6-yl,
4-(methylthio)phenyl, 4-methoxyphenyl,
2-benzo[1,3]dioxol-5-yl, 4-isopropenyl-
cyclohex-1-enyl, 3,4,5-trimethoxyphenyl

2.4.2 With acid halides

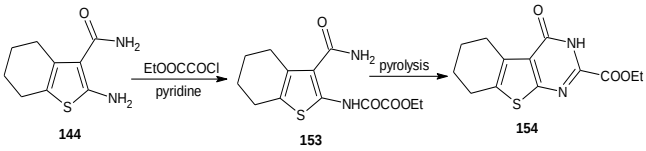
Condensation of compound **146** with chloroacetyl chloride in dry tetrahydrofuran and catalytic amount of triethylamine led to the formation of 3-[(chloroacetyl)-amino]-2-thiophene **150**, which reacted with different amines to afford 3-substitutedamino-2-thiophene **151**. The later compound reacted with 2*N* sodium hydroxide to give 2-substitutedthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **152** [99].



146 **150** **151** **152**

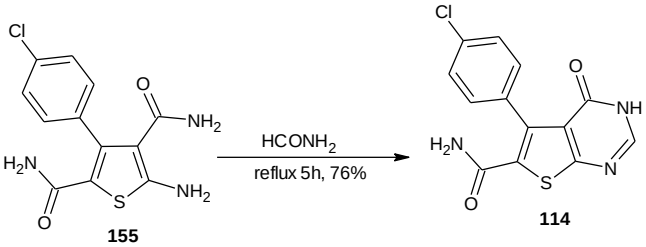
R^1R^2 = piperdinyl, morpholinyl, *N*-methylpiperazinyl, *N*-benzylpiperazinyl, pyrrolidinyl

Similarly, treatment of compound **144** with ethyloxalyl chloride in dry pyridine gave ethyl *N*-[3-(aminocarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl]-oxamate (**153**), which converted into thieno[2,3-*d*]pyrimidine derivative (**154**) on pyrolysis at 260°C [101].



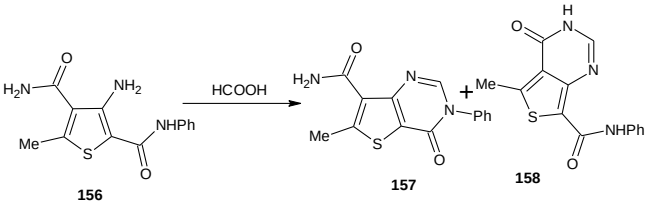
2.4.3 With formamide

Cyclocondensation of dicaroxamide derivative **155** with formamide afforded thieno[2,3-*d*]pyrimidine **114** [102].



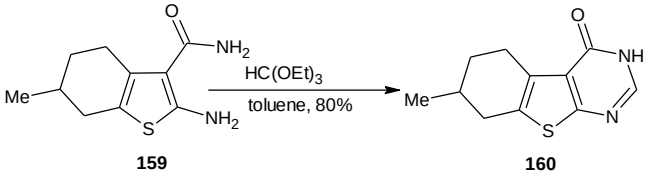
2.4.4 With formic acid

Treatment of formic acid with 3-amino-4-carbamoyl-5-methyl-2-(*N*-phenylcabamoyl)thiophene (**156**) gave mixture of 6-methyl-4-oxo-3-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-7-carboxamide (**157**) and 5-methyl-4-oxo-3,4-dihydrothieno [2,3-*d*] pyrimidine-7-carboxanilide (**158**) in 81and 7% yields, respectively [103].



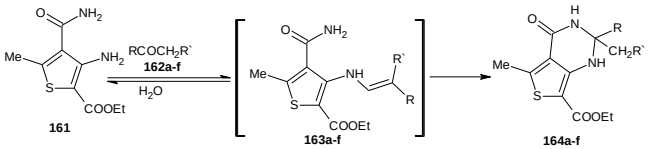
2.4.5 With triethylorthoformate

Cyclocondensation of 2-amino-6-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**159**) [14] with triethylorthoformate afforded 7-methyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4-one (**160**) [104].



2.4.6 With 1,3-dicarbonyl compounds

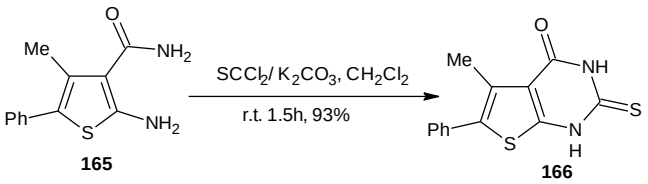
Reactions of ethyl 3-amino-4-cabamoyl-5-methyl-thiophene-2-carboxylate (**161**) with carbonyl compounds (acetylacetone, benzoylacetone, ethyl acetoacetate, acetoacetanilide, ethyl benzoylacetate and *α*-cyanoacetophenone) **162a-f** gave intermediate enamine **163a-f**, which cyclized to afford thieno[3,4-*d*]pyrimidines **164a-f** [105].



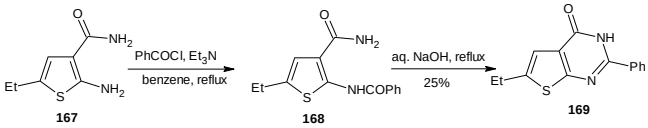
a, R = Me, R` = COMe; **b**, R = Me, R` = COPh;
c, R = Me, R` = CO 2Et; **d**, R = Me, R` = CONHPh;
e, R = Ph, R` = CO 2Et; **f**, R = Ph, R` = CN

2.4.7 With halogenated compounds

Cyclization of 2-amino-4-methyl-5-phenyl-thiophene-3-carboxamide (**165**) [14] by effect of thiophosgene in dichloromethane afforded 5-methyl-6-phenyl-2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**166**) in excellent yield [17].



When 2-amino-5-ethylthiophene-3-carboxamide (**167**) was allowed to react with benzoyl chloride it gave the carboxamido derivative **168**. Heating compound **168** with aqueous sodium hydroxide, 6-ethyl-2-phenylthieno[2,3-*d*] pyrimidin-4(1*H*)-one (**169**) is produced [47].



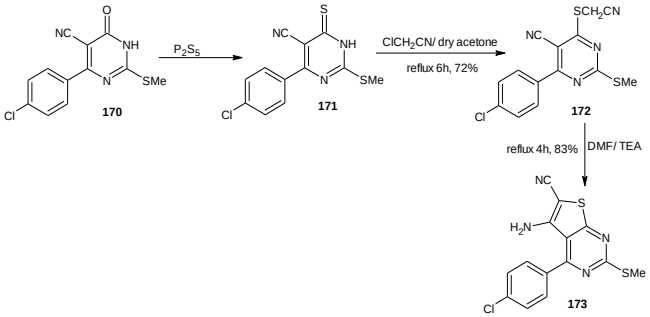
3. Annulations of Thiophene on Pyrimidine Ring

The starting susbtituted pyrimidines are less readily accessible for the synthesis of thienopyrimidines. The location of the ring sulphur in thieno[2,3-*d*]pyrimidines suggests that pyrimidines bearing a sulphu

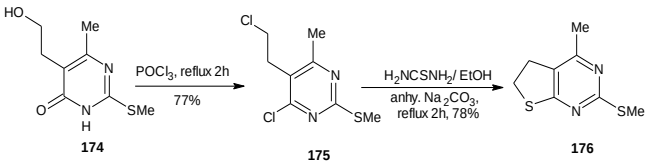
r at C-6 would serve as good candidates for developing the thiophene ring. whereas, pyrimidines with a sulphur function at C-5 represent the most efficient precursors for the synthesis of thieno[3,2-*d*]pyrimidines.

3.1 From uracil and thiouracil derivatives

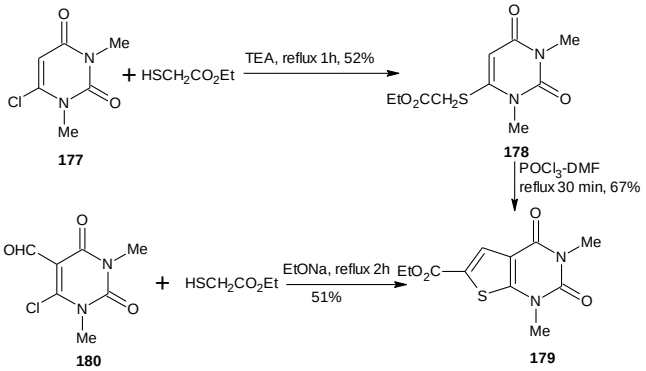
Thiouracils represent important starting materials which cooperate in construction of the target thienopyrimidines. Thiation of thiouracil derivative **170** [106] using phosphorus pentasulphide in dry pyridine afforded thiated product **171** [107]. Alkylation of **171** with chloroaceto-nitrile furnished 4-(4-chlorophenyl)-6-[(cyanomethyl)thio]-2-(methylthio)pyrimidine-5-carbonitrile (**172**). Base-induced intramolecular cyclization of **172** afforded 5-amino-4-(4-chlorophenyl)-2-(methylthio)thieno[2,3-*d*] pyrimidine-6-carbonitrile (**173**) [108].



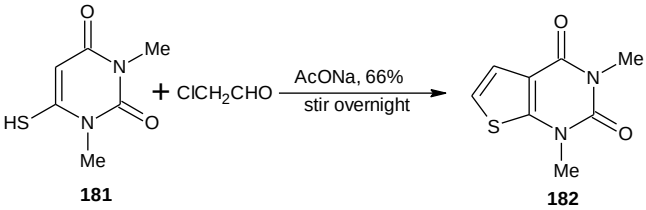
Also, treatment of 5-(2-hydroxyethyl)-6-methyl-2-methylthiopyrimidin-4(3*H*)-one (**174**) with phosphorus oxychloride gave 4-chloro-5-(2-chloroethyl)-6-methyl-2-methylthiopyrimidin-4(3*H*)-one (**175**), which was reacted with thiourea in presence of anhydrous sodium carbonate to yield 5,6-dihydro-2-methylthio-4-methylthieno[2,3-*d*] pyrimidine (**176**) [109].



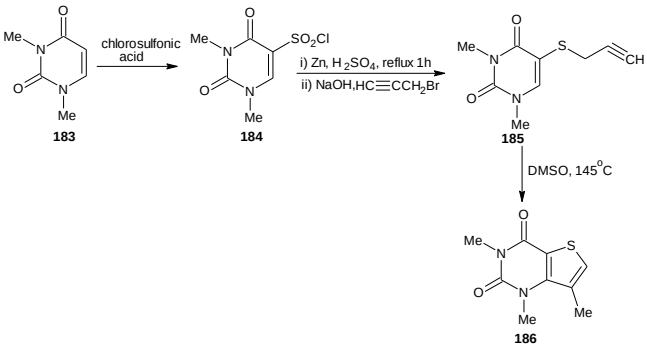
Moreover, condensation of 6-chloro-1,3-dimethyluracil (**177**) [110] with ethyl 2-mercaptoacetate gave 6-ethoxycarbonyl-methylthio-1,3-dimethyluracil (**178**), which underwent the Vilsmeier-Haack reaction to afford 6-ethoxycarbonyl-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**179**). Compound **179** can be also obtained from cyclocondensation of 6-chloro-5-formyl-1,3-dimethyluracil (**180**) with ethyl 2-mercaptoacetate [111,112].



When 6-mercaptouracil (**181**) [113] was allowed to react with chloroacetaldehyde in the presence of sodium acetate at room temperature, 1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4-(1*H*, 3*H*)-dione (**182**) was obtained [112].



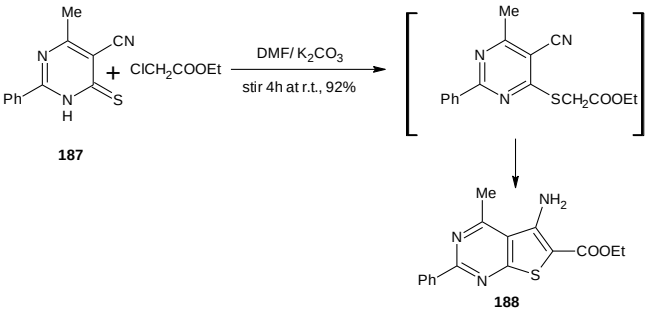
Also, treatment of 1,3-dimethyluracil (**183**) with chlorosulfonic acid afforded 5-chloro-sulfonyl-1,3-dimethyluracil (**184**) [114], which was reduced on refluxing with zinc dust and sulfuric acid. Alkylation of the resulting 1,3-dimethyl-5-thiouracil derivative **184** with propargyl bromide afforded 5-(2-propynylthio)uracil **185**, which underwent cyclization in dimethyl sulfoxide to give 1,3,6-trimethylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**186**) in good yield [115].



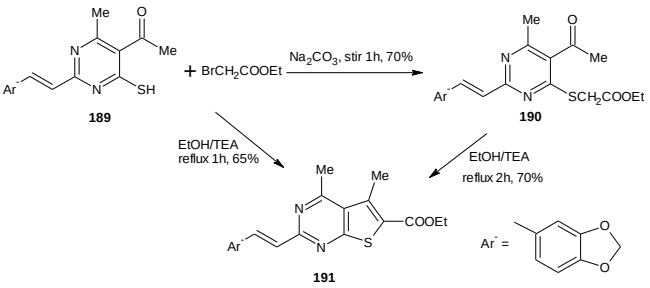
3.2 From thioxopyrimidine derivatives

Cyclization of 6-thioxopyrimidine **187** [116,117] with ethyl chloroacetate in DMF in the presence of excess of anhydrous potassium carbonate at room temperature

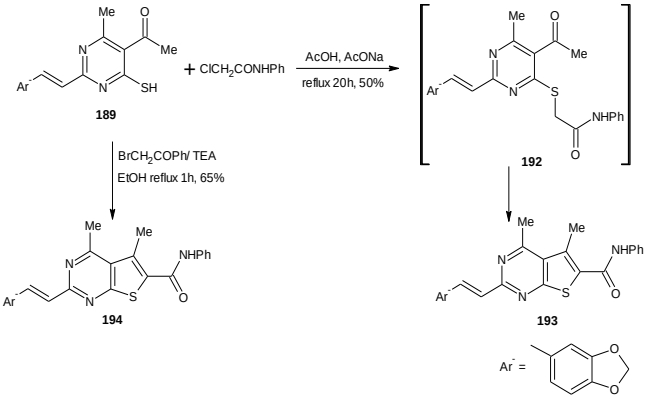
formed the nonisolable *S*-alkylated intermediate, which *via* nucleophilic substitution and intramolecular cyclo-condensation gave thieno[2,3-*d*]pyrimidine derivative **188** [118].



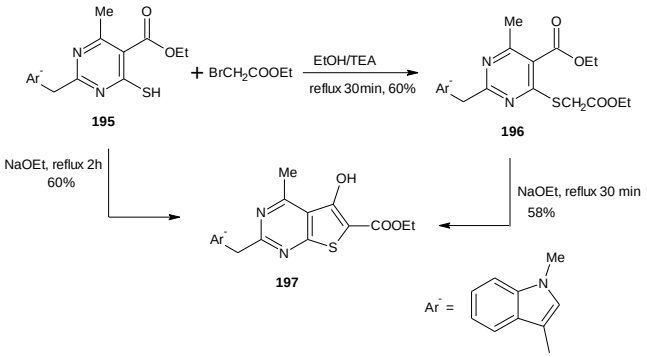
Also, condensation of 4-mercaptopyrimidine derivative **189** with ethyl bromoacetate in the presence of sodium carbonate yielded ethyl (2-(5-acetyl-2-(benzo[*d*][1,3] dioxol-5-yl)vinyl)-6-(methylpyrimidin-4-yl)-sulfanyl) acetate (**190**), which cyclized on refluxing in ethanol containing catalytic amount of triethylamine to afford thieno[2,3-*d*]pyrimidinederivative **191**. In addition, compound **191** can be prepared directly from compound **189** with ethyl bromoacetate in the presence of triethyl-amine in refluxing ethanol [119].



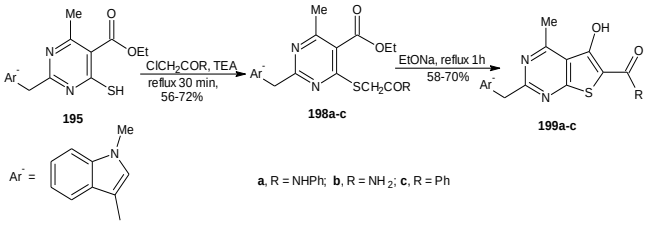
Moreover, treatment of compound **189** with *N*-phenyl-chloroacetamide in presence of anhydrous sodium acetate gave thieno[2,3-*d*]pyrimidine **193** *via*the non-isolated intermediate**192**. While, reaction of compound **189** with phenacylbromide in the presence of TEA in refluxing ethanol furnished thieno[2,3-*d*]pyrimidine derivative **194** [119].



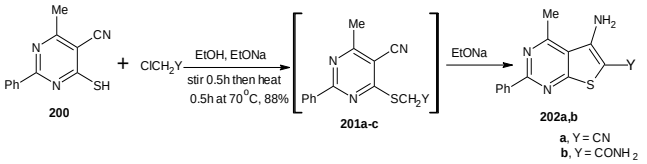
In the same manner, alkylation of 6-mercaptopyrimidine **195** [120] with ethyl bromoacetate in the presence of TEA produced 6-ethoxycarbonylmethylmercaptopyrimidine **196**, which was refluxed with sodium ethoxide to yield 3-hydroxythieno[2,3-*d*]pyrimidine **197**. However, the latter compound was also prepared directly from compound **195** on refluxing with ethyl bromoacetate in the presence of sodium ethoxide [121].



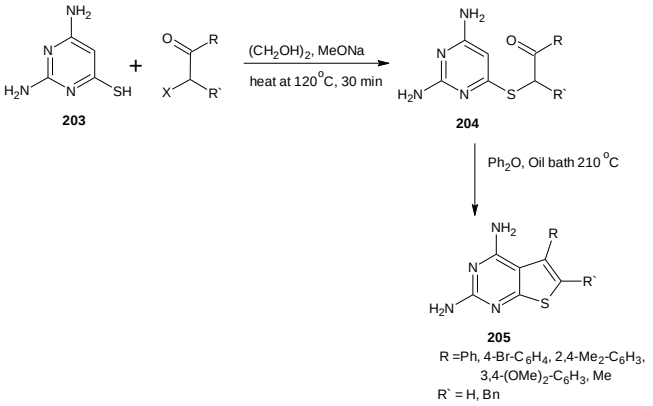
Reaction of compound **195** with chloro reagents, namely, chloro-*N*-phenylacetamide, chloroacetamide and phenacyl chloride in refluxing ethanol containing TEA as a catalyst afforded 2-substitutedmercaptopyrimidines **198a-c**. The latter derivativesunderwent intramolecular cyclization using sodium ethoxide yielding the corresponding fused thieno-pyrimidines **199a-c** [121].



Moreover, 4-methyl-2-phenyl-6-mercaptopyrimidine-5-carbonitrile (**200**) was reacted with chloroacetonitrile and/or chloroacetamide in the presence of sodium ethoxide to give *S*-alkylated derivatives as intermediates **201a,b** which upon heating cyclized to the corresponding thieno[2,3-*d*]pyrimidines **202a,b** [122,123].



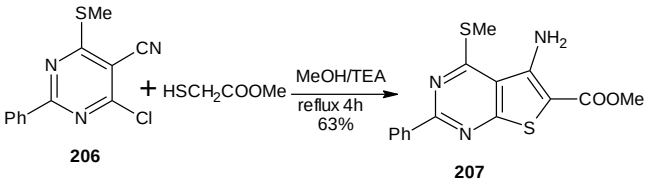
In addition to, 2,4-diamino-6-mercaptopyrimidine (**203**) [124] was reacted with α-haloketones to afford the desired 2,4-diaminothieno[2,3-*d*]pyrimidine derivatives **205** through an intermediate pyrimidyl sulfide derivatives **204** [125].



203 204 205

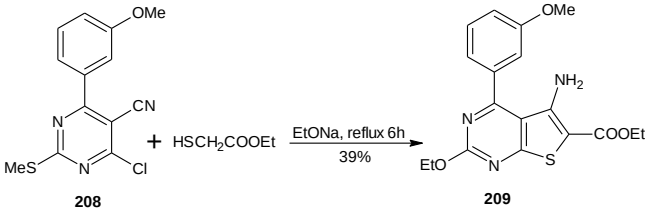
3.3 From Chloropyrimidine derivatives

Substitution of methyl thioglycolate for the chlorine atom in 4-chloro-6-methylthio-2-phenyl-pyrimidine-5-carbonitrile (**206**) in the presence of TEA afforded thieno[2,3-*d*]pyrimidine derivative **207** [126].



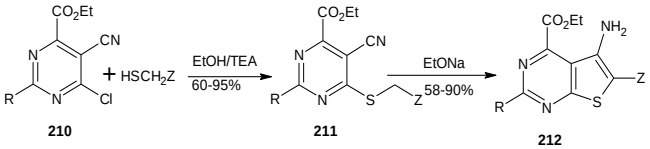
206 207

Also, cyclocondensation of 4-chloro-6-(3-methoxyphenyl)-2-methylthiopyrimidine-5-carbonitrile (**208**) with ethyl thioglycolate yielded 3-amino-2-carbethoxy-6-ethoxy-4-(3-methoxyphenyl)thieno[2,3-*d*]pyrimidine (**209**) [127].



208 209

Similarly, 6-chloropyrimidine-5-carbonitriles **210** were subjected to react with mercaptoacetic acid derivatives to give the corresponding 6-substitutedpyrimidine-5-carbonitriles **211**, which cyclized by the effect of sodium ethoxide to afford 5-aminothieno[2,3-*d*]pyrimidines **212** [128].

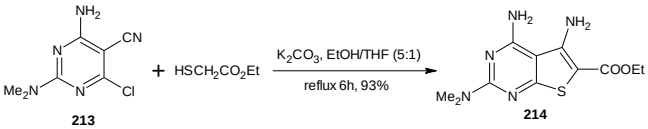


210 211 212

R = -NMe2, -NEt2, pyrrolidin-1-yl, piperidin-1-yl

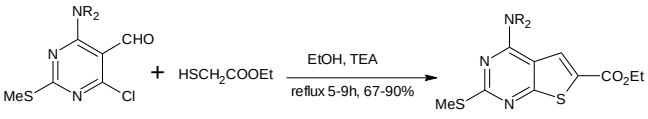
Z = CO2Et, CONH2

Moreover, ethyl thieno[2,3-*d*]pyrimidine-6-carboxylate **214** was prepared in good yield by the reaction of 2-(dimethylamino)pyrimidine **213** with ethyl 2-mercapto-acetate in refluxing EtOH/THF (5:1) [129].



213 214

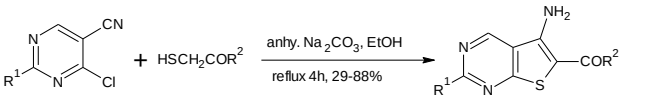
Also, heating of pyrimidine-5-carbaldehydes **215a-c** with ethyl mercaptoacetate at reflux in the presence of TEA yielded the corresponding ethyl 2-methylthiothieno[2,3-*d*] pyrimidine-6-carboxylate derivatives **216a-c** [130].



215a-c 216a-c

a, R2 = Me
b, R2 = -(CH2)4
c, R2 = -(CH2)5

Furthermore, 4-chloro-2-substitutedpyrimidine-5-carbo-nitrile **217a-c** were allowed to react with one equivalent of mercaptoacetic acid derivatives in refluxing ethanol containing powdered sodium carbonate to afford the corresponding 5-aminothieno[2,3-*d*]pyrimidines **218a-f** [131].



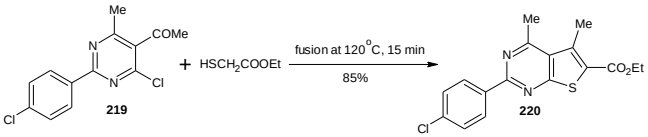
217a-c

a, R1 = MeS;
b, R1 = Ph;
c, R1 = Me2N

218a-f

a, R1 = MeS; R2 = OEt;
b, R1 = Ph; R2 = OMe;
c, R1 = Ph; R2 = NHPh;
d, R1 = Ph; R2 = NH-2-naphthyl;
e, R1 = Me2N; R2 = OEt;
f, R1 = Me2N; R2 = NHPh

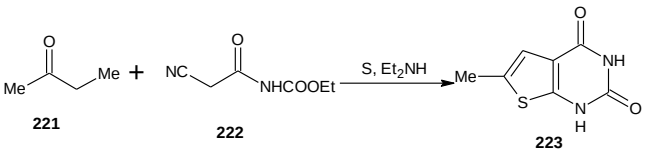
In addition to, condensation of chloropyrimidine derivative **219** with ethyl 2-mercaptoacetate under fusion conditions yielded ethyl 2-(*p*-chlorophenyl)-4,5-dimethylthieno[2,3-*d*] pyrimidine-6-carboxylate (**220**) [132].



219 220

4. Synthesis of Thienopyrimidines from Acyclic Compounds

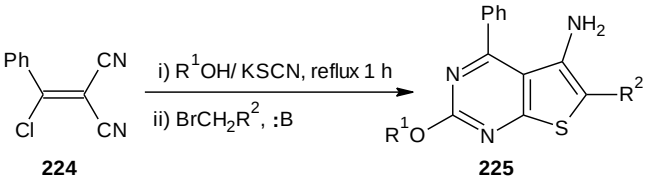
Treatment of methylethyl ketone **221**, *N*-cyanoacetyl urethane **222** and sulfur in the presence of diethyl amine yielded 2,4-dioxo-6-methylthieno[2,3-*d*]pyrimidine **223** in one step in an excellent yield [132].



221 222 223

Also, the reaction of α-cyano-β-chlorocinnamonitrile **224** with KSCN , ROH and active bromomethylene derivatives ($BrCH_2X$) afforded the corresponding thieno[2,3-*d*]

pyrimidine derivatives **225** [133].



224 **225**

R^1 = alkyl; R^2 = acyl, $CONH_2$, alkoxycarbonyl, CN

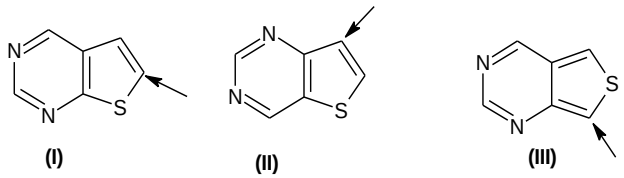
5. Reactions of Thienopyrimidines

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 susbtituents in the performed thienopyrimidine structure. In addition to, many studies were devoted to the use of various thienopyrimidine derivatives in the synthesis of linearly and angularly polyannelated heterocyclic systems. There are some of these reactions attributed to thiophene ring and other due to pyrimidine ring.

5.1 Reactions attributed to thiophene ring

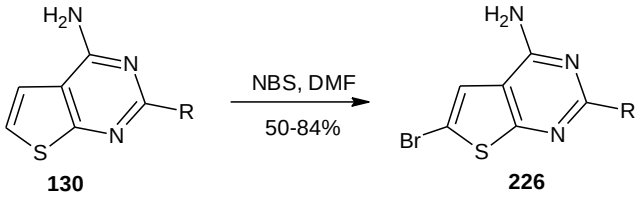
5.1.1 Reactions at thiophene carbons

Electrophilic substitutions like halogenation, Vilsmeier formylation, nitration and alkylation, were demonstrated in thieno[2,3-*d*]pyrimidines (**I**) and thieno [3,4-*d*]pyrimidines (**III**) involved position 6 and equivalent position 7, respectively, which is typical of thiophene itself and suggested a weak influence of annelation with the pyrimidine ring. A different situation is observed for electrophilic substitution in thieno[3,2-*d*]pyrimidines (**II**), 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 occurred at position 7.



5.1.1.1 Halogenation

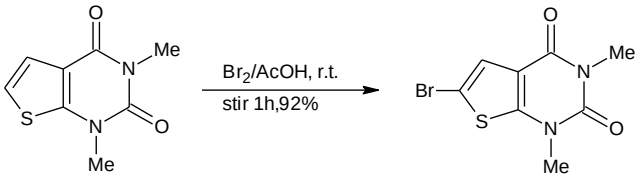
Bromination of compound **130** with mild bromonating agent, *N*-bromosuccinimde (NBS), in dimethyl formamide afforded 4-amino-6-bromo-2-subutitutedthieno[2,3-*d*]pyrimidines **226** [88].



130 **226**

R = 2-methylfuran-5-yl, Ph

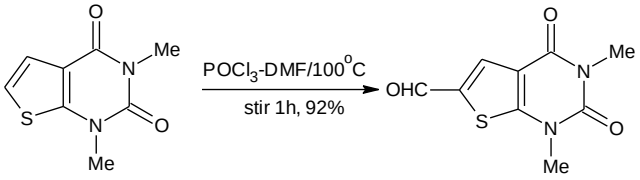
Also, 6-bromo-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**227**) was formed by addition of a solution of bromine dissolved in acetic acid to thieno-pyrimidine **182** [112].



182 **227**

5.1.1.2 Vilsmeier-Haack reaction

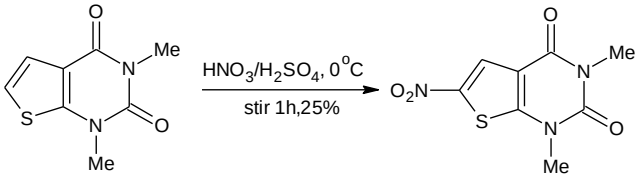
The Vilsmeier-Haack reaction of compound **182** using phosphorus oxychloride and DMF resulted in the formation of 6-formyl-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**228**) [112].



182 **228**

5.1.1.3 Nitration

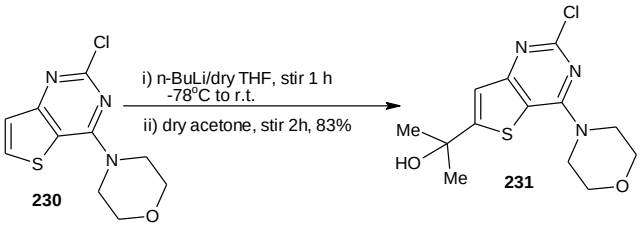
Thieno[2,3-*d*]pyrimidine **182**was nitrated using a solution of fuming nitric acid in concentrated sulfuric acid to afford 6-nitro-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4 (1*H*,3*H*)-dione (**229**) [112].



182 **229**

5.1.1.4 Alkylation

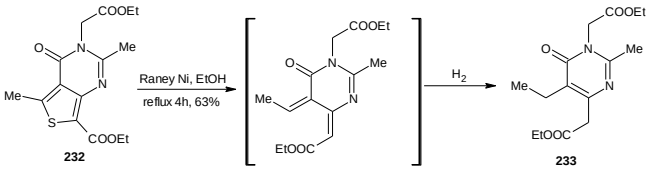
2-(2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl) propan-2-ol (**231**) was obtained from treatment of 2-chloro-4-morphlin-4-ylthieno[3,2-*d*]pyrimidine (**230**) with *n*-BuLi followed by addition of dry acetone[70].



230 231

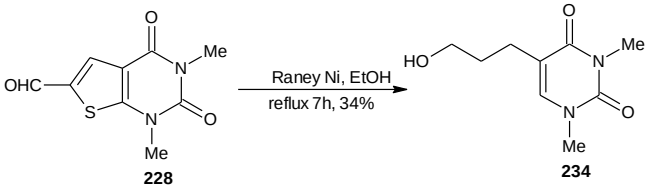
5.1.2 Ring opening of the thiophene ring

Ethyl 3-(2-ethoxy-2-oxoethyl)-2,5-dimethyl-4-oxo-3,4-dihydrothieno[3,4-*d*]pyrimin-dine-7-carboxylate (**232**) was underwent desulfurization under the action of Raney nickel to yield ethyl 4-(ethoxycarbonylmethyl)-5-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-1-yl-acetate (**233**) [105].



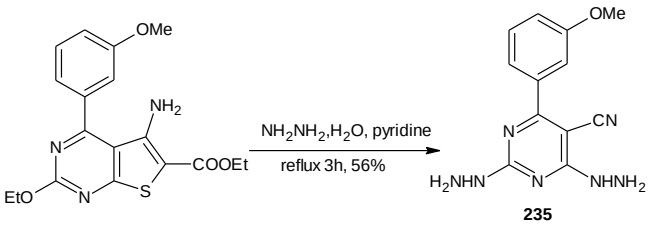
232 233

In the same way, hydrogenation of 6-formylthieno[2,3-*d*] pyrimidine **228** with Raney nickel under 50 atmospheres induced desulfurization to give 5-(3-hydroxypropyl)-1,3-dimethyluracil (**234**) [112].



228 234

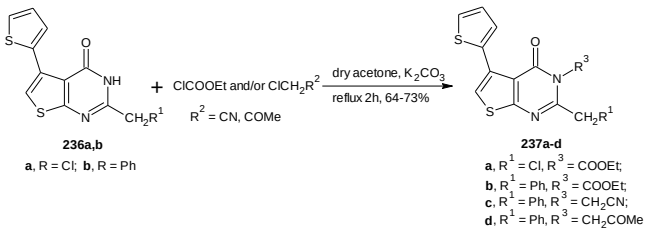
Also, when compound **209** allowed to react with hydrazine hydrate, it gave unexpectedly a ring opened compound, 2,4-dihydrazino-6-(3-methoxyphenyl)-pyrimidine-5-carbonitrile (**235**) [134].



209 235

5.2 Reactions attributed to nitrogen of the pyrimidine ring

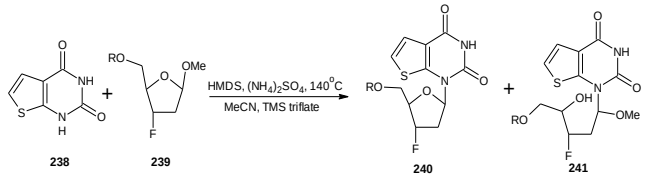
Treatment of 5-(2-thienyl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one **236a,b** with ethyl chloroformate and/or chloroacetonitrile in the presence of potassium carbonate gave the corresponding 3-substitutedthieno[2,3-*d*] pyrimidine **237a-c** [135].



236a,b
a, R = Cl; **b**, R = Ph

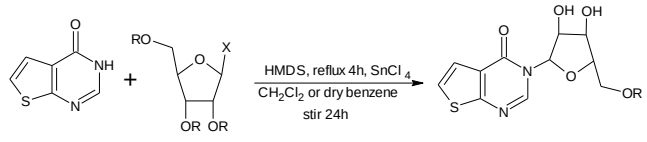
237a-d
a, R^1 = Cl, R^3 = COOEt;
b, R^1 = Ph, R^3 = COOEt;
c, R^1 = Ph, R^3 = CH_2CN;
d, R^1 = Ph, R^3 = CH_2COMe

Silylation of thieno[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione (**238**) with 1,1,1,3,3,3-hexamethyl-disilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate gave the corresponding silylated compounds, which condensed with methyl 3-fluoro-2,3-dideoxy-5-*O*-(4-phenylbenzoyl)-β-D-*erythro*-pentofuranoside (**239**) in acetonitrile using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a catalyst according to the method of Vorbrüggen [136]to yield the corresponding thieno[2,3-*d*] pyrimidin-2,4(1*H*,3*H*)-dione **240** in 56% yield and the acyclic nucleoside **241** in 17% yield [137].



238 239 240 241

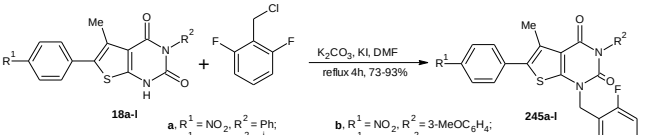
Similarly, condensation of the silylated heterocycle thieno[2,3-*d*]pyrimidin-4-one **242** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**243a**) in the presence of stannic chloride or with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**243b**) in the presence of mercuric oxide and mercuric bromide yielded 3-β-D-ribofuranosylthieno[2,3-*d*] pyrimidin-4-one (**244**) [138].



242 243a,b 244

a, R = COPh, X = $MeCO_2$;
b, R = COMe, X = Br

Also, thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **18a-l** was alkylated with 2,6-difluorobenzyl chloride in the presence of potassium carbonate to furnish the corresponding 1-(2,6-difluorobenzyl)thieno[2,3-*d*] pyrimidin-2,4(1*H*,3*H*)-diones **245a-l** [28].

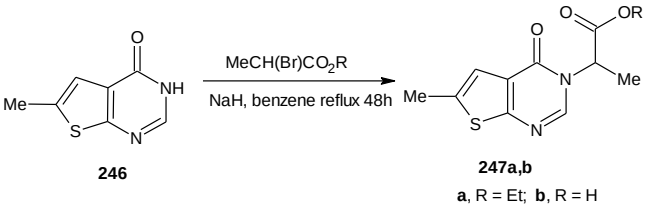


18a-l 245a-l

a, R^1 = NO_2, R^2 = Ph; **b**, R^1 = NO_2, R^2 = 3-$MeOC_6H_4$;
c, R^1 = OMe, R^2 = ^{t}Bu; **d**, R^1 = OMe, R^2 = cyclohexyl;
e, R^1 = OMe, R^2 = Bn; **f**, R^1 = OMe, R^2 = Ph;
g, R^1 = OMe, R^2 = 2-$MeOC_6H_4$; **h**, R^1 = OMe, R^2 = 4-$MeOC_6H_4$;
i, R^1 = OMe, R^2 = 4-$MeOC_6H_4$; **j**, R^1 = OMe, R^2 = 2-ClC_6H_4;
k, R^1 = OMe, R^2 = 3-ClC_6H_4; **l**, R^1 = OMe, R^2 = 4-ClC_6H_4

Alkylation of thienopyrimidinone **246** with ethyl 2-bromopropionate and/or 2-bromopropionic acid gave ethyl

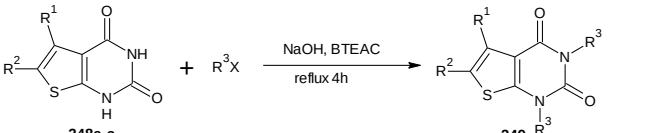
2-(6-methyl-4-oxothieno[2,3-*d*]pyrimidin-3(4*H*)-yl)propanoate (**247a**) and/or 2-(6-methyl-4-oxothieno [2,3-*d*]pyrimidin-3(4*H*)-yl)propanoic acid (**247b**), respectively [139].



246 **247a,b**

a, R = Et; **b**, R = H

Condensation of thieno[2,3-*d*]pyrimidindionederivatives **248a-c** with alkyl halide in the presence of benzyltriethylammonium chloride (BTEAC) yielded 1,3-dialkylthieno[2,3-*d*] pyrimidindione **249** [140].



248a-c
a, $R^1 = R^2$ =Me;
b, R^1R^2 = -$(CH_2)_4$-;
c, R^1 =Ph, R^2 = H

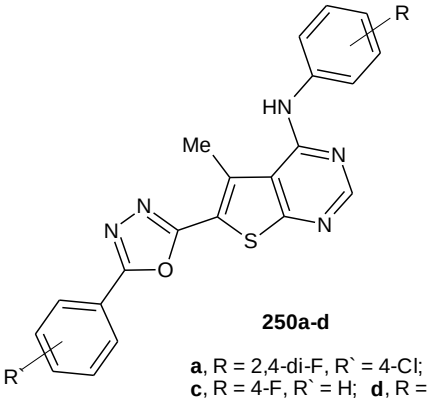
249
R^3 = Me, Et, Pr, Bu, allyl

6. APPLICATIONS OF THIENOPYRIMIDINES

Thienopyrimidines are interesting heterocyclic compounds and a number of derivatives of these compounds display therapeutic activity as antimicrobial [141-144], antiviral [145,146], anti-inflammatory [147,148], antidiabetic [149], antioxidant [150], antitumor [151-155] and anticancer agents [155,156]. Despite the breadth of biological activities displayed by these agents, the antibacterial activity of this class of compounds has been underexplored.

Moreover, thieno[2,3-*d*]pyrimidines have fascinated importance in medicinal chemistry, exhibiting pharma-cological and therapeutic properties such as antidepressant [158], antiplatelet [159], antihypertensive [160], herbicidal [161] and plant growth regulatory properties [162].

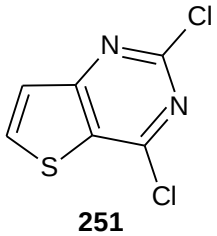
The compounds having thieno[2,3-*d*]pyrimidines in combination with 1,3,4-oxadiazoles exhibited greater antioxidant activity. 4-Substitutedaminothieno[2,3-*d*] pyrimidines **250a-d** showed excellent, almost equivalent to that of standards, where the presence of electron donating substituent on both sides of thienopyrimidine ring enhances the activity and electron withdrawing groups decrease [82].



250a-d

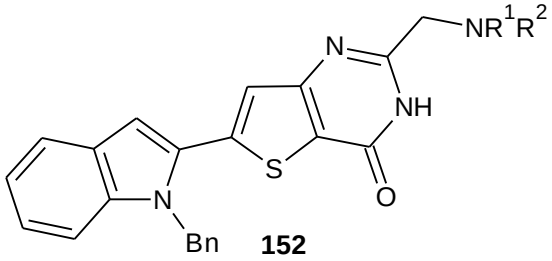
a, R = 2,4-di-F, R` = 4-Cl; **b**, R = 2,4-diF, R` = H;
c, R = 4-F, R` = H; **d**, R = 4-F, R`= 4-Cl

Also, 2,4-dichlorothieno[3,2-*d*]pyrimidine (**251**) is one of the intermediates for synthesizing anticancer medicines [163].



251

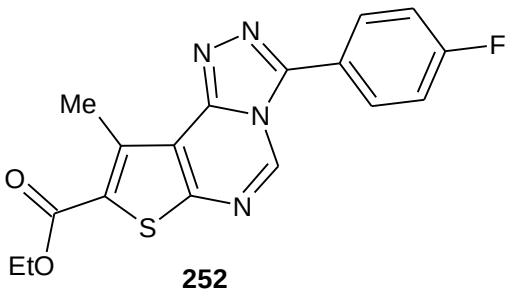
Moreover, biological assays on endothelial cell tube formation proved thieno[2,3-*d*]pyrimidine derivative **152** as a new anti-angiogenic lead compound that showed to be more efficient in inhibiting endothelial cell tube formation induced by VEGF (vascular endothelial growth factor) and compound **152** did not cause any cytotoxic side effect to endothelial cells [99].



152

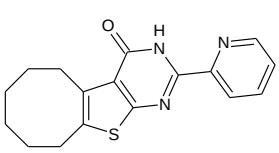
R^1R^2 = piperdinyl

The antibacterial activity of thieno[2,3-*d*]pyrimidine derivative **252** was comparable with that of ampicillin against *B. subtilis*. Also, the antifungal activity of compound **252** was about half that of fluconazole against *C. albicans* [164].

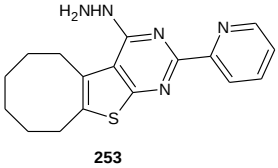


252

Moreover, thieno[2,3-*d*]pyrimidines **143a** and **253** showed potent anticancer activity at low concenrations against most of the used human tumor cell lines when compared to doxorubicin as potent anticancer drug [95].

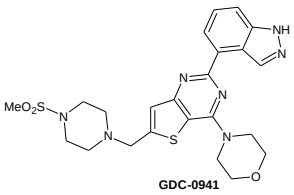


143a

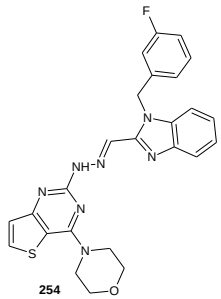


253

Thienopyrimidine derivative **254** showed higher cytotoxic activities against H460 (human lung cancer), HT-29 (human colon cancer) and MDA-MB-231 (human breast cancer) cell lines which were 3.8, 1.7 and 66.5 times active than GDC-0941 (2-(1*H*-Indazol-4-yl)-6-((4-(methyl-sulfonyl)-1-piperazinyl)methyl)-4-(4-morpholinyl)thieno [3,2-*d*]pyrimidine), respectively [70].



GDC-0941



254

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Synthesis of novel bioactive derivatives of 3-(4-chlorophenyl)-2-hydrazino-5,6,7,8-tetrahydrobenzo(*b*)thieno [2,3-*d*]pyrimidine-4(3*H*)-ones. Eur. *J. Med. Chem.* **44**, 4721 (2009).

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