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Chemistry of 2-aminothiophene-3-carboxamide and related compounds

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This review describes the synthesis and reactions of 2-aminothiophene-3-carboxamides as building blocks for the syntheses of polyfunctionalized heterocyclic compounds.

Key Words: 2-Aminothiophene-3-carboxamides, syntheses, reactivity, reactions, heterocycles

Introduction

Substituted 2-aminothiophene-3-carboxamides are versatile building blocks for the synthesis of agrochemicals, dyes, and pharmacologically active compounds.[1−3] Several methods were reported in the literature for the preparation of these materials.[4−31] The most convergent and well-established classical approach for the preparation of 2-aminothiophenes is Gewald's method.[32] Our review deals with the effective use of 2-aminothiophene-3-carboxamides in the synthesis of different polyfunctional heterocyclic compounds. A review including the interesting biological and medicinal activities of substituted 2-aminothiophenes was published recently by Puterová et al.[33]

Synthesis

Gewald devised the most facile and promising set of synthetic routes leading to 2-aminothiophene with a carboxamide group in position 3 and alkyl, aryl, cycloalkyl, and hetaryl groups in positions 4 and 5. Three

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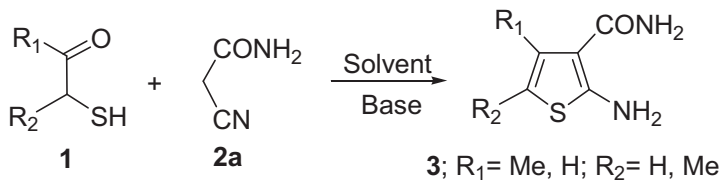
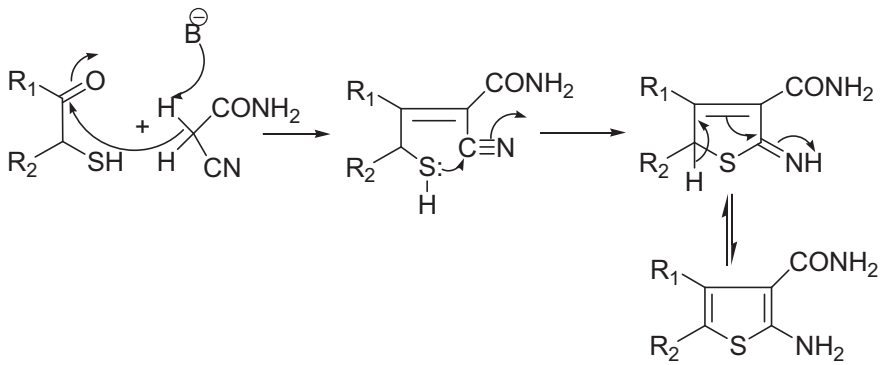
major variations of this reaction have been described in detail. The first version[34–48] consists of a single step, by treatment of α-mercaptoaldehyde or an α-mercaptoketone with cyanoacetamide **2a** in a solvent such as ethanol, dimethylformamide (DMF), dioxane, or water, in the presence of a basic catalyst such as triethylamine (TEA) or piperidine at 50 °C.

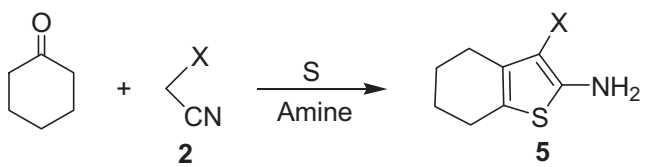


$\alpha-$Mercaptoaldehyde or α-mercaptoketone is often generated in situ by the reaction of alkali sulfides with the corresponding α-halocarbonyl compounds. This version has a few drawbacks; the starting compounds are unstable and difficult to prepare. The mechanism of this reaction is as follows in Scheme 1.[34–48]



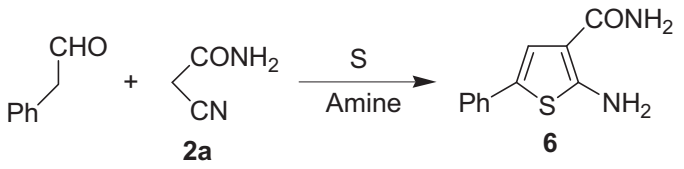
Scheme 1.

The second version of the Gewald reaction[32,38–43] consists of a one-pot procedure that is very extensively used for this synthesis. The convenient technique includes the condensation of ketones with cyanoacetamide or N-substituted derivatives **2** and a sulfur element in a solvent such as ethanol, DMF, or dioxane in the presence of amine as dimethylamine, morpholine, or TEA at room temperature.

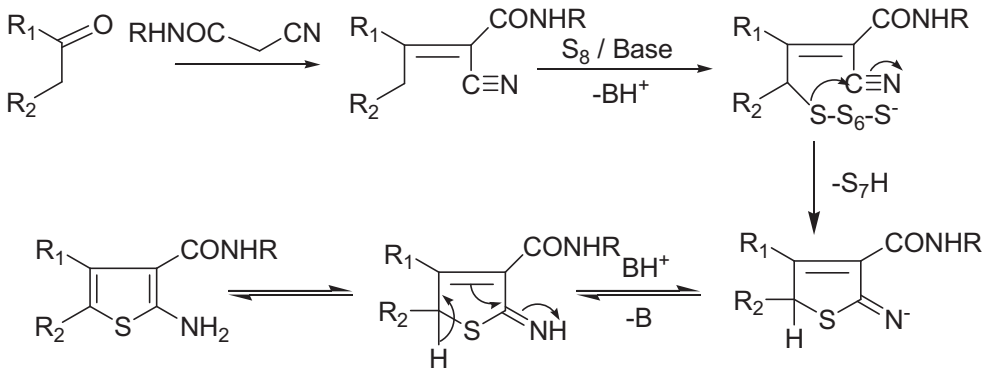


2, **5a**, X= $CONH_2$; **b**, X= $CONHCH_3$; **c**, X= $CONHC_2H_5$;
d, X= $CONHC_6H_5$; **e**, X= $CSNH_2$; **f**, X= $CONHNH_2$

Aldehydes such as phenylacetaldehyde were used instead of ketones in the above reaction to give 2-amino-5-phenylthiophene-3-carboxamide (**6**).[32]

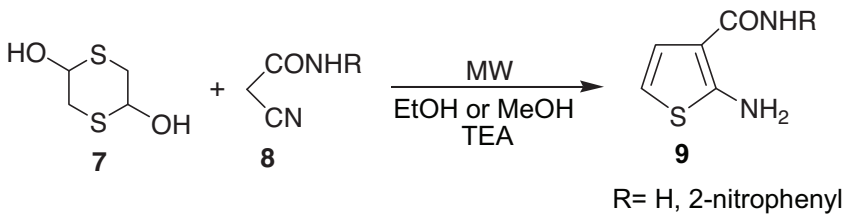


The mechanism of this reaction is as follows in Scheme 2.[32,38–43]

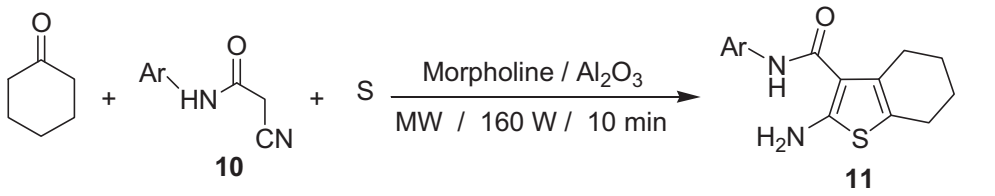


Scheme 2.

Microwave irradiation (MW) has become an important method in organic synthesis and could be applied to a wide range of reactions within short times and with high yields. The microwave irradiation of 1,4-dithiane-2,5-diol(thioacetaldehyde dimmer) (**7**) with cyanoacetamide or 2-cyano-N-(2-nitrophenyl)acetamide (**8**) in boiling ethanol or methanol containing a catalytic amount of TEA furnished corresponding 2-aminothiophene-3-carboxamide derivative **9**.[49,50]

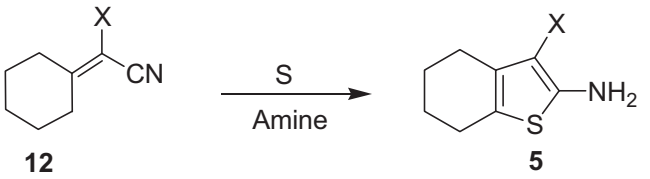


Furthermore, a new synthesis of substituted-2-aminothiophene-3-carboxamide **11** was achieved via a 1-pot MW-assisted Gewald reaction using aluminum oxide as a solid support in the presence of morpholine as a basic catalyst and under solvent-free conditions for several minutes.[51]



10, **11a**, Ar= C_6H_4-4-OMe; **b**, Ar= C_6H_4-4-Me;
c, Ar =C_6H_4-3-Cl-4-F ; **d**, Ar= C_6H_4-4-CF_3

α,β-Unsaturated nitrile **12** was prepared by a Knoevenagel-Cope condensation followed by treatment with sulfur and amine,[34,38,42,52–63] and this method gave high yields. Alkyl and aryl ketone do not yield thiophenes in the 1-step modification, but gave acceptable yields in the 2-step techniques.

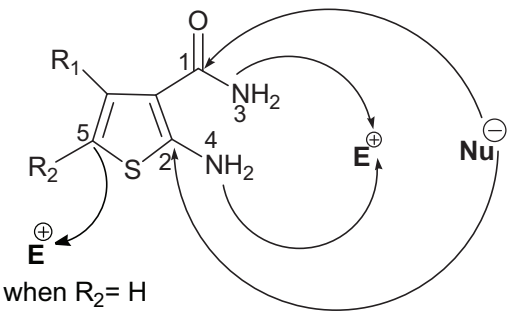


12 **5**

5, **12a**, X= $CONH_2$; **b**, X= $CONHC_6H_4$-3-CF_3; **c**, X=$CONHC_6H_4$-3-OCH_3;
d, X= $CONHC_6H_4$-4-Cl; **e**, X=$CONHC_6H_4$-4-Br; **f**, X= $CONHC_6H_4$-4-I;
g, X= $CONHC_6H_4$-4-CF_3; **h**, X= 4-antipyrinyl

Reactivity

2-Aminothiophene-3-carboxamide derivatives could be treated with various reagents, such that the attack can take place at 5 possible positions. The nucleophiles are able to attack the carbon atom of the carbonyl group at position 1 and carbon 2 at position 2, while the electrophiles attack the amino group of the carboxamido at position 3, the amino group at position 4, and carbon atom 5 at position 5.



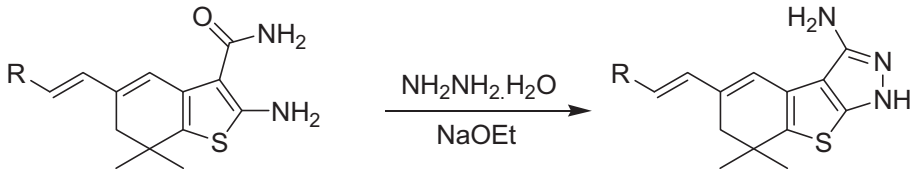
Reactions

The reactions of 2-aminothiophene-3-carboxamide with numerous reagents are classified separately in a single category due to the huge number of references. We have arranged this large volume of data in terms of the type of heterocyclic, starting with 5- and 6-membered rings in order to increase the number of hetero atoms. Such systematic treatment provided a clear idea about the synthetic possibilities of the methods and may be useful in selecting the direction of further research.

Formation of 5-membered rings with 2 hetero atoms

Formation of thieno[2,3-d]pyrazolo derivatives

Pyrazolo derivatives **14** were prepared by the reaction of 2-aminothiophene-3-carboxamides **13** with hydrazine hydrate in sodium ethoxide.[64]



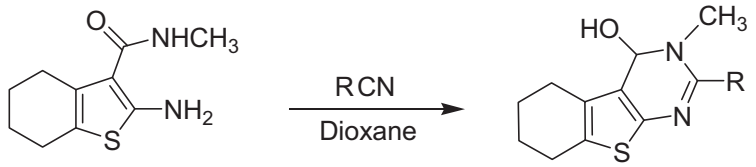
13 **14**

13, **14a**, R= C_6H_5; **b**, R= C_6H_4-2-Cl; **c**, R= C_6H_3-3,4-Cl_2; **d**, R= C_6H_4-4-OCH_3;
e, R= C_6H_2-3,4,5-$(OCH_3)_3$; **f**, R= C_6H_3-3-OCH_3,4-OH; **g**, R= C_6H_4-4-NO_2;
h, R= C_6H_3-4-Cl; **i**, R= C_6H_4-2-OCH_3

Formation of 6-membered rings with 2 hetero atoms

Synthesis of thieno[2,3-d]pyrimidine derivatives

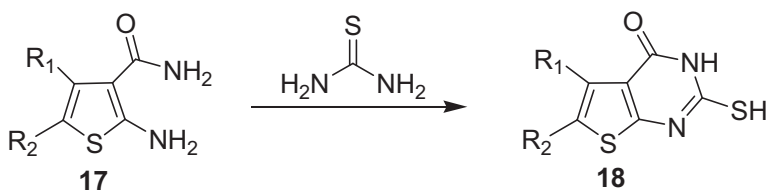
Dave et al.[65] reported that the reaction of 2-aminothiophene-3-carboxamide derivatives **15** with nitriles in dioxane in the presence of hydrochloric acid yielded corresponding pyrimidine derivatives **16**.



15 **16**

16a, R= Me; **b**, R= Ph; **c**, R= CH_2CO_2Et; **d**, R= CH_2Ph;
e, R= CH_2CH_2Cl; **f**, R= CH:CHPh; **g**, R= C_6H_4-4-Cl;
h, R= pyridyl

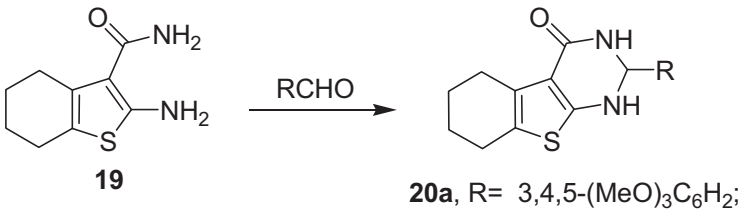
2-Mercaptothieno[2,3-d]pyrimidin-4-(3H)-one derivatives **18** were prepared by the cyclocondensation of 2-aminothiophene-3-carboxamides **17** with thiourea.[66]



17 **18**

17, **18a**, R_1= H, R_2= Me; **b**, R_1=R_2= Me

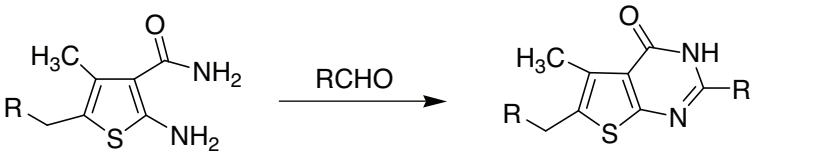
Thienopyrimidines **20** were obtained in yields of 58%-92% by the condensation of **19** with different aldehydes.[67]



19

20a, R= 3,4,5-$(MeO)_3C_6H_2$;
b, R= 4-MeO C_6H_4;
c, R= 2-Cl C_6H_4;
d, R= 3,4-$(MeO)_2C_6H_3$;
e, R= 4-MeC_6H_4

It was found that the reaction of 2-amino-4-methylthiophene-3-carboxamide (**21**) with aromatic aldehydes gave corresponding thienopyrimidine derivatives **22**.[67]

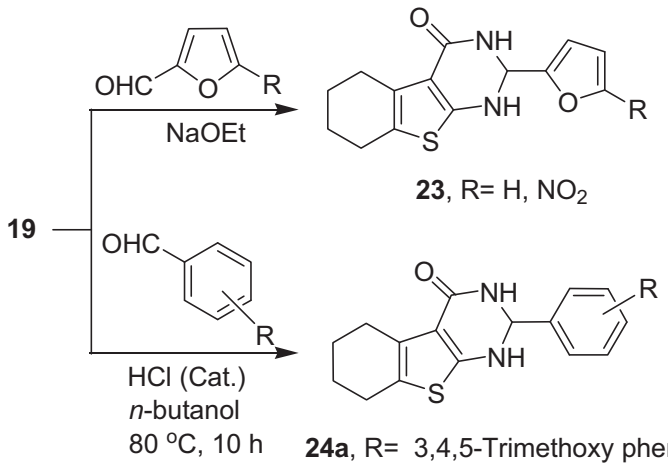


21

22a, R= Ph;
b, R= 3,4-$(MeO)_2C_6H_3$;
c, R= 3-pyridyl

In addition, the reaction of furfurals with **19** in sodium ethoxide furnished thieno[2,3-d]pyrimidin-4-ones **23**.[68] Similarly, some cyclocondensation products (**24**) were obtained from the reaction of different aromatic aldehydes with **19** in n-butanol in the presence of hydrochloric acid (Scheme 3).[69]

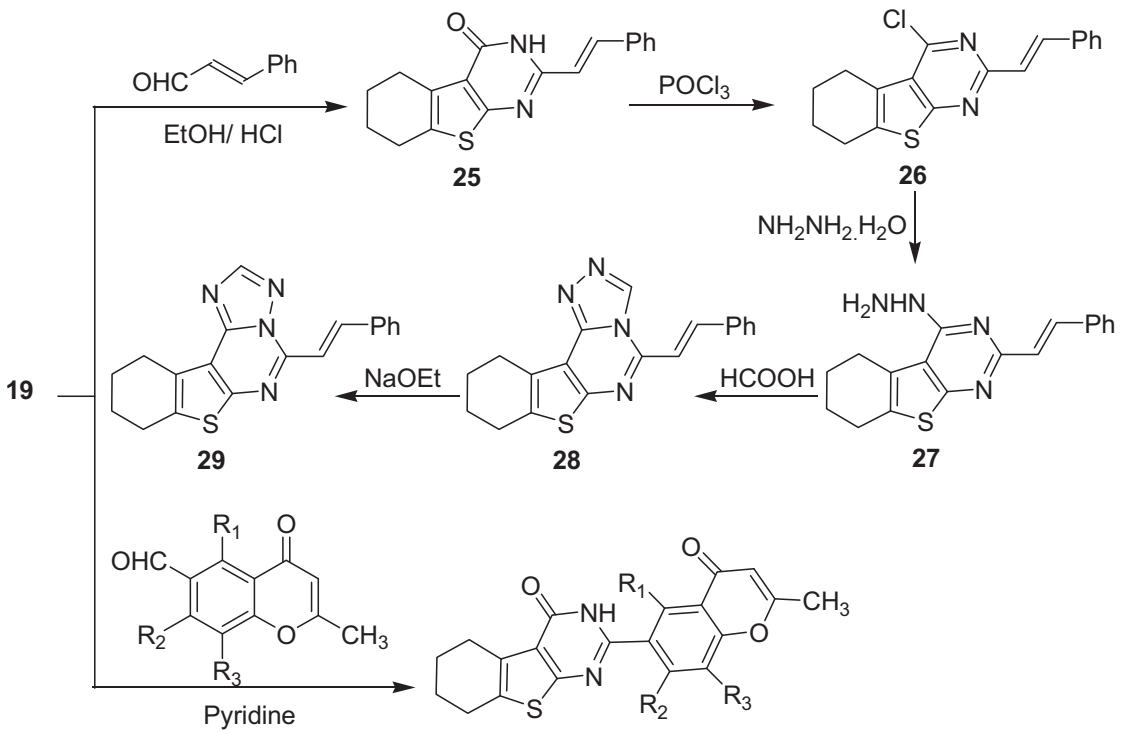
On the other hand, the reaction of cinnamaldehyde with **19** in ethanol in the presence of dry hydrogen chloride gas afforded corresponding 2-stryl-thienopyrimidine **25**.[70] Treatment of **25** with phosphorus oxychloride yielded **26**, which, upon reaction with hydrazine hydrate, gave 4-hydrazino-2-styryl-thieno[2,3-d]pyrimidine derivative **27**. Triazolopyrimidine **28** could be obtained through the cyclization of **27** with formic acid. Triazolopyrimidine derivative **28** was converted into its isomeric structure (**29**) upon refluxing in a sodium ethoxide/ethanol mixture. Furthermore, it was reported recently that the reaction of compound **19** with 6-carboxaldehyde chromenes in boiling pyridine furnished corresponding pyrimidines **30** (Scheme 4).[71]



23, R= H, NO_2

24a, R= 3,4,5-Trimethoxy phenyl;
b, R= 4-Hydroxy-naphthalen-1-y;
c, R= 2-Bromo-3,4-dimethoxy phenyl;
d, R= 3-Acetyloxy phenyl;
e, R= 3-Chloro-4-hydroxy-5-methoxy phenyl

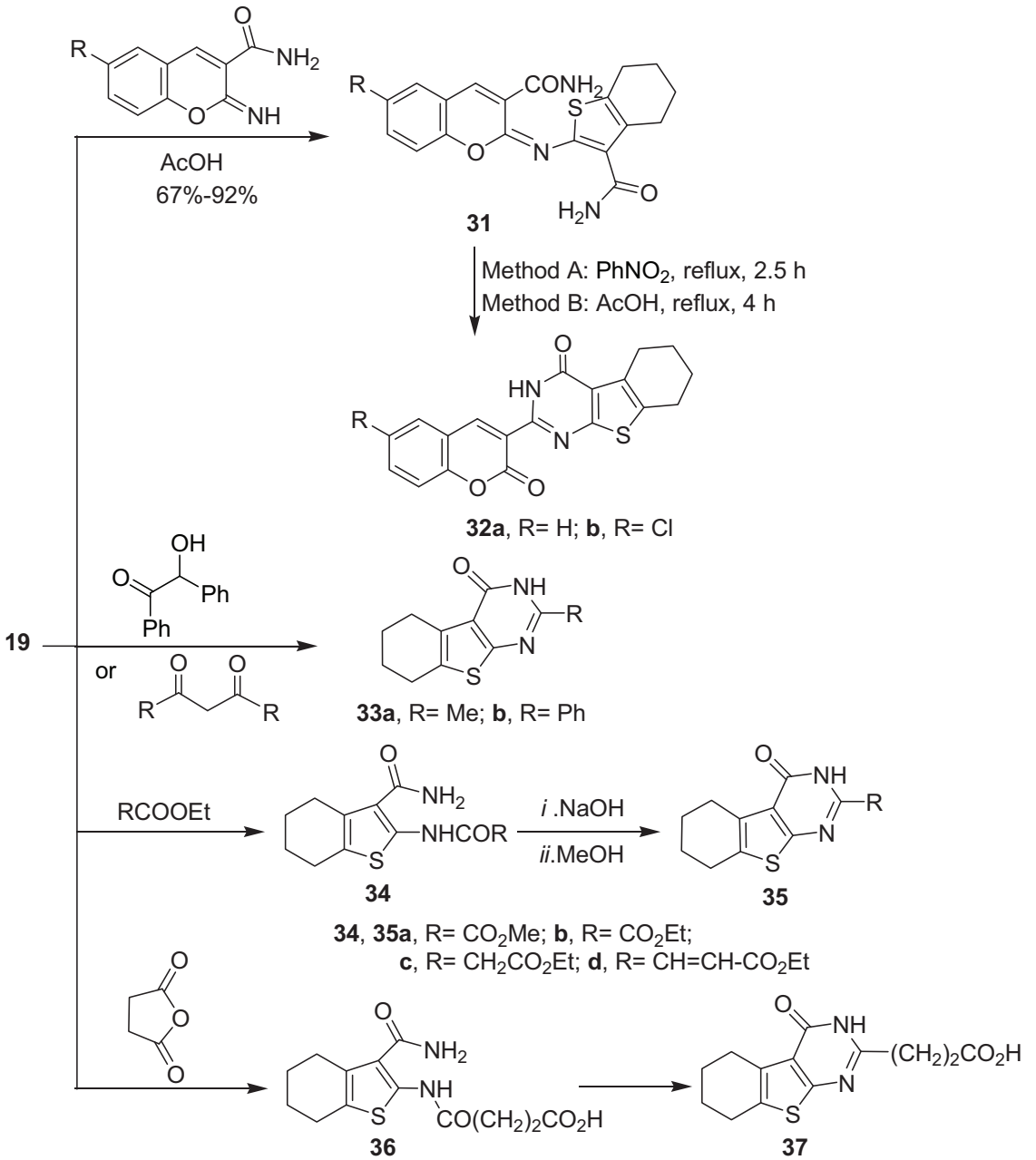
Scheme 3.



30a, R_1= OCH_3, R_2= OH, R_3= H;
b, R_1= R_2= OCH_3, R_3= H;
c, R_1= R_2= OH, R_3= Br;
d, R_1= OCH_3, R_2= OH, R_3= NO_2

Scheme 4.

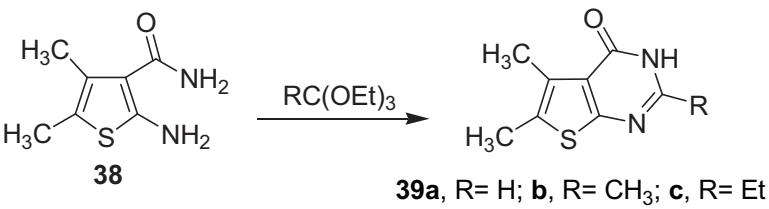
Maksym et al.[72] introduced a novel method for the synthesis of compounds containing thiophene, pyrimidine, and coumarin ring systems. Thus, the reaction of **19** with 2-imino-2H-1-benzopyran-3-carboxamides in glacial acetic acid (AcOH) yielded **31**, which, upon refluxing in appropriate solvents, gave thieno[2,3-d]pyrimidin-4-ones **32a** and **32b**. The cyclocondensation of **19** with acetyl acetone or 2-hydroxy-1,2-diphenylethanone in ethanol containing hydrochloric acid yielded corresponding thieno[2,3-d]pyrimidin-4-ones **33a** and **33b**.[73,74]



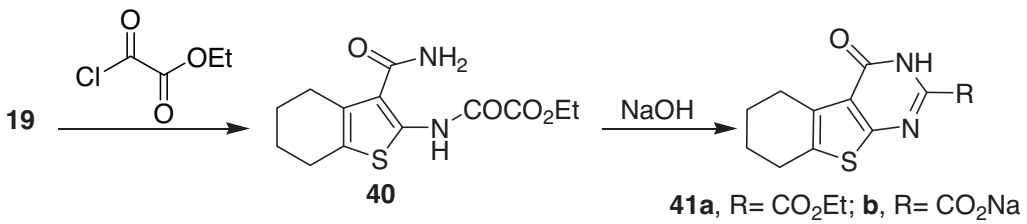
Scheme 5.

The refluxing of **19** with a variety of diesters for 1.5-2 h gave **34a-34d**, which cyclized and esterified with the use of sodium hydroxide to form thienopyrimidines **35a-35d**.[75,76] Similarly, the heating of **19** and succinic anhydride gave 4-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylamino)-4-oxobutanoic acid (**36**), which cyclized in a basic medium to give corresponding thienopyrimidine derivative **37** (Scheme 5).[77]

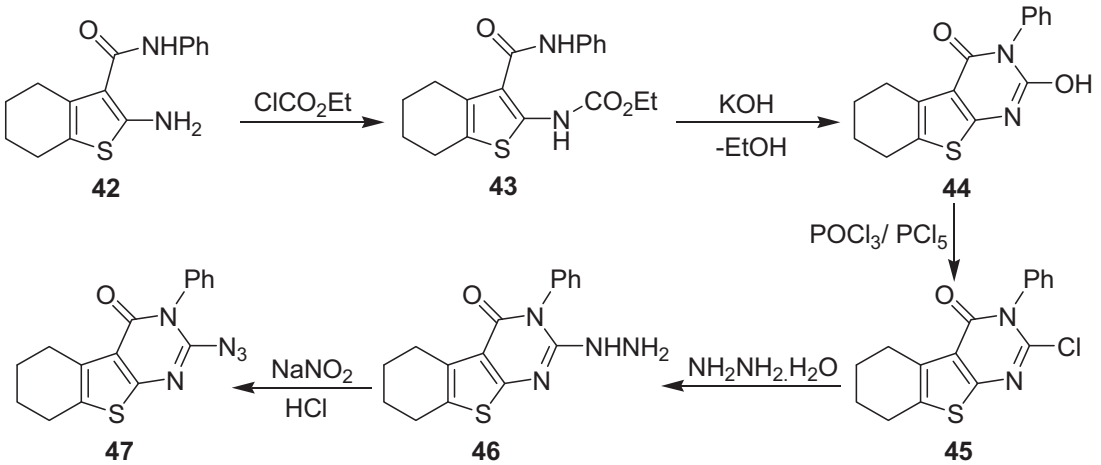
The treatment of **38** with different orthoesters in ethanol containing a catalytic amount of tungstophosphoric acid gave corresponding thienopyrimidinone derivatives **39a-39c**.[78]



Compound **40** was obtained by reacting **19** with ethyl 2-chloro-2-oxoacetate, which cyclized in sodium hydroxide to give corresponding thienopyrimidines **41a** and **41b** (Scheme 6).[79–81]



Scheme 6.

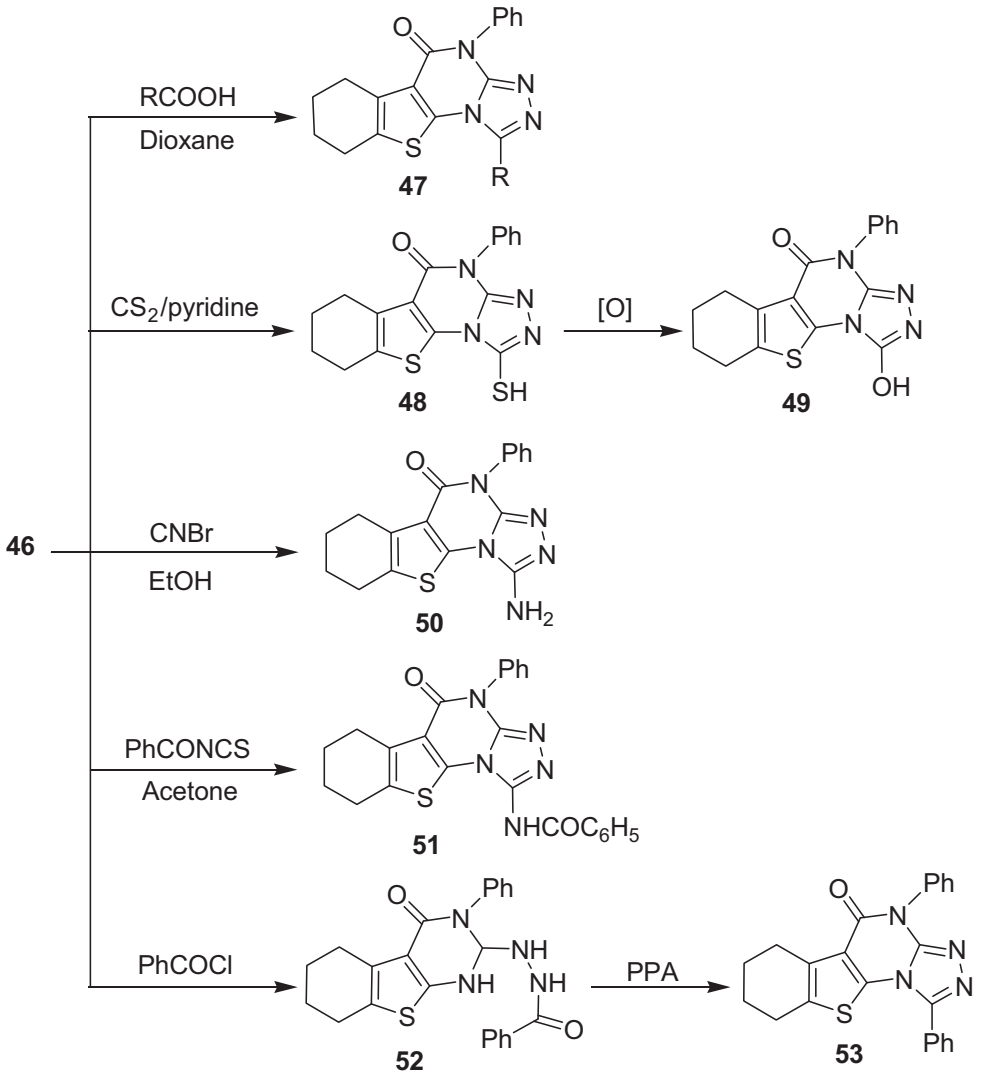


Scheme 7.

In addition, compound **42**, upon treatment with ethyl chloroformate in pyridine, gave **43**, which cyclized with potassium hydroxide to yield thienopyrimidinone derivative **44**. Treatment of **44** with a mixture of phosphorus oxychloride ($POCl_3$) and phosphorus pentachloride (PCl_5) gave **45**. Nucleophilic displacement

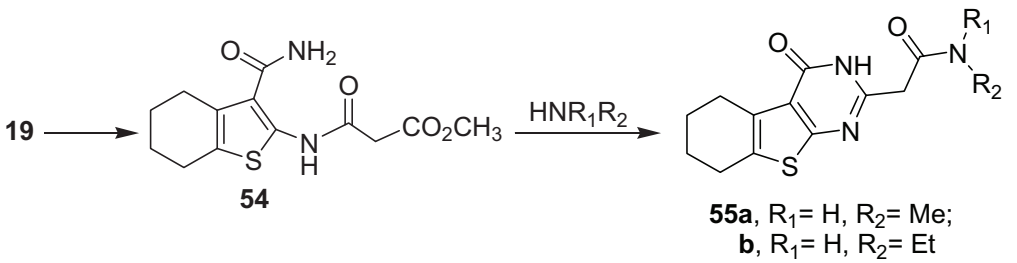
of the chlorine atom in compound **45** with hydrazine hydrate gave 2-hydrazino-thienopyrimidin-4-one (**46**). Diazotization of **46** with sodium nitrite solution and 50% concentrated hydrochloric acid at 0-5 °C afforded 2-azido-thienopyrimidin-4-one derivative **47** (Scheme 7).[82]

Various approaches have been used to synthesize the condensed triazolopyrimidines, involving cyclization of 2-hydrazino derivatives **46** with a variety of single-carbon donors. The reaction of **46** with aromatic acids in dioxane/$POCl_3$, CS_2/pyridine, CNBr/EtOH, benzoyl isothiocyanate in acetone, or benzoyl chloride followed by polyphosphoric acid gave the corresponding triazolopyrimidine derivatives **47-51** and **53**, respectively (Scheme 8).[82]



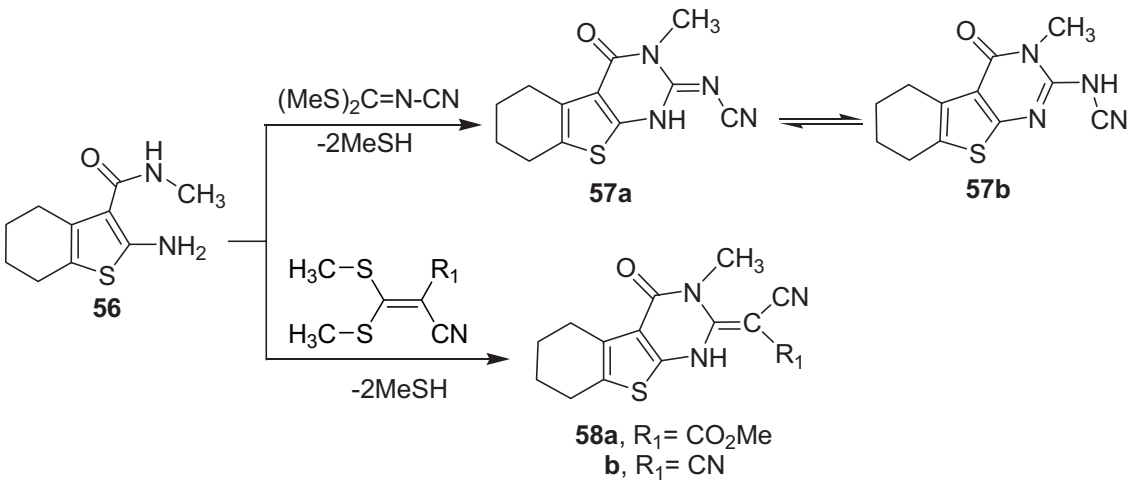
Scheme 8.

Compound **54** was obtained by the reaction of **19** with methyl chloroacetate in a basic medium. Cyclization of **54** was accomplished by reaction with different amines to give thienopyrimidines **55** (Scheme 9).[83]



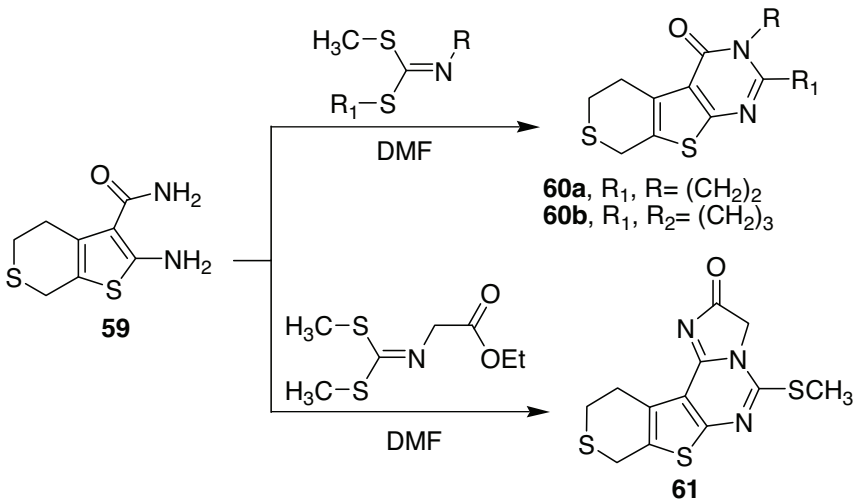
Scheme 9.

It was reported that treatment of **56** with bis-methylthiomethylene compounds in DMF gave thieno[2,3-d]pyrimidin-2-ylidenes **57a** and **57b** and **58a** and **58b** (Scheme 10).[84]



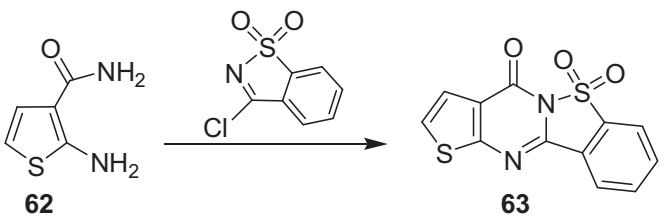
Scheme 10.

Furthermore, new heteroannulation reactions of 2-amino-5,7-dihydro-4H-thieno[2,3-c]thiopyran-3-carboxamid (**59**) with ethyl 2-(bis(methylthio)methyleneamino)acetate and its related reagents led to the formation of thiopyrano and imidazopyrimidine derivatives **60** and **61**, respectively, as a 1-pot reaction (Scheme 11).[85]

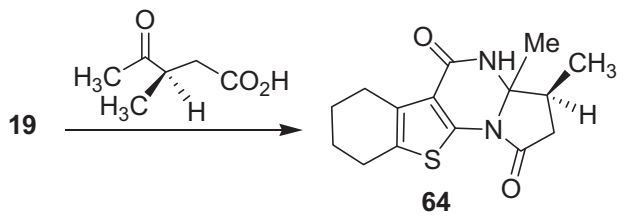


Scheme 11.

Thienopyrimidinebenzoisothiazole **63** was obtained by treating 2-aminothiophene-3-carboxamide **62** with pseudosaccharin chloride.[86]



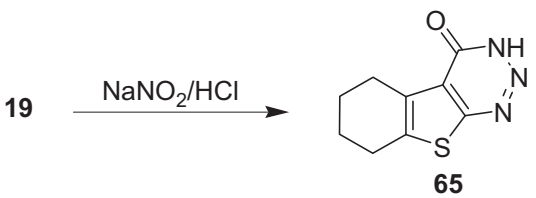
Compound **19** was refluxed with levulinic acid in a high-boiling solvent to give thienopyrimidine derivative **64**.[87]



Formation of 6-membered ring with 3 hetero atoms

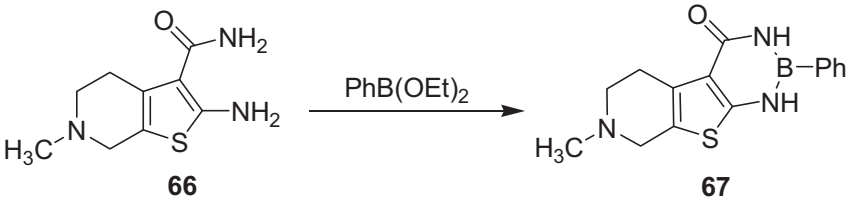
Formation of thieno[2,3-d]-1,2,3-triazine derivatives

Thienotriazine **65** was prepared by diazotization followed by the cyclization of compound **19**.[88]



Formation of thieno[2,3-d]-1,3-diaza-2-borin pyrimidin-4-one derivatives

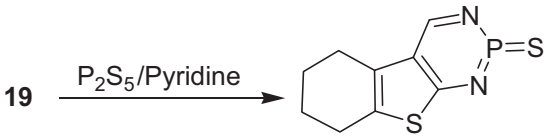
It was reported that 2-aminothiophene-3-carboxamides **66** were cyclized with phenylboronic esters to give **67**.[89]



66 **67**

Formation of thieno[2,3-d]-1,2,3-diazaphosphino-2-thione pyrimidine

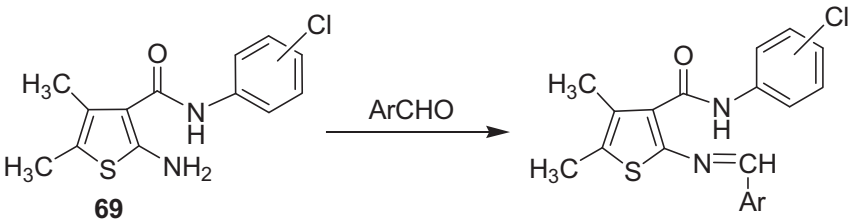
Treatment of **19** with phosphorous pentasulfide in pyridine yielded diazaphosphinane derivative **68**.[90]



68

Miscellaneous reactions

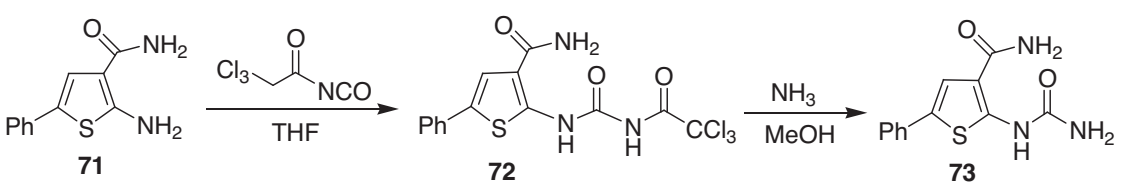
Condensation of 2-aminothiophene-3-carboxamide **69** with different aromatic aldehydes afforded corresponding Schiff bases **70**.[91]



69 **70**

Ar= 2-Cl-C_6H_4, 4-Cl-C_6H_4, 2-OH-C_6H_4, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-$N(CH_3)_2$-C_6H_4, 3,4-$(MeO)_2$-C_6H_3, 3,4,5$(MeO)_3$-C_6H_2

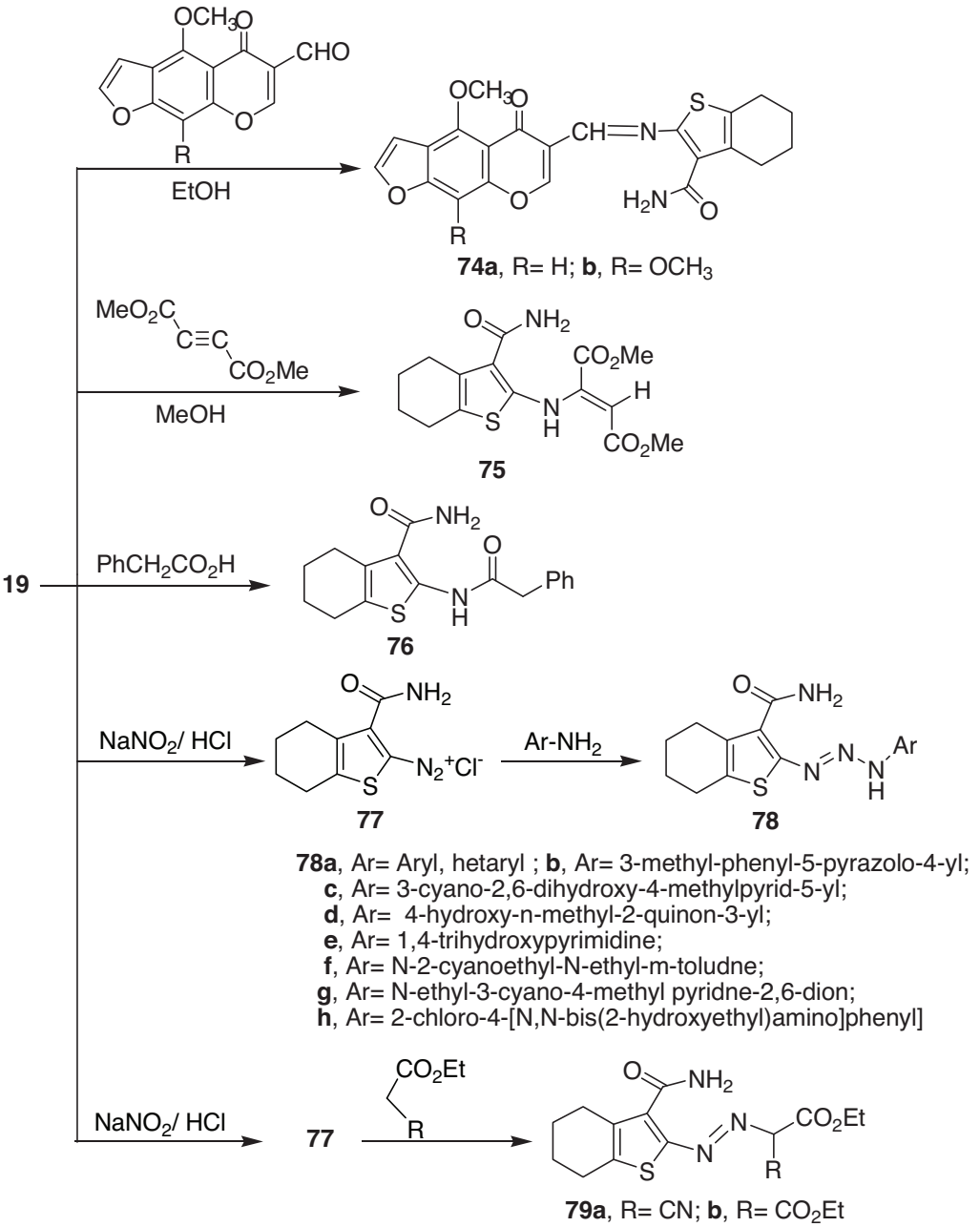
2-Ureidothiophene-3-carboxamide derivative **73** was synthesized by the addition reaction of **71** with an isocyanate derivative in tetrahydrofuran (THF) followed by treatment of the formed trichloroacetamide (**72**) with ammonia in methanol (Scheme 12).[92]



71 **72** **73**

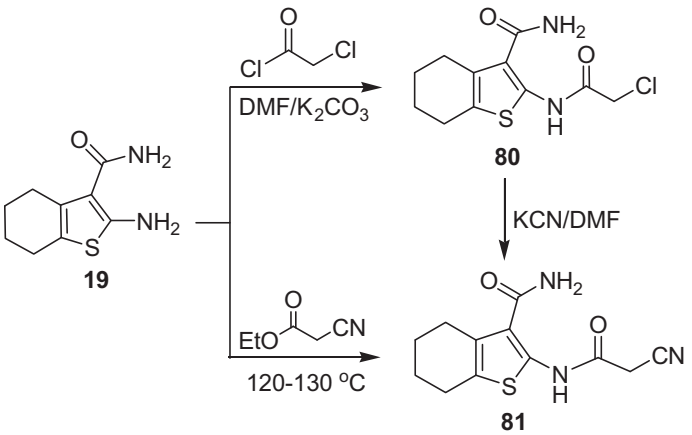
Scheme 12.

The reaction of **19** with furo[3,2-g]chromene-6-carbaldehydes in boiling ethanol gave Schiff bases **74**.[71] The Michael addition of **19** to dimethyl acetylenedicarboxylate led to the formation of N-vinylated product **75**.[93] Amidation of **19** with phenyl acetic acid yielded 2-(2-phenylacetylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (**76**).[94] Diazotization of **19** gave diazonium salts **77**, which were coupled with different aromatic amines to afford diazo compounds **78** as a disperse dye.[95] Benzothiophene-2-yl-hydrazonoesters **79** were also obtained by the coupling of diazonium salt **77** with ethyl cyanoacetate or diethyl malonate (Scheme 13).[96]



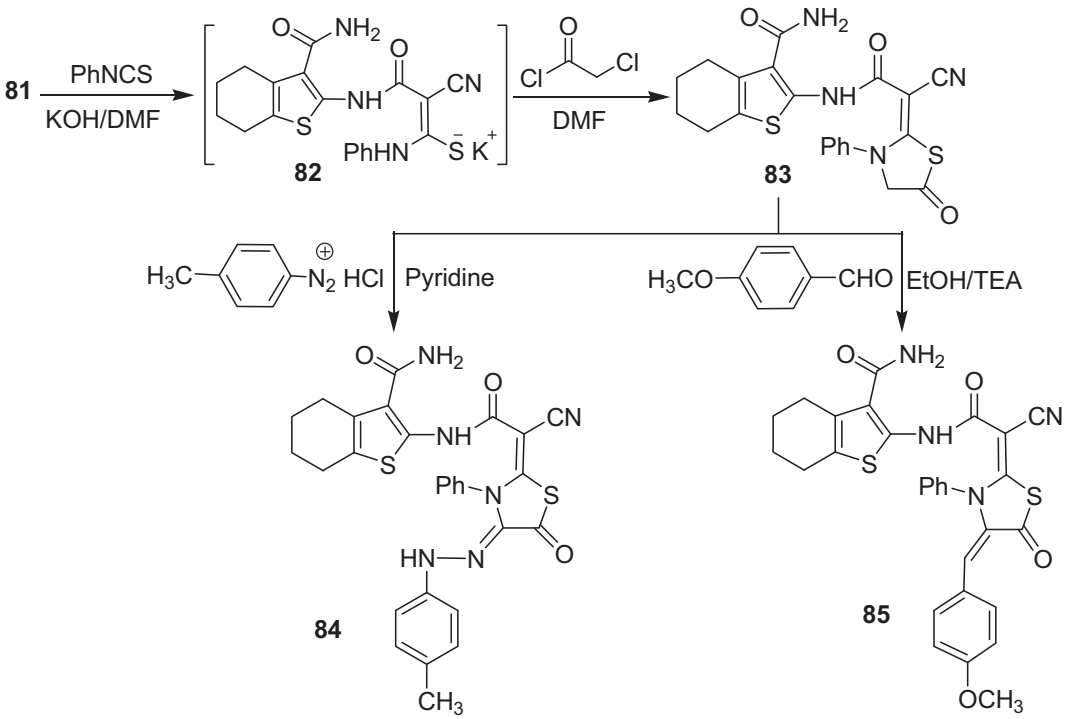
Scheme 13.

Chloroacetylation of **19** with chloroacetyl chloride in dry DMF catalyzed by anhydrous potassium carbonate at 0 °C yielded chloroacetamido derivative **80**.[83] 2-(2-Cyanoacetylamino)thiophene **81** was obtained by the reaction of **80** with potassium cyanide in DMF at 70 °C. Compound **81** was also obtained by another synthetic route with high yield and purity, via the fusion of **19** with ethyl cyanoacetate at 120-130 °C (Scheme 14).[97]



Scheme 14.

The base-catalyzed reaction of **81** with phenyl isothiocyanate yielded (nonisolable) thiocarbamoyl intermediate **82**,[98] which was cyclized with chloroacetyl chloride in dry DMF to give **83**.[97] The diazo-coupling of

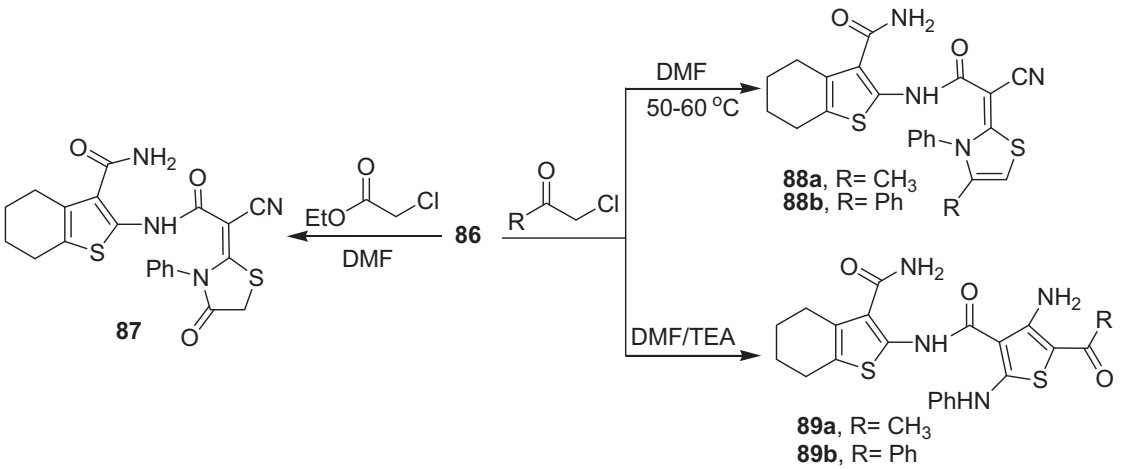


Scheme 15.

83 with p-tolyldiazonium chloride in pyridine afforded **84**.[97] The refluxing of **83** with p-anisaldehyde in DMF catalyzed by TEA gave **85** (Scheme 15).[97]

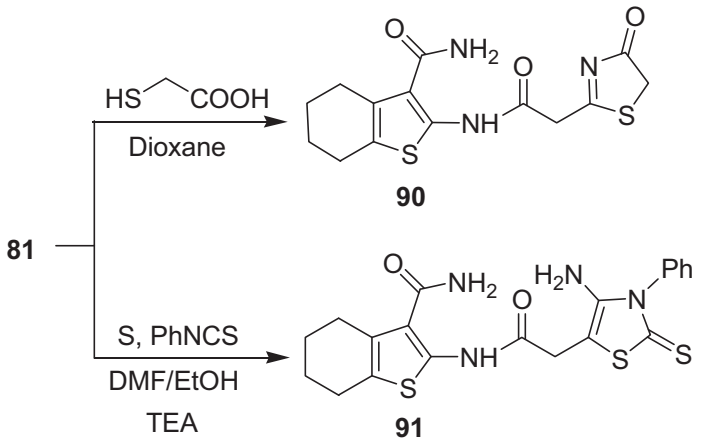
Acidification of potassium salt **82** with dilute hydrochloric acid yielded corresponding thioamide derivative **86**.[98]

Compound **86** underwent cyclization when treated with equimolecular amounts of α-halo compounds, namely chloroacetone, phenacyl chloride, or ethyl chloroacetate in DMF, to afford thiazolidin-4-one **87** and thiazolylidine derivatives **88a** and **88b**, respectively. Compounds **87, 88a**, and **88b** were also obtained in a high yield by the reaction of **86** with α-halo compounds in a mixture of ethanol and DMF.[98] Refluxing of **83** with chloroacetone or phenacyl chloride in DMF catalyzed by TEA yielded thiophenes **89a** and **89b**, respectively (Scheme 16).[98]



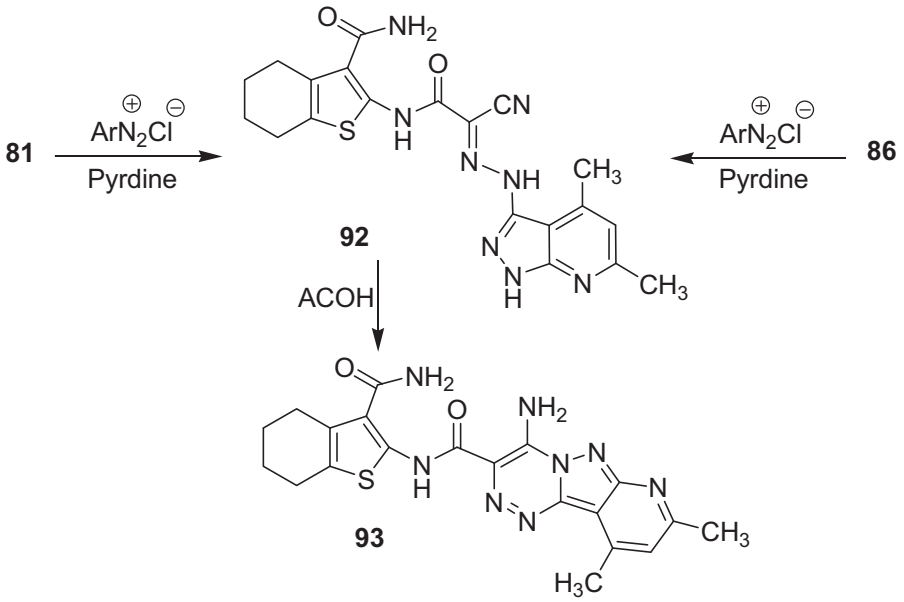
Scheme 16.

The reaction of **81** with thioglycolic acid gave corresponding 4-oxothiazolidinone derivative **90**. The stirring of **81** with sulfur and phenyl isothiocyanate in a mixture of DMF and ethanol containing TEA at 60 °C yielded 2-thioxothiazoline derivative **91** (Scheme 17).[98]



Scheme 17.

The diazo-coupling of **81** with the appropriate diazonium chlorides in pyridine afforded arylhydrazono derivative **92**. Hydrazono derivative **92** was also obtained by diazo-coupling of thiocarbonyl derivative **86** with the same diazonium chloride in pyridine.[97] The refluxing of **92** in AcOH gave corresponding cyclized triazine derivative **93** (Scheme 18).[97]



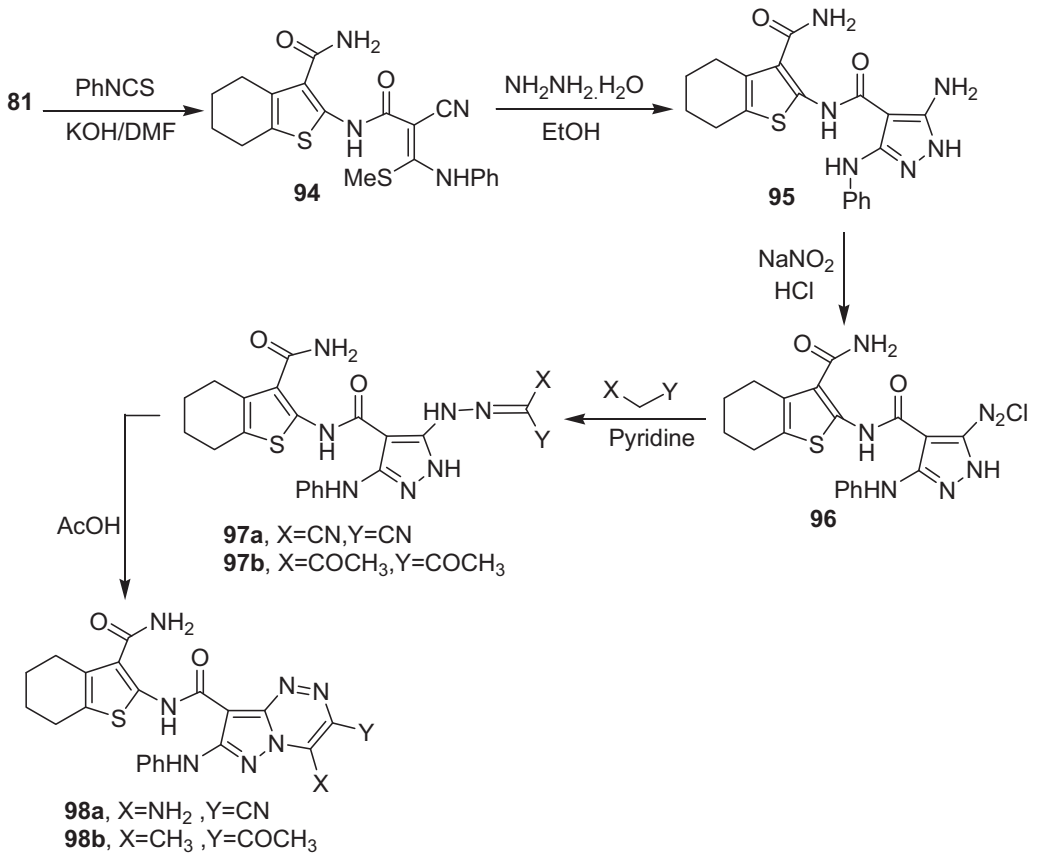
Scheme 18.

The treatment of **81** with phenyl isothiocyanate in DMF containing potassium hydroxide at room temperature followed by treatment with dimethylsulfoxide (DMSO) afforded corresponding ketene N,S-acetal derivative **94**.[97] 5-Amino pyrazole derivative **95** was achieved by the reaction of **94** with hydrazine hydrate in ethanol.[97] Diazotization of **95** with sodium nitrite and concentrated HCl gave corresponding diazonium chloride **96**, which, upon coupling with malononitrile or acetylacetone in pyridine, gave corresponding hydrazonopyrazolo derivatives **97a** and **97b**, respectively. The refluxing of **97a** and **97b** in AcOH gave target pyrazolotriazine derivatives **98a** and **99b**, respectively (Scheme 19).[97]

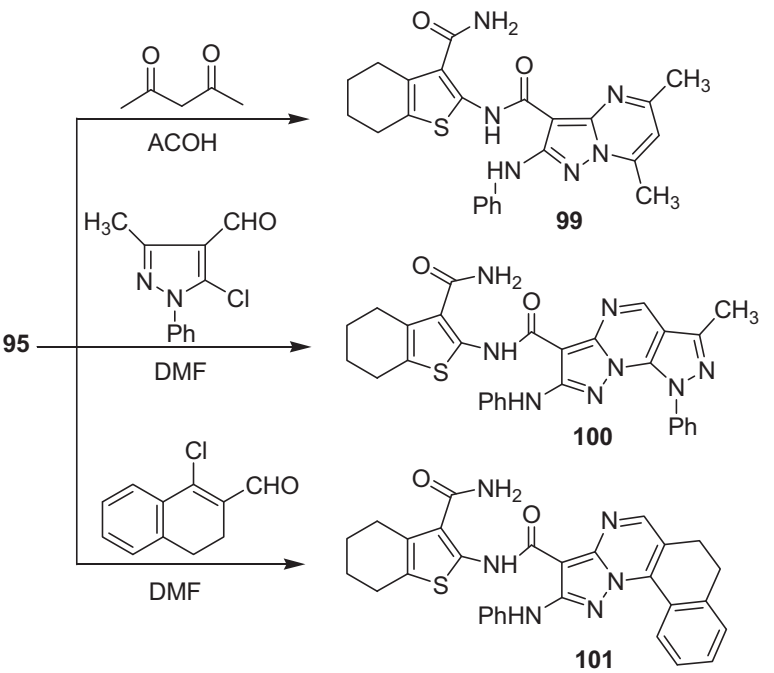
Cyclocondensation of **17** with acetyl acetone in boiling acetic acid afforded corresponding pyrazolo[1,5-a]pyrimidines **21**.[97] The reaction of **95** with 5-chloro-3-methyl-phenylpyrazolo-4-carboxaldehyde or 1-chloro-3,4-dihydro-naphthalene-2-carboxaldehyde in DMF gave pyrazolo[1,5-a]pyrimidines **100** and **101**, respectively (Scheme 20).[97]

The reaction of **95** with a Mannich base such as 1-phenyl-3-(pipridin-1-yl)propan-1-one hydrochloride in AcOH afforded pyrazolo[1,5-a]pyrimidine **102**.[97] Cyclocondensation of **95** with 2,5-hexadione in boiling acetic acid furnished corresponding pyrrole derivative **103** (Scheme 21).[97]

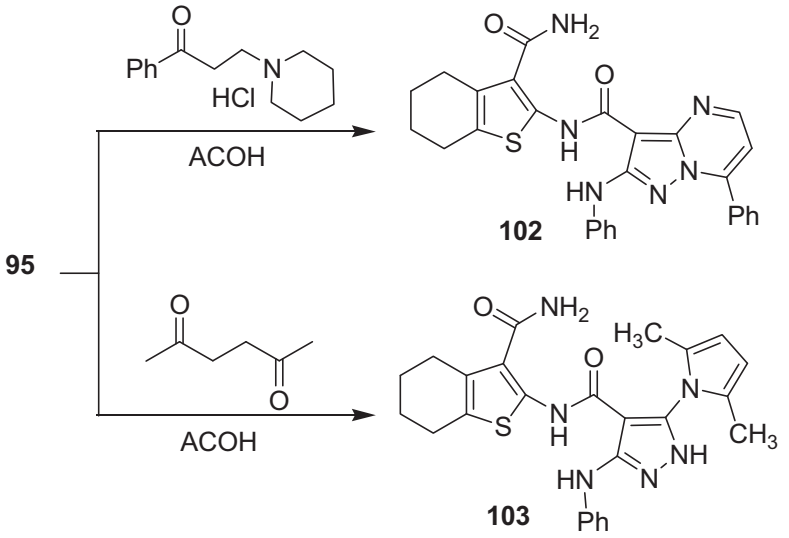
The reaction of **81** with dimethylformamide-dimethylacetal (DMF-DMA) in dry xylene afforded **104**, which could be transformed to pyrazole derivative **105** upon heating with hydrazine hydrate.[97] Cyclocondensation of **81** with 1-nitroso-β-naphthol and salicylaldehyde in boiling ethanol catalyzed by piperidine furnished naphto[2,3-b][1,4]oxazine **106** and 2-imino-2H-chromene **107**, respectively (Scheme 22).[97]



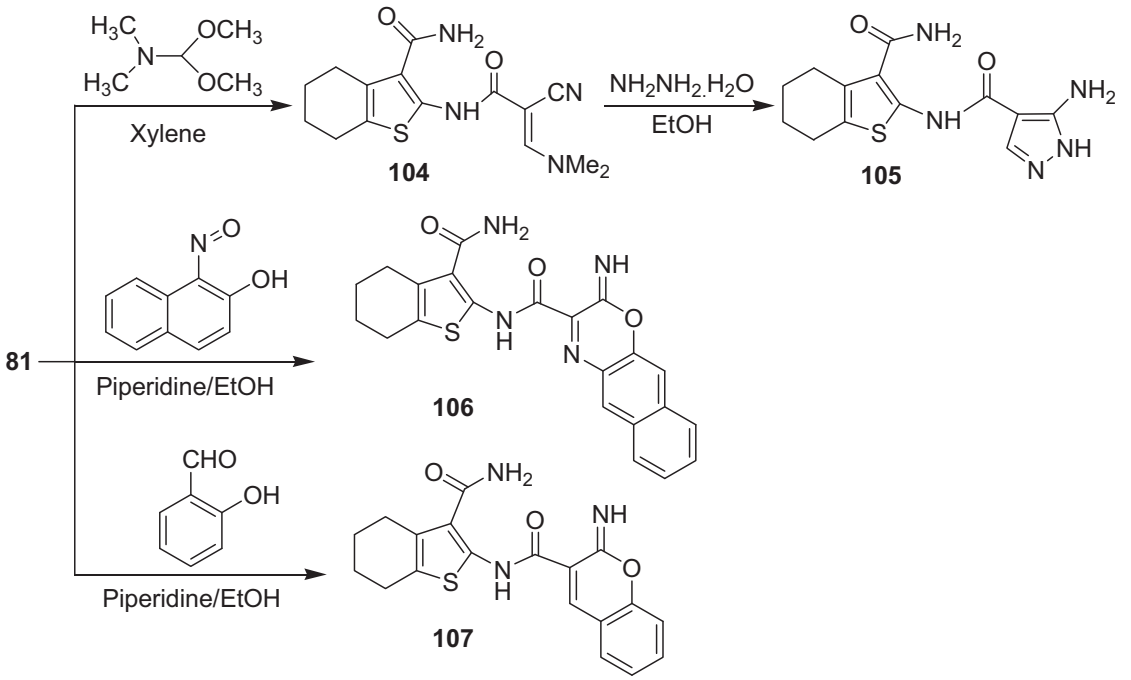
Scheme 19.



Scheme 20.

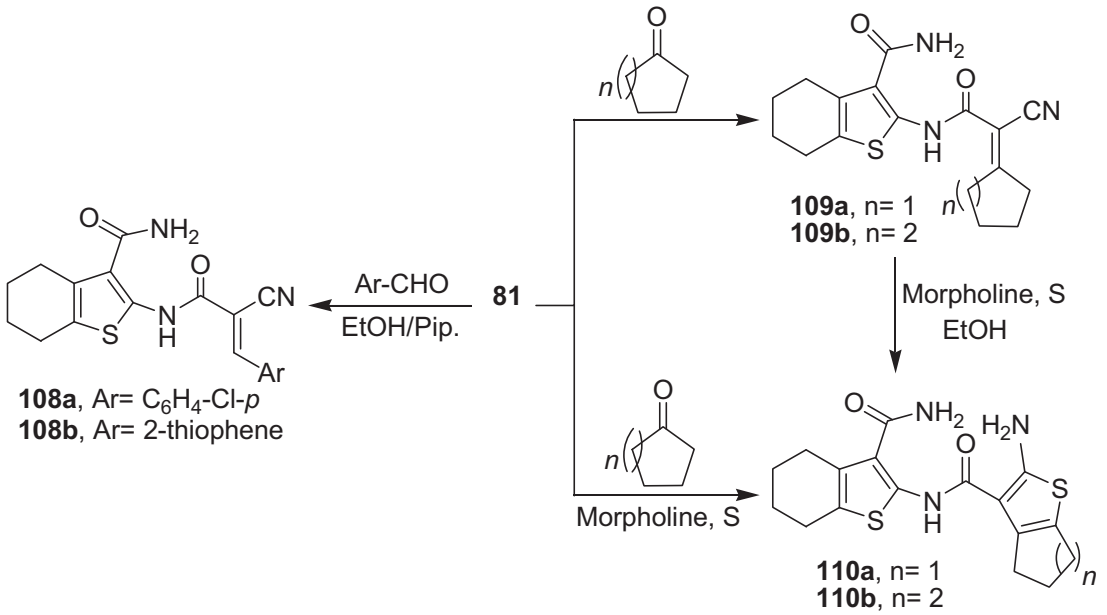


Scheme 21.



Scheme 22.

Condensation of **81** with different aromatic aldehydes in ethanol catalyzed by piperidine furnished arylidene derivatives **108a** and **108b**.[98] Similarly, condensation of **81** with different cyclic ketones such as cyclopentanone and cyclohexanone in ethanol containing sodium acetate furnished desired compounds **109a** and **109b**.[98] The reaction of **109a** or **109b** with elemental sulfur in ethanol catalyzed by morpholine yielded **110a** and **110b**, respectively. Compounds **110a** and **110b** were prepared by another method via a 1-pot Gewald's reaction of **81** with the same previous ketones and elemental sulfur in ethanol catalyzed by morpholine (Scheme 23).[98]



Scheme 23.

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References

1. Lütjens, H.; Zickgraf, A.; Figler, H.; Linden, J.; Olsson, R. A.; Scammells, P. J. *J. Med. Chem.* **2003**, *46*, 1870-1877.
2. Nikolakopoulos, G.; Figler, H.; Linden, J.; Scammells, P. J. *Bioorgan. Med. Chem.* **2006**, *14*, 2358-2365.
3. Pillai, A. D.; Rani, S.; Rathod, P. D.; Xavier, F. P.; Vasu, K. K.; Padh, H.; Sudarsanam, V. *Bioorgan. Med. Chem.* **2005**, *13*, 1275-1283.
4. Steinkopf, W. *Liebigs Ann. Chem.* **1914**, *403*, 17-44.
5. Pedersen, E. B.; Lawesson, S. O. *Tetrahedron* **1974**, *30*, 875-878.
6. Hartman, S.; Sullivan, F. F. (U.S. Plywood-Champion Paper, Inc.) U.S. 1969, 3,424,270; *Chem. Abstr.* **1969**, *70*, 69118g.
7. Hartmann, H.; Scheithauer, S. *J. Prakt. Chem. Chem. Ztg.* **1969**, *311*, 827-843.
8. Baird, D. B.; Costello, A. T.; Fishwick, B. R.; McClelland, R. D.; Smith, P. *German Patent* **1975**, 394, 366; *Chem. Abstr.* **1975**, *83*, 114196.
9. Baird, D. B.; Costello, A. T.; Fishwick, B. R.; McClelland, R. D.; Smith, P. *German Patent* **1973**, 2, 304, 201; *Chem. Abstr.* **1973**, *79*, 127402.
10. King, F. D.; Walton, D. R. M. *J. Chem. Soc. Chem. Commun.* **1974**, 256-257.

11. Consiglio, G.; Arnone, C.; Spinelli, D.; Noto, R. *J. Chem. Soc. Perkin Trans. 2* **1981**, 642-644.
12. Consiglio, G.; Noto, R.; Spinelli, D. *J. Chem. Soc. Perkin Trans. 2* **1979**, 222-223.
13. Spinelli, D.; Consiglio, G.; Noto, R. *J. Heterocycl. Chem.* **1977**, *14*, 1325-1329.
14. Spinelli, D.; Consiglio, G. *J. Chem. Soc. Perkin Trans. 2* **1975**, 989-992.
15. Spinelli, D.; Consiglio, G.; Noto, R. *J. Chem. Soc. Perkin Trans. 2* **1976**, 1495-1496.
16. Meth-Cohn, O.; Narine, B. *Synthesis* **1980**, *2*, 133-135.
17. Campaigne, E.; Monroe, P. A. *J. Am. Chem. Soc.* **1954**, *76*, 2447-2450.
18. Hurd, C. D.; Moffat, J. *J. Am. Chem. Soc.* **1951**, *73*, 613-615.
19. Galvez, C.; Gareia, F. *J. Heterocycl. Chem.* **1981**, *18*, 851-853.
20. Binder, D.; Habison, G.; Noe, C. R. *Synthesis* **1977**, *4*, 255-256.
21. Hartmann, H. *J. Prakt. Chem.* **1967**, *36*, 50-72; *Chem. Abstr.* **1967**, *67*, 82017f.
22. Hartmann, H.; Mayer, R. *Z. Chem.* **1966**, *5*, 151-152; *Chem. Abstr.* **1966**, *63*, 5621h.
23. Rajappa, S.; Advani, B. G. *Tetrahedron Lett.* **1969**, *10*, 5067-5068.
24. Smutny, E. J. *J. Am. Chem. Soc.* **1969**, *91*, 208-209.
25. Augustin, M.; Rudorf, W. D.; Schmidt, U. *Tetrahedron* **1976**, *32*, 3055-3061.
26. Krapf, H.; Riedl, P.; Sauer, J. *Chem. Ber.* **1976**, *109*, 576-596; *Chem. Abstr.* **1976**, *84*, 33433f.
27. Baird, D. B.; Barben, I. K.; Fishwick, B. R.; Holland, J. M. *German Patent* **1976**, 2, 526, 086; *Chem. Abstr.* **1976**, *84*, 135461.
28. Stacy, G. W.; Eck, D. L. *Tetrahedron Lett.* **1967**, *8*, 5201-5204.
29. Eck, D. L.; Stacy, G. W. *J. Heterocycl. Chem.* **1969**, *6*, 147-151.
30. Faull, A. W.; Hull, R. *J. Chem. Res. Synop.* **1979**, 240-241; *Chem. Abstr.* **1980**, *92*, 41284p.
31. Faull, A. W.; Hull, R. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1078-1082.
32. Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94-100; *Chem. Abstr.* **1976**, *64*, 8118c.
33. Puterová, Z.; Krutošíková, A.; Végh, D. *Nova Biotechnologica* **2009**, *9*, 167-173.
34. Gewald, K. *Angew. Chem.* **1961**, *73*, 114; *Chem. Abstr.* **1961**, *55*, 12383e.
35. Gewald, K. *Chem. Ber. Recl.* **1965**, *98*, 3571-3577.
36. Gronowitz, S.; Fortea-Laguna, J.; Ross, S.; Sjoberg, B.; Stjernstrom, N. E. *Org. Sulfur Symp.* **1966**, 119-141; *Chem. Abstr.* **1968**, *68*, 113742r.
37. Eilingsfeld, H.; Niess, R. *German Patent* **1974**, 2, 042, 984; *Chem. Abstr.* **1972**, *76*, 140495.
38. Tinney, F. J.; Sanchez, J. P.; Nogas, J. A. *J. Med. Chem.* **1974**, *17*, 624-630.
39. Robba, M.; Lecomte, J. M.; de Sévricourt, M. C. *B. Soc. Chim. Fr.* **1974**, 2864-2870.
40. Cruceyra, A.; Gomez-Parra, V.; Madronero, R. *Anal. Quim.* **1977**, *73*, 265-268; *Chem. Abstr.* **1977**, *87*, 201452.
41. Hromatka, O.; Binder, D.; Stanetty, P.; Marischler, G. *Monatsheft Chem.* **1976**, *107*, 233-239; *Chem. Abstr.* **1976**, *84*, 17054c.
42. Weber, K. H.; Daniel, H. *Liebigs Ann. Chem.* **1979**, *1979*, 328-333; *Chem. Abstr.* **1979**, *90*, 204054p.
43. Hromatka, O.; Binder, D.; Stanetty, P. *Monatsheft Chem.* **1973**, *104*, 709-714.

44. Binder, D.; Stanetty, P. *J. Chem. Res. Synop.* **1981**, *4*, 102; *Chem. Abstr.* **1981**, *95*, 62074x.
45. Nippon Kayaku Co. Ltd. *Japan Kokai Tokkyo Koho*, **1981**, JP81143245; *Chem. Abstr.* **1982**, *96*, 87016.
46. Binder, D.; Hromatka, O.; Noe, C. R.; Hillebrand, F.; Veit, W.; Blum, J. E. *Arch. Pharm.* **1980**, *313*, 587-602.
47. Binder, D.; Hromatka, O.; Noe, C. R.; Bara, Y. A.; Feifel, M.; Habison, G.; Leierer, F.; Blum, J. E. *Arch. Pharm.* **1980**, *313*, 636-644.
48. Gewald, K. *Khim. Geteroosikl. Soedin.* **1976**, 1299-1315; *Chem. Abstr.* **1977**, *86*, 55307.
49. Walser, A.; Flynn, T.; Mason, C. *J. Heterocycl. Chem.* **1991**, *28*, 1121-1125.
50. Hesse, S.; Perspicace, E.; Kirsch, G. *Tetrahedron Lett.* **2007**, *48*, 5261-5264.
51. Manhas, M. S.; Rao, V. V.; Seetharaman, P. A.; Succardi, D.; Pazdera, J. *J. Chem. Soc. C* **1969**, 1937-1938.
52. Elslager, E. F.; Jacob, P.; Werbel, L. M. *J. Heterocycl. Chem.* **1972**, *9*, 775-782.
53. Mayer, R.; Gewald, K. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 294-306; *Chem. Abstr.* **1976**, *66*, 85721w.
54. Gewald, K. *Chem. Heterocycl. Comp*. **1976**, *12*, 1077-1090; *Chem. Abstr.* **1977**, *86*, 55307.
55. Arya, V. P.; Ghate, S. P. *Indian J. Chem.* **1971**, *9*, 1209-1212.
56. Gompper, R.; Kutter, E. *Angew. Chem.* **1962**, *74*, 251; *Chem. Abstr.* **1962**, *60*, 511f.
57. Gewald, K.; Schael, J. *J. Prakt. Chem.* **1973**, *315*, 39-43; *Chem. Abstr.* **1973**, *78*, 124379k.
58. Shvedov, V. I.; Grinev, A. N. (S. Ordzhonikidze All-Union Chem. Pharm. Sci. Res. Inst., Moscow) *Khim. Geterosilk. Soedin.* **1966**, *4*, 515-518; *Chem. Abstr.* **1967**, *66*, 37711w.
59. Koebel, R. F.; Needham, L. L.; De Witt Blanton, C. Jr. *J. Med. Chem.* **1975**, *18*, 192-194.
60. Noravyan, A. S.; Mkrtehyan, A. P.; Dzhagtspanyan, I. A.; Akopyan, R. A.; Vartanyan, S. A. *Khim. Farm. Zh.* **1977**, *11*, 38-42; *Chem. Abstr.* **1978**, *88*, 37739.
61. Tinney, F. J. *US Patent* **1971**, 3, 558, 606; *Chem. Abstr.* **1971**, *74*, 141896.
62. Naumann, B.; Bohm, R.; Fulop, F.; Bernath, G. *Pharmazie* **1996**, *51*, 4-6.
63. Zhang, M.; Harper, R. W. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1629-1634.
64. Desai, J. M.; Shah, V. H. *Indian J. Chem.* **1997**, *36B*, 668-674.
65. Dave, K. G.; Shishoo, C. J.; Devani, M. B.; Kalyanaraman, R.; Ananthan, S.; Ullas, G. V.; Bhadti, V. S. *J. Heterocycl. Chem.* **1980**, *17*, 1497-1500.
66. Sauter, F.; Deinhammer, W. *Monatsh. Chem.* **1973**, *104*, 1593-1598; *Chem. Abstr.* **1974**, *80*, 82868c.
67. Cruceyra, A.; Gomez, P. V.; Modronero, R. *Ann. Quim.* **1975**, *71*, 103-106; *Chem. Abstr.* **1975**, *83*, 131544s.
68. Laboratorios Made, S. A. Span. **1975**, 409,863; *Chem. Abstr.* **1977**, *86*, 89872g.
69. Jennings, L. D.; Kincaid, S. L.; Wang, Y. D.; Krishnamurthy, G.; Beyer, C. F.; McGinnis, J. P.; Miranda, M.; Discafani, C. M.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4731-4735.
70. Shishoo, C. J.; Devani, M. B.; Ullas, G. V.; Ananthan, S.; Bhadti, V. S. *J. Heterocycl. Chem.* **1985**, *22*, 825-830.
71. Magd El-Din, A. A.; Atta, S. M. Sh.; Abd El-All, A. S.; Galal, S. A.; Abdalah, M. M. *World J. Chem.* **2009**, *4*, 112-116.
72. Bilokin, Y. V.; Vasylyev, M. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. *Tetrahedron* **1999**, *55*, 13757-13766.
73. Manhas, M. S.; Amin, S. G.; Rao, V. V. *Synthesis* **1977**, *5*, 309-310; *Chem. Abstr.* **1977**, *87*, 84932n.

74. Shaban, M. A.; Mohamed, M. S.; Kamel, M. M.; El-Zanfally, S. H. *B. Fac. Pharm.* **1990**, *28*, 17-19; *Chem. Abstr.* **1992**, *117*, 48485y.
75. Boehm, R.; Elsner, B.; Drewitz, B. *German Patent* **1981**, 222,709,1980,6; *Chem. Abstr.* **1983**, *98*, 3493j.
76. Böhm, R.; Pech, R. *Pharmazie* **1983**, *38*, 136-137.
77. Pech, R.; Schleiermacher, E.; Boehm, R. *Pharmazie* **1989**, *44*, 860-861; *Chem. Abstr.* **1990**, *113*, 40617a.
78. Davoodnia, A.; Bakavoli, M.; Barakouhi, G.; Tavakoli-Hoseini, N. *Chinese Chem. Lett.* **2007**, *18*, 1483-1486.
79. Temple, D. L. *Appl.* **1975**, 611,955,19; *Chem. Abstr.* **1978**, *88*, 37829p.
80. Temple, D. L. *Appl.* **1977**; 92; *Chem. Abstr.* **1979**, *91*, 74644p.
81. Temple, D. L. *US Patent* **1977**, 826,591,71; *Chem. Abstr.* **1980**, *92*, 58803e.
82. Pathak, U. S.; Gandhi, N. V.; Singh, S.; Warde, R. P.; Jain, K. S. *Indian J. Chem.* **1992**, *31B*, 223-229.
83. Sauter, F.; Stanetty, P.; Schrom, E. *Arch. Pharm.* **1977**, *310*, 337-343; *Chem. Abstr.* **1977**, *87*, 84931m.
84. Wagner, G.; Boehm, N.; Leistner, S. *Pharmazie* **1993**, *48*, 20-23.
85. Sauter, F.; Fröhlich, J.; Ahmed, E. K. *Monatsheft Chem.* **1996**, *127*, 319-324.
86. Sauter, F.; Deinhammer, W. *Monatsheft Chem.* **1974**, *105*, 1249-1251; *Chem. Abstr.* **1975**, *82*, 140053n.
87. Manhas, M. S.; Sugiura, M.; Chawla, H. P. S. *J. Heterocycl. Chem.* **1978**, *15*, 949–953; *Chem. Abstr.* **1979**, *90*, 23370t.
88. Sauter, F.; Deinhammer, W. *Monatsheft Chem.* **1973**, *104*, 1586-1592; *Chem. Abstr.* **1974**, *80*, 82895j.
89. Arya, V. P. *Ind. J. Chem.* **1977**, *15B*, 267-268; *Chem. Abstr.* **1977**, *87*, 102397y.
90. El-Sherief, A. M. Sh.; Micky, J. A. A.; Shmeiss, N. A. M. M.; El-Gharieb, G. *Phosphorus, Sulfur and Silicon* **2003**, *178*, 439-451.
91. Shetty, K. S. M.; Somashekar, V.; Mohan, S. *Asian J. Chem.* **2004**, *16*, 623-627.
92. Janetka, J. W.; Almeida, L.; Ashwell, S.; Brassil, P. J.; Daly, K.; Deng, C.; Gero, T.; Glynn, R. E.; Horn, C. L.; Ioannidis, S.; Lyne, P.; Newcombe, N. J.; Oza, V. B.; Pass, M.; Springer, S. K.; Su, M.; Toader, D.; Vasbinder, M. M.; Yu, D.; Yu, Y.; Zabludoff, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4242-4248.
93. Fondjo, E. S.; Döpp, D.; Henkel, G. *Tetrahedron* **2006**, *62*, 7121-7131.
94. Fancelli, D.; Pevarello, P.; Varasi, M. *PCT Int. Appl.* **2001**, 98,290, *US Appl.* 596,550,200; 85 pp.; *Chem. Abstr.* **2002**, *136*, 69729p.
95. Hallas, G.; Towns, A. D. *Dyes Pigments* **1996**, *31*, 273-289.
96. Mohareb, R. M.; Sherif, S. M.; Gaber, H. M.; Ghabrial, S. S.; Aziz, S. I. *Heteroatom Chem.* **2004**, *15*, 15-20.
97. Gouda, M. A.; Berghot, M. A.; Abd El-Ghani, G. E.; Khalil, A. M. *Eur. J. Med. Chem.* **2010**, *45*, 1338-1345.
98. Khalil, A. M.; Berghot, M. A.; Abd El-Ghani, G. E.; Gouda, M. A. *Synth. Commun.* **2010**, *40*, 1658-1669.