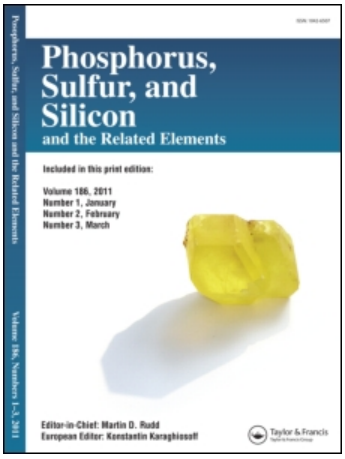

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
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RECENT TRENDS IN THE CHEMISTRY OF THIENOPYRIDAZINES

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Online publication date: 11 August 2010

To cite this Article El-Dean, Adel M. Kamal , Gaber, Abd El-Aal M. , El-Gaby, Mohamed S. A. , Eyada, Hassan A. and Al-Kamali, Ahmed S. N.(2004) 'RECENT TRENDS IN THE CHEMISTRY OF THIENOPYRIDAZINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 2, 321 — 344
To link to this Article: DOI: 10.1080/10426500490262324
URL: http://dx.doi.org/10.1080/10426500490262324

Phosphorus, Sulfur, and Silicon, 179:321–344, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490262324

RECENT TRENDS IN THE CHEMISTRY OF THIENOPYRIDAZINES

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(Received June 20, 2003; accepted August 4, 2003)

This review describes the synthesis of thieno[2,3-c]pyridazine, thieno [3,2-c]pyridazine, thieno[2,3-d]pyridazine and thieno[3,4-d]pyridazine derivatives and their reactions.

Keywords: Thieno[2,3-c]pyridazine; thieno[3,2-c]pyridazine; thieno [2,3-d]pyridazine and thieno[3,4-d]pyridazine derivatives

Thienopyridazine derivatives are important compounds because of their broad range of biological and pharmacological effects. Thieno[2,3-d]pyridazine derivatives, for example, have been evaluated pharmacologically and used for potent and selective phosphodiesterase IV inhibitor,[1,2] immunosuppressants,[3] antiarrhythmic,[4] antibiotic,[5] antiasthmatic,[6] antiinflammatory,[7] antispasmodic,[8] antitumor,[9] potentiated pentobarbital sleep,[10] antipsychotic, anxiolytic,[11] and anticonvulsant[12] activities.

Also, thieno[3,4-d]pyridazine derivatives were used as serotonin antagonists and alpha adrenergic blocking agents,[13] modules of protein tyrosine phosphatases (PT-Pases),[14] antimicrobials,[15] blood platelet aggregation inhibitors.[16] and enhanced fibrinolytic activity in intact and spleenectomized rats.[17]

There are four positional isomers of thienopyridazines are known (**1**, **2**, **3**, and **4**) as a result of fusion of thiophene to the pyridazine nucleus: thieno[2,3-c]pyridazine **1**, thieno[3,2-c]pyridazine **2**, thieno[2,3-d]-pyridazine **3** and thieno[3,4-d]pyridazine **4**.

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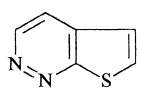
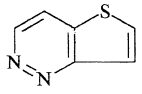
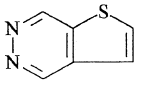


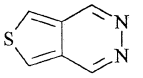
thieno[2,3-c]pyridazine
1



thieno[3,2-c]pyridazine
2



thieno[2,3-d]pyridazine
3



thieno[3,4-d]pyridazine
4

The literature survey revealed that there are some methods for the preparation of the different classes of thienopyridazine derivatives.

SYNTHESIS OF THIENO[2,3-c]PYRIDAZINES

Two synthetic routes have been used for the synthesis of thieno[2,3-c]pyridazine either starting with the thiophene moiety or the pyridazine ring.

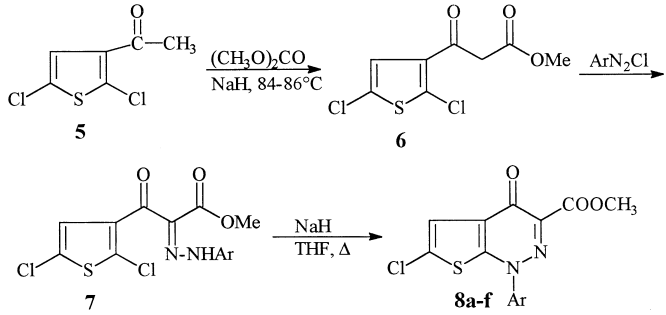
From Thiophene Derivatives

Condensation of 3-acetyl-2,5-dichlorothiophene **5** with dimethyl carbonate in the presence of sodium hydride gave the β-ketoester **6**, which was coupled with the appropriate arenediazonium chlorides to produce the hydrazones **7**. Cyclization of the latter compounds by the sodium hydride in tetrahydrofuran gave the thieno[2,3-c]pyridazines[18] **8a–f** (Scheme 1).

From Pyridazine Derivatives

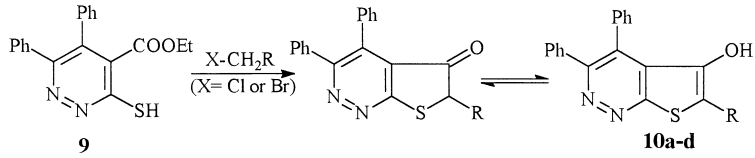
Suitably substituted pyridazine derivatives have been used as starting materials for the synthesis of thieno[2,3-c]pyridazines. Thus, the reaction of ethyl 5,6-diphenyl-3-mercaptopyridazine-4-carboxylate **9** with phenacyl bromide, chloro-*N*-arylacetamides, chloroacetonitrile, ethyl chloroacetate, or chloroacetone furnished the corresponding 4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazines[19] **10a–d** (Scheme 2).

Kamal El-Dean et al.[20] have reported that thieno[2,3-c]pyridazine derivatives **12a,b** have been obtained from the reactions between 4-acetyl-5,6-diphenylpyridazine-3(2*H*)-thione **11** and ethyl chloroacetate or p-chlorophenacyl chloride (Scheme 3).



Compound	Ar	Yield (%)
8a	C_6H_5	55
8b	C_6H_4F-p	52
8c	C_6H_4Cl-p	60
8d	C_6H_4Br-p	63
8e	$C_6H_4OCH_3$-p	52
8f	$C_6H_4CH_3$-p	56

SCHEME 1

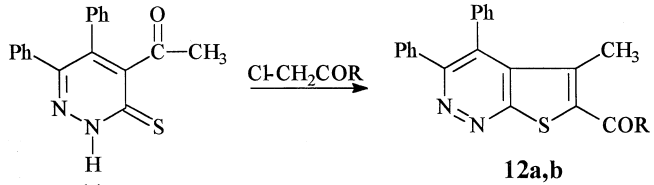


Compound	R	Yield (%)
10a	COC_6H_5	90
10b	COC_6H_4Br-p	95
10c	$CONHC_6H_5$	84
10d	$CONHC_6H_4CH_3$-p	86

SCHEME 2

Some new 4,5-di(2-furyl)thieno[2,3-c]pyridazine derivative **14** was prepared starting with 5,6-di(2-furyl)4-cyanopyridazine-3(2*H*)-thione **13**, which reacted with chloroacetonitrile to produce the corresponding thieno[2,3-c]pyridazine derivative[21] (Scheme 4).

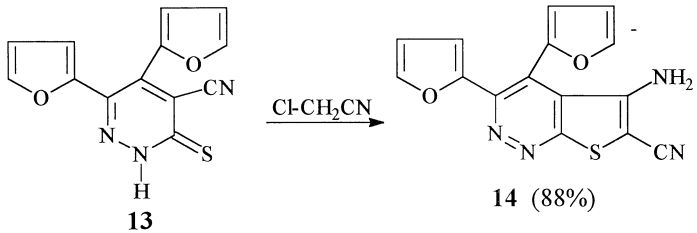
Thieno[2,3-c]pyridazine derivatives[22] **16a–c** have been obtained from the reaction between 4-cyano-5,6-diphenylpyridazine-3(2*H*)-thione **15** with *N*-substituted chloroacetamide in refluxing ethanol



11 12a,b

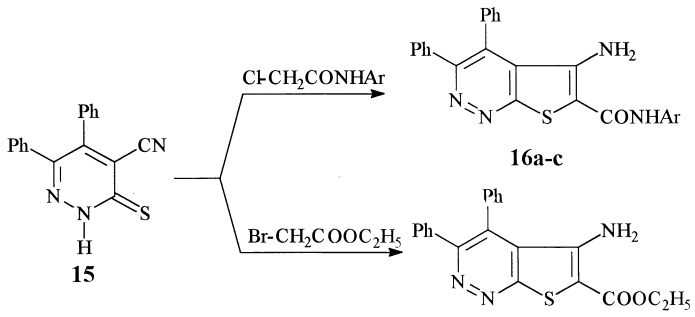
Compound	R	Yield (%)
12a	OC_2H_5	52
12b	C_6H_4Cl-p	50

SCHEME 3



13 14 (88%)

SCHEME 4



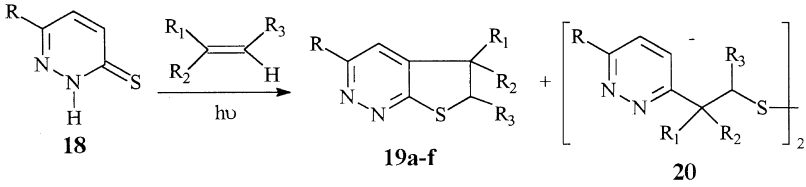
15 16a-c 17

Compound	Ar	Yield (%)
16a	C_6H_5	54
16b	$C_6H_4OCH_3$-p	64
16c	C_6H_4Cl-p	66

SCHEME 5

in the presence of anhydrous K_2CO_3. Also, treatment[23] of compound **15** with ethyl bromoacetate gave thieno[2,3-c]pyridazine derivative **17** (Scheme 5).

Photoaddition[24] of olefines to 3(2*H*)-pyridazine thiones **18** produced both thieno[2,3-c]pyridazines **19a–f** and 3-substituted pyridazine disulfides **20** (Scheme 6).

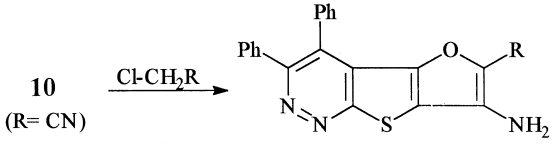


Compound	R	R_1	R_2	R_3	Yield (%)
19a	CH_3	CH_3	CH_3	H	52
19b	CH_3	CH_3	CH_3	CH_3	49
19c	H	CH_3	CH_3	H	39
19d	H	CH_3	CH_3	CH_3	50
19e	CH_3	C_2H_5O	H	H	21
19f	CH_3	CH_3COO	H	H	25

SCHEME 6

REACTIONS OF THIENO[2,3-c]PYRIDAZINES

The reaction of 4,5-diphenyl-3-hydroxy-2-cyano-thieno[2,3-c]-pyridazine **10** (R = CN) with chloroacetonitrile or ethyl chloroacetate afforded 3-amino-7,8-diphenyl-furo[2′,3′:4,5]thieno[2,3-c]pyridazine **21** and **22** respectively[19] (Scheme 7).

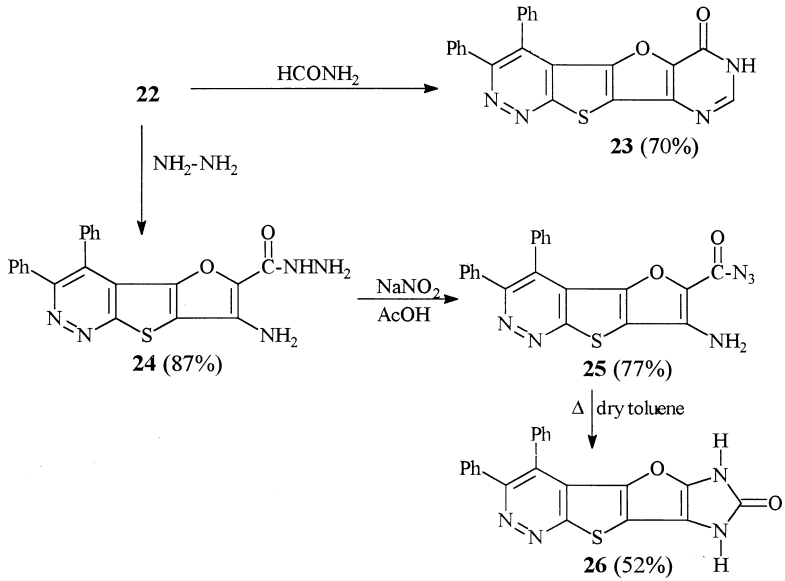


21, R= CN (54%)
22, R= $COOC_2H_5$ (84%)

SCHEME 7

Cyclocondensation of compound **22** with formamide gave 3,4-dihydro-6,7-diphenyl-4-oxopyrimido[4″,5″:4′5′]furo[2′,3′:4,5]thieno[2,3-c]pyridazine **23**. The reaction of **22** with hydrazine hydrate yielded

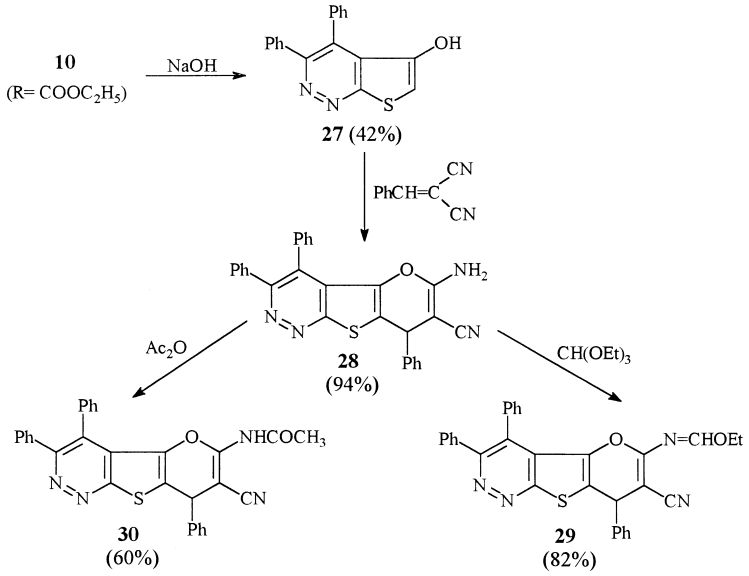
the carbohydrazide **24**, which on treatment with sodium nitrite in glacial acetic acid, gave the corresponding carbonylazide **25**. On refluxing of **25** in dry toluene, the imidazolo[4″,5″:4,5]furo[2′,3′:4,5]thieno-[2,3-c]pyridazine **26** was obtained via Curtius rearrangement followed by intramolecular cyclization[19] (Scheme 8).



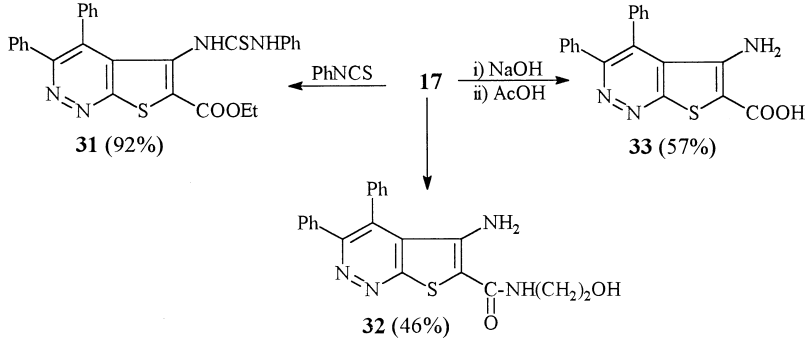
SCHEME 8

Treatment of **10** (R = $COOC_2H_5$) with an ethanolic solution of sodium hydroxide resulted in hydrolysis followed by spontaneous decarboxylation to give 4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazine **27**. The cycloaddition reaction of **27** with benzylidenemalononitrile afforded 2-amino-3-cyano-4,8,9-triphenyl-4H-pyrano[2′,3′:4,5]thieno[2,3-c]pyridazine **28** in quantitative yield. The reactivity of compound **28** was tested via its reaction with triethyl orthoformate and acetic anhydride[19] and furnished ethoxymethylene **29** and acetamide **30** derivatives respectively (Scheme 9).

When the *ortho*-aminoester **17** was allowed to react with some reagents as phenyl isothiocyanate and ethanolamine the corresponding thiourea **31** and amide **32** were obtained. Saponification of compound **17** with an ethanolic solution of sodium hydroxide followed by acidification[25] with acetic acid resulted in the formation of the carboxylic acid **33** (Scheme 10).



SCHEME 9

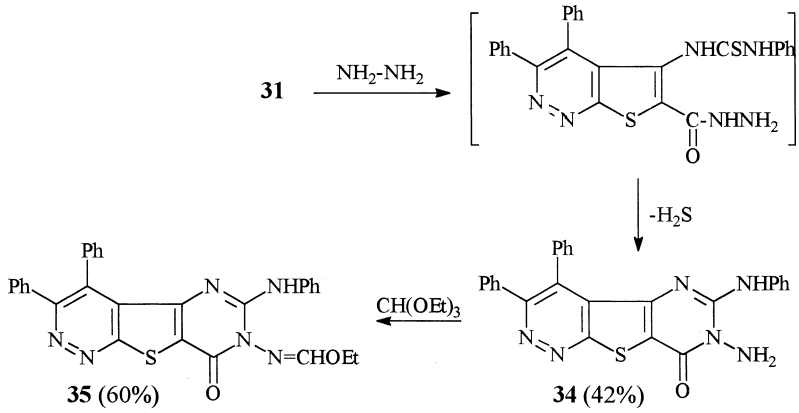


SCHEME 10

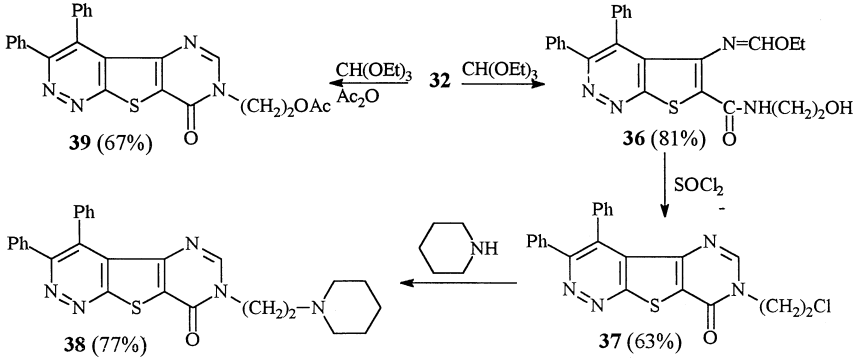
The thiourea derivative **31** was reacted with hydrazine hydrate to give pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine **34** which upon treatment with triethyl orthoformate afforded ethoxymethylene derivative[25] **35** (Scheme 11).

Compound **32** was used as a key intermediate for synthesizing some pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazines **37–39**[26] (Scheme 12).

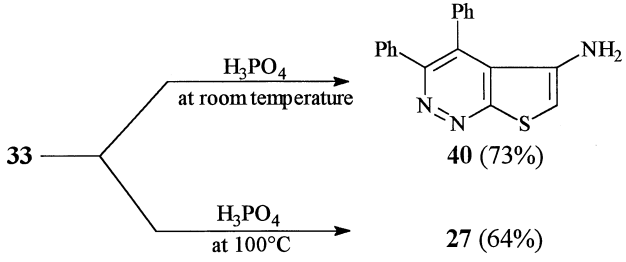
Upon treatment of the aminocarboxylic acid **33** with orthophosphoric acid at room temperature, decarboxylation occurred to afford 3-amino-4,5-diphenylthieno[2,3-c]pyridazine[26] **40**. However, reaction



SCHEME 11



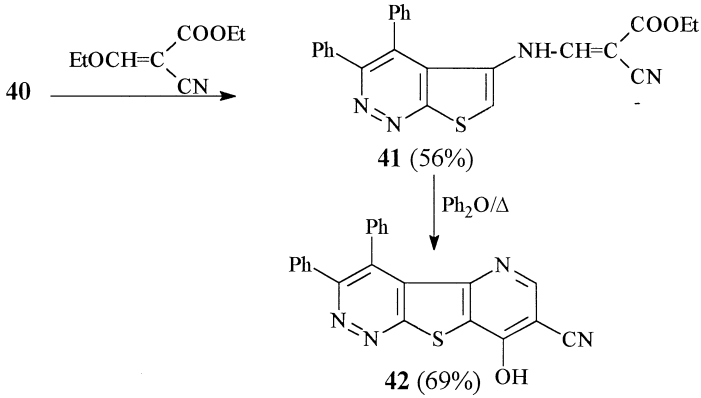
SCHEME 12



SCHEME 13

of **33** with orthophosphoric acid at 100°C yielded the corresponding hydroxy compound **27** which was identical to that previously obtained[19] (Scheme 13).

The reaction of 3-amine-4,5-diphenyl-thieno[2,3-c]pyridazine **40** with ethoxymethylenecyanoacetate produced compound **41** which upon boiling in diphenylether cyclized into pyridothienopyridazine derivative[26] **42** (Scheme 14).

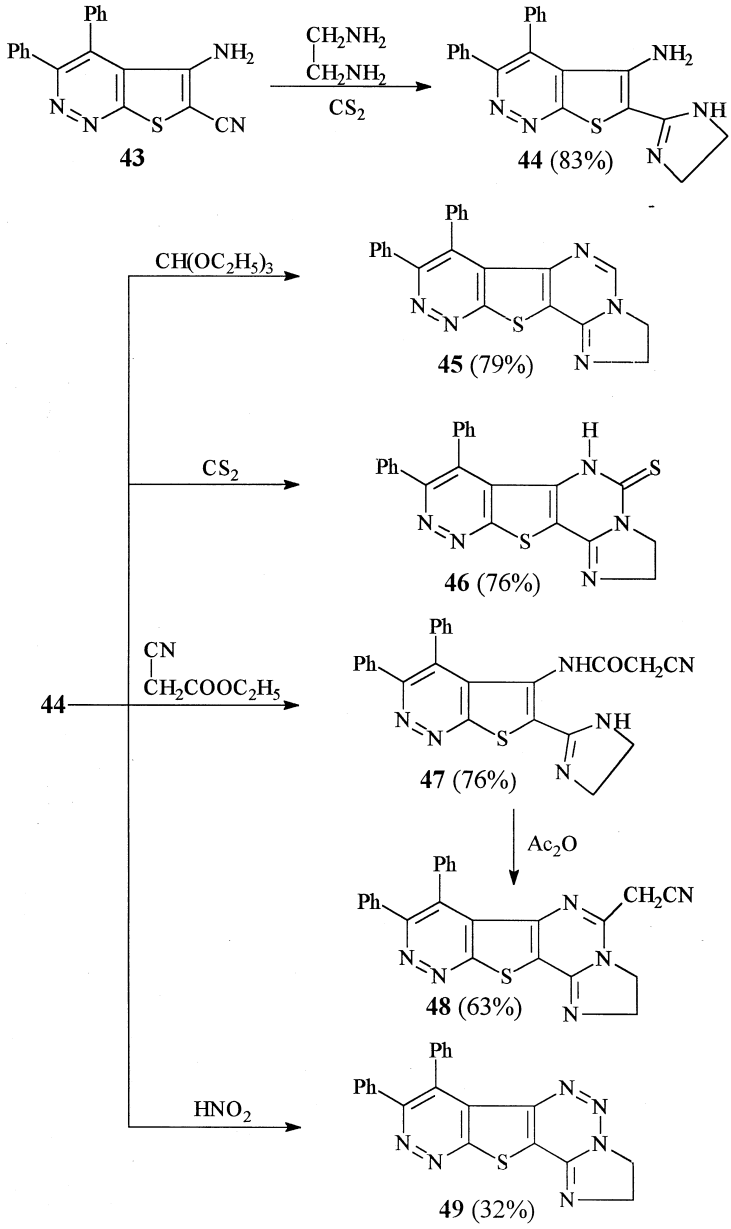


SCHEME 14

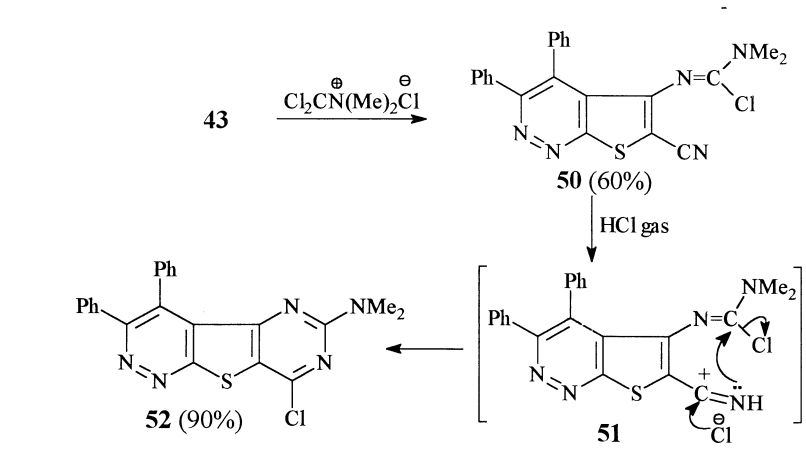
Incorporating the imidazole ring in thienopyridazine systems was achieved by reaction of 2-aminocarbonitrile **43** with ethylenediamine in the presence of carbon disulfide to give imidazolyl derivative **44**. Reaction of **44** with triethyl orthoformate, carbon, disulfide, and ethyl cyanoacetate furnished imidazolopyrimidothieno[2,3-c]pyridazines **45**, **46**, and **48** respectively. The triazine analogue **49** was obtained upon treatment of **44** with nitrous acid[27] (Scheme 15).

On treatment of compound **43** with (dichloromethylene) dimethylammonium chloride in refluxing 1,2-dichloroethane gave the amide halide **50**, which underwent smooth cyclization to yield the corresponding fused pyrimidothienopyridazine **52** by the reaction with dry hydrogen chloride[28] (Scheme 16).

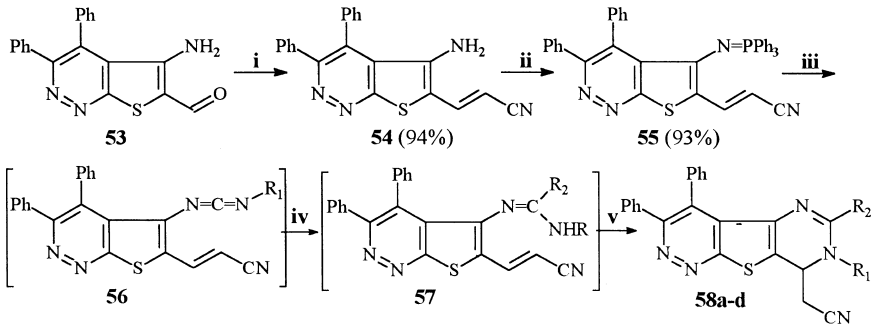
5-Amino-3,4-diphenylthieno[2,3-c]pyridazine-6-carboxaldehyde **53** reacted with an equimolecular quantity of the appropriate phosphoranes to give good yield of 6-vinylthienopyridazine (Scheme 17). The iminophosphorane **55** was very readily obtained from **54** by treatment with triphenylphosphine in the presence of triethylamine in dry tetrahydrofuran. Iminophosphorane **55** underwent a Wittig type reaction with isocyanates to give the highly reactive carbodiimide intermediate **56** which in turn was converted by a one-pot procedure into



SCHEME 15



SCHEME 16



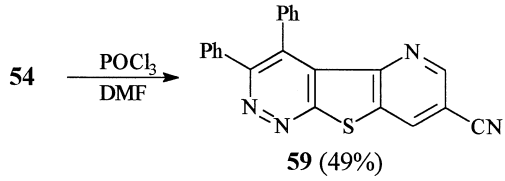
i: $Ph_3\overset{+}{P}CH_2C\overset{-}{N}Cl$, $HN(CH_2)_5$, THF, ii: Ph_3P, C_2Cl_6, NEt_3, THF, 60°C
iii: R_1NCO, THF, iv: amine, v: NaOEt, r.t.

Compound	R_1	R_2	Yield (%)
58a	C_6H_5	$N(CH_3)_2$	58
58b	C_6H_5	Piperidino	67
58c	C_6H_5	4-Methylpiperazino	56
58d	C_6H_5	Thiomorpholino	66

SCHEME 17

the corresponding heterocycles **58a–d**, via initial addition of an amine to the carbodiimide cumulenic system followed by intramolecular heteroconjugate addition annulation[29] (Scheme 17).

The vinylthienopyridazine **54** underwent an unusual pyridine ring closure under Vilsmeier conditions to form the pyridothienopyridazine[30] **59** (Scheme 18).

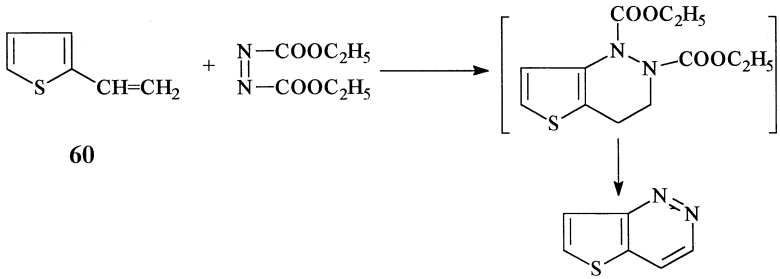


59 (49%)

SCHEME 18

SYNTHESIS OF THIENO[3,2-c]PYRIDAZINES

Thieno[3,2-c]pyridazine derivative **61** was obtained by the [4 + 2] cycloaddition reaction of 2-vinylthiophene **60** with diethylazodicarboxylate in refluxing acetonitrile[31,32] (Scheme 19).



60

61 (small yield)

SCHEME 19

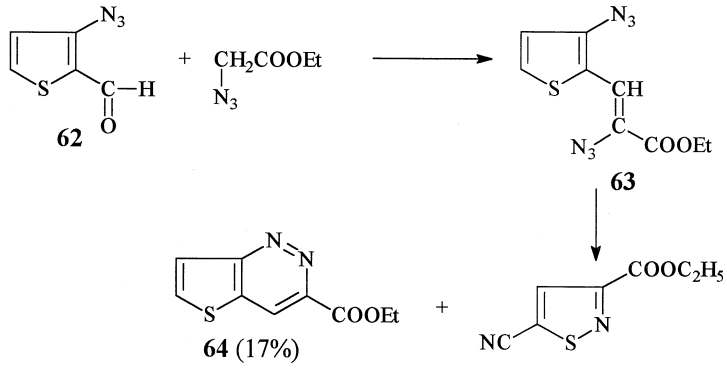
Condensation reaction of 3-azidothiophene-2-carboxaldehyde **62** with ethyl azidoacetate in presence of sodium ethoxide furnished the azidothiophene[33] **63**. Thermolysis[34] of azidothiophene **63** in refluxing toluene for 0.5 h resulted in ring cleavage with extrusion of acetylene giving 19% isothiazole with 17% thieno[3,2-c]pyridazine **64** (Scheme 20).

Cyclocondensation of thiophene derivative **65** with hydrazine acetate afforded thieno[3,2-c]pyridazine[35] **66** (Scheme 21).

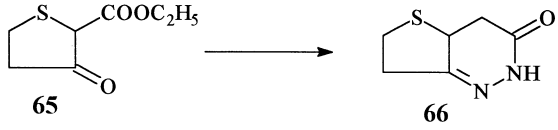
SYNTHESIS OF THIENO[2,3-d]PYRIDAZINES

From Thiophene Derivatives

Treatment of 3-bromothiophene[6] **67** with one equivalent of n-butyllithium and 3-cyanopyridine followed by treatment with another

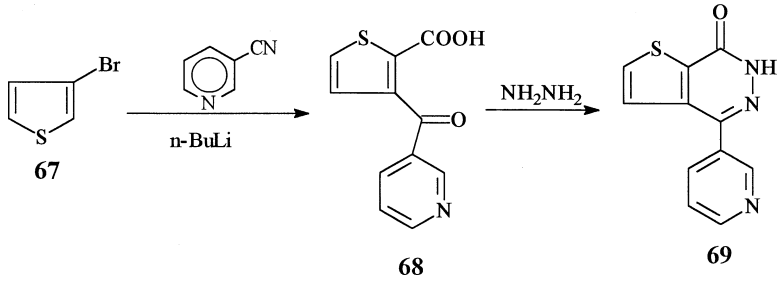


SCHEME 20



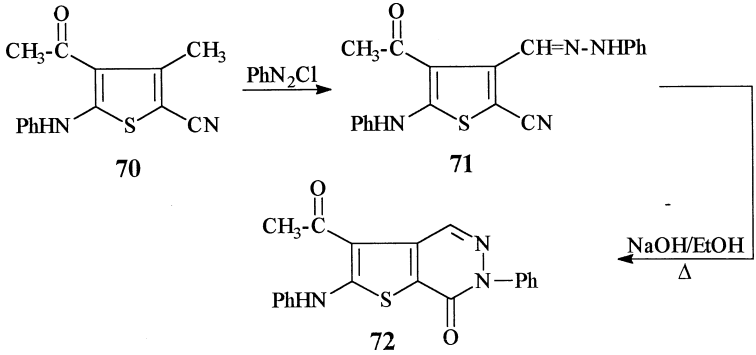
SCHEME 21

equivalent of n-butyllithium and dry ice, and hydrolysis with diluted hydrochloric acid gave **68** (Scheme 22). Cyclization of the latter compound with hydrazine yielded thieno[2,3-d]pyridazine derivative **69** in a low yield of 10%.



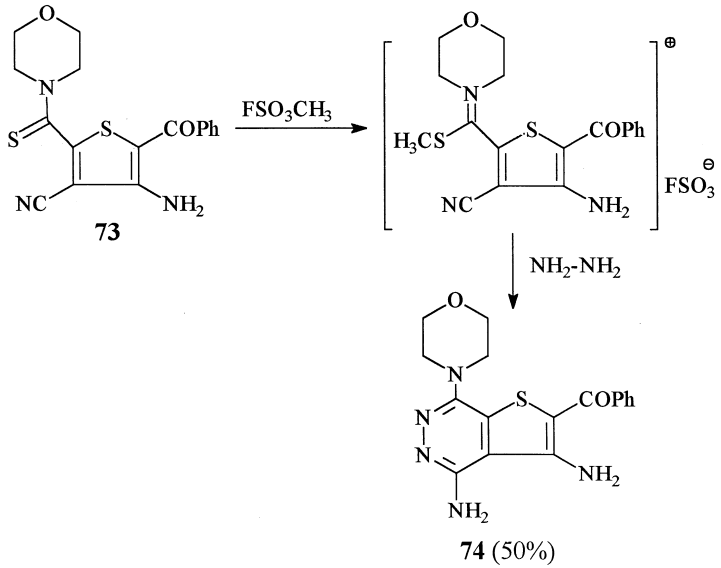
SCHEME 22

3-Methyl-4-acetyl-5-phenylaminothiophene-2-carbonitrile **70** was coupled with benzenediazonium chloride to give hydrazone derivative **71** which undergoes readily cyclization when heated in ethanol/sodium hydroxide solution to afford the thieno[2,3-d]pyridazine derivative[36] **72** in 67% yield (Scheme 23).



SCHEME 23

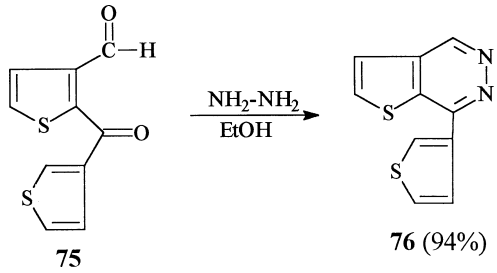
S-Alkylation[37] of the thiophene derivative **73** at the thioamide sulfur followed by hydrazinolysis gives the thieno[2,3-d]pyridazine **74** (Scheme 24).



SCHEME 24

4-(3-Thienyl)-thieno[2,3-d]pyridazine **76** was prepared from the reaction of 2-(thiophene-3-carbonyl)-thiophene-3-carboxaldehyde **75** with hydrazine hydrate[38] (Scheme 25).

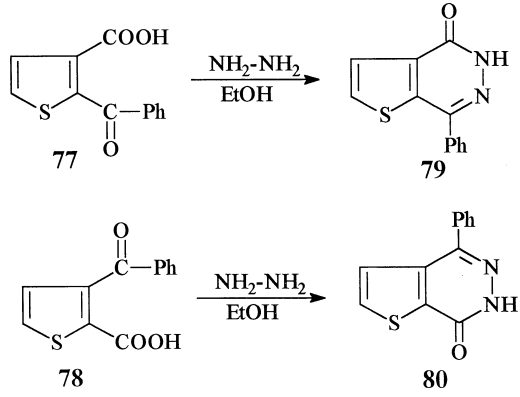
Thieno[2,3-d]pyridazine-4-ones **79** and thieno[2,3-d]pyridazine-7-ones **80** were prepared by the reactions of 2-benzoyl-3-thiophene



75 **76** (94%)

SCHEME 25

carboxylic acid **77** and 3-benzoyl-2-thiophene carboxylic acid **78** with hydrazine hydrate in ethanol,[7] which were used as antiinflammatory agents (Scheme 26).

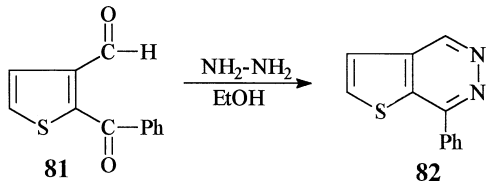


77 **79**

78 **80**

SCHEME 26

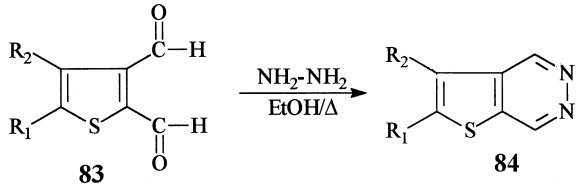
The reaction of 2-benzoyl-3-formylthiophene **81** with hydrazine hydrate gave thieno[2,3-d]pyridazine **82** which was exhibited potentiated pentobarbital sleep activity[10] (Scheme 27).



81 **82**

SCHEME 27

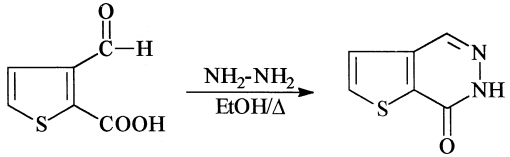
Cyclocondensation of 2,3-diformylthiophene derivatives **83** with hydrazine hydrate in ethanol afforded thieno[2,3-d]pyridazine derivatives[39,40] **84** (Scheme 28).



83 **84**

SCHEME 28

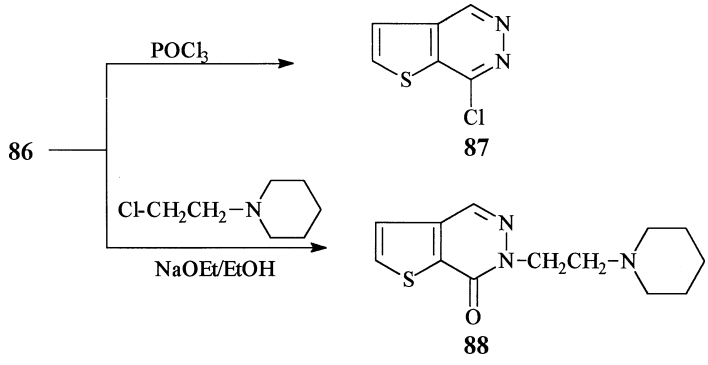
The 1-oxo-1,2-dihydrothieno[2,3-d]pyridazine **86** was synthesized by reacting 3-formylthiophene-2-carboxylic acid **85** with hydrazine hydrate in ethanol[41] (Scheme 29).



85 **86** (80%)

SCHEME 29

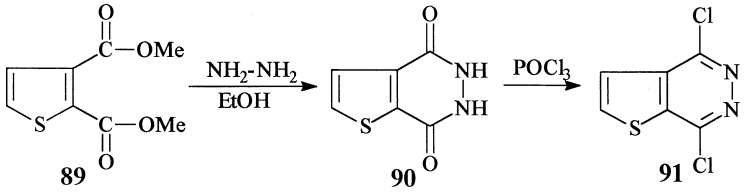
Robba et al.[42,43] have reported that the reaction of **86** with phosphorus oxychloride and 1-chloro-2-piperidinoethane in sodium ethoxide yielded 1-chlorothieno[2,3-d]pyridazine **87** and 1-oxo-1,2-dihydro-2-(β-piperi-dinoethyl)thieno[2,3-d]pyridazine **88** respectively (Scheme 30).



87 **88**

SCHEME 30

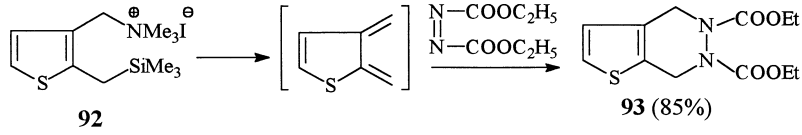
The reaction of 2,3-bis(carbomethoxy)thiophene **89** with hydrazine hydrate afforded thieno[2,3-d]pyridazine derivative **90** which on heating with phosphorus oxychloride gave 1,4-dichlorothieno[2,3-d]pyridazine[44] **91** (Scheme 31).



89 90 91

SCHEME 31

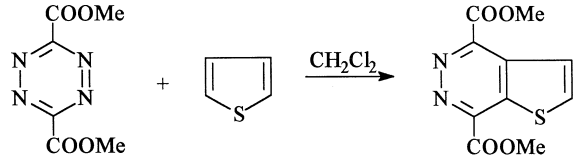
2,3-Dimethylene-2,3-dihydrothiophene is generated in situ[45] from 3-(trimethylammonium methyl)-2-(trimethylsilylmethyl)thiophene iodide **92** by a fluoride trapped in [4 + 2] cycloaddition reaction with diethyl azodicarboxylate to furnish thieno[2,3-d]pyridazine **93** (Scheme 32).



92 **93** (85%)

SCHEME 32

Also, thieno[2,3-d]pyridazine derivative **95** was prepared by [4 + 2] cycloaddition reaction of 3,6-bis(methoxycarbonyl)tetrazine **94** with thiophene in dichloromethane[46] (Scheme 33).

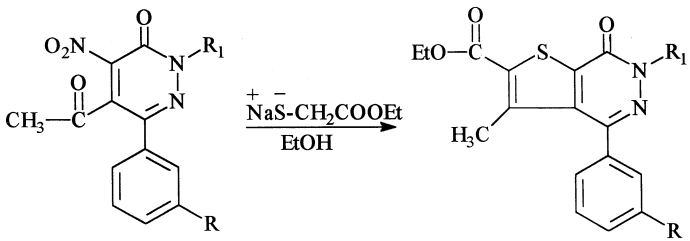


94 **95** (12%)

SCHEME 33

From Pyridazine Derivatives

Cyclocondensation of 5-acetyl-2-substituted-4-nitro-6-aryl-3(2*H*)-pyridazinone **96** with sodium ethyl thioglycolate in absolute ethanol at room temperature afforded the thieno[2,3-d]pyridazine derivatives[1,47] **97a–d** (Scheme 34).



96 **97a-d**

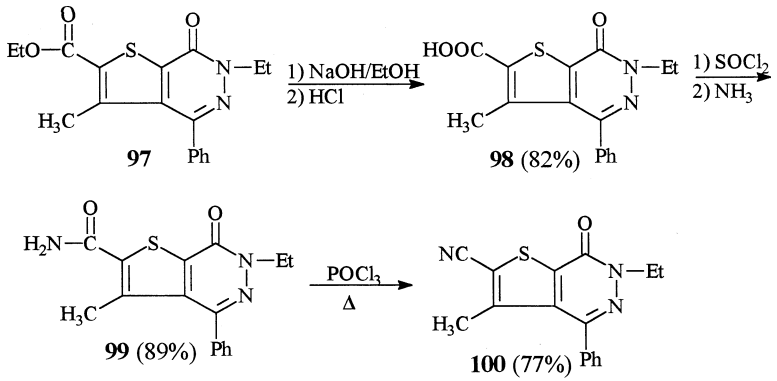
Compound	R_1	R_2	Yield (%)
97a	H	CH_3	46
97b	H	C_6H_5	40
97c	NO_2	CH_3	61
97d	Cl	CH_3	38

SCHEME 34

REACTIONS OF THIENO[2,3-d]PYRIDAZINES

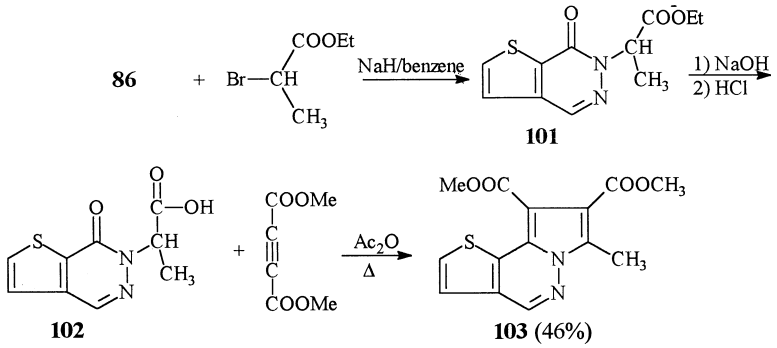
Recently,[2] 2-cyano-6-ethyl-3-methyl-4-phenylthieno[2,3-d]pyridazin-7-(6*H*)-one **100** was prepared by hydrolysis of ethyl 6,7-dihydro-6-ethyl-3-methyl-7-oxo-4-phenylthieno [2,3-d]pyridazine-2-carboxylate **97** (R = H, $R_1 = C_2H_5$) by heating with ethanolic sodium hydroxide, followed by acidification with hydrochloric acid gave the carboxylic acid derivative **98**. Treatment of the latter compound with thionyl chloride, followed by quenching with aqueous ammonia, afforded the amide **99** which was converted into the cyano derivative **100** by heating with phosphorus oxychloride (Scheme 35).

Alkylation of thieno[2,3-d]pyridazin-7(6H)-one **86** with ethyl 2-bromopropionate gave the *N*-propionate thieno[2,3-d]pyridazine derivative **101**. Saponification of **101** with sodium hydroxide followed by acidification with hydrochloric acid yielded the acid **102**. Cycloaddition reaction of **102** with dimethyl acetylenedicarboxylate



SCHEME 35

in acetic anhydride furnished pyrrolo[1,2-g]thieno[2,3-d]pyridazine derivative[48] **103** (Scheme 36).



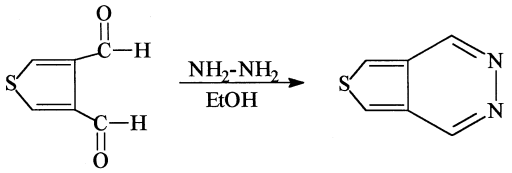
SCHEME 36

SYNTHESIS OF THIENO[3,4-d]PYRIDAZINES

From Thiophene Derivatives

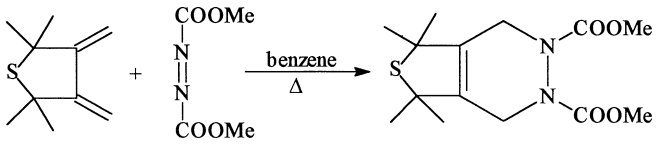
Thieno[3,4-d]pyridazine **105** was prepared by the treatment of 3,4-diformylthiophene **104** with hydrazine hydrate[49] (Scheme 37).

Also, thieno[3,4-d]pyridazine derivative **107** was obtained by [4 + 2] cycloaddition reaction of 3,4-dimethylene thiophene **106** and dimethyl azodicarboxylate in refluxing dry benzene[50] (Scheme 38).



104 105

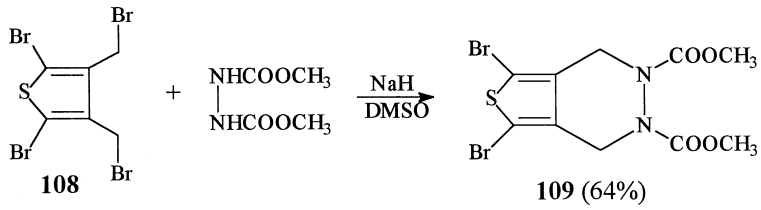
SCHEME 37



106 **107** (80%)

SCHEME 38

Treatment of 2,5-dibromo-3,4-bis(bromomethyl)thiophene **108** with dimethylhydrazodicarboxylate (DMHD) in the presence of sodium hydride in dimethylsulfoxide produced 1,2,3,4-tetrahydro-N,N′-dicarbomethoxy-6,8-dibromothieno[3,4-d]pyridazine[51] **109** (Scheme 39).



108 **109** (64%)

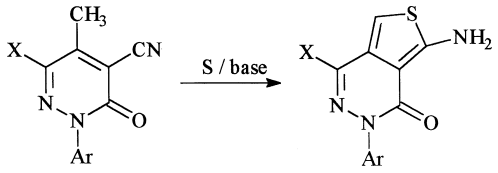
SCHEME 39

From Pyridazine Derivatives

Elnagdi et al.[52–55] have reported that 4-methyl pyridazin-5-yl-carbonitriles **110** react with elemental sulfur in the presence of base in dioxane under reflux to yield the corresponding thieno[3,4-d]pyridazines **111** (Scheme 40).

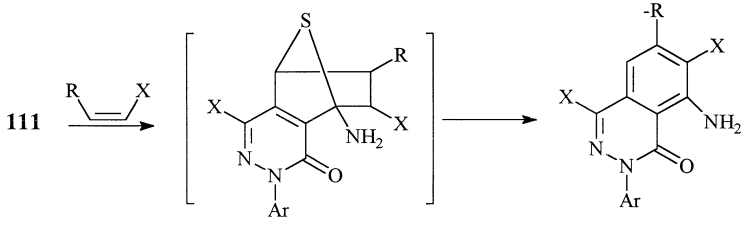
REACTIONS OF THIENO[3,4-d]PYRIDAZINES

The reactivity[56,57] of thieno[3,4-d]pyridazines **111** toward dienophiles as acrylonitrile and ethyl acrylate was investigated and furnished phthalazines **113**, via intermediacy of **112** (Scheme 41).



110 **111**

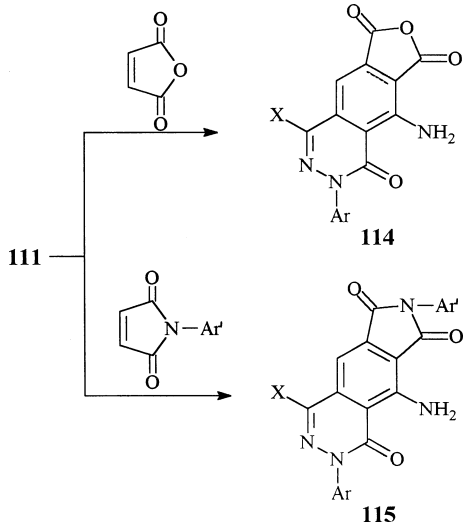
SCHEME 40



112 **113**

SCHEME 41

Similarly, maleic anhydride and *N*-arylmaleimide with thienopyridazines **111** yielded the condensed pyridazines **114** and **115** respectively[57] (Scheme 42).



SCHEME 42

CONCLUSIONS

It is observed from the literature survey that there are four positional isomers of thienopyridazines as a result of fusion of thiophene to the pyridazine nucleus: thieno[2,3-c]pyridazine, thieno[3,2-c]pyridazine, thieno[2,3-d]pyridazine, and thieno[3,4-d]pyridazine. Thienopyridazine derivatives were prepared either starting with the thiophene moiety or the pyridazine ring. A considerable number of thienopyridazines described in this article have been reported to exhibit interesting biological properties.

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