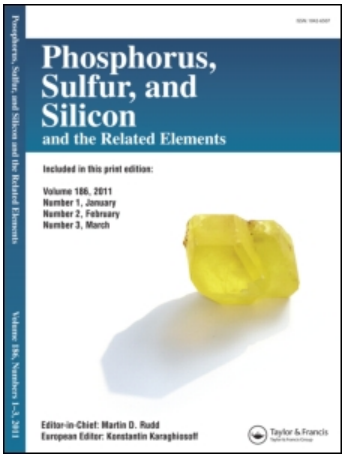

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Recent Trends in the Chemistry of Thienopyridines

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RECENT TRENDS IN THE CHEMISTRY OF THIENOPYRIDINES

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The nomenclature, synthesis, and reactions of various isomeric thienopyridines as well as their applications are reviewed.

Keywords: Applications; pyridothienopyrimidines; pyridothienotriazines; reactions; synthesis; thienopyridines

The earliest method for the preparation of thienopyridines was reported by Steinkopf and Lutzkendorf[1] who applied the Skraup reaction on 2-aminothiophene to obtain thieno [2,3-b]pyridine (**1**) in a low yield. During the 35 years that followed, there were very few publications in this field and those that did appear mostly were concerned with approaches to thiophene analogs of indigo dyes.[2] Between 1950 and 1970 a certain amount of work on thienopyridines was reported.[3,4]

Further work was in progress between 1971 and 1980, which is significant for two main reasons. First, the obvious theoretical interest in the behavior of systems that contain and fused together a π-excessive and a π-deficient ring were studied. Second, the search for pharmacologically active substances has led to the synthesis of analogs of various quinolines and isoquinolines in which the benzene ring is replaced by thiophene. During the last two decades, a large number of reports concerning thienopyridines in general have appeared owing to a wide variety of their applications in biochemistry, medicine, and industry.

The recent trends in the chemistry of isomeric thienopyridines as well as their applications are included in this review.

The author thanks all of his coworkers for their dedication and hard work, and he wishes especially to thank Prof. Dr. A. E. Abdel-Rahman, Prof. Dr. H. S. El-Kashef, and Prof. Dr. Sh. M. Radwan for their help in revising this review.

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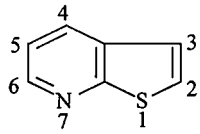
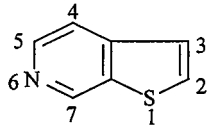
NOMENCLATURE

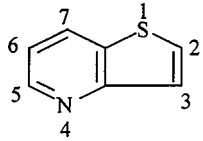
By *ortho* condensation of a thiophene nucleus with pyridine, six thienopyridines are possible. These thienopyridines fall into two groups: those that are analogs of quinoline, the [b]-fused systems **1–3**, and those that are analogs of isoquinoline, the [c]-fused systems **4–6**:



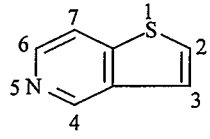
1
Thieno[2,3-b]pyridine



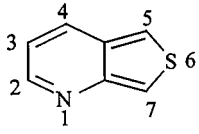
4
Thieno[2,3-c]pyridine



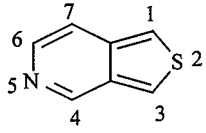
2
Thieno[3,2-b]pyridine



5
Thieno[3,2-c]pyridine



3
Thieno[3,4-b]pyridine



6
Thieno[3,4-c]pyridine

The thienopyridines **1**, **2**, and **4**, and their related compounds have received great attention in the literature. Very little work has been reported on thieno[3,4-b]- and [3,4-c]pyridines **3** and **6**; the parent substances were first prepared in 1970,[4] but they were found to be much less stable than the other four isomers.

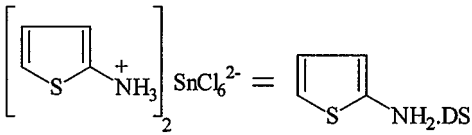
SYNTHESIS OF THIENO[2,3-b]PYRIDINES

Synthetic approaches to thienopyridines are conveniently considered under two main headings according to which heterocyclic ring is constructed. Lately, two new methods have been reported: One involves intramolecular Diels-Alder reaction of some butynylthio-heterocycles and the other is a one-pot reaction.

Synthesis Involving Formation of The Pyridine Ring

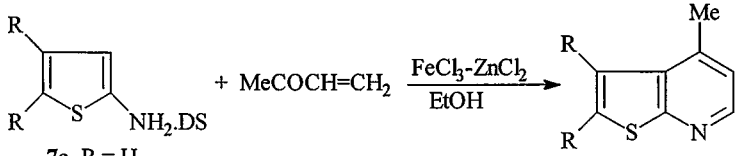
From 2-Aminothiophenes

The preparation of thieno[2,3-b]pyridine (**1**) from 2-aminothiophene already has been mentioned.[1] In fact, Steinkopf and Lutzkendorf did not employ the free amine but used the tin double salt of 2-aminothiophene; such salts will be represented as follow (e.g., **7a**).



7a, DS = double salt

The reaction of methyl vinyl ketone with 2-aminothiophene double salts **7a**,**b** was reported to give the corresponding thieno[2,3-b]pyridine derivatives **8a**,**b**.[5,6]



7a, R = H
7b, R = Me

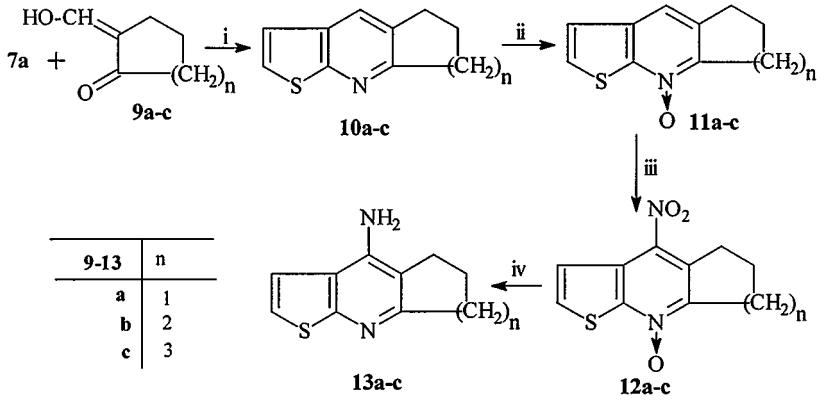
8a, R = H
8b, R = Me

The cycloalka[e]thieno[2,3-b]pyridines (**10a–c**) were synthesized from the reaction of 2-aminothiophene double salt (**7a**) with the corresponding 2-hydroxymethylenecycloalkanones (**9a–c**).[7] Compounds **10a–c** were converted into 4-aminocycloalka[e]thieno[2,3-b]pyridines (**13a–c**) via three steps.[7]

Adachi et al.[8] reported that the reaction of 2-aminothiophene derivatives **14** with alkyl or aryl 2-acetyl-3-(3′-nitrophenyl)acrylates (**15**) gives the 4,7-dihydrothieno[2,3-b]pyridine derivatives **16**.

From 2-Aminobenzo[b]thiophene-3-thiocarboxaldehyde

Treatment of 2-aminobenzo[b]thiophene-3-thiocarboxaldehyde (**17**) with a three-fold excess of diethyl acetylenedicarboxylate in benzene at room temperature followed by heating of the crude reaction mixture (after removal of the benzene solvent) at 110°C under vacuum (15 mmHg) for 3 h afforded, beside the sulfide **21**, the desired benzothieno[2,3-b]pyridine **20** in 40% yield.[9] The pathway of this reaction would

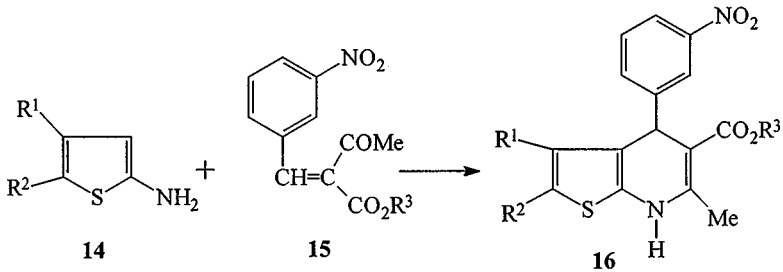


i: $ZnCl_2$; ii: Magnesium monoperoxyphthalate/AcOH ; iii: H_2SO_4-HNO_3; iv, Fe/AcOH

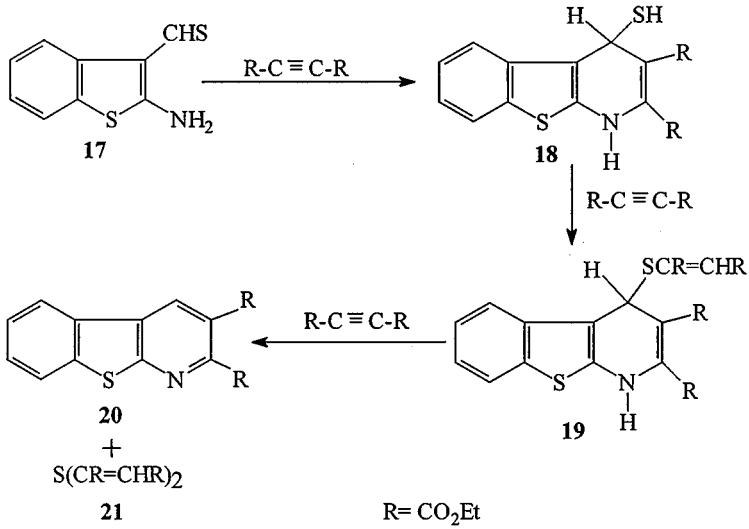
involve initial formation of the thiol intermediate **18** through nucleophilic addition of the amino group of **17** to the alkyne and subsequent intramolecular cyclization of the resulting enamine onto the thioformyl function. Further reaction of **18** with the alkyne would give the vinyl sulfide derivative **19**, which could then afford the aromatized thienopyridine **20** by formal elimination of a $HS(EtO_2C)C{=}CH(CO_2Et)$ unit, in turn being trapped by the alkyne to give the isolated sulfide **21**.[9]

From 2-Aminothiophene-3-carboxylic Acids or Their Alkyl Esters

Recently, a new method for the synthesis of valuable thieno[2,3-b] pyridine derivatives **23a–f** starting from the corresponding ethyl 2-aminothiophene-3-carboxylates **22a–c** has been reported.[10–12]

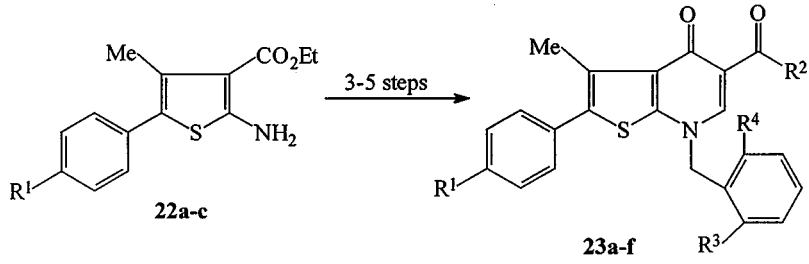


R^1= alkyl, Ph, substituted phenyl; R^2 = H, alkyl, alkoxycarbonyl, R^3= alkyl, alkoxyalkyl, aralkyl;

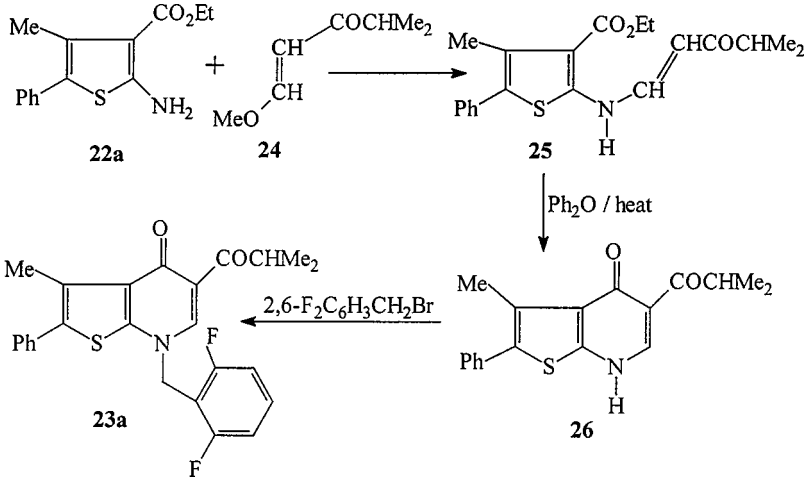


For example, the reaction of ethyl 2-amino-4-methyl-5-phenylthiophene-3-carboxylate (**22a**) with 1-methoxy-4-methyl-1-penten-3-one (**24**) gave the compound **25** which was cyclized into thieno[2,3-b] pyridine derivative **26** by heating in diphenyl ether. The latter compound was N-alkylated with 2,6-difluorobenzyl bromide to give the target compound **23a**.[12]

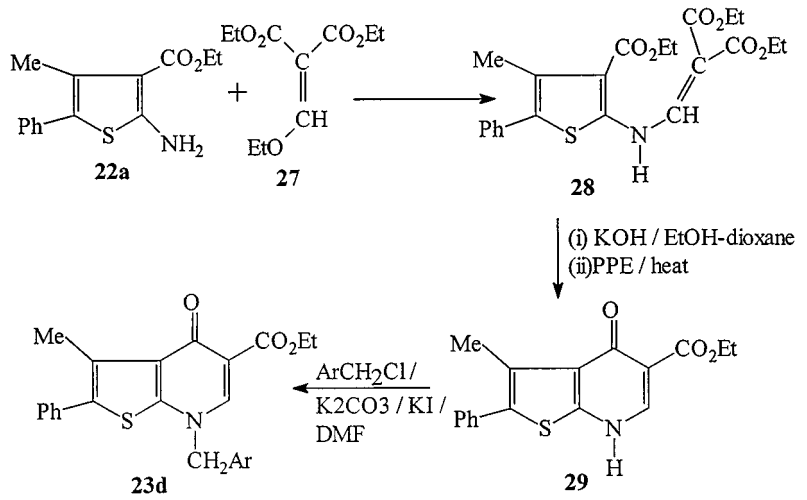
Also, the reaction of **22a** with diethyl ethoxymethylenemalonate (**27**) gave the thiophene derivative **28**. The alkaline hydrolysis of the



23	R^1	R^2	R^3	R^4	Ref.
a	H	$CHMe_2$	F	F	12
b	H	Ph	F	F	10
c	NO_2	Ph	F	F	10
d	H	OEt	F	F	11
e	OMe	OEt	OMe	H	10
f	NO_2	OEt	F	F	11

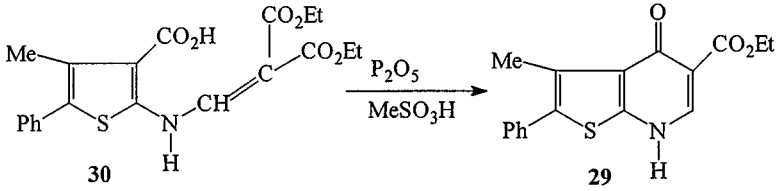


3-ethyl ester group of **28** followed by subsequent ring closure produced thieno[2,3-b]pyridine derivative **29**. The reaction of compound **29** with 2,6-difluorobenzyl chloride afforded compound **23d**.[11]

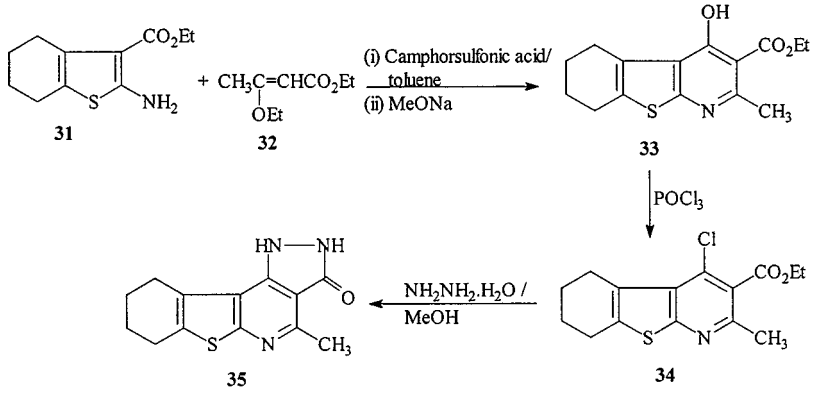


Also, cyclization of 2-aminothiophene-3-carboxylic acid derivative **30** into thieno[2,3-b]pyridine **29** derivative was achieved by heating with P_2O_5 in $MeSO_3H$.[13]

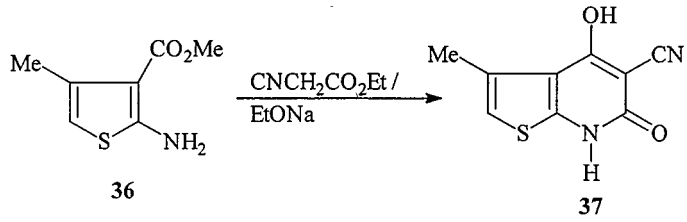
Ethyl 4-hydroxy-2-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-b] pyridine-3-carboxylate (**33**) was prepared by reaction of compound **31** with ethyl 3-ethoxycrotonate (**32**) in toluene containing camphorsulfonic acid followed by cyclization of the resulting intermediate with sodium methoxide.[14] Treatment of **33** with phosphorus oxychloride



gave the 4-chloro derivative **34** which was reacted with hydrazine hydrate in methanol to afford the fused tetracyclic compound **35**.[14]



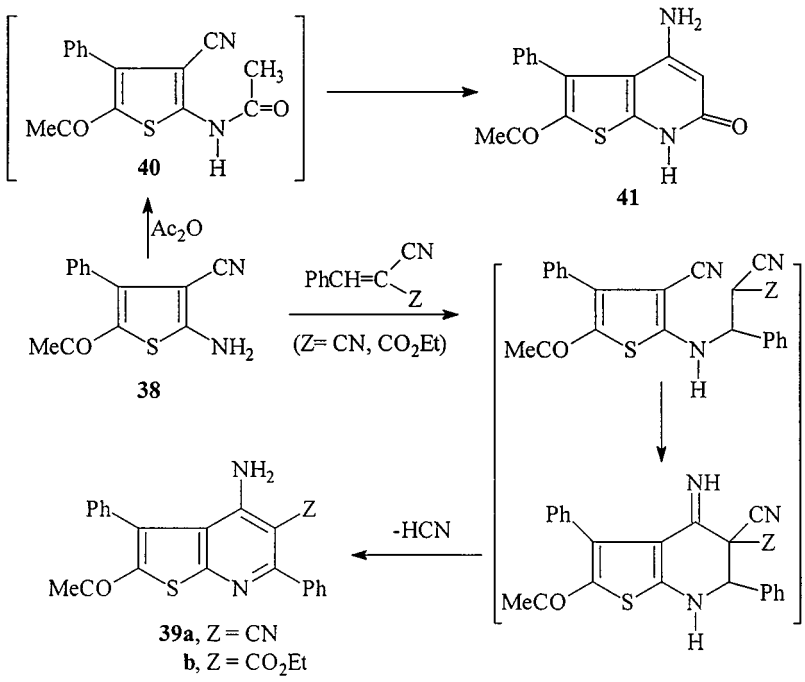
The cyclocondensation of methyl 2-amino-4-methylthiophene-3-carboxylate (**36**) with ethyl cyanoacetate in the presence of sodium ethoxide afforded 6,7-dihydro-4-hydroxy-3-methyl-6-oxothieno[2,3-b] pyridine-5-carbonitrile (**37**).[15]



From o-aminothiophenecarbonitriles

Both benzylidenemalononitrile and ethyl benzylidenecyanoacetate were reacted with 5-acetyl-2-amino-4-phenylthiophene-3-carbonitrile (**38**) to give the thieno[2,3-b]pyridines **39a**,**b**. This reaction is assumed to proceed via addition of the amino group of thiophene derivative **38** to the activated double bond of the reagent followed by cyclization and elimination of HCN.[16] Refluxing compound **38** with acetic anhydride led to the formation of thienopyridine derivative **41**.[16] The latter reaction

involves the formation of N-acetyl derivative **40** which underwent intramolecular cyclization to furnish the thienopyridine derivative **41**.[16]

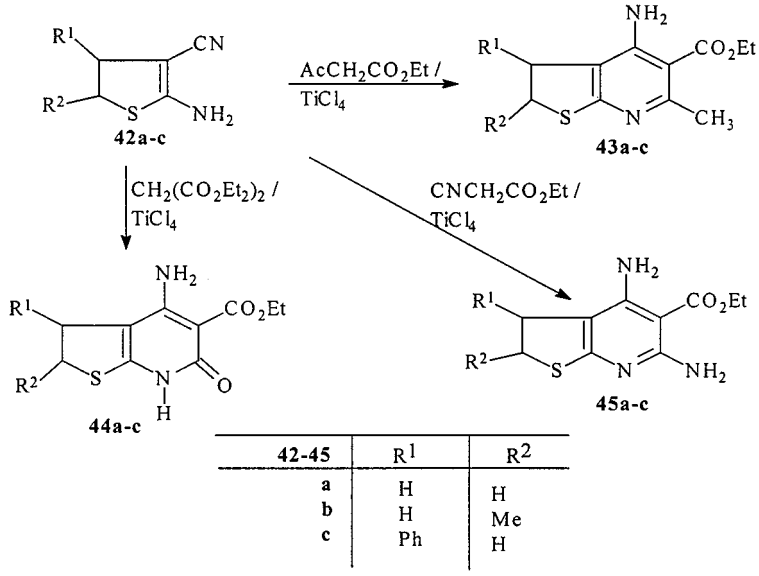


The reaction of 2-amino-4,5-dihydrothiophene-3-carbonitriles **42a–c** with ethyl acetoacetate, diethyl malonate, and ethyl cyanoacetate in the presence of $TiCl_4$ afforded the thieno[2,3-b]pyridines **43a–c**, **44a–c**, and **45a–c** respectively.[17]

Also, the *o*-aminothiophenecarbonitriles **46a**,[18] **46b**,[19] and **47a–c**[20] were used as starting materials for other thieno[2,3-b]pyridine derivatives.

From thienyl-β-ketoesters

Thienyl-β-ketoester **48** was condensed with triethyl orthoformate in acetic anhydride to produce the 3-ethoxyacrylate derivative **49**, which in turn was reacted smoothly with the appropriate alkyl[21] or aryl[22] amines in an addition-elimination sequence to generate the respective 3-aminoacrylates **50a–p**. These enaminoketoesters exist in (*Z*)- and (*E*)- forms in solution where the former isomer is predominant. Treatment of compounds **50a–p** with sodium hydride in DMF afforded the



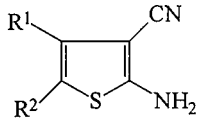
42-45	R^1	R^2
a	H	H
b	H	Me
c	Ph	H

corresponding methyl 2-chloro-7-alkyl or aryl-4,7-dihydro-4-oxo-thieno [2,3-b]pyridine-5-carboxylates (**51a–p**). Mild saponification of the latter esters furnished the target acids **52a–p**.

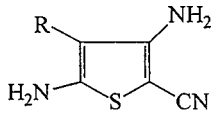
Synthesis Involving Formation of the Thiophene Ring

From 2-Chloropyridine-3-carboxaldehydes

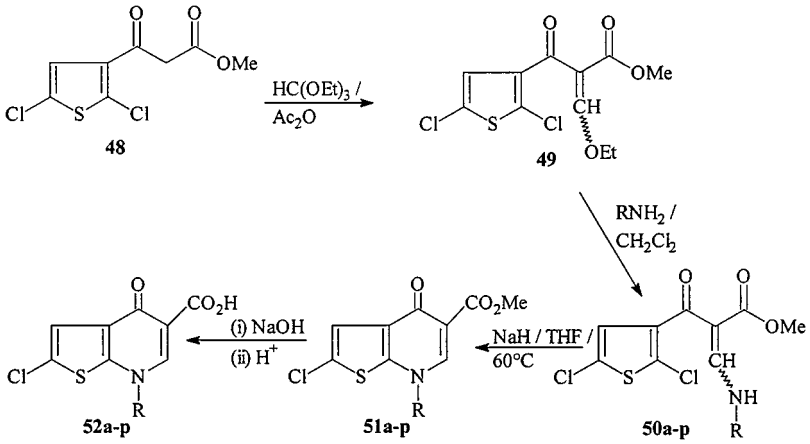
The synthesis of ethyl 4-aryl-4,7-dihydro-5-methoxycarbonyl-6-methylthieno[2,3-b]pyridine-2-carboxylates (**54**) was accomplished by refluxing of 2-chloro-1,4-dihydropyridine-3-carboxaldehydes **53** with an equimolar amount of ethyl thioglycolate in dry ethanol in the presence of sodium ethoxide under an inert atmosphere.[23] The reaction takes place by nucleophilic attack of the thioglycolate anion, generated in situ under the basic condition, at the carbon bearing the chlorine atom followed by intramolecular cyclization and dehydration to



46a, R^1 =Me, R^2 = MeCO
b, R^1 = Ph, R^2 = CN

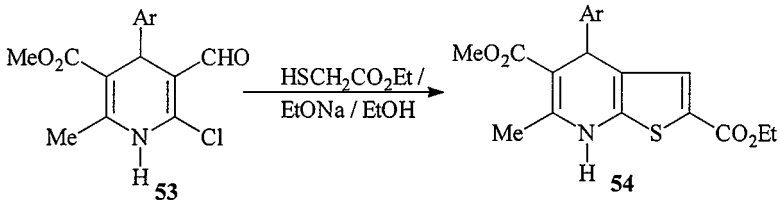


47a, R =CN
b, R =CO_2Et
c, R =CONHPh



50–52	R	Ref.	50–52	R	Ref.
a	Et	21	**i**	4-BrC_6H_4	22
b	cyclopropyl	21	**j**	4-HOC_6H_4	22
c	$CHMe_2$	21	**K**	4-$MeOC_6H_4$	22
d	$(CH_2)_2Me$	21	**l**	4-MeC_6H_4	22
e	CMe_3	21	**m**	2-FC_6H_4	22
f	Ph	22	**n**	2,4-$F_2C_6H_3$	22
g	4-FC_6H_4	22	**o**	2-$MeOC_6H_4$	22
h	4-ClC_6H_4	22	**p**	2-MeC_6H_4	22

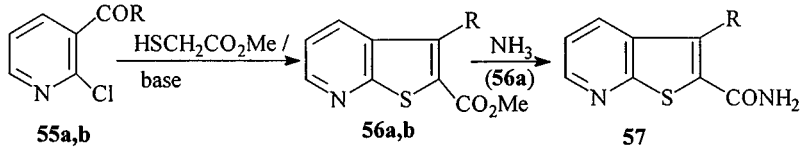
afford dihydrothieno[2,3-b]pyridines **54** as stable crystalline solids in good yields.[23]

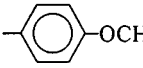


Ar =Ph, 2-ClC_6H_4, 3-$NO_2C_6H_4$, 4-MeO_2C-C_6H_4

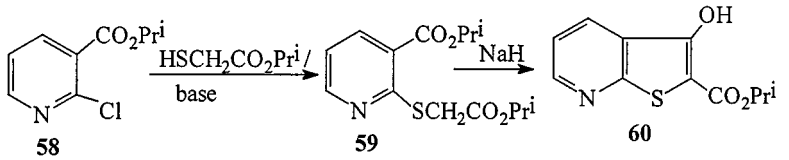
From 3-Aroyl-, Heteroaroyl-, or Alkoxycarbonyl-2-chloropyridines

The reaction of 3-aroyl[24] or 3-(2′-thenoyl)[25]-2-chloropyridines **55a**,**b** with methyl thioglycolate was patented to give the thieno[2,3-b]pyridines **56a**,**b**. On treatment of **56a** with ammonia, the amide **57** was obtained.[24]



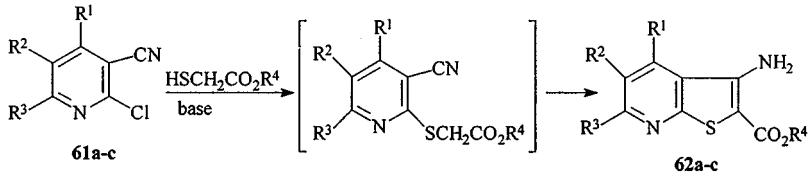
56a, 57, R=  $OCH_2CH_2CH_2NMe_2$, **56b**, R = 2-thienyl

The reaction of isopropyl 2-chloronicotinate (**58**) with isopropyl thioglycolate gave the compound **59** which was cyclized into isopropyl 3-hydroxythieno[2,3-b]pyridine-2-carboxylate (**60**) on treatment with sodium hydride for a long time.[26]



From 2-Chloropyridine-3-carbonitriles

Alkyl 3-aminothieno[2,3-b]pyridine-2-carboxylates **62a–c** were prepared from the reaction of **61a–c** with alkyl thioglycolate in the presence of a basic catalyst.[27–29]

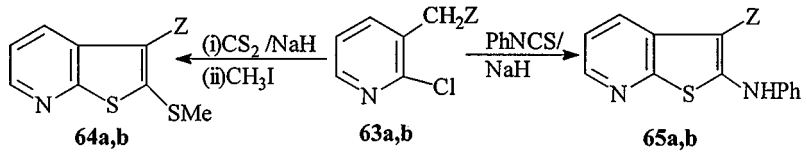


61, 62	R^1	R^2	R^3	R^4	Ref.
a	—$(CH_2)_4$—		H	Et	27
b	H	H	Me	Me	28
c	H	CO_2Et	Me	Et	29

From Ethyl (2-Chloro-3-pyridyl)acetate or 2-Chloro-3-pyridylacetonitrile

Ethyl (2-chloro-3-pyridyl)acetate (**63a**) or 2-chloro-3-pyridylacetonitrile (**63b**), which have a methylene group activated by the ester or nitrile functionality, when reacted with carbon disulfide in the presence of sodium hydride followed by treatment with methyl

iodide, gave 2-methylmercaptothieno[2,3-b]pyridine derivatives **64a** and **64b**.[30,31] Similarly, the reaction of **63a**,**b** with phenyl isothiocyanate produced the corresponding anilinothieno[2,3-b]pyridines **65a**,**b**.[32]

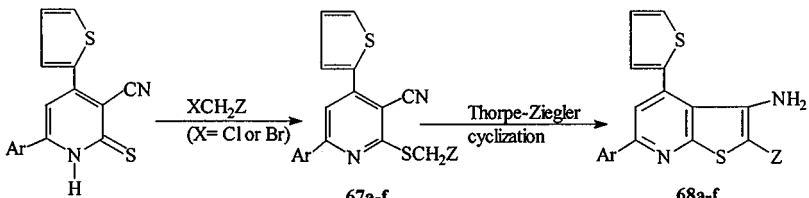


64a,b **63a,b** **65a,b**

63-65	Z
a	CO_2Et
b	CN

From 3-Cyanopyridine-2(1H)-thiones

Substituted 3-cyanopyridine-2(1*H*)-thiones were used extensively in the synthesis of a large number of functionally substituted thieno[2,3-b] pyridines. Thus, the reaction of 3-cyanopyridine-2(1*H*)-thiones **66a**,**b** with phenacyl bromide, ethyl chloroacetate, or chloroacetamide gave the *S*-alkylated products **67a–f**. Upon heating of the latter compounds with sodium ethoxide in ethanol, they underwent intramolecular Thorpe-Ziegler cyclization to give the corresponding thieno[2,3-b]pyridine deivatives **68a–f**.[33]

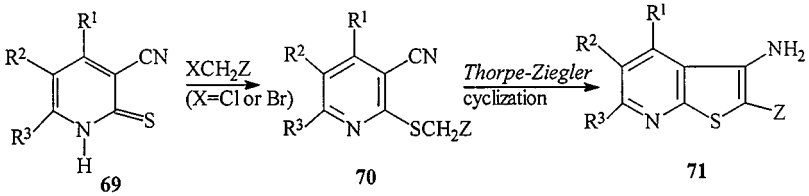


66a, Ar = Ph
b, Ar = 4-ClC_6H_4 **67a-f** **68a-f**

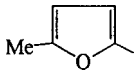
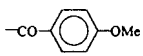
66-68	Ar	Z	66-68	Ar	Z
a	Ph	COPh	d	4-ClC_6H_4	CO_2Et
b	4-ClC_6H_4	COPh	e	Ph	$CONH_2$
c	Ph	CO_2Et	f	4-ClC_6H_4	$CONH_2$

Similarly, 2-functionalized 3-aminothieno[2,3-b]pyridine derivatives of the type **71** were prepared from the reaction of 3-cyanopyridine-2(1*H*)-thiones **69** with the respective halo compounds such as chloroacetone, phenacyl bromides, chloroacetic acid, ethyl chloroacetate,

chloroacetamide, chloro-*N*-arylacetamides, or chloroacetonitrile followed by cyclization of the resulting intermediates **70**.[34–44]



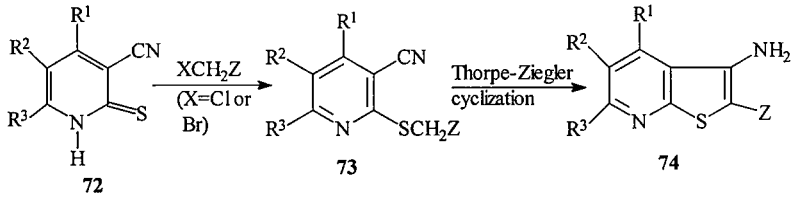
69 **70** **71**

R^1	R^2	R^3	Z	Ref.
H	H	n-Pr	COPh, CO_2Et, $CONH_2$, CN	34
H	Et	Me	COPh, CO_2Et, $CONH_2$, CN	34
Me	H	Me	$CONH_2$, CONHPh, $CONHC_6H_4Me(4)$, $CONHC_6H_4Cl(4)$	35
CH_2OMe	H	Me	COAr, $CONH_2$, CONHPh	36
Ph	H	Ph	COPh, CO_2Et, CO_2H	37
Me	H	CH_2OH	COAr, CO_2H, CO_2Et, $CONH_2$	38
4-ClC_6H_4	H	Me	$CONH_2$, CONHPh	39
2-furyl	H	Me	$CONH_2$, CONHPh	39
PhCH=CH	H	Ph	COMe	40
	H	Me	COPh, $COC_6H_3Cl_2(3,4)$, $COC_6H_4Br(4)$, CONH2	41
CF_3	H	2-thienyl	$CONH_2$, CONHPh, $CONHC_6H_4Cl(4)$	42
Ph	H	2-benzimidazolyl	COMe, COPh, CO_2Et, $CONH_2$, CONHPh	43
SMe		H	CO_2Et, $CONH_2$	44

Also, the reaction of trisubstituted 3-cyanopyridine-2(1*H*)-thiones of the type **72** with the appropriate α-haloketones, α-haloesters, chloroacetamide, or chloroacetonitrile produced the pentasubstituted thiopyridines **73**. When the latter compounds were heated with strong base such as potassium hydroxide or sodium alkoxide, they underwent intramolecular Thorpe-Ziegler cyclization to give the thieno[2,3-b] pyridine derivatives **74**.[45–53]

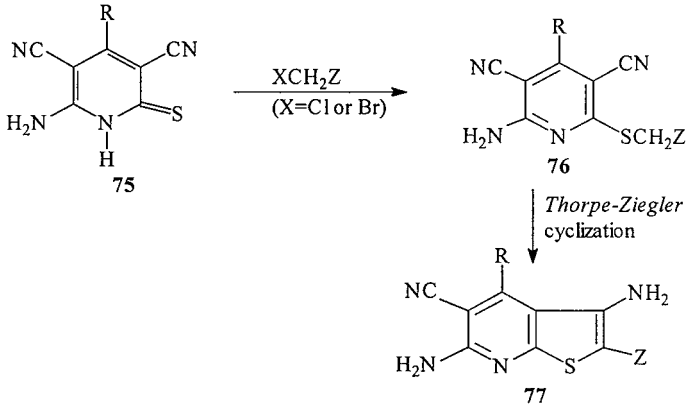
Moreover, the polyfunctionally substituted thieno[2,3-b]pyridines of the type **77** were prepared from the reaction of the appropriate 3-cyanopyridine-2(1*H*)-thiones **75** with the respective halo compounds followed by cyclization of the resulting intermediates **76**.[54,55]

The above mentioned sequence was extended for synthesizing some cycloalka[e]thieno[2,3-b]pyridines **80** and was started from the appropriate 3-cyanocycloalka[b]pyridine-2(1*H*)-thiones **78**.[56–58]



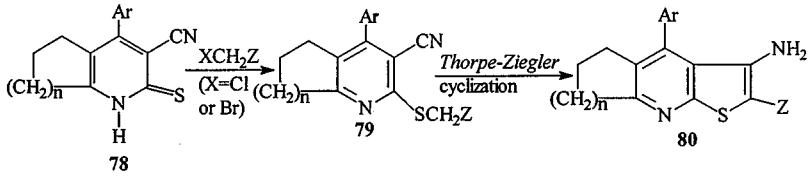
72 73 74

R^1	R^2	R^3	Z	Ref.
Et	PhNHCO	Me	$COC_6H_4Cl(4)$, 2-thenoyl	45
Me	Me	Me	$CONH_2$, CN	46
ph	Me	ph	COPh, CO_2Et, $CONH_2$, CN	46
Ph	CO_2Et	Me	CO_2Me	47
4-$MeOC_6H_4$	CO_2Et	Ph	COMe, COPh, $COC_6H_4Cl(4)$	48
4-ClC_6H_4	CO_2Et	Ph	COMe, COPh, COC_6H_4Cl (4)	48
4-ClC_6H_4	CO_2Et	Me	COMe, COC_6H_4Cl (4), CO_2Et, $CONH_2$	49
2-furyl	CO_2Et	Me	COMe, COC_6H_4Cl (4), CO_2Et, $CONH_2$	49
4-$MeOC_6H_4$	COMe	Me	$COCH_3$, CO_2Et	50
4-ClC_6H_4	COMe	Me	$COCH_3$, CO_2Et	50
4-$MeOC_6H_4$	COMe	Me	$CONH_2$	51
4-ClC_6H_4	COMe	Me	$CONH_2$	51
2-furyl	PhNHCO	Me	$COC_6H_3Cl_2(3,4)$, CO_2Et	52
Ph	CN	OEt	CN	53



75 76 77

R	Z	Ref.
n-Pr	CO_2Me, $COC_6H_4Cl(4)$	54
CH_2CHMe_2	CO_2Me, $COC_6H_4Cl(4)$	54
Pr^t	CO_2Me, $COC_6H_4Cl(4)$	54
4-BrC_6H_4	$COC_6H_4Br(4)$, $COC_6H_4Cl(4)$, $CONH_2$	55
4-FC_6H_4	$COC_6H_4Br(4)$, $COC_6H_4Cl(4)$, $CONH_2$	55
3-FC_6H_4	$COC_6H_4Br(4)$, $COC_6H_4Cl(4)$, $CONH_2$	55
2,4-$(EtO)_2C_6H_3$	$COC_6H_4Br(4)$, $COC_6H_4Cl(4)$, $CONH_2$	55
4-$NO_2C_6H_4$	$COC_6H_4Br(4)$, $COC_6H_4Cl(4)$, $CONH_2$	55



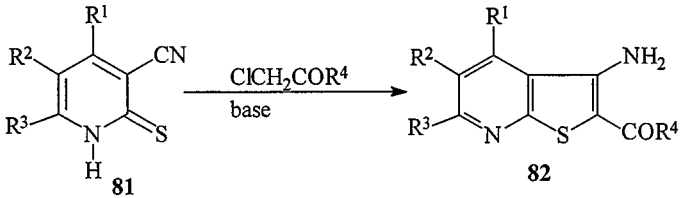
n	Ar	Z	Ref.
1	Ph	CO_2Et, $CONH_2$	56
1	4-$MeOC_6H_4$	CO_2Et, $CONH_2$	56
1	Ph	CONHPh, $CONHC_6H_4Me(4)$, $CONHC_6H_4Cl(4)$, CN	57
1	4-$MeOC_6H_4$	CONHPh, $CONHC_6H_4Me(4)$, $CONHC_6H_4Cl(4)$, CN	57
1	4-ClC_6H_4	CONHPh, $CONHC_6H_4Me(4)$, $CONHC_6H_4Cl(4)$, CN	57
2	Ph	COMe	58
2	4-$MeOC_6H_4$	COMe, CO_2Et, $CONH_2$	58
2	4-ClC_6H_4	COMe	58

When the reaction of 3-cyanopyridine-2(1*H*)-thiones **81** or **83** with some α-haloketones or alkyl chloroacetate was carried out in a high boiling point solvent such as pyridine[62] or in the presence of a relatively strong base such as potassium carbonate,[59,61,66] potassium hydroxide,[60] or sodium alkoxide,[63–65,67] the corresponding thieno[2,3-b]pyridine derivatives **82**[59–65] and **84**[59,66,67] were directly obtained. Similarly, the compounds **85** were reacted with chloroacetonitrile and/or chloroacetamide in the presence of potassium carbonate[59,69,70] or sodium methoxide[68] to give the target 2-functionalized 3-aminothieno[2,3-b] pyridines **86**.[59,68–70]

When the compounds **87** were allowed to react with chloroacetone, ethyl chloroacetate, or chloroacetonitrile in the presence of potassium carbonate, the 2-functionalized 3-aminothieno[2,3-b]pyridine derivatives **88** were obtained.[59] Similarly, the cycloalka[d]thieno[2,3-b]pyridines **90** were prepared from the reaction of **89** with phenacyl bromide in DMF containing potassium carbonate.[71] Moreover, the heterocyclothienopyridines **92** were prepared from the reaction of 3-cyanopyridine-2(1*H*)-thiones **91** with the respective chloro compounds.[72]

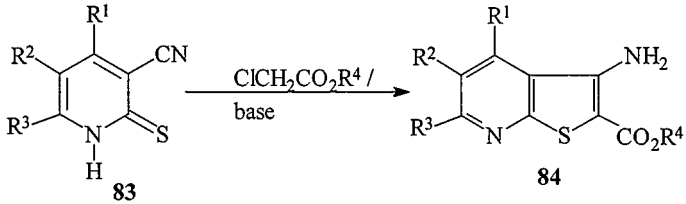
3-Cyanopyridine-2(1*H*)-thiones of the type **69** ($R^2 = H$) were reacted with bromonitromethane, which has a methylene group of high activity in the presence of triethylamine to give 3-amino-2-nitrothieno[2,3-b] pyridine derivatives **93**.[73]

Some heterocyclic compounds incorporating two thieno[2,3-b]pyridine moieties in their structures were prepared via two methods. First, the reaction of compound **94** with two molar ratios of



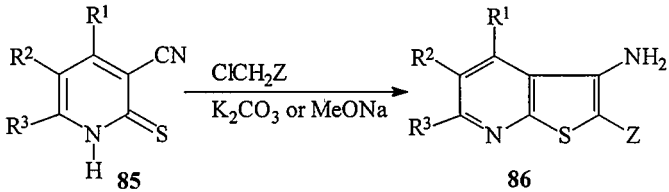
81 82

R^1	R^2	R^3	R^4	Ref.
H	H	Me	Me	59
Me	H	Me	Me	59
styryl	H	Me	Me	59
styryl	H	styryl	Me	59
H	H	Ph	Ph	60
Me	H	Ph	Ph	60
Me	H	NH_2	Ph	61
Et	CN	NH_2	Ph	62
CO_2Et	H	Me	Me or Bu^t	63
CO_2Et	H	Me	Ar	63
CO_2Et	H	Me	5-chloro-2-thienyl	63
Me	PhN=N	Me	Ph	64
Ph	4-ClC_6H_4N=N	Ph	Ph	65
Ph	4-BrC_6H_4N=N	Ph	Ph	65
Ph	4-MeC_6H_4N=N	Ph	Ph	65
Ph	4-$MeOC_6H_4N$=N	Ph	Ph	65
Ph	4-$NO_2C_6H_4N$=N	Ph	Ph	65



83 84

R^1	R^2	R^3	R^4	Ref.
H	H	Me	Et	59
Me	H	Me	Et	66
styryl	H	Me	Et	59
styryl	H	styryl	Et	59
H	H	Ph	Et	67
Me	H	Ph	Et	67
Me	Me	Me	Et	67
Me	$PhCH_2$	Me	Et	67
4-BrC_6H_4	H	Me	Me	67
Me	H	4-BrC_6H_4	Me	67

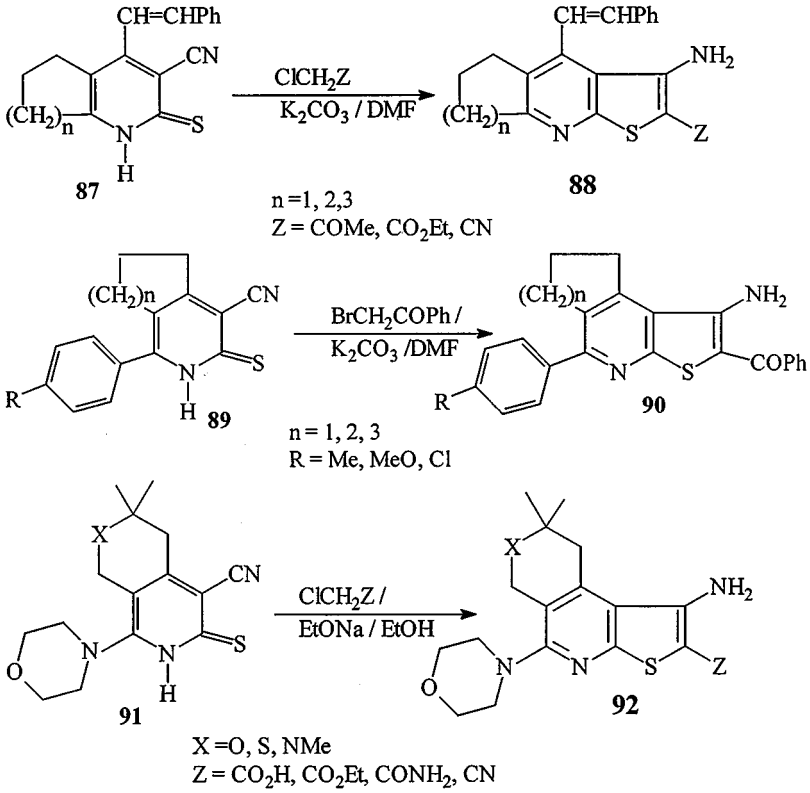


85 **86**

R^1	R^2	R^3	Z	Ref.
H	H	Me	CN	59
Me	H	Me	CN	59
styryl	H	Me	CN	59
styryl	H	styryl	CN	59
Ph	H	Me	$CONH_2$	68
Ph	H	Me	CN	68
Me	H	Ph	$CONH_2$	68
Me	H	Ph	CN	68
Ph	H	Ph	CN	68
Me	H	4-ClC_6H_4	CN	68
4-ClC_6H_4	H	Me	CN	68
4-ClC_6H_4	H	Ph	$CONH_2$	68
4-ClC_6H_4	H	Ph	CN	68
4-ClC_6H_4	H	4-ClC_6H_4	$CONH_2$	68
4-ClC_6H_4	H	4-ClC_6H_4	CN	68
4-BrC_6H_4	H	Me	$CONH_2$	68
Me	H	4-BrC_6H_4	$CONH_2$	68
Me	Me	Me	$CONH_2$	68
Me	Me	Me	CN	68
Me	CH_2Ph	Me	$CONH_2$	68
Me	CH_2Ph	Me	CN	68
H	CO_2Et	Et	$CONH_2$	69
Ph	CN	OEt	$CONH_2$	70

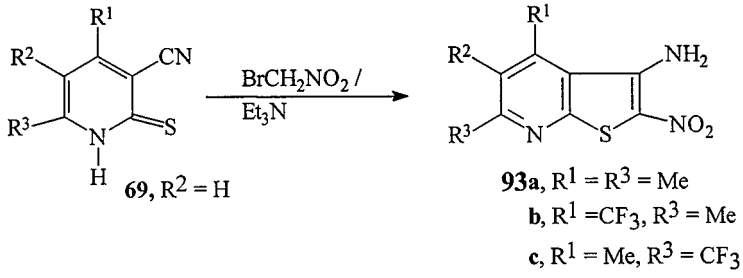
chloroacetamide yielded the compound **95** which underwent intramolecular Thorpe-Ziegler cyclization upon treatment with sodium ethoxide to furnish the thieno[2,3-b]pyridine derivative **96**.[74]

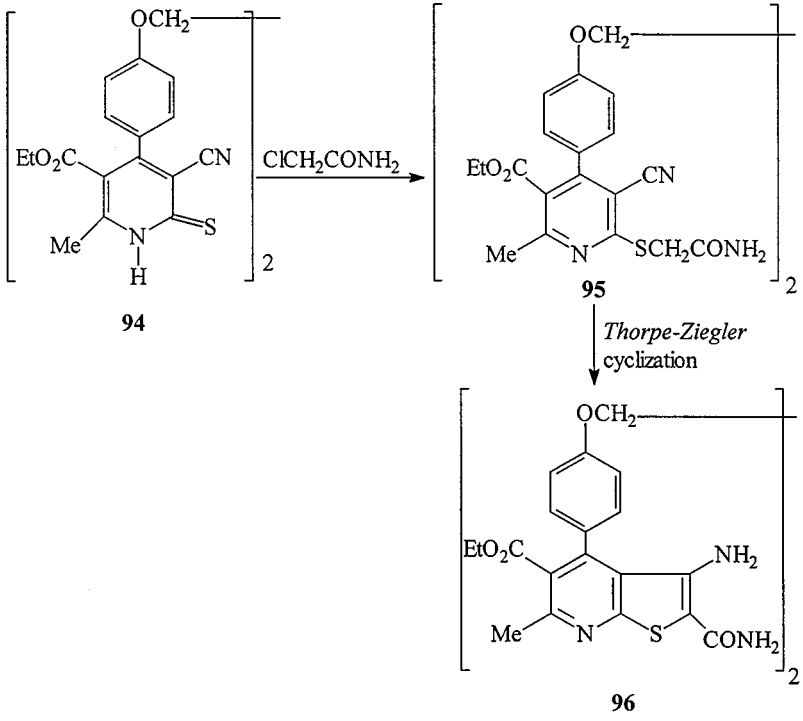
Second, when the compounds **69** were allowed to react with 1,3-dichloroacetone (in 2:1 molar ratios) by refluxing in ethanol containing triethylamine, the products were identified as **97a–d**.[75] Cyclization of **97a–d** into the desired thienopyridines **98a–d** was achieved by heating with sodium methoxide in methanol. The latter compounds also were prepared by the reaction of **69** with 1,3-dichloroacetone in the presence of sodium methoxide as a basic catalyst.[75] Diazotization of **98a–d** using sodium nitrite and H_3PO_4 AcOH mixture led to the formation of the pentacyclic systems **99a–d**.[75]



From 3-Cyano-1,2,5,6-tetrahydro-2-thioxopyridines

The reaction of 4-aryl-3-cyano-5-ethoxycarbonyl-6-oxo-1,2,5,6-tetrahydro-2-thioxopyridines (**100**) with chloroacetone, phenacyl bromide, ethyl chloroacetate, or chloroacetamide in the presence of equimolar quantity of sodium ethoxide gave the S-alkylated derivatives **101**. Upon heating of the latter compounds with KOH





in methanol, the corresponding thieno[2,3-b]pyridines **102** were obtained.[76]

From 1,4-Dihydro-3-cyanopyridine-2-thiols

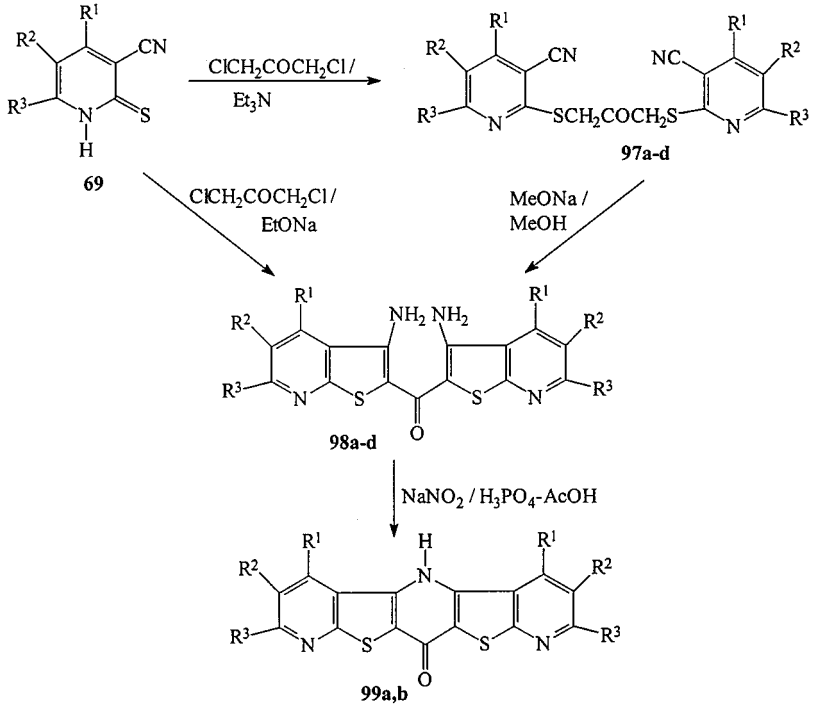
When the piperidinum 1,4-dihydro-3-cyanopyridine-2-thiolates **103** were reacted with iodoacetamide or chloroacetonitrile followed by cyclization of the resulting intermediates **104**, the corresponding 4,7-dihydrothieno[2,3-b]pyridines **105** were isolated.[77,78]

From Other Pyridine Derivatives

Heating 2-phenacylthionicotinic acid (**106**) with polyphosphoric acid at 100°C produced 2-benzoyl-3-hydroxythieno[2,3-b]pyridine (**107**).[79]

The reaction of sodium 3-carbamoyl-5-(4′-pyridyl)pyridine-2-thiolate (**108**) with iodoacetamide gave the pyridine derivative **109** which was cyclized to give the thieno[2,3-b] pyridine derivative **110**.[80]

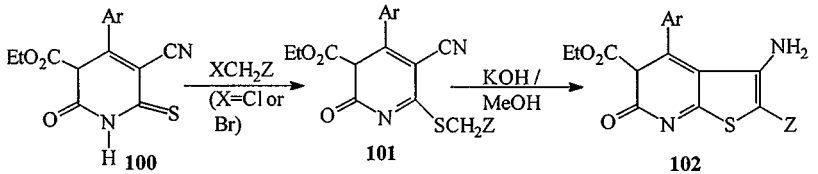
The *N*,*N*-dimethyl-2-benzylthionicotinamide (**111**) was cyclized into thieno[2,3-b]pyridine derivative **112** in the presence of potassium tert-butoxide.[81]



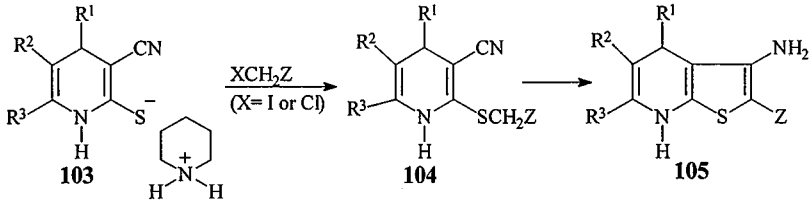
97–99	R^1	R^2	R^3
a	Me	H	Me
b	4-BrC_6H_4	H	Me
c	Me	H	Ph
d	SMe	CN	NH_2

Synthesis Involving Intramolecular Diels-Alder Reaction

Some heterocycles carrying a dienophilic side chain were observed to undergo intramolecular Diels-Alder reaction to give heterocyclic



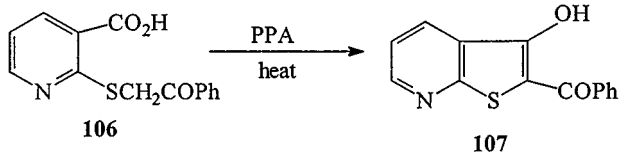
Ar = Ph, 4-ClC_6H_4, 2-furyl
Z = COMe, COPh, CO_2Et, $CONH_2$

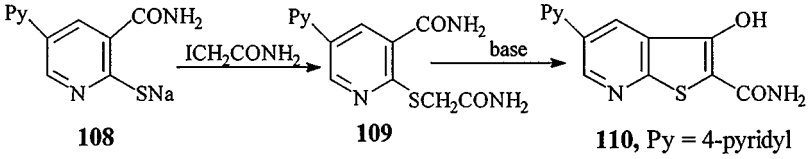


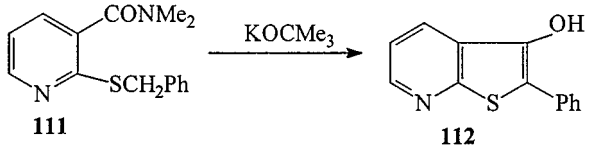
104–105	R^1	R^2	R^3	Z	Ref.
a	Ph	CO_2Et	Ph	$CONH_2$	77
b	3-pyridyl	CO_2Et	Ph	$CONH_2$	77
c	2-furyl	$CONHC_6H_4OMe(4)$	Me	CN	78

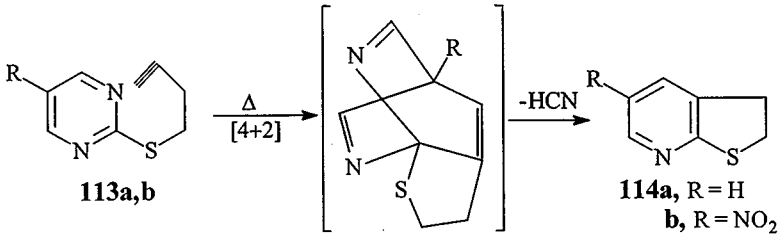
annelated pyridines viz. thieno[2,3-b]pyridines. Thus, heating 2-(3′-butynylthio)pyrimidines **113a**,**b** in nitrobenzene at 210°C under nitrogen atmosphere resulted in the formation of the corresponding 2,3-dihydro-thieno[2,3-b] pyridines **114a**,**b**.[82]

De Bie et al.[83] reported that heating of 2-(3′-butynylthio)pyrazine (**115**) leads to the formation of a mixture of **114a** and **118** via an intramolecular Diels-Alder reaction. Similar reactions of **116** or **117** were reported to give the corresponding thieno[2,3-b]pyridines **119** or **120** as the exclusive products.







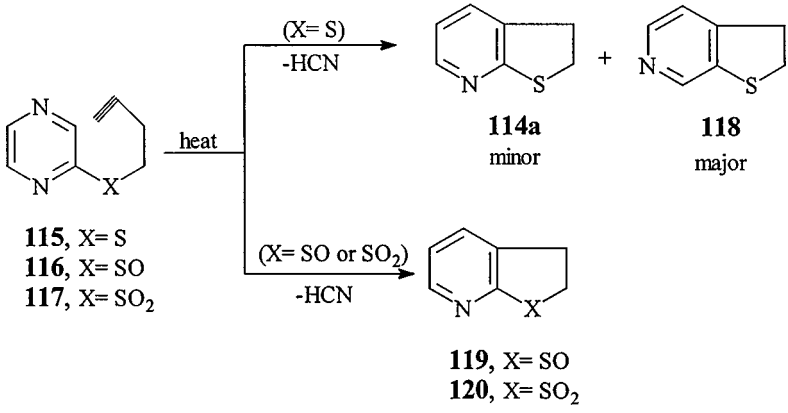


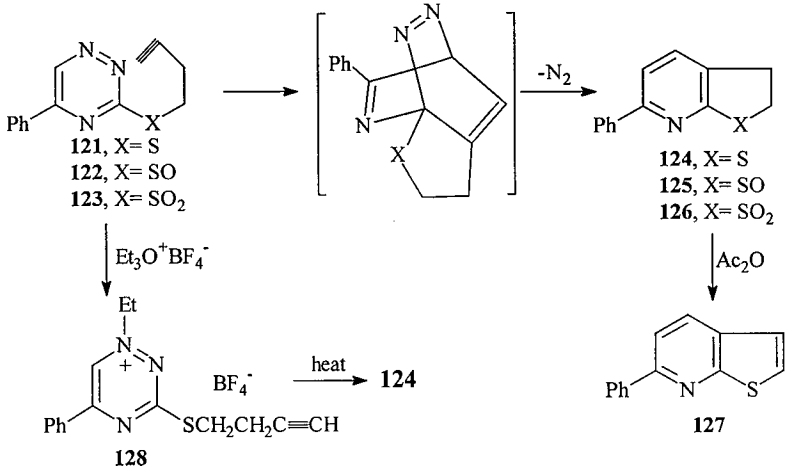
In a similar manner, the thieno[2,3-b]pyridine derivatives **124**, **125**, and **126** were obtained from the corresponding alkynylthio-1,2,4-triazines **121**, **122**, and **123**. Heating **125** with acetic anhydride led smoothly to 6-phenylthieno[2,3-b]pyridine (**127**).[84] Also, 2,3-dihydro-6-phenylthieno[2,3-b]pyridine (**124**) was obtained by quaternization of **121** with $Et_3O^+BF_4^-$ followed by heating of the resulting triazinium salt **128** in acetone, ethanol, or dioxane. This cyclization proceeds also via intramolecular Diels-Alder reaction.[85]

One-Pot Synthesis of Thieno[2,3-b]pyridines

Sherif et al.[86] reported that the reaction of 2-aminoprop-1-en-1,1,3-tricarbonitrile (**129**) with acetylacetone in the presence of elemental sulfur and triethylamine gives thieno[2,3-b]pyridine derivative **130**.

Also, the reaction of **129** with phenyl isothiocyanate followed by cyclization with phenacyl bromide,[87] ethyl chloroacetate, or α-chloroacetoacetanilide[88] furnished the thieno[2,3-b]pyridines **131a–c**.



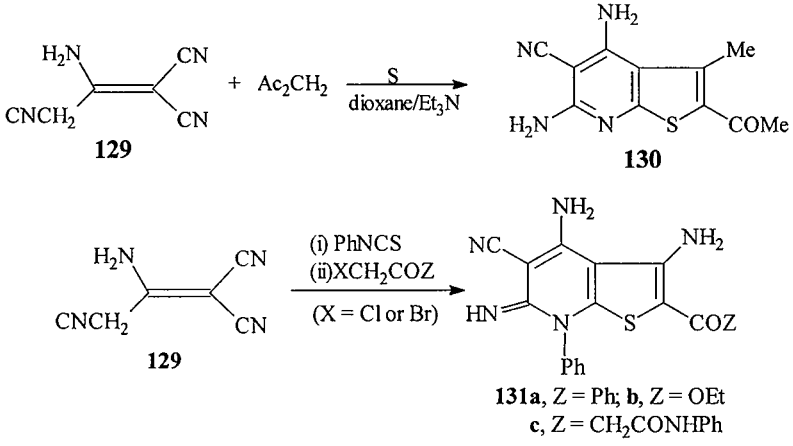


REACTIONS OF THIENO[2,3-b]PYRIDINES

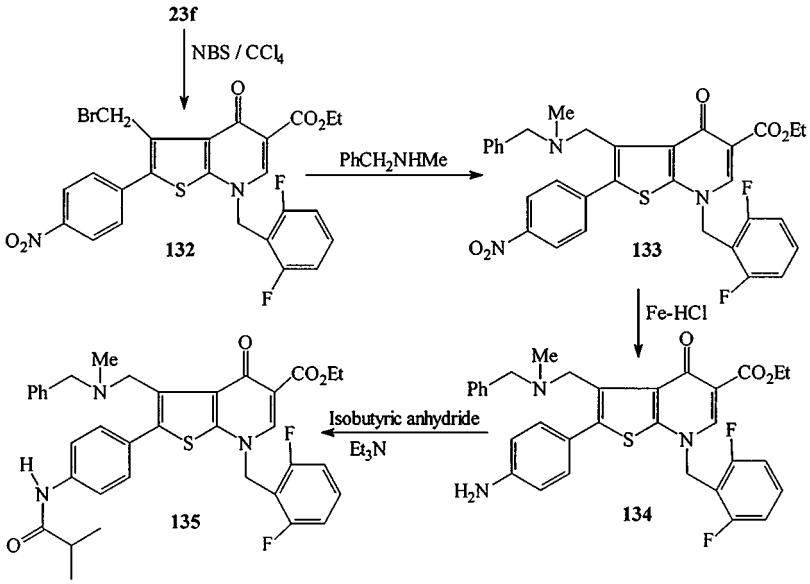
The forward reactions of functionally substituted-thieno[2,3-b]pyridines with a variety of reagents have been reported to give other thieno[2,3-b]pyridine derivatives as well as a large number of their fused heterocyclic systems. Most of these reactions are summarized below.

Reactions of 5-Functionalized 4,7-Dihydro-4-oxothieno[2,3-b]pyridines

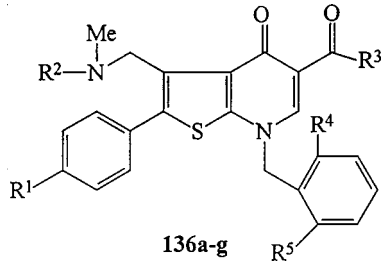
Radical bromination of the thienopyridine derivative **23f** gave the bromomethyl compound **132** which was reacted with *N*-benzylmethylamine to furnished the compound **133**. Reduction of **133** with iron



powder-concentrated HCl produced the amino compound **134** which was converted into the amide **135** by acylation with isobutyric anhydride.[11]

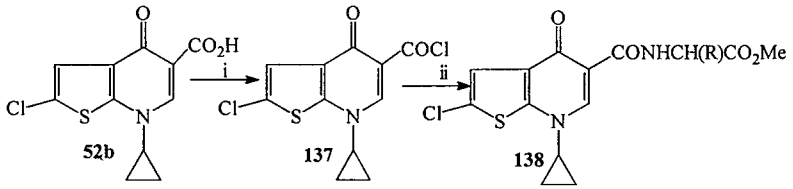


Similar reactions were performed on other thieno[2,3-b]pyridines to produce the corresponding products **136a–g**.[10,11,89–91]



Compound 136	R^1	R^2	R^3	R^4	R^5	Ref.
a	MeO	$PhCH_2$	OEt	OMe	H	11, 89
b	MeO	$PhCH_2$	OEt	F	F	11
c	NH_2	$PhCH_2$	$CHMe_2$	F	F	90
d	MeO	$PhCH_2$	OEt	F	F	89
e	OH	$PhCH_2$	Ph	F	F	91
f	$OCH_2CH{=}CH_2$	$PhCH_2$	Ph	F	F	91
g	EtCONH	$PhCH_2$	Ph	F	F	10

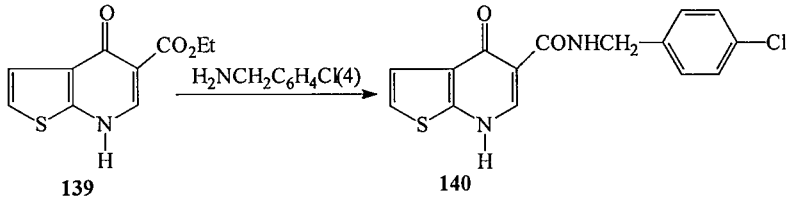
The reaction of 2-chloro-4,7-dihydro-7-cyclopropyl-4-oxothieno [2,3-b]pyridine-5-carboxylic acid (**52b**) with thionyl chloride gave the acid chloride **137**, which in turn was reacted with L-α-aminoesters hydrochloride to give the target thieno[2,3-b]pyridine derivatives **138**.[92]



i: $SOCl_2$; ii: $Cl^- H_3N^+CH(R)CO_2Me$ / pyridine

R = Me, CHMe, CH_2CHMe_2, $CH(Me)CH_2Me$, Ph, CH_2Ph, $CH_2C_6H_4OH(4)$

In contrast, the thieno[2,3-b]pyridine derivative **140** was prepared in a one-pot reaction via treatment of **139** with 4-chlorobenzylamine.[93]

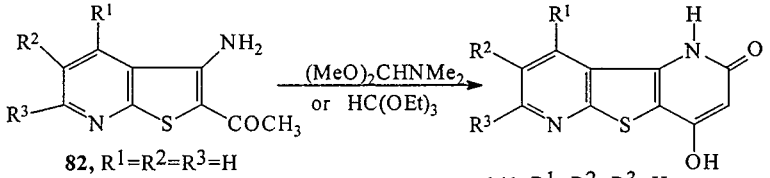


Reactions of 2-Acetyl-, Aroyl-, or Heteroaroyl-3-amino-thieno[2,3-b]pyridines

The cyclocondensation of 2-acetyl-3-aminothieno[2,3-b]pyridine (**82**) with *N*,*N*-dimethylformamide dimethylacetal or triethyl orthoformate gave 4-hydroxypyrido[2′,3′:4,5]thieno[2,3-b]pyridine-2(1*H*)-one (**141**).[94] The methyl analog **143** was prepared by intramolecular cyclization of **142** under basic conditions.[95]

The reaction of 2-acetyl-3-amino-4,6-dimethylthieno[2,3-b] pyridine (**82**) with some aldehydes by heating in ethanol and in the presence of sodium hydroxide was reported to give 2-substituted 7,9-dimethylpyrido-[2′,3′:4,5]thieno[2,3-b]pyridine-4(1*H*)-ones (**144a–c**).[96]

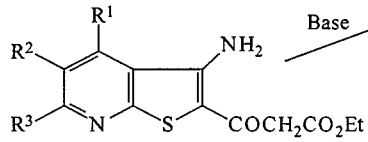
In contrast, when a similar reaction of **80** with some aromatic aldehydes was performed at 50–55°C, the products were identified as β-aminochalcones **145a–e**.[58] The reactivity of **145a–c** as chalcones were tested upon treatment with hydrazine hydrate where the pyrazoline derivatives **146a–c** were obtained. Cyclization of **145a–c** into the corresponding tetrahydropyridine derivatives **147a–c** was achieved by heating with orthophosphoric acid at 100°C.[58]



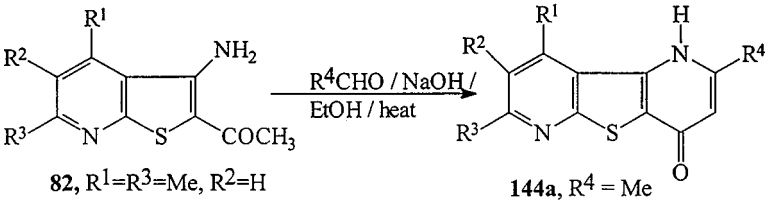
82, $R^1=R^2=R^3=H$

141, $R^1=R^2=R^3=H$

143, $R^1=R^2=$, H, $R^3=Me$



142, $R^1=R^2=$, H, $R^3=Me$

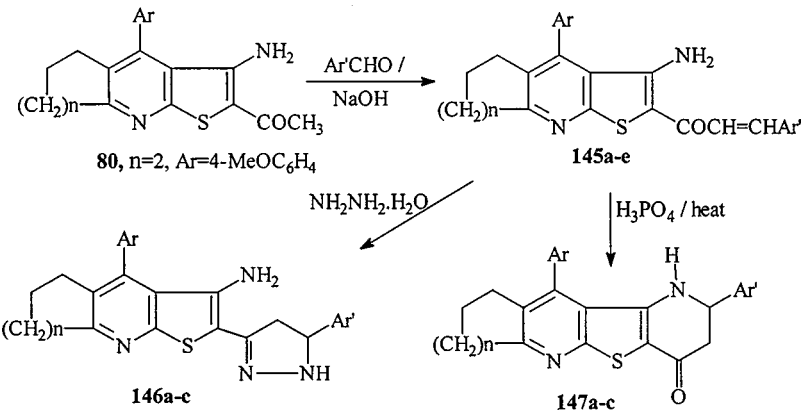


82, $R^1=R^3=Me$, $R^2=H$

144a, $R^4 = Me$

b, $R^4 = 4\text{-}ClC_6H_4$

c, $R^4 = 4\text{-}NO_2C_6H_4$



80, n=2, Ar=4-$MeOC_6H_4$

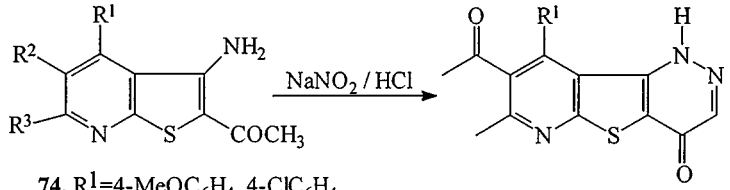
145a-e

146a-c

147a-c

145–147	Ar	Ar′
a	Ph	Ph
b	4-$MeOC_6H_4$	Ph
c	4-$MeOC_6H_4$	4-$MeOC_6H_4$
d	4-$MeOC_6H_4$	3,4-methylenedioxyphenyl
e	4-ClC_6H_4	Ph

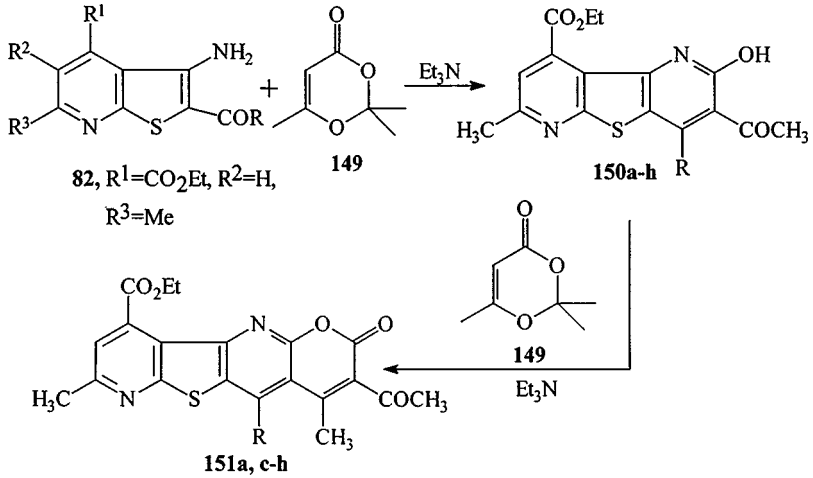
On the other hand, the reactivity of the enaminoacetyl moiety of compounds **74** was tested via its reaction with nitrous acid where the pyridothienopyridazinones **148a**,**b** were obtained.[50]



74, R^1=4-$MeOC_6H_4$, 4-ClC_6H_4
R^2=COMe
R^3=Me

148a, R^1 = 4-$MeOC_6H_4$,
b, R^1 =4-ClC_6H_4,

The triethylamine-catalyzed reaction of ethyl 2-acyl-, aroyl-, or heteroaroyl-3-amino-6-methylthieno[2,3-b]pyridine-4-carboxylates (**82**) with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**149**) gave the corresponding pyridothienopyridine derivatives **150a–h**.[63] The latter compounds reacted further with **149** to produce the fused pyranopyridothienopyridines **151a–h**.[63] Only compound **150b** did not give **151b**.[63] This may be due to the steric effect of the tert-butyl group.



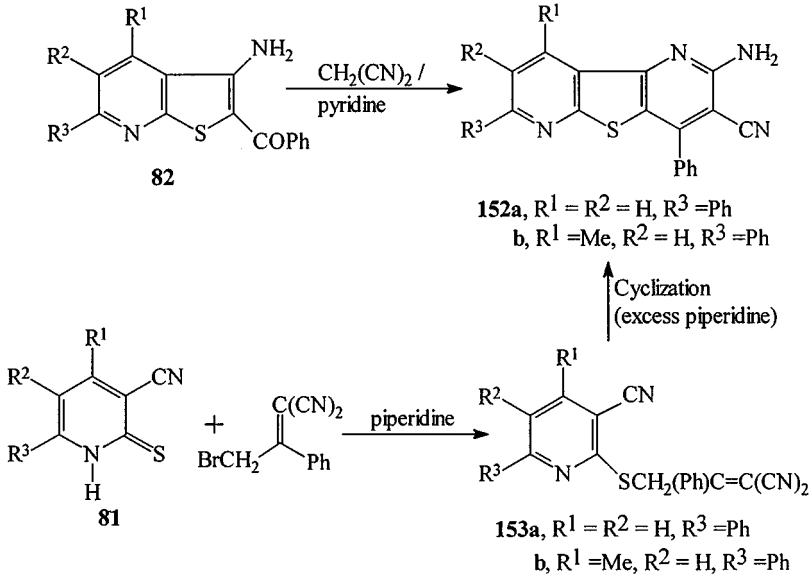
82, R^1=CO_2Et, R^2=H,
R^3=Me

150a-h

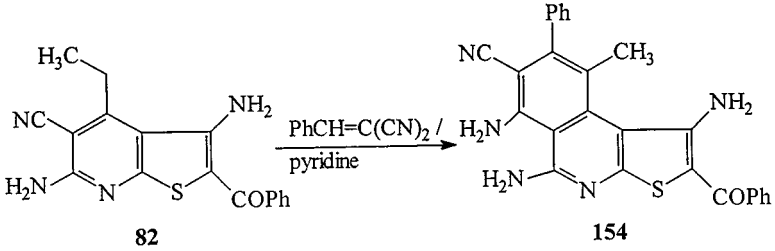
151a, c-h

Compound	R	Compound	R
150a, 151a	Me	**150e, 151e**	4-$NO_2C_6H_4$
150b	Bu^t	**150f, 151f**	3-$CF_3C_6H_4$
150c, 151c	Ph	**150g, 151g**	2,4-$Cl_2C_6H_4$
150d, 151d	4-$MeOC_6H_4$	**150h, 151h**	5-chloro-2-thienyl

The cyclocondensation of **82** with malononitrile by refluxing in pyridine afforded the corresponding pyridothienopyridine derivatives **152a**,**b**.[60] The latter compounds also were synthesized by reaction of 3-cyanopyridine-2(1H)-thiones **81** with 1-bromomethyl-1-phenyl-2-cyano-acrylonitrile followed by cyclization of the resulting products **153a**,**b**.[60]



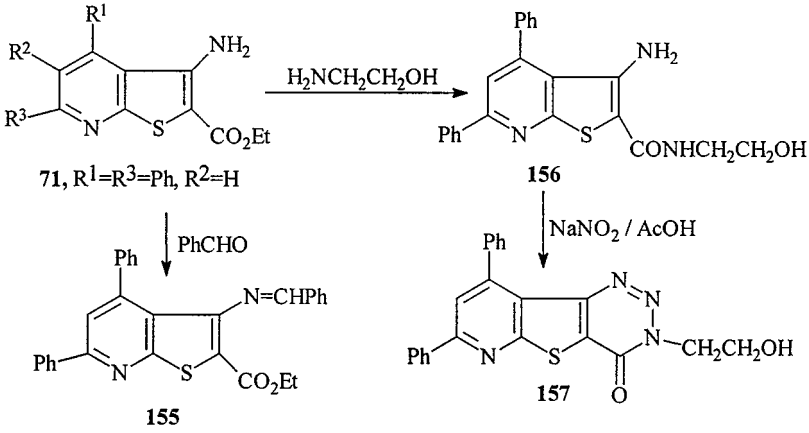
The reaction of thienopyridine derivative **82** with benzylidene-malononitrile in boiling pyridine resulted in the building of a benzo moiety to furnish the thienoisoquinoline derivative **154** in good yield.[62]



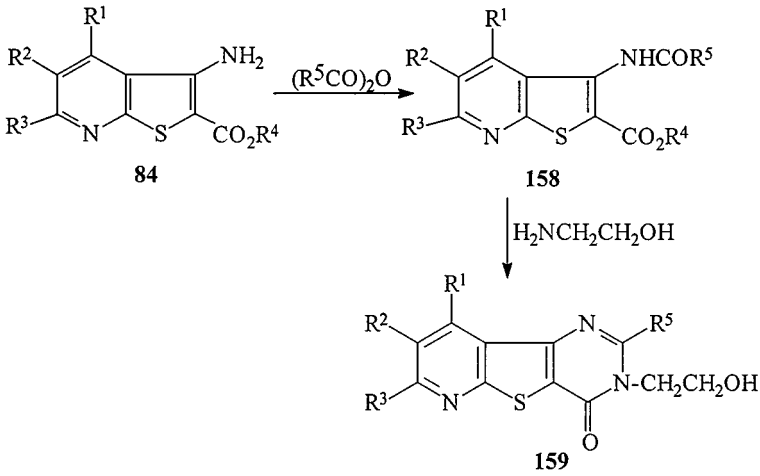
Reaction of Alkyl 3-Aminothieno[2,3-b]pyridine-2-carboxylates

Ethyl 4,6-diphenyl-3-aminothieno[2,3-b]pyridine-2-carboxylate (**71**) was condensed with benzaldehyde to give the Schiff's base **155**.[37] Also,

the reaction of **71** with ethanolamine yielded the thieno[2,3-b]pyridine derivative **156** which, upon treatment with nitrous acid, furnished pyridothienotriazinone **157**.[68]



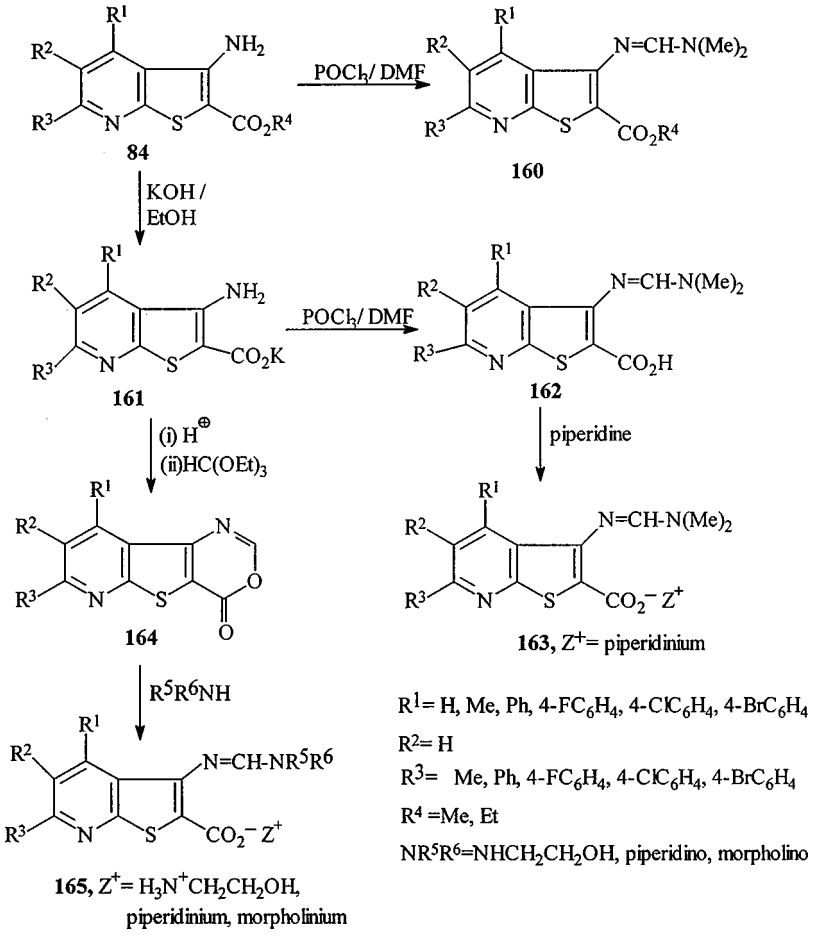
The acylation of *o*-aminoesters **84** with some acid anhydrides afforded the acylated derivatives **158**, which in turn were reacted with ethanolamine to afford pyridothienopyrimidines **159**.[67]



R^1=H, Me,4-BrC_6H_4; R^2=H, Me, $PhCH_2$
R^3=Me, Ph, 4-BrC_6H_4; R^4=Me ,Et; R^5=Me, Et

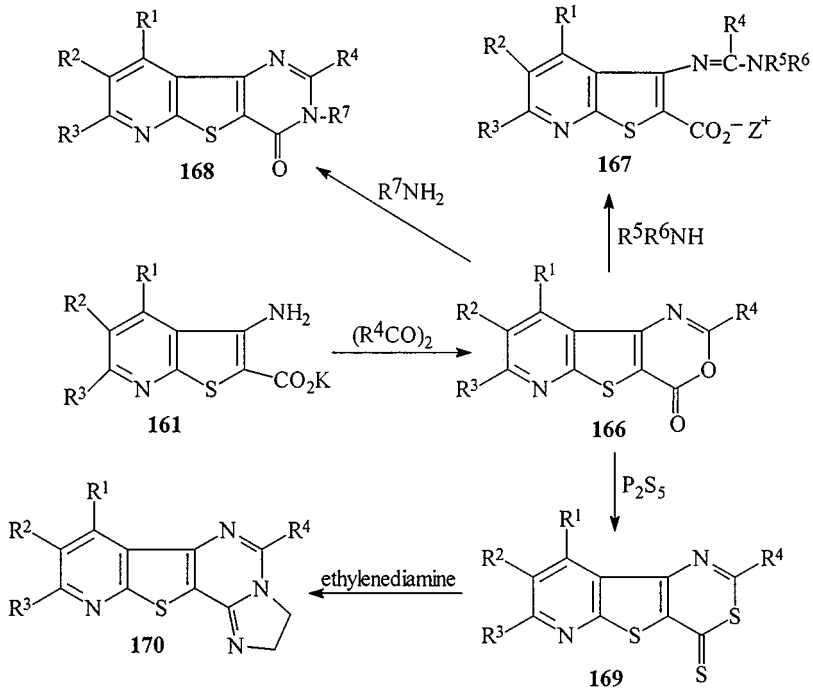
On treatment of *o*-aminoesters **84** with Vilsmeier reagent ($POCl_3$-DMF), the amidine derivatives **160** were obtained.[97] Saponification of

84 with alcoholic potassium hydroxide gave the potassium salt of the corresponding acids **161** which were also reacted with Vilsmeier reagent to give N-(2-carboxythieno[2,3-b]pyridin-3-yl)formamidines **162**. The latter compounds were interacted with piperidine to give the piperidinium salts **163** (Z^+ = piperidinium). The potassium salts **161** were converted into the corresponding acids which were reacted with triethyl orthoformate to produce the oxazinone derivatives **164**. The latter compounds in turn were reacted with ethanolamine, piperidine or morpholine to furnish the compounds **165**.[97]



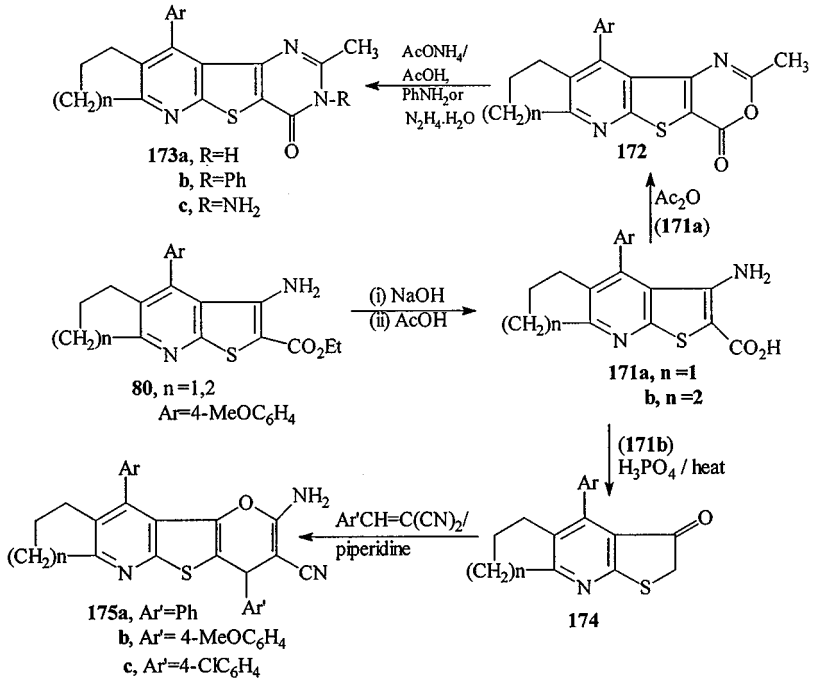
The cyclocondensation of **161** with acid anhydrides resulted in the formation of the 2-alkyl-oxazinone derivatives **166** which, upon reaction with secondary amines, afforded **167**.[98] The oxazinones **166** were

recyclized into the corresponding pyridothienopyrimidinone derivatives **168** upon treatment with primary amines.[99] On heating of **166** with phosphorus pentasulfide in xylene, the 1,3-thiazine-4-thione **169** was obtained. The latter compound was reacted with ethylenediamine to afford the imidazolinopyridothienopyrimidines **170**.[100]



In the same manner, the esters **80** were hydrolyzed to produce the corresponding acids **171a**,**b**.[56,58] The compound **171a** was converted into the oxazinone **172**, which in turn was reacted with ammonium acetate/acetic acid, aniline, or hydrazine hydrate to afford the corresponding pyrimidinones **173a–c**.[56] On the other hand, heating of **171b** with orthophosphoric acid at 100°C led to decarboxylation followed by hydrolysis of the amino group (which isomerizes to the imino form)

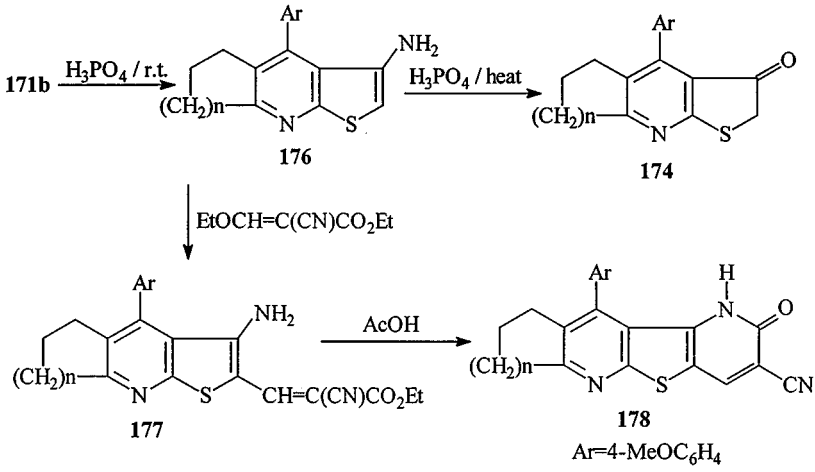
affording the ketone **174**. The latter compound underwent a cycloaddition reaction with arylmethylenemalononitriles to give the pyran derivatives **175a–c**.[58]



When the above decarboxylation was carried out at room temperature, the amino compound **176** was obtained. The compound **176** also was converted to **174** upon heating with orthophosphoric acid at 100°C.[58] The interaction of **176** with ethyl α-cyano-β-ethoxyacrylate gave thieno[2,3-b]pyridine derivative **177** which was cyclized into cyanopyridone derivative **178** by heating in acetic acid.[58]

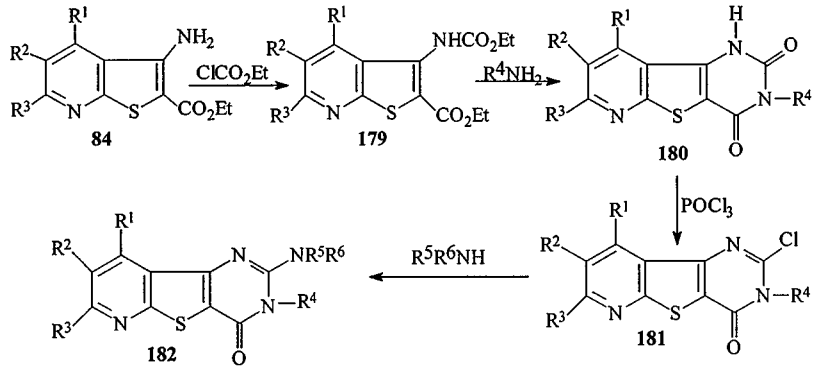
The reaction of *o*-aminoesters **84** with ethyl chloroformate gave the acylated compounds **179** which were cyclized with some primary amines to afford the pyridothienopyrimidine-2,4(1*H*,3*H*)-dione derivatives **180**. Chlorination of **180** to produce 2-chloropyrimidinones **181** was achieved by heating with phosphorus oxychloride. The compounds **181** underwent nucleophilic substitution reactions with some aliphatic or heterocyclic amines to afford the pyridothienopyrimidine derivatives **182**.[101]

Cyclocondensation of aminoesters of the type **71** with some isothiocyanates in boiling pyridine led to the formation of pyridothienopyrimidine-4(3*H*)-ones (**183**).[102] The compounds **183** were S-methylated



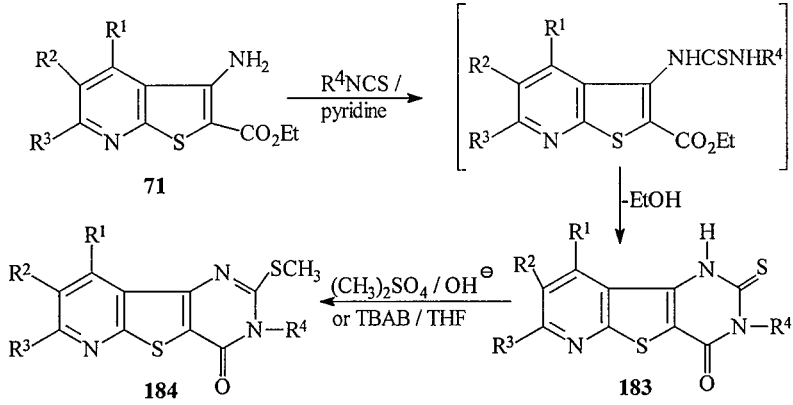
using dimethyl sulphate in alkaline medium to afford 2-methylthiopyrimidinones **184**.[102] The latter compounds also were prepared under solid-liquid phase transfer conditions in which tri-*n*-butyl ammonium bromide was used as a catalyst and THF as a solvent.[102]

The reaction of ester **79** with hydrazine hydrate afforded the 3-aminothieno[2,3-b]pyridine-2-carbohydrazide derivative **185** which was used as a synthon for other thienopyridines. Thus, the cyclocondensation of **185** with acetylacetone gave the pyrazolyl derivative **186**. Heating of **185** with formic acid or acetic anhydride led to the formation of cyclopenta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones **187** and **188** respectively. Also, diazotization of compound **185** gave the carboazide **189**. Upon heating of **189** in dry toluene, it underwent



R^1=H, Me, CO_2Et; R^2 =H; R^3=Me, Ph; R^4= Et, n-Bu, $CH_2CH_2N(Et)_2$

NR^5R^6=NH_2, $NHCH_2CH_2OH$, $NHCH_2CH_2N(Et)_2$, NHBu(n), NHPh, piperidino, morpholino



R^1 =Ph; R^2= H; R^3 = 4-MeC_6H_4, 4-$MeOC_6H_4$,

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

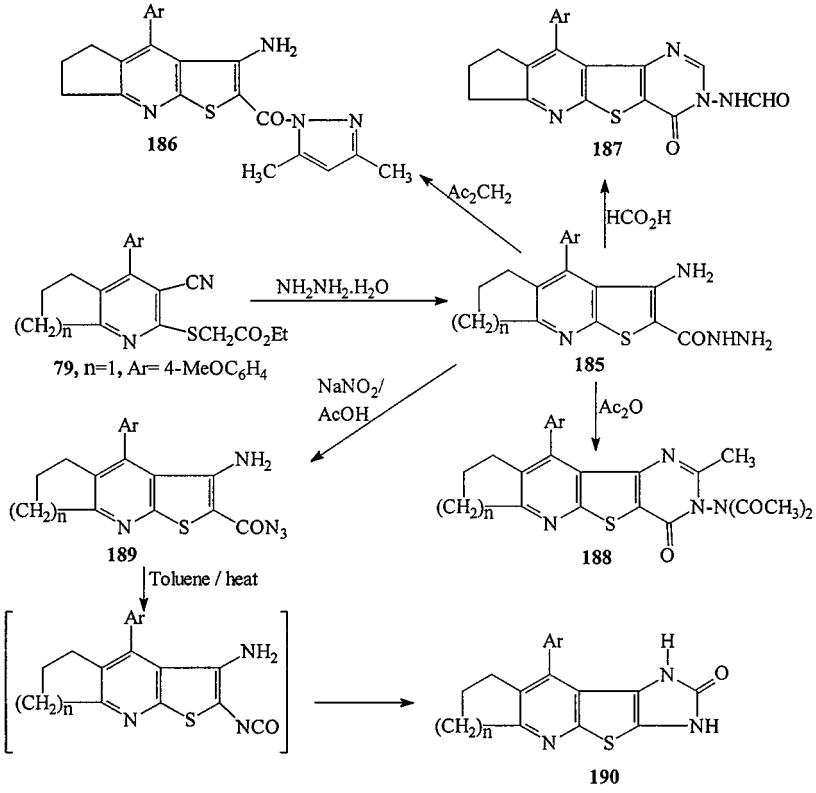
Curtius rearrangement followed by intramolecular cycloaddition reaction to furnish the imidazothienopyridine derivative **190**.[56]

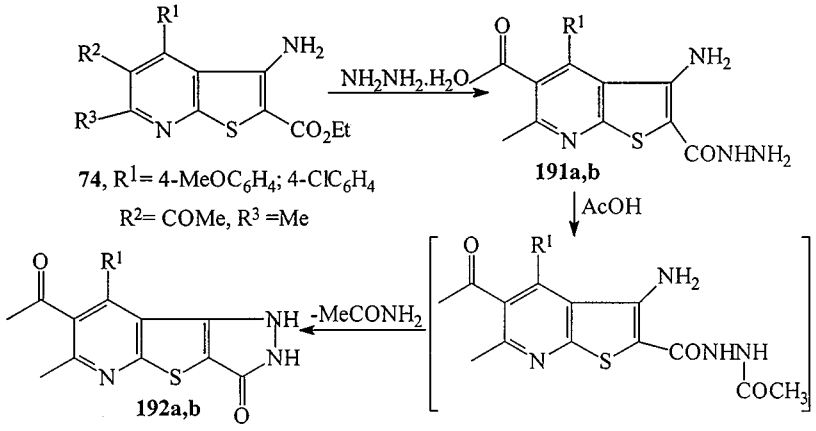
The reaction of *o*-aminoesters **74** with hydrazine hydrate led to the formation of the carbohydrazides **191a**,**b**, which upon heating in glacial acetic acid, furnished the corresponding pyrazolinothienopyridines **192** via elimination of ammonia.[50] The pathway of this reaction may be including initial formation of the acethydrazide derivative as an intermediate, which underwent a ring closure reaction to afford **192a**,**b** by losing of acetamide.

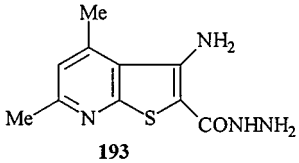
The cyclocondensation of 3-amino-4,6-dimethylthieno[2,3-b]-pyridine-2-carbohyrazide (**193**) with some chalcones in the presence of an acidic catalyst gave the pyrazoline derivatives **194**.[102]

Also, the reaction of carbohydrazide derivative **193** with a variety of 1,3-diketones in glacial acetic acid afforded the corresponding pyrazole derivatives **195**.[104] Moreover, the compound **193** was reacted with some ethoxymethylenes **196** or ketene dithioacetals **197** to afford the substituted aminopyrazoles **198** and **199** respectively.[104] The cycloaddition reaction of **193** with some arylazoacetylacetones or arylazomalononitriles gave the azo dyes **200** and **201** respectively.[105]

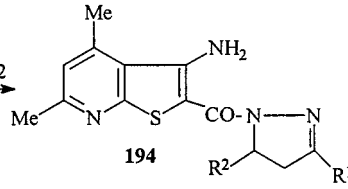
The reaction of **193** with equimolar amount of aromatic aldehydes was reported to give N^1-arylmethylene-3-amino-4,6-dimethylthieno[2,3-b] pyridine-2-carbohydrazides (**202**).[35] The interaction of **202** with carbon disulfide in heated pyridine gave the 1,3-thiazine derivative **203** instead of the expected pyrimidinthiones **204**.[106] The recyclization of **204** with primary amines gave the thioxopyrimidinones **205a–d** which also were prepared by the reaction of compounds **71** with carbon disulfide.[106]





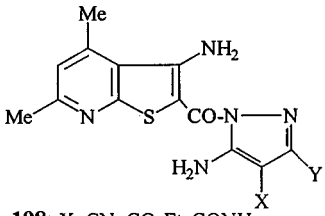


193

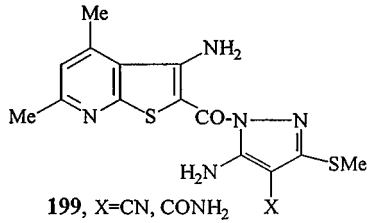


194

R^1, R^2 =Me, Ph; 2-furyl, Ph; Ph, 2-thienyl; 2-furyl, 2-furyl



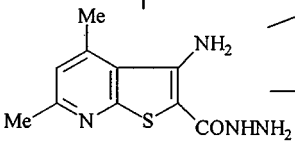
198; X=CN, CO_2Et, $CONH_2$, Y= H, Me



199, X=CN, $CONH_2$

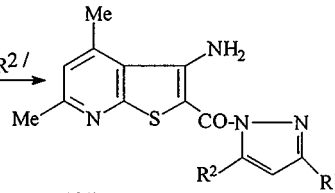
EtOC(Y)=C(X)CN **(196)**

$(MeS)_2C$=C(X)CN **(197)**



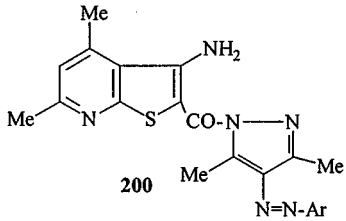
193

$R^1COCH_2COR^2$ / AcOH



195, R^1= H, Me, CF_3; R^2=H, Me, CF_3, Ph, 2-theinyl

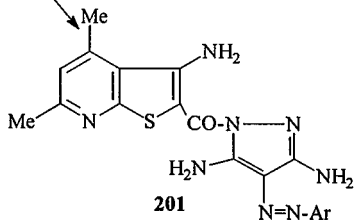
$ArNH-N=C(COMe)_2$



200

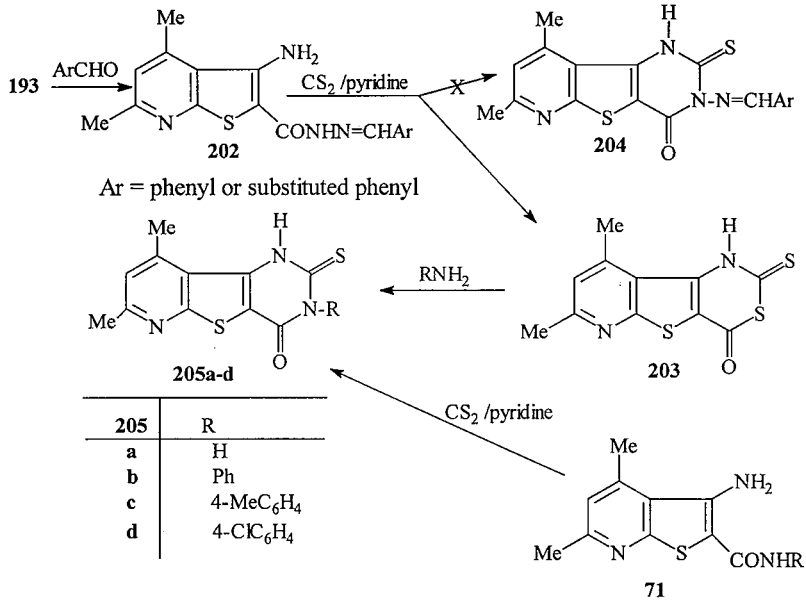
Ar=Ph, 2-MeC_6H_4, 2-ClC_6H_4, 2-CNC_6H_4, 2-$NO_2C_6H_4$,4-$MeCONHC_6H_4$

$ArNH-N=C(CN)_2$



201

Ar=Ph, 2-MeC_6H_4, 2-ClC_6H_4, 2-CNC_6H_4, 2-$NO_2C_6H_4$,4-$MeCONHC_6H_4$



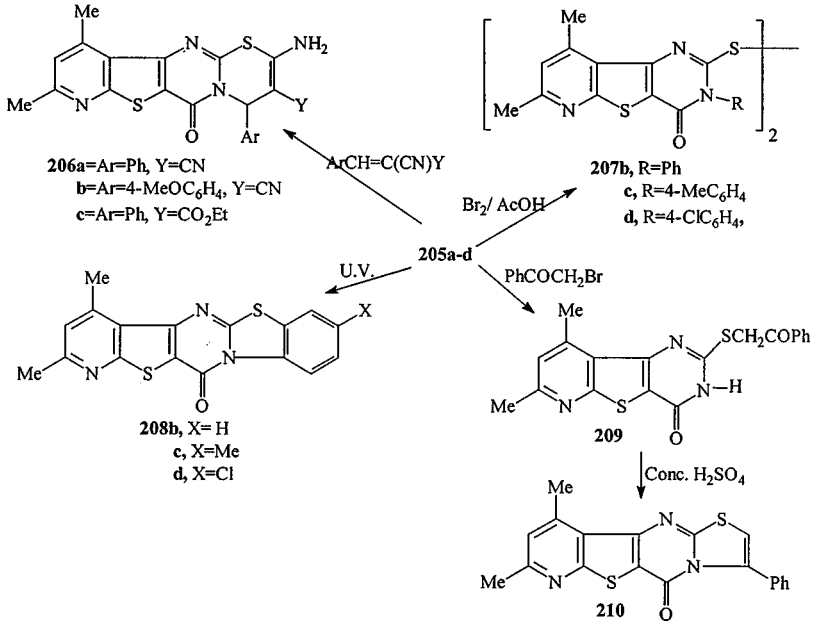
205	R
a	H
b	Ph
c	4-MeC_6H_4
d	4-ClC_6H_4

The compound **205a** (R = H) was reacted with arylmethylenemalononitriles or ethyl benzylidenecyanoacetate to produce the corresponding pyridothienopyrimidothiazine derivatives **206a–c**. On treatment of **205b–d** with bromine in acetic acid, the disulfide derivatives **207b–d** were obtained. UV irradiation of **205b–d** in dioxane under aerobic conditions resulted in a cyclodehydrogenation and formation of pyridothieno-pyrimidobenzthiazoles **208b–d**. The alkylation of **205a** with phenacyl bromide produced the ketone derivative **209** which was cyclized by using concentrated sulfuric acid to give thiazolopyridothienopyrimidinone **210**.[106]

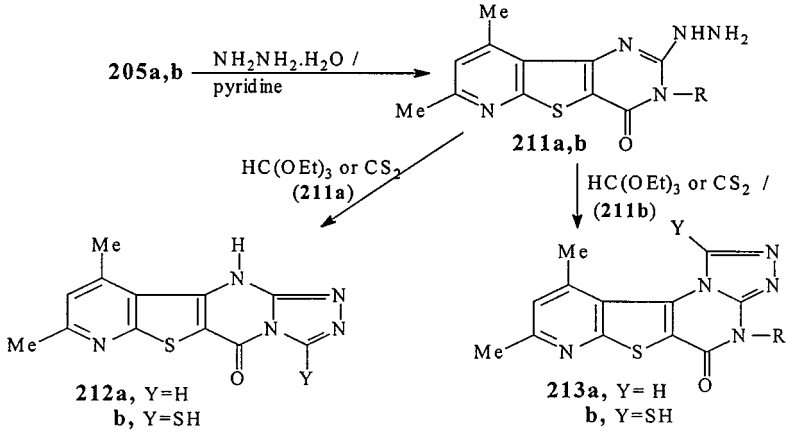
Heating compounds **205a**,**b** with hydrazine hydrate in pyridine resulted in the formation of the hydrazino derivative **211a**,**b**. The reaction of **211a** with triethyl orthoformate or with carbon disulfide produced the *s*-triazolopyridothienopyrimidines **212a**,**b**. Similar reactions of **211b** gave the compounds **213a**,**b**.[106]

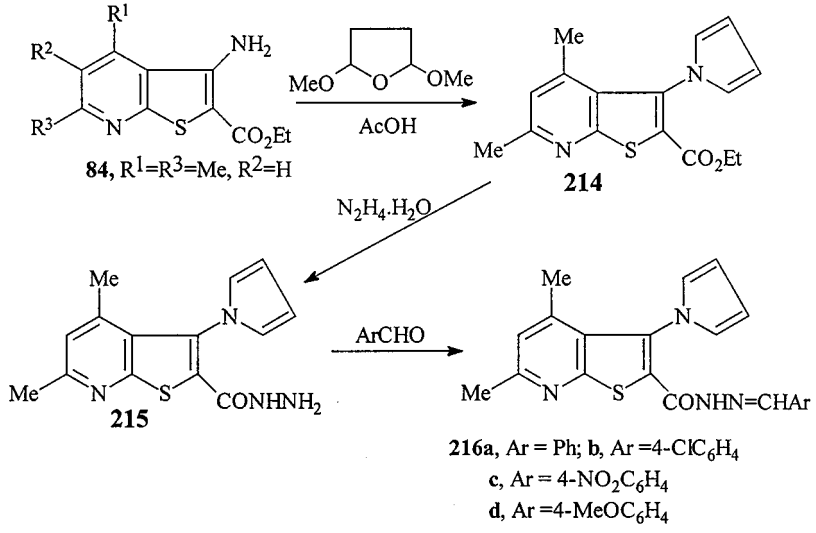
The conversion of the amino group of compound **84** into pyrryl moiety was achieved by using 2,5-dimethoxytetrahydrofuran in boiling acetic acid, where the pyrryl derivative **214** was obtained. Hydrazinolysis of **214** afforded the carbohydrazide **215** which in turn was condensed with aromatic aldehydes to give the hydrazones **216a–d**.[107]

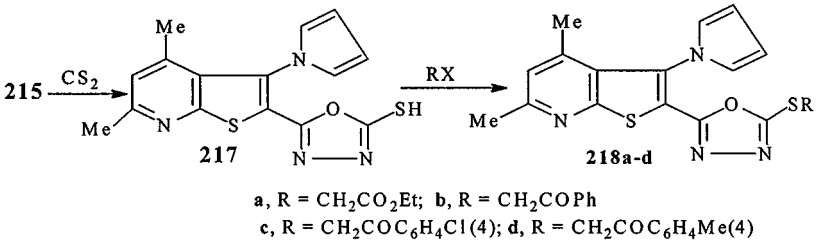
The interaction of **215** with carbon disulfide in heated pyridine gave oxadiazolethiol derivative **217** which was reacted with some halogen compounds to give the *S*-alkylated derivatives **218a–d**.[107]

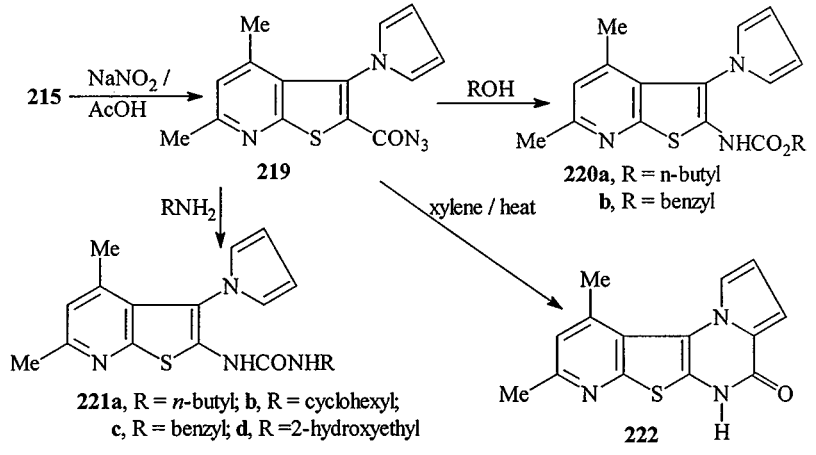


The reaction of **215** with nitrous acid gave the acid azide **219**. The latter compound underwent Curtius rearrangement in boiling alcohols or in boiling xylene in the presence of amines to afford the carbamates **220a**,**b** or urea derivatives **221a–d** respectively. However, heating of **219** in an inert solvent of high boiling point such as xylene, in the absence of any reactive entity led to the formation of pyrazinethione derivative **222**.[107]

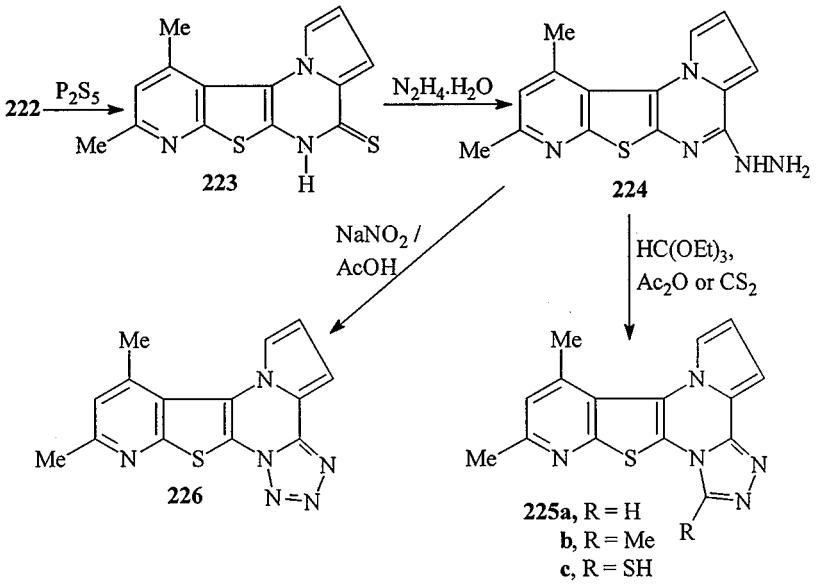








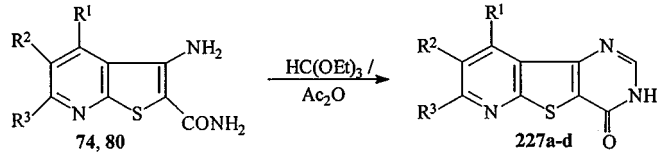
Thiation of pyrazinone **222** was undertaken using phosphorus pentasulfide in boiling pyridine to give the pyrazinethione **223**. Treatment of **223** with hydrazine hydrate gave the hydrazino compound **224** which underwent some ring closure reactions with triethyl orthoformate, acetic anhydride, or cabon disulfide to give the fused pentacyclic systems **225a–c**. Diazotization of **224** produced the tetrazolo compound **226**.[107]



Reactions of 3-Aminothieno[2,3-b]pyridine-2-carboxamides and Their *N*-Aryl Derivatives

When *o*-aminoamides of the type **74**[51] or **80**[56] were allowed to condense with triethyl orthoformate in the presence of acetic anhydride, pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-one derivatives **227a–d** were obtained.

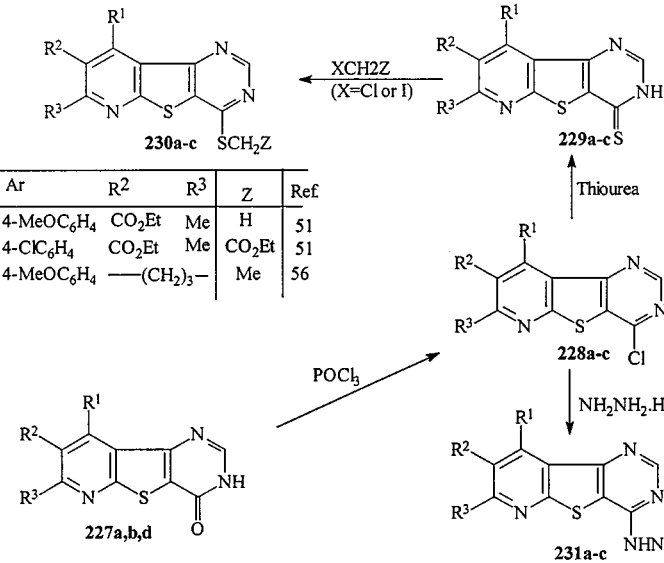
Chlorination of **227a**,**b**,**d** by boiling with phosphorus oxychloride produced the 4-chloropyrimidine derivatives **228a–c** in good yields. Reaction of **228a–c** with thiourea afforded the promising pyrimidine-4(3*H*)-thione derivatives **229a–c** which, upon treatment with some halo compounds, furnished 4-alkylthiopyrimidines **230a–c**. When the chloro compounds **228a–c** were allowed to react with hydrazine hydrate in refluxing ethanol, the expected hydrazino compounds **231a–c** were obtained.



	R^1	R^2	R^3	Ref.
74a	4-$MeOC_6H_4$	CO_2Et	Me	51
74b	4-ClC_6H_4	CO_2Et	Me	51
80a	Ph	—$(CH_2)_3$—		56
80b	4-$MeOC_6H_4$	—$(CH_2)_3$—		56

227	R^1	R^2	R^3	Ref.
a	4-$MeOC_6H_4$	CO_2Et	Me	51
b	4-ClC_6H_4	CO_2Et	Me	51
c	Ph	—$(CH_2)_3$—		56
d	4-$MeOC_6H_4$	—$(CH_2)_3$—		56

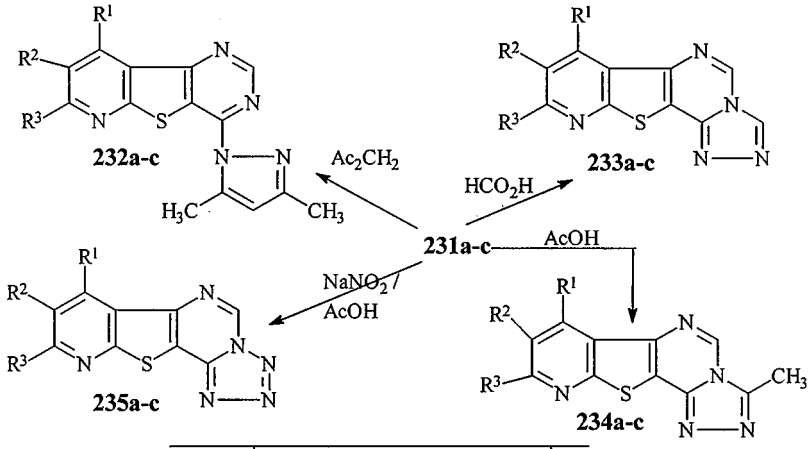
The cyclocondensation of **231a–c** with acetylacetone afforded the 3,5-dimethylpyrazolyl derivatives **232a–c**. The fused tetracyclic compounds **233a–c** and **234a–c** were prepared by treating **231a–c** with formic or with acetic acid respectively. Diazotization of **231a–c** using sodium nitrite and acetic acid produced the tetrazolo derivatives **235a–c**.



230	Ar	R^2	R^3	Z	Ref.
a	4-$MeOC_6H_4$	CO_2Et	Me	H	51
b	4-ClC_6H_4	CO_2Et	Me	CO_2Et	51
c	4-$MeOC_6H_4$	—$(CH_2)_3$—		Me	56

	R^1	R^2	R^3	Ref.
227a	4-$MeOC_6H_4$	CO_2Et	Me	51
227b	4-ClC_6H_4	CO_2Et	Me	51
227d	4-$MeOC_6H_4$	—$(CH_2)_5$—		56

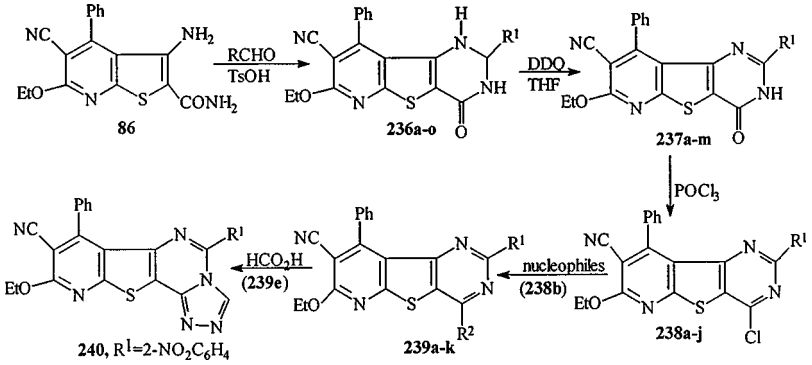
228,229 231	R^1	R^2	R^3	Ref.
a	4-$MeOC_6H_4$	CO_2Et	Me	51
b	4-ClC_6H_4	CO_2Et	Me	51
c	4-$MeOC_6H_4$	—$(CH_2)_3$—		56



232-235	R^1	R^2	R^3	Ref.
a	4-$MeOC_6H_4$	CO_2Et	Me	51
b	4-ClC_6H_4	CO_2Et	Me	51
c	4-$MeOC_6H_4$	—$(CH_2)_3$—		56

On treatment of *o*-aminoamides **86** with the appropriate aldehydes in refluxing toluene containing *p*-toluenesulfonic acid with azeotropic removal of water, **86** underwent cyclization to give the 8-cyano-7-ethoxy-4-oxo-9-phenyl-2-substituted-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidines (**236a–o**) in good yields. Dehydrogenation of compounds **236a–m** to give **237a–m** was achieved by heating of the former compounds with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in THF for a few hours. The pyridothienopyrimidinones **237a–j** were reacted with phosphorus oxychloride to yield the expected 4-chloropyrimidines **238a–j**. The compound **238b** showed a remarkable reactivity of its chloro substituent toward some nucleophilic reagents to produce the pyridothienopyrimidine derivatives **239a–k**.[70] Heating of compound **239e** with formic acid gave the *s*-triazolo derivative **240**.[70]

On the other hand, treatment of *o*-aminoamides of the type **74** or **80** in AcOH-H_2SO_4 mixture with sodium nitrite solution at low temperature resulted in diazotization followed by self coupling to afford the corresponding pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-4(3*H*)-one derivatives **241a–c**[42,51] and **242a**,**b**.[56] Compound **242a** underwent N-alkylation reaction upon treatment with some halo compounds viz. phenacyl bromide, ethyl chloroacetate, or chloroacetamide, in DMF containing anhydrous K_2CO_3 to afford the triazinone derivatives **243a–c**.[56]



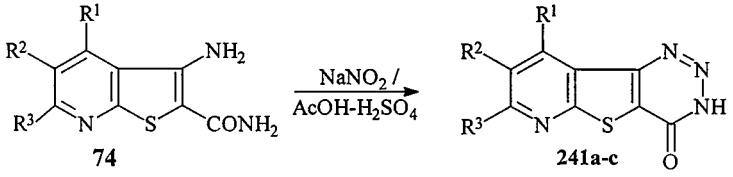
236–238	R^1	**236–238**	R^1	**239**	R^2
a	$2\text{-ClC}_6\text{H}_4$	**l**	$3\text{-(OH),-3-MeOC}_6\text{H}_3$	**a**	Morpholino
b	$2\text{-NO}_2\text{C}_6\text{H}_4$	**m**	PhCH_2	**b**	Piperidino
c	$4\text{-ClC}_6\text{H}_4$	**n**	$2,4,5\text{-(MeO)}_3\text{C}_6\text{H}_2$	**c**	4-Benzylpiperazino
d	$4\text{-NO}_2\text{C}_6\text{H}_4$	**o**	$\text{CH}_2\text{CH}_2\text{Cl}$	**d**	4-(4′-nitrophenyl) piperazino
e	Ph			**e**	NHNH_2
f	$4\text{-MeC}_6\text{H}_4$			**f**	$\text{NH(CH}_2)_2\text{CH}_3$
g	$2\text{-MeOC}_6\text{H}_4$			**g**	$\text{NH(CH}_2)_3\text{CH}_3$
h	$2,6\text{-Cl}_2\text{C}_6\text{H}_3$			**h**	$\text{NH(CH}_2)_2\text{OH}$
i	$4\text{-FC}_6\text{H}_4$			**i**	$\text{NH(CH}_2)_2\text{Ph}$
j	$3,4\text{-(OCH}_2\text{O)C}_6\text{H}_3$			**j**	OC_2H_5
k	$4\text{-OHC}_6\text{H}_4$			**k**	N_3

Similarly, diazotization of *o*-aminoamides **86** using sodium nitrite and AcOH-H_2SO_4 mixture at low temperature produced the corresponding pyridothienotriazinones **244**.[68]

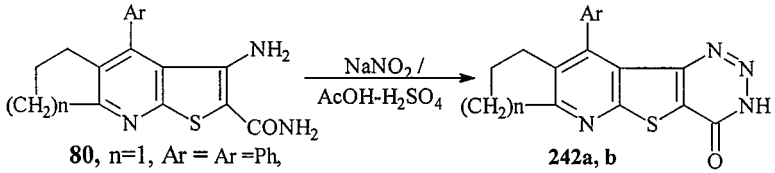
More recently,[58] we reported that the reaction of *o*-aminoamide **80** with some aldehydes produces the tetrahydropyrimidines **245a–c**. When the compound **80** was allowed to react with cyclopentanone or cyclohexanone. The products were identified as spiro compounds **246a**,**b** rather than the expected Schiff's bases **247a**,**b**.

Similar reactions also were carried out on *o*-aminoamide **71** to obtain valuable fluorine-containing thieno[2,3-b]pyridine derivatives **248a–c** and **249a**,**b**.[42]

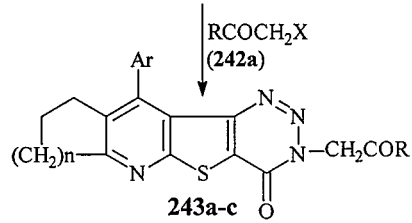
Moreover, 3-amino-2-(*N*-aryl)carbamoylthieno[2,3-b]pyridines **80** were reacted with triethyl orthoformate or with nitrous acid to give the corresponding 3-arylpyridothienopyrimidines **250** or 3-arylpyrido thienotriazines **251** respectively.[57]



241	R^1	R^2	R^3	Ref.
a	CF_3	H	2-thienyl	42
b	4-$MeOC_6H_4$	COMe	Me	51
c	4-ClC_6H_4	COMe	Me	51



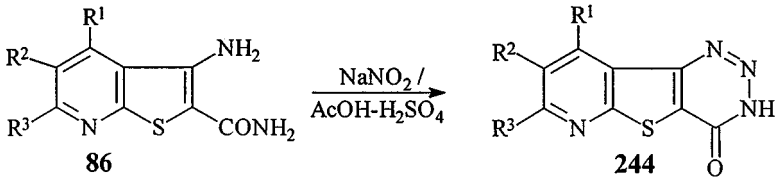
243	R
a	Ph
b	OEt
c	NH_2



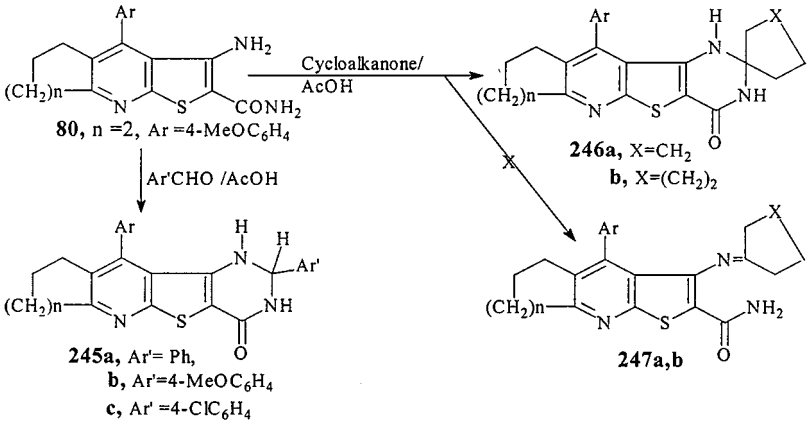
Reactions of 3-Aminothieno[2,3-b]pyridine-2-carbonitriles

Heating 3-aminothieno[2,3-b]pyridine-2-carbonitriles **71** with formamide at reflux temperature led to the formation of 4-aminopyridothieno-pyrimidines **252a**,**b**.[34]

The condensation of *o*-aminocarbonitrile **80** with triethyl orthoformate afforded the methanimidate derivative **253** which reacted with



R^1 = Me, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 3-pyridyl, 4-pyridyl, CO_2Me, $CONH_2$, CONH(Bu^n), piperidinocarbonyl; R^2 = H, Me, $PhCH_2$, 4-$CNC_6H_4CH_2$; R^3 = Me, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 2-naphthyl, 2-furyl

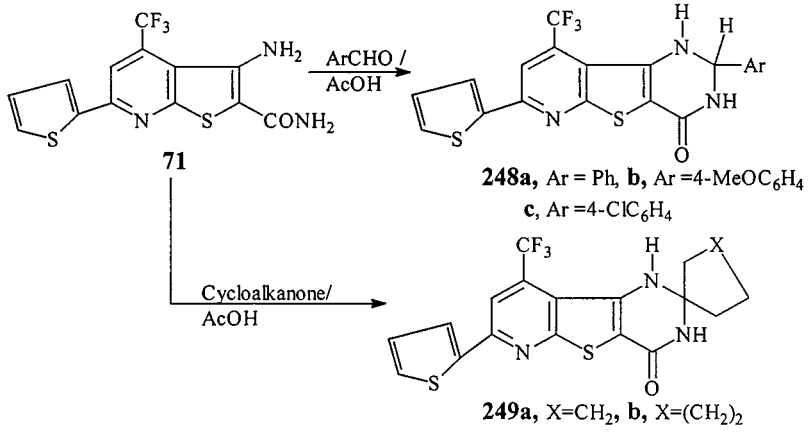


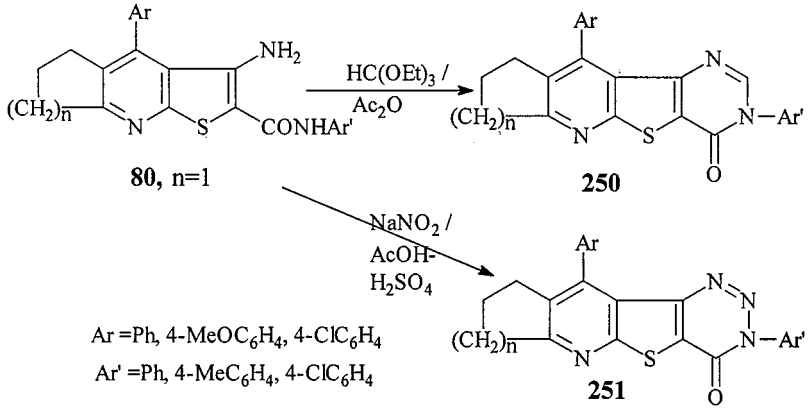
hydrazine hydrate at room temperature to give pyridothienopyrimidine **254**. The latter compound underwent a ring closure reaction upon treatment with triethyl orthoformate to give *s*-triazolo compound **255**.[57]

The reaction of compound **254** with acetylacetone under neat conditions led to the formation of methyl-*s*-triazole derivative **257** instead of the expected triazepine **256**. The compound **257** also was obtained upon heating of **254** with acetic anhydride.[57]

The interaction of **80** with carbon disulfide or with phenyl *iso*-thiocyanate gave the dithioxopyrimidine **258** and thiourea derivative **259** respectively. The compound **259** was cyclized into **260** by refluxing in methanol containing sodium methoxide.[57]

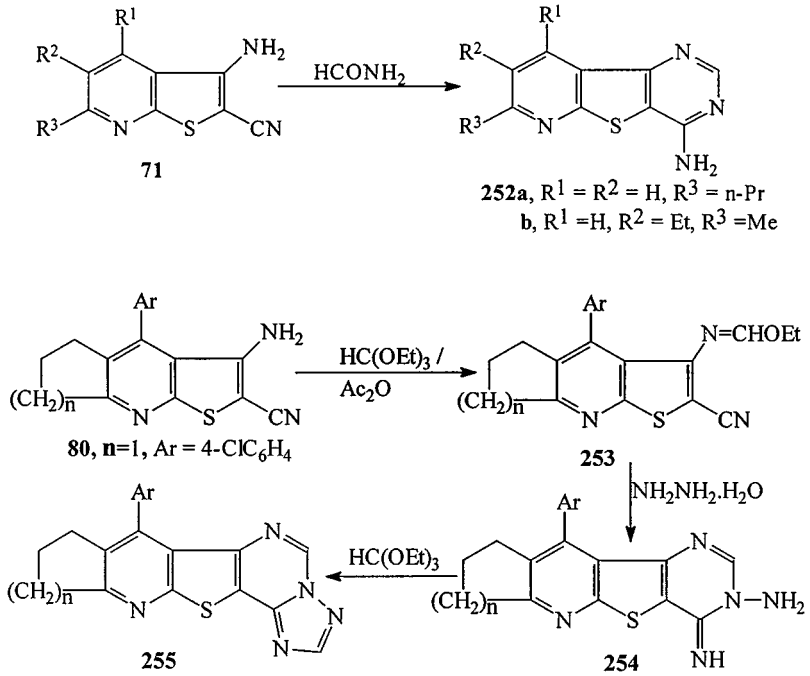
Treatment of *o*-aminocarbonitriles **86** in AcOH-HCl mixture with sodium nitrite solution at low temperature afforded 4-chloropyrido

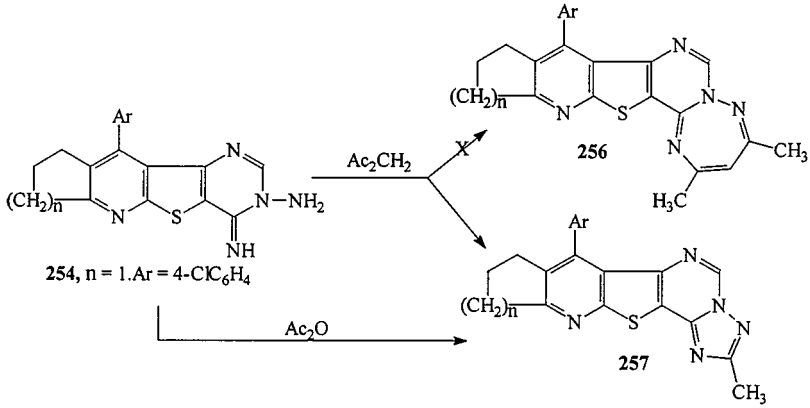


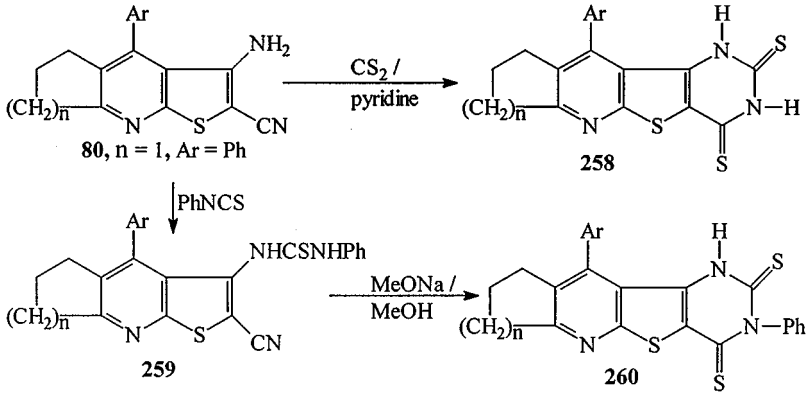


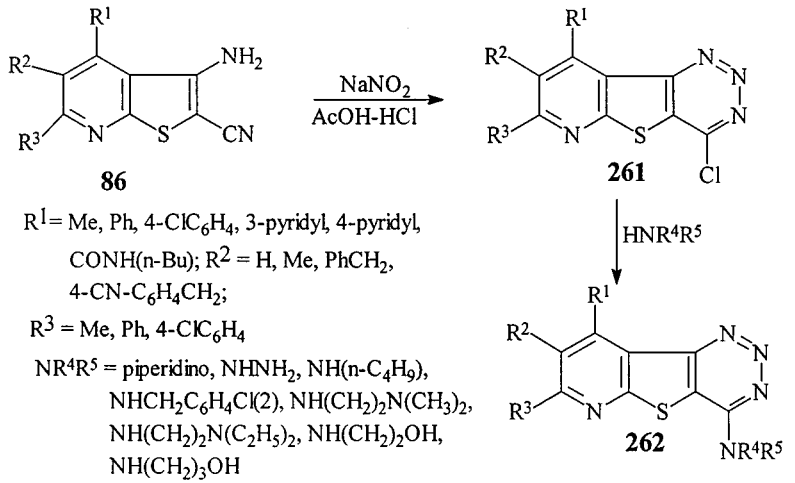
[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine derivatives **261**.[68] Most of the latter compounds were reacted with a variety of N-nuleophiles to produce the corresponding 4-substituted pyridothienotriazines **262**.[68]

Incorporating the imidazoline or tetrahydropyrimidine moieties into thieno[2,3-b]pyridine structure was achieved on conversion of the nitrile group of compounds **86** into the imidazolinyl or tetrahydropyrimidinyl residues followed by some subsequent reactions.[108] Thus,







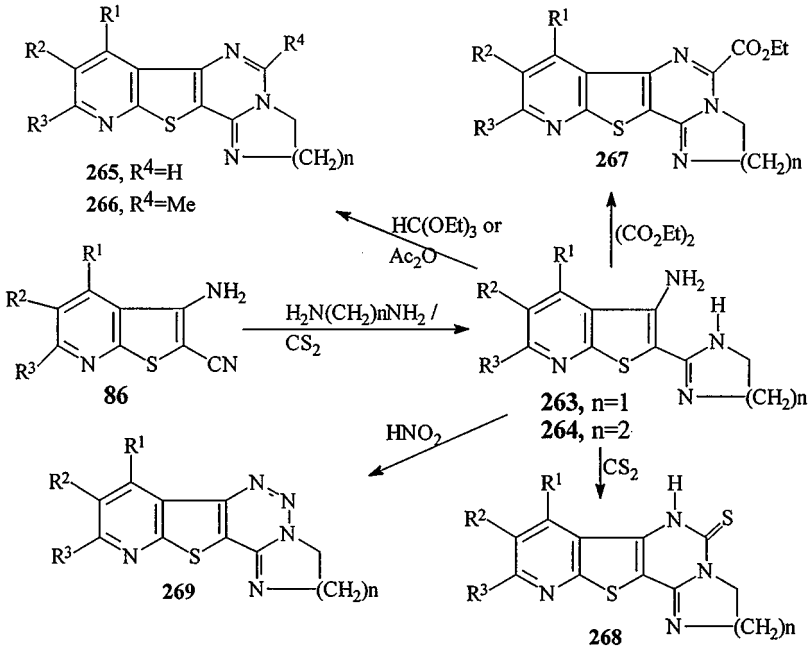


R^1 = Me, Ph, 4-ClC_6H_4, 3-pyridyl, 4-pyridyl, CONH(n-Bu); R^2 = H, Me, $PhCH_2$, 4-CN-$C_6H_4CH_2$;

R^3 = Me, Ph, 4-ClC_6H_4

NR^4R^5 = piperidino, $NHNH_2$, NH(n-C_4H_9), $NHCH_2C_6H_4Cl(2)$, $NH(CH_2)_2N(CH_3)_2$, $NH(CH_2)_2N(C_2H_5)_2$, $NH(CH_2)_2OH$, $NH(CH_2)_3OH$

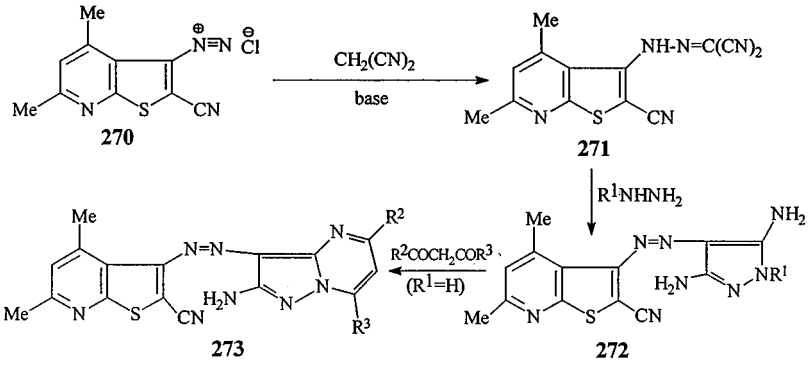
the reaction of **86** with ethylenediamine or 1,3-diaminopropane gave the imidazolines **263** and 3,4,5,6-tetrahydropyrimidines **264** respectively.[108] The compounds **263** and **264** were reacted with some reagents such as triethyl orthoformate, acetic anhydride, diethyl oxalate, or carbon disulfide to afford the condensed pyridothienopyrimidines **265**, **266**, **267**, and **268** respectively. The triazinone analogs **269** were obtained from the reaction of **263** or **264** with nitrous acid.[108]



R^1= H, Me, 4-BrC_6H_4; R^2 = H, Me; R^3 = Me, Ph, 4-BrC_6H_4; n =1,2

When the diazoinium salt of 3-amino-2-cyanothieno[2,3-b]pyridine (**270**) was allowed to couple with malononitrile, the hydrazomalononitrile derivative **271** was isolated. The reaction of **271** with some hydrazino compounds produced the diaminopyrazolyl derivatives **272**. Compound **272** (R^1 = H) underwent cyclocondensation reactions with the appropriate 1,3-diketones in acetic acid to give the pyrazolopyrimidines **273**.[109]

On the other hand, regioselective reduction of *o*-aminocarbonitrile **74** with diisobutylaluminium hydride (DIBAl-H) led to the aldehyde **274** which upon treatment with primary aromatic amines afforded the corresponding aldimines **275a–c**. Treatment of **275a–c** with triphenylphosphine/triethylamine/hexachloroethane system in



R^1= H, Me, Ac, Ph, $SO_2C_6H_4$, COPh, isonicotinyl, phthalazinyl

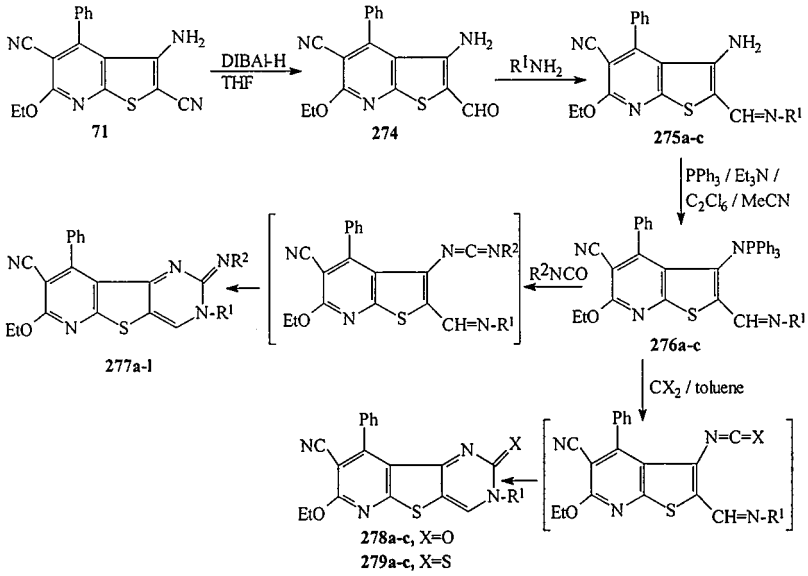
R^2 = Me, CF_3; R^3 = Me, Ph, CF_3, 2-thienyl, 2-furyl

dry acetonitrile afforded the key intermediate **276a–c**. Reaction of iminophosphoranes **276a–c** with some isocyanates by refluxing in toluene resulted in the formation of triphenylphosphine oxide and 2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidines **277a–l** in moderate yields.[53] The mechanism for these conversions involves initial aza-Wittig reaction between the iminophosphoranes and the isocyanate to give a carbodiimide that is a highly reactive intermediate and undergoes readily electrocyclic ring-closure to give the cyclic valence tautomers **277a–l**. Heating **276a–c** in a sealed tube at 120°C with carbon dioxide or carbon disulfide in toluene gave rise to the fused pyrimidines **278a–c** and **279a–c** respectively. The formation of the latter compounds can be understood to occur by initial aza-Wittig reaction between iminophosphoranes **276a–c** and carbon dioxide or carbon disulfide to give the corresponding isocyanate or isothiocyanate as intermediates; these last cyclize spontaneously to **278a–c** and **279a–c** respectively.[53]

Reactions of Other Thieno[2,3-b]pyridine Derivatives

Treatment of 5-aminolthieno[2,3-b]pyridine derivative **280** with 2,4-difluorophenyl *iso*-cyanate gave the urea derivative **281**.[110]

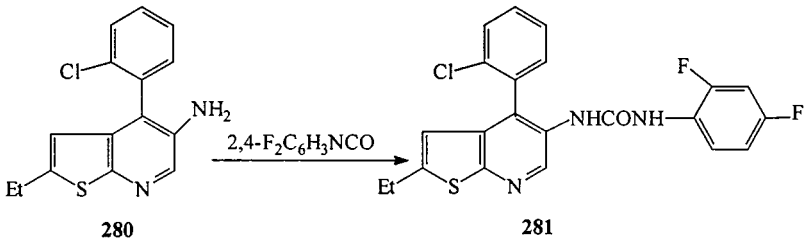
Bromination of compound **130** using bromine/AcOH gave 2-bromoacetylthieno[2,3-b]pyridine **282**, which upon treatment with potassium cyanide in ethanol produced 2-cyanoacetyl derivative **283**. The reaction of **283** with equimolar amount of malononitrile in the presence of anhydrous ammonium acetate yielded compound **285**. The formation of **285** was considered to proceed via the intermediacy of **284** which underwent intramolecular cyclization via addition of its methyl

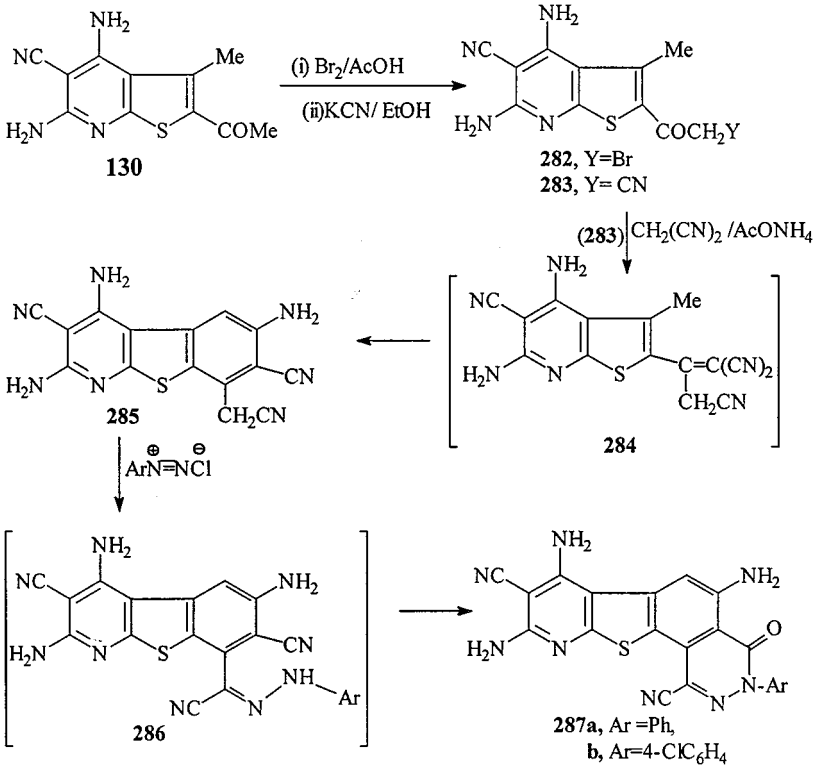


group to a CN function. When **285** was allowed to couple with aryldiazonium chloride, the pyridothienophthalazine derivatives **287a**,**b** were isolated. This reaction was assumed to proceed via formation of arhydrazones **286a**,**b** followed by cyclization and hydrolysis of the imino group.[86]

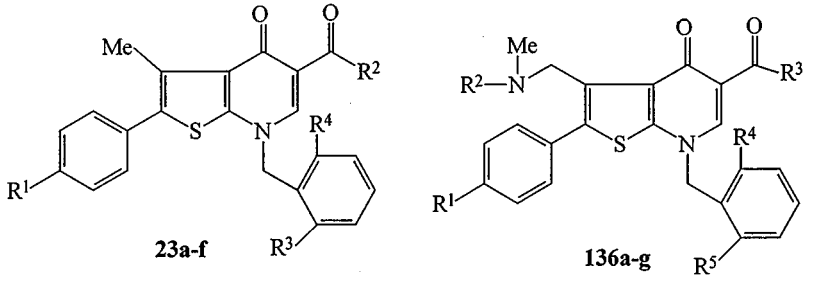
APPLICATIONS OF THIENO[2,3-b]PYRIDINES

Thieno[2,3-b]pyridine ring systems have proved to be an interesting class of heterocycles. Most of the aforementioned thieno[2,3-b]pyridine derivatives are reported to possess anticipated biological activities. Some of them are known to exhibit a variety of medicinal and industrial applications.

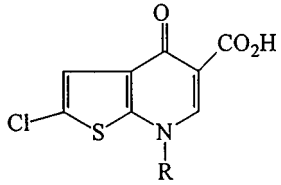




For example, the thieno[2,3-b]pyridines **23a–f** and **136a–g** are useful as gonadotropin-releasing hormone antagonists.[10–12,89–91]

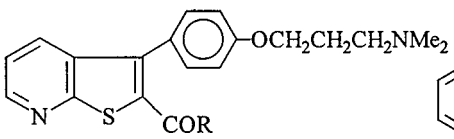


2-Chloro-7-alkyl- or aryl-4,7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acids (**52a–p**) are reported to possess good antibacterial activities especially against *Escherichia coli*.[21,22,111]

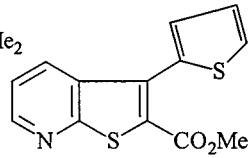


52a-p

The compounds **56a** and **57** are patented to be useful as hematinics, antitumor agents and as immunostimulants.[24] The compound **56b** is used for compacting phytopathogenic fungi.[25]

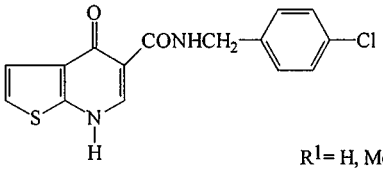


56a, R =OMe
57, R=NH_2

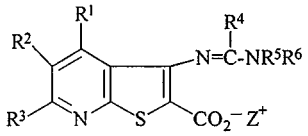


56b

The 4,7-dihydrothieno[2,3-b]pyridine derivative **140** showed a considerable antiviral activity.[93] Most of the compounds **167** showed inhibitory activity against different lipoxygenases.[98]



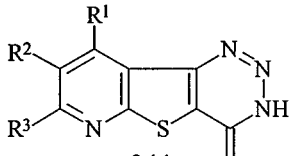
140



167

R^1= H, Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, R^2= H
R^3= Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4;R^4 =Me, Et
NR^5R^6= piperidino, morpholino; Z^+= piperidinium, morpholinium

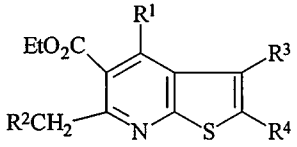
Most of the pyridothienotriazine derivatives **244** are reported to exihibit respectable antianaphylactic activities.[68]



244

R^1= Me, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 3-pyridyl, 4-pyridyl, CO_2Me, $CONH_2$, $CONH(Bu^n)$, piperidinocarbonyl; R^2 = H, Me, $PhCH_2$, 4-$CNC_6H_4CH_2$;
R^3 = Me, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 2-naphthyl, 2-furyl

The thieno[2,3-b]pyridine derivatives **288** are used as antiinflammatory agents, particularly agent for treating arthritis and bone resorption inhibiting agents.[112]



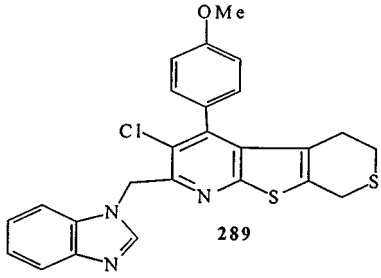
288

R^1= Ph, di-and trimethoxyphenyl

R^2=Et_2N, triazolyl, imidazolyl, pyrrolidinyl, piperidino, mrpholino

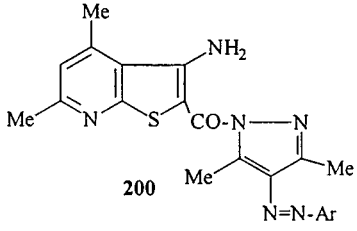
R^3=R^4=Me,R^3R^4 =$CH_2SCH_2CH_2$, $CH_2NR_4CH_2CH_2$, R^4 = Me, Et, Pr, benzyl

Thieno[2,3-b]pyridine derivative **289** is useful as an antiinflammatory drug particularly as a remedy for arthritis.[113]



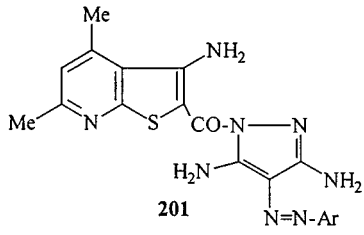
289

On the other hand, the dyes **200** and **201** were applied to polyesters and polyamide fibers, and their spectral and fastness properties were measured.[105]



200

Ar=Ph, 2-MeC_6H_4, 2-ClC_6H_4, 2-CNC_6H_4, 2-$NO_2C_6H_4$,4-$MeCONHC_6H_4$

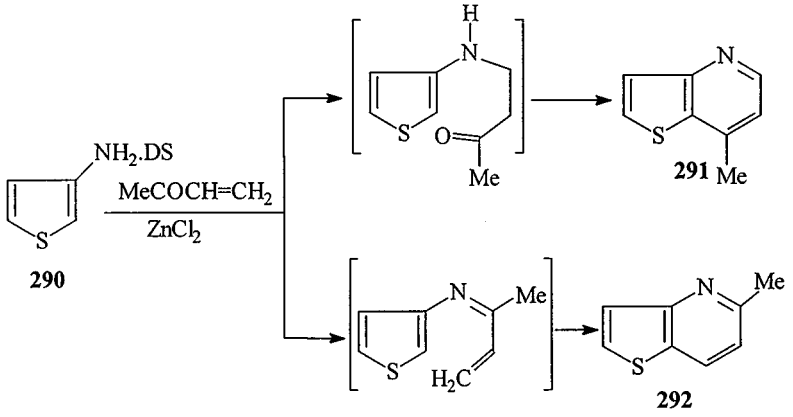


201

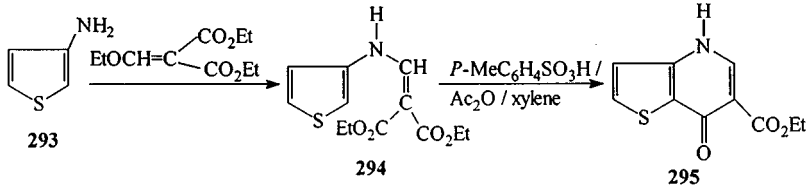
Ar=Ph, 2-MeC_6H_4, 2-ClC_6H_4, 2-CNC_6H_4, 2-$NO_2C_6H_4$,4-$MeCONHC_6H_4$

SYNTHESIS, REACTIONS AND APPLICATIONS OF THIENO[3,2-b]PYRIDINES

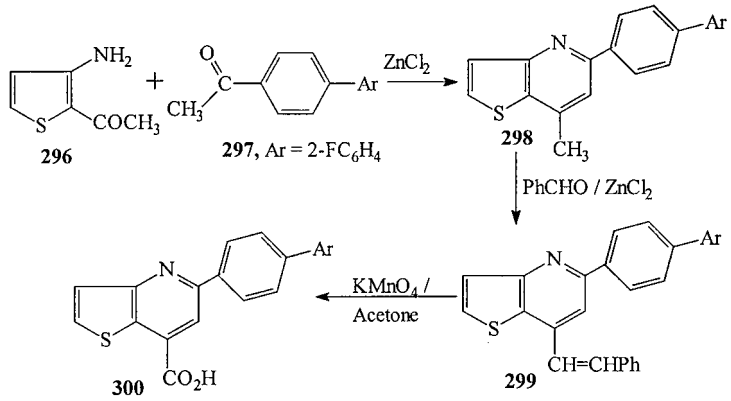
The reaction of methyl vinyl ketone with 3-aminothiophene double salt **290** was reported to give a mixture of products that arising from Michael addition (**291**) predominating over that from the Schiff's base (**292**).[6]



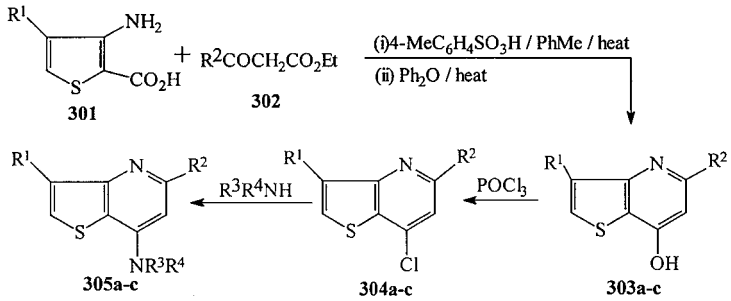
Refluxing thiophene derivative **294**, which was obtained from the reaction of 3-aminothiophene **293** with diethyl ethoxymethylene-malonate, with *p*-toluenesulfonic acid and acetic anhydride in xylene afforded ethyl 4,7-dihydro-7-oxothieno[3,2-b]pyridine-6-carboxylate (**295**) in high yield.[114,115] The compound **295** and its derivatives are useful as antihypertensive or antibacterial agents.[114,115]

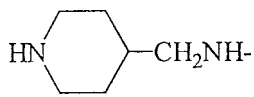
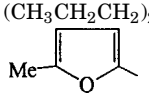


2-Acetyl-3-aminothiophene (**296**) was condensed with 4-(2′-fluorophenyl)-acetophenone (**297**) in the presence of anhydrous zinc chloride to give thieno[3,2-b]pyridine derivative **298**. The reaction of **298** with benzaldehyde produced the styryl derivative **299**, which underwent oxidation reaction upon treatment with $KMnO_4$ to afford the corresponding acid **300**.[116]

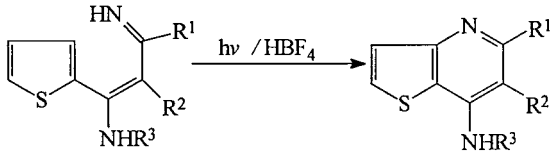


The reaction of 3-aminothiophene-2-carboxylic acids **301** with some β-ketoesters **302** in boiling toluene, in the presence of *p*-toluenesulfonic acid, followed by heating of the resulting products in diphenyl ether at 220°C, afforded the corresponding thieno[3,2-b]pyridine derivatives **303a–c**. Chlorination of **303a–c** to give the chloro compounds **304a–c** was achieved by boiling in phosphorus oxychloride. The compounds **304a–c** underwent nucleophilic displacement upon treatment with amines to furnish thieno[3,2-b]pyridine derivatives **305a–c**.[117–119] The latter compounds are useful in the diagnosis and treatment of anxiety.[117–119]



303–305	R^1	R^2	NR^3R^4	Ref.
a	H	4-FC_6H_4		117
a	2,4,6-$Me_3C_6H_2$	Me	$(CH_3CH_2CH_2)_2N$-	118
c	H	4-FC_6H_4		119

Irradiation of 3-(2′-thienyl)-2-alkene imines **306a**,**b** in the presence of tetrafluoroboric acid resulted in photocyclization and formation of thieno[3,2-b]pyridine derivatives **307a**,**b**.[120] The formation of these compounds could be explained with a mechanism involving a six-electrocyclic process.[120]



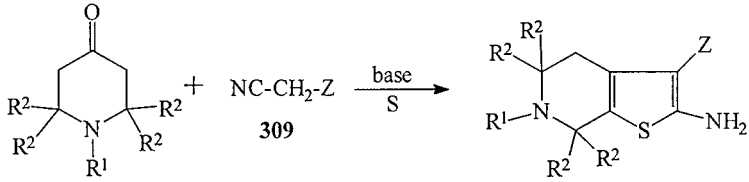
306a,b

307a, R^1 =Ph, R^2 =Me, R^3=Ph

307b, R^1 =4-$MeOC_6H_4$, R^2 =H, R^3=cyclohexyl

SYNTHESIS, REACTIONS AND APPLICATIONS OF THIENO[2,3-c]PYRIDINES

Most of the known thieno[2,3-c]pyridine derivatives were prepared by Gewald reaction. Thus, the reaction of 4-piperidone derivatives **308** with some active methylene nitriles **309a–c** and elemental sulfur under Gewald conditions gave the corresponding 3-functionalized 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine derivatives (**310a–i**).[121–126]

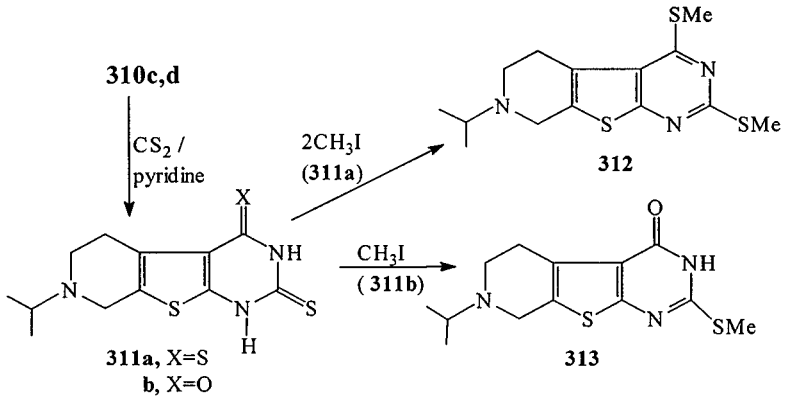


308

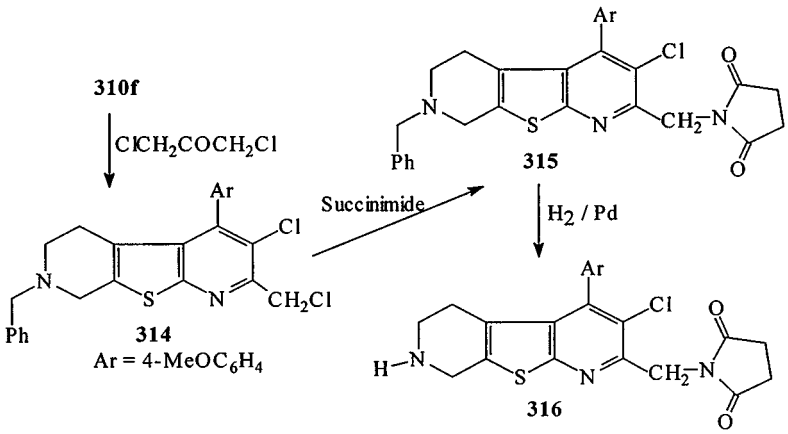
310a-i

310	R^1	R^2	Z	Ref.
a	H	Me	CO_2Et	121
b	H	Me	CN	121
c	$CHMe_2$	H	CN	122
d	$CHMe_2$	H	$CONH_2$	122
e	$CHMe_2$	H	CO_2Et	122
f	$PhCH_2$	H	$COC_6H_4OMe(4)$	123
g	MeCO	H	$COC_6H_4Cl(2)$	124
h	MeCO	H	CO_2Et	125
i	4-ClC_6H_4CO	H	$COC_6H_3(OMe)_2(3, 4)$	126

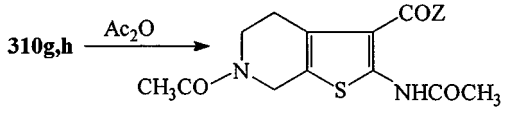
Reaction of **310c** or **310d** with carbon disulfide gave the corresponding pyridothienopyrimidines **311a**,**b** which upon treatment with methyl iodide in the presence of sodium acetate afforded the methylated products **312** and **313**.[122]



The reaction of **310f** with 1,3-dichloroacetone afforded the pyridothienopyridine **314** which upon treatment with succinimide gave a 58% yield of 2-(succinimidylmethyl) derivative **315**.[123] The latter compound underwent Pd-catalyzed debenzylation to give **316**.[123]

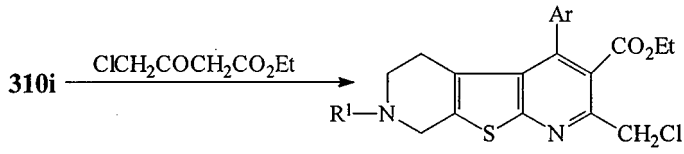


The compounds **310g,h** were converted to the *N*-acetylated derivatives **317a**,**b** which are useful for treatment of inflammation, rheumatoid arthritis and allergy.[124,125]



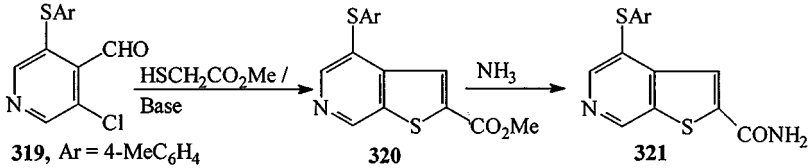
317a, Z = 2-ClC_6H_4; **b**, Z = OEt

The reaction of **310i** with ethyl chloroacetoacetate yielded the pyridothienopyridine derivative **318** which is useful as anti inflammatory agent.[126]



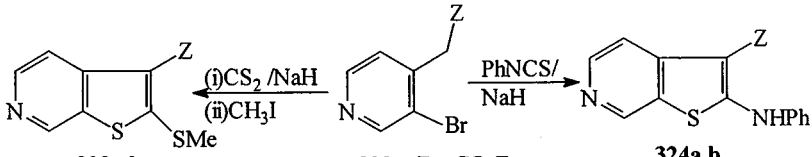
318, R^1= 4-ClC_6H_4CO-
Ar =3,4-$(MeO)_2C_6H_3$

5-Chloro-3-(4′-tolylthio)pyridine-4-carboxaldehyde (**319**) was cyclocondensed with methyl thioglycolate to give thieno[2,3-c]pyridine **320** which upon treatment with ammonia furnished the amide **321**.[127]



319, Ar = 4-MeC_6H_4 **320** **321**

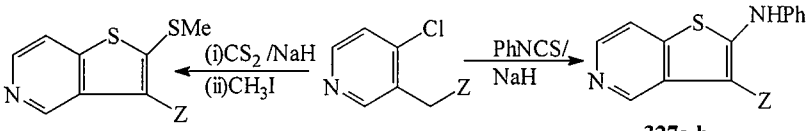
The reaction of 3-bromopyridine derivatives **322a**,**b** with carbon disulfide in the presence of sodium hydride followed by treatment with methyl iodide gave thieno[2,3-c]pyridines **323a**,**b**.[29,30] Similarly, the reaction of **322a**,**b** with phenyl isothiocyanate afforded the corresponding anilinothieno[2,3-c]pyridine derivatives **324a**,**b**.[31]



323a,b **322a, Z = CO_2Et,**
b, Z = CN **324a,b**

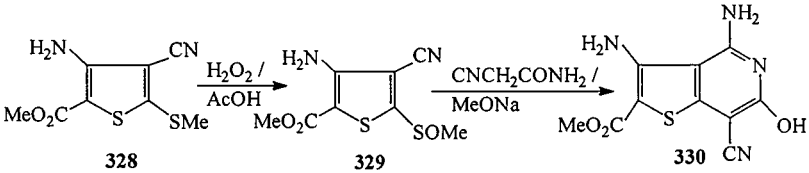
SYNTHESIS AND APPLICATIONS OF THIENO[3,2-c]PYRIDINES

In analogy to the above reactions, the thieno[3,2-c]pyridine derivatives **326a**,**b**[29,30] and **327a**,**b**[31] were prepared from chloropyridine derivatives **325a**,**b**.



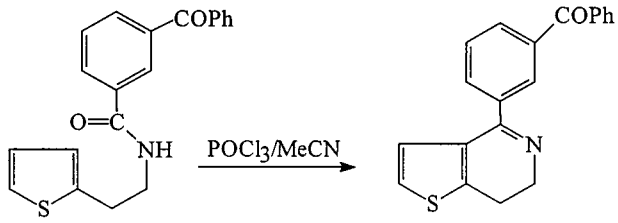
326a,b **325a**, Z = CO_2Et; **b**, Z = CN **327a,b**

Treatment of methyl 4-amino-3-cyano-2-methylthiophene-5-carboxylate (**328**) with hydrogen peroxide in acetic acid gave the sulfoxide derivative **329** which was reacted with cyanoacetamide in the presence of sodium methoxide to give polyfunctional thieno[3,2-c] pyridine **330**.[128]



328 **329** **330**

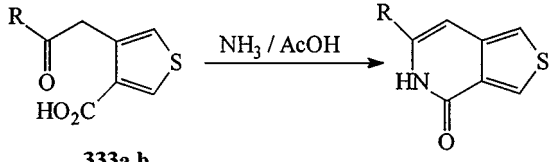
The dihydrothieno[3,2-c]pyridine derivative **332** was prepared by heating of compound **331** with phosphorus oxychloride in acetonitrile. Compound **332** was used for treatment of epilepsy.[129]



331 **332**

SYNTHESIS OF THIENO[3,4-c]PYRIDINES

The cyclocondensation of 4-(2′-oxopropyl)- or 4-phenacyl-thiophene-3-carboxylic acid (**333a**,**b**) with ammonia in acetic acid furnished thieno[3,4-c]pyridine derivatives **334a**,**b**.[130]



333a,b **334a**, R =Me
b, R =Ph

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