Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

β-Mercaptoalkanoic carboxylic esters: versatile synthons in heterocyclic chemistry

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To cite this Article Chandrasekhar, Batchu(2008) 'β-Mercaptoalkanoic carboxylic esters: versatile synthons in heterocyclic chemistry', Journal of Sulfur Chemistry, 29: 2, 187 — 240
To link to this Article: DOI: 10.1080/17415990701784667
URL: http://dx.doi.org/10.1080/17415990701784667

Journal of Sulfur Chemistry
Vol. 29, No. 2, April 2008, 187–240

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β-Mercaptoalkanoic carboxylic esters: versatile synthons in heterocyclic chemistry

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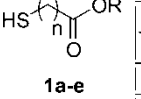
Dedicated to Dr. C. Someswara Rao on the occasion of his 72nd birthday

(*Received 21 May 2007; final version received 07 October 2007*)

This review presents approaches to the synthesis of heterocyclic annelated thiophenes of the last 35 years. Annelated thiophenes have been reported by the cyclocondensation reaction of β-mercaptoalkanoic carboxylic esters with 1,3-bifunctional substrates such as α-haloenones, β-haloenones, α-halogenoacrylic acid derivatives. The reaction takes place by nucleophilic addititon, followed by Dieckmann cyclization with the elimination of hydrogen halide. In case of other substrates such as β-chlorocinnamonitriles, β-haloacrylonitriles, arylsulfonylacrylonitriles, α,β-unsaturated nitriles, Dieckmann–Thorpe–Ziegler cyclization occurs resulting in aminothiophene derivatives. Functionalized annulated thiophene derivatives have potent industrial applications because of significant biological properties.

Keywords: β-mercaptoalkanoic carboxylic esters; cyclocondensation; Thorpe–Ziegler cyclization; Dieckmann cyclization; Michael addition; Knoevenagel-type condensation

This review article deals with approaches to the synthesis of a wide range of mono and polycyclic heterocycles utilizing β-mercaptoalkanoic carboxylic esters **1a–e**.



1a-e

1	n	R
a	1	Me
b	1	Et
c	2	Me
d	2	Et
e	CHMe	Me

1. Introduction

Synthetic organic chemistry involves specially designed reagents, which are readily generated and used for further exploitation. An important example of such a reagent is β-mercaptoalkanoic carboxylic ester. A large number of reports on the utility of this reagent have been published.

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ISSN 1741-5993 print/ISSN 1741-6000 online

DOI: 10.1080/17415990701784667
http://www.informaworld.com

The emphasis of this review is placed on the literature published since 1970. Patents have in general not been included to keep the bulk of this review in a manageable size.

The main objective of this survey is to provide a comprehensive account of the synthetic utility of β-mercaptoalkanoic carboxylic esters, especially in building various heterocycles and also to highlight their potential in developing better chemothrapeutic agents. The present review is divided into five sections based on the nature of heterocylces synthesized or employed or on the type of reaction used. The reactions of β-mercaptoalkanoic carboxylic esters leading to the formation of monocyclic, bicyclic, tricyclic, tetracyclic and miscellaneous heterocylic compounds are all reviewed in detail.

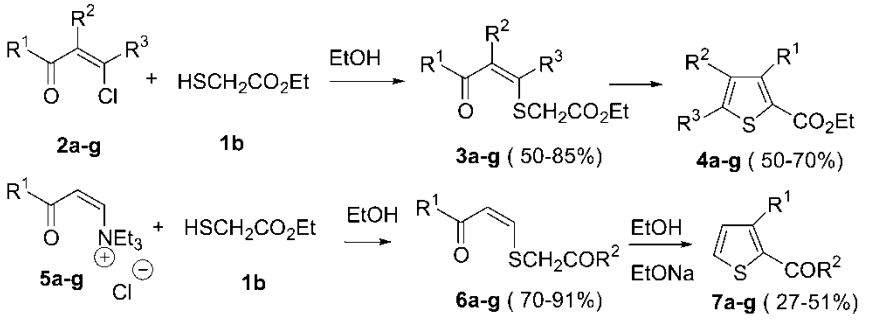
2. Monocyclic derivatives

2.1. *2-Functionalized thiophenes*

The use of 1,3-bifunctional substrates in the synthesis of thiophene derivatives has been described in the literature (*1*). Alberola *et al.* (*2*) have reported the synthesis of functionalized thiophenes. The reaction of methyl thioglycolate with acetylene-dicarboxylates (*3*) has been exploited in the preparation of 3-hydroxythiophenes. The 3-substituted enones with a better leaving group such as 3-chloroenones (*4*) **2a–g** or acylenammonium chlorides **5a–g** on reaction with ethyl thioglycolate **1b** in the presence of NaOEt/EtOH gave ethyl thiophenecarboxylates **4a–g**. On the other hand, acylenammonium chlorides are easily transformed, in high yields, into the intermediates **6a–g** when refluxed in ethanol with α-mercapto derivatives **1b** for 1 or 2 h. The transformation of these intermediates to obtain 2-functionalized thiophenes **7a–g** is carried out in good to moderate yields by cyclization with sodium ethoxide in ethanol at reflux or room temparature (Scheme 1).

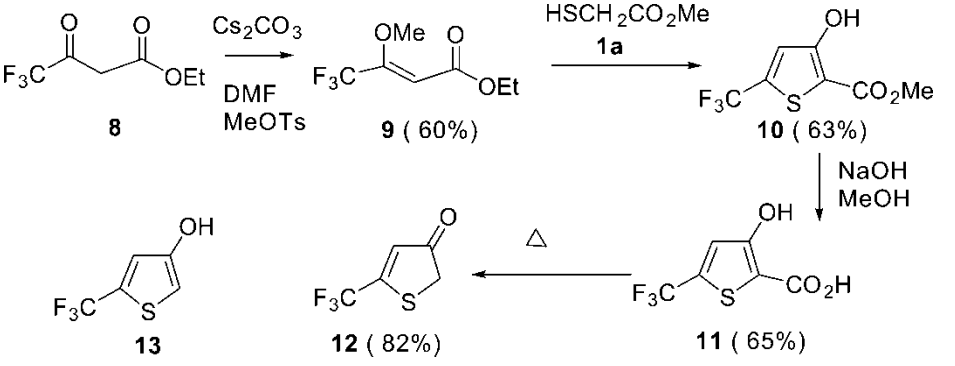
2.2. *4-Hydroxy-2-trifluoromethylthiophene*

The concept of bioisosterism has been widely utilized as a mechanism-based rational design to lead optimization in the discovery of new drugs and agrochemicals (*5*). A common structural motif present in a number of commercial as well as experimental herbicides, insecticides and fungicides is the α,α,α-trifluoro-*m*-cresol moiety. Karp *et al.* (*6*) have reported the synthesis



	R^1	R^2	R^3		R^1	R^2	R^3		R^1	R^2	R^3		R^1	R^2	R^3
a	Et	H	H	**c**	4-NO_2-C_6H_4	H	H	**e**	Me	Me	Me	**g**	Me	H	Ph
b	4-MeO-C_6H_4	H	H	**d**	Me	H	Me	**f**	Ph	H	Me				

Scheme 1.



Scheme 2.

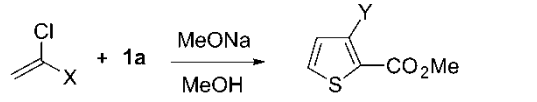
of 4-hydroxy-2-trifluoromethylthiophene **13**, a putative thiophene bioisostere of α,α,α-trifluoro-*m*-cresol as the inhibitor of phytoene desaturase (*7*), a key enzyme in the biosynthesis of carotenoids (*8*). The 3-alkoxy-4,4,4,-trifluorocrotonate ester (*9*) should serve as a suitable tetrolate synthon. Thus, the treatment of ethyl 4,4,4-trifluoroacetoacetate **8** with Cs_2CO_3 and methyl *p*-toluenesulfonate afforded ethyl 3-methoxy-4,4,4-trifluorocrotonate **9** in 60% yield. The strong electron withdrawing nature of the trifluoromethyl group allows for the exclusive *O*-alkylation of the β-keto ester. Cyclocondensation of **9** with methyl thioglycolate **1a** in methanolic KOH occurred smoothly to give methyl 3-hydroxy-5-trifluoromethylthiophene-2-carboxylate **10** (*10*) in 63% yield. Saponification afforded the acid **11** in 65% yield. Compound **11** readily underwent thermal decarboxylation upon heating the solid to 100 °C affording compound **13** in 82% yield, predominantly in the enol form, in the ratio of 8.5:1 (Scheme 2).

2.3. *3-Hydroxy-and 3-aminothiophenes*

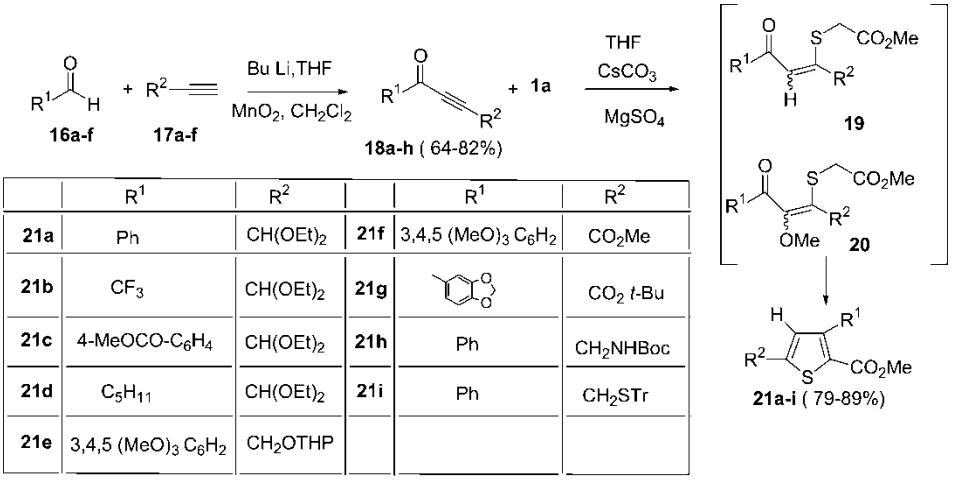
The synthesis of methyl 3-amino- and 3-hydroxy-2-thiophene carboxylates by Fiesselmann (*11*) involves the base induced condensation of methyl thioglycolate with 2,3-dihalogenopropionitrile and 2,3-dihalogenopropionate esters, respectively. Huddleston and Barker (*12*) reported the modified Fiesselmann process and have obtained good yields of thiophene derivatives (**15a**) and (**15b**). The 2-halogenoacrylic acid derivatives (**14a, b**) on reaction with methyl thioglycolate **1a**, in the presence of sodium methoxide, furnished thiophene derivatives. Presumably, the reaction sequence leading to the thiophene ring involves the Michael addition of the thioglycolate anion to the acrylic acid derivative, followed by a Thorpe or Dieckmann-type cyclization with the elimination of HCl (Scheme 3).

2.4. *2,3,5-Trisubstituted thiophenes*

Various substituted thiophenes have found many applications in the pharmaceutical field and especially in the search of new semiconductors (*13, 14*). Obrecht *et al.* (*15*) have reported



Scheme 3.



	R^1	R^2		R^1	R^2
21a	Ph	$CH(OEt)_2$	**21f**	3,4,5 $(MeO)_3$ C_6H_2	CO_2Me
21b	CF_3	$CH(OEt)_2$	**21g**		CO_2 *t*-Bu
21c	4-MeOCO-C_6H_4	$CH(OEt)_2$	**21h**	Ph	CH_2NHBoc
21d	C_5H_{11}	$CH(OEt)_2$	**21i**	Ph	CH_2STr
21e	3,4,5 $(MeO)_3$ C_6H_2	CH_2OTHP			

Scheme 4.

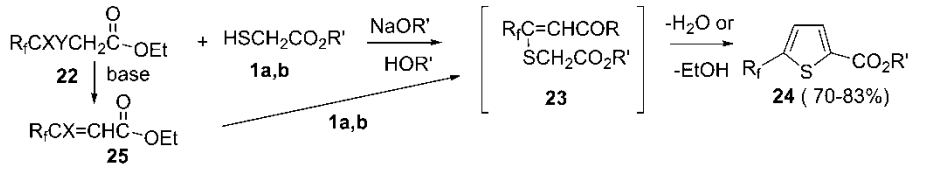
that the acetylinic ketones are excellent precursors for the synthesis of substituted thiophenes and quinolines (*16*). 2,3,5-Trisubstitated thiophenes of type **21a–i**, adopting a tandem *Michael*-addition/intramolecular *Knoevenagel*-condensation strategy (*17*) were also reported by the authors. The treatment of aldehydes **16a–f** with the alkynyllithium reagents derived from acetylenes **17a–f** furnished the expected acetylinic ketones, **18a–h** (*18–20*) after oxidation with MnO_2 in CH_2Cl_2, in 64–82% yield. The treatment of acetylinic ketones **18** with one equivalent of methyl thioglycolate **1b** in THF resulted in the quantitative formation of an E/Z-mixture of *Michael* adducts **19, 20**, which were transformed into the 2,3,5-trisubstituted thiophens **21a–i**, with an overall yield of 60–90% by the addition of MeOH and 20 mol% Cs_2CO_3 (mixed with predried $MgSO_4$) at 0 °C and stirring for 1–2 h at room temperature (Scheme 4).

2.5. *2-Trifluoromethyl-or 2-(1,1-difluoroalkyl)thiophenes*

Fluorine-bearing heterocyclic compounds are important in both the academic and industrial fields. The regioselective replacement of hydrogen in a molecule by a fluorine or fluoroalkyl group may have profound influence on the biological and physical properties of such compounds (*21*). α-Fluoroalkyl acetates **22** have proved to be versatile precursors in the synthesis of fluoroalkylthiophenes. Guan *et al.* (*10*) reported the synthesis of such compounds with alkyl 2-sulfanylacetates **1a,b**. α-Fluoroalkylcarbonyl compounds **22** in presence of NaOMe on treatment with methyl-2-sulfanylacetate **1a** in methanol at room temperature for ∼5 h to afforded 2-fluoroalkyl-4-hydroxy-5-methoxycarbonylthiophene **24** in high yields. Under basic conditions, **22** underwent dehydrohalogenation to give intermediate **25**, which were attacked by the nucleophilic thiols **1a, b** at the β-position and afforded intermediate **23**. Such intermediates underwent intramolucular condensation and dehydration to afford the target product **24** (Scheme 5).

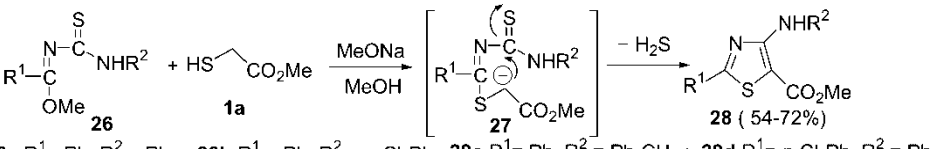
2.6. *Aminothiazole derivatives*

Aminothiazoles constitute excellent precursors of a large variety of biologically active compounds such as antibiotics, β-lactams and antibacterials (*22*). Dridi *et al.* (*23*) reported the synthesis of aminoethoxycarbonylthiazole derivatives from *N*-functionalized imidates (*24–26*). Refluxing equimolar quantities of methyl thioglycolate **1a** and *N*-thiocarbamoylimidates **26** in methanol



	R_fCXY	R_f	R'		R_fCXY	R_f	R'
24a	CF_3CBr_2	CF_3	Me (75%)	**24e**	$Cl(CF_2)_4$	$Cl(CF_2)_3$	Me (83%)
24b	CF_3CFBr	CF_3	Me (72%)	**24f**	$PhCH{=}CHCF_2CF_2$	$PhCH{=}CHCF_2$	Me (72%)
24c	CF_3CF_2	CF_3	Et (75%)	**24g**	$CH_3(CH_2)_5CF_2CF_2$	$CF_3(CH_2)_5CF_2$	Me (70%)
24d	$ClCF_2CF_2$	$ClCF_2$	Me (72%)	**24h**	$(MeO)_2C(CH_2)_2CF_2CF_2$	$MeO_2C(CH_2)_2CF_2$	Me (80%)

Scheme 5.



28a R^1 = Ph, R^2 = Ph; **28b** R^1 = Ph, R^2 = *p*-Cl-Ph; **28c** R^1 = Ph, R^2 = Ph-CH_2 ; **28d** R^1 = *p*-Cl-Ph, R^2 = Ph

Scheme 6.

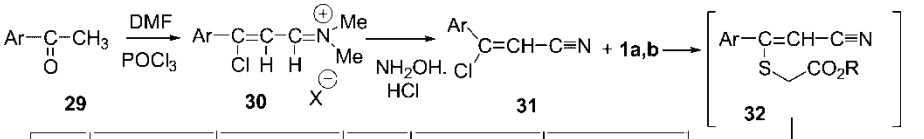
with an excess of NaOMe gives the desired 4-aminothiazoles **28**. Presumably, this is a two-step reaction, formation of the *N*-thio-carbamoylthioimidate **27** intermediate, which on cyclization affords aminothiazole **28** (Scheme 6).

2.7. *5-Aryl-2-alkoxycarbonyl thiophenes*

Hartmann (*27*) reported the synthesis of β-chlorocinnamonitriles **31** starting from acetophenones **29**, dimethylformamide (DMF), $POCl_3$ and hydroxylamine hydrochloride (*28, 29*). The reaction involves the intermediate 3-chloro-2-propeniminium salts **30**, which are versatile synthons in organic chemistry, especially in the synthesis of heterocyclic compounds (*30*). β-Chlorocinnamonitriles **31** can be converted to 5-aryl-3-amino-2-alkoxycarbonylthiophene **33** by the reaction with α-mercaptoacetic esters **1a, b** in the presence of a base. The reactants probably interact by the primary substitution of the chloro-substitutent in **31** by the mercapto group of **1** followed by a Dieckmann–Thorpe cyclization of the resulting in 3-aryl-3-alkoxycarbonylmethylmercaptoacrylonitriles **32**. The best yields of **33** are obtained when alkaline hydroxides in alcoholic solution are used as bases (Scheme 7).

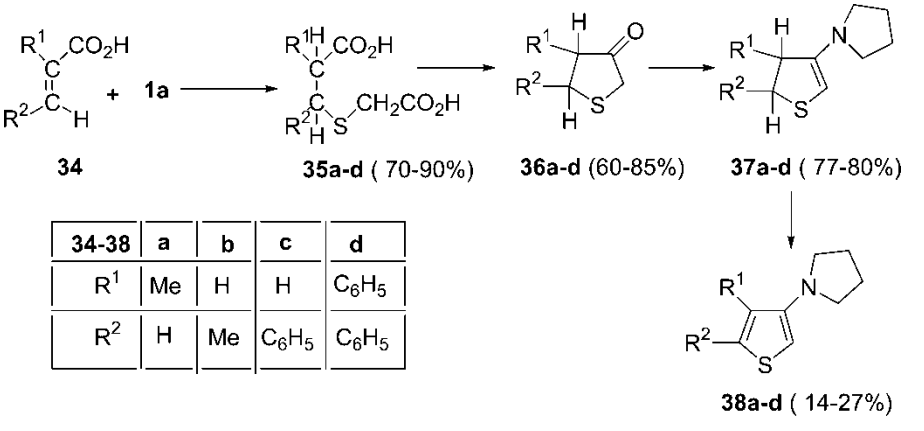
2.8. *3-Pyrrolidinylthiophenes*

In the reactivity of 3-(1-pyrrolidinyl)-thiophenes (*31*), the carbon–carbon double bond constitutes part of a heteroaromatic $[4n + 2]$ π-electron system, the reactivity of these 1-pyrrolidinyl heteroarenes is of the same order of magnitude as in 'normal' enamines (*32*). Alkyl- and aryl-substituted 3-(1-pyrrolidinyl)-thiophenes **38** were obtained (*33*) by a four-step synthesis. The initial step is the addition of methyl mercaptoacetate to a propenoic acid **34** under basic conditions (70–90% yield). Ring-closure of the dicarboxylic acid **35** was performed with lithium acetate as catalyst in acetic anhydride. The condensation of the cyclic thioketone **36** with pyrrolidine



	Ar	R		Ar	R
33a	C_6H_5	Et (66%)	**33f**	4-MeO-C_6H_4	Et (55%)
33b	4-Cl-C_6H_4	Me (76%)	**33g**	4-C_6H_5-C_6H_4	Et (70%)
33c	4-Cl-C_6H_4	Et (98%)	**33h**	4-C_6H_5-C_6H_4	Me (79%)
33d	4-Br-C_6H_4	Et (81%)	**33i**	4 -NO_2-C_6H_4	Me (80%)
33e	4-MeO-C_6H_4	Me (82%)	**33j**	2-$C_{10}H_7$	Me (84%)

Scheme 7.



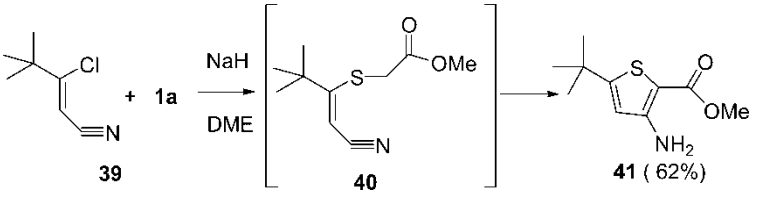
34-38	**a**	**b**	**c**	**d**
R^1	Me	H	H	C_6H_5
R^2	H	Me	C_6H_5	C_6H_5

Scheme 8.

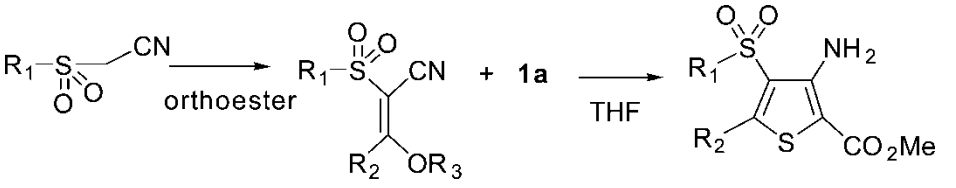
and subsequent aromatization of the enamine **37** (30–80% yield) was performed using standard methods (*34*) to result in **38** (Scheme 8).

2.9. *3-Aminothiophenecarboxylate esters*

Substituted 3-amino-2-thiophenecarboxylate esters were reported to exhibit anti-inflammatory activity (*35*). Redman *et al.* (*36*) reported the synthesis of 5-substituted-3-aminothiophene-2-carboxylate **41** by the condensation of β-haloacrylonitrile **39** (*27*) with methyl thioglycolate **1a** using NaH in DMF. This reaction involves the formation of a *cis*-β (alkylthio) acrylonitrile **40** followed by base catalyzed cyclization leading to the formation of aminothiophene **41** (Scheme 9).



Scheme 9.



42a-g **43a-i** (26-70%) **44a-i** (31-70%)

42	R_1	43-44	R_1	R_2	R_3
a	Ph	a	Ph	H	Et
b	4Cl-Ph	b	4-ClPh	H	Et
c	4-F-Ph	c	4-F-Ph	H	Et
d	4-Me-Ph	d	4-MePh	H	Et
e	2-NO_2-Ph	e	2-NO_2-Ph	H	Et
f	2-CO_2Me-Ph	f	2-CO_2Me-Ph	H	Et
g	Me	g	4-Cl-Ph	Me	Me
		h	2-NO_2-Ph	Me	Me
		i	4-Cl-Ph	Et	Et

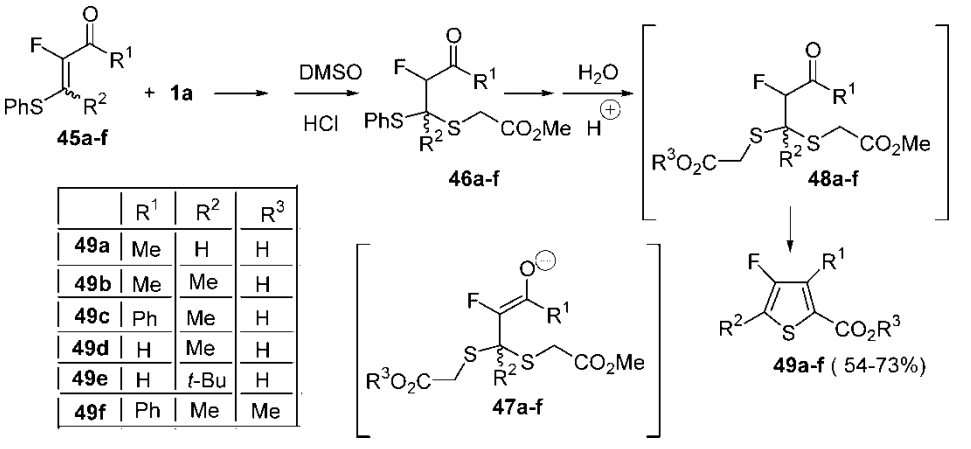
Scheme 10.

2.10. *4-Arylsulfonyl-2-thiophenecarboxylates*

The 3-amino-4-arylsulfonylthiophene-2-carboxylates are reported to have anti-viral activity. Stephens *et al.* (*37*) reported a Fiesselmann-type (*38*) synthesis of a series of methyl 3-amino-4-arylsulfonylthiophene-2-carboxylates containing non-heteroatom substituents at the 5-position by reaction of 3-alkoxy-2-arylsulfonylacrylonitriles with methyl thioglycolate in the presence of triethylamine. The reaction of substituted arylsulfonylacetonitriles **42** with an *ortho* ester derivative in the presence of acetic anhydride/zinc chloride gave 3-alkoxy-2-arylsulfonylacrylonitriles **43** (*39*). The reaction of acrylonitriles **43** with methyl thioglycolate **1a** in refluxing THF for 2-5h using Et_3N furnished the 3-amino 4-aryl sulfonylthiophene-2-carboxylates **44** (Scheme 10).

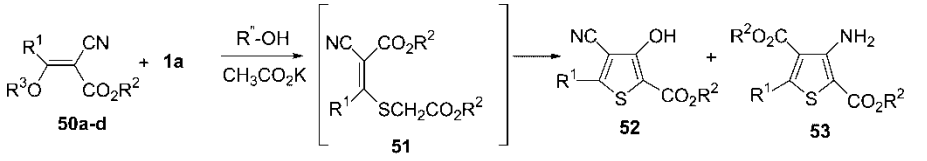
2.11. *Substituted α-carboxy-γ-fluorothiophenes*

Fluorothiophenes are potent intermediates, for pharmacological or agrochemical active products (*40*). α-Carboxy-γ-fluorothiophenes **49** were synthesized by Andres *et al.* (*41*) from α-fluoroenones **45** by the condensation with methyl thioglycolate **1a** in DMSO. γ-Fluorothiophenes **49** has been obtained *via* an unclassical nucleophilic vinylic substitution mechanism. The first enolic intermediates **47** can be trapped by an acid hydrolysis to give saturated dithianes **48** or **47**, which can be cyclized to fluorothiophenes with an excess of base. The fluoro-carbanion lone pair repulsion in **46** increasing the negative charge density on oxygen-atom associated with the nucleo-fugacity of the thio groups SR seem responsible for this particular situation (*42*) (Scheme 11).



	R^1	R^2	R^3
49a	Me	H	H
49b	Me	Me	H
49c	Ph	Me	H
49d	H	Me	H
49e	H	*t*-Bu	H
49f	Ph	Me	Me

Scheme 11.



	R^1	R^2	R^3	R'	R"		R^1	R^2	R^3	R'	R"
52a	Me	Me	Me	Me	Me (28%)	**53a**	Me	Me	Me	Me	Me (28%)
52b	Me	Et	Me	Me	Me (28%)	**53b**	Me	Et	Me	Me	Me (28%)
52c	Et	Me	Et	Me	Me (35%)	**53c**	Et	Me	Et	Me	Me (35%)
52d	Et	Et	Et	Me	Me (47%)	**53d**	Et	Et	Et	Me	Me (47%)

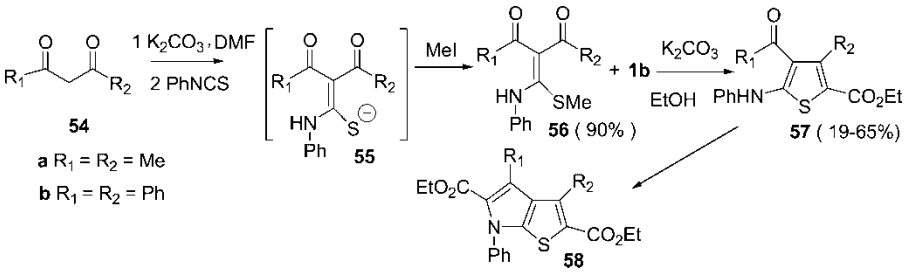
Scheme 12.

2.12. *3-Substituted thiophenes*

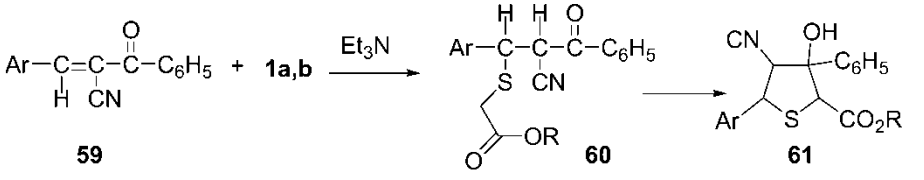
Thiophene derivatives have been reported for their application in the synthesis of useful compounds (*43–45*). Most thiophenes from two-component pathways are formed by the reaction of 3-thionate salts of acrylic esters or acrylonitriles with halogen compounds. Saito and Kambe (*46*) reported the synthesis of 3-hydroxy- or 3-aminothiophenes **52** or **53**, respectively, from 3-alkoxy-2,3-unsaturated nitriles **50** and mercaptoacetic esters **1a, b** in refluxing alcohol. Reaction of nitriles **50a–d** with mercaptoacetic esters **1a, b** in the presence of potassium acetate in the appropriate alcohol gave **52a–d** and **53a–d** in good yields. The reaction goes through the intermediate **51**, which was easily converted to thiophenes **52** and **53** under alkaline conditions (Scheme 12).

2.13. *4-Aminothiophenes*

Ketene dithioacetals are the key intermediates for the preparation of a large number of heterocyclic structures (*47*). Sommen *et al.* (*48*) reported the synthesis of ketene phenylamino methylthioacetals **56** by reacting β-diketones **54** with phenyl isocyanates in a basic medium (K_2CO_3/DMF), followed by methyl iodide (*49*). The thiophene derivatives **57** were prepared by the cyclization reaction of ethyl thioglycolate **1b** with thioacetals **56** by the displacement of the thiomethyl



Scheme 13.



	Ar	R		Ar	R
a	C_6H_5	Me	**d**	4-Cl-C_6H_4	Me
b	4-MeC_6H_4	Me	**e**	2-Cl-C_6H_4	Me
c	4-$NO_2C_6H_4$	Me	**f**	C_6H_5	Et

Scheme 14.

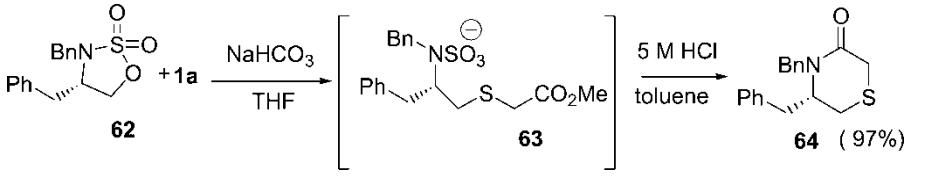
group of ketene dithioacetal. The condensation of **57** with ethyl bromoacetate furnished thieno[2,3b]pyrroles in good yields (Scheme 13).

2.14. *Aryl-3-phenyltetrahydrothiophene*

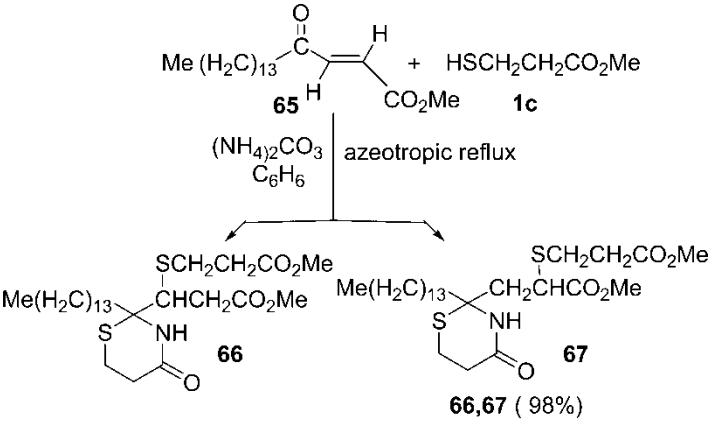
α,β-Unsaturated nitriles (*50*) are valuble intermediates in the synthesis of heterocylces. One-step synthesis of 7*H*-thiazolo[3,2-*a*]pyridine derivatives from α-cyanocinnamic esters and mercaptoacetic esters in the presence of triethylamine was reported (*51*). Kamble *et al.* (*52*) reported the formation of thioether group by the addition of thiol to an olefin, which can be utilized to carry out a Dieckmann synthesis of a 3-oxotetrahydrothiophene from an α-mercapto ester, and an α,β-unsaturated nitrile (*53*). The reaction of benzylidinebenzoylacetonitriles **59** with mercaptoacetic esters **1a,b**, in the presence of triethylamine, gave 2-alkoxycarbonyl-5-aryl-4-cyano-3-hydroxy-3-phenyltetrahydrothio-phenes **61** without the isolation of intermediate thioethers **60** (Scheme 14).

2.15. *Thiomorpholin-3-ones*

Cyclic sulfates and cyclic sulfamidates represent a versatile class of functionalized and enantiomerically pure electrophiles. As a result, these reactive alkylating agents are finding increasing synthetic applications across a range of areas (*54*). 1,2-cyclic sulfamidates **62** (*55*) provide an attractive entry to *N*−heterocycles by allowing the key C–N bond stereochemistry to be defined at the outset and retained. The approach is outlined in the scheme by Williams *et al.* (*56*), using methyl thioglycolate **1a** as the other component. A six-ring *N*-heterocycle **64** is formed



Scheme 15.



Scheme 16.

by a regioselective nucleophile displacement on **62** and subsequent lactamization (involving the adjacent acetate fragment in **63**) (Scheme 15).

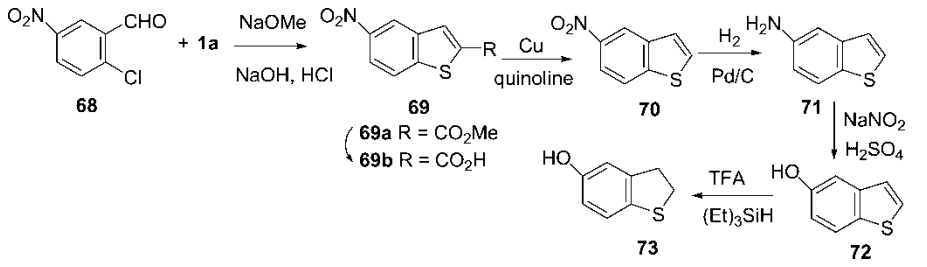
2.16. *Heterocyclic derivatives of long-chain fatty acids*

Thiazolidinedione derivatives of long-chain fatty acids are reported as physiologically active natural products (*57*), which control the biochemical processes of different systems. Mustafa *et al.* (*58*) reported the synthesis of thiazinanones from (*E*)-methyl 4-oxo-octadec-2-enoate **65** (*59*). Azeotropic reflux of **65** with methyl 3-mercaptopropionate **1c** and ammonium carbonate afforded the thiazinane, as a mixture of isomers **66** and **67** (Scheme 16).

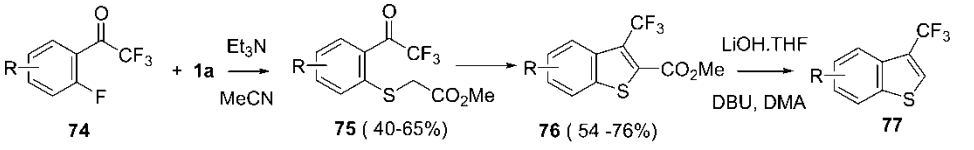
3. Bicyclic derivatives

3.1. *5-Hydroxy-2,3-dihydrobenzothiophene*

The 5-Hydroxy-2,3-dihydrobenzofurans are reported as the antioxidant-based inhibitors of leuko-triene biosynthesis (*60*). The synthesis of 5-hydroxy-2,3-dihydrobenzothiophene **73**, the isoelectronic di-hydrobenzothiophene was reported by Zambias and Hammond (*61*). Addition of a methanolic solution of 2-chloro-5-nitrobenzaldehye **68** to a 50 °C solution of methyl thioglycolate **1a** and sodium methoxide in methanol afforded the methyl ester **69a**, which may be isolated (95%) or directly saponified. Acidification with conc. HCl then affords **69b** as precipitate in 90% yield. Decarboxylation of **69b** with copper in quinoline (*62*), followed by catalytic reduction (*63*) afforded amine **71** in 62% yield. Diazotization and displacement of **71** in H_2SO_4 acid afforded **72** in 59% yield. Reduction with triethylsilane in TFA (*64*) gave 5-hydroxy-2,3-dihydrobenzothiophene **73** in 30% yield (Scheme 17).



Scheme 17.



a; R = H (62%), **b**; R = 5-Br (65%), **c**; R = 5-Cl (40%), **d**; R = 5-CN (63%), **e**; R = 4-Br (41%)

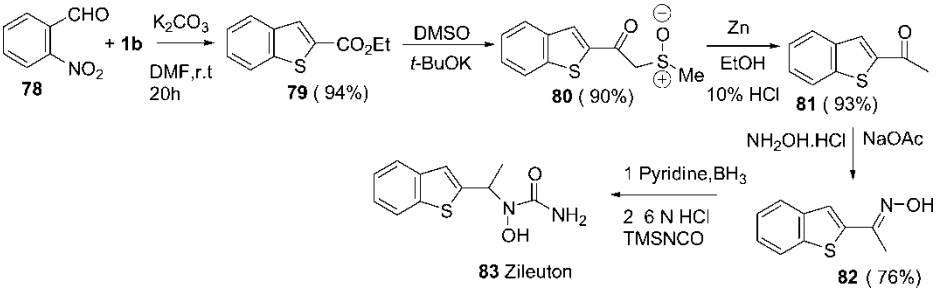
Scheme 18.

3.2. *3-Trifluoromethylbenzothiophenes*

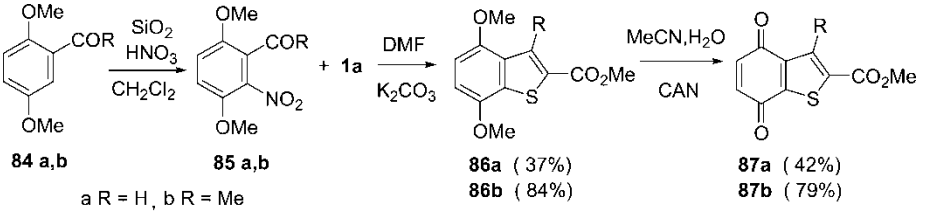
The trifluoromethyl group is a very valuable substituent to include in any organic series because of the unique physical and biological properties it confers (*65*). Owton (*66*) reported a scaleable route to 3-trifluoromethylbenzo[*b*]thiophenes **77** (*67*) that could provide substituents in the 5 position. The reaction of substituted 2-fluoro-2′,2′,2′-trifluoroacetophenones **74** with methyl thioglycolate **1a** in triethylamine at room teprature in acetonitrile gave the methyl 3-trifluoromethyl-5-cyanobenzo[*b*]thiophene-2-carboxylate **76** through the keto intermediate **75**. Hydrolysis of the methyl esters was accomplished in near quantitative yield with lithium hydroxide in THF/water (19:1) at room temprature. Decarboxylation was accomplished in good yield with DBU in dimethylacetamide at 200 °C for 1 h in a CEM MARS microwave reactor to furnish **77** (*68*) (Scheme 18).

3.3. *2-Acetylbenzothiophene*

Zileuton is the first selective 5-LO (lipoxygenase inhibitor) to establish efficacy for therapeutic agents in asthma and ulcerative colitis (*69*). 2-Acetylbenzo[*b*]thiophene is the key intermediate for the synthesis of Zileuton. Kolasa and Brooks (*70*) have reported the synthesis of 2-acetylbenzothiophene from 2-nitrobenzaldehyde **78**. Reaction of *o*-nitrobenzaldehyde **78** with ethyl mercaptoacetate **1b** in DMF and K_2CO_3 provided ethyl 2-benzo[*b*]thiophenecarboxylate **79** in 94% yield. The application of β-ketosulfoxide as an intermediate for the transformation of the ester **79** into the desired 2-acetyl analog **81** was then employed. Treatment of the ester **79** with potassium *t*-butoxide in DMSO provided the β-ketosulfoxide intermediate **80** in 90% yield. Reduction of the sulfoxide with a suspension of zinc dust in 10% NH_4Cl-ethanol at 0 °C for 1 h afforded 2-acetylbenzo[*b*]thiophene **81** as a crystalline product in 93% yield. The oxime **82** was prepared by reacting **81** with $NH_2OH \cdot HCl$ and sodium acetate. The oxime **82** is converted to the Zileuton **83** by reduction with pyridine borane and 6 N HCl to provide the corresponding hydroxylamine. The hydroxylamine is treated with trimethylsilylisocyanate to form the *N*-hydroxyurea **83** (Scheme 19).



Scheme 19.



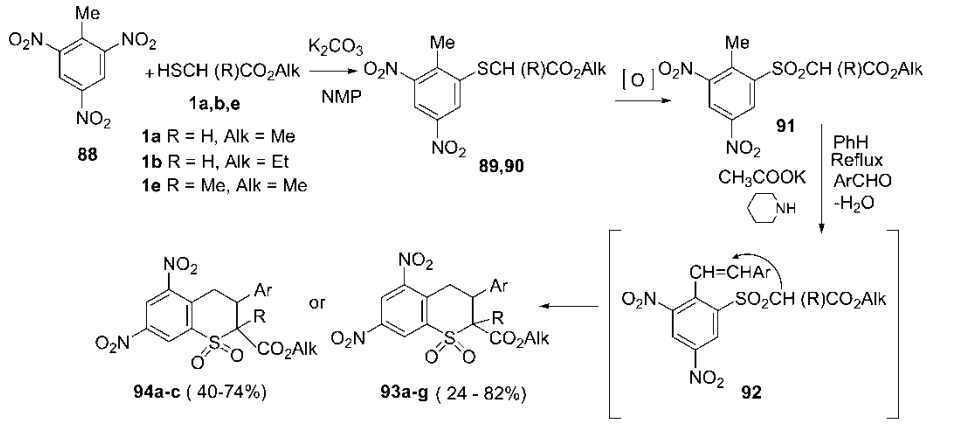
Scheme 20.

3.4. *Benzothiophene-4,7-quinones*

Benzo[*b*]thiophene-4,7-quinones are known as antitumoral heteroanalogues of the antitumor drugs daunomycin and mitoxantrone, which contain this structural subunit (*71*). Valderrama and Valderrama (*72*) reported the synthesis of these heterocylces based on the method of Beck (*73*) in which the thiophene ring formation occurs from 2,5-dimethoxybenzaldehyde **84**. The oxidative demethylation, which is a well-established method to prepare heterocyclic quinones, was applied to the synthesis of **87a, b**. The nitration of 2,5-dimethoxycarbonyl compounds (**84a, b)** with nitric acid-impregnated silica gel (*74*) gave nitro derivatives (**85a, b**). The reaction of **85a, b** with methyl thioglycolate **1a** was carried out in DMF in the presence of K_2CO_3 which afforded the corresponding benzo[*b*]thiophene **86**. The mechanism of the cyclization of *o*-nitroketo derivatives with methyl thioglycolates in basic medium is unknown. However, it is reasonable to assume that thiophene ring formation involves thiol anion displacement of the activated nitro group followed by base-catalyzed aldol-condensation. Oxidative demethylation of 4,7-dimethoxybenzo[*b*]thiophenes **86** was carried out by reaction with cerium (IV) ammonium nitrate (CAN) in acetonitrile-water solution to afford benzo[*b*]thiophene-4,7-quinones **87** (Scheme 20).

3.5. *Thiochroman 1,1-dioxide derivatives*

Tartakovskii *et al.* (*75*) reported the chemical utilization of an explosive material 2,4,6-trinitrotoluene (*76*). The authors report the transformation of 2,4,6-trinitrotoluene (TNT) **88** into benzo-fused heterocylces. The synthesis of thiochroman-1,1-dioxide derivatives is described on the basis of TNT. In the reaction with mercaptoacetic acid ester **1a, b**, only one of the *ortho*-nitro groups is replaced in the presence of K_2CO_3 in *N*-methylpyrrolidone (NMP) or DMF at 20 °C. The product, sulfides **89, 90**, was oxidized to the corresponding sulfone **91**. The reaction of sulfones **90** and **91** with aromatic aldehydes was conducted under Knoevenagel reaction conditions as described below. Equimolar amounts of **90** or **91** and an aromatic aldehyde ArCHO were reacted together in benzene in the presence of a catalytic amount of piperidinium acetate and

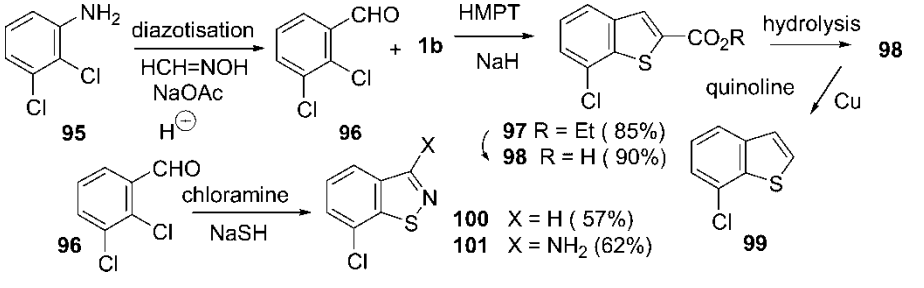


Scheme 21.

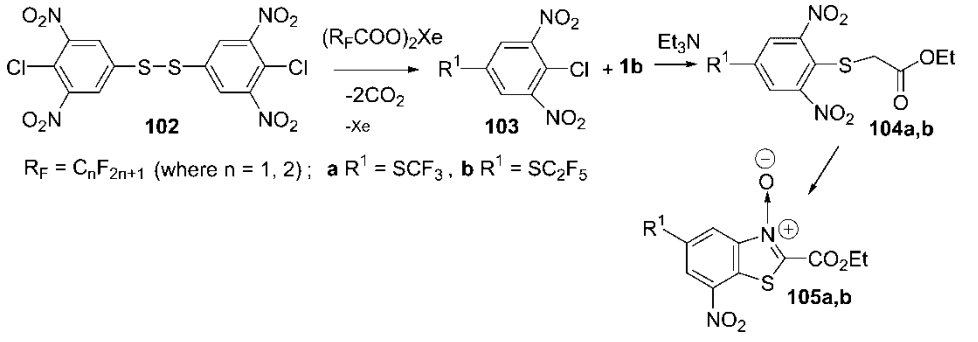
with the continuous removal of water to form 5,7-dinitrochroman-1,1-dioxide **93, 94**. Condensation of the aldehyde group with methyl group of **90** initially afforded stilbene **92**, which later underwent intramolecular Michael addition of the reactive methylene group at the double bond (Scheme 21).

3.6. *7-Substituted benzothiophenes and 1,2-benzoisathiazoles*

The 7-substituted benzo[*b*]thiophenes and 1,2-benzoisothiazoles are difficult to synthesize (*77*). Rahman and Scrowston (*78*) reported the synthesis of 7-chloro and 7-nitroderivatives of each system in connection with a study of biologically active compounds. 2,3-dichlorobenzaldehyde **96** has been obtained in 55% yield by the treatment of 2,3-dichloroaniline **95** with formaldoxime, followed by acidic hydrolysis of the initially formed product (Beech's method) (*79*). Initial attempts to selectively replace the 2-chloro atom in the 2,3-dichlorobenzaldehyde **96** by a sulfur nucleophile were unsuccessful. However, the use of ethyl mercaptoacetate in hexamethylphosphoric triamide (HMPT) and NaH effectively displaced the 2-chloro atom and the product cyclized spontaneously to give ethyl 7-chlorobenzo[*b*]thiophene-2-carboxylate **97** in 85% yield. This was converted into 7-chlorobenzo[*b*]thiophene **99** by hydrolysis, and decarboxylation with copper in quinoline. Treating 2,3-dichlorobenzaldehyde **96** with sodium hydrogen sulfide in HMPT at 60–80 °C gave-3-chloro-2-mercapto-benzaldehyde sodium salt. This reacted with chloramines to provide 7-chloro-1,2-benzisothiazole **100** and **101** (Scheme 22).



Scheme 22.



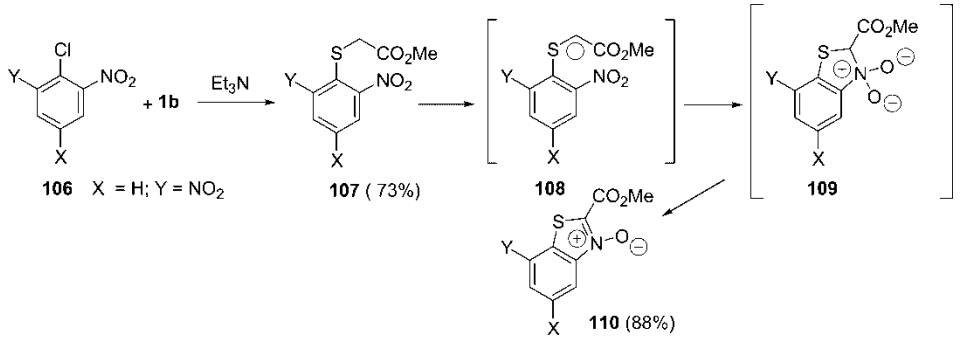
Scheme 23.

3.7. *Perfluoroalkylbenzothiazole N-Oxide*

The replacement of the hydrogen atom in aromatic and heterocyclic systems by perfluoro alkyl groups may significantly affect the physical and biological properties of such molecules (*80*). The introduction of 'superlipophilic' perfluoroalkylthio groups such as SR_F ($R_F = CF_3$, C_2H_5, etc.), which have the highest lipophilicity indices, may substantially enhance the biological effect of the resultant compound (*81*). Perfluoroalkylation of bis (4-chloro-3,5-dinitrophenyl)disulfide **102** (*82*), gave 2,6-dinitro-1-chloro-4-perfluoroalkylthio-benzene **103a, b**. Sipyagin *et al.* (*83*) reported that the reaction of **103a, b** with ethyl thioglycolate **1b** gave benzothiazole *N*-oxide **105** (*84*). In this case, the ethyl thioglycolate fragment resulting the formation of intermediates **104a,b** replaces the chlorine atom. Subsequent intramolecular condensation with the nitro group led to heterocyclisation giving **105a, b** (Scheme 23).

3.8. *2-Alkoxycarbonylbenzothiozol-3-oxides*

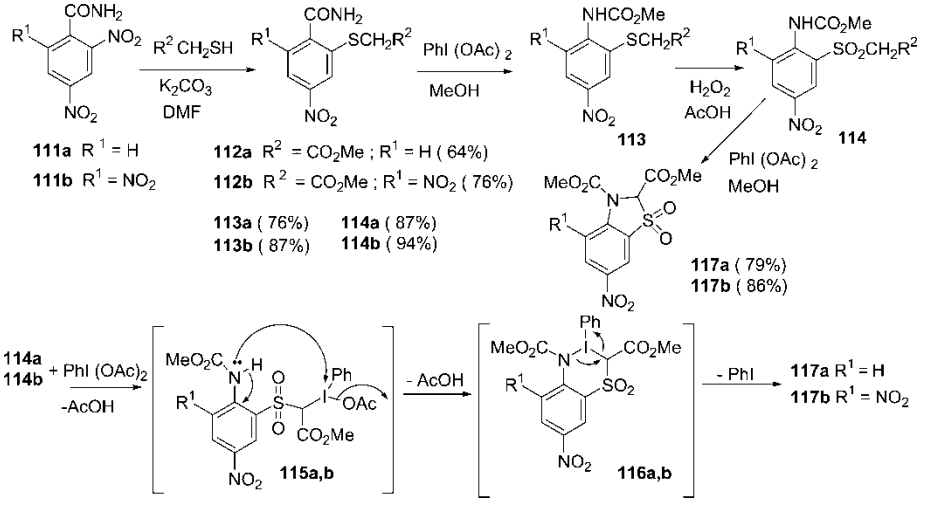
Wagner *et al.* (*85*) have described the base catalyzed reaction of substituted 2-nitrochlorobenzenes **106** with esters of sulfanylethanoic acid to give the correspondingly substituted 2-alkoxycarbonylbenzo[*d*]thiazol-3-oxides. Dudova *et al.* (*86*) described that 2,6-dinitrochlorobenzene **106** reacts with methyl thioglycolate **1a** in methanol (with triethylamine as catalyst) to give 2-methoxycarbonyl-7-nitrobenzo[*d*]thiazol-3-oxide **110**, through the 'open' substituted methyl (2,6-dinitrophenylsulfanyl)ethanoate **107**. It proceeds as a multi-step reaction (*87, 88*). The first step in the cyclization involves a base-catalyzed deprotonation of the methylene group to afford the corresponding carbanion **108**, which then intramolecularly attacks the nitrogen atom of nitro group to afford **109**. The ionization of the hydroxyl group leads to the formation of the final product **110** (Scheme 24).



Scheme 24.

3.9. *Benzothiazol-1,1-dioxide and 1,4-benzothiazin-3-ones*

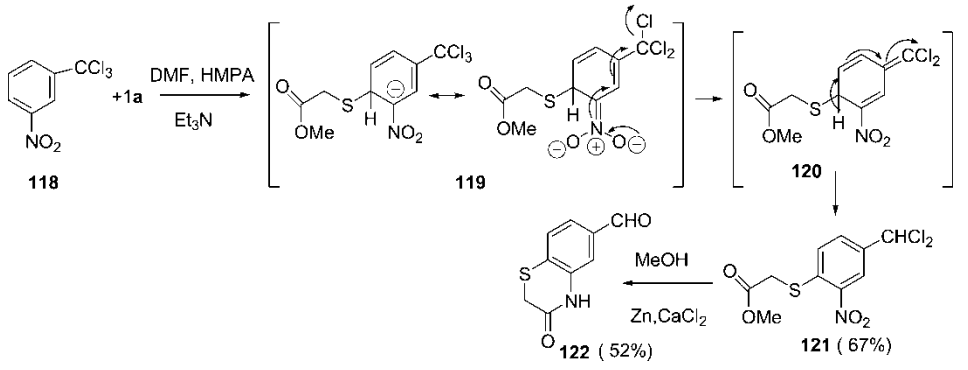
Transformations of polynitroarenes into various valuable products such as sulfur- and nitrogen-containing heterocylces have been developed (*89*). The conversion of 2,4-di- and 2,4,6-trinitrobenzamide **111a, b** to 2,3-dihydrobenzothiazol-1,1-dioxides are well known types of heterocycles employed in the preparation of biologically active compounds (*90*). The methods reported by Gerasyuto *et al.* (*91*) involve the introduction of sulfur-containing substituents into the position *ortho*-to the amido group. The transformation of the amido group to the methoxycarbonyl-amino group was followed by heterocyclization of the compounds in the presence of a base or an oxidant. The reaction of benzamides **111a, b** with methyl thioglycolate **1a** in DMF in the presence of K_2CO_3 gave 2-alkylthiobenzamides **112a, b**. The 2-alkylthiobenzamides **112a, b** were converted to methyl carbamates **113a, b** under the action of diacetoxyiodobenzene (DAIB) in MeOH by the modified procedure (*92*). The oxidation of urethanes **113a, b** with H_2O_2 gave 5,5-dioxides **114a, b**. The interaction of **114a, b** with DAIB in MeOH furnished 2,3-bis(methoxycarbonyl)-2,3-dihydrobenzothiazol-1,1-dioxide **117a, b** in 79 and 87% yield, respectively. The transformation of urethanes **114a, b** into benzothiazenes **117a, b** apparently involves the generation of iodine intermediates structures **115**, **116** at the carbon atom of the methylene group, followed by intramolecular cyclization, followed by the elimination of AcOH and PhI (Scheme 25).



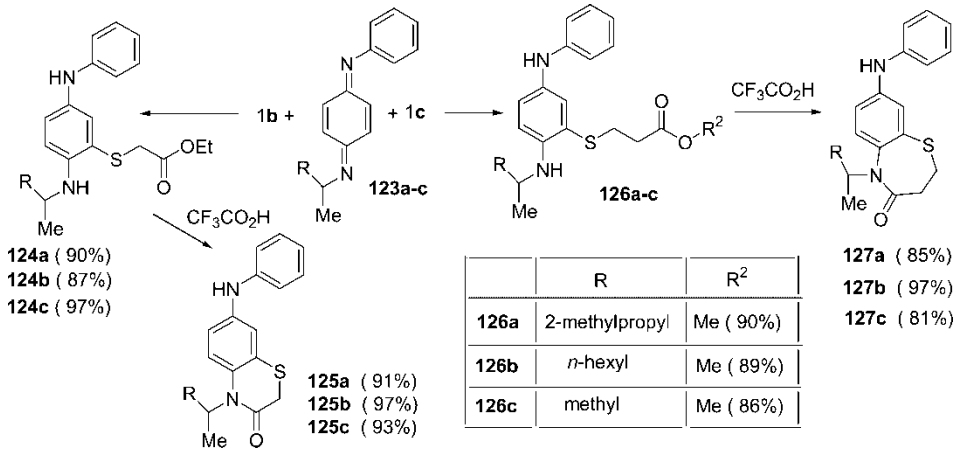
Scheme 25.

3.10. *1,4-Benzothiazine-3-one*

Tele nucleophilic aromatic substitution in carbocyclic and heterocyclic arenes is a very important reaction from both the academic and industrial point of views (*93, 94*). Giannopoulos *et al.* (*95*) reported the reactions of 1-nitro-3-trichloromethylbenzene **118** (*96*) with methyl thioglycolate **1a** in DMF at ambient temperature with HMPA as the catalyst in triethylamine, followed by aqueous work-up gave nitro-ester **121** in 67% yield. The reductive cyclization of **121** with Zn and $CaCl_2$ in aqueous methanol gave 1,4-benzothiazine-3(4*H*)-one **122** in 52% yield. The reaction occurs by the addition of nuclophile to the sixth position resulting in the intermediate **119, 120**, the elimination of a chloride ion and 1,5-hydrogen shift from the sixth position to the exocyclic carbon leading to a 2-substituted-5-dichloromethylnitrobenzene (Scheme 26).



Scheme 26.



	R	R^2
126a	2-methylpropyl	Me (90%)
126b	*n*-hexyl	Me (89%)
126c	methyl	Me (86%)

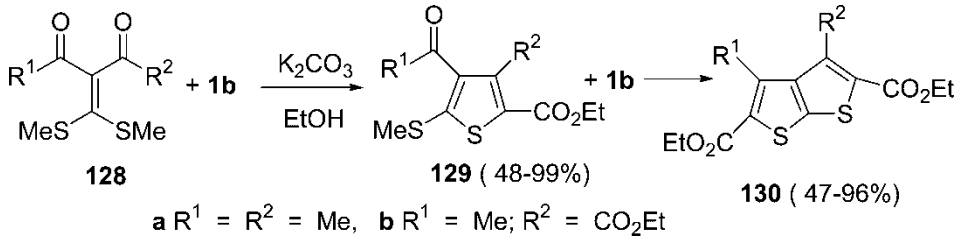
Scheme 27.

3.11. *1,5-Benzothiazepin-4-one and 1,4-benzothiazin-3-ones*

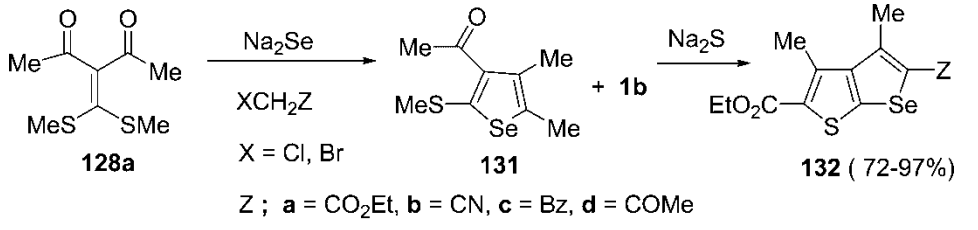
Benzothiazepinones and benzothiazinones have been of great interest due to the broad spectrum of biological activities of these types of compounds (*97, 98*). Katritzky *et al.* (*99*) have reported the synthesis of benzothiazepinones **127a–c** (*100*) and benzothiazinones **125a–c** from 1,4-benzoquinone diimines. The nucleophilic addition of methyl 3-mercaptopropanoate **1c** to benzoquinone diimines **123a–c** proceeds regioselectively by the addition at the C-3 position of benzoquinoid ring forming methyl 3-[5-anilino-2[(1,3-dimethylbutyl)amino]phenylsulfonyl] propanoate **126a–c**. The cyclization of compounds **126a–c** by heating with TFA at 70 °C gave the desired cyclized **127a–c**. In a similar way, 2*H*, 1,4-benzothiazin-3(4*H*)-ones **125a-c** were reported in 87–97% yield, from benzoquinone diimines **123a–c** with ethyl thioglycolate (Scheme 27).

3.12. *2,3,4,5-Functionalized thienothiophenes*

Substituted thieno[2, 3-*b*]thiophenes and the methods of their preparation have been known since the 1950s. One of the most recent synthetic pathways for their preparation is based on the cyclization of Ketene dithioacetals (*101–103*), obtained from carbon disulfide, in basic media. The ability of thioglycolate to replace a methylsulfanyl group of ketene dimethylthioacetals **128** has been investigated by Sommen *et al.* (*104*). The authors reported the formation of thiophenes **129** from



Scheme 28.



Scheme 29.

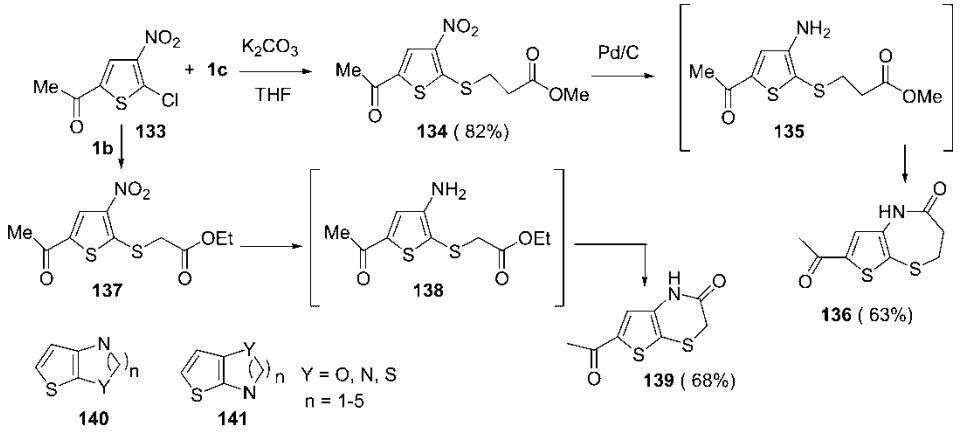
ketene methylthioacetals using ethyl thioglycolate **1b** in a basic medium [K_2CO_3/EtOH] by the replacement of one methyl sulfanyl group. The reaction of 5-methyl sulfanylthiophenes **129** with a second equivalent of ethyl thioglycolate under basic conditions resulted in thieno[2,3-*b*]thiophenes **130** in excellent yields (Scheme 28).

3.13. *Selenothiophenes*

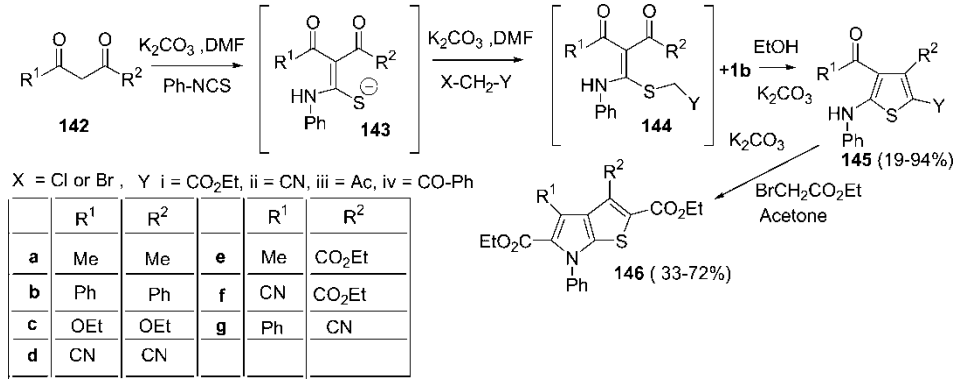
Selenium has gained great importance in the past few years not only for its role as an essential trace nutrient but also for bringing out some specific biological activities (*105, 106*). Sommen *et al.* (*107*) reported the synthesis of substituted selenolo [2,3-*b*]thio-phenes from ketene dithioacetals (*108*). Ketene dithioacetals **128a** on reaction with sodium selenide in the presence of activated halides give 5-methylsulfanyl-selenophenes **131**. The reaction of selenophenes **131** with ethyl thioglycolate **1b** in DMF and K_2CO_3 gave selenolo[2, 3-*b*]thiophenes **132** in good to excellent yields (Scheme 29).

3.14. *Thienoannelated O,N and S,N-heterocycles*

The chemistry of thienoannelated *O*, *N*- and *S*, *N*-heterocycles was studied by Puschmann and Erker (*109*) to obtained compounds with the following basic structure **140,141**. Halogenated nitrothiophenes were selected as the starting materials and followed by nucleophilic substitution with the corresponding reagents to provide the desired result. Ring closure occurs after the reduction of the nitro group if for instance an ester group is present in the structure. Reaction of 5-acetyl-2-chloro-3-nitrothiophene **133** with methyl 3-mercapto-propionate **1c** by using potassium carbonate in THF resulted in **134**. The catalytic hydrogenation of the nitro group with 10% Pd/C resulted not only the reduction of the nitro group but also in the cyclization of the amine **135** to the expected lactam **136**. Compound 6-acetyl-1*H*-thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one **139** was synthesized in a similar way. Component **133** reacted with ethyl mercaptoacetate **1b** to give **137**. Reduction and cyclization led to **139** in a 68% yield. This approach provides a methodology to synthesize thieno[2,3-*b*][1,4]thiazepines **136** and thieno[2,3-*b*][1,4]thiazines **139** (Scheme 30).



Scheme 30.



	R^1	R^2		R^1	R^2
a	Me	Me	**e**	Me	CO_2Et
b	Ph	Ph	**f**	CN	CO_2Et
c	OEt	OEt	**g**	Ph	CN
d	CN	CN			

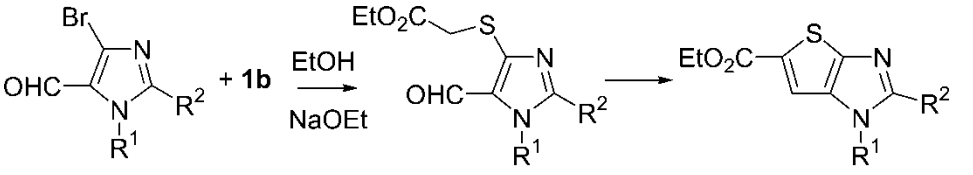
Scheme 31.

3.15. *Thienopyrroles*

Owing to the interesting biological properties of thienopyrroles (*110*), Sommen *et al.* (*111*) developed new preparation methods based on the use of active methylene compounds and isothiocyanates. The one-pot method (*49*) for the preparation of aminothiophenes **145**, precursors of thieno[2,3-*b*]pyrroles **146** is reported recently by the authors. The first is the condensation of activated methylene compounds **142** with alkyl or aryl isothiocyanates in a basic medium, which is well documented in the literature (*112, 113*). The condensation of the intermediate salt ketene-*N*,*S*-acetal **143** with alkyl bromoacetate leads to the corresponding aminothioacetal **144**, which smoothly undergoes a Dieckmann or Thorpe–Ziegler cyclization in basic medium at room temparature. The formation of the pyrrole-fused ring was achieved by prolonged reflux of **145** in acetone for 4–5 days in the presence of 1.5 equivalent of an alkyl bromoacetates (*114*). The methylsulfanyl group can act as a leaving group in the presence of thioglycolate and lead to the expected thienopyrroles **146** (Scheme 31).

3.16. *Thienoimidazoles*

Thieno[3,4-*d*]imidazoles have attracted interest particularly as intermediates for biotin (*115*). Iddon *et al.* (*116*) have reported the synthesis of thieno[2,3-*d*]imidazole from bromoaldehydes



147 **148** **149** (65-70%)

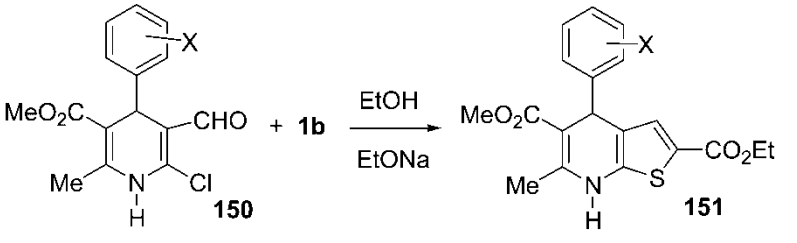
	R^1	R^2		R^1	R^2
a	CH_2Ph	H	**f**	CH_2OMe	SPh
b	$CH_2C_6H_4OMe$-4	H	**g**	CH_2OEt	SMe
c	$CH_2C_6H_3(OMe)_2$-3,4	H	**h**	CH_2Ph	SCH_2Ph
d	CH_2OMe	H	**i**	CH_2Ph	SPh
e	CH_2OMe	SCH_2Ph			

Scheme 32.

147 (*117*). The 1*H*-thieno[2,3-*d*]imidazoles **149** can be prepared in 65–70% yield by heating the corresponding bromoaldehyde **147** with ethyl thioglycolate **1b** in refluxing EtOH for 4 h in the presence of sodium ethoxide. Shorter reaction times allow the intermediate sulfide **148** involved in these reactions to be isolated (Scheme 32).

3.17. *Thienopyridines*

Thieno[2,3-*b*]pyridines are very attractive heterocyclic systems mainly due to their biological activity, useful for multiple pharmacological applications. Thus, dihydrothieno [2,3-*b*]pyridine has shown effects such as calcium antagonists (*118*) and have also been used in the treatment of epilepsy, Alzheimer's disease and Huntington's chorea (*119*). The synthesis of 4,7-dihydrothieno[2,3-*b*]pyridines **151** was accomplished by Martin *et al.* (*120*) by refluxing *o*-chloroformyl substituted 1,4-dihydropyridines **150** with an equimolar amount of ethyl mercaptoacetate **1b** in the presence of sodium ethoxide and dry ethanol under an inert atmosphere. The reaction takes place by the nucleophilic attack of the anion of the mercaptoacetate, generated in basic medium, at the carbon bearing the chlorine atom, followed by 5-*exo-trig* cyclization (*121*) and dehydration to afford **151** as stable crystalline solids in good yields (Scheme 33).

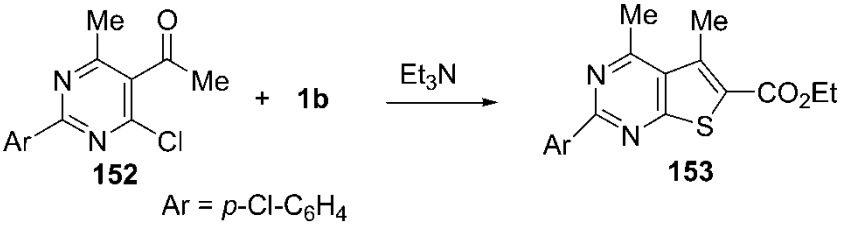


a x = H (66%) ; **b** x = *o*-Cl (70%) ; **c** x = *m*-NO_2 (80%) ; **d** x = *p*-CO_2Me (66%)

Scheme 33.

3.18. *Thienopyrimidines*

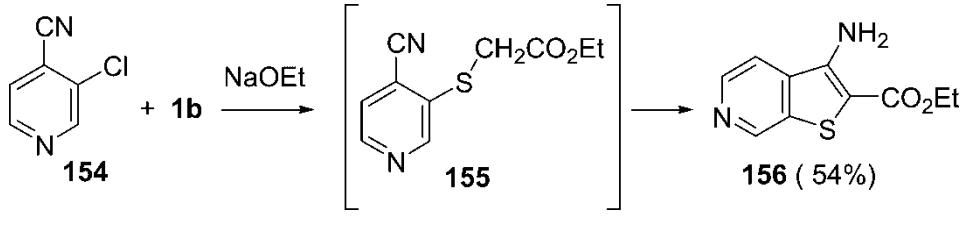
Fused pyrimidine derivatives exhibit interesting biological as well as medicinal applications (*122, 123*). Thiophene ring is constructed readily on pyrimidine by reacting β-halogenocarbonyl compounds **152** with ethyl 2-mercaptoacetate **1b** in the presence of a base (*124*). Bahaie *et al.* (*125*) reported thieno[2,3-*d*]pyrimidine **153** by the treatment of the 4-chloropyrimidine derivative **152** with ethyl 2-mercaptoacetate in the presence of triethylamine (Scheme 34).



Scheme 34.

3.19. *Thienopyridines*

The 3-chloroisonicotinonitrile **154** (*126*) is a valuable heterocyclic synthon due to the potential sites for nucleophilic addition. Despite the juxtaposition of the chloro and cyano groups, chemospecificity is possible, thus affording a variety of 3,4-disubstituted pyridines and other heterocylces not readily accessible by conventional literature procedures. The chemoselective reaction of **154** with ethyl thioglycolate **1b** in DMF in the presence of NaOEt was reported by LaMattina and Taylor (*127*) to afford the thieno[2,3-*c*] pyridine **156** in 54% yield. Presumably, the first step in this reaction is the aromatic nucleophilic displacement of chloride to afford the corresponding displacement product **155** (Scheme 35).

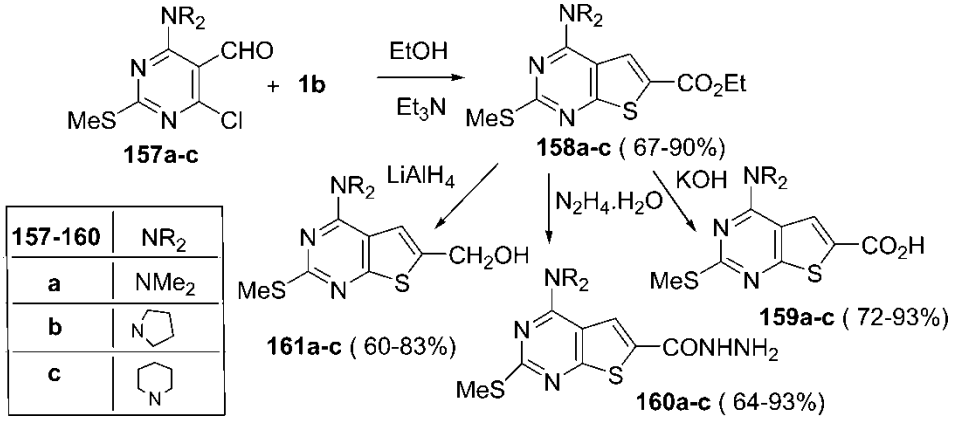


Scheme 35.

3.20. *4-Dialkylamino-2-methylthiothienopyrimidines*

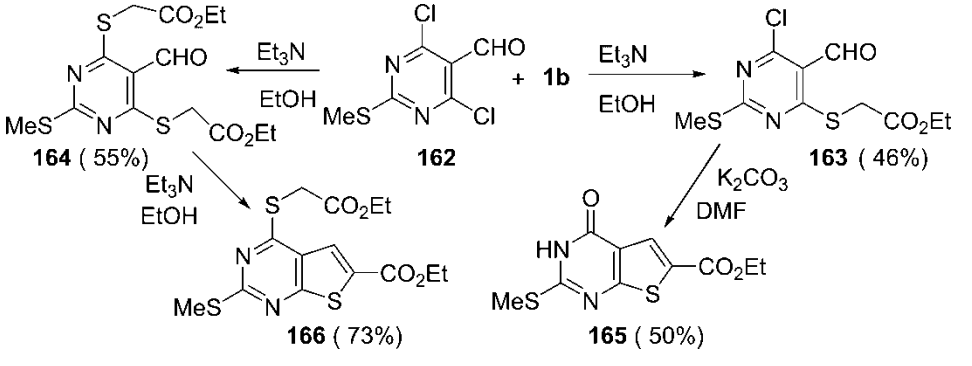
Thieno[2,3-*d*]pyrimidines and compounds containing the thienopyrimidine fragment as well as their pyridine analogs display useful pharmacological properties (*128, 129*). Tumkevicius and Kaminskas (*130*) reported the synthesis of 6-substituted thieno[2,3-*d*]pyrimidines, which may be used as intermediates for the synthesis of classic and lipophilic antifolates (*131*). The 6-chloro-4-dialkylamino-2-methylthiopyrimidine-5-carbaldehydes **157** on heating with ethyl mercaptoacetate **1b** at reflux in the presence of triethylamine gave ethyl esters of 4-dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids **158**. The hydrolysis of esters **158** to give

the corresponding acids **159** was carried out at room temprature using a solution of KOH in aqueous EtOH. Hydrazides **160** were obtained in 64–93% yield only upon prolonged heating of esters **158** under reflux conditions with excess of hydrazine hydrate. The reduction of esters **158** with LAH proceeds at room temprature and leads to the corresponding (thieno[2,3-*d*] pyrimidin-6-yl) methanols **161** (Scheme 36).



Scheme 36.

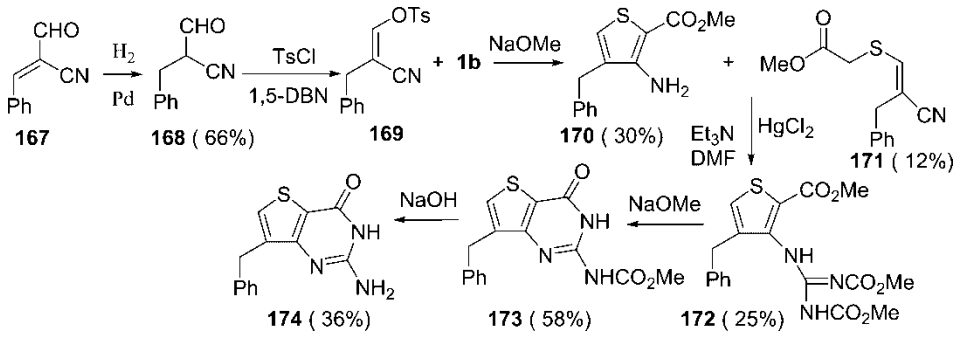
The 4,6-disubstituted-2-methylthiothieno[2,3-*d*] pyrimidine derivatives with potential biological activity were reported by Tumkevicius *et al.* (*132*). Treatment of carbaldehyde **162** (*133*) with ethyl mercaptoacetate **1b** at room temprature in the presence of triethylamine (the replacement of one or two chloro atoms depend on the amount of ethyl mercaptoacetate) took place and the respective compounds **163, 164** were formed. Carbaldehydes **163, 164** under basic conditions underwent a cyclodehydration reaction at 50 °C to give thienopyrimidines **165, 166** (Scheme 37).



Scheme 37.

3.21. *7-Substituted-2-aminothienopyrimidines*

Derivatives of the thieno[3,2-*d*]pyrimidine ring systems have been reported as inhibitors of the enzyme purine nucleoside phosphorylase (*134*). Morris *et al.* (*135*) have reported the synthesis of thienopyrimidines by the annelation of the methyl 3-amino-4(3-phenylmethyl)thiophene-2-carboxylate, **170**. The catalytic reduction of 2-cyano-3-phenyl-propenal **167** (*136*) gave **168**,



Scheme 38.

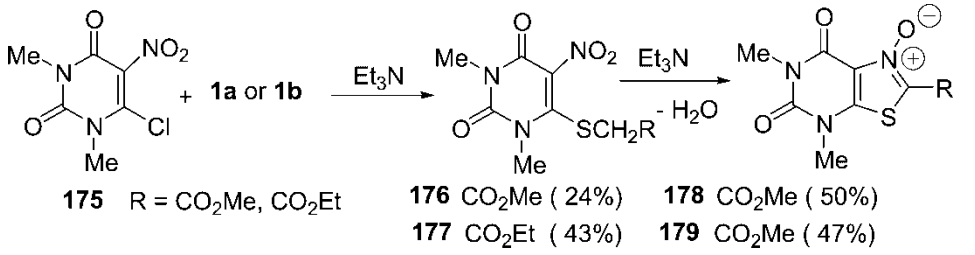
which was treated directly with 1,5-diazabicyclo-[4.3.0]non-5-ene and tosyl chloride to obtain the tosylate **169**. Displacement of the tosyl group with the anion of methyl thioglycolate **1a** (generated *in situ* from one equivalent of methyl mercaptoacetate and two equivalents of sodium methoxide) in refluxing methanol gave **170**. Condensation of **170** with 1,3-dicarbomethoxy-2-methyl-2-thiopseudourea **171** in presence of mercury (II) chloride gave the guanidine adducts **172**. Cyclization of **172** occurred with the concomitant loss of carbamate group to afford **173**. The remaining carbamate group was hydrolyzed with warm aqueous sodium hydroxide to obtain thieno[3,2-*d*]pyridine **174** in 36% yield (Scheme 38).

3.22. *Thiazolopyrimidine-1-oxide*

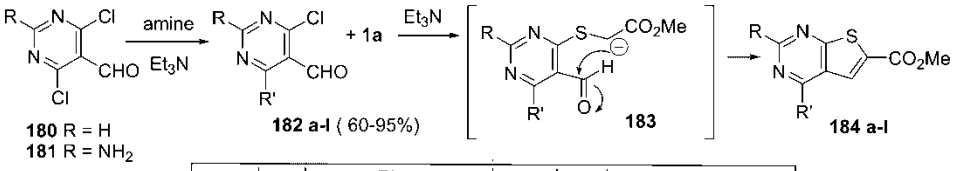
Thiazolo[5,4-*d*] pyrimidine ring system would be of medicinal interest (*137*) since it can be considered at first glance as a thia analog of purine by virtue of the five-membered ring to the pyrimidine nucleus. Senga *et al.* (*138*) have reported the syntheses of thiazolo[5,4-*d*] pyrimidine *N*-oxides by the cyclization of *o*-nitrochlorouracil with thioglycolic esters. The reaction of 6-chloro-1,3-dimethyl-5-nitrouracil **175** (*139*) and methyl or ethyl thioglycolate **1a** or **1b** in ethanol in the presence of triethylamine gave the corresponding 2-alkoxycarbonyl-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*, 6*H*)dione 1-oxides **178** and **179** in 50 and 47% yield, respectively. The reaction of **175** with mercaptans leading to **178, 179** apparently consists of the initial formation of the intermediates **176, 177** followed by the base catalyzed dehydrative cyclization (Scheme 39).

3.23. *Thienopyrimidines*

Thienopyrimidines are reported to have diverse biological activities (*140*). Clark *et al.* (*141*) have reported the syntheses of several thieno[2,3-*d*]pyrimidines which later converted into thieno[2,3-*d*:4,5-*d*′] dipyrimidines. The 4,6-Dichloropyrimidine-5-carbaldehyde **180** (*142*) and



Scheme 39.



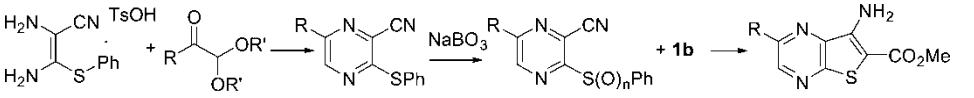
	R	R'		R	R'
184a	H	NH_2 (30%)	**184g**	NH_2	NH_2 (68%)
184b	H	NHMe (80%)	**184h**	NH_2	NHEt (71%)
184c	H	NMe_2 (78%)	**184i**	NH_2	NEt_2 (70%)
184d	H	NEtPh (89%)	**184j**	NH_2	NHPh (65%)
184e	H	$N(CH_2)_4$ (90%)	**184k**	NH_2	NEtPh (60%)
184f	H	morpholine (70%)	**184l**	NH_2	morpholine (83%)

Scheme 40.

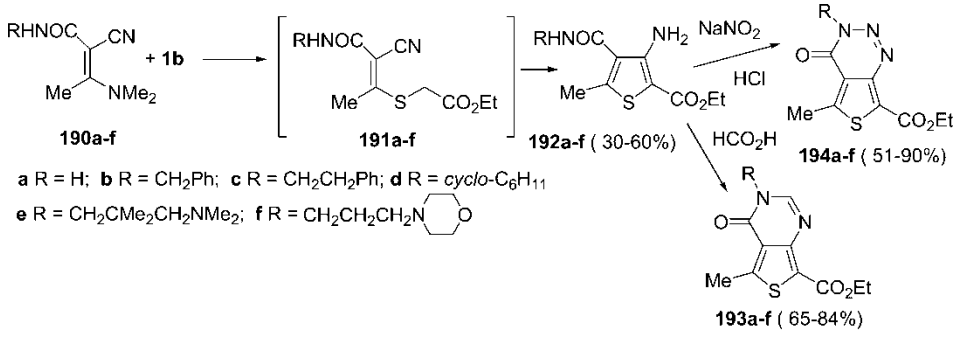
2-amino-4,6-dichloropyrimidine-5-carbaldehyde **181** (*143*) were used as starting materials for all the thienopyrimidines by building a thiophene ring around the positions 5 and 6 via a Dieckmann-type intramolecular process. Treatment of pyrimidines **180** and **181** with 1 mol equivalent of the respective amine and TEA resulted in the replacement of one of the two equivalents chlorine atoms to furnish the 4-substituted derivatives in high yield. Reaction with the one molecular equivalent of methyl thioglycolate **1a** and two moles of Et_3N in refluxing methanol replaced the remaining chlorine atom in each of the pyrimidines **182**. The reaction proceeded *via* a postulated intermediate **183** to furnish, after the loss of water, the corresponding methyl thieno[2,3-*d*]pyrimidine-6-carboxylates **184** (Scheme 40).

3.24. *7-Amino-3-phenylthienopyrazines*

Thieno[2,3-*b*]pyrazines and pyrazines have found wide uses in pharmaceuticals and also in agrochemistry (*144–146*). The general method of synthesizing thieno[2,3-*b*]pyrazines has been to treat 3-cyano-2-halopyrazines with thioglycolates and the base cyclization of the resulting 3-cyano-2-*S*-acyl-mercaptopyrazines to yield the desired thieno[2,3-*b*] pyrazines (*146, 147*). Zhang *et al.* (*148*) reported an alternative synthesis of **187** by the use of 2,3-diamino-3-phenylthioacrylonitrile **185** (*149*) for the synsthesis of pyrazine **187**, also followed the practical large-scale conversion of sulfide to sulfone (leaving group). The protected α-ketoaldehyde derivative, 2,2-diethoxyacetophenone **186** was condensed with 3-phenylthiopyrazine carbonitrile (**185**) in the presence of excess TFA in 2-propanal to give methylthiopyrazine **187** in 81% yield. Presumably, an imine is first formed between 2-amino group of compound **185** and the ketone carbonyl group of **186**, and then subsequent cyclization gives pyrazine **187**. Oxidation of the phenylthio group in **187** as the mixture of sulfoxide and sulfone (1:7.3) was accomplished with sodium perborate (*150*) in a mixture of acetic acid and chloroacetic acid. Treatment of the 1:7.3 mixture of (**187, 188**) with methyl thioglycolate **1a** in ethanol with Hunig's base yielded the compound **189** in 93% yield (Scheme 41).



Scheme 41.



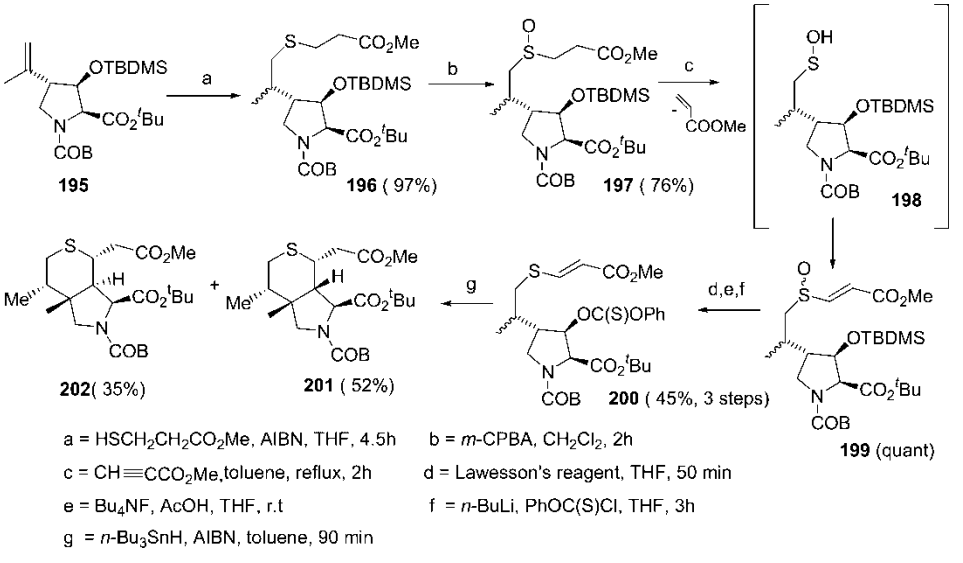
Scheme 42.

3.25. *Functionalized thienopyrimidines, thienotriazines*

The Thorpe–Ziegler reaction is one of the most promising routes in the chemistry of five-membered heterocycles. This reaction makes it possible to obtain the variously substituted thiophenes (*151*). A general approach to the synthesis of functionalized 3-aminothiophenes and studies of their transformation into fused heterocyclic systems containing a thiophene fragment was investigated by Ryndina *et al.* (*152*). The 2-cyano-3-dimethylaminobut-2-enamide derivatives **190a–f** on reaction with ethyl thioglycolate **1b** in the presence of K_2CO_3 gave the 2-alkylthiocarboxylate olefins **191a–f**. This was followed by Thorpe–Ziegler cyclization to furnish ethyl 3-amino-4-*N*-R-carbamoyl-5-methylthiophene-2-carboxylates **192a–f**. From thiophenes **192a, b, d, f**, one can obtain the substituted ethyl 3,4-dihydrothieno[3,4-*d*]pyrimidine-7-carboxylates **193a–d** by reaction with formic acid. Diazotization of thiophenes **192a–e** with sodium nitrite containing acetic acid, HCl at 20 °C yielded thieno[3,4-*d*]-1,2,3-triazines **194a–e** (Scheme 42).

3.26. *8-Aza-3-thiabicyclononanes*

Radical-mediated cyclizations are extensively used for the construction of heterocyclic systems (*153*). The synthesis of confirmationally restricted kainods **201** and **202** were reported (*154, 155*) through free radical cyclization of β-thioacrylates. Bilokin *et al.* (*156*) reported the synthesis of 8-aza-3-thiabicyclononanes mainly by the anti-Markovnikov addition of methyl 2-mercaptopropionate **1c** to the isopropenyl group of **195** (*157*). The resulting sulfides **196** (mixture of C-1′epimers) were selectively oxidized to sulfoxides **197**. Sulfoxides, which carry an acidic methylene group in the β-position, underwent facile thermolysis to give the corresponding sulfenic acid. The emerging sulfenic acid **198** can be trapped *in situ* by alkynes (*158*). Extension of this reaction allowed the metathetic transformation of sulfoxides **197** into α, β-unsaturated sulfoxide **199** by heating the former with excess of methyl propiolate. Selective reduction with Lawesson's reagent of the unsaturated sulfoxide **199** to the corresponding thioenolate (*159*) was followed by desilylation and thionocarbonation to give the desired β-thioacrylate-thionocarbonate derivatives **200** carrying the β-thioacrylate function as radical acceptor and the thionocarbonate function as radical precursor. The *n*-Bu_3SnH/AIBN induced free radical cyclization of thionocarbonates **200** (1:1 mixture of two epimers at C-1′) gave 8-aza 3-thia-bicyclo[4,3.0]nonanes **201** and **202**. Formation of two, rather than four isomers, is attributed to a different directive effect of the C-1′ methyl group in the two C-1′ epimers **200** (Scheme 43).

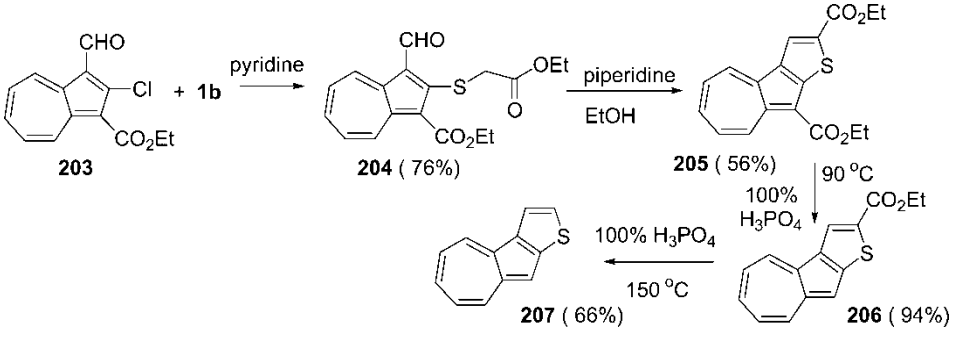


Scheme 43.

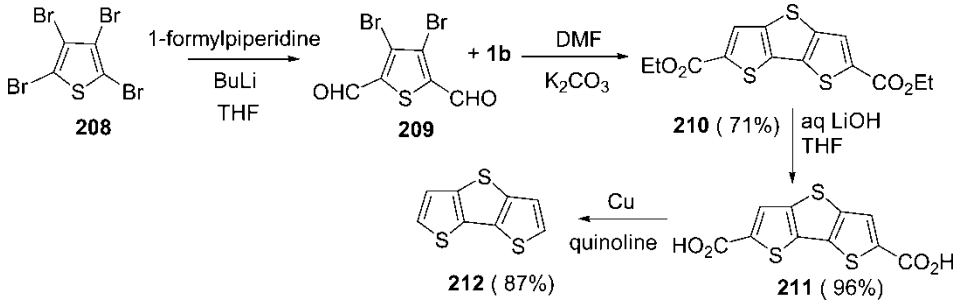
4. Tricyclic derivatives

4.1. *Azuleno[2,1-b]thiophene*

Azuleno[2,1-*b*]thiophene, which is a polycyclic aromatic compound containing a heterocycle, is of interest in its physical properties and chemical behaviour (*160*). Yamane *et al.* (*161*) reported the synthesis of **207** from 2-chloro-3-formylazulene-1-carboxylate **203** (*162*) in about four steps. When ethyl 2-ethoxycarbonylmethylthio-3-formylazulene-1-carboxylate **204**, prepared by the reaction of ethyl 2-chloro-3-formylazulene-1-carboxylate **203** with ethyl mercaptoacetate **1b**, was heated with piperidine in EtOH, cyclization occurred to afford the diethylazuleno[2,1-*b*]thiophene-2,9-dicarboxylate **205** in moderate yield. The compound **205**, on treatment with conc. phosphoric acid at 90 °C, furnished ethyl azuleno[2,1-*b*]thiophene-2-carboxylate **206**. When the ester **206** was heated at 150 °C in conc. phosphoric acid, decarbonylation occurred to give azuleno[2,1-*b*]thiophene **207** (Scheme 44).



Scheme 44.



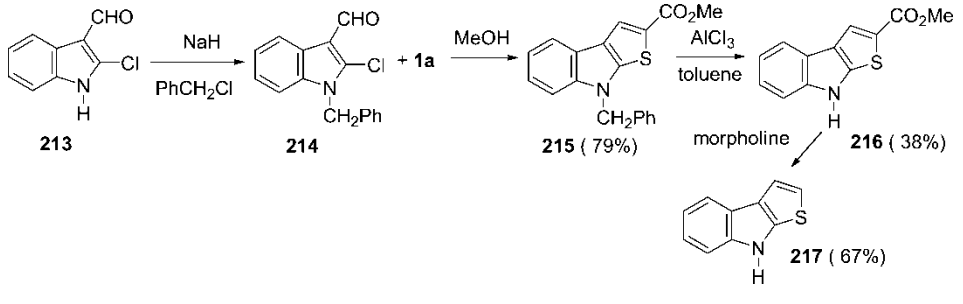
Scheme 45.

4.2. *Dithieno[3,2-b: 2′,3′-d] thiophene*

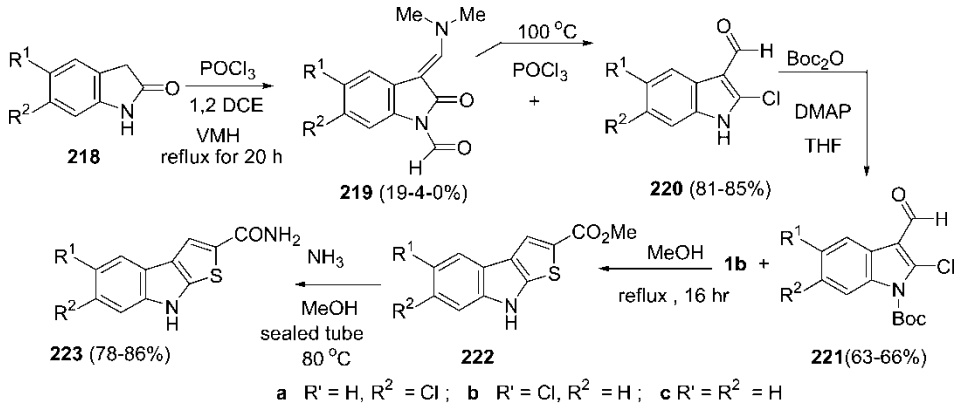
Dithieno[3,2-*b*:2′,3′ − *d*]thiophene (DTT) **212** has emerged as an important building block in the synthesis of a wide variety of optoelectronic materials. Polymers with DTT as the repeating unit have been prepared by electrochemical and photochemical oxidation (*163, 164*), and recently DTT dioxide has been incorporated in thiophene oligomers (*165*). Frey *et al.* (*166*) reported dilithiation of tetrabromothiophene **208** with butyl lithium which resulted into 3,4-dibromothiophene-2,6-dicarbaldehyde **209** after quenching with 1-formyl-piperidine. Reaction of dialdehyde **209** with ethyl mercaptoacetate **1b** in the presence of excess base in DMF gave diethyl 2,6-DTT-dicarboxylate **210** as a result of a double annelation process (*167*) which was easily saponified with LiOH to form, after acidification, the corresponding dicarboxylic acid **211**. Decarboxylation of **211** with copper and quinoline afforded DTT **212** in overall yield of 47% (Scheme 45).

4.3. *Thieno[2, 3-b]indole*

The 6-Chlorothieno[2,3-*b*]indole-2-carboxamide and thienodoline has been described as a new plant growth-regulating substance produced by a *Streptomycete* strain (*168*). Olesen *et al.* (*169*) reported the synthesis for methyl thieno[2,3-*b*]indole-2-carboxylate **216** as well as the parent ring system thieno[2,3-*b*]indole **217**. 2-chloroindole-3-carbaldehyde **213** was protected with benzyl chloride to give 1-benzyl-2-chloroindole-3-carbaldehyde **214**. The annulation reaction of **214** with methyl thioglycolate **1a** gave methyl thieno[2,3-*b*]indole carboxylate **216** in methonol with dry K_2CO_3 as base. Deprotection of **215** with $AlCl_3$ in toluene at reflux gave methyl thieno[2,3-*b*]indole-3-carboxylate **216**. Thieno[2,3-*b*]indole **217** was isolated by heating **216** in morpholine *via* the morpholino amide (Scheme 46).



Scheme 46.



Scheme 47.

4.4. *Thienodoline*

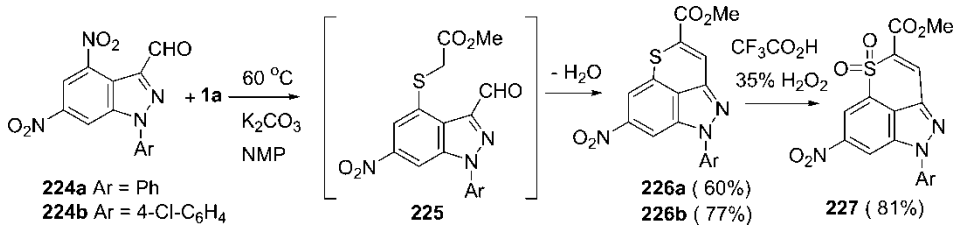
Thienodoline **223** was isolated from the culture broth of *Streptomyces albogriseolus* MJ286-76F7 and shown to have both growth-promoting and inhibiting activities in rice seedlings (*170*). Engqvist *et al.* (*171*) have reported the synthesis from 2,6-dichloroindole-3-carboxaldehyde **220** in three steps from oxindoles **218** (*172*). The first oxindoles **218** were pretreated with $POCl_3$, then treated with a fresh solution of Vilsmeier reagent at 0 °C, and finally heated at reflux for 20 h to afford a mixture of dichloroindole-3-carbaldehydes **220a, b** and chloro-3-(dimethylaminomethylene)-1-formyloxindoles compunds **219a, b**. The **219a, b** were readily converted into **220a, b** in good yields by refluxing in neat $POCl_3$. Aldehydes **220a, b** were subsequently protected using di-*tert*-butyldicarbonate (Boc_2O) and 4-(dimethylamino) pyridine (DMAP) in THF. The protected indole deriative **221** was heated with methyl thioglycolate **1a** and K_2CO_3 in MeOH yielding the ester **222** in 70% yield. When **222** was treated with ammonia in MeOH in a sealed tube at 80 °C for 6 days, **223** was obtained in an overall yield of 27% (Scheme 47).

4.5. *1H-thiopyrano[4,3,2–cd] indazoles*

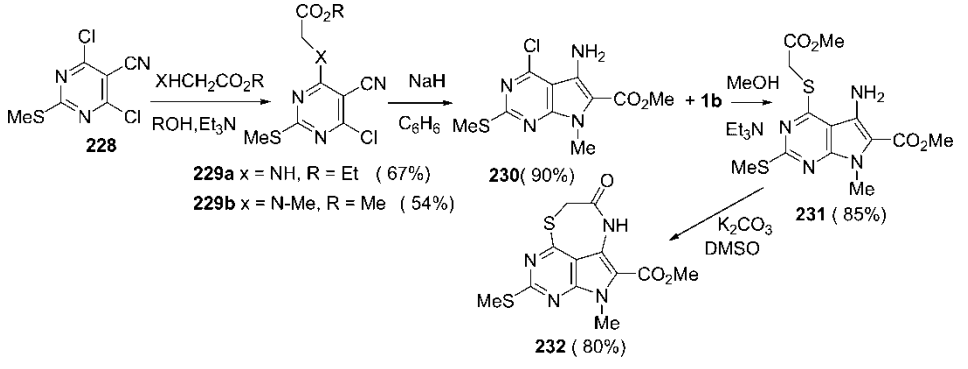
Tricyclic heteroaromatic systems, such as 1*H*-thiopyrano[4,3,2-*cd*]indazoles, were reported to show pharmacological properties (*173*). 1-Aryl-3-formyl-4,6-dinitro-1*H*-indazoles **224** can be used to prepare 14π-electron *peri*-annelated tricyclic heteroaromatic systems (*174*). Starosotnikov *et al.* (*175*) reported the reaction of 3-formyl-4,6-dinitroindazoles **224** with methyl thioglycolate **1b** in NMP or DMF in the presence of solid K_2CO_3 afforded the corresponding *peri*-annelated tricyclic heteroaromatic compounds, namely methyl 1-aryl-7-nitro-1*H*-thiopyrano[4,3,2-*cd*]indazole-4-carboxylates **226a, b**. Presumably, the 4-NO_2 group is first replaced by the treatment with thioglycolate-K_2CO_3 system to furnish the intermediate **225**. The formyl group in **225** undergoes the base-catalyzed intramolecular condensation with the active methylene group of the SCH_2CO_2Me side chain affording **226**. Tricyclic derivative **226** is easily and selectively oxidized on treatment with aqueous H_2O_2 in CF_3COOH to afford the corresponding sulfone **227** (Scheme 48).

4.6. *Thieno-and pyrrolopyrimidines peri-fused with 1,4-thiazepine*

Thieno[2,3-*d*] and pyrrolo[2,3-*d*]pyrimidine are reported to possess antiviral activities (*176*). *Peri*-fused heterocycles, containing thieno[2,3-*d*]pyrimidine skeleton, were reported by the



Scheme 48.

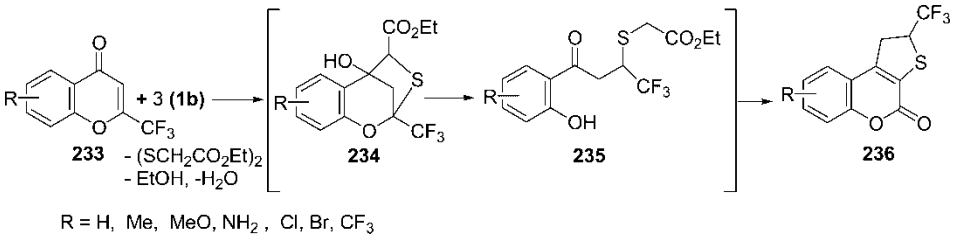


Scheme 49.

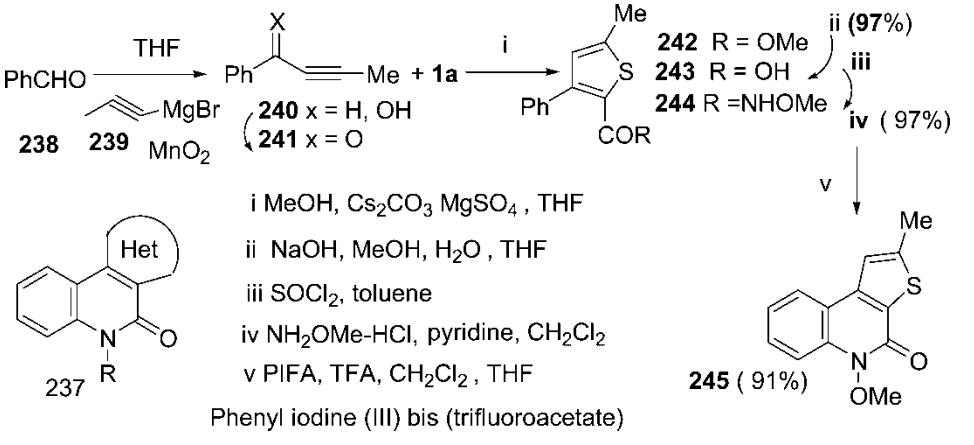
cyclocondensation of 4,5-diaminothieno[2,3-*d*] with either nitrous acid or with a one- or two-carbon C-electrophiles (*177*). Tumkevicius *et al.* (*178*) reported the reaction of 4,6-dichloro-2-methylthiopyrimidine-5-carbonitrile **228** (*134*) with methyl or ethyl esters of glycine and sarcosine in the presence of triethylamine to give the substitution products of one chlorine atom the corresponding 4-(alkoxycarbonylmethyl-amino)-6-chloro-2-methylthio-pyrimidine-5-carbonitriles **229a, b**. Upon the reaction of **229a, b** with sodium hydride in benzene, cyclization occurred resulting in pyrrolopyrimidine derivatives **230**. Heating **230** with methyl mercaptoacetate **1a** with triethylamine at reflux gave the acyclic intermediate **231**. When **231** was heated in DMSO in the presence of K_2CO_3 intramolocular cyclization occurred to yield 6-thia-2,3,5,9-tetraazabenz[*cd*] azulene **232** (Scheme 49).

4.7. *Dihydrothienocoumarins*

Trifluoromethylated heterocylces continue to be of great industrial interest in view of medicinal and biomedical applications (*66*) and therefore the development of new methods to incorporate the CF_3 group into organic compounds remains an important area of research (*179*). Sosnovskikh *et al.* (*180, 181*) have shown that the reaction of 2-trifluromethyl chromones **233** with three equivalents of ethyl mercaptoacetate in the presence of triethylamine afforded dihydrothienocoumarins **236** in high yield. These compounds are the key intermediates in the synthesis of triazolo- and tetrazolo-pyridazines (*182*), which exhibit different types of biological activity (*183*). The mechanism for the redox (*184*) formation of coumarins **236** is not obvious but it is most likely that it begins with the addition of the mercapto group to the C(2) atom and the resulting Michael adduct undergoes reversible cyclization to form bridged structure **234**. The reductive opening of bicyclic **234** or ring opening of the Michael adduct followed by reduction under the action of an excess of ethyl mercaptoacetate **1b** led to sulfanyl acetate **235**, which undergoes two intramolecular cyclizations involving the ketone and ester carbonyl groups to produce coumarin **236** (Scheme 50).



Scheme 50.



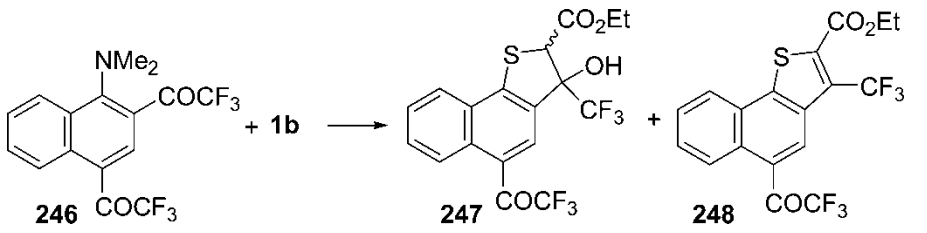
Scheme 51.

4.8. *Thienoquinolin-4-one*

Naturally occurring and synthetically produced heterocycle-fused quinolines and quinolinones of type **237** have attracted the interest of the research community on account of their significant antiinflammatory, antitumor and antibacterial properties (*185*). Phenyliodine (III) *bis* (trifluoroacetate) (PIFA) promoted aryl–heteroaryl coupling reaction has been employed to synthesise a series of phenanthridines, phenanthridinones starting from *N*-arylbenzamides (*186*). Herrero *et al.* (*187*) reported the reaction of benzaldehyde **238** with 1-propynylmagnesium bromide **239** to afford the propargylic alchol **240**. Oxidation with manganese oxide provided the corresponding ketone **241** (*188*), which underwent conjugate addition with methyl thioglycolate **1a** and subsequent cyclization under basic conditions yielding the methyl ester **242** in an excellent yield of 87% overall (four steps). The ester group hydrolyzed under basic conditions and the resulting free carboxylic acid **243** was transformed into the amide **244** by the treatment of corresponding acyl chloride derivative with methoxylamine. The PIFA-mediated oxidative cyclization of amide **244** gave quinolinone **245** in 37% yield (Scheme 51).

4.9. *2,3-Dihydronaphthothiophenes*

N, *N*-Dimethyl-2,4-bis(trifluoroacetyl)-1-napthylamine **246** is a useful building block for the construction of naphthalene-fused heterocyclic compounds bearing trifluoromethyl groups, which are expected to show interesting biological activities (*189*). Okada *et al.* (*190*) reported the reaction of **246**, which is easily prepared by bistrifluoro acetylation of *N*, *N*-dimethyl-1-naphthylamine, with ethyl thioglycolate in refluxing acetonitrile for 1 h gave 2,3-dihydronaphtho[1,2-*b*]thiophene

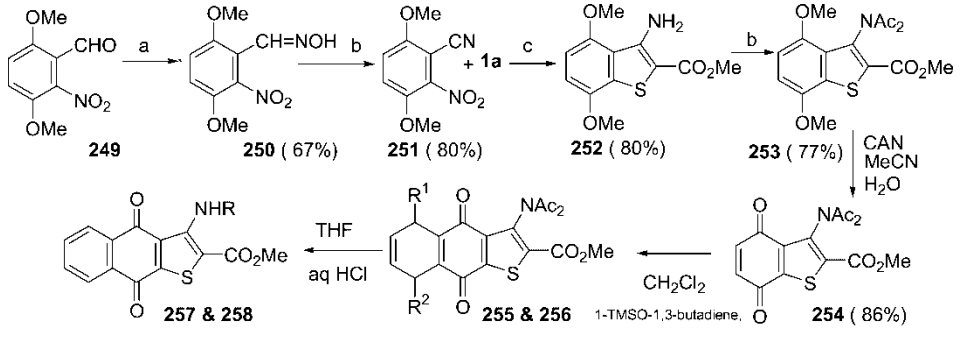


Scheme 52.

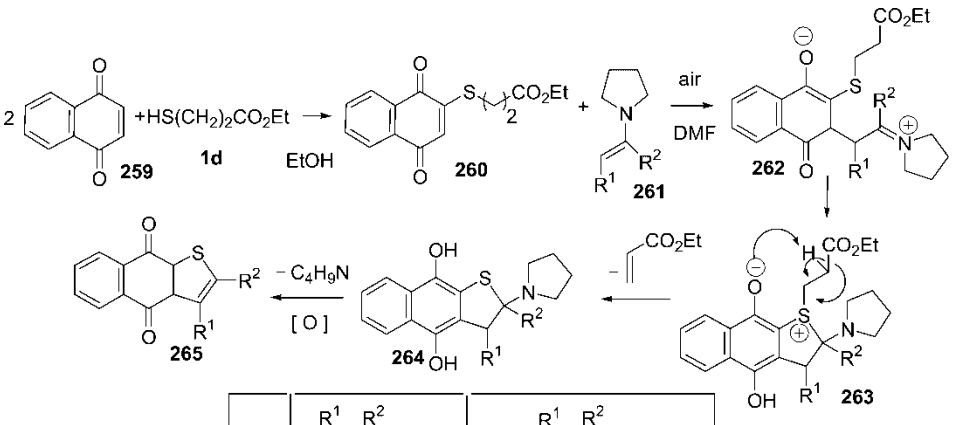
247 and naphtho[1,2-*b*] thiophene **248** in 40 and 53% yields, respectively. The aromatic nucleophilic Me_2N-SCH_2CO_2Et exchange reaction of **246** with ethyl thioglycolate **1b** takes place to give an intermediate 2,4-bis(trifluoroacetyl)-1-naphthylethoxycarbonylmethylsulfide, which undergoes intramolecular nucleophilic attack of its active *S*-methylene carbon onto the carbonyl carbon of the trifluoroacetyl group to afford dihydronaphthothiophene **247**. Dehydration of **247** by heating provides naphtho-thiophene **248** (Scheme 52).

4.10. *Benzo-and naphthothiophenequinones*

Natural and synthetic quinonoid compounds are well-known substances, which possess a variety of biological properties such as antibacterial, antifungal, antiprotozoal, antitumor activity (*191*). The thiophene ring-containing quinones showed promising antiprotozoal activity against *trypanosome cruzi* and strains of *Leishmania spp* (*192*). The synthesis of *ortho*-aminoesters **252** *via* the cyclization of 3,6-dimethoxy-2-nitrobenzonitrile **251** with methyl thioglycolate **1a** was described by Valderrama *et al.* (*193*). 3,6-dimethoxy-2-nitrobenzaldehyde **249** (*74*) was converted into 2,5-dimethoxy-6-nitrobenzonitrile **251** by reaction with hydroxylamine followed by the dehydration of 3,6-dimethoxy-2-nitrobenzadehyde oxime **250** with acetic anhydride. Protection of the amino group in **252** as the corresponding amide **253** was done by the acetylation of **252** with Ac_2O at room temprature. Oxidative deprotection using CAN gave the corresponding stable quinone, methyl 3-diacetylamino-4,7-dioxo-4,7-dihydrobenzo[*b*] thiophene-2-carboxylate **254** in 86% yield. The reaction of **254** and the diene at room temparature gave a mixture of regioisomers **255** and **256** which, by reaction with 5% HCl in THF, gave a mixture of methyl 3-amino-4,9-dioxo-4,4a,5,8,8a,9-hexahydronaphtho[2,3-*b*]thiophene-2-carboxylate **257** and methyl 3-acetylamino-4,9-dioxo-4,4a,5,8,8a,9-hexahydronaphtho[2,3-*b*]thiophene-2-carboxylate **258** in 74 and 26% yields, respectively (Scheme 53).



Scheme 53.



	R^1 R^2		R^1 R^2
265a	-$(CH_2)_3$- (72%)	**265d**	-$(CH_2)_6$- (71%)
265b	-$(CH_2)_4$- (69%)	**265e**	Me Et (56%)
265c	-$(CH_2)_5$- (71%)	**265f**	Et *n*-Pr (59%)

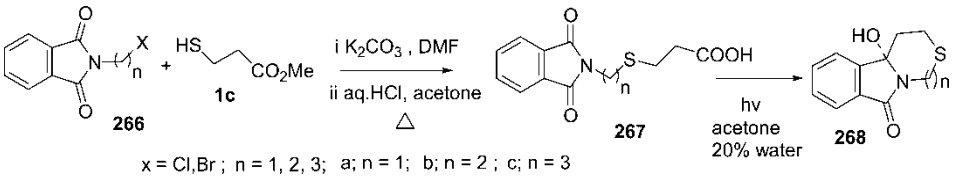
Scheme 54.

4.11. *2, 3-Disubstituted naphthothiophene-4, 9-diones*

Heterocycles based on thiophenequinone skeleton have received considerable attention because of their synthetic, biological and industrial importances (*194–197*). Kobayashi *et al.* (*198*) reported the synthesis of 2,3-disubstituted naphtho[2,3-*b*] thiophene-4,9-diones **265**. The treatment of 1,4-naphthaquinone **259** with ethyl 3-mercaptopropanoate **1d** in EtOH at room temparature afforded the sulfenyl quinone **260**. The reaction of **260** with enamine **261** in toluene afforded the corresponding naphthothiophene quinones **265**. The first step is the formation of intermediate adducts **262** by the addition of an enamine to the sulfenyl quinone **260** at the 3-position in a 1,4-addition manner. Cyclization of the sulfur to the iminium carbon gave the sulfonium ion intermediate **263**. The elimination of ethyl propeonate affords the hydroquinone intermediate **264**. Oxidation followed by the elimination of pyrrolidine gives rise to **265** (Scheme 54).

4.12. *Sulfur containing tricyclic ring systems*

The photoinduced electron transfer (PET) reactivity of phthalimides has been intensively studied during the last decade (*199*). In the photochemical cyclization of ω-imidocarboxylates **267**, the carboxylate anion acts as the electron-donor and the electronically excited imido group as electron acceptor. Alkyl (*ω*-imidoalkyl) sulfides have shown excellent donor activity for electron transfer reactions yielding sulfur-containing macrocycles (*200*). *N*-(hydroxyalkyl)phthalimides were prepared by Gricsbeck *et al.* (*201*), from phthalic anhydride and the corresponding amino alcohols (*202*). Transformation of the hydroxy group into the halogenated phthalimide was achieved using PBr_3. The phthalimidoalkylsulfanylcarboxylic acids (thioethers) **267** were readily available from the halogenated phthalimides **266** and the methyl mercaptocarboxylates **1c** followed by hydrolysis (*203*). Under irradiation at 300 nm in acetone/water mixture, the potassium salts of substrates **267** cyclized with concomitant extrusion of CO_2 to give tricyclic product **268**. In all cases, the activation of the electron donor terminus involved decarboxylation and thus the generation of a primary radical at the terminal carbon atom. This phenomenon demonstrates that these reactions are initiated by means of one electron oxidation of the sulfur atom (*204*). An intramolecular



Scheme 55.

PET mechanism involving the thioether as the electron-donating species and the triplet excited phthalimide as the electron accepting species (*205*) has been established for direct excitation of the chromophore (Scheme 55).

4.13. *9-Methyl-thiazinquinoline-2,5,10-trione*

Pyridoacridine alkaloids of basic skeleton **276** are secondary metabolites of marine invertebrates, which have shown a wide range of biological activity (*206*). They vary in structure in having different side chain appendages fused to the ring C. *Shermilamine **A*** and ***B*** **277, 278** have a 2*H*-1,4-thiazine-3(4*H*)-one ring fused to ring C. 2-Acetamido-5-bromo-1,4-benzoquinone **270** was easily prepared from the corresponding 4-bromo-*N*-(2,5-dimethoxyphenyl)acetamide **269** (*207*) by oxidative demethylation using CAN (*208*). Townsend and Jackson (*209*) further carried the reaction of **270** with azadiene **271** (*210*) in acetonitrile, followed by methyl thioglycolate, to obtain **272, 273** in 28 and 10% yield, respectively. Both compounds **272** and **273** when heated in 6 M HCl produced the amino acid **274**, which cyclizes on treatment with DCC-DMAP to afford thiazinone **275** (Scheme 56).

4.14. *Thienopyridines*

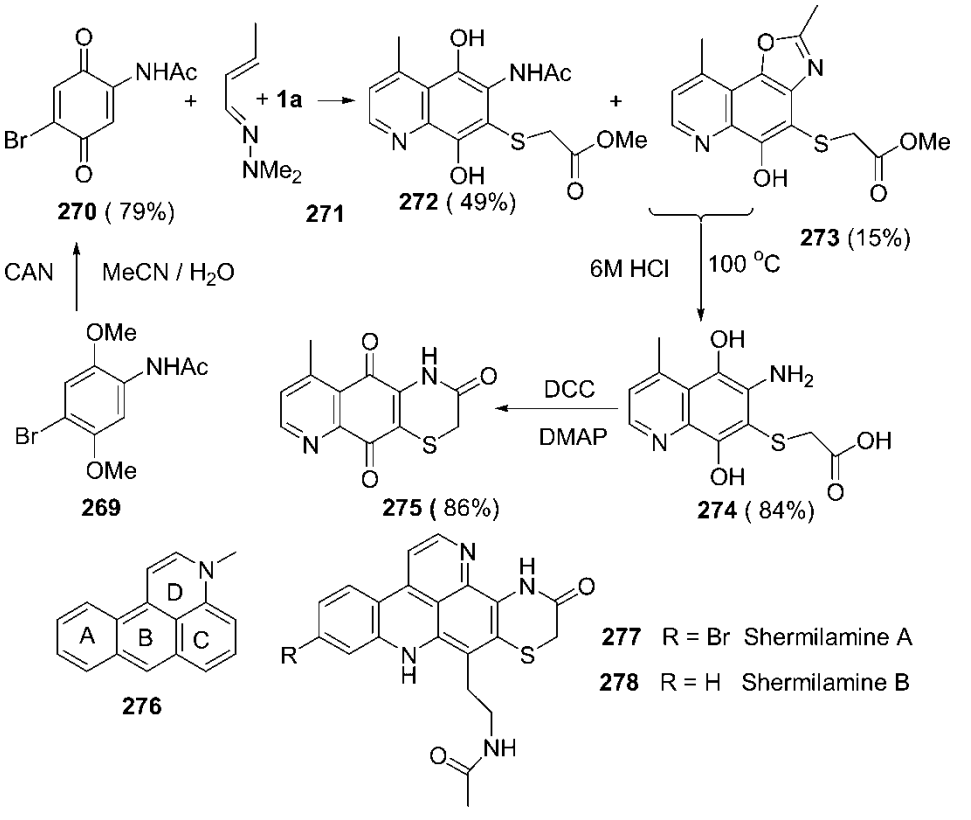
Koyama *et al.* (*211*) and Meth-Cohn and Narine (*212*) have reported the formylation of acetanilides using the Vilsmeier–Haack reaction, which results in the formation of 2-chloro-3-formyl-fused pyridines. 2-chloro-3-formyl-6-bromothienopyridine **280** was obtained by the Vilsmeier–Haack reaction of 5-bromo-2-acetamidothiophene **279** (*213*) in good yields. The reaction of chloraldehyde **280** with methyl mercaptoacetate **1a** in the presence of DMF and K_2CO_3 gave the bis thieno[2,3-*b*]pyridine **281** (Scheme 57).

4.15. *Dithienoazepines*

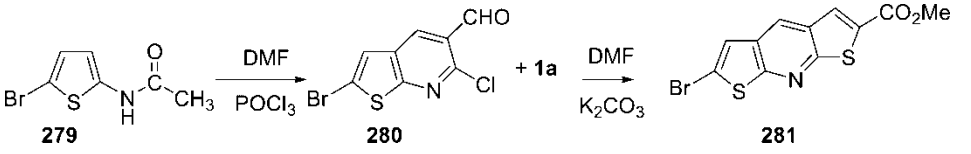
Di-β-chlorovinyl aldehydes **282** appear to be useful starting materials for the synthesis of a wide range of tricyclic systems. Aubert *et al.* (*214*) have reported the synthesis of bis thiophene isosteres of dibenzo[*b*,*f*]azepines **283** (*215*). These analogs appear to be of special interest because the replacement of one or both of the flanking benzene rings of the related dibenzo[*b*,*e*]azepines by a thiophene ring has been achieved and leading to compounds with useful biological activities (*216*). Di-β-chlorovinyl aldehydes **282** were converted in one step into the dithieno[*b*, *f*]azepines **283** in good yields by condensation with ethyl 2-mercaptoacetate **1b** and triethylamine in pyridine (Scheme 58).

4.16. *Thieno[2,3-b]pyridines*

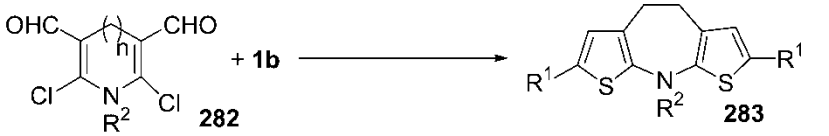
Thieno[2,3-*b*]pyridine derivatives containing various substituents in the pyridine ring have been synthesized. In 4,6-dichlorinated compounds, the chlorine atom at C-4 is preferentially replaced



Scheme 56.



Scheme 57.

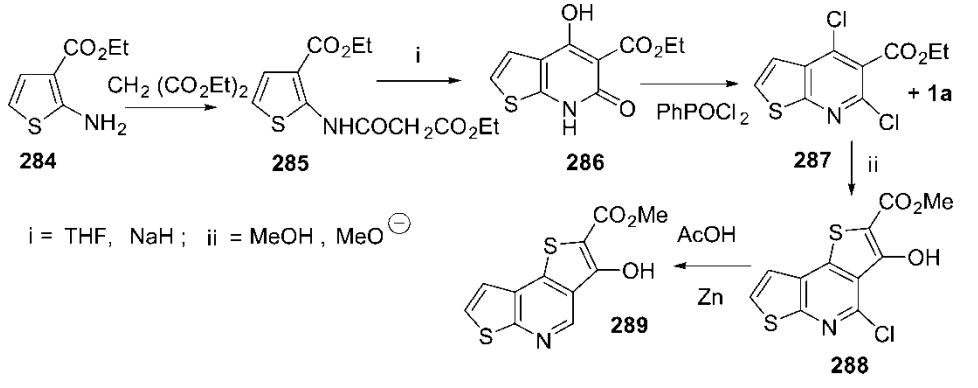


1 n = 0, 1, 2 $R^1 = CO_2Et$, $R^2 = CH_2Ph$, CH_2CO_2Et, $(CH_2)_3NMe_2$

	R^1	R^2			R^1	R^2	
282a	CO_2Et	CH_2Ph	(83%)	**283a**	CO_2Et	CH_2NMe	(65%)
282b	CO_2Et	CH_2CO_2Et	(83%)	**283b**	CO_2Et	CH_2Ph	(6%)
282c	CO_2Et	Ph	(68%)	**283c**	H	CH_2Ph	(60%)
282d	CO_2Et	H	(40%)	**283d**	CO_2Et	H	(40%)

Scheme 58.

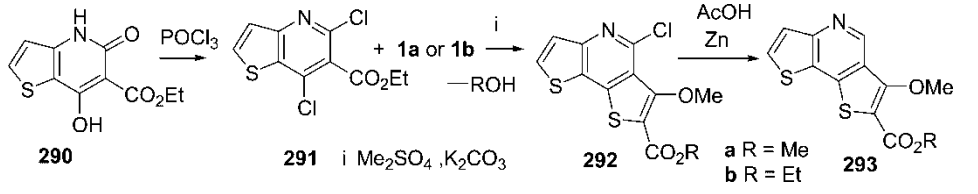
by nucleophiles. Barker *et al.* (*217*) have reported the synthesis of thienopyridines from ethyl 2-aminothiophene-3-carboxylate **284** (*218*). The reaction of **284** with diethylmalonate gave the corresponding amide **285**, which undergoes cyclization on treatment with NaH/THF. The cyclic amide **286** on reaction with $PhPOCl_2$ gave the 2,4-dichlorothienopyridine **287**. The reaction of ethyl 2,4-dichloroquinoline-3-carboxylate with methyl mercaptoacetate **1a** in the presence of NaOEt and EtOH gave thienopyridine derivative **288**. The reduction of **288** with zinc and acetic acid gave **289** (Scheme 59).



Scheme 59.

4.17. *Thieno[3,2-b]pyridines*

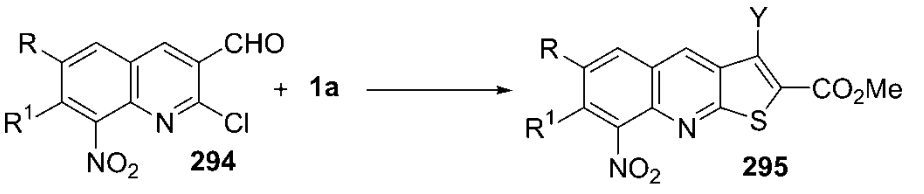
Barker *et al.* (*219*) have reported the treatment of 6-ethoxycarbonyl-7-hydroxy-thieno[3,2-*b*]pyridin-5(4*H*)-one **290** with $POCl_3$, which furnished the dichloro compound **291**. The reaction of **291** with methyl thioglycolate **1a** followed by methylation gave the tricyclic ester **292**. The angular nature of the resulting tricylic substances was established by correlation with **293** (*220*). Reductive dechlorination of **292** with zinc and acetic acid gave the tricyclic ester **293** (Scheme 60).



Scheme 60.

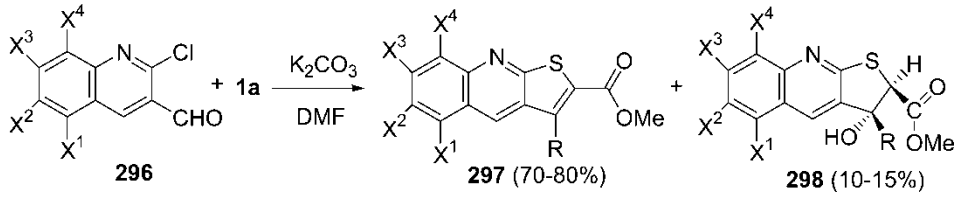
4.18. *Thienoquinoline derivatives*

Bhat and Bhaduri (*221*) have reported the synthesis of nitrothieno[2,3-*b*]quinoline derivatives. Reaction of 2-chloro-6,7-dimethoxy-3-formyl-8-nitroquinoline (*222*) **294** with methyl thioglycolate **1a** in the presence of potassium carbonate gave 2-carbomethoxy-1,7-dimethoxy-8-nitrothieno[2,3-*b*]quinoline and 2-carbomethoxy-6,7-dimethoxy-3-hydroxy-8-nitrothieno[2,3-*b*]quinoline **295** (Scheme 61).



a; R = R^1 = OMe; **b**; R = R^1 = OEt; **c**; y = H; **d**; y = OH

Scheme 61.



296	x^1	x^2	x^3	x^4
a	H	H	H	H
b	H	OMe	H	H
c	H	OMe	OMe	H
d	OMe	OMe	OMe	H

296	x^1	x^2	x^3	x^4
e	H	OEt	OEt	H
f	H	OMe	OMe	NO_2
g	H	OEt	OEt	NO_2

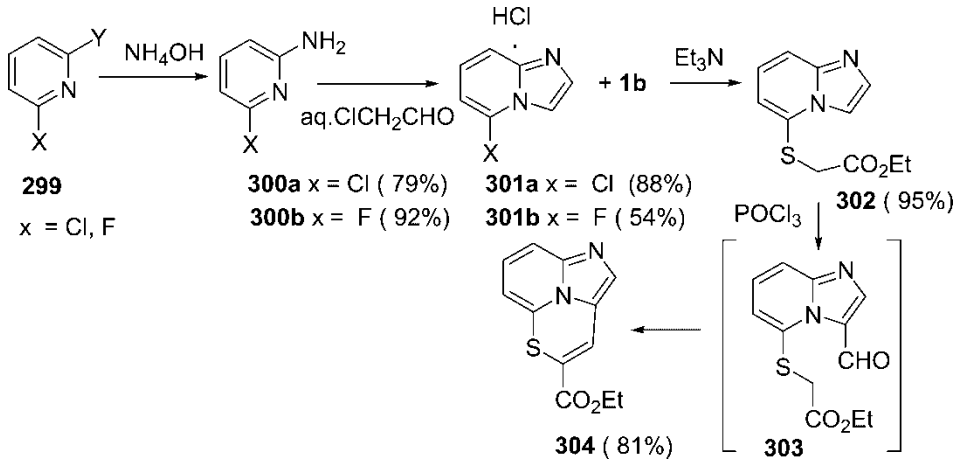
Scheme 62.

4.19. *Thienoquinolines*

The synthesis of 2,3-dihydrothieno[2,3-*b*]quinolines reported earlier (*223*) involves several steps and it cannot be used to incorporate substituents at positions 2 and 3. Bhat and Bhaduri (*224*) reported the synthesis of 2-methoxycarbonylthieno[2,3-*b*]quinolines **297** and 3-hydroxy-2-methoxycarbonyl-2,3-dihydrothieno[2,3-*b*]quinolines **298**. These compounds may be substituted in the 3,5,6,7 and/or 8 positions. The synthesis of compounds **298** involves intermolecular cyclocondensation. The reaction of 2-chloro-3-formylquinolines **296** (*225*) with methyl mercaptoacetate **1a** in DMF in the presence of anhydrous potassium carbonate afforded 2-methoxycarbonylthieno[2,3-*b*]quinolines **297** in 70–80% yields along with 3-hydroxy-2-methyoxycarbonyl-2,3-dihydrothieno[2,3-*b*] quinolines **298**, which was isolated in 10–15% yields following column chromatography. The reaction of compounds **298** with acetic anhydride/pyridine afforded the dehydration products **297** in almost quantitative yield (Scheme 62).

4.20. *5-Thia-1,8b-diazaacenapthylene derivatives*

The 5-thia-1,8*b*-diazaacenaphthilenes are new cyclazines with fused tricyclic ring systems having an internal nitrogen atom and 5,6 and 6-members (*226*). Ikemoto *et al.* (*227*) reported the synthesis of ethyl (imidazo[1,2-*a*]pyridin-5-ylthio)acetate **302** by thioglycolation of 5-halogenoimidazo[1,2-*a*]pyridine **301** (*228*) using Et_3N in DMF. 2,6-Dichloropyridine **299**, when treated with ammonia, gave 2-aminopyridine **300**, which, on condensation with chloroacetaldehyde, furnished **301**. The cyclazine **304** was synthesized by the formylation of **302** at the 3-position of imidazo[1,2-*a*]pyridine in the presence of $POCl_3$, DMF (*229*) followed by intramolecular condensation (Scheme 63).



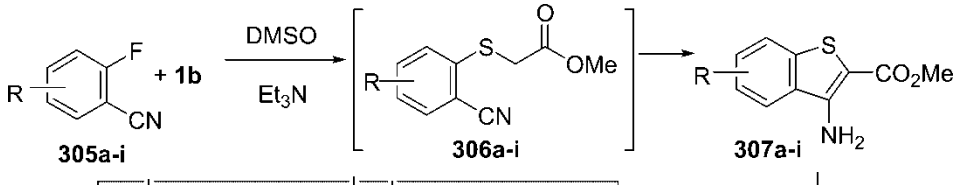
Scheme 63.

4.21. *Benzothienopyrimidines*

Substituted[1]benzothieno[3,2-*d*]pyrimidones are used as precursors for the preparation of inhibitors of tyrosine kinase (*230*). The intermediate 3-amino[1]-benzothiophene-2-carboxylate esters **307** have been prepared by Bridges and Zhou (*231*) through displacement from both 2-chloro (*232*) and 2-nitrobenzonitrile (*73*) and by the reaction of a malonate anion with 3-chlorobenzoisoxazoles.(*233*). Nucleophilic displacement of an *ortho*-halobenzonitrile **305** with a thioglycolate anion **1a**, followed by spontaneous base induced aldol cyclization of intermediate **306**, afforded the 3-amino[1]benzothiophene-2-carboxylate ester **307**. This can be further cyclized with a formate equivalent in a Niementowski synthesis (*234*) to give the desired tricyclic pyrimidones **308** (Scheme 64).

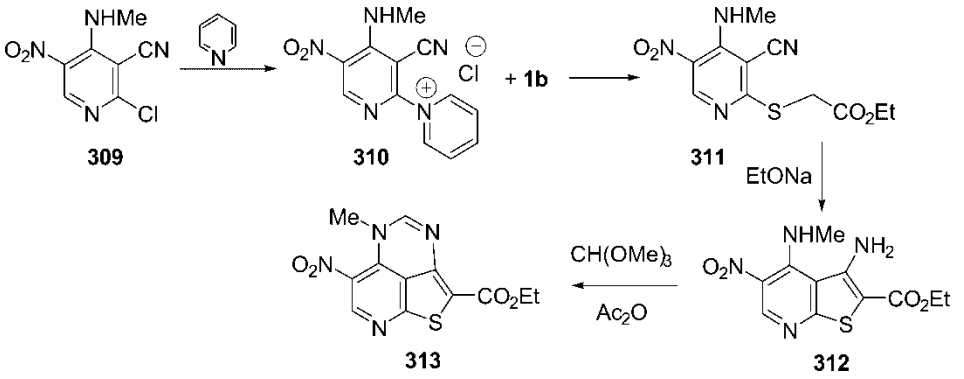
4.22. *Thienopyrimidine*

Krichevsky *et al.* (*235*) reported that the reaction of 2-Chloro-3-cyano-4-methylamino-5-nitropyridine **309**, the main key intermediate for the synthesis of condensed pyridines, proceeds



a	R =H	**g**	R = 8-NO_2
b	R = 9-MeO	**h**	R = 7-NHEt, 8-F
c	R = 6-MeO	**i**	R = 7-NH_2,8-F
d	R = 7-MeO	**j**	R = 7-NH_2
e	R = 8-MeO	**k**	R = 7-NO_2
f	R = 7, 8-$(MeO)_2$	**i**	R = 7-SCH_2CO_2Me

Scheme 64.



Scheme 65.

extremely well in spite of the presence at they position of a strong electron-donating substituent. The chlorine at position 2 is replaced under nucleophilic attack to form the pyridyl-2-pyridinium salt **310**. The reaction of pyridinium salt **310** with thioglycolic ester **1b** resulted in the formation of 3-cyano-2-ethoxycarbonylmethylthio-4-methylamino-5-nitropyridine **311**. Under the action of sodium ethoxide, the latter smoothly underwent Thorp–Ziegler cyclization (*151*) with the formation of 3-amino-2-ethoxycarbonyl-4-methylamino-5-nitrothieno[2,3-*b*]pyrimidine **312**. The bicyclic compound **312**, when heated with ethyl orthoformate, leads to the formation of pyrimidine ring involving the 3-NH_2 and 4-NHMe groups, resulting in the formation of the expected thienopyrimidine derivative **313** (Scheme 65).

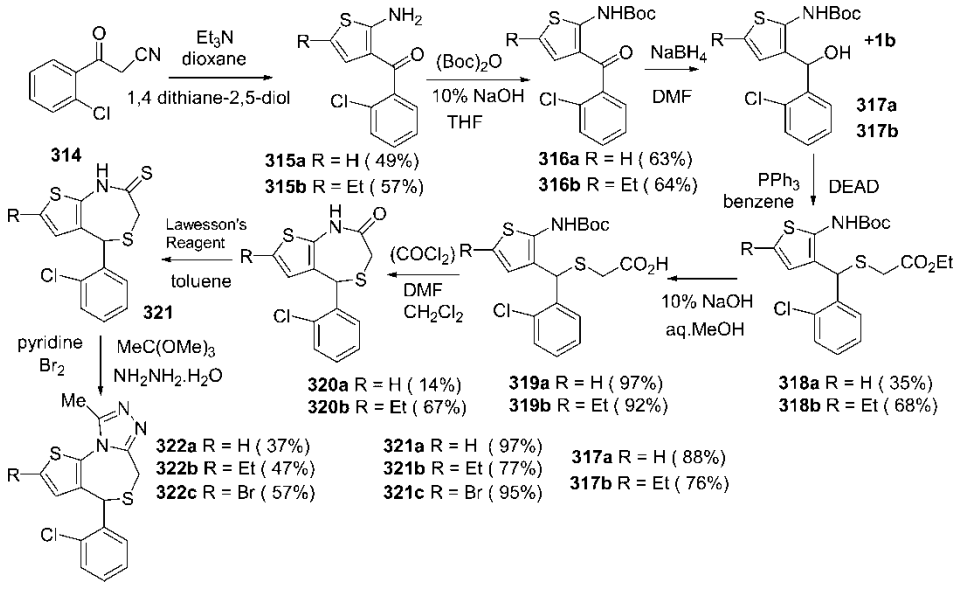
4.23. *Thienotriazolothiazepines*

Thienotriazolodiazepine derivatives were reported to exhibit anti-platelet activating factor activity (*236*). Nagaoka *et al.* (*237*) have reported the synthesis of structurally related analog, thienotriazolothiazepines, from α-cyanoketones (*238*). α-cyanoketone **314** was treated with 1,4-dithiane-2,5-diol and Et_3N to give the 2-aminothiophene or its analog **315**, respectively. Protection of the amino group of **315** with *t*-butoxycarbonyl group **316** followed by reduction ($NaBH_4$, DMF) furnished the alcohol **317**. The alcohols were treated under Mitsunobu conditions (Ph_3P, DEAD, ethyl thioglycolate, benzene) to provide the sulfides **318**, which were hydrolyzed to the corresponding carboxylic acids **319**. Cyclization of **319** to the thiazepine **320** was affected *via* the acid chloride by a treatment with oxalyl chloride and trifluoroacetic acid **320**. Treatment of **320** with Lawesson's reagent (*239*) gave thioamide **321**, which was converted into the thienotriazolo-thiazepine **322** by the successive treatment with hydrazine monohydrate and trimethyl orthoacetate (Scheme 66).

5. Tetracyclic derivatives

5.1. *7-Polyfluoroalkylnorkhellins*

The natural product furochromone khellin (4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*] chromen-5-one) obtained from the fruits and seeds of *Ammi visnaga L.* possesses a high antiatherosclerotic and lipid-altering activity (*240*). In view of the unique biological properties displayed by khellin on the one hand and by many fluorinated heterocyclic compounds (*66*) on the other hand, Sosnovskikh *et al.* (*184*) have described the synthesis of 7-polyfluoroalkylnorkhellins, which are reactive building blocks for khellin derivatives. Condensation of khellinone **323** with R^FCO_2Et in the presence



Scheme 66.

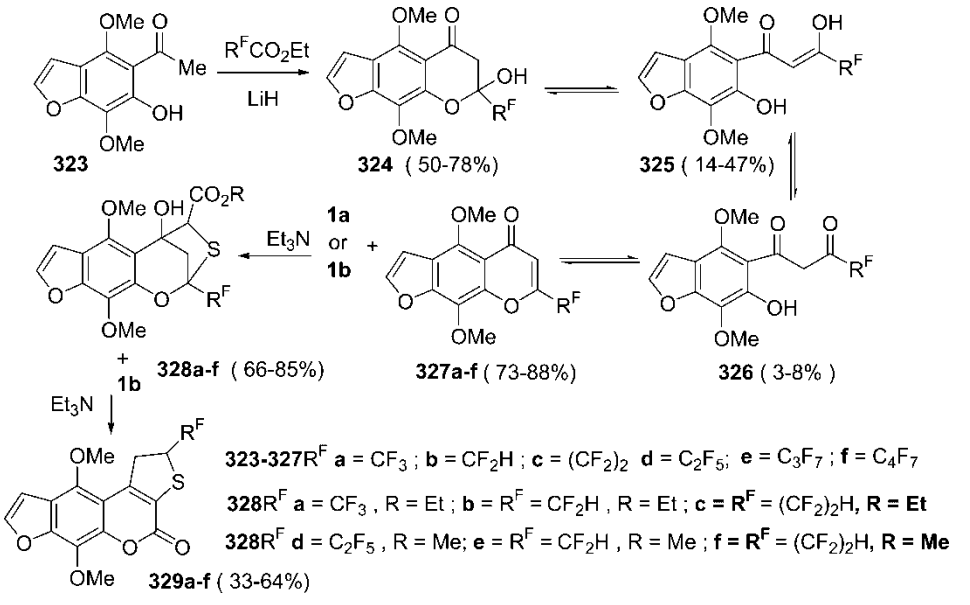
of LiH in refluxing THF proceeded at the acetyl group of **323** and afforded benzofuran derivatives, which are a cyclic hemiketal form **324** of the corresponding β-diketones in DMSO-d_6. In contrast to **324**, the ^{1}H NMR spectra of compounds in $CDCl_3$ exhibited three sets of signals: one of them corresponded to the furochromanone form **324** (50–78%) and, the others, to the ketoenol form **325** (14–47%) and diketo forms **326** (3–8%). Refluxing of furochromanones **324–326** in acetic acid with a catalytic amount of HCl afforded 7-polyfluoroalkylnorkhellins **327** in good to high yields. The reaction of 7-polyfluoro-alkylnorkhellins **327** with alkyl mercaptoacetates in the presence of Et_3N for 2 days at room temperature yielded **328** in 66–85% yield. Treatment of **328** with ethyl mercaptoacetate **1b** under similar conditions gave dihydro-thienopsoralens **329** in moderate yield (Scheme 67).

5.2. *Annelated N,S-heterocycles*

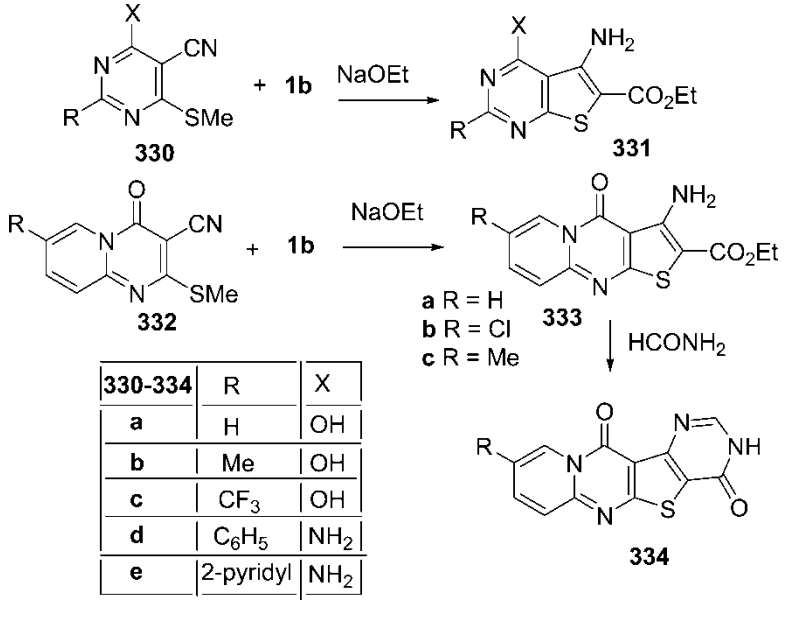
The therapeutic importance of pyrimidines and annulated pyrimidines derivatives as antibacterial agents (*241*) has aroused considerable interest to synthesize thienopyrimidines as isosteres of pyrimidines. Saxena *et al.* (*242*) reported the synthesis of condensed sulfur heterocylces **331** and **334** using ethyl mercaptoacetate **1b** as a reagent. 5-cyano-6-methylsulfanyl pyrimidines **330** on reaction with ethyl mercaptoacetate underwent base-catalyzed condensation and cyclization to yield thieno[2,3-*d*]pyrimidines **331**. Similarly, 2-methylsulfanyl-4-oxo-4*H*-pyrimido[1,2-*a*]pyrimidine-3-carbonitriles **332** on base catalyzed condensation and cyclization reaction with **1b**, at reflux temperature provided pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine **333**. Further cyclization furnished a tetracyclic heterocycle, 9-methyl-12*H*-pyrido[1,2-*a*] pyrimido[4′,5′:4,5]thieno[2,3-*d*] pyrimidine 4,12 (3*H*)-dione **334** after refluxing in formamide (Scheme 68).

5.3. *Benzothienonaphthridines*

Ivanov *et al.* (*243*) and Yalysheva *et al.* (*244*) have shown that the hydrolytic opening of 5-cyano-6-(2-dimethylaminovinyl)-1-phenylpyrimidine-4-one **335** followed by instant recyclization of



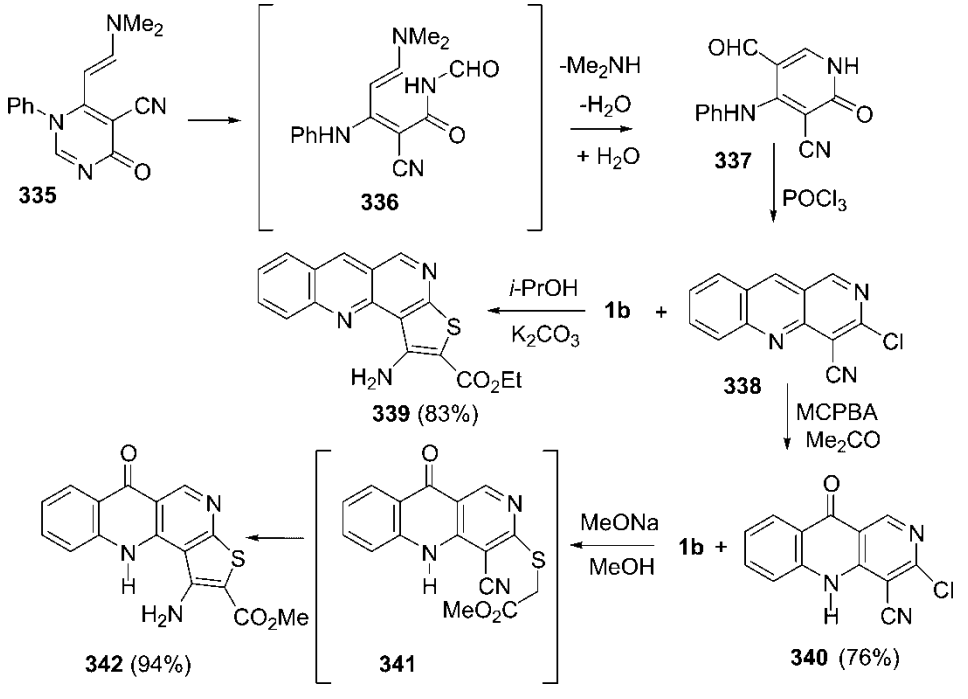
Scheme 67.



330-334	R	X
a	H	OH
b	Me	OH
c	CF_3	OH
d	C_6H_5	NH_2
e	2-pyridyl	NH_2

Scheme 68.

336 gave 4-anilino-3-cyano-5-formylpyridine-2-one **337** in acidic media (*151*). Heating of formylpyridone **337** in $POCl_3$ in the presence of $Et_3N.HCl$ affords 3-chloro-4-cyanobenzo-[*b*][1,6]napthyridine **338**. The reaction of **339** with available *S*-, *C*- and *N*-nucleophiles afforded stable sigma adducts at position 10. In the base-catalyzed, reactions of compound **338** with ethyl thioglycolate in *i*-PrOH underwent *in situ* Thorpe–Ziegler (*151*) cyclization to furnish benzo[*b*]thieno[2,3-*h*][1,6]naphthyridine **339**. The synthesis of 3,10-disubstituted 4-cyanobenzo[*b*][1,6]naphthyridines with different substituents in these positions of the rings was

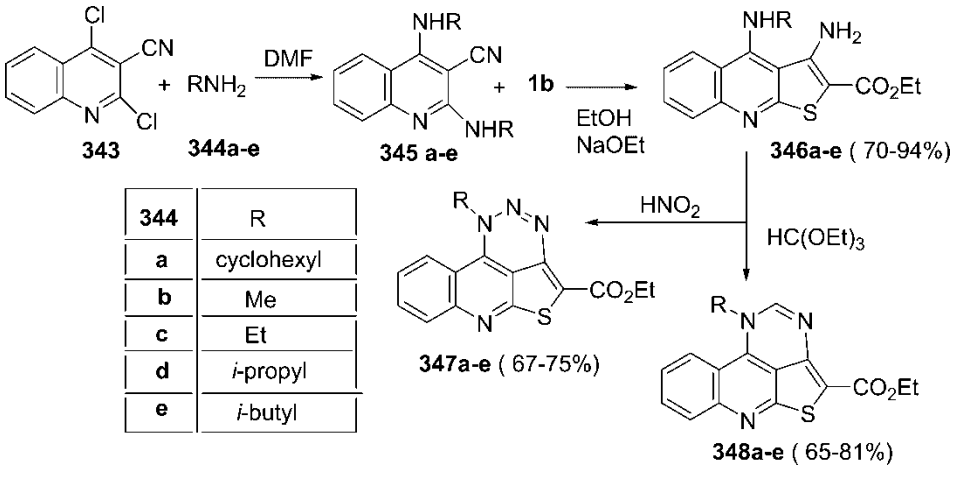


Scheme 69.

reported by Ivanov *et al.* (*245*) in order to study σ-adducts formed by *S*-nucleophiles (*246*). The oxidation of 3-chloro-4-cyanobenzo[*b*][1,6] napthyridine with *m*-chloroperbenzoic acid in refluxing acetone gave 10-oxoderivative **340** in a good yield. The structure of compound **340** shows that it can react with nucleophiles at position 3, while posititon 10 would remain intact. 1-Amino-2-ethoxycarbonyl-6-oxo-6,11-dihydrobenzo [*b*]thieno[2, 3-*h*][1,6]naphthyridine **342** was prepared by refluxing **340** with methyl mercaptoacetate **1a** in the presence of MeOH and NaOMe as a basic catalyst. It can be assumed that the thiolate anion attacks position 3 to yield 3-methoxycarbonylmethylthio derivative **341**, which subsequently undergoes the Thorpe–Ziegler cyclization (*151*) to give tetracyclic product **342** (Scheme 69).

5.4. *5-Thia-tetra-and triazaacephenanthrylenes*

Thienoquinolines have drawn much attention due to their considerable biological and pharmacological activities as antitumor and drug-resistant modulators (*247*). Mekheimer *et al.* (*248*) reported the synthesis of periannelated tetracyclic pyrimidothioquinoline ring systems. 2,4-dichloroquinoline-3-carbonitrile **345** (*249*) was reacted with alkylamine **344** to provide intermediate **345** into the first nucleophilic substitution taking place at the fourth position (*250*). The synthesis of 2-carbethoxy-3-aminothienoquinoline **346** was accomplished by refluxing **345** with a equimolecular amount of ethyl mercaptoacetate **1b** in dry EtOH and in the presence of excess NaOEt to afford diaminothienoquinolines **346** as stable crystalline solids in 70–94% yield. When compounds **346** were reacted with sodium nitrite in a 70% solution of H_2SO_4 at $-5\,^{\circ}C$, the corresponding ethyl 1-alkyl-1*H*-5-thia-1,2,3,6-tetraazaacephenanthrylene-4-carboxylates **347** were formed in good yield. When compounds **346** were refluxed with excess of triethyl orthoformate, ethyl 1-alkyl-1*H*-5-thia-1,3,1-triazaacephenanthrylenes-4-carboxylates **348** were isolated as the only reaction product (Scheme 70).



344	R
a	cyclohexyl
b	Me
c	Et
d	*i*-propyl
e	*i*-butyl

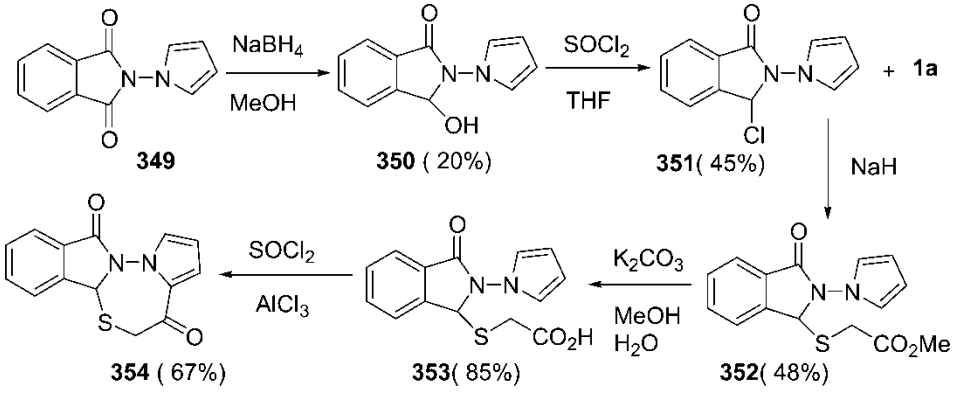
Scheme 70.

5.5. *Pyrrolothiadiazepinoisoindole*

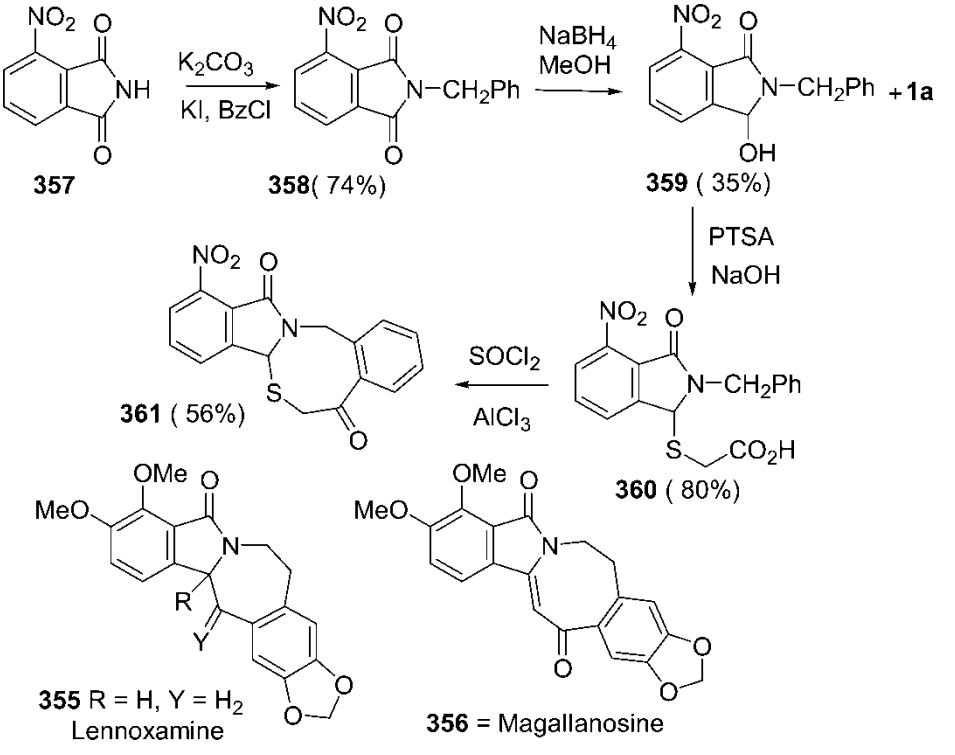
Pyrrolyl isoindole type of compounds containing thia-diazocine ring were reported with potential pharmacological activity (*251, 252*). Guesdon *et al.* (*253*) have reported the synthesis of fused dioxaza-ring compounds starting from *N*-hydroxyphthalimide. 1-Phthalimidopyrrole **349** was prepared by the acidic condensation of 1-aminophthalimide with 2,5-diethoxy-tetrahydrofuran (*254*). Reduction of **349** with $NaBH_4$ at 5 °C in MeOH led to the hydroxy lactam **350** (*255*). The action of thionyl chloride in THF results in chlorolactam **351**. The reaction of **351** with thiolate anion generated by the action of sodium hydride on methyl thioglycolate **1a** gave ester **352**. Saponification of the ester group of **352** led to the expected acid **353**. Intramolecular cyclization of the acid chloride derivatives under Friedel–Crafts conditions gave the pyrrolothiadiazepino isoindole **354** (Scheme 71).

5.6. *Isoindolobenzothiazocine derivatives*

Mono (or poly) hydroxylated and methoxylated dihydroisoindolones units are present in a large number of interesting classes of benzazepine and benzazocine alkaloids. These structures are



Scheme 71.



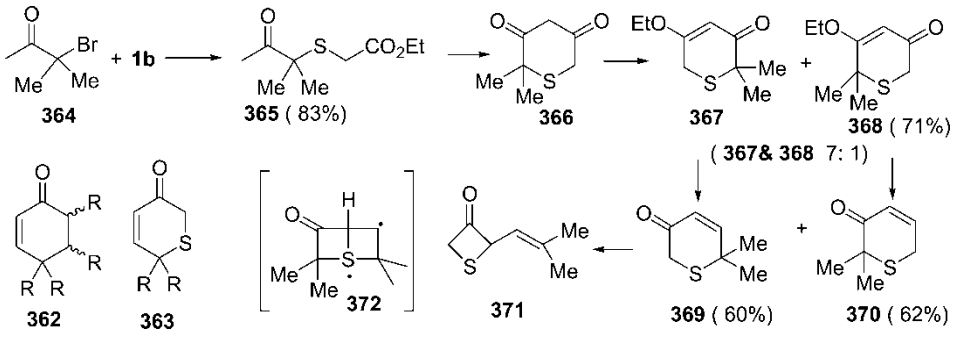
Scheme 72.

exemplified by lennoxamine **355** and magallanosine **356** extracted from the Chilean berberidaceae, *Berberis darwinii* Hook (*256*). Chihab-Eddine *et al.* (*257*) have reported the synthesis of tricyclic thioanalog systems annelated to isoindolone. 3-Nitrophthalimide **357** was *N*-alkylated with benzyl choride under solid–liquid phase transport catalysis using anhydrous potassium carbonate as base and a mixture of potassium iodide and crown ether 18-C-6 as the catalyst (*258*) to get *N*-benzylated product **358**. This imide was subjected to reduction using the excess of $NaBH_4$ (*7*) in methanol to get ω-carbinol lactam **359**. Treatment of hydroxylactam with an excess of methyl thioglycolate **1a** and a catalytic amount of PTS followed by saponification gave **360**. The acid derivative under Friedel–Crafts cyclodehydration conditions gave the cyclic ketone **361** (Scheme 72).

6. Miscellaneous

6.1. *2-(Alk-1-enyl)thietan-3-ones*

2*H*,6*H*-thiin-3-ones of type **363** are the subject of interest for their photochemistry (*259*) wherein C(5) in **362** is replaced by an *S*-atom (*260*). Margaretha (*261*) has reported the preparation of these types of compounds **370, 371**. The reaction of 3-bromo-3-methylbutan-2-one **364** with ethyl mercaptoacetate **1b** affords ethyl 4,4-dimethyl-5-oxo-3-thiahexanoates **365**. Treatment of these esters with NaOMe in MeOH gives 2,2-dimethyl- and 2,2,6,6-tetramethylthiane-3,5-dione **366**. Conversion of these dicarbonyl compound to their corresponding ethyl enol ethers (**367**, **368**) followed by the reduction with $LiAlH_4$ gave 2*H*,6*H*-thiin-3-ones (**369**, **370**). When irradiated (350 nm) in either MeCN or *i*-PrOH, these heterocylces efficiently isomerised to 2-(alky-1-enyl) thietan-3-ones **371**. The thiinone–thietanone rearrangement appears to proceed through



Scheme 73.

sulfuranyl-alkyl singlet biradical intermediate **372,** which is not sensitive to the stability, displaced radical group (Scheme 73).

6.2. *3-Substituted isothiochromans*

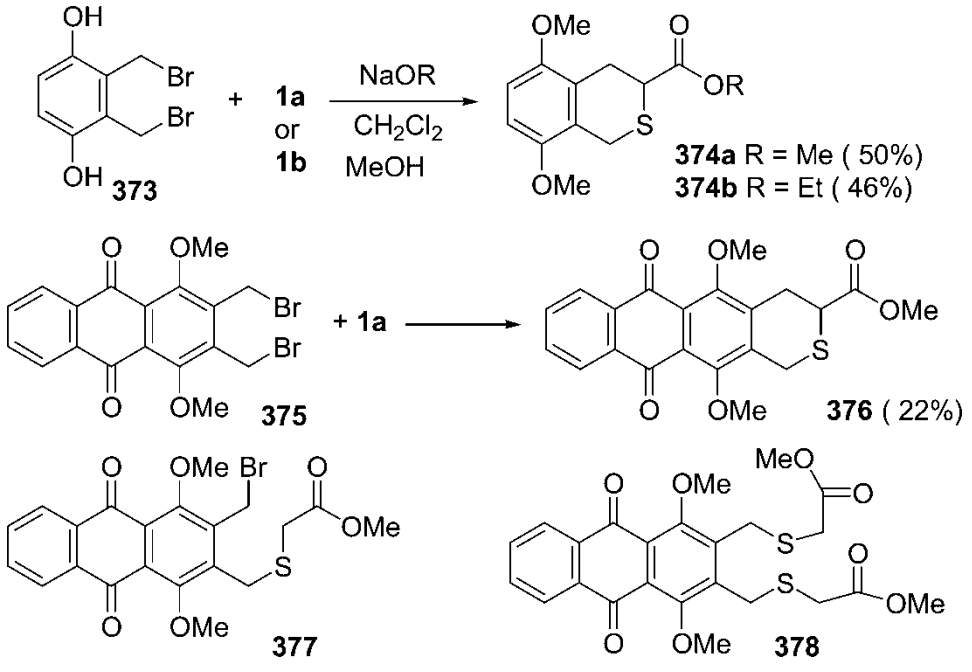
The pharmacology of isothiochroman derivatives has been extensively investigated because these compounds have been found to possess a diverse spectrum of biological activity (*262*) including antitussive (*263*), sedative (*264*) and muscle relaxant effects (*265*). Recently, isothiochromans have been shown to be a useful synthon for the preparation of heterocyclic anthracyclinone analogs (*265*). Xu *et al.* (*266*) have described a one-pot synthesis of isothiochromans from benzyl dibromide **373**. The dibromide **373** is readily available (*267*) by the bromination of 2,3-dimethyl-1,4-dimethoxybenzene with *N*-bromosuccinimide. The treatment of **373** with α-thiocarbonyl compounds **1a** and sodium methoxide in DCM and MeOH (1:1) gave moderate yields of the desired heterocyclic compounds **374**. The heterocyclic analog of anthracyclinone **376** was prepared in the same manner from dibromide **375** (*268*) with methyl thioglycolate. The low yield is that the one-pot reaction proceeds first with *S*-alkylation to form intermediate **377,** which then undergoes intramolecular C-alkylation through the ester enolate to give the product **376**. Intermediate **377**, however, can also undergo a second *S*-alkylation to form **378** (Scheme 74).

6.3. *1,4-Benzoxathiepins and 4,1-benzothiazepines*

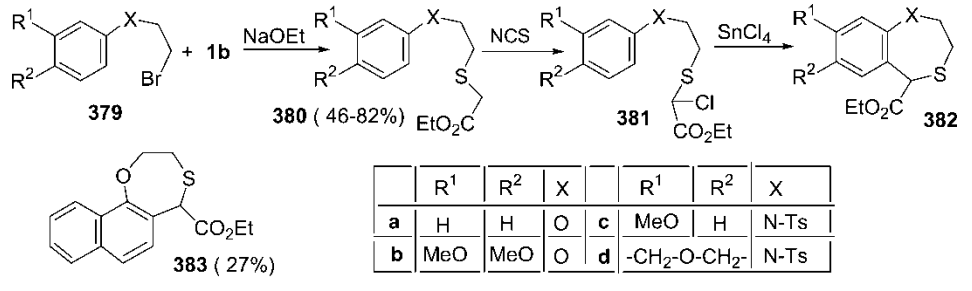
The condensed seven-membered heterocylces have been the subject of intensive synthetic studies since they possess a wide spectrum of pharmacological activities (*269*). Ishibashi *et al.* (*270*) have reported the synthesis of condensed seven-membered heterocylces such as 2,3-dehydro-5*H*-1,4-benzoxathiepins and 1,2,3,5-tetrahydro 4,1-benzothiazepines by the intramolecular Friedel–Crafts reaction of arenes with α-acyl-α-chlorosulfides (*271*). Substituted arenes **379** on reaction with ethyl thioglycolate in the presence of sodium ethoxide gave the corresponding sulfide **380**. The treatment of the chlorides **381,** that were prepared *in situ* from sulfide **380** and *N*-chlorosuccinimide, with stannic chloride in methylene chloride at room temparature, gave 1,4-benzoxathiepin compounds **382** in 22% yield. 1,4-benzoxathiepin derivative **383** was prepared in an analogous manner (Scheme 75).

6.4. *Thienothiopyrans*

Polycyclic compounds obtained by the annelation of a pyrimidine ring on to thieno[3,2-*c*] thiopyrans have shown antibacterial and antiparasitic activities (*272*). Mandal *et al.* (*273*)

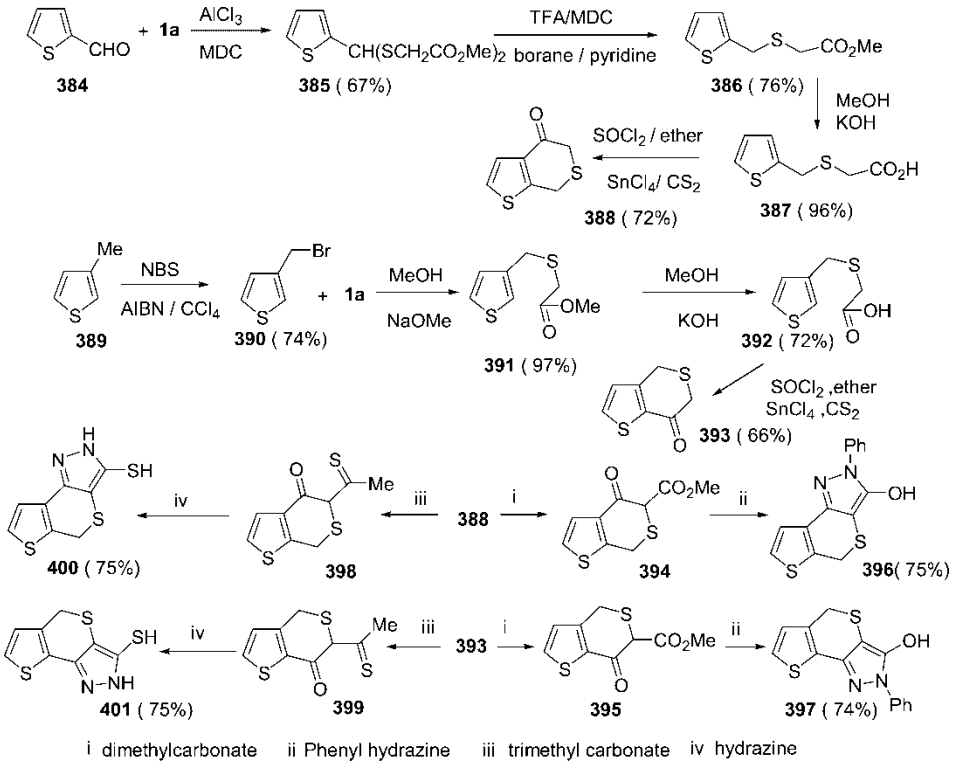


Scheme 74.



Scheme 75.

have reported the synthesis of annelated thieno[2,3-*c*]- and thieno[3,2-*c*]thiopyrans from 7*H* thieno[2,3-*c*]thiopyran-4(5*H*)-one **388** and 4*H*-thieno[3,2-*c*]thio-pyran 7(6*H*)-one **393**. The ketone **388** was synthesized from the thiophene-2-carbaldehyde **384** in excellent overall yield. Treatment of carbaldehyde **384** with 2 mol of methyl mercaptoacetate **1a** in DCM in the presence of anhydrous aluminum chloride at room temparature afforded 2-[bis(methylsulfanylacetyl)methyl]thiophene **385** in 67% yield after purification by column chromatography. Selective removal of one of the acetal groups in the latter was achieved with pyridine-borane in the presence of TFA to give ester **386**. Hydrolysis of the ester group in **386** and cyclization of resulting acid were carried out using methanolic KOH, thionyl chloride and stannic tetrachloride. The ketone **393** was synthesized from 3-methylthiophene **389** in good overall yield. Side chain bromination of **389** proceeded in 74% yield to afford 3-bromomethylthiophene (*274*). Treatment of **390** with methyl mercaptoacetate in the presence of NaOMe afforded methyl 2-(3-thienylmethylsulfanyl)acetate **391** in 97% yield. Hydrolysis of the ester function and cyclization of the resulting acid was accomplished in a manner analogous to **388.**

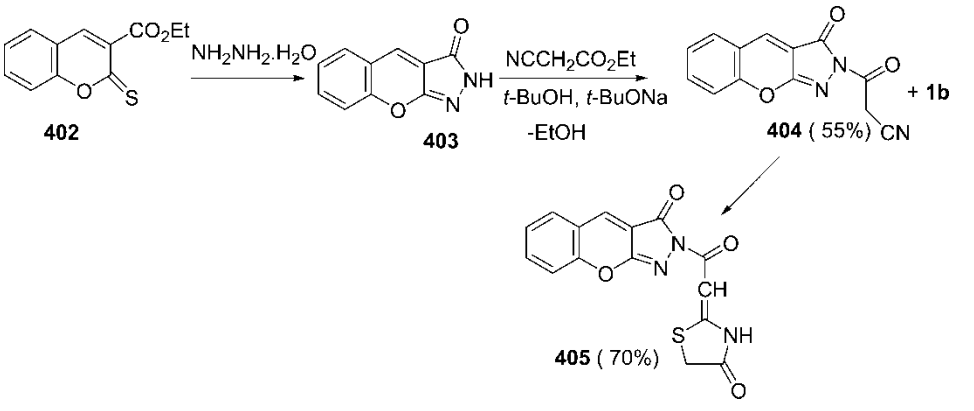


Scheme 76.

The β-oxoesters **394** and **395** exist entirely in the enolic form in solid phase (*275*). The β-oxoesters **394** and **395** were obtained from **388** and **393,** respectively, upon treatment with dimethyl carbonate in the presence of NaH. The β-oxo esters **394** and **395** reacted with phenylhydrazine in hot MeOH to afford the tricyclic compounds, 3-hydroxy-2-phenyl-2,5-dihydrothieno[3′,2′:4,5]thiopyran[3,2-*c*]pyrazole **396** and 3-hydroxy-2-phenyl-7,5-dihydro-thieno[2′,3′:4,5]thiopyrano[3,2-*c*]pyrazole **397** in 75 and 74% yield, respectively. The ketones **388** and **393** also reacted with dimethyl trithiocarbonate in the presence of potassium *t*-butoxide to give β-oxodithioesters **398** and **399**. The β-oxodithioesters **398** and **399** when reacted with hydrazine hydrate in refluxing ethano1 to afford the tricyclic compounds 3-mercapto-2,5-dihydrothieno[3′,2′:4,5]thiopyrano[3,2-*c*]pyrazole **400** and 3-mercapto-2,5-dihydrothieno[2′,3′:4,5]thiopyrano[3,2-*c*]pyrazole **401** in 75% yields (Scheme 76).

6.5. *Benzopyranopyrazolothiazolidinone*

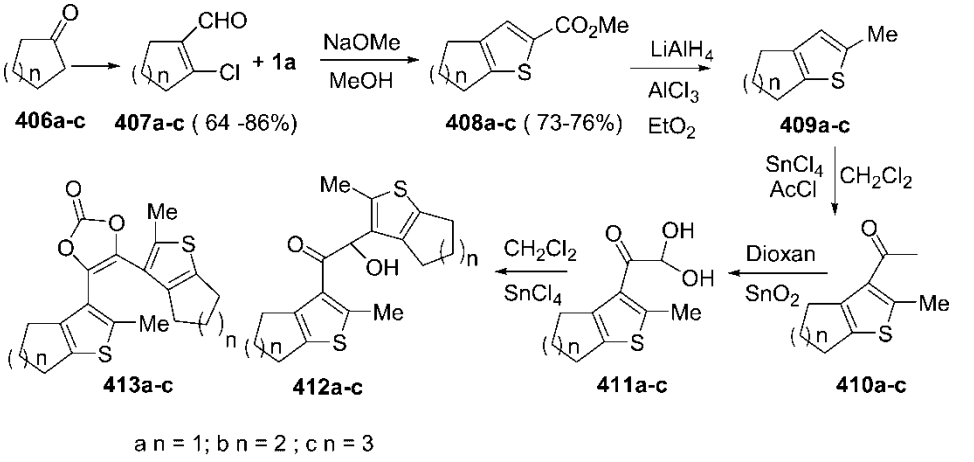
Many heterocyclic compounds containing the coumarin moiety show antibacterial and antibiotic activity (*276*). Khodiary (*277*) reported the synthesis of poly-fused heterocylces containing pyran, pyrazole, thienyl and substituted benzene derivatives. Benzopyrano[2, 3-*c*]pyrazol-3-one **403** was prepared from the reaction of 3-carbethoxy-benzopyran-2-thione **402** with hydrazine hydrate in a good yield (*278*). The reaction of ethyl cyanoacetate in the presence of sodium *t*-butoxide afforded the *N*-cyanoacetyl derivative **404** in 43% yield *via* the elimination of ethanol. Resulting compound **404** with ethyl mercaptoacetate gave the corresponding 4-thiazolidinone derivatives **405** in good yield (Scheme 77).



Scheme 77.

6.6. *Methylthiophenes*

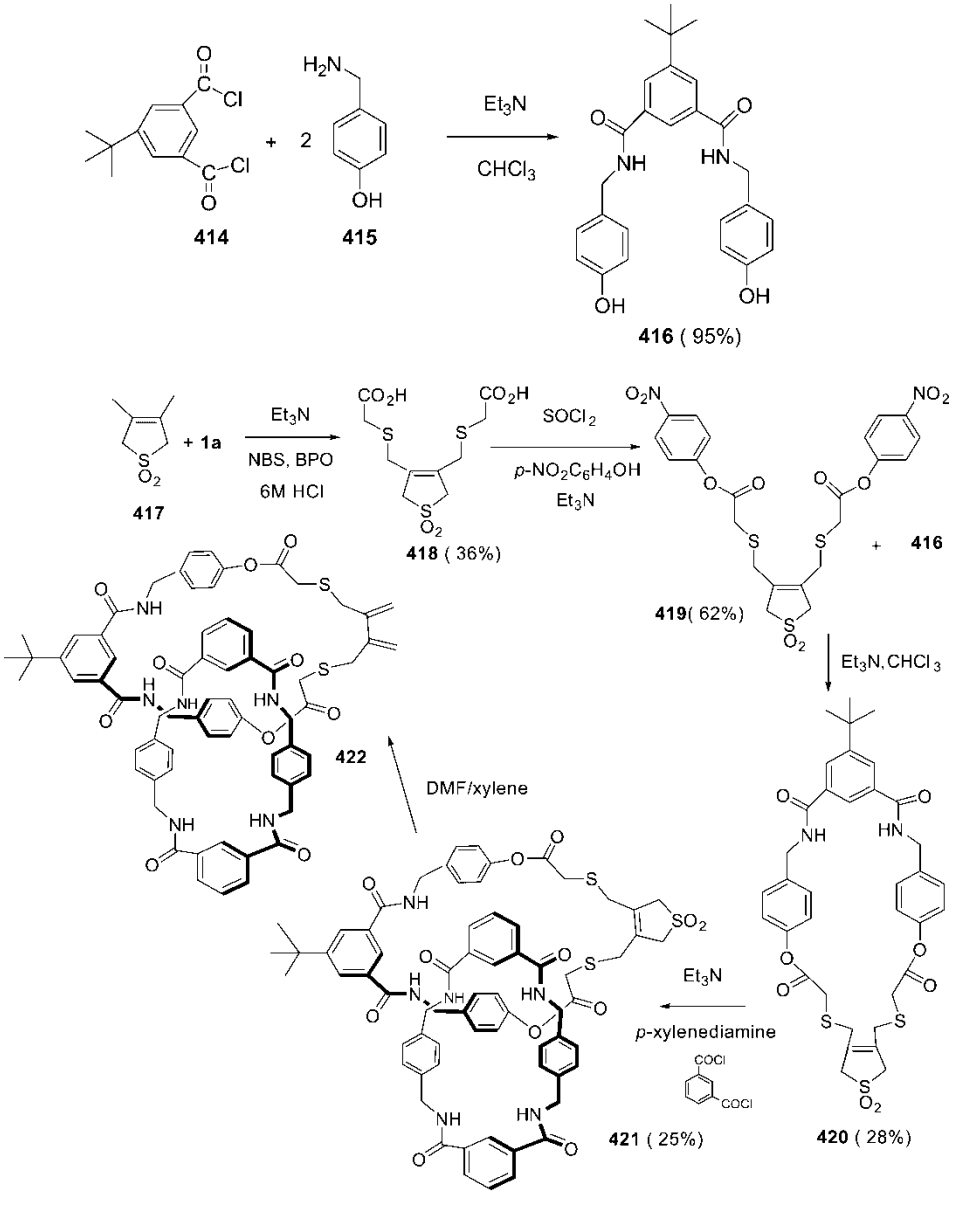
Functionally substituted 1,2-dithienylethene derivatives are of great interest for the progress of the chemistry of photochromic 1,2-dihetero-arylethenes (*279*). 2-Methylthiophenes are widely used for the synthesis of photochromic dihetero-arylethenes as prospective elements of 3D optical memory (*280, 281*). Krayushkin *et al.* (*282*) reported a three-step approach for the synthesis of the methylthiophenes **409** starting from ketones. The first step is the reaction of ketones **406** in $POCl_3$/DMF at 40 °C leading to the chloraldehydes **407** in 64–86% yields (*283*). The reaction of chloraldehydes **407** with methyl thioglycolate **1a** in methanolic NaOMe proceeded readily to provide the methyl thiophene carboxylates **408** in 73–76% yield (*284*). $LiAlH_4$ and $AlCl_3$ can reduce the esters **408** in Et_2O solution to methylthiophenes **409** in good yields. The thiophene **409** was used for the synthesis of 1,3-dioxa-2-one heterocyclic-bridged fragment **410**. The better acetylation of **409** gave acetyl derivative **410**, which, on oxidation with SeO_2, gave the gem diol **411**. The reaction of **411** with $SnCl_4$ gave acyloin **412**. Reaction of **412** with excess of 1,1′-carbonyldiimidazole leads to 4,5-di-(2-methyl-4,5,6,7-tetrahydrobenzo-[b]-thiophen-3-yl)-1,3-dioxol-2-one **412** in high yield. It was demonstrated that 1,3-dioxol-2-one derivative **413b** derived from 2-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene **409b** is a thermally irreversible photochromic compound (Scheme 78).



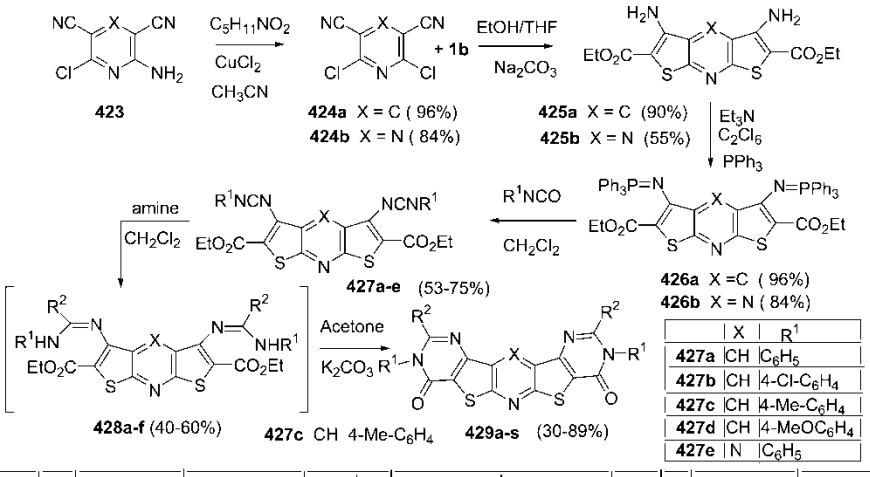
Scheme 78.

6.7. *Catenane ring*

Interlocked molecules such as rotaxane, catenane and trefoil knot (*285*) have attracted the attention recently due to the advances in the chemistry of non-covalent bonding systems. 'Unlock–lock approach' (*286, 287*) is a good example of successful technique for modifications of an interlocked compound with the change of conductivity. The annulation-ring scission sequence, with initial annulation on the ring component to introduce a new connectivity followed by successive scission of the original bonding, is the protocol reported by Watanabe *et al.* (*288*). The [2] Catenane 422 I bearing a 1,3-diene moiety was reported as a typical example of annulation-ring scission sequence by the authors. Bisphenol **416** was synthesized from 5-tert-butylisophthaloyl chloride **414** and



Scheme 79.



	X	R^1
427a	CH	C_6H_5
427b	CH	4-Cl-C_6H_4
427c	CH	4-Me-C_6H_4
427d	CH	4-MeOC_6H_4
427e	N	C_6H_5

	X	R^1	R^2		X	R^1	R^2		X	R^1	R^2
428a	CH	C_6H_5	Thiomorpholino	**429e**	CH	4-Cl-C_6H_4	Morpholino	**429o**	CH	4-Me-C_6H_4	*i*-propylamino
428b	CH	C_6H_5	Diethylamino	**429f**	CH	4-Cl-C_6H_4	Piperidino	**429p**	N	C_6H_5	Thiomorpholino
428c	CH	C_6H_5	Morpholino	**429g**	CH	4-Me-C_6H_4	Morpholino	**429q**	N	C_6H_5	Morpholino
428d	CH	4-MeO-C_6H_4	Morpholino	**429h**	CH	4-MeO-C_6H_4	Piperidino	**429r**	N	C_6H_5	Piperidino
428e	CH	4-Cl-C_6H_4	Piperidino	**429i**	CH	4-MeO-C_6H_4	Morpholino	**429s**	N	C_6H_5	*i*-propylamine
428f	CH	C_6H_5	*i*-propylamino	**429j**	CH	4-MeO-C_6H_4	Piperidino	**429t**	N	4-Cl-C_6H_4	Morpholino
429a	CH	C_6H_5	Diethylamine	**429k**	CH	C_6H_5	*n*-butylamino	**429u**	N	4-Cl-C_6H_4	Piperidino
429b	CH	C_6H_5	Thiomorpholino	**429l**	CH	C_6H_5	*i*-propylamino	**429v**	N	4-Me-C_6H_4	Morpholino
429c	CH	C_6H_5	Morpholino	**429m**	CH	4-Cl-C_6H_4	*i*-propylamino	**429w**	N	4-Me-C_6H_4	Piperidino
429d	CH	C_6H_5	Piperidino	**429n**	CH	4-Me-C_6H_4	*i*-propylamino	**429x**	N	4-MeO-C_6H_4	Morpholino
								429y	N	4-MeO-C_6H_4	Piperidino

Scheme 80.

4-hydroxyphenylmethyl amine **415**. Sulfolene **417**, derived from 2,3-dimethyl-1,3-butadiene, was first brominated to afford **417**, which was followed by reaction with methyl thioglycolate. Subsequent hydrolysis afforded **418**, which was converted to the corresponding active ester **419**. Macrolactam **420** was prepared by the 1:1 cyclization of bisphenol **416** and active ester **419** under highly dilute conditions. Secondary amide groups of **420** provided hydrogen-bonding sites that can interact with other secondary amide groups for the construction of the interlocked structure. The cyclization of isophthaloyl dichloride and *p*-xylenediamine in the presence of **420** afforded [2]catenane **421** (*289*) in 25% yield. Deprotection by thermolysis of **421** at 150 °C gave [2]catenane **422** by the elimination of SO_2 from the sulfolene moiety (Scheme 79).

6.8. *Pyrido and pyrazinodithienodipyrimidine 4,8(3H, 9H) dione*

Synthetic heterocycles containing a fused pyrimidine ring have significant biological activity, particularly in cancer and virus researches (*290*). Iminophosphoranes derived from *N*-aminoheterocylces are valuable precursors for the preparation of fused heterocylces, which may be neutral, cationic or mesoionic (*291*). Vilarelle *et al.* (*292*) have reported the synthesis of fused pyrimidines based on the tandem aza-Wittig heterocumulene-mediated annulation strategy (*293*). Pentaheterocyclic compounds **429a–y** were obtained in an one-pot reaction of the corresponding

iminophosphoranes of heteroaromaticβ-enamino esters **426a, b** with isocyanates followed by hetrocyclization on addition of amines. The starting compounds for the aza-Witting reaction heterocyclisation sequence were prepared from the readily available heterocyclic β-enaminoesters **425a, b**. First, 2,6-dichloropyridine-3,5-dicarbonitrile **424** and 2,6-dichloropyrazine-3,5-dicarbonitrile **424** were formed by the nitrosation reaction of the corresponding 2-aminoderivatives **423** (*294*) following a previously described procedure (*295*). The thiophene rings were added on the pyridine and pyrazine rings by condensing **424a, b** with ethyl 2-mercaptoacetate **1b** in the presence of an equimolecular amount of potassium carbonate in refluxing ethanol to give ethyl 3,5-diamino-dithieno[3′,2′ − *e* :2,3-*b*]pyridine-2,6-dicarboxylate **425a** and ethyl 3,5-diamino-dithieno[3′,2′ − *e*:2,3-*b*]pyrazine-2,6-dicarboxylate **425b** in good yields. The key iminophosphoranes **426a, b** were obtained by the modified Kirsanov reaction of the β-enaminoesters **425a, b** with *in situ* prepared dichlorotriphenylphosphorane using a hexachloroethane-triphenylphosphine-triethylamine reagent system (*296*). Aza-Wittig reaction of bisiminophosphoranes **426a, b** with arylisocyanates followed by hetero-cyclization on addition of secondary amines directly affords substituted pyrido [5″6″:4,5:3″2″:4′,5′]dithieno[3,2-*d*:3′,2-*d*′]di-pyrimidine-4,8 (3*H*,9*H*)-dione **429a–o** and pyrazino[5″,6″:4,5; 3″2″:4′,5′]dithieno[3,2-*d*:3′2′ − *d*′]dipyrimidine 4,8(3*H*, 9*H*)-dione **429p–y** (Scheme 80).

7. Conclusions

The reactions of β-mercaptoalkanoic carboxylic esters elaborated in this review can be summarized as follows. These esters react with active methylene compounds such as α,β-unsaturated esters and acetylenic ketones. In the case of unsaturated esters and ketones, annelated thiophenes are formed through nucleophilic addition followed by intramolecular cyclocondensation. Reactions with unsaturated carbonyl compounds containing halogen proceed through nucleophilic addition. The intermediates in these reactions are transformed to other useful compounds by intramolecular transformation including cyclization by the elimination of the hydrogen halide. On the other hand, reactions with unsaturated carbonyl compounds containing nitrile group such as β-chlorocinnamonitrile, β-haloacrylonitrile, α,β-unsaturated nitriles lead to the formation of aminothiophens derivatives through Dieckmann–Thorpe–Ziegler cyclization. β-Mercaptoalkanoic carboxylic esters can also be used in reactions involving multiple bonds and as cyclocondensing agents.

Acknowledgements

The author thanks Dr S.R. Ramadas, Professor of Chemistry (Retd), IIT-Chennai and Dr S.P. Hiremath, President Indian Council of Chemists for their technical help and constant encouragement.

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