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The latest achievements in thienothiophene chemistry †

V P Litvinov

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Abstract. Data on methods of synthesis, physicochemical characteristics, reactivity and biological activities of isomeric thienothiophenes and their analogues and some of their properties of practical importance are summarised and analysed. The present review covers the last 25 years. The bibliography includes 417 references.

I. Introduction

In the last 25 years, annelated heterocyclic systems have attracted considerable attention both from a theoretical standpoint and in view of their various practical applications. This interest is evidenced by a sharply increasing number of publications devoted to various aspects of the chemistry of fused thiophenes. For example, about 300 papers have been published during 90 years since the discovery of thienothiophenes (in 1886)[1] up to the publication of the most recent reviews devoted to this field of chemistry,[2–5] whereas the number of such papers has considerably increased in the last 10 – 15 years. The character of publications has also changed. In recent years, procedures for the synthesis of annelated derivatives and the physicochemical properties, reactivity and potentially useful properties of isomeric thienothiophenes and their analogues have attracted growing interest. In particular, the percentage of studies on practical applications of such systems exceeded 30% of the total number of publications. To represent information on the chemistry of this class of fused heterocycles in more detail, it is worthwhile to discuss not only investigations performed in the last decade but also earlier studies, which have not been included in the latest review[2] on this problem or those reported more recently.

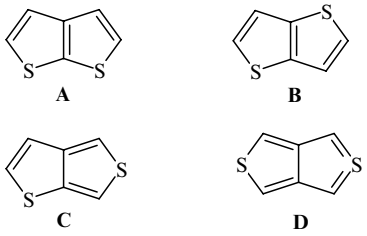
II. Methods of synthesis

Data presented in this Section are classified according to the nature of the starting compounds involved in the synthesis of isomeric thienothiophenes.

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Compounds characterised by three modes of fusion of the thiophene rings, *viz*., [2,3-*b*] (structure **A**), [3,2-*b*] (**B**) and [3,4-*b*] (**C**), have attracted most attention. These isomers are referred to as conventional (or classical) thienothiophenes, because structures of the type **D** ([3,4-*c*]-fusion) are much less accessible.



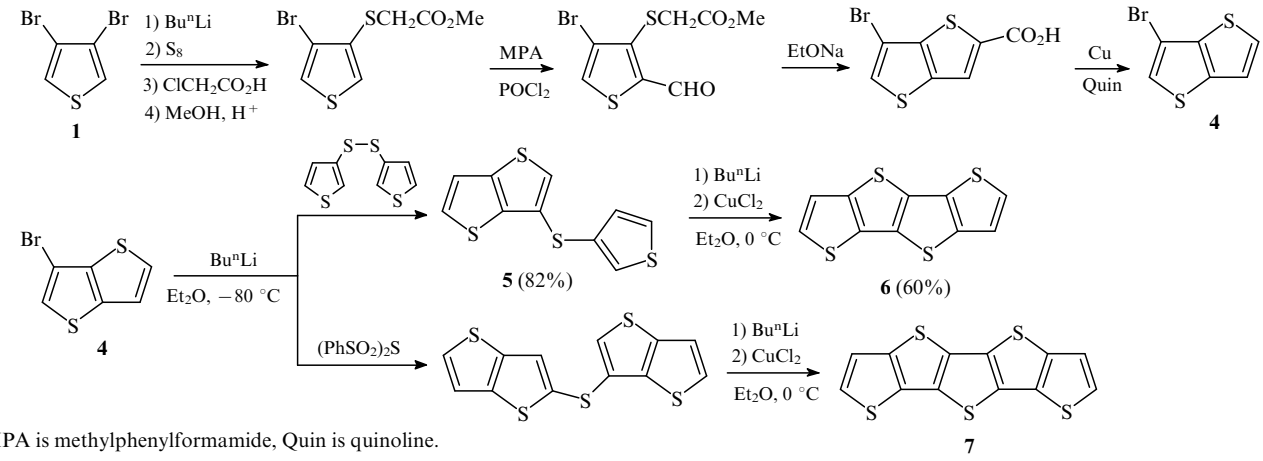
For isomeric thienothiophenes, both general methods of synthesis and original procedures applicable only to the preparation of particular types of compounds have been developed. In recent years, along with conventional methods based on thiophene derivatives as substrates, other approaches using, in particular, cyclopropenethiones, dithiynes and dithiolium salts have been successfully designed. Special sections in the review deal with high-temperature synthesis of annelated thienothiophenes and procedures used for the preparation of particular representatives of this class of heterocycles.

1. Thiophene derivatives in the synthesis of thienothiophenes

Bromine derivatives of thiophene are most widely used for the preparation of isomeric thienothiophenes and related systems. A classical example of this approach is illustrated by the following transformation sequence: formylation of 3,4-dibromothiophene (**1**) through a lithium derivative, repeated metallation and treatment with elemental sulfur and methyl bromoacetate. The closure of the second heterocycle occurs in the presence of sodium alkoxide. Decarboxylation of the resulting 4-bromothieno[2,3-*b*]thiophene-2-carboxylic acid (**2a**) affords 3-bromothieno[2,3-*b*]thiophene (**3a**).[6] The reaction with the use of selenium instead of sulfur produced 4-bromoselenopheno[2,3-*b*]thiophene-2-carboxylic acid (**2b**) and 4-bromoselenopheno[2,3-*b*]thiophene (**3b**).

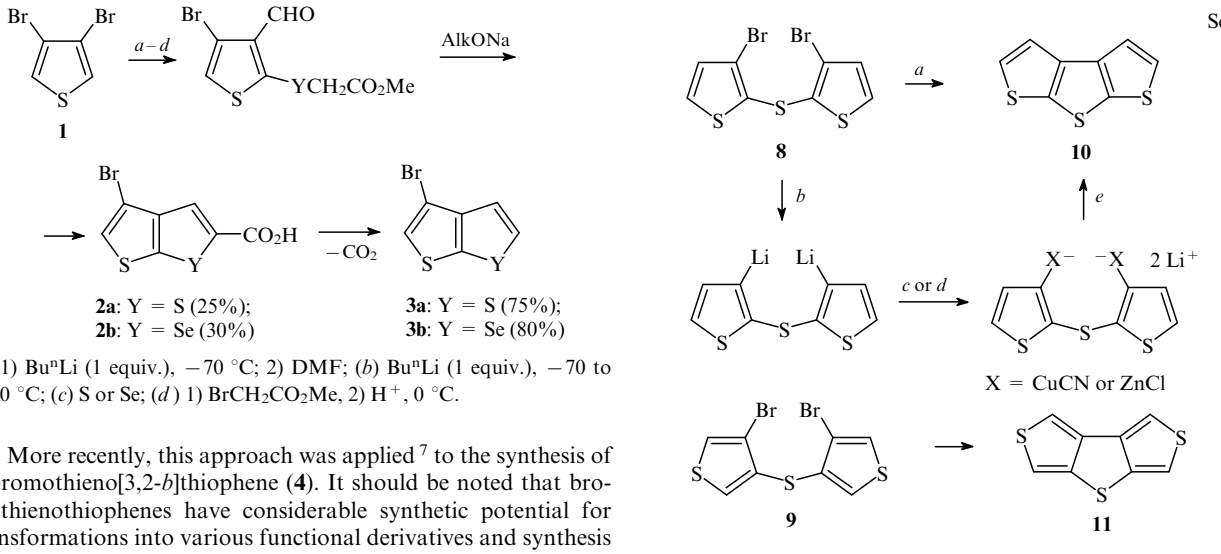
† Dedicated to Academician Yurii Bubnov on the occasion of his 70th birthday.

Scheme 1



MPA is methylphenylformamide, Quin is quinoline.

Scheme 2

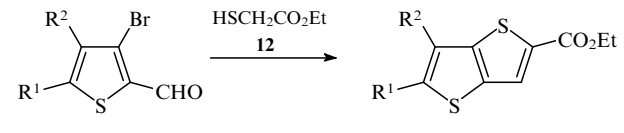


(*a*) 1) Bu^{n}Li (1 equiv.), −70 °C; 2) DMF; (*b*) Bu^{n}Li (1 equiv.), −70 to −20 °C; (*c*) S or Se; (*d*) 1) $BrCH_2CO_2Me$, 2) H^+, 0 °C.

More recently, this approach was applied [7] to the synthesis of 3-bromothieno[3,2-*b*]thiophene (**4**). It should be noted that bromothienothiophenes have considerable synthetic potential for transformations into various functional derivatives and synthesis of polyannelated thiophenes. For example, treatment of bromide **4** with Bu^{n}Li and then with di(3-thienyl) disulfide affords sulfide **5**. Oxidative cyclisation of the latter gives tetrathienocene **6**. Pentathienocene **7** was prepared according to an analogous scheme (Scheme 1).

Three approaches to the synthesis of dithieno[2,3-*b*:3′,2′-*d*]thiophene (**10**) and dithieno[3,4-*b*:3′,4′-*d*]thiophene (**11**) starting from di(bromothienyl) sulfides **8** and **9** were developed.[8,9] One procedure (conditions *a*) involves cyclisation of sulfides **8** and **9** with hexamethyldistannane catalysed by a palladium complex. Two other procedures involve lithiation, the formation of organocopper (conditions *b*, *c*, *e*) or organozinc (conditions *b*, *d*, *e*) derivatives and their oxidation by molecular oxygen (Scheme 2).

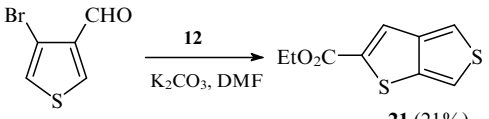
Bromine-substituted thiophenecarbaldehydes were used as the starting compounds in the synthesis of isomeric thienothiophenes.[10] The second sulfur-containing ring can be constructed using ethyl thioglycolate (**12**). The reactions of 3-bromine-substituted thiophene-2-carbaldehydes **13**–**15** with ester **12** are most often carried out in DMF in the presence of K_2CO_3 as a base.[10–15] These reactions produce thieno[3,2-*b*]thiophene-5-carboxylates **16**–**18**, whose yields vary substantially depending on the structure of the starting aldehyde. The reaction of 3,4,5-tribromo derivative **15** with ethyl thioglycolate **12** was studied under different conditions. It should be noted that the reaction in boiling anhydrous ethanol in the presence of EtONa afforded ethyl 2,3-dibromothieno[3,2-*b*]thiophene-5-carboxylate (**18**), whereas the reaction in the presence of even traces of water *in situ* was accompanied by hydrolysis of ester **18** to the corresponding carboxylic acid. In liquid ammonia, the reaction proceeds apparently through the replacement of the bromine atom (by an $S_{RN}1$ mechanism).

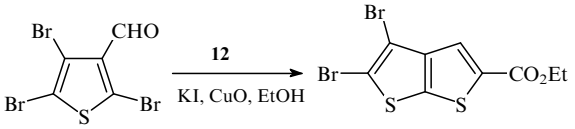


Conditions	Yield (%)	
	10	**11**
a	75	78
b, *c*, *e*	37	40
b, *d*, *e*	~70	~70

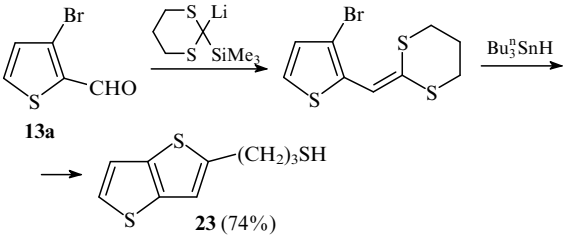
Substrate (product)	R^1	R^2	Reaction conditions	Yield (%)	Ref.
13a (**16a**)	H	H	DMF, K_2CO_3, 20 °C	95	11–13
13b (**16b**)	Me	Br	DMF, K_2CO_3, 20 °C	73	15
14 (**17**)	Br	H	DMF, K_2CO_3, 20 °C	8	10
15 (**18**)	Br	Br	DMF, K_2CO_3, 20 °C	61	10
15 (**18**)	Br	Br	EtONa, EtOH (anhydr.), 78 °C	72	10
15 (**18**)	Br	Br	NH_3 (liquid)	66	10

Analogously, thienothiophene systems **21** and **22** were derived from thiophene-3-carbaldehydes **19** and **20**, respectively [10] (*cf.* Ref. 16). Compounds **18**, **21** and **22** provide examples of isomeric thienothiophenes, which were prepared according to the same procedure but are characterised by different modes of fusion of the five-membered sulfur-containing heteroaromatic rings.

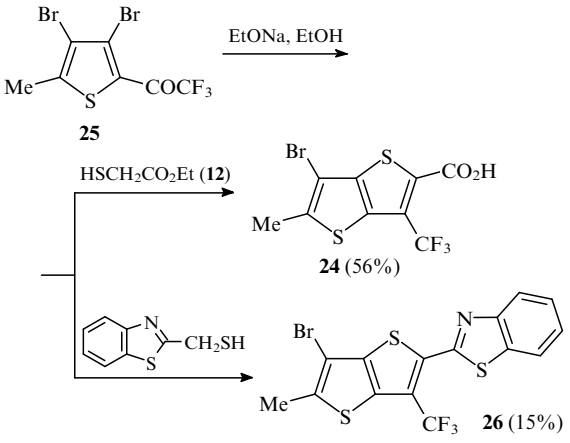




3-Bromothiophene-2-carbaldehyde **13a** served also as the starting compound in the synthesis of thieno[3,2-*b*]thiophene **23** containing the mercaptopropyl substituent.[17]

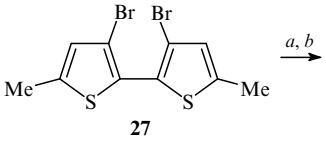


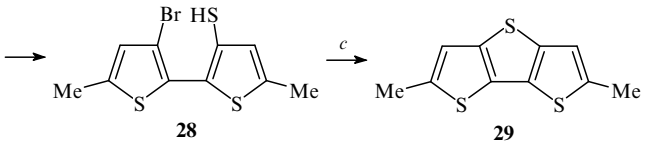
6-Bromo-5-methyl-3-trifluoromethylthieno[3,2-*b*]thiophene-2-carboxylic acid (**24**) was synthesised by the reaction of dibromo-substituted thienyl ketone **25** with ethyl thioglycolate **12** in an ethanolic solution of sodium alkoxide.



Under analogous conditions, the reaction with 2-mercaptomethylbenzothiazole afforded the corresponding 2-(benzothiazol-2-yl)thieno[3,2-*b*]thiophene derivative **26**.[14,15]

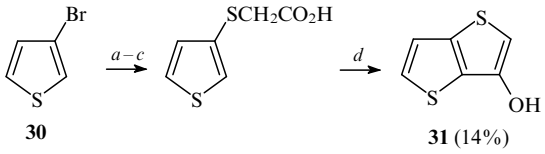
Treatment of 3,3′-dibromo-5,5′-dimethyl-2,2′-bithiophene (**27**) with Bu^{n}Li and then with elemental sulfur produced 3-bromo-3′-mercapto-5,5′-dimethyl-2,2′-bithiophene (**28**). In the presence of Cu_2O and alkali, the latter undergoes cyclisation to 2,6-dimethyldithieno[3,2-*b*:2′,3′-*d*]thiophene (**29**).[14,18] Compounds **26** and **29** were used to design new photochromic substances.[14,15,18]





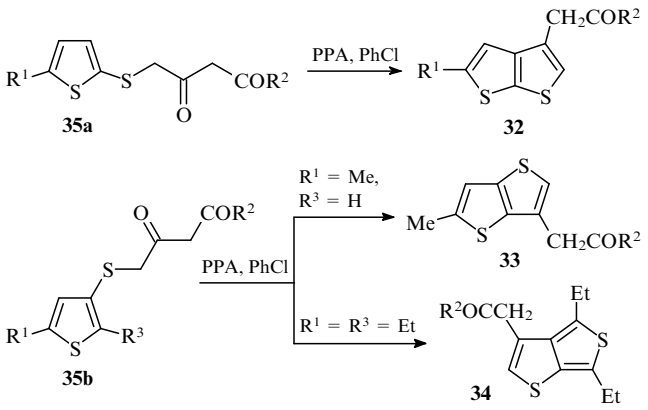
(*a*) Bu^{n}Li, C_6H_{14}, −70 °C; (*b*) S_8, −35 °C; (*c*) Cu_2O, KOH, DMF.

An analogous method was used [19] to introduce the thiol group into 3-bromothiophene **30** in the synthesis of 3-hydroxythieno[3,2-*b*]thiophene (**31**).



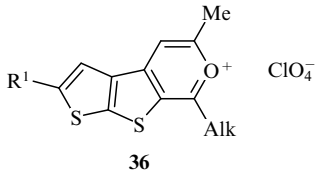
(*a*) Bu^{n}Li, −70 °C; (*b*) S_8, −70 °C, 20% NH_4Cl; (*c*) $ClCH_2CO_2H$, 40–45 °C; (*d*) H_2SO_4, 95–100 °C.

Procedures were developed [20–22] for the preparation of isomeric thienothiophenes **32**–**34** by cyclisation of methyl γ-thienylthioacetoacetates **35a**,**b** derived from substituted 3-bromothiophenes. Cyclisation occurs in chlorobenzene in the presence of polyphosphoric acid (PPA).



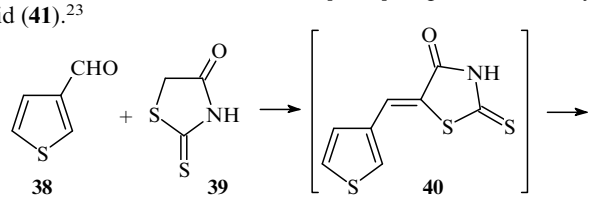
R^1 = Me, Et; R^2 = Me, OMe; R^3 = H, Et.

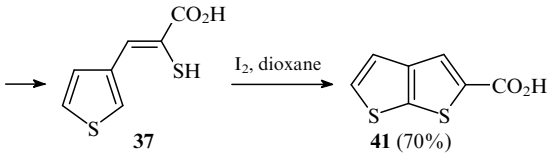
Acylation of thienothiophene derivatives **32** and **33** in an aliphatic acid anhydride–70% perchloric acid system was demonstrated to give the corresponding pyrylium salts **36** (for compounds **32**, R^2 = Me).



R^1 = Me, Et.

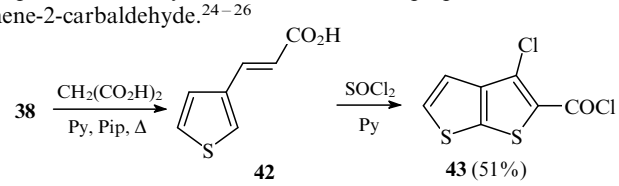
The synthesis of isomeric thienothiophenes and benzothienothiophenes was successfully carried out starting from thiophenecarbaldehydes and their derivatives. Treatment of 2-mercapto-3-(3-thienyl)acrylic acid (**37**), which was prepared in quantitative yield from thiophene-3-carbaldehyde (**38**) and 2-thioxothiazolidin-4-one (**39**) through intermediate **40**, with two equivalents of iodine in dioxane afforded thieno[2,3-*b*]thiophene-2-carboxylic acid (**41**).[23]





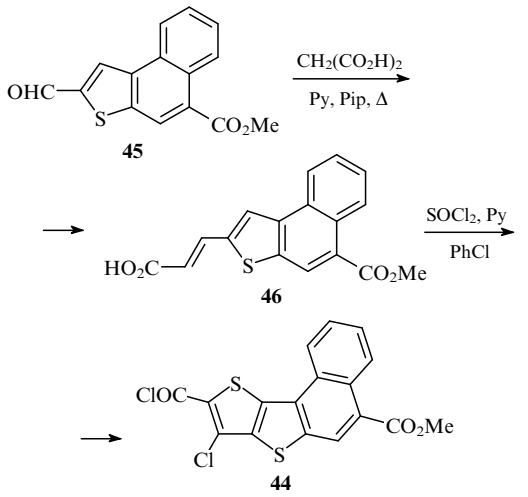
37 **41** (70%)

Condensation of thiophene-3-carbaldehyde **38** with malonic acid (Doebner reaction) in a mixture of pyridine (Py) and piperidine (Pip) performed with heating affords (*E*)-3-(3-thienyl)acrylic acid (**42**), whose treatment with thionyl chloride in pyridine produces 3-chlorothieno[2,3-*b*]thiophene-2-carboxylic acid chloride (**43**).[24,25] Analogously, 3,5-dichlorothieno[3,2-*b*]-thiophene-2-carboxylic acid chloride was prepared from thiophene-2-carbaldehyde.[24–26]



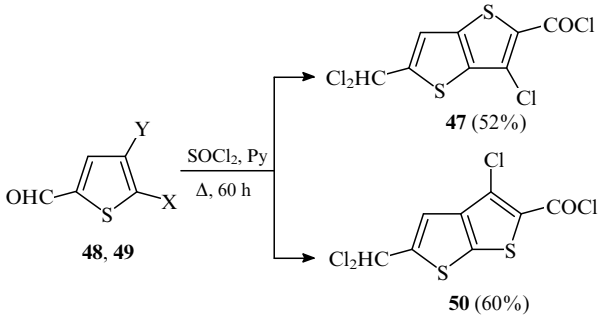
42 **43** (51%)

The same methodology was employed in the synthesis of a more complex heterocyclic system, *viz*., 3-chloro-6-methoxycarbonylnaphtho[2′,1′:2,3-*b*]thieno[4,5-*d*]thiophene-2-carboxylic acid chloride (**44**). Annelated thiophenecarbaldehyde **45** reacts with malonic acid in boiling pyridine containing two drops of piperidine to give unsaturated acid **46**, which undergoes cyclisation to acid chloride **44** upon mixing with thionyl chloride in chlorobenzene with a small admixture of pyridine.[27]



45 **46** **44**

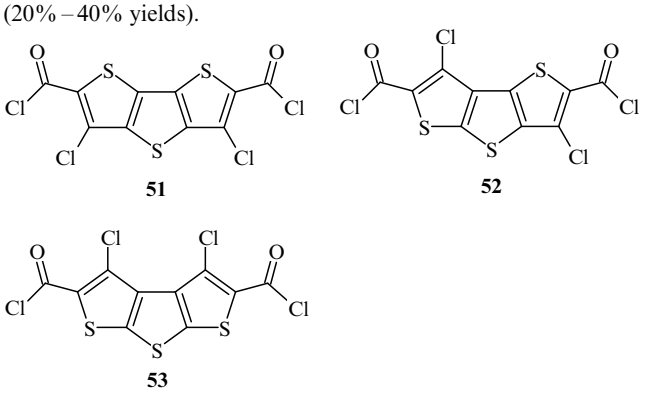
3-Chloro-5-dichloromethylthieno[3,2-*b*]thiophene-2-carboxylic acid chloride (**47**) was synthesised by the reaction of thionyl chloride in pyridine with 5-formylthiophen-2-ylacrylic acid **48**.[28] 3-Chloro-5-dichloromethylthieno[2,3-*b*]thiophene-2-carboxylic acid chloride (**50**) was prepared analogously starting from isomer **49**.



48, **49** **47** (52%) **50** (60%)

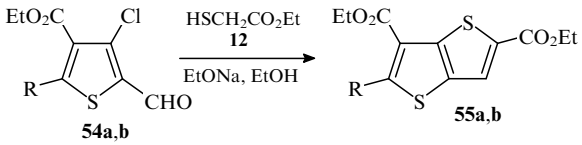
X = CH=CHCO$_2$H, Y = H (**48**); X = H, Y = CH=CHCO$_2$H (**49**).

This method was applied to the synthesis of dithienothiophenes **51**–**53** from isomeric thiophenediacrylic acids (20%–40% yields).



51 **52** **53**

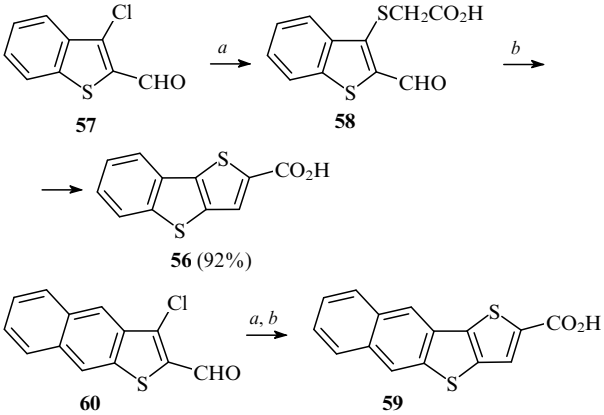
The synthesis of thieno[3,2-*b*]thiophenes and their benzo- and naphthoannelated analogues was carried out starting from 4-chloro-5-formylthiophene-3-carboxylic esters. For example, the reaction of 2-substituted ethyl 4-chloro-5-formylthiophene-3-carboxylates **54a**,**b** with ethyl thioglycolate **12** afforded the corresponding thieno[3,2-*b*]thiophene derivatives **55a**,**b** in rather high yields.[29,30]



54a,**b** **55a**,**b**

R = Me (**a**), PhNH (**b**).

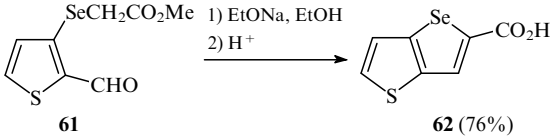
An analogous approach was employed in the synthesis of benzo[*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid (**56**) and naphtho[2,3-*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid (**59**) from substituted benzo[*b*]thiophene-2-carbaldehyde **57**[31] (through thioglycolic acid derivative **58**) and naphtho[2,3-*b*]thiophene-2-carbaldehyde **60**, respectively.[32]



57 **58** **56** (92%) **60** **59**

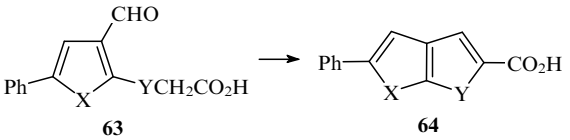
(*a*) HSCH$_2$CO$_2$H; (*b*) 30% KOH, 80–90 °C, 30 min.

Substituted thiophenecarbaldehydes were also used in the synthesis of thienothiophene-related systems. For example, cyclisation of thiophene-containing methyl selanylacetate **61** in the presence of EtONa in ethanol afforded selenopheno[3,2-*b*]thiophene-5-carboxylic acid (**62**).[33,34]



61 **62** (76%)

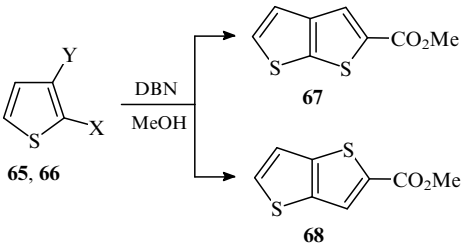
Furo-, pyrrolo-, selenopheno- and thieno[2,3-*b*]thiophene-2-carboxylic acids **64** were synthesised from various heterocyclic 2-chalcogenoacetic acids **63**.[35]



63 **64**

X = NMe, O, S; Y = S, Se.

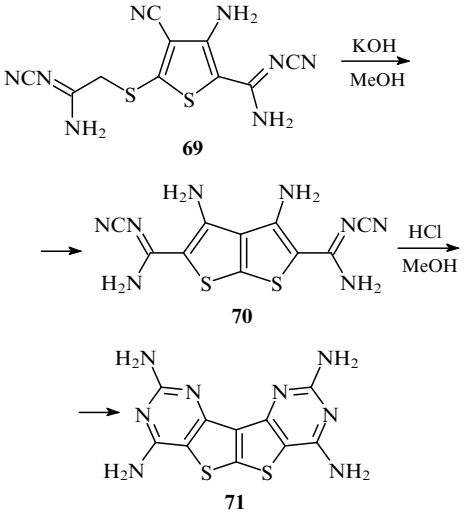
Cyclisation of isomeric thiophenes **65** and **66** containing the aldehyde function and the SCH_2CO_2Me group at positions 2 and 3 by the reactions with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) affords methyl thieno[2,3-*b*]- (**67**) and -[3,2-*b*]thiophene-2-carboxylates (**68**), respectively.[36]



65, **66** **67** **68**

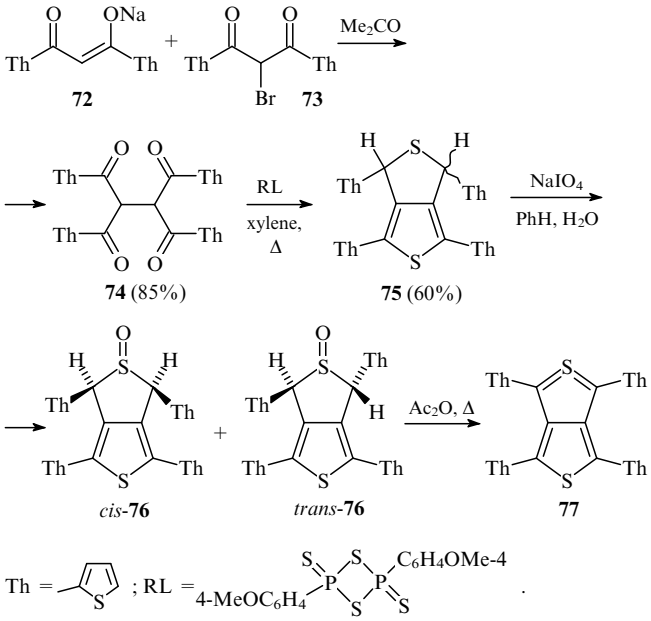
X = SCH_2CO_2Me, Y = CHO (**65**);
X = CHO, Y = SCH_2CO_2Me (**66**).

Intramolecular condensation was used also in the synthesis of more complex substances, including thienothiophenes containing various functional groups. The ester and nitrile functions can serve as the 'carbonyl component'.[37,38] Among examples of the synthesis of the thienothiophene system, worthy of mention is the transformation of thiophene-4-carbonitrile **69** in the reaction with KOH giving rise to 3,4-diamino-2,5-di[amino(cyanoimine)methyl]thieno[2,3-*b*]thiophene (**70**), which is cyclised to symmetrical tetracycle **71**.[39,40]



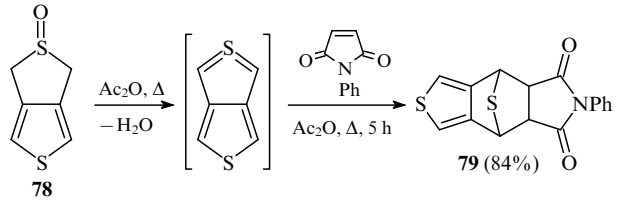
69 **70** **71**

Thiophene derivatives were also used in the synthesis of derivatives of the fourth, the so-called non-classical, isomer of thienothiophene, *viz*., thieno[3,4-*c*]thiophene.[41,42] For example, the reaction of a sodium salt of dithenoylmethane (**72**) and bromodithenoylmethane (**73**) in acetone produced 1,1,2,2-tetra-2-thenoylethane (**74**). Sulfonation of the latter with Lawesson's reagent (RL) in boiling xylene afforded a mixture of two stereoisomeric 1,3-dihydrothieno[3,4-*c*]thiophenes (**75**). This mixture was oxidised without purification and then chromatographed on silica gel (CCl_4 as the eluent) to isolate individual *cis*- and *trans*-sulfoxides **76**. Dehydration of an unseparated mixture of isomers **76** in boiling acetic anhydride under nitrogen produced 1,3,4,6-tetra-2-thienylthieno[3,4-*c*]thiophene (**77**) in 84% yield, whereas the yield of the product in an analogous transformation of the *cis*-isomer of **76** decreased to 68%.[41]



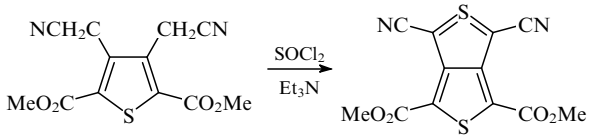
72 **73** **74** (85%) **75** (60%) *cis*-**76** *trans*-**76** **77**

Unsubstituted thieno[3,4-*c*]thiophene was synthesised for the first time by Pummerer dehydration of 1*H*,3*H*-thieno[3,4-*c*]thiophene 2-oxide (**78**).[42] This compound was characterised using chemical traps (for example, as adduct **79** with *N*-phenylmaleimide).[43]



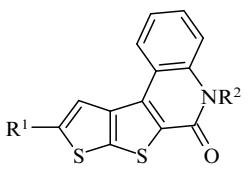
78 **79** (84%)

The reaction of thienyldinitrile **80** with thionyl chloride in the presence of triethylamine gives thieno[3,4-*c*]thiophene **81** containing only electron-withdrawing substituents.[44,45] This compound is very stable in the solid state.



80 **81** (70%)

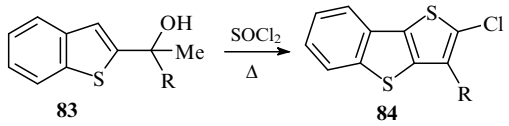
Multistep syntheses involving aldol condensation of thiophene-3-carbaldehyde **38** with malonic acid or the Heck reaction using 3-bromothiophene **30** or 4-bromothiophene-2-carboxylate produced thieno[3′,2′:4,5]thieno[2,3-*c*]quinolones **82**, which exhibit high antitumour activity.[46]



82

R^1 = H, MeO_2C, $Me_2N(CH_2)_3NH$, $Me_2N(CH_2)_3NPh$;
R^2 = H, $Me_2N(CH_2)_3$.

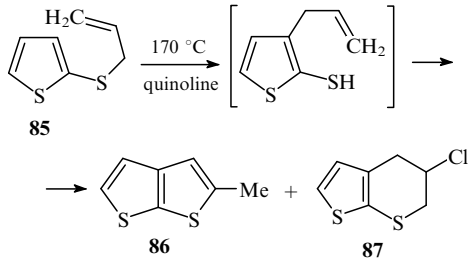
Benzothiophenes **83** containing the tertiary alcoholic group undergo cyclisation in the presence of thionyl chloride.[47] The reaction affords benzo[*b*]thieno[3,2-*b*]thiophenes **84**.



83 **84**

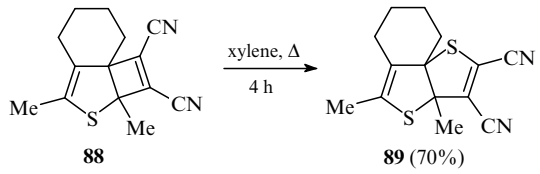
R = Pr^i, Bu^t.

Isomeric thienothiophenes can also be synthesised from other thiophene derivatives. In the studies of the 3,3-sigmatropic rearrangement of allyl 2-thienyl sulfide (**85**), 2-methylthieno[2,3-*b*]thiophene (**86**) and 3-chloro-3,4-dihydro-2*H*-thieno[2,3-*b*]thiopyran (**87**) were isolated from the reaction mixture in a total yield of up to 60%.[48–50]



85 **86** **87**

Refluxing of sulfur-containing tricyclic dinitrile **88** in xylene was found to give 3*a*,5-dimethyl-3*aH*-6,7,8,9-tetrahydrobenzo[*c*]thieno[3,2-*b*]thiophene (**89**).[51]



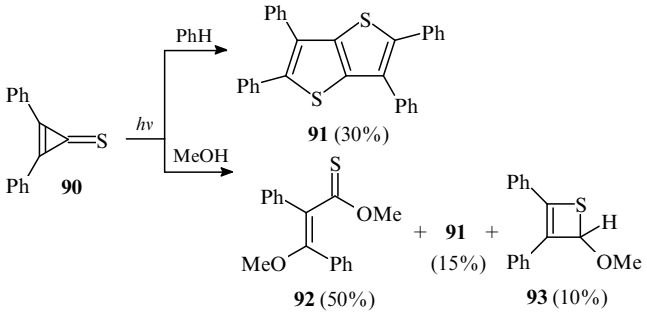
88 **89** (70%)

Analysis of the above methods for the synthesis of thienothiophenes and their analogues based on thiophene derivatives demonstrates that mono- and dibromo-substituted thiophenes are most often and successfully used as the starting compounds. It should be noted that intramolecular cyclisation of compounds derived from the above-mentioned thiophenes serves as the key step in this approach. In this step, vicinal carbonyl functions (generally, formyl or acyl) interact with fragments containing the activated methylene group.

2. Cyclopropenethiones in the synthesis of thienothiophenes

Cyclopropenethiones are transformed into thienothiophenes both under irradiation and on heating. However, this method has not received wide acceptance because the starting compounds are difficult to prepare and also because of low yields of the desired products.

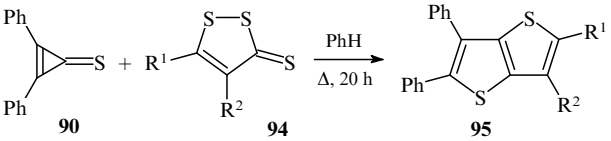
Photodimerisation of 2,3-diphenylcyclopropenethione (**90**) in benzene[52] occurs regioselectively to give the expected 2,3,5,6-tetraphenylthieno[3,2-*b*]thiophene (**91**). This reaction in methanol



90 **91** (30%) **92** (50%) **91** (15%) **93** (10%)

afforded methyl 1-methoxy-2-phenylthiocinnamate (**92**) as the major product; in addition, thienothiophene **91** and 3,4-diphenyl-2-methoxythiethane (**93**) were isolated as by-products.[53, 54]

Refluxing of cyclopropenethione **90** with 4,5-disubstituted 1,2-dithiol-3-thiones **94** in anhydrous benzene in the dark is accompanied by elimination of two sulfur atoms to form thieno[3,2-*b*]thiophenes **95**.[55]

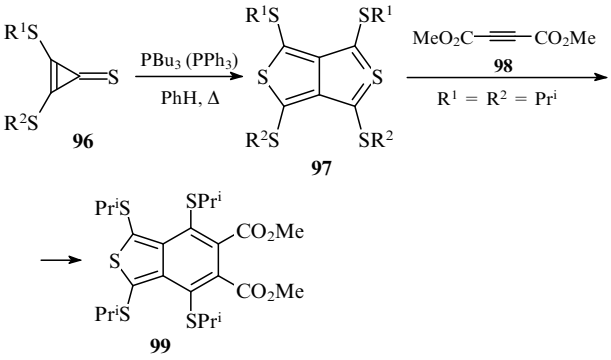


90 **94** **95**

R^1 = R^2 = Me, Ph; R^1–R^2 = $(CH_2)_4$, $(CH=CH)_2$.

Refluxing of 1,2-dithiole-3-thione **94** (R^1 = R^2 = Ph) with powdered copper in chlorobenzene (6.5 h) led to its cyclisation to thienothiophene **91** in 39% yield.[56, 57]

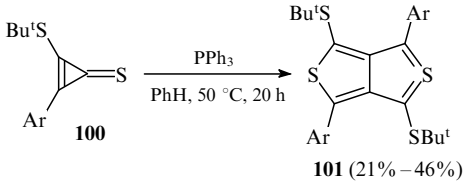
In the presence of triphenyl- or tributylphosphine, 2,3-di-(alkylthio)cyclopropenethiones **96** are dimerised (refluxing in benzene under nitrogen, 4 h) to 1,3,4,6-tetra(alkylthio)-thieno[3,4-*c*]thiophenes (**97**) in moderate yields.[58, 59] The authors of the cited study also demonstrated that thienothiophene **97** (R^1 = R^2 = Pr^i) is involved in cycloaddition with dimethyl acetylenedicarboxylate (**98**) to form 5,6-dimethoxycarbonylbenzo[*c*]-thiophene (**99**).



96 **97** **98** **99**

R^1 = Pr^i, Bu^t; R^2 = Me, Et, Pr^i, Bu^t.

More recently,[60, 61] 1,4-bis(*tert*-butylthio)-3,6-diarylthieno[3,4-*c*]thiophenes **101** were prepared by treatment of cyclopropenethiones **100** with triphenylphosphine (benzene, 50 °C, argon atmosphere).



100 **101** (21%–46%)

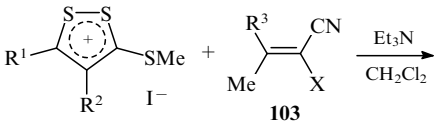
Ar = Ph, thien-2-yl.

An analogous procedure involving the reaction of cyclopropenethiones with tributylphosphine was employed in the synthesis of substituted thieno[3,2-*b*]thiophenes.[62]

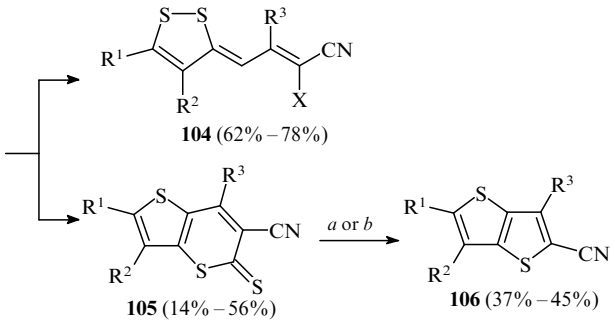
3. Dithiynes in the synthesis of thienothiophenes

The use of dithiynes for the preparation of thienothiophenes is exemplified by four types of reactions. For example, 3-methylthio-1,2-dithiolium ions **102** react with malonic acid derivatives **103** to give γ-dithiolylidene nitriles **104** and 6-cyanothieno[3,2-*b*]thiopyranothiones **105**. Oxidation of the latter with H_2O_2 in acetic acid or successive treatment of **104** and **105** with NaOH and $BrCH_2CN$ affords 2-cyanothieno[3,2-*b*]thiophenes **106**.[63] This method was

applied to the synthesis of a rather broad range of nitrile-containing thienothiophenes promising for further modifications.



102 **103**

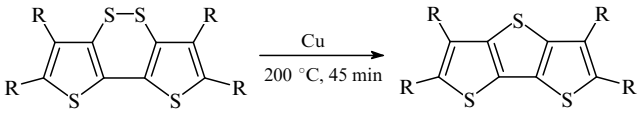


104 (62% – 78%)

105 (14% – 56%) **106** (37% – 45%)

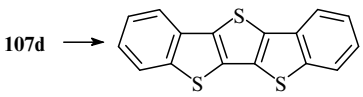
R^1 = H, Bu, SMe, Ph, 4-$MeOC_6H_4$; R^2, R^3 = Ph, 4-$MeOC_6H_4$; X = CN, CO_2Et; (*a*) H_2O_2, AcOH; (*b*) 1) NaOH, 2) $BrCH_2CN$.

Heating of dithienoannelated 1,2-dithiynes **107a – c** with powdered copper (200 °C, 45 min) afforded dithieno[3,2-*b*:2′,3′-*d*]thiophenes **108a – c**.[64,65] An analogous transformation of benzoannelated dithiyne **107d** [R – R = $(CH=CH)_2$] produced bis(benzo[4,5]thieno)[3,2-*b*:2′,3′-*d*]thiophene (**108d**).[66]



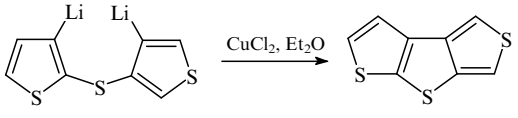
107a – c **108a – c** (50% – 70%)

R = H (**a**), Me (**b**), Ph (**c**).



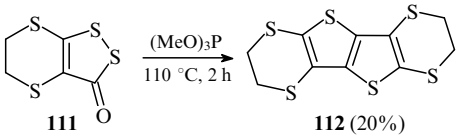
108d (53%)

Unsubstituted dithienothiophene **108a** has been synthesised earlier by treating 2,2′-dilithium 3,3′-dithienyl sulfide with copper dichloride in diethyl ether.[67] This method was also successfully applied to oxidative cyclisation of the corresponding dilithium dithienyl sulfide **109** giving rise to dithieno[2,3-*b*:3′,4′-*d*]thiophene (**110**) (29% yield).[68] The above-described dithieno[2,3-*b*:3′,2′-*d*]thiophene (**10**) (32%) and dithieno[3,4-*b*:3′,4′-*d*]thiophene (**11**) (31%) were synthesised analogously (see Section II.1).[68]



109 **110** (29%)

Heating of a suspension of 4,5-ethylenedithio-1,2-dithiol-3-one (**111**) in trimethylphosphite under nitrogen (110 °C, 2 h) afforded 2,3:5,6-bis(ethylenedithio)thieno[3,2-*b*]thiophene (**112**).[69]



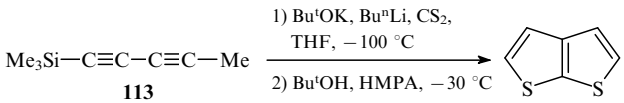
111 **112** (20%)

It should be noted that almost all the above-described reactions gave products in low yields. Hence, this approach is of theoretical rather than preparative interest.

4. Carbon disulfide in the synthesis of thienothiophenes

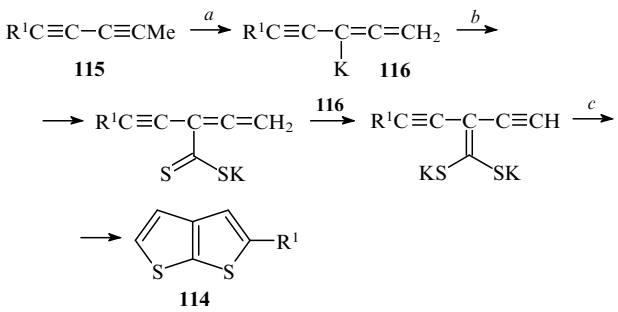
Methods based on the reactions of carbon disulfide with compounds containing conjugated triple-bond systems or the active methylene group are rather successfully employed in the synthesis of thienothiophenes. Generally, these procedures involve many steps, which require a thorough preparation and purification of the reagents and solvents.

Unsubstituted thieno[2,3-*b*]thiophene was synthesised in satisfactory yield from trimethylsilylpenta-1,3-diyne (**113**) under very mild conditions. In this procedure, the reagents should be added in a reverse order: n-butyllithium is initially added to a suspension of Bu^tOK in dry THF at −100 °C followed by the addition of alkyne at −80 °C, CS_2 at −100 °C and a solution of Bu^tOH in dry HMPA at −30 °C.[70]



113 (47%)

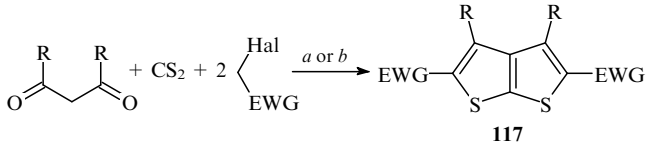
In the studies,[71–73] a one-pot procedure was developed for the synthesis of thieno[2,3-*b*]thiophenes **114** using diynes **115** and CS_2 as the building blocks (in 44% – 48% yields). Allene derivative **116** was detected as an intermediate. If the trimethylsilyl group is present as a substituent at the triple bond, it is eliminated during the reaction (as in the above-considered reaction).



115 **116** **114**

R^1 = Me_3Si (H for **114**), Alk, $N(Alk)_2$, SAlk;
(*a*) Bu^nLi, Bu^tOK, THF, C_6H_{14}; (*b*) CS_2, −100 °C; (*c*) Bu^tOH, HMPT (HMPT is hexamethylphosphorous triamide).

A technologically convenient one-pot synthesis of 2,5-functionalised thieno[2,3-*b*]thiophenes **117** starting from 1,3-diketones was proposed. In this procedure, carbon disulfide and alkylating agents containing electron-withdrawing groups are used. The reaction proceeds either in dry DMF in the presence of anhydrous KF as a promoter for condensation (36% – 67% yields)[74] or under phase-transfer catalysis conditions (78% – 93% yields)[75] (see also Ref. 76).

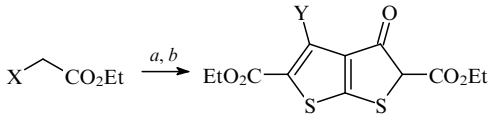


117

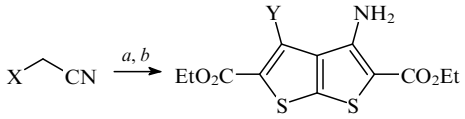
R = Me, Ph, 4-MeC_6H_4 (*p*-Tol); Hal = Br, Cl; EWG = CN, Ac, CO_2Et, CONHPh, CONH-thiazol-2-yl;
(*a*) KF, DMF; (*b*) K_2CO_3, Bu^n_4NBr, PhH, H_2O.

More recently,[77] this approach was extended to the synthesis of oxo- and amino-substituted thieno[2,3-*b*]thiophenes. Compounds containing the active methylene group (3-keto esters, malononitrile, ethyl cyanoacetate or 3-ketonitrile) were used as the starting reagents, and ethyl bromoacetate or bromoacetic acid

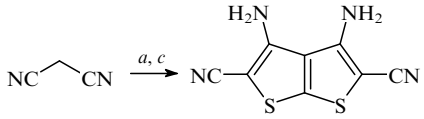
nitrile served as the alkylating agent. The yields of thienothiophenes were 61% – 87%.



X = Ac, CN; Y = Me, NH_2;

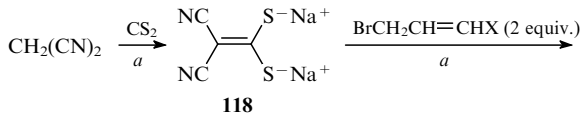


X = Piv, CN; Y = Bu^t, NH_2;

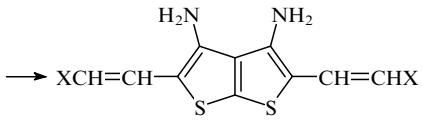


(*a*) CS_2, K_2CO_3, DMF; (*b*) $BrCH_2CO_2Et$ (2 equiv.); (*c*) $BrCH_2CN$ (2 equiv.); Piv = $Bu^tC(O)$.

The reactions of carbon disulfide with malononitrile in the presence of sodium methoxide in methanol followed by treatment of the resulting dicyanodithioacetate **118** with γ-bromocrotonic acid derivatives can also be assigned to this reaction type.[78] These reactions give diamino-substituted thienothiophenes **119** as the final products.



118

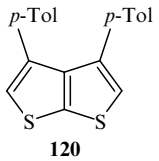


119 (45% – 78%)

X = CN, CO_2Me; (*a*) MeONa, MeOH.

Dinitrile **118** was also used in the synthesis of other thieno[2,3-*b*]thiophene derivatives.[79] Various tri- and tetrasubstituted thieno[2,3-*b*]thiophenes were prepared according to modifications of this procedure.[80 – 83]

The synthesis of *peri*-substituted 3,4-diarylthienothiophene **120** from $(4\text{-}MeC_6H_4CH_2)_2CO$ through the corresponding ketene dithioacetal, Dieckmann cyclisation, hydrolysis and decarboxylation was described in the study.[84]

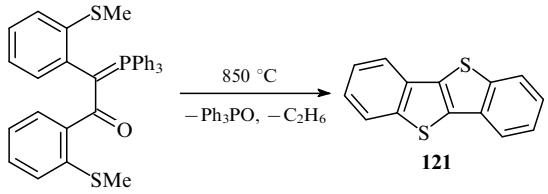


120

5. High-temperature synthesis

High-temperature synthesis of sulfur-containing heteroaromatic systems has attracted attention of researchers (predominantly, of Russian scientists) in the last 30 years. This method assumes the use of both a broad range of the starting substrates (aliphatic, aromatic, heteroaromatic compounds) and various sulfur donors (elemental sulfur, hydrogen sulfide, dialkyl sulfides).

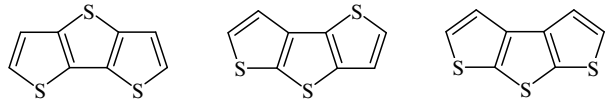
Friedmann was the first to describe the formation of thienothiophenes under pyrolysis conditions in 1916.[85 – 88] The reaction of aliphatic or aromatic hydrocarbons with sulfur proceeds at 270 – 320 °C and high pressure. More recently, this method was applied to the synthesis of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene (**121**) in yields of up to 50% starting from benzyl bromide and its derivatives,[89,90] 1,2,3-trichloro-1,2-diphenylethane[91] or *o*-halotoluenes[92] at 200 – 280 °C. Compound **121** was also prepared in 36% yield by tandem radical cyclisation of 2-methylthiophenyl-substituted phosphorus ylide **122** under conditions of flash vacuum pyrolysis at 850 °C.[93,94]



122 **121**

In addition, thienothiophene **121** was synthesised by gas-phase pyrolysis of benzotrichloride at 400 °C in a hydrogen sulfide atmosphere (67% yield).[95]

1,2-Dichloroethylene reacts with hydrogen sulfide in the gas phase at 420 – 520 °C in a quartz tube. The reaction produced a complex mixture, in which thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene were detected (in a total yield of 4.5%).[96,97] Thieno[2,3-*b*]thiophene was prepared by the gas-phase reaction of 2-chlorothiophene with hydrogen sulfide and acetylene at 600 °C.[98] The reaction with the use of dimethyl selenide instead of acetylene afforded a mixture of dithienothiophene **108a** and dithieno[3,2-b;2,3-*d*]thiophene (**123**) (3% yield).[99] The formation of dithienothiophene **10** along with other products was observed upon thermolysis (500 – 600 °C) of 2,2′-dithienyl sulfide under an atmosphere of nitrogen and hydrogen sulfide,[100] whereas dithienothiophenes **10** and **108a** were generated in a hydrogen sulfide atmosphere.[101]



108a **123** **10**

Thieno[2,3-*b*]thiophene was also prepared by the high-temperature reaction of 2-chlorothiophene with acetylene and hydrogen sulfide[102,103] or dimethyl sulfide[103] and by the reaction of thiophene-2-thiol with acetylene.[104] An analogous reaction of 2-chlorothiophene with a mixture of diethyl di- and trisulfides produces a mixture of thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene in 10% – 32% yields.[105] This reaction in the presence of acetylene affords a mixture of thienothiophenes in somewhat higher yield (36%).[106]

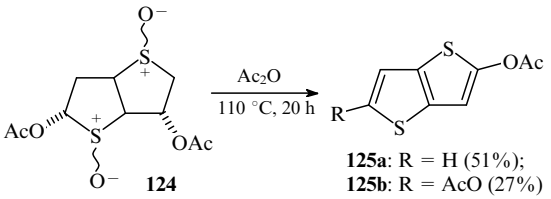
A mixture of thiophene and isomeric thienothiophenes (in a total yield of 85%) was prepared by the gas-phase reaction of dimethyl sulfide, diethyl disulfide, diethyl trisulfide and diethyl tetrasulfide with acetylene.[107] It was also found that gaseous allyl 2-thienyl sulfide is transformed into a mixture of thiophene-2-thiol, bis(2-thienyl) sulfide and 2-methylthieno[2,3-*b*]thiophene at 350 – 410 °C; in the presence of acetylene, the reaction gives these products along with thieno[2,3-*b*]thiophene.[108] Thermolysis (at 540 °C) of a mixture of di(prop-1-enyl) sulfide and 2-chloro(or bromo)thiophene affords a mixture of thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene.[109]

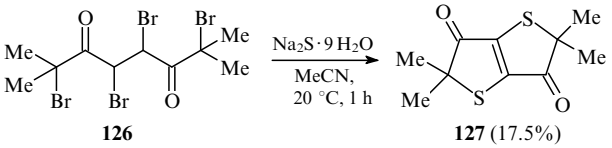
Therefore, the advantage of this method is that the starting compounds are readily available. Among the drawbacks are the necessity of using special apparatus, the formation of a large number of by-products in almost all reactions and low yields of the desired compounds.

6. Other methods for the synthesis of thienothiophenes and their analogues

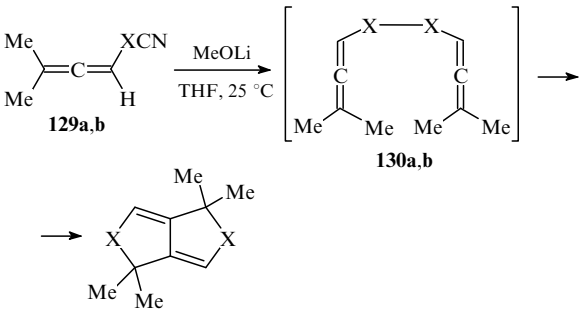
There are a few original procedures, which were used to prepare particular representatives of this class of heterocyclic compounds and their selenium and tellurium-containing analogues. The most interesting procedures are considered below.

Among other approaches to the synthesis of thienothiophenes, worthy of mention are the Pummerer rearrangement of disulfoxide **124** giving a mixture of 2-acetylthieno[3,2-*b*]thiophenes **125a**,**b**[110] and the reaction of 2,4,5,7-tetrabromo-2,7-dimethyl-3,6-octanedione (**126**) with sodium sulfide hydrate yielding 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene-3,6-dione (**127**).[111]



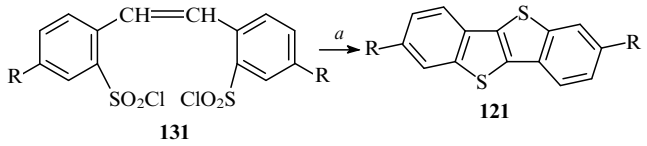


Substituted tetrahydrothieno[3,4-*c*]thiophene (**128a**) and its selenium analogue (**128b**) were synthesised by the reactions of lithium methoxide with γ,γ-dimethylallenyl thio(or seleno)cyanates **129a**,**b**.[112–114] The multistep mechanism of this reaction involves the formation of bis(dimethylallenyl) chalcogenides **130a**,**b** as the key intermediates, which undergo successive [3,3]-sigmatropic rearrangement and double Michael addition of a chalcogen-containing group.



X = S (**a**), Se (**b**).

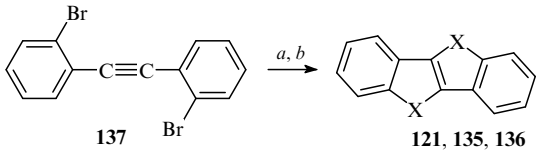
A new procedure was developed for the synthesis of benzoannelated thienothiophene based on reduction of stilbene-2,2′-disulfochloride (**131**) with concentrated hydroiodic acid in acetic acid.[115–118] This approach is applicable also to the synthesis of 2,7-disubstituted derivatives of thienothiophenes **121** starting from the corresponding 4,4′-disubstituted disulfochlorides.



R = H (79%), NH_2; (*a*) 55% HI, AcOH, 100 °C, 8 h.

Diethyl 2,2′-dinitro-(*E*)-stilbene-4,4′-dicarboxylate **132** proved to be a convenient starting compound in the synthesis of diethyl benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene-2,7-dicarboxylate (**133**) and its selenium analogue **134** (Scheme 3).[119]

Sulfur-, selenium- and tellurium-containing heteroaromatic systems **121**, **135** and **136** were prepared by successive treatment of 2,2′-dibromodiphenylacetylene (**137**) with *tert*-butyllithium and chalcogens in anhydrous tetrahydrofuran at −80 °C under argon.[120]



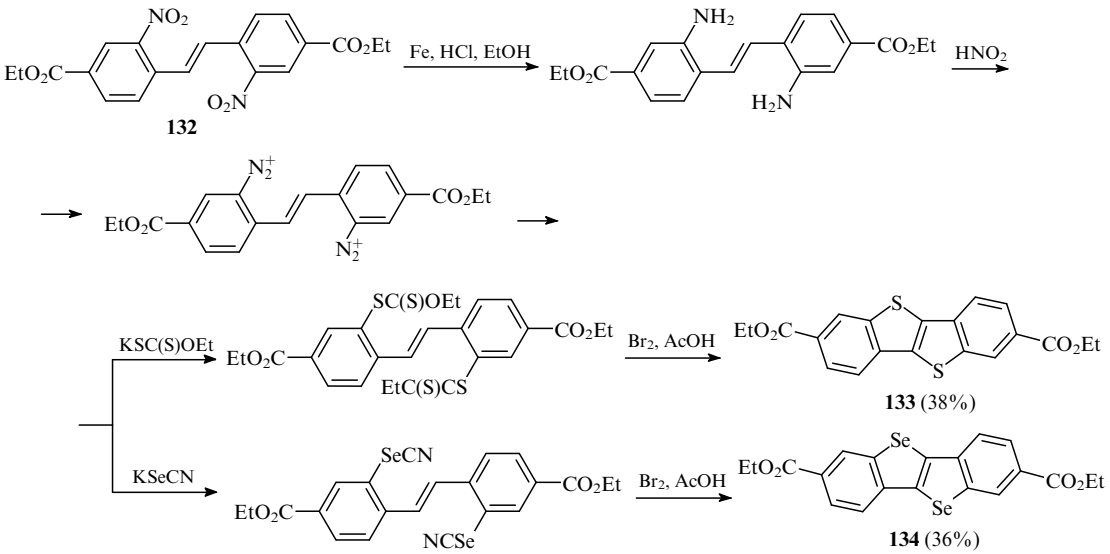
X = S (**121**, 49%), Se (**135**, 52%), Te (**136**, 55%);
(*a*) Bu^tLi, THF, −80 °C, Ar; (*b*) chalcogen (S, Se or Te).

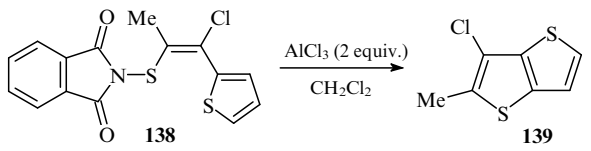
A selenium modification of the Claisen rearrangement of propargylselenochalcogenophenes was employed in the synthesis of fused bicyclic systems, *viz*., thieno[2,3-*b*]-2*H*-selenopyran, thieno[3,2-*b*]-2*H*-selenopyran, 5-methylselenopheno[2,3-*b*]tellurophene and 5-methylselenopheno[3,2-*b*]thiophene.[121]

The reactions of sulfur with dimethylformamide dimethylacetal[122] and 2,5-dimethylhex-3-yne-2,5-diol[123] give substituted thieno[3,2-*b*]thiophenes.

The reaction of sulfenamide **138** with two equivalents of aluminium chloride produces 3-chloro-2-methylthieno[3,2-*b*]thiophene (**139**) in satisfactory yield.[124]

Scheme 3





138 **139**

Methyl 3-hydroxythieno[2,3-*b*]thiophene-2-carboxylates were also synthesised by cyclisation of substituted methyl 3-hydroxythiophene-2-carboxylates.[125]

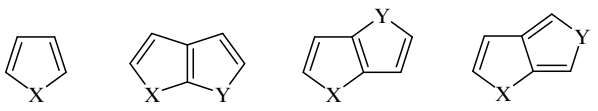
Therefore, the above data demonstrates the diversity of synthetic approaches to thienothiophene derivatives.

III. Reactivity and chemical transformations

Heteroatoms in the five-membered π-excessive heteroaromatic compounds are responsible for the chemical behaviour of the molecules as a whole. The heteroatoms not only give electrons to form an aromatic π-electron system but also determine the direction of the attack of electrophilic or nucleophilic agents. In fused π-excessive heterocycles containing two or more heteroatoms, the reactivity of compounds and their physical properties are substantially affected by both the mutual arrangement of the heteroatoms and the electronic effects associated with their nature.

1. Reactivity

First studies of the reactivity of thienothiophenes and their analogues by quantum-chemical methods were carried out in the mid-1970s.[2, 5, 126] More recently,[127, 128] the reactivity of thiophene, selenophene, various isomeric thienothiophenes, selenophenothiophenes, selenophenoselenophenes and their various C-protonated forms (σ complexes) in electrophilic substitution reactions was estimated by the semiempirical LCAO SCF MO method for all valence electrons (CNDO/2). The charges on the carbon atoms Q_c (static index) and the localisation energy Λ^+ (dynamic index; in the CNDO/2 approximation, this index is determined as $\Lambda^+ = E_{total}M - E_{total}MH^+$, where $E_{total}M$ and $E_{total}MH^+$ are the total energies of the aromatic molecule and its σ complex with a proton, respectively) were used as the reactivity indices. The method of reactivity indices supplemented by a 'pseudoatom' approach (pseudoatoms simulate an electrophilic agent) provides a correct interpretation of experimental data on electrophilic substitution in fused heteroaromatic systems containing various heteroatoms. In addition, the values of Q_c and Λ^+ (relative to position 3 in thiophene) indicate that the direction of electrophilic attack depends on the nature and size of the attacking species. This effect is mainly responsible for the difference in the reactivity of substrates.



140, 141 **142 – 144** **145 – 147** **148 – 151**

The results of calculations made it possible to arrange the relative reactivities of different positions in compounds **140 – 151** in electrophilic substitution reactions in the following theoretical series: C(4) (**150**) > C(4) (**148**) > C(4) (**151**) > C(4) (**149**) > C(6) (**150**) > C(6) (**148**) > C(6) (**151**) C(6) (**149**) > C(2) (**146**) > C(2) (**145**) > C(5) (**146**) > C(2) (**147**) > C(2) (**143**) > C(2) (**149**) > > C(2) (**142**) > C(2) (**148**) > C(2) (**144**) > C(2) (**151**) > C(5) (**143**) > C(2) (**150**) > C(2) (**140**) > C(2) (**141**) > C(3) (**149**) > > C(3) (**143**) > C(3) (**148**) > C(3) (**144**) > C(3) (**151**) > C(3) (**142**) > C(3) (**150**) > C(4) (**143**) > C(3) (**146**) > C(3) (**145**) > C(3) (**147**) > C(6) (**146**) > C(3) (**147**) > C(3) (**140**).[5] This series was confirmed experimentally. For example, the following series of reactivities of different positions in these compounds was obtained in studies of acetylation, formylation and chlorination of thiophene (**140**), thieno[2,3-*b*]thiophene (**142**) and thieno[3,2-*b*]thiophene (**145**): C(2) (**145**) > C(2) (**142**) > C(2) (**140**) > C(3) (**142**) > C(3) (**145**) > C(3) (**140**).[129] In formylation, position 4 in thieno[3,4-*b*]thiophene (**148**) was found[130] to be more readily subjected to the attack of an electrophilic species compared to position 6.

The detritiation rate was studied for thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**), dithieno[2,3-*b*:3′,2′-*d*]thiophene (**10**), dithieno[3,2-*b*:2′,3′-*d*]thiophene (**108a**) and dithieno[2,3-*d*:2′,3′-*d*]thiophene (**123**), which are specially labelled with the ^3H isotope at each position, in trifluoroacetic acid or its mixture with acetic acid.[131, 132] All thiophene systems were demonstrated to be rather active in electrophilic substitution reactions. The reactivity of the corresponding α and β positions slightly increases in going from thiophene to thienothiophenes and increases to an even larger extent in going from thienothiophenes to dithienothiophenes.

The comparative reactivities in electrophilic substitution of selenopheno[3,2-*b*]thiophene (**143**) and -selenophene (**144**) with respect to thieno[3,2-*b*]thiophene (**142**) were studied by the method of competitive reactions.[133] The reactivity was found to change in the following order: **144** > **143** > **142**. This series agrees well with a higher substitution rate in selenophene compared to thiophene in acetylation, formylation and chlorination reactions.

Competitive metallation of two-component systems, *viz*., thieno[3,2-*b*]thiophene (**142**) and selenopheno[3,2-*b*]thiophene (**143**), selenophenothiophene **143** and thiophene (**140**), selenophenothiophene **143** and selenophene (**141**), thiophene (**140**) and selenophene (**141**), was investigated.[34] The reactions were carried out with a deficient amount of Bu^nLi in anhydrous diethyl ether at 25 ± 1 °C followed by hydrolysis with heavy water. Mass-spectrometric analysis of the products demonstrated that the relative reactivities of the compounds increase in the following order: **143** > **142** > **141** > **140**.[34]

The reactivities of thieno[2,3-*b*]thiophene (**142**) and selenopheno[2,3-*b*]thiophene (**143**) were also compared using competitive acetylation of their mixture with thiophene (**140**) or selenophene (**141**) by acetyl chloride in the presence of tin chloride ($CHCl_3$, 25 °C).[35] The selenophene rings were found to be more reactive than the thiophene ring.

The above examples demonstrate that the theoretical estimates of the reactivities of the compounds in electrophilic substitution reactions most typical of aromatic systems agree well with the experimental data.

2. Chemical transformations

In the last 20 years, studies of chemical transformation of isomeric thienothiophenes have been aimed primarily at examining the possibilities of using these substrates in the synthesis of new polyannelated heteroaromatic systems and compounds possessing practically useful properties. These compounds can exhibit both electron-withdrawing and electron-donating properties and they were used in the synthesis of numerous charge-transfer complexes. Thienothiophene derivatives have found application as medicines, pesticides, conducting polymers, liquid and clathrate crystals, organic conductors or superconductors, photosensitive receptors, materials for optoelectronics (nonlinear optical chromophores), dyes, *etc*. The most typical reactions of this class of compounds (metallation, condensation and photochemical cyclisations) clearly illustrate their high synthetic potential.

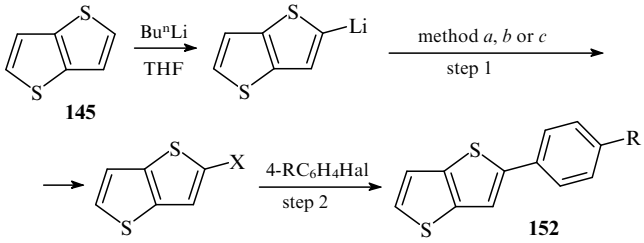
a. Metallation

Lithiation (generally, with n-butyllithium) is most often and successfully used in the synthesis of various functionalised thienothiophenes. The lithium intermediates thus formed can react with various electrophiles.

For example, thieno[3,2-*b*]thiophene (**142**)[134 – 141] and its alkyl derivatives[136, 137, 142, 143] are readily metallated with n-butyllithium at the α position, which can be used for the preparation of α-substituted thienothiophenes. This method was employed to introduce such substituents as Br,[139] I,[134] MgBr,[143] ZnCl, $SnBu_3$,

$B(OH)_2$,[135] SeMe, TeMe,[136] SR (R = Me, n-$C_{18}H_{37}$),[137] SMe,[141] SEt,[142] SO_2Me, SO_2NH_2,[137] CHO [140] and CO_2Me.[137]

Lithium derivatives of thieno[3,2-*b*]thiophene (**145**) were used in the synthesis of 2-arylthieno[3,2-*b*]thiophenes **152** through various organometallic (or -boron) intermediates.[135]



R = H, NO_2, CN, CO_2Me, SO_2Me; Hal = Br, I.

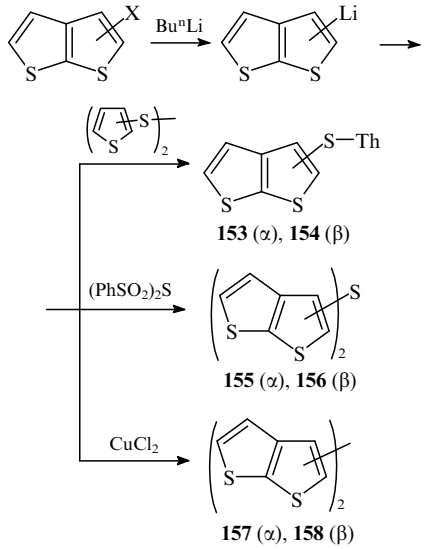
Method X		Reaction conditions		Yields (%)
		Step 1	Step 2	
a	ZnCl	$ZnCl_2$, THF	$Pd(dba)_2$, PPh_3, DMF	10–85
b	$B(OH)_2$	$B(OBu^n)_3$, THF	$Pd(PPh_3)_4$, $Ba(OH)_2$, DME	40–55
c	$SnBu^n_3$	Bu^n_3SnCl, THF	$Pd(PPh_3)_4$, dioxane	<60

dba is dibenzylideneacetone, DME is 1,2-dimethoxyethane.

Metallation of thieno[3,2-*b*]thiophene **145** with two equivalents of Bu^{n}Li affords the 2,5-dilithium derivative, whose treatment with various reagents [CO_2, DMF, $(MeS)_2$, $(PhS)_2$, $(Me_3Si)_2$, $(Bu^tMe_2Si)_2$] gives the corresponding disubstituted thienothiophene.[15, 138, 144]

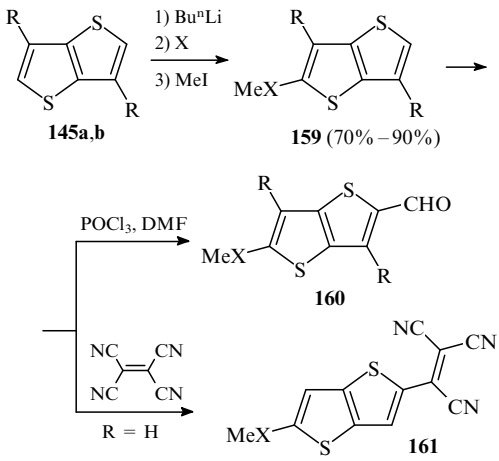
Exchange halogen–lithium reactions provide an approach to thienothiophene sulfides **142** and **145**, which were used in the synthesis of tetrathienocene **6** and pentathienocene **7** (see Section II.1).[7, 145]

Lithium intermediates served as the starting compounds in the synthesis of the corresponding 2(α)- or 3(β)-substituted derivatives of thienyl sulfides **153** and **154**, thieno[2,3-*b*]thienyl sulfides **155** and **156** and thieno[2,3-*b*]thienylthieno[2,3-*b*]thiophenes **157** and **158**.[146]



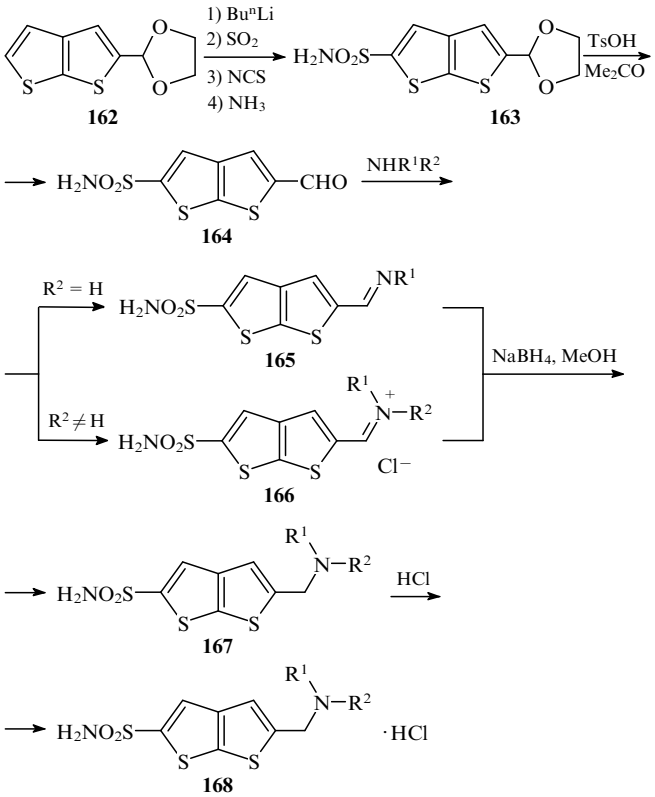
X = Br, I.

Lithiation of thieno[3,2-*b*]thiophenes **145a**,**b** gives 2-lithium derivatives, whose treatment with chalcogens and iodomethane affords chalcogenides **159**.[136] Vilsmeier–Haack formylation of the latter produces aldehydes **160**, whereas the reaction with tetracyanoethylene in DMF affords 5-tricyanovinyl derivatives **161**.



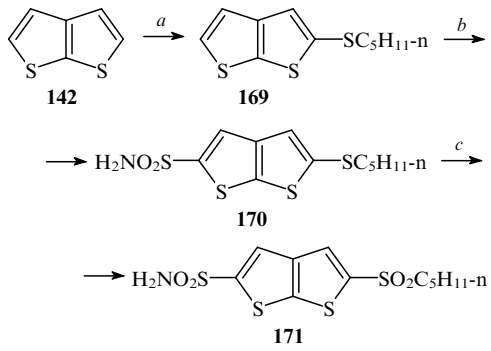
R = H (**a**), Me (**b**); X = S, Se, Te.

Organolithium derivatives served as intermediates in the synthesis of 5-amino-substituted thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-sulfonamides possessing biological activities. These compounds are carbonic anhydrase inhibitors (CAIs)[36, 147] and non-peptide fibrinogen receptor antagonists.[148] For example, the introduction of the sulfamoyl group into the dioxolane derivative of thieno[2,3-*b*]thiophene **162** can be efficiently performed by metallation with butyllithium at position 5 followed by treatment of the reaction mixture with SO_2, *N*-chlorosuccinimide (NCS) and ammonia. The acetal protection in the resulting 5-[1,3]dioxolan-2-ylthieno[2,3-*b*]thiophene-2-sulfonamide **163** was removed[36] by transacetalation giving rise to aldehyde **164** in high yield. The latter reacts with various primary and secondary amines to form imines **165** or immonium salts **166**, respectively, whose reduction with sodium borohydride affords tertiary amines **167**. Transformations of the amines into hydrochlorides **168** produced water-soluble salts, which were tested for biological activities. The same synthetic approach was applied to the synthesis of the corresponding thieno[3,2-*b*]thiophene analogues.



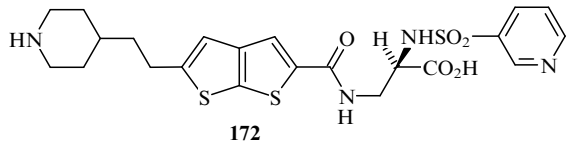
R^1, R^2 = H, Alk.

The reaction of thieno[2,3-*b*]thiophene (**142**) with Bu^{n}Li affords a lithium intermediate, whose treatment with elemental sulfur and bromopentane produces sulfide **169**. Regioselective *N*-sulfonation of the latter was successfully carried out by the successive reactions with Bu^{n}Li, SO_2 and hydroxylamino-*O*-sulfonic acid. Selective oxidation of sulfide **170** with potassium peroxymonosulfate afforded sulfone **171**.[147]



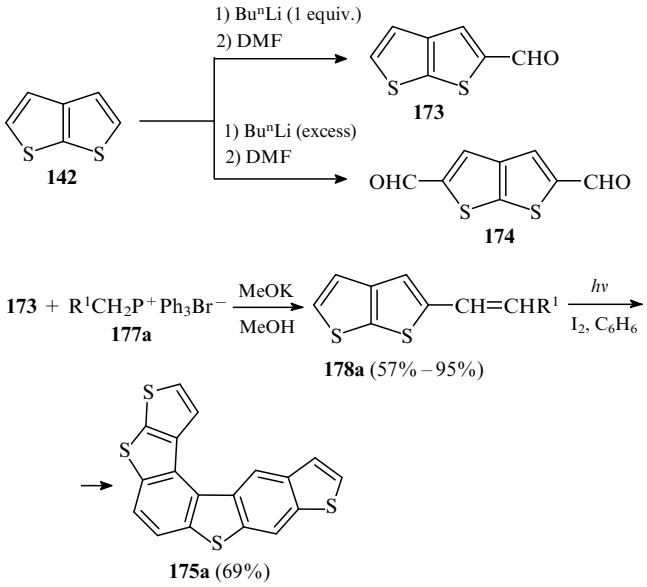
(*a*) 1) Bu^{n}Li, 2) S_8, n-$C_5H_{11}Br$; (*b*) 1) Bu^{n}Li, 2) SO_2, 3) hydroxylamino-*O*-sulfonic acid; (*c*) K_2SO_5.

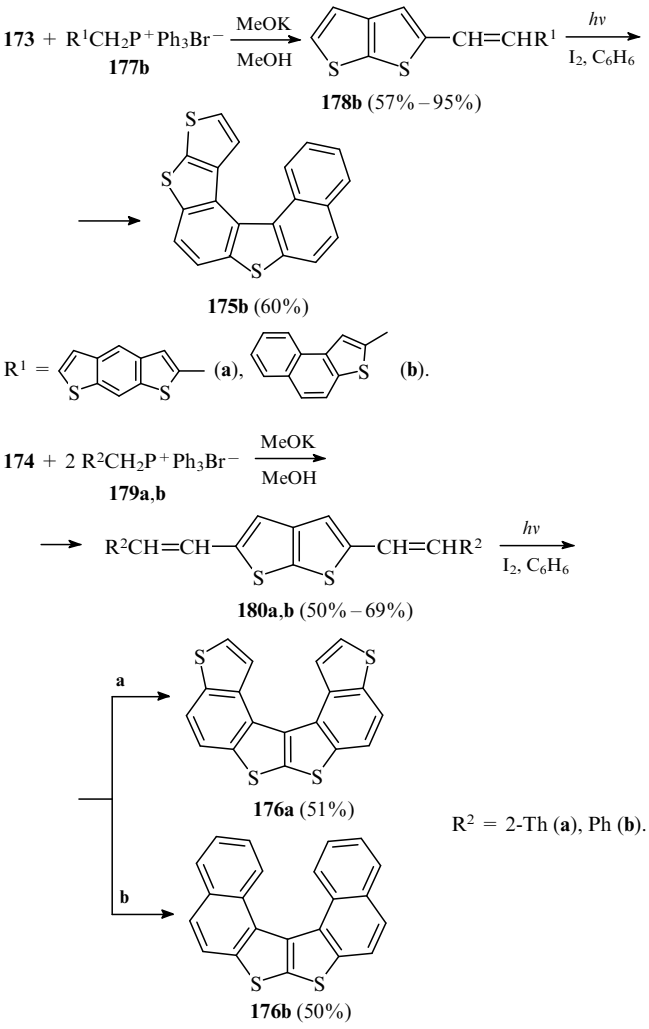
An analogous approach was employed in the synthesis of sulfonamide **172**, which is a potential non-peptide fibrinogen receptor antagonist.[148]



Metallation was involved also as the first step in the synthesis of di-, tri- and tetramers of 3,6-disubstituted thieno[3,2-*b*]thiophene (**145**) and selenopheno[3,2-*b*]selenophene (**147**).[143] These compounds are of practical interest. Many thiophene oligomers exhibit biological activity, which is enhanced upon exposure to visible light.[149]

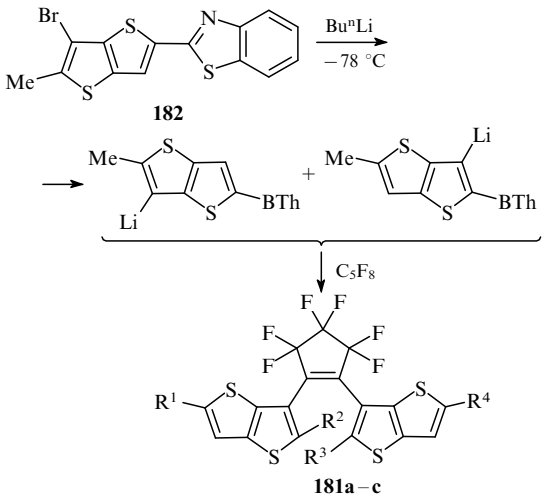
Metallation of thieno[2,3-*b*]thiophene (**142**) followed by the reactions of the resulting mono- and dilithium derivatives with dimethylformamide afforded aldehydes **173** and **174**, which served as the starting compounds in the synthesis of heterohelicenes **175a**,**b** and **176a**,**b**.[150]





The Wittig reaction of aldehyde **173** with phosphonium salts **177a**,**b** gives alkenes **178a**,**b**, and the double Wittig reaction of dialdehyde **174** with phosphonium salts **179a**,**b** affords alkenes **180a**,**b**. Irradiation of suspensions of alkenes **178a**,**b** and **180a**,**b** in benzene in the presence of iodine produces heterohelicenes **175a**,**b** and **176a**,**b**.

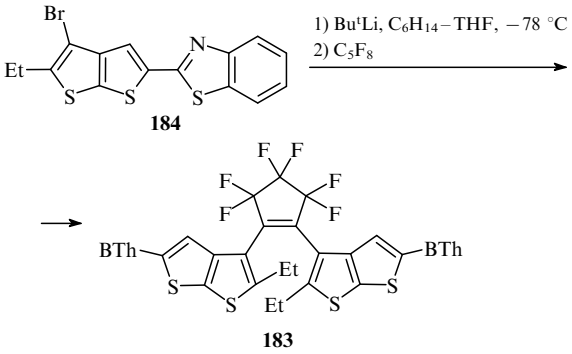
With the aim of synthesising new photochromic dihetarylethenes, *viz*., 5-substituted 1,2-bis(thieno[3,2-*b*]thiophen-3-yl)perfluorocyclopentenes **181a**–**c**, 2-(benzothiazol-2-yl)-6-bromo-5-



$R^1 = R^4$ = BTh, $R^2 = R^3$ = Me (**a**); $R^1 = R^3$ = BTh, $R^2 = R^4$ = Me (**b**); $R^2 = R^3$ = BTh, $R^1 = R^4$ = Me (**c**); BTh is benzothiazol-2-yl.

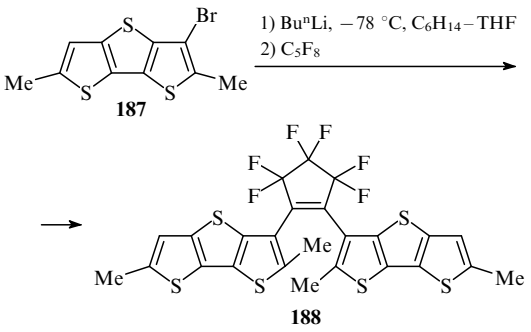
methylthieno[3,2-*b*]thiophene (**182**) was subjected to metallation. A mixture of lithium derivatives produced by this reaction was treated with octafluorocyclopentene (C_5F_8).[14, 15]

The thieno[2,3-*b*]thiophene analogue of compound **181**, *viz*., 1,2-bis{2-ethyl-5-(benzothiazol-2-yl)thieno[2,3-*b*]thiophen-3-yl}-hexafluorocyclopentene (**183**), was synthesised according to an analogous procedure starting from (5-benzothiazol-2-yl)-3-bromo-2-ethylthieno[2,3-*b*]thiophene (**184**).[151]

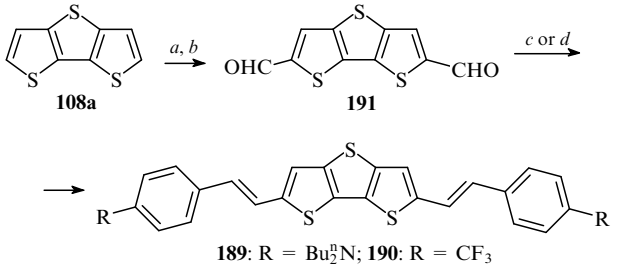


Dithieno[3,2-*b*:2′,3-*d*]thiophene (**108a**) served as a building block in the design of photochromic materials for optical memory. Photochromic compounds **185** and **186** (Scheme 4) were prepared in satisfactory yields by successive transformations involving initial metallation of dithienothiophene **108a** with Bu^{n}Li at −78 °C.[152]

Photochromic 1,2-bis(2,6-dimethylthieno[3,2-*b*:2′,3′-*d*]thiophen-3-yl)hexafluorocyclopentene (**188**) was synthesised [18] starting from 3-bromo-2,6-dimethylthieno[3,2-*b*:2′,3′-*d*]thiophene (**187**) according to a procedure described in the studies.[14, 15]

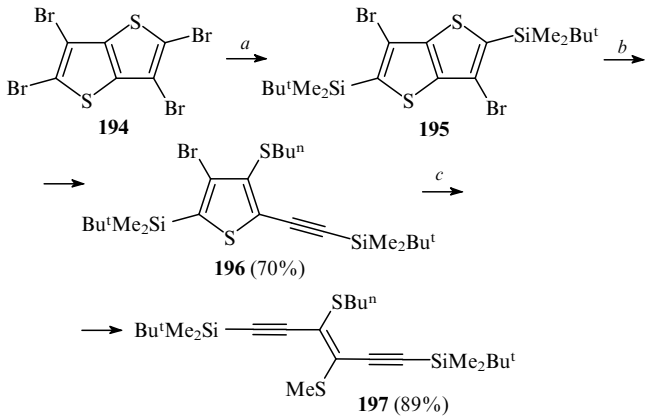


An analogous methodology was employed in the synthesis of new quadrupole photophores **189** and **190**, which have high two-photon excited fluorescence. Conjugated dithienothiophene **108a** was used as the starting compound. The reactions of dialdehyde **191** (see Ref. 153) with phosphonium salt **192** (2.1 equiv.) or phosphonate **193** (2.2 equiv.) in the presence of phase-transfer catalysts [154] afforded compounds **189** and **190**, respectively, in 80% – 90% yields.[155] After crystallisation, these compounds were isolated as pure *E* isomers.



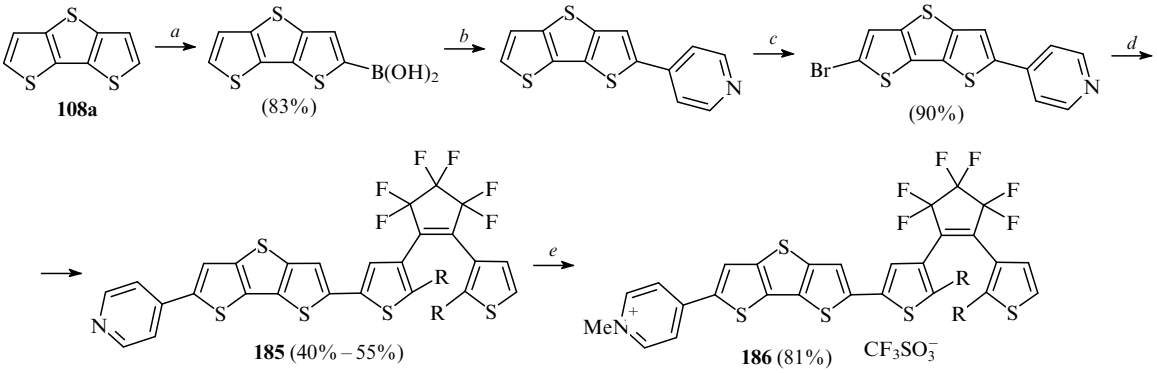
(*a*) Bu^{n}Li, THF, −78 °C; (*b*) DMF, −78 °C; (*c*) 4-Bu$^n_2$NC$_6$H$_4$CH$_2$P$^+$Ph$_3$I$^-$ (**192**), Bu^{t}OK, CH_2Cl_2, 20 °C, 5 h; (*d*) 4-F_3CC$_6$H$_4$CH$_2$P(O)(OEt)$_2$ (**193**), NaH, THF, 20 °C, 24 h.

Polyfunctional thiophenes and enediynes were synthesised through the cleavage of the heterocycle in 3-lithiated thieno[2,3-*b*]- and -[3,2-*b*]thiophenes, 3,4-dilithiated thieno[2,3-*b*]thiophenes and 3,6-dilithiated thieno[3,2-*b*]thiophenes.[15, 156, 157] For example, tetrabromothieno[3,2-*b*]thiophene (**194**) [158] was successively treated with two equivalents of n-butyllithium (THF, 20 °C) and two equivalents of Bu^{t}Me$_2$SiCl to prepare dibromide **195**, which was treated with one equivalent of n-butyllithium. The corresponding bromothiophene **196** was isolated by flash chromatography on silica gel. Treatment of **196** with Bu^{n}Li (1 equiv.) and excess iodomethane afforded enediyne **197**. Both steps of ring opening can be carried out without isolation of intermediates (the so-called tandem process).[157]



(*a*) 1) Bu^{n}Li (2 equiv.), THF, 20 °C, 2) Bu^{t}Me$_2$SiCl (2 equiv.); (*b*) Bu^{n}Li (1 equiv.), −78 °C; (*c*) Bu^{n}Li (1 equiv.), 0 °C, MeI.

Scheme 4

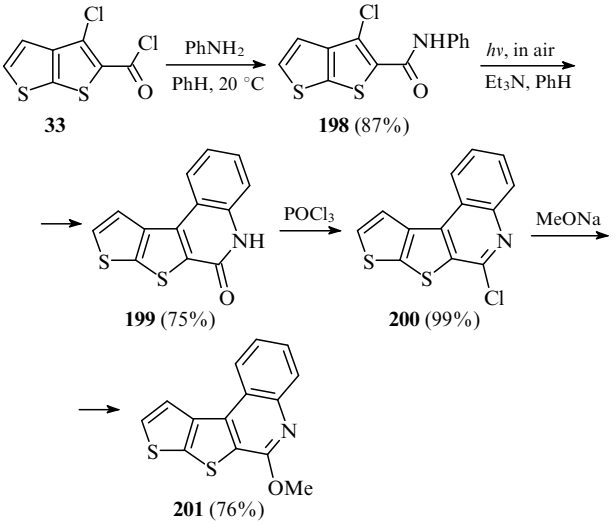


(*a*) 1) Bu^{n}Li, THF −78 °C; 2) B(OBu^i)$_3$; (*b*) 4-bromopyridine, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, H$_2$O – THF; (*c*) NBS, CHCl$_3$ – AcOH; (*d*) 1,2-bis[2-hexyl-5-(dihydroxyboryl)thiophen-3-yl]hexafluorocyclopentene, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, H$_2$O – THF; (*e*) CF_3SO_3Me, CH_2Cl_2; R = n-hexyl; NBS is *N*-bromosuccinimide.

The above reactions exemplify the wide range of applications of metallation of thienothiophenes, which allows one to prepare new derivatives of this class of heterocycles, including those having practically useful properties.

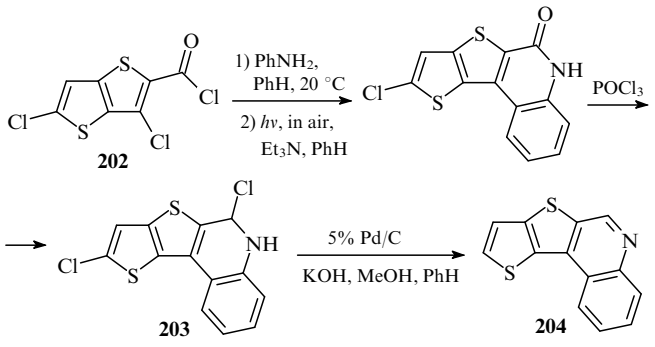
b. Photocyclisation

In the last decade, photocyclisation [159] of thienothiophenes and their derivatives (primarily, of amides) has attracted considerable attention as a convenient method for the synthesis of sulfur-containing polyannelated heterocyclic systems.[25, 27, 160–166] Two examples of the synthesis of such compounds are given below. The reaction of aniline with 3-chlorothieno[2,3-*b*]thiophene-2-carboxylic acid chloride **43** produced *N*-phenylthieno[2,3-*b*]thiophene-2-carboxamide **198**.[24, 25] Photocyclisation of the latter in benzene containing a small amount of triethylamine gave thieno[3′,2′:4,5]-thieno[2,3-*c*]quinolin-2-one (**199**), whose chlorination with $POCl_3$ afforded 6-chlorothieno[3′,2′:4,5]thieno[2,3-*c*]quinoline (**200**). The reaction of compound **200** with sodium methoxide produced the corresponding methoxy derivative **201**. All steps of this transformation sequence gave products in good yields.



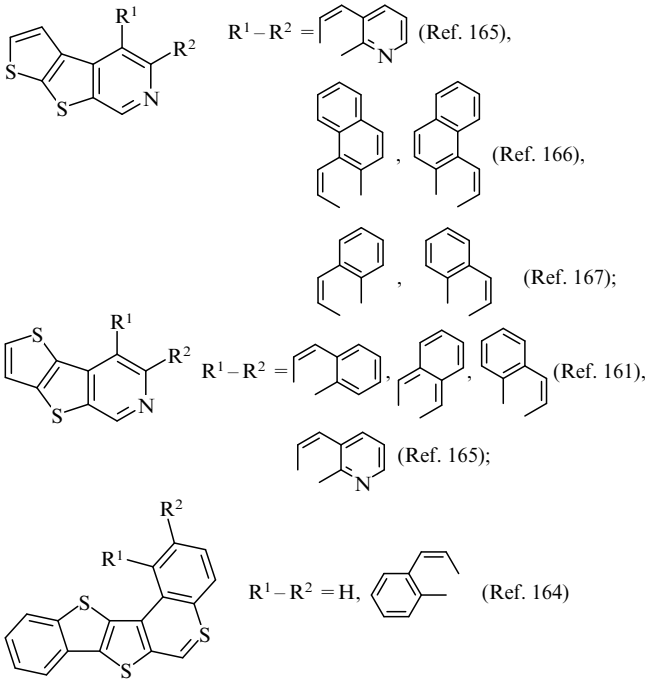
33 **198** (87%) **199** (75%) **200** (99%) **201** (76%)

6,9-Dichlorothieno[2′,3′:4,5]thieno[2,3-*c*]quinoline (**203**) was synthesised from 3,5-dichlorothieno[3,2-*b*]thiophene-2-carboxylic acid chloride (**202**). Catalytic dechlorination of **203** afforded unsubstituted thieno[2′,3′:4,5]thieno[2,3-*c*]quinoline (**204**).[25]

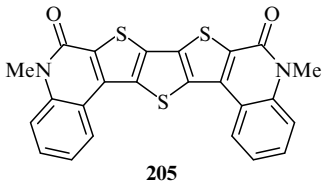


202 **203** **204**

This procedure was employed to prepare various polyannelated thienothiophene- and benzo[*b*]thiophene-containing systems starting from thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-carboxylic acid chlorides. The structures of these compounds and references to their synthesis are given below.



Dithieno[3,2-*b*:2′,3′-*d*]thienyl[2″,3″-*c*:2″,3″-*c*′]-5,10-*N*,*N*′-dimethylquinoline-6,9-dione (**205**) was synthesised by double photochemical dehydrohalogenation of the corresponding thieno[3,2-*b*:2′,3′-*d*]thiophene-2,6-dicarboxanilide.[167]

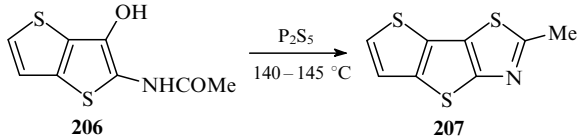


205

Conjugated thiophene polymers are of interest because of their electrical and optical properties. In this connection, photochemical polymerisation of dithieno[3,2-*b*:2′,3′-*d*]thiophene **108a** and dithieno[3,4-*b*:3′,4′-*d*]thiophene **11** was studied. Irradiation of solutions containing dithienothiophene and an electron acceptor (for example, *p*-dinitrobenzene, CCl_4) gives rise to polythienothiophenes with molecular mass of $\sim 10^4$. The radical cation of the starting thienothiophene is efficiently generated by photoinduced electron transfer from the excited state of the monomer to an electron acceptor. The subsequent coupling reaction affords polymers.[168, 169]

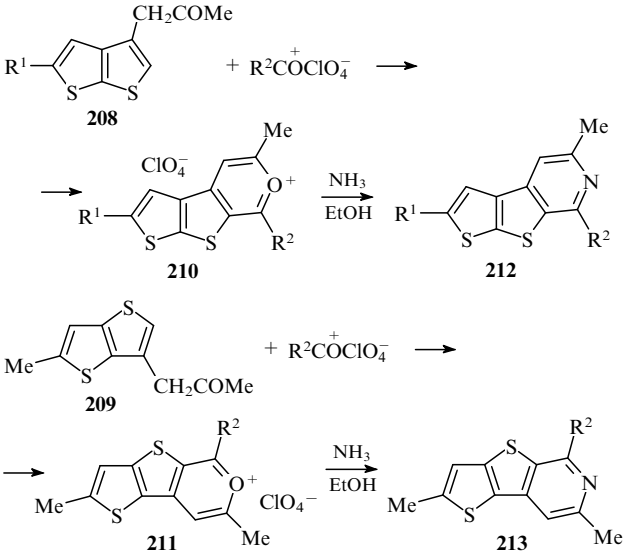
c. Fused thienothiophenes and their reactions

To construct additional heterocycles fused to the thienothiophene system, a number of approaches other than the above-mentioned photocyclisations were used. For example, heating of 2-acetylamino-3-hydroxythieno[3,2-*b*]thiophene (**206**) in the presence of P_2S_5 afforded 2-methylthieno[3,2-*b*]thieno[3,2-*d*]thiazole (**207**).[19] Isomeric 2-methylthieno[2,3-*b*]thieno[3,2-*d*]thiazole was prepared by oxidation of 2-thioacetylaminothieno[2,3-*b*]thiophene with $K_3Fe(CN)_6$ in aqueous alkali.[170]



206 **207**

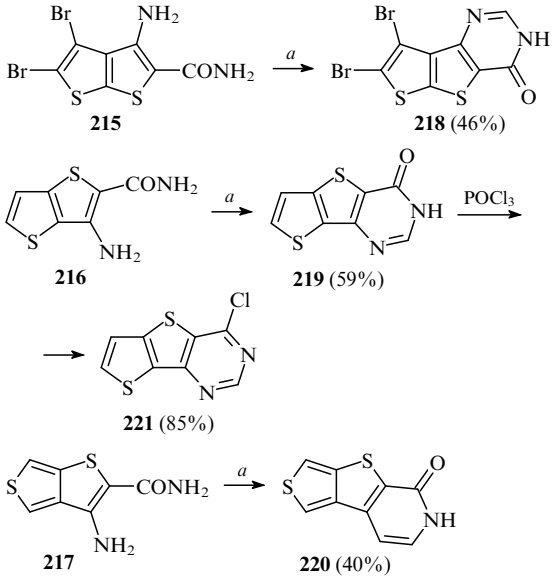
Acylation of 3-acetonyl-5-alkylthieno[2,3-*b*]thiophenes **208** and 3-acetonyl-5-methylthieno[3,2-*b*]thiophenes **209** in a mixture of aliphatic acid anhydride and perchloric acid (actually, acylium perchlorate) was demonstrated [171] to occur at the free α position followed by cyclisation and formation of perchlorates of tricyclic pyrylium salts **210** and **211** (yields > 80%). The latter are transformed into thieno[2′,3′:5,4]- (**212**) and -[2′,3′:4,5]thieno[2,3-*c*]pyridines **213** in yields of higher than 90% by passing ammonia through their suspensions.



R^1 = Me, Et; R^2 = Me, Et, Bu^n.

Functionalised thieno[2,3-*b*]thiophenes **214** were transformed according to conventional procedures into the following tri- and tetracyclic systems: thienopyrimidines, thieno-1,3-oxazines, bis-(thieno-1,2,3-triazines), dithieno-1,4-oxazepines [38] (presented in Scheme 5) and fused thieno[2,3-*b*]thiophenes containing pyridine, pyrimidine, thiazine, thiazole, oxadiazole, isoxazole, pyrazole, pyridazine, piperazine, pyrrolopiperazine and other heterocyclic fragments.[172–175]

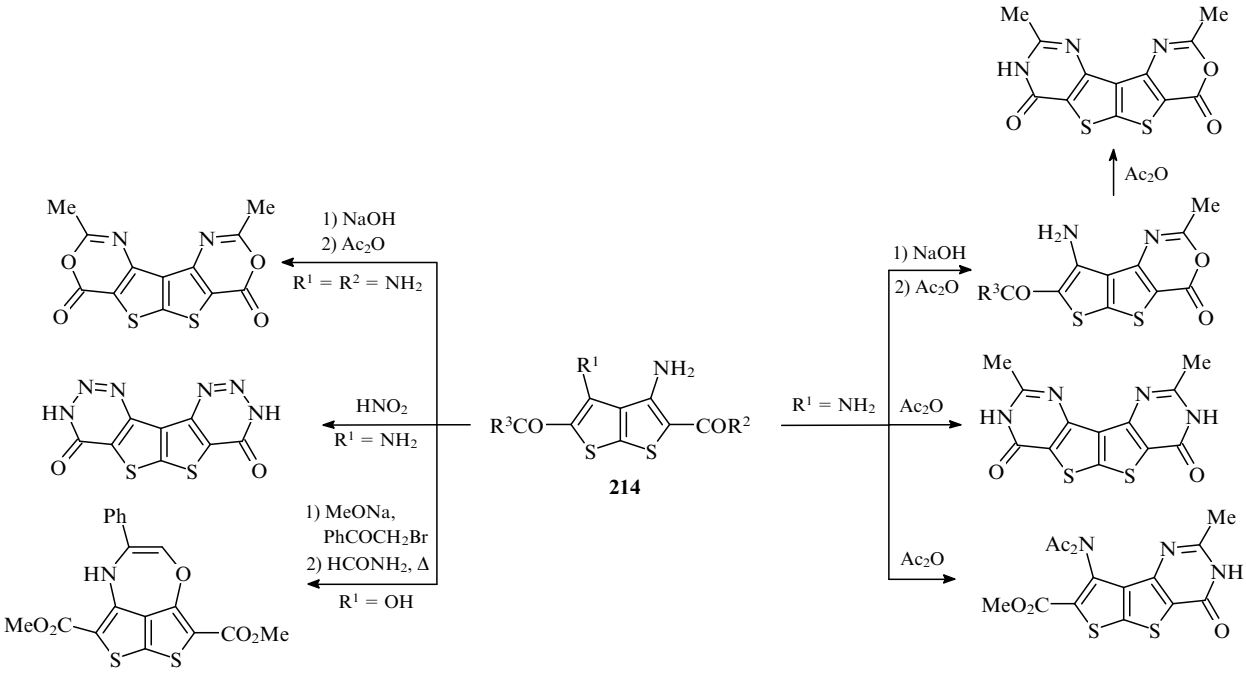
The reactions of thienothiophenes **215**, **216** and **217** containing the amino- and carboxamide groups in the adjacent positions with triethyl orthoformate in boiling acetic anhydride produce thieno[2′,3′:4,5]- (**218**), thieno[3′,2′:4,5]- (**219**) and thieno[3′,4′:4,5]thieno[3,2-*d*]pyrimidin-7(6*H*)-ones (**220**), respectively.[10] The reaction of thienopyrimidine **219** with $POCl_3$ affords 7-chloro derivative **221**.



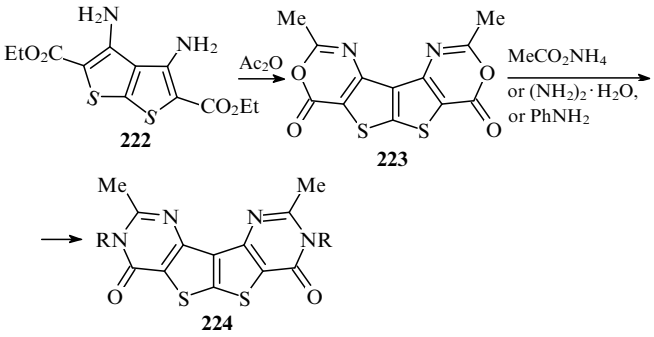
(*a*) $CH(OEt)_3$, Ac_2O, Δ, 1.5 h.

Treatment of diethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate (**222**) with acetic anhydride afforded symmetrical tetracyclic derivative **223**, whose reactions with ammonium acetate, hydrazine hydrate or aniline produced its nitrogen analogues **224**.[172]

Scheme 5

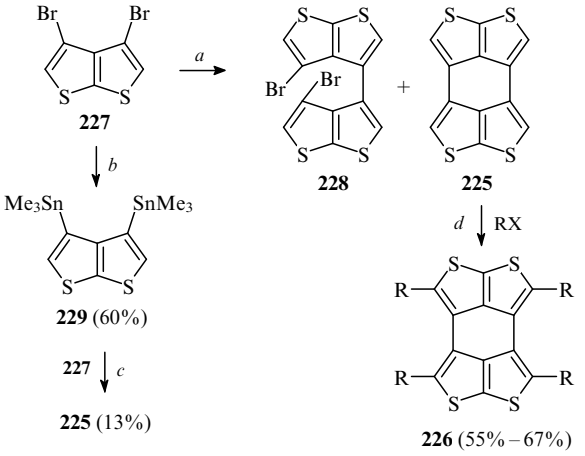


R^1 = NH_2, OH; R^2 = NH_2, OMe, Ph; R^3 = NH_2, OMe, Ph.



R = H, NH_2, Ph.

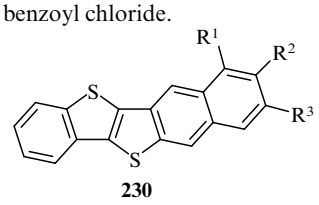
2,3,6,7-Tetrathiabenzo[1,3-*cd*:4,6-*c*′*d*′]dipentalene (**225**) and its derivatives **226** are new fused polynuclear heteroarenes isoelectronic with perylene. Dipentalene **225** was prepared for the first time by dimerisation of thieno[2,3-*b*]thiophene (**142**).[172] More recently, it was found that catalytic reduction of 3,4-dibromothieno[2,3-*b*]thiophene (**227**) with an excess of activated zinc in the presence of bis(triphenylphosphine)nickel(II) chloride and tetraethylammonium iodide afforded only 4,4′-dibromo-3,3-bis(thieno[2,3-*b*]thiophene) (**228**) (in a maximum yield of 28%).[176] However, the reaction in the presence of a larger amount of the nickel catalyst afforded also dipentalene **225**. Optimisation of the reaction conditions made it possible to increase the yield of the latter to only 14%. An alternative procedure was employed to transform thienothiophene **227** into trimethylstannyl derivative **229**. The reaction of thienothiophene **227** with organotin intermediate **229** in the presence of the palladium triphenylphosphine complex afforded dipentalene **225** (13% yield). Derivatives **226** were prepared by lithiation of dipentalene **225** followed by the reaction with the corresponding alkyl iodide or dialkyl disulfide.[79]



RX = MeI, EtI, $(MeS)_2$, $(EtS)_2$; R = Me, Et, SMe, SEt;
(*a*) $(Ph_3P)_2NiCl_2$, Me_4NI, Et_4Ni, Zn (excess), PhH, Δ; (*b*) Bu^nLi (2 equiv.), Me_3SnCl (2 equiv.), Et_2O–TMEDA, −80 °C; (*c*) $(Ph_3P)_4Pd$, PhMe, 70 °C; (*d*) LDA, THF, −10 °C; TMEDA is *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, LDA is lithium diisopropylamide.

The oxidation potential of heteroarene **225** is equal to that of perylene, and compound **225** forms an analogous complex with iodine having rather high conductivity (0.11 S cm^{-1}). However, it appeared that complexes of all derivatives **226** with iodine have low conductivity. In addition, compounds **225** and **226** form charge-transfer complexes with strong electron acceptors, such as 7,7,8,8-tetracyanoquinodimethane (TCNQ), 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane ($TCNQF_4$), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and 1,1,2,3,4,4-hexacyano-1,3-butadiene (HCBD).[79,176] However, the majority of these π complexes are low-conducting powdered polymers, whereas complexes of tetrakis(methylthio) derivatives **226** (R = SMe) form crystalline radical-cation salts with a conductivity of about 10^{-3} S cm^{-1}.

Friedel–Crafts condensation of benzo[*b*]thieno[3,2-*b*]thiophene-2-carboxylic acid chloride with *m*- and *p*-xylene affords ketones, which undergo Elbs pyrolysis (420 °C, 15 min) to form pentacyclic derivative **230**.[177] Analogous products were prepared from benzo[*b*]thieno[3,2-*b*]thiophene and (di)methyl homologues of benzoyl chloride.



$R^1 = R^2 = R^3 = H$;
R^1 = Me, $R^2 = R^3 = H$;
R^2 = Me, $R^1 = R^3 = H$;
R^3 = Me, $R^1 = R^2 = H$.

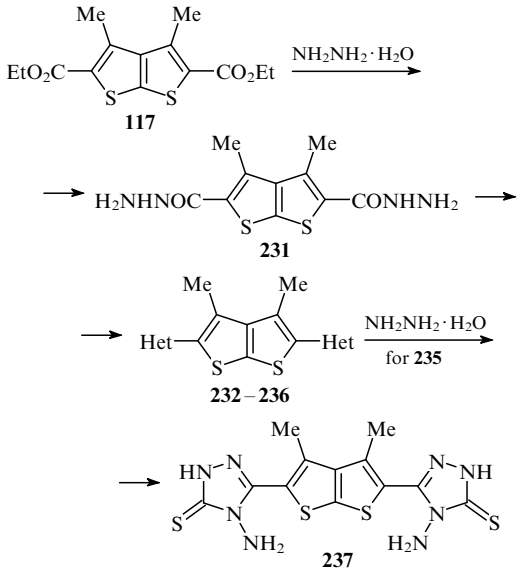
Cyclisation of benzo[*b*]thieno[3,2-*b*]thiophene-2-butyric acid in the presence of P_2O_5 gives benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene (**121**) in 80% yield.[178]

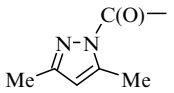
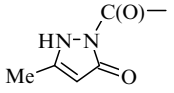
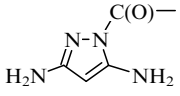
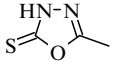
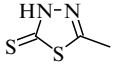
d. Other transformations

This Section deals with the most interesting reactions of thienothiophenes giving rise to various sulfur-containing heterocyclic systems.

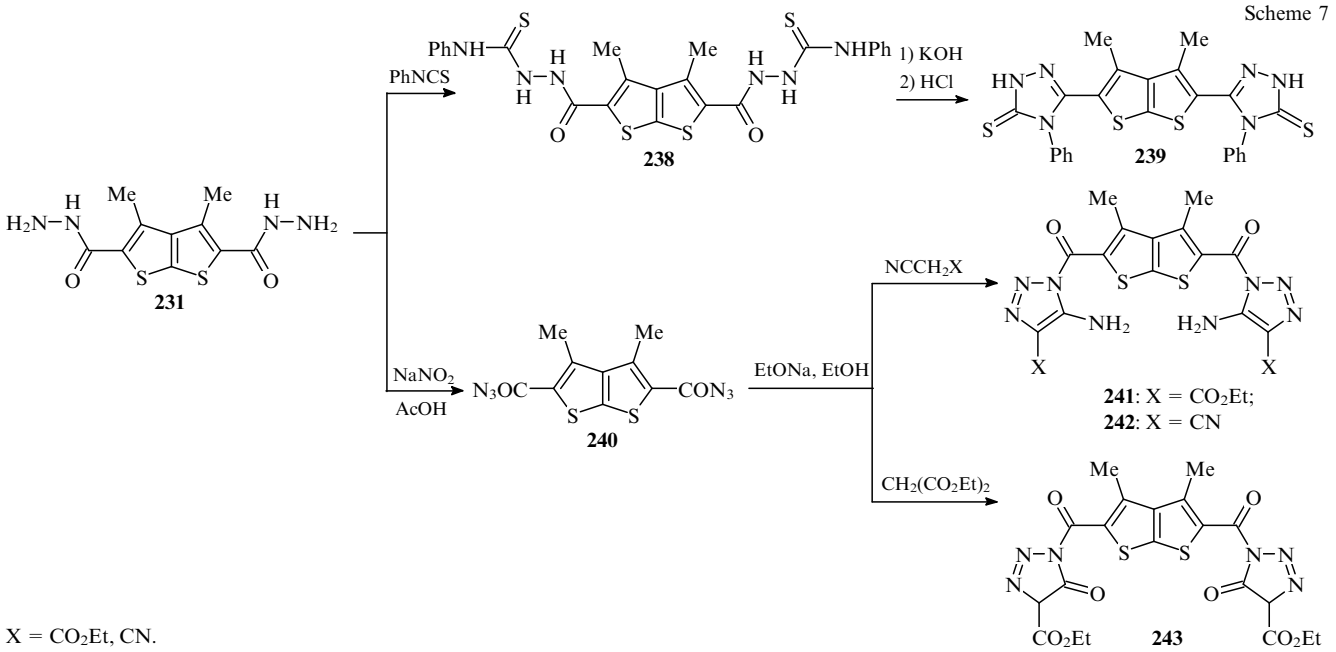
The reaction of diethyl 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate (**117**, R = Me, EWG = CO_2Et) with hydrazine hydrate afforded dihydrazide **231**, which was subjected to various transformations (Scheme 6). For example, the reactions with acetylacetone, ethyl acetoacetate or malononitrile[75] are accom-

Scheme 6



Compound	Het	Reaction conditions	Yield (%)
232		CH_2Ac_2, fusion	88
233		$AcCH_2CO_2Et$, EtOH, AcOH	79
234		$CH_2(CN)_2$, EtOH, Pip	73
235		1) CS_2, KOH, 2) HCl	82
236		1) CS_2, KOH, 2) H_2SO_4	85

Scheme 7

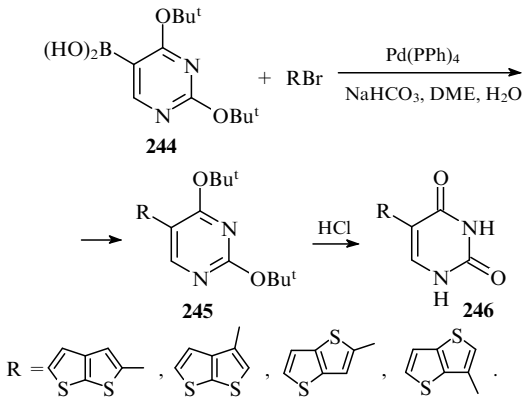


X = CO_2Et, CN.

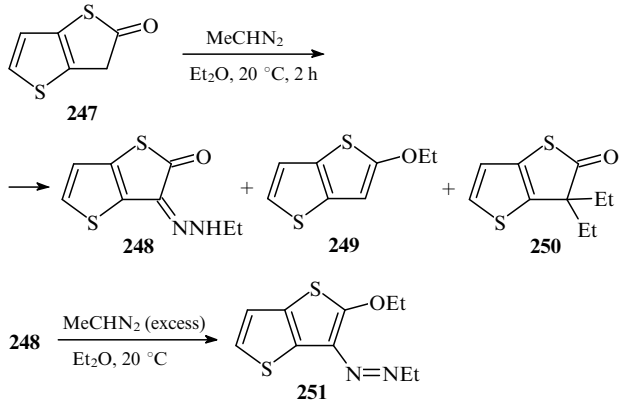
panied by the closure of the exocyclic pyrazole ring to form the corresponding derivatives **232**–**234**. The reaction of dihydrazide **231** with carbon disulfide in the presence of KOH followed by decomposition with dilute HCl or concentrated H_2SO_4 produces di(oxadiazole) (**235**) or di(thiadiazole) derivative (**236**). Condensation of di(oxadiazolyl)thienothiophene **235** with hydrazine hydrate affords di(triazolyl)thienothiophene **237** (Scheme 6).

Dihydrazide **231** was also used in the synthesis of thienothiophenes containing triazole substituents. For example, the reaction with phenyl isothiocyanate in ethanol produces di(*N*-phenylthiocarbamoyl)carbohydrazide **238**, whose treatment with KOH followed by acidification affords compound **239**. Diazotisation of dihydrazide **231** with a 10% sodium nitrite solution in acetic acid gives diazide **240**. The reactions of the latter with compounds containing the active methylene group, *viz*., ethyl cyanoacetate, malononitrile or diethyl malonate, in the presence of sodium ethoxide, yield the corresponding ditriazole derivatives **241**–**243** (Scheme 7).

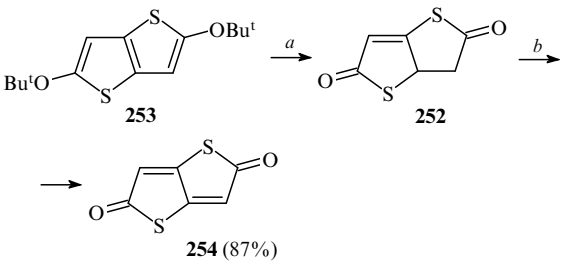
In the presence of zero-valent palladium complexes as the catalyst, 2,4-di-*tert*-butoxypyrimidine-5-boronic acid (**244**) reacts with the bromine derivatives of thieno[2,3-*b*]- (**142**) and thieno[3,2-*b*]thiophene (**145**).[179,180] This reaction was used to introduce fragments of isomeric thienothiophenes at position 5 of 2,4-di-*tert*-butoxypyrimidine. The resulting compounds **245** were transformed into uracils **246** in quantitative yields.

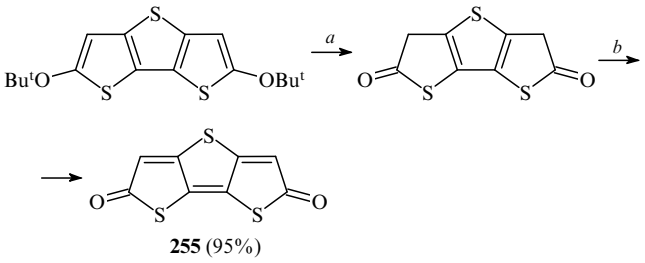


After the reaction of thieno[3,2-*b*]thiophen-2(3*H*)-one (**247**) with diazoethane in diethyl ether, thieno[3,2-*b*]thiophene-2,3-dione 3-ethylhydrazone (**248**), 2-ethoxythieno[3,2-*b*]thiophene (**249**) and 3,3-diethylthieno[3,2-*b*]thiophen-2-one (**250**) were isolated from the reaction mixture.[181] The reaction of hydrazone **248** with diazoethane yielded 2-ethoxy-3-ethylazothieno[3,2-*b*]thiophene (**251**).



Dehydrogenation of dione **252**, which was prepared by treatment of 2,5-di(*tert*-butoxy)thieno[3,2-*b*]thiophene (**253**) with *p*-toluenesulfonic acid, with DDQ in dioxane gave 2,5-dioxothieno[3,2-*b*]thiophene (**254**).[182] 2,6-Dioxothieno[3,2-*b*]-thieno[2′,3′-*d*]thiophene (**255**) was prepared according to an analogous procedure.

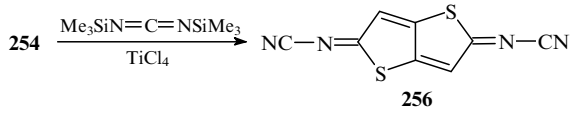




255 (95%)

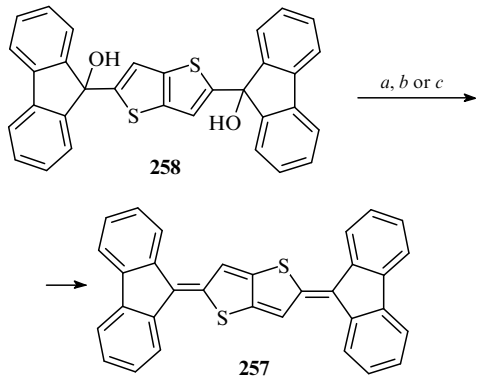
(*a*) TsOH, PhH, Δ, 2 h; (*b*) DDQ, dioxane, Δ, 5 h.

Dicyanodiimide **256** and its various derivatives were synthesised starting from dione **254**. These compounds form high-conducting charge-transfer complexes.[183]



256

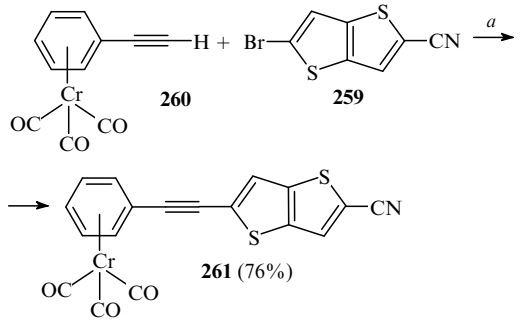
Fluorenylidene derivative **257** was synthesised from diol **258** according to three procedures: by heating without a solvent (35% yield) and by irradiation for 5–10 h in the solid state (~10%) or in a solution in CH_2Cl_2 (86%). Irradiation was carried out using a high-pressure mercury lamp through a Pyrex filter.[184]



257

(*a*) > 200 °C; (*b*) *hv*; (*c*) *hv*, CH_2Cl_2.

Recently, the first example of Pd-catalysed coupling of bromothienothiophene **259** with the chromium tricarbonyl complex with phenylacetylene (**260**) giving rise to complex **261** has been published.[185]

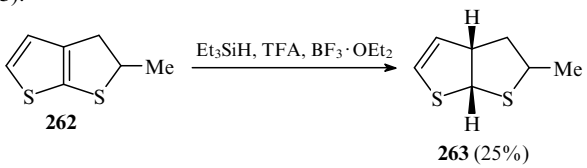


260 **259** **261** (76%)

(*a*) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, Δ.

Catalytic liquid-phase oxidation of 3-methylthieno[2,3-*b*]- and -[3,2-*b*]thiophenes in the presence of cobalt acetate and NaBr in acetic acid (90–110 °C) gave rise to thieno[2,3-*b*]thiophene-2-carboxylic acid (**41**) and the 3-formyl derivative, respectively.[186] The kinetic data provide evidence that electron transfer from the peroxy radical to Co^{2+} is the rate-determining step.

Ionic hydrogenation of 2-methyl-2,3-dihydrothieno[2,3-*b*]-thiophene (**262**) affords *cis*-2,8-dithiabicyclo[3.3.0]octane (**263**).[187]



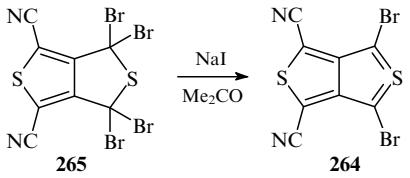
262 **263** (25%)

TFA is trifluoroacetic acid.

Desulfation of methyl 5,6-dibromo-3-chlorothieno[3,2-*b*]thiophene-2-carboxylate with a Ni–Al melt in a 10% NaOD–D_2O solution produced methyl heptanoate containing 96% of deuterium.[188]

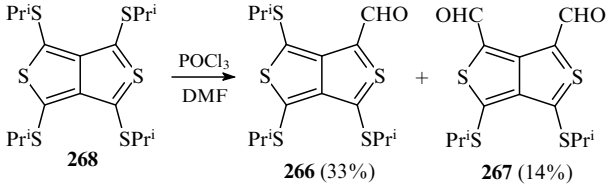
As mentioned above, thieno[3,4-*c*]thiophene is very difficult to synthesise compared to all other isomeric thienothiophenes. A few derivatives are known: tetraphenyl-,[189–191] tetrakis(alkylthio)-,[58] tetra(2-thienyl)-,[42] tetrabromo-, 1,3-dibromo-4,6-dicyano-, 1,3-dibromo-4,5-bis(methoxycarbonyl)-,[192] 1,4-bis(*tert*-butylthio)-3,6-diphenyl- and 3,6-di(2-thienyl)thieno[3,4-*c*]thiophenes.[61]

The synthesis of 1,3-dibromo-4,6-dicyanothieno[3,4-*c*]thiophene (**264**) by the reaction of tetrabromide **265** with NaI in acetone is the first example of the synthesis of a stable thieno[3,4-*c*]thiophene derivative.[193]



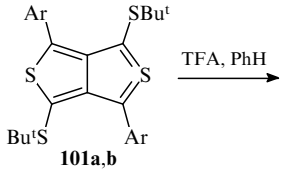
265 **264**

Mono- (**266**) and diformyl derivatives **267**, which were prepared by formylation of 1,3,4,6-tetrakis(isopropylthio)thieno[3,4-*c*]thiophene (**268**) with the Vilsmeier reagent, also proved to be rather stable.[194]

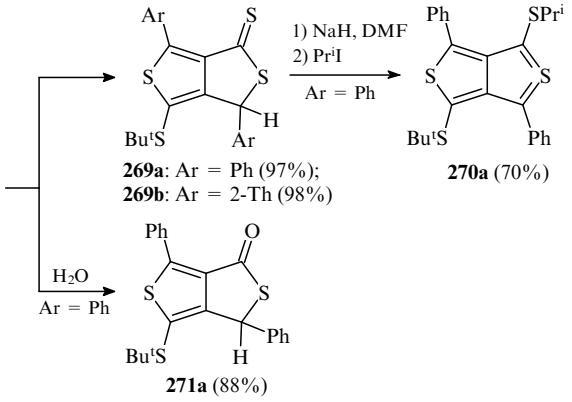


268 **266** (33%) **267** (14%)

The reactions of thienothiophenes **101a**,**b** with trifluoroacetic acid are accompanied by protonation of the thienothiophene system, resulting in the Bu^t–S bond cleavage to form the corresponding thieno[3,4-*c*]thiophene-1(3*H*)-thione (**269a**,**b**).[60,61] Treatment of thienothiophene **269a** with sodium hydride and isopropyl iodide leads to regeneration of the thieno[3,4-*c*]thiophene system to give 1-(*tert*-butylthio)-3,6-diphenyl-4-(isopropylthio)thieno[3,4-*c*]thiophene (**270a**). The reaction of thienothiophene **101a** with trifluoroacetic acid in the presence of 10 equivalents of water is accompanied by elimination of one sulfur-containing group to form 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophen-1(3*H*)-one (**271**).



101a,**b**



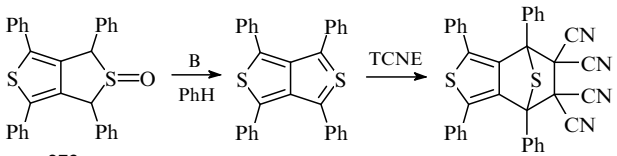
269a: Ar = Ph (97%);
269b: Ar = 2-Th (98%)

270a (70%)

271a (88%)

Cycloaddition of thienothiophenes **101a**,**b** to *N*-phenylmaleimide and dimethyl acetylenedicarboxylate was described in the study.[61]

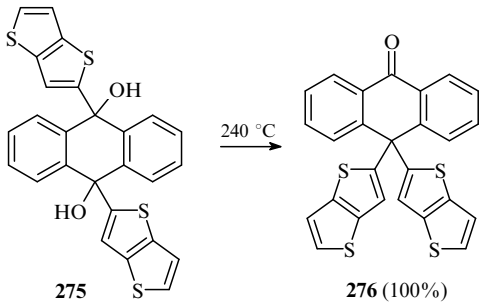
1,3,4,6-Tetraphenylthieno[3,4-*c*]thiophene (**272**) was derived from a mixture of *cis*- and *trans*-sulfoxides **273** by dehydration with bases [$Ba(OH)_2$, MeMgBr, EtMgBr, MeLi, LDA]. Product **272** was isolated either directly or as adduct **274** with tetracyanoethylene (TCNE).[194]



273 **272** (9%–77%) **274** (76%)

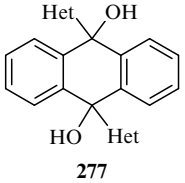
B is a base.

The reactions of thienothiophene derivatives in the absence of a solvent were also described in the literature. For example, the solid-state thermally induced rearrangement of 9,10-dihydroxy-9,10-bis(thieno[3,2-*b*]thiophen-2-yl)-9,10-dihydroanthracene (**275**) occurs at 240 °C and gives 10,10-bis(thieno[3,2-*b*]thiophen-2-yl)anthrone (**276**).[195]

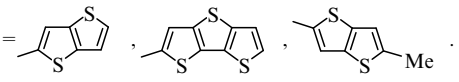


275 **276** (100%)

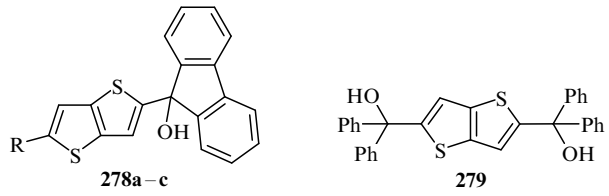
(Thienothienyl)anthracenes **277** were subjected to analogous transformations to prepare the corresponding anthrones.



277

Het =  .

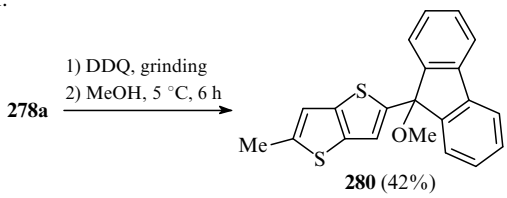
(Hydroxyfluorenyl)thieno[3,2-*b*]thiophenes **278a**–**c** and their diphenyl analogue **279** were subjected to methanolysis.[196] Substitution of the hydroxy function with the methoxy group requires specific reactions conditions for each substrate.



278a–**c** **279**

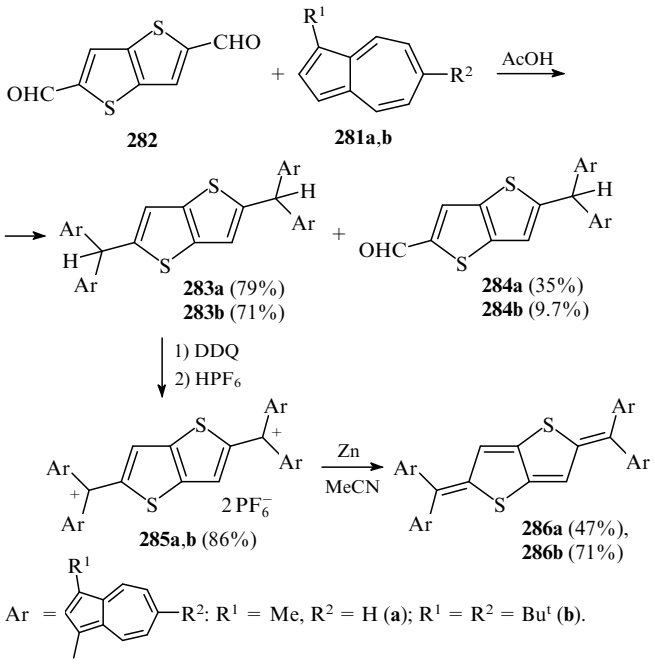
R = Me (**a**), Cl (**b**), 9-hydroxyfluoren-9-yl (**c**).

For example, 2-(9-methoxyfluoren-9-yl)thieno[3,2-*b*]thiophene (**280**) was prepared by careful grinding an equimolar mixture of 5-(9-hydroxyfluoren-9-yl)-2-methylthieno[3,2-*b*]thiophene (**278a**) with DDQ followed by storage of the resulting dark-green powder in methanol at a temperature below 5 °C for 6 h.



278a **280** (42%)

The reaction of 1-methyl- or 1,6-di-*tert*-butylazulenes (**281a**,**b**) with 2,5-diformylthieno[3,2-*b*]thiophene **282** in acetic acid afforded diazulenylmethylthieno[3,2-*b*]thiophenes **283a**,**b** along with products **284a**,**b** resulting from the reaction at one aldehyde group.[197] The reaction of thienothiophenes **283a**,**b** with two equivalents of DDQ produced dications, which were isolated as stable hexafluorophosphates **285a**,**b** by treating the reaction mixture with a 60% HPF_6 aqueous solution. Treatment of salts **285a**,**b** with zinc powder in acetonitrile afforded 2,5-bis[di(azulenyl)methylene]-2,5-dihydrothieno[3,2-*b*]thiophenes (**286a**,**b**).



282 **281a**,**b**

283a (79%)
283b (71%)

284a (35%)
284b (9.7%)

285a,**b** (86%)

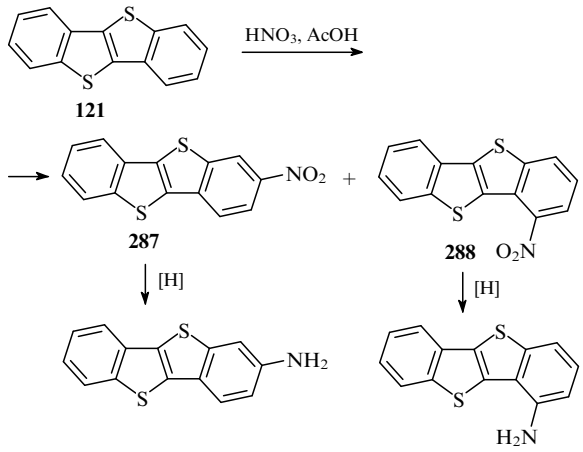
286a (47%),
286b (71%)

Ar = R^2: R^1 = Me, R^2 = H (**a**); R^1 = R^2 = Bu^t (**b**).

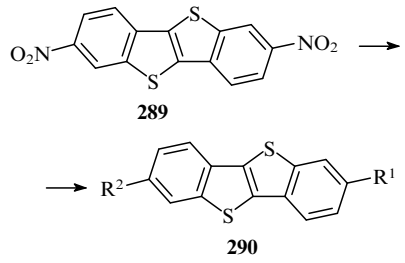
Electrophilic substitution reactions were studied for thienothiophenes annelated with one or two benzene rings. For example, benzo[*b*]thieno[2,3-*b*]- and -[3,2-*b*]thiophenes and their 3-methyl derivatives undergo bromination, Vilsmeier–Haack formylation and Friedel–Crafts acylation at position 2. These results agree well with the calculated electron densities.[32, 198–200] If these compounds contain the methyl group at position 2, bromination occurs at position 3, whereas the direction of acylation of 2-methylbenzo[*b*]thieno[2,3-*b*]thiophene depends on the reaction conditions and the reaction produces either a 3- or 6-acetyl

derivative. Bromination of 3-formyl-substituted benzo[*b*]thienothiophenes affords 2-bromo derivatives, whereas the reactions with 2-formyl-substituted derivatives are accompanied by a loss of the formyl group to give, respectively, 2,3-dibromobenzo[*b*]thieno[2,3-*b*]- or 2,6-dibromobenzo[*b*]thieno[3,2-*b*]thiophenes. Nitration of 2-formyl derivatives also leads to the replacement of the formyl group and the formation of 2-nitro derivatives as the major product.[200]

Nitration of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene **121** containing two fused benzene rings was studied. The reaction of **121** with concentrated nitric acid ($d = 1.51$ g cm^{-3}) in acetic acid produced 2- (**287**) and 4-nitro derivatives (**288**), which were reduced to the corresponding amines.[201]



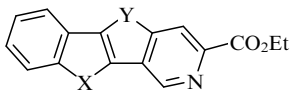
Earlier,[202] it has been reported that nitration of benzothienobenzothiophene **121** with a mixture of nitric and acetic acids led to substitution at the carbon atoms in both rings to give 2,7-dinitrodibenzo[*b*]thieno[3.2-*b*]thiophene **289** in low yield. The latter was transformed according to conventional synthetic procedures into derivatives **290** containing various electron-donating and electron-withdrawing substituents.[116]



$R^1 = R^2 = NH_2$; $R^1 = NH_2$, $R^2 = NO_2$; $R^1 = R^2 = Cl$; $R^1 = R^2 = Br$;
$R^1 = OH$, $R^2 = Cl$; $R^1 = NH_2$, $R^2 = Cl$; $R^1 = NO_2$, $R^2 = OH$;
$R^1 = OMe$, $R^2 = NO_2$, $R^1 = NH_2$, $R^2 = OMe$; $R^1 = R^2 = NHAc$;
$R^1 = R^2 = NHCOCF_3$; $R^1 = NO_2$, $R^2 = NHCOCF_3$; $R^1 = NHAc$,
$R^2 = Cl$; $R^1 = NHAc$, $R^2 = OMe$.

Nitration of 2-benzoyl- and 4-acetylaminobenzo[*b*]thieno-[3,2-*b*]thiophenes with nitric acid occurs predominantly at the *ortho*-position with respect to the substituent to give the nitro derivative, whose deacylation and reduction affords 1,2- and 3,4-diaminobenzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophenes in high yields.[203]

Thermal decomposition of azidoacrylates, which were prepared by condensation of ethyl azidoacetate with heteroaromatic aldehydes, produced a series of the previously unknown fused heteroaromatic analogues of isoellipticine **291**.[204]



X, Y = S, Se.

The above-considered transformation convincingly demonstrate a high synthetic potential of thienothiophene derivatives.

IV. Molecular structures and physical properties

Theoretical aspects of the structures, reactivities and physicochemical properties of isomeric thienothiophenes have attracted attention of a wide range of researchers. Earlier investigations of these problems have been covered in reviews[2,205] and other publications (see, for example, Refs 206–212).

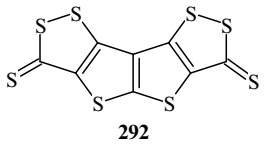
1. Structures

In the last 25 years, X-ray diffraction analysis has been particularly widely used (along with other methods) to determine the structures of thienothiophenes. For example, the crystal structures of the following compounds were established by X-ray diffraction: 3,4-dibromothieno[2,3-*b*]thiophene,[79] 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene-2,6-dione (**127**) [the main chromophoric system of the thioindigo-like dye having the *trans*-(*S*)-*trans*-(*S*)-*trans*-configuration],[111,213] (5-benzoyloxymethyl)thieno[2,3-*b*]thiophene-5-sulfamide 6,6-dioxide,[147] nitronyl nitroxide and imino nitroxide free radicals bound to isomeric thieno[2,3-*b*]- and -[3,2-*b*]thiophenes,[214] 2,3:5,6-bis(ethylenedithio)thieno[3,2-*b*]thiophene,[69] 1,2-bis{2-methyl-5-(2-benzothiazolyl)-6-trifluoromethylthieno[3,2-*b*]thiophen-3-yl}hexafluorocyclopentane,[17] 2,5-bis(dicyanomethylene)-2,5-dihydrothieno[3,2-*b*]thiophene[159] and the 3,6-dimethylselenopheno[3,2-*b*]thiophene dimer.[143]

Recently, it has been demonstrated that 2,5-bis(9-hydroxyfluoren-9-yl)thieno[2,3-*b*]- and -[3,2-*b*]thiophenes form crystalline inclusion guest–host complexes with EtOH, Pr^{n}OH, Pr^{i}OH, DMSO, Me_2SO and benzene, and the structures of these clathrates were established by X-ray diffraction.[215–223]

The structures of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**272**),[224] 1,4-bis(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene, 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene-1(3*H*)-thione and 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]-thiophen-1(3*H*)-one[61] were also characterised by X-ray diffraction.

Study of the crystal structure of sulfur-containing heterocyclic compound **292**, which was prepared by the reaction of diethyl dihydroxythieno[2,3-*b*]thiophene-2,5-dicarboxylate with Lawesson's reagent in the presence of sulfur, revealed the presence of a three-dimensional S–S interaction.[225]



The π-electron systems of thiophene, isomeric thienothiophenes and other fused sulfur-containing compounds (58 compounds, including those annelated with the benzene and naphthalene rings) were considered from the viewpoint of the degree of contribution of the sulfur atom to the ability of the probable resonance structures to include the hydrocarbon portion of the molecule.[226]

Bicyclic conjugated systems consisting only of five-membered heterocycles were studied theoretically. The authors used the topological resonance energy (TRE) as a new aromaticity index,[227] which correctly predicts the aromatic behaviour of all groups of isomeric heteroaromatic systems, including thienothio-

phenes. These isomers are referred to as positional isomers, because they formally differ only in the position of σ-bivalent heteroatoms and can be considered as a special group in accordance with the mode of their annelation. The calculated TREs agree well with the experimental values.[227, 228]

To study the effect of the nature of the heteroatom on the aromatic system, the photoelectron spectra of thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**),[229] thieno[2,3-*b*]selenophene (**143**), selenopheno[3,2-*b*]selenophene (**147**), thieno[2,3-*b*]pyrrole, selenopheno[2,3-*b*]pyrrole, pyrrolo[2,3-*b*]pyrrole and selenopheno[3,2-*b*]pyrrole[230] were measured and analysed. The replacement of the sulfur atom with selenium causes slight changes in all characteristics in accordance with the simple excitation theory. The replacement of the sulfur or selenium atom with the NH group influences the π-electron system. In this case, an increase in the resonance integral of the bonds including the heteroatom is compensated by a strong destabilising inductive effect due to N–H bond polarity. The efficient electronegativity of the NH group was found to differ only slightly from that of the sulfur atom.[230]

Thieno[3,2-*b*]thiophene (**145**), thieno[3,2-*b*]thieno[2′,3′-*d*]thiophene (**108a**), thieno[2″,3″:4′,5′]thieno[2′,3′-*d*]thieno[3,2-*b*]thiophene (**6**) and dithieno[2,3-*d*:2′,3′-*d*′]thieno[3,2-*b*:4,5-*b*′]thiophene (**7**) were studied by gas-phase and solid-state photoelectron spectroscopy.[145] For tetrathienocene **6**, the ionisation energy for the gas phase (7.22 eV) differs substantially from that for the solid state (4.86 eV), resulting in an increase in the polarisation energy by 2.36 eV, which is larger than the calculated value (1.83 eV). This phenomenon was interpreted in terms of intramolecular orbital interactions for the solid state of polythienothiophene **6**. This interaction is not observed for lower homologues (thienothiophenes **145** and **108a**).

Recently, among isomeric thienothiophenes, thieno[3,4-*c*]thiophenes have attracted most attention from both the theoretical and spectroscopic points of view as 10π-electron heterocycles having a non-classical structure.[61, 224, 231–239] Examination of the photoelectron and UV-Vis absorption spectra of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**240**)[236] confirmed the singlet aromatic ground state of the molecule predicted by quantum-chemical calculations[224] (by the MINDO/3 method without allowance for d-orbital interactions).

In the π-electron approximation of the MO LCAO SCF method, a procedure was developed on the basis of the Longuet–Higgins model to account for the d orbitals of the sulfur atoms. The chemical shifts in the ^{1}H and ^{13}C NMR spectra, the lowest singlet–singlet and singlet–triplet transitions and the dipole moments of a series of sulfur-containing heterocyclic systems, including thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**) and thieno[3,4-*c*]thiophene, were calculated.[240] These results are in agreement with experimental data.

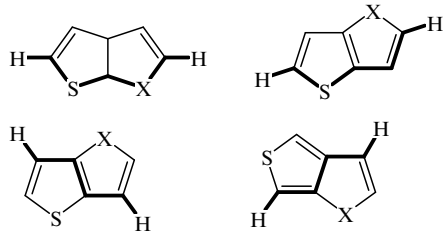
The multiplicity of the ground state, p-stability ('aromaticity'), the order and energy of the electron-excited and ionic states of thieno[3,4-*c*]thiophene were studied.[235] In particular, this compound was demonstrated to have 'aromaticity' analogous to that of thiophene, but it is much less stable due to a specific structure of its highest occupied molecular orbital.

2. NMR spectra

NMR spectroscopy along with and combined with other physicochemical methods is rather widely used to study the chemical structures of thienothiophenes and their heteroanalogs. In the study,[241] CNDO/2 calculations were carried out for selenophene and [2,3-*b*]-, [3,2-*b*]- and [3,4-*b*]-annelated thienoselenophenes **143**, **144**, **146** and **149**–**151**. Correlations between the calculated electron density and experimental ^{77}Se NMR chemical shifts in the spectra of these compounds were revealed. The chemical shifts were demonstrated to depend substantially on both the total and π-electron density on the selenium atom.

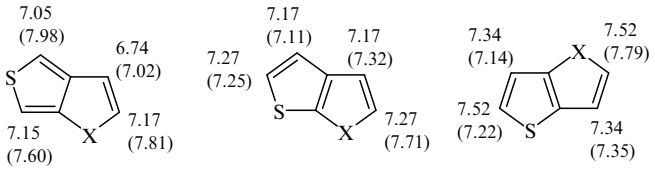
The ^{1}H, ^{13}C and ^{77}Se NMR spectra of selenopheno[2,3-*c*]thiophene (**149**),[242] selenopheno[2,3-*b*]selenophene (**144**),[243] selenopheno[3,2-*b*]selenophene (**146**),[244] selenopheno[3,4-*b*]selenophene (**151**)[245] and a series of 2-substituted selenopheno[2,3-*b*]-selenophenes[246] and -[3,2-*b*]selenophenes[247] were measured and analysed.

The ^{1}H NMR spectra of isomeric thienothiophenes, selenophenothiophenes and their derivatives[130, 248, 249] revealed long-range spin–spin coupling through five and six bonds located in a 'direct zigzag' system. This phenomenon is analogous to that observed in a series of other bicyclic systems including sulfur, nitrogen and oxygen atoms [see, for example, Ref. 250].



X = S, Se.

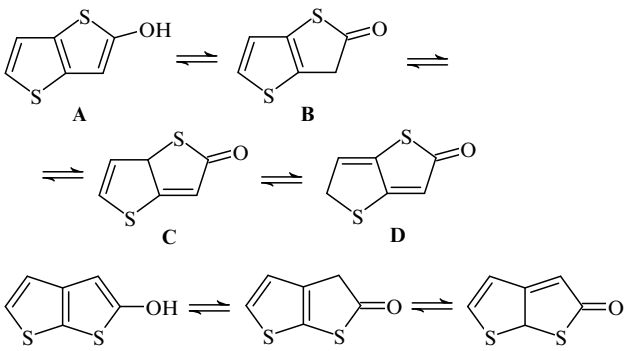
It was also concluded that the signals for the α- and β-protons of isomeric thieno- and selenophenothiophenes are characteristic of different modes of fusion of heterocyclic rings.[205] The chemical shifts of annelated thiophenes with X = S are given below (the values for X = Se are given in parentheses).

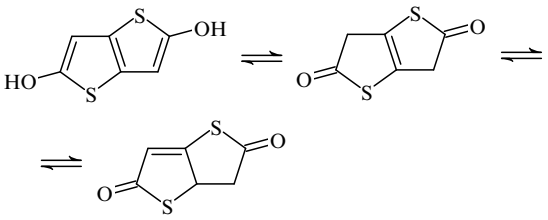


X = S, Se.

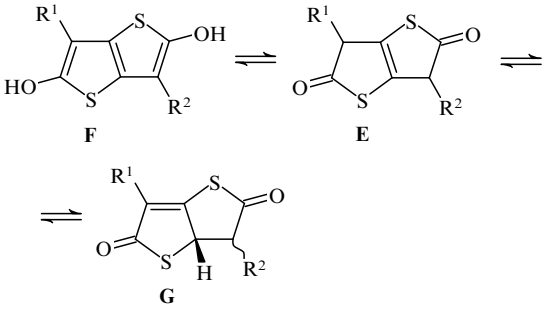
The spectra of isomeric selenophenothiophenes are characterised also by spin–spin coupling between the ^{77}Se atom (spin 1/2) and protons of the selenophene fragment[249] analogous to that observed in selenides of the thiophene series.[251]

Tautomerism of 2-hydroxythieno[2,3-*b*]- and -[3,2-*b*]thiophenes, 2,5-dihydroxythieno[3,2-*b*]thiophene and their alkyl- and aryl-substituted derivatives was also examined by NMR spectroscopy.[252, 253] These compounds were demonstrated to occur predominantly as thiolactones rather than in the hydroxy form. For the thieno[2,3-*b*]thiophene system, this equilibrium is completely shifted to thieno[2,3-*b*]thiophen-2(3*H*)-ones, whereas the forms **B** and **D** were found for [3,2-*b*]-fused systems. The effect of the nature and positions of the substituents on the tautomeric equilibrium was discussed.





Alkyl- and aryl-substituted 2,5-dihydroxythieno[3,2-*b*]thiophenes appeared to occur exclusively as dithiolactones. In no case was the hydroxy form of these compounds was detected.[253] The results of NMR spectroscopy demonstrated that 2,3-dihydrothieno[3,2-*b*]thiophene-2,5-dione (**E**) is a favourable structure. The tautomer **F** was detected only for the unsubstituted compound. However, this tautomer is readily transformed into the tautomer **E**. For 6-substituted compounds, two stereoisomers of the form **G** are observed; these stereoisomers have opposite configurations at the C(6) atom.

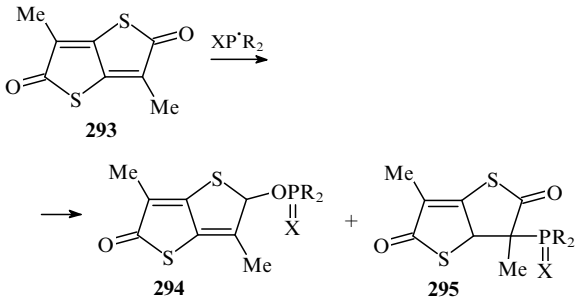


R^1 = H, Me, Bu^t, Ph; R^2 = H, Me, Ph.

The effects of the nature and positions of the substituents on stability of tautomeric forms were discussed.

3. ESR spectra

The reactions of the diphenylphosphoryl ($OP^{\bullet}Ph_2$) and diethoxyphosphoryl [$OP^{\bullet}(OEt)_2$] radicals with 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione (**293**) were studied by ESR spectroscopy.[254] Both reactions produce the oxygen-containing (**294**) and cyclic (**295**) adducts. The hyperfine coupling constants of the former adducts are close to those of analogous oxygen-containing adducts of Group IVB organometallic radicals.[255] The attack can occur on the carbon atoms at positions 3, 6 or 4, 5 of the ring. In the former case, the structure of the adduct is similar to that of the substituted allylic system, and the ESR spectra would be expected to show methyl splitting with the constant of $\sim$10 Hz. The reactions of dione **293** with the $SP^{\bullet}Et_2$ and $P^{\bullet}Ph_2$ radicals afforded predominantly derivatives **294**, although the ESR signals of cyclic adduct **295**, which was generated simultaneously with **294**, were recorded.

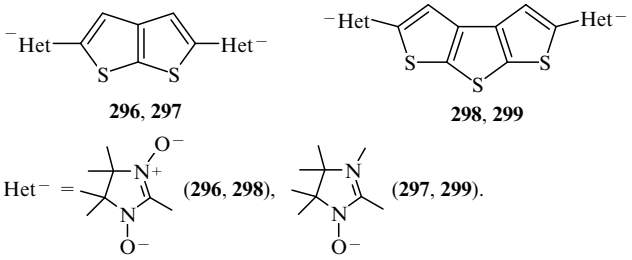


X = O: R = Ph, OEt; X = S, R = Et; X is absent, R = Ph.

The hyperfine coupling constants for paramagnetic adducts of the $M^{\bullet}R_3$ (M = Si, Ge, Sn) radicals with dithienyl and bis(thieno[2,3-*b*]- and -[3,2-*b*]thienyl) ketones were measured and compared with those of the diarylhydroxymethyl radicals. These results were confirmed by INDO calculations and indicate that the $2p_z$ orbital is involved in the O–M bond in dithienyl derivatives.[256]

Complexation of dibenzo-18-crown-6 ether with 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione **293**,[257] homolytic aromatic silylation of 2-cyanothieno[2,3-*b*]- and -[3,2-*b*]thiophenes,[258] addition of silyl radicals to 3,6-dimethylthieno[3,2-*b*]thiophene-2,5-dione and 5-benzylidene-3,6-dimethylthieno[3,2-*b*]thiophen-2-one[259] and the conformational behaviour of the dithieno[3,2-*b*:2′,3′-*d*]thiophene-2,6-dicarbaldehyde radical anions[260] were studied by ESR spectroscopy.

Diradical species **296**–**299**, in which two nitronyl nitroxide (ONC=NO) or imino nitroxide (NCNO) radical centres are bound to the thieno[2,3-*b*]thiophene and thieno[2,3-*b*]-thieno[3′,2′-*d*]thiophene chromophores, were investigated. Their intramolecular exchange coupling in frozen solutions and the magnetic sensitivity at low temperatures were examined by ESR spectroscopy.[261,262]



4. UV spectra

The nature and properties of the ground and first low-lying excited states of the thieno[3,2-*b*]thiophene (**145**) molecule were investigated in a series of spectroscopic studies.[263–268]

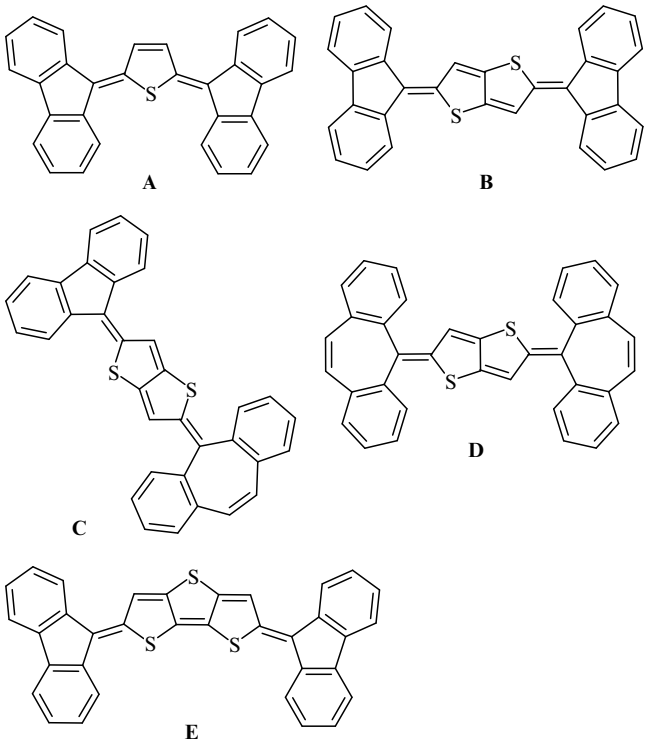
The first UV spectrum of thienothiophene **145** in the gas phase was recorded in 1956.[263] However, some details of the spectrum have remained uninterpreted because of the complicated spectral pattern. Only 20 years later, complete spectroscopic study, including IR and UV-Vis spectroscopy, of this compound was carried out both in the gas phase and in the crystalline state.[269] Two systems of intense absorption bands at 36 000–40 000 cm^{-1} were assigned to two electron transitions in the excited state, whereas a very weak band observed in the spectrum of the crystal at 34 394 cm^{-1} was assigned to a singlet–triplet transition caused by spin–orbit coupling. Calculations by the LCAO method with the STO/3G basis set[270] confirmed the assignment of the electron transitions.

The possibility of using the liquid-crystal linear dichroism (LCLD) technique for the assignment of electron transitions was exemplified by two models of chromophores with high (phenylthiol) and low (thienothiophene **145**) symmetry.[271] The LCLD spectrum of the thienothiophene chromophore revealed a new band, which has not been observed earlier, and confirmed the theoretical results.[270]

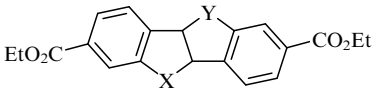
The thieno[3,2-*b*]thiophene (**145**), selenopheno[3,2-*b*]thiophene (**146**) and selenopheno[3,2-*b*]selenophene (**151**) charge-transfer complexes based on tetracyanoethylene (TCNE) were studied by UV and IR spectroscopy. The absorption spectra recorded in CCl_4 and CH_2Cl_2 show numerous charge-transfer bands.[272] A comparison with photoelectron spectra of other donors demonstrated that these bands appear due to transitions from two different occupied orbitals of the donor to unoccupied orbitals of the acceptor. The calculated ionisation potentials of the donors are consistent with the photoelectron spectroscopic data.

The quinoid compounds **A**, **B** and **E** have similar UV spectra, although the absorption maximum is shifted to longer wave-

lengths by approximately 50 nm with increasing number of thiophene rings.[182] The observed absorption maxima agree with the values calculated by the Pariser–Parr–Pople (PPP) method with allowance for restricted configuration interactions. For the **B**–**C**–**D** series, the long-wavelength band is shifted to higher frequencies in going from the first to the last compound, in spite of an increase in π-conjugation in this series of compounds. This may be a consequence of steric interactions between the phenyl fragment and the quinoid thienothiophene system, resulting in a deviation of the seven-membered ring from the plane. The discrepancy between the observed and calculated electron transitions for the long-wavelength band in the compounds **C** and **D** also confirms a non-planar structure of the total π-system of these molecules.



The UV spectra of 3,6-dimethylthieno[3,2-*b*]thiophene, 3,6-dimethylselenopheno[3,2-*b*]selenophene, their dimers, trimers and tetramers,[143] 2,2,5,5-tetramethylthieno[3,2-*b*]thiophene-3,6-dione,[111,211] and derivatives of benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene **121**[115] and compounds **300**–**305**[119] were measured and analysed.



300–**305**

X = Y = NMe (**300**); X = Y = S (**301**); X = Y = Se (**302**); X = NMe, Y = S (**303**); X = NMe, Y = Se (**304**); X = S, Y = Se (**305**).

The strongest absorption maximum in the UV-Vis spectra of compounds **300**–**305** is observed between 331 nm (for **301**) and 354 nm (for **300**); the longest-wavelength absorption is most intense, and the maximum is observed between 367 nm (for **301**) and 426 nm (for **300**). All compounds, except for **302**, show fluorescence: compound **300** shows strong fluorescence, whereas compounds **301** and **305** exhibit relatively weak fluorescence due, apparently, to the effect of the heavy atom.

The UV spectra of a homologous thienocene series show a shift of the long-wavelength band to the red region characterised by a good linear correlation with the number of the thiophene rings. A comparison of the UV spectra of heterohelicenes **175a**,**b** and **176a**,**b**[273–275] with the spectra of benzohelicenes[274,275] demonstrated that the longest-wavelength band (α band) is shifted to higher frequencies (by approximately 30 nm), whereas the positions of the second and third bands (p and β bands, respectively) are only slightly different.

The twist angles of the phenyl ring relative to the plane of the bicyclic fragment in 2-phenylthieno(or selenopheno)[2,3-*b*]thiophenes, -furans and analogous *N*-methylpyrroles were determined from absorption spectra and data on molecular refraction.[276]

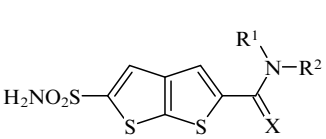
V. Fields of application

Earlier, the practical use of thienothiophenes has been limited primarily to the preparation of polymethine dyes, transition metal complexes,[2] as well as the synthesis of *N*-(aminoalkyl)thieno[3,2-*b*]thiophene-2-carboxamide derivatives, which were proposed as antidepressants and antitumor agents,[277] and the synthesis of benzo[*b*]thienobenzo[*b*]thiophenes, which are used as pesticides.[200,278] In recent years, the field of applications of these compound has been substantially extended due to the synthesis of numerous derivatives of this class of compounds. The introduction of pharmacophoric substituents into thienothiophene molecules and the use of these compounds in the synthesis of annelated systems gave rise to new types of biological activities. The discovery of unusual optical, electrical and complexation properties made it possible to prepare new materials for modern technology.

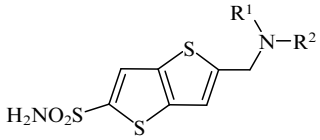
1. Biological activity

Since many thiophene-containing compounds, including annelated compounds, exhibit biological activities,[279–282] the structure–activity relationships for this series of heterocycles have attracted considerable attention. Studies are aimed both at using thienothiophenes as building blocks and searching for new types of biological activity of fused systems containing various central fragments.[38,81]

For example, 5-substituted thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-sulfonamides **306**–**312** were synthesised and proposed as glaucoma medicines.[36,147,283–289] In the cited studies, the substituents at position 5 were varied to increase solubility in water and achieve pK_a minimising binding of the iris pigment. The best results were obtained in tests of compound **306** [R^1 = $(CH_2)_2O(CH_2)_2OMe$, R^2 = $(CH_2)_2OMe$].[36]



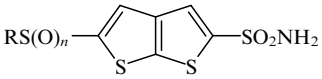
306: X = H_2; **307**: X = O



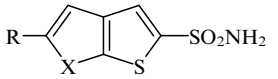
308

R^1 = Me, $(CH_2)_2OH$, $(CH_2)_2CH(OH)CH_2OH$, $(CH_2)_2NMe_2$, $(CH_2)_2S(O)Me$, $(CH_2)_2O(CH_2)_2OMe$, $(CH_2)_2N(CH_2CH_2)_2O$, $(CH_2)_2N(CH_2CH_2)_2S$;

R^2 = H, Me $(CH_2)_2OH$, $(CH_2)_2OMe$.



309: *n* = 0;
310: *n* = 2



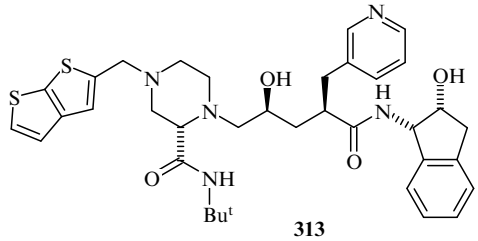
311: X = S;
312: X = SO_2

R = n-C_5H_{11}, $(CH_2)_3OH$, $(CH_2)_3N(CH_2CH_2)_2O$.

The results of pharmacological studies of the potential non-peptide fibrinogen receptor antagonist, *viz*., thieno[2,3-*b*]thiophene-based compound **172**, were reported.[148,290]

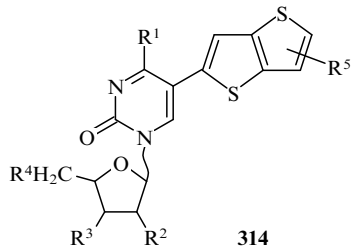
A series of thieno[2,3-*b*]thiophene-based HIV protease inhibitors were synthesised and tested.[291,292] At low concentrations, these inhibitors are efficient against HIV, and some of them provide a satisfactory plasma level in animals upon peroral administration. Among compounds of this series, compound **313**

proved to be the most promising (IC_{50} = 0.12 nM and IC_{95} = 6–12 nM).[291]



313

Pyrimidine nucleosides **314** containing the thieno[3,2-*b*]thiophene substituent hold promise against HIV and hepatitis B and were covered by a patent.[293]

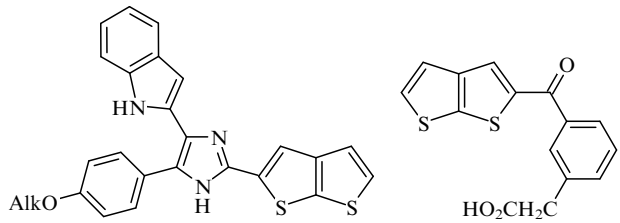


314

R^1 = OH, NH_2; R^2 = H, F, OH, OMe; R^3 = H, F, OH;
R^4 = OH, $(CH_2)_nP(O)(OMe)_2$; R^5 = H, C_1-C_{10}-Alk, Hal; n = 0, 1.

2-(Thienothienylglycyl)cephalosporin[294,295] and 2-(thienothienylphenyl)carbapenam derivatives[296] possess antibacterial properties.

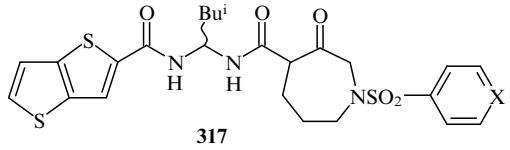
Patents covered procedures for the preparation of 4(5)-(3-indolyl)imidazoles **315**, which are useful for treatment of central nervous system function disorders, cerebrovascular dementia, senile dementia and memory or learning disorder,[297] the synthesis of thieno[2,3-*b*]thienyl-containing carboxylic acids **316** and their derivatives used as analgetics, inflammation and thrombosis inhibitors[298,299] and the synthesis of thieno[3,2-*b*]thiophene-2-carboxamides used as cyclooxygenase and lipoxygenase inhibitors.[300]



315

316

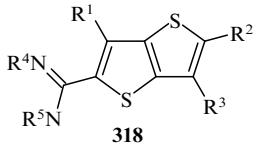
Thieno[3,2-*b*]thiophene-2-carboxamides **317**, which were prepared as mixtures of diastereomers and separated by high-performance liquid chromatography, were covered by patents as cysteine protease inhibitors.[301–305]



317

X = N, N^+-O^-.

Amidines of the thieno[3,2-*b*]thiophene series **318** were covered by patents as urokinase inhibitors.[306]



318

R^1 = H, NH_2, Hal; R^2, R^3 = H, Hal, HO, NH_2, NO_2;
R^4, R^5 = H, C_1-C_6-Alk.

Thieno[2,3-*b*]- and -[3,2-*b*]thiophene-2-carboxylic acids and their benzo[*b*]annelated analogues were synthesised and their lipid-reducing properties were investigated.[307] A number of hydrazides and sulfonamides of the thienothiophene series were covered by patents as pesticides.[308,309]

It was found that the smells given off by heated food include those of compounds formed by the reaction of thienothiophene-containing 4-hydroxy-5-methyl-3(2*H*)-furanones with cysteine or H_2S.[310] Thieno[3,2-*b*]thiophene derivatives were used in combinatorial synthesis to compile chemical libraries with the aim of examining the biological action of these compounds.[311]

2. Other areas of practical applications

Sulfur-containing heteroaromatic compounds, particularly, fused compounds having an extensive conjugated system can be used as building blocks for preparing organic conductors,[312–315] magnetic[316] and photosensitive receptors,[317] materials for optoelectronics,[318,319] *etc*. These compounds most often belong to charge-transfer complexes.[320–322] A rational combination of conducting polymers[323] and magnetic materials[324,325] requires the presence of precursors containing functional groups, which can enhance π-conjugation in the system as a results of condensation.

a. Complexation properties of isomeric thienothiophenes

Isomeric thienothiophenes and their derivatives are of considerable interest as electron donors or acceptors for the design of new types of charge-transfer complexes and as ligands coordinating metal ions. As mentioned above (see Section IV.4), charge-transfer complexes of some five-membered fused heteroaromatic systems with tetracyanoethylene were studied by UV and IR spectroscopy and their relative stabilities were discussed using the association constants and enthalpies of formation.[272]

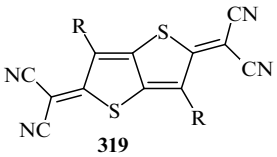
Thieno[2,3-*b*]thiophene and -[3,2-*b*]thiophene containing two 9-hydroxyfluoren-9-yl groups as substituents form charge-transfer complexes with 1,2,4,5-tetracyanobenzene (TCNB), which show fluorescence in the solid state.[222,326] Benzo[*b*]thieno[3,2-*b*]thiophene forms charge-transfer complexes with various organic acceptors.[327]

In recent years, dithienothiophenes have attracted considerable attention because these compounds have three various types of π-conjugation, which play a decisive role in the donor ability of these compounds.[7–9,157,215,218,328–333] Two higher homologues of fused polythiophenes, *viz*., thienocenes **6** and **7**, which are isoelectronic with chrysene and picene, respectively, but contain many fewer peripheral hydrogen atoms, were also used as precursors of organic conductors.[7,145,315]

As mentioned above (see Section III.2.c, and Ref. 334), 2,3,6,7-tetrathiabenzo[1,3-*cd*:4,6-*c*′*d*′]dipentalene (**225**) and its derivatives **226** form charge-transfer complexes with strong electron acceptors (TCNQ, $TCNQF_4$, DDQ and HCBD), most of which have a low conductivity.

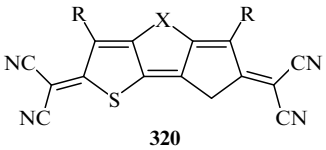
New fused thienothiophene, *viz*., 2,3:5,6-bis(ethylenedithio)-thieno[3,2-*b*]thiophene (**112**), was used to prepare conducting organic salts.[69]

Examples of the use of 2,5-bis(dicyanomethylene)-2,5-dihydrothieno[3,2-*b*]thiophenes (**319**) and -2,6-dihydrothieno[3,2-*b*:2′,3′-*d*]thiophenes **320** as electron acceptors were reported, and the resulting charge-transfer complexes have a very high (up to metallic) conductivity.[157]



319

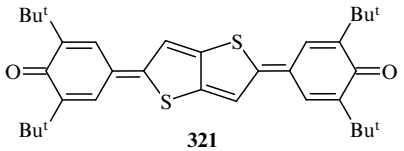
R = H, Br



320

X = S: R = H, Br;
X = SO, SO_2: R = H

2,5-Bis(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-2-ylidene)-2,5-dihydro-1,4-dithiapentalene (**321**) is also a promising electron acceptor for the formation of complexes.[335]



321

Dinuclear complexes of Group VIB (Cr, Mo, W)[336, 337] and Group VIII (Pt)[338] metal ions with 3,6-dimethylthieno[3,2-*b*]- and dithieno[3,2-*b*:2′,3′]thiophene as ligands were synthesised and studied.

b. Thienothiophenes as liquid and clathrate crystals

In the last 15 years, the liquid-crystalline properties of azomethines, azines, vinylenes and hexatrienes containing the thiophene or thieno[3,2-*b*]thiophene fragment were examined. Their thermal and optical properties were compared with those of analogous compounds of the benzene series.[144, 339] Taking into account particular characteristics, these compounds were proposed as materials for various purposes of modern technology.

Certain thieno[2,3-*b*]- and -[3,2-*b*]thiophene derivatives can be used in liquid-crystalline mixtures for electrooptical switches and evaluation devices.[340–342]

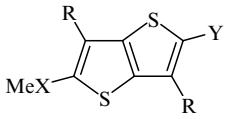
Benzo[*b*]thieno[3,2-*b*]benzo[*b*]thiophene-2,7-dicarboxylate derivatives exhibit properties of smectic liquid crystals, whose stability depends on the length and nature of terminal chains. Samples of these liquid crystals show pronounced photoconducting behaviour.[343]

Liquid-crystal linear dichroism of the thieno[3,2-*b*]thiophene molecule has been examined.[271]

Recently,[7, 145, 182, 215–223, 344–347] a series of new compounds possessing host-type complexation properties, for example, 2,5-bis(9-hydroxyfluoren-9-yl)thieno[3,2-*b*]thiophene (**278c**), were introduced into crystals of complexes. Such compounds are referred to as 'clathrate crystals'.[348]

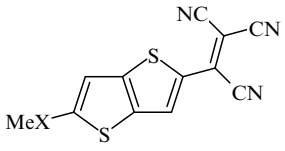
c. Materials for nonlinear optics

The recently discovered physical and chemical properties of thieno- and dithienothiophenes make it possible to use these fused heteroaromatic compounds for the design of new nonlinear optical materials. For example, the following two conjugated chromophoric charge-transfer systems were synthesised:[136] thieno[3,2-*b*]thiophenes **322**, which contain simultaneously electron-donating and electron-withdrawing substituents, and trinitriles **323**, which are heteroaromatic chromophores due to formation of charge-transfer complexes. The first hyperpolarisability (β) of these compounds was determined by electric-field-induced second-harmonic (EFISH) generation; the replacement of the oxygen atom with sulfur leads to a substantial increase in β, which remains unchanged in going to other chalcogens (Se or Te).



322

X = O, S, Se;
Y = CHO, NO_2;
R = H, Me

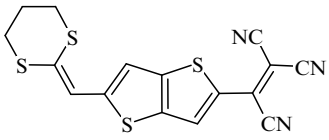


323

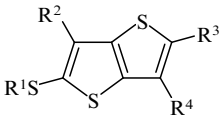
X = O, S, Se, Te

2-(1,3-Dithian-2-ylidenemethyl)-5-(tricyanovinyl)thieno[3,2-*b*]thiophene (**324**) was used to prepare nonlinear optical polymers.[349]

Substituted thioethers of thieno[3,2-*b*]thiophenes **325** possess analogous optical properties. The procedure for their preparation was covered by a patent.[350]



324



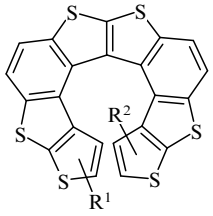
325

R^1 = C_1–C_{22}-Alk, CH = $C(CN)_2$; R^2, R^3, R^4 = H, Me;
R^2 = H, R^3 = NO_2, R^4 = CN, NO_2.

Thienothiophene-containing chromophores bearing the TCNQ group as an acceptor are as thermally stable as analogous chromophores containing the strong tricyanovinyl substituent but they are characterised by a substantially larger second-order optical nonlinearity.[351]

Many thieno[3,2-*b*]thiophene derivatives are important synthons for the design of new functional materials possessing chromophoric, conducting or nonlinear optical properties.[134, 137, 182, 183, 350, 352, 353]

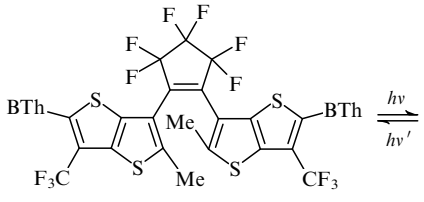
Materials containing hexathiaoctahelicene derivatives **326**, which show high third-harmonic generation and are resistant to thermal and optical laser action, were constructed.[354]



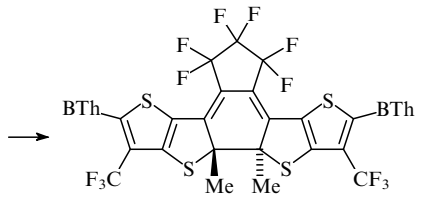
326

R^1, R^2 = H, C_1–C_6-Alk, C_1–C_6-OAlk, OH, NO_2, CN, CHO, Hal.

Photochromic compounds **181** were synthesised on the basis of benzothiazole derivatives of thieno[3,2-*b*]thiophene (see Section III.2). Their open (colourless, **181a**) and cyclic (coloured, **181b**) forms have high thermal stability, which makes it possible to perform repeated direct and reverse photoinduced transitions **181a** ⇆ **181b** with retention of the structure.[14, 15]

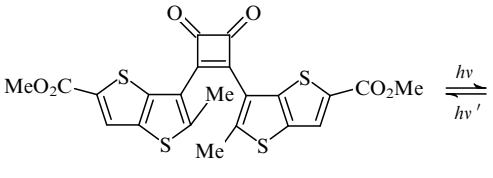


181a

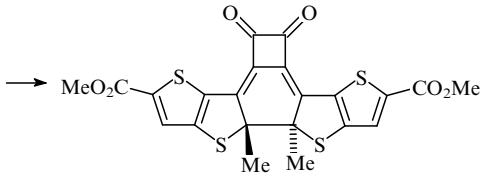


181b

Analogous cyclobutenedione derivatives of thieno[3,2-*b*]thiophene **327** were synthesised in continuing studies of the use of thienothiophenes for the design of new photochromic materials.[355, 356] Under UV irradiation (λ = 313 nm), compound **327** forms thermally stable (in the dark) cyclic form **327b**, which is again transformed into open form **327a** under irradiation with visible light (λ = 578 nm).

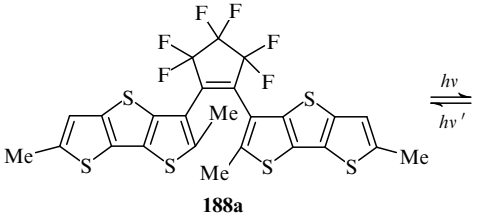


327a

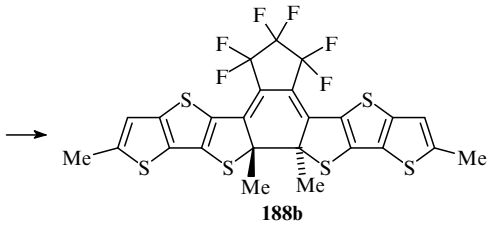


327b

The photochromic characteristics of 1,2-bis(2,6-dimethyldithieno[3,2-*b*:2′,3′-*d*]thiophen-3-yl)hexafluorocyclopent-1-ene (**188**) were studied in an acetonitrile solution.[18] The photocyclisation **188a** → **188b** was carried out under UV irradiation at λ = 313 nm, and the reverse reaction was performed under irradiation at λ = 578 nm. The long-wavelength absorption maxima for open form **188a** and cyclic form **188b** are 290 and 612 nm, respectively, which are comparable with the corresponding characteristics of benzothiazole derivatives.[14, 15]

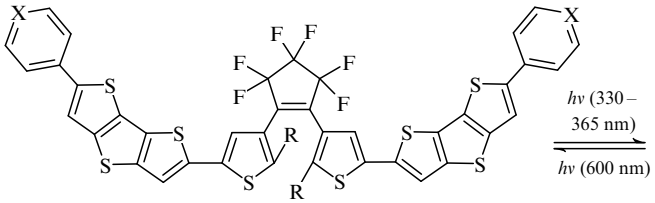


188a

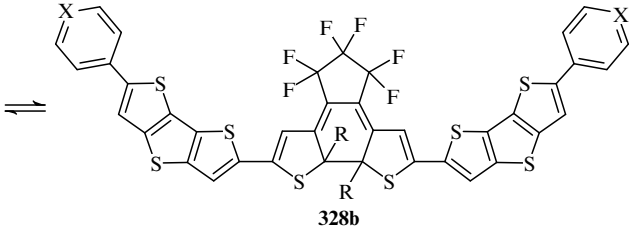


188b

Compounds **328a**,**b**, which have an extensive conjugation between two fused dithienothiophene fragments, were synthesised in the study.[152] High thermal stability, fatigue strength, sensitivity to the diode laser wavelength, nearly quantitatively reversible interconversion and, particularly, ability to perform nondestructive data reading give a real possibility to use these compounds as photoswitching elements in practice.



328a



328b

R = n-C_6H_{13} ; X = N or $MeN^+(CF_3SO_3)^-$.

New quadrupolar photophores **189** and **190**, which contain fragments exhibiting very high two-photon absorption and simultaneously have high quantum yield, were synthesised.[155] Other dithienothiophene-containing nonlinear-optical chromophores were also prepared and have found use as optical relays of a new type.[153]

Benzo[*b*]annelated thieno[3,2-*b*]thiophenes were covered by patents as organic photoconductors[357] and fluorescent bleaching agents.[358]

d. Conjugated polymers

In recent years, the number of publications on photochemical and electrochemical polymerisation of thienothiophenes and their polyannelated analogues has been increased sharply. These compounds form conjugated polymers possessing unique properties. Since this field of thienothiophene chemistry is beyond the scope of the present review, only the references to such studies are given.[7, 143, 167, 169, 347, 359–381]

Studies of copolymerisation of a new class of highly efficient optical chromophores with thieno- and dithienothiophenes as linking units led to the design of conducting polymers.[169, 353, 382–391] Poly(thieno[3,4-*b*]thiophenes), which are stable conducting polymers, have attracted particular attention. These compounds were prepared by electrochemical polymerisation of thieno[3,4-*b*]thiophene and its derivatives. These polymers hold promise, in particular, as new materials for electrochromic devices.[392–405]

A new class of silicon-containing copolymers were synthesised by the Heck reaction of distyrylsilane monomers with thiophene and thieno[3,2-*b*]thiophene derivatives, their luminescence properties were studied, and these polymers were demonstrated to be promising electroluminescent materials.[406, 407]

The electropolymerisation kinetics of 3,6-dimethylthieno[3,2-*b*]thiophene was studied by cyclic voltammetry, chronoamperometry and chronopotentiometry on glassy carbon in the presence of a 0.1 M $LiClO_4$ solution.[408]

3. Dyes

A few publications were devoted to the use of thienothiophene derivatives for the design of new dyeing materials. For example, diazotisation of aminothienothiophene derivatives afforded disperse azo dyes for colouring synthetic or polyester fibres.[409–411] Thieno[3,2-*b*]thienylidenebis(benzoquinones) were covered by a patent as dyes for optical recording devices.[412]

New electro- and photoactive multifunctional dyes were designed on the basis of dithienothiophenes.[413–415] The pigment properties of 2,2,5,5-tetramethyl-2,3,5,6-tetrahydrothieno[3,2-*b*]thiophene (**127**) were compared with those of analogous compounds containing the thioindigoid fragment, and thienothiophene **127** was demonstrated to belong to indigoid dyes.[113, 213]

Compounds of the thieno[2,3-*b*]thiophene (**142**), thieno[3,2-*b*]thiophene (**145**), dithieno[3,2-*b*:2′,3′-*d*]thiophene (**108a**) and thieno[2′,3′:4,5]thieno[2′,3′-*d*]thieno[3,2-*b*]thiophene (**6**) series were also covered by a patent as components (in amounts of 0.01%–0.8%) for the preparation of nonaqueous electrolyte solutions.[416]

VI. Conclusion

In the chemistry of heterocyclic compounds, the end of the 20th century was marked by a growing interest in fused systems, as evidenced, in particular, by a snowballing increase in the number of publications in this field of chemistry. Analysis of the data published in the literature in the last 25 years demonstrates that the theoretical, synthetic, physicochemical and, particularly, practical aspects of the chemistry of thienothiophenes and their analogues attract growing attention of researchers working in different fields.

The range of practical applications of isomeric thienothiophene derivatives and their O-, N-, S-, Se-, Te-containing and fused analogues is very wide, from real prospects for the design of new medicines (due to a wide spectrum of pharmacological activities) to the design of the previously unknown liquid and clathrate crystals, charge-transfer complexes (organic conductors, magnetic and photosensitive receptors), electroconducting polymers, new nonlinear optical materials necessary for informational technologies, dyes, *etc*.[417]

The further development of the chemistry of fused chalcogen-containing heterocycles will be, apparently, associated with the introduction of various pharmacophoric groups at different positions of the molecules with the aim of preparing new efficient medicines and also with the use of these heterocycles as building blocks for the design of new highly conjugated heterocyclic systems as promising technological materials of the 21th century.

I hope that the present review will be not only helpful to researchers dealing with the chemistry of heterocyclic compounds but also will attract attention of researchers working in other fields of science, such as pharmacology, technology, optoelectronics, *etc*.

I thank Professor M M Krayushkin, who has successfully combined the development of methods for the synthesis of the previously unknown thienothiophene derivatives and the use of these compounds for the design of new photochromic materials in his recent studies (see, for example, Ref. 417), for the idea to write this review and help in analysing published data.

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