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

Cyclization of Nitriles as Synthetic Route to 2-and 3-Aminothiophenes

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To cite this Article Litvinov, V. P. , Sharanin, Yu. A. and Babichev, F. S.(1986) 'Cyclization of Nitriles as Synthetic Route to 2-and 3-Aminothiophenes', Journal of Sulfur Chemistry, 6: 2, 97 — 128
To link to this Article: DOI: 10.1080/01961778608082495
URL: http://dx.doi.org/10.1080/01961778608082495

Sulfur Reports
Volume 6(2), August 1986, pp. 97–135

Printed in the United Kingdom.

CYCLIZATION OF NITRILES AS SYNTHETIC ROUTE TO 2- AND 3-AMINOTHIOPHENES

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(Received August 3, 1985)

This review is concerned with the preparation of 2- and 3-aminothiophenes, their hydrogenated derivatives, and fused systems by cyclization of nitriles. Substantial attention is given to the procedures for the synthesis of nitriles since they occur as intermediates in most reactions leading to aminothiophenes.

KEY WORDS: 2-Aminothiophenes, 3-aminothiophenes, Gewald reaction

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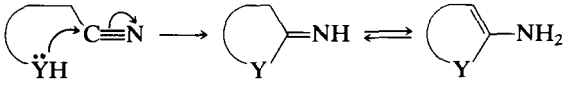
I. INTRODUCTION

In the past two decades the number of publications dealing with various aspects of the chemistry of thiophene and its derivatives has greatly increased. Among thiophene derivatives, amino derivatives of the thiophene series, their hydrogenated analogs, and fused systems incorporating aminothiophene rings make up an important group of substances; many of them have found practical applications as pharmaceuticals, pesticides, dyestuff intermediates, and in other fields of fine organic synthesis.

At the same time the reviews on thiophene chemistry now available[1–4] fall behind in the presentation of the latest accomplishments in the synthetic chemistry of aminothiophenes. Among general techniques for the preparation of aromatic amines, reduction of nitro,[5,6] nitroso,[7,8] and azo compounds,[9,10] exchange of the amino group for a halogen,[11,12] rearrangements of azides (Curtius)[13,14] and amides (Hofmann),[15,16] and certain other techniques are of only limited applicability to aminothiophenes.[2–4] For that reason cyclization of nitriles according to the scheme



(I) **(II)** **(III)**

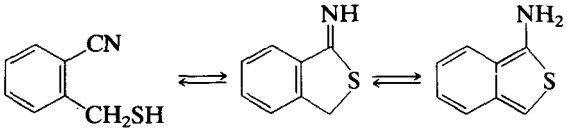
is of considerable preparative importance. With Y = S in (I), 2-aminothiophenes are formed. 3-Aminothiophenes can be prepared by the Thorpe reaction from (I) containing sulphur between the reactive centers Y (an activated CH_2 group) and CN.

It should be borne in mind that generally, because of the presence of two reactive centers (YH as nucleophile and the nitrile carbon atom as an electrophile) compounds (I) can undergo cyclization to imines (II) which are, as a rule, stabilized as amines (III). Reactions involving the formation of (I), which mostly cannot be isolated, therefore provide a means of preparing 2- and 3-aminothiophenes. Numerous examples of such transformations can be found in the literature. At the same time the monograph by Taylor and McKillop[17] only includes data on enaminonitriles of the thiophene series available at the time of its publication. Other reviews[17–25] discuss separate, often not very important, points pertaining to the problem. The same topic is discussed in the reviews[25–27] which are not as comprehensive as one could wish. This prompted us to undertake a general survey of literature data concerning the synthesis of 2- and 3-aminothiophenes. Especial attention has been given to work published during the past decade.

II. SYNTHETIC ROUTES TO 2-AMINOTHIOPHENES

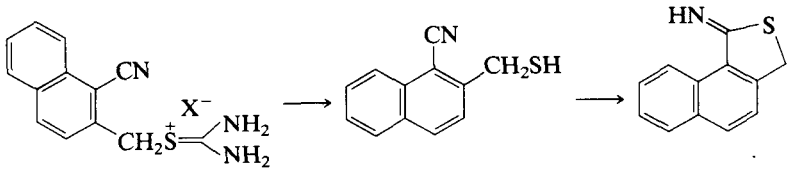
Unsubstituted 2- and 3-aminothiophenes are rather labile, and the former were believed to be far less stable than the latter. Stacy and Eck[28,29] were, however, able to isolate 2-aminothiophene (m.p. 12–13 °C) by treating its hydrochloride with dry ammonia in methylene chloride. The hydrochloride was made by cyclization of *cis*-2-(benzylthio)crotononitrile. 2-Aminothiophene was purified from hexane/methylene chloride at reduced temperature under nitrogen.[29] An attempt to prepare 2-aminothiophene by extracting an alkaline solution with benzene resulted in the isolation of 2,5-bis(cyanomethyl)-1,4-dithiane in 25% yield because of intermediate formation of 3-mercaptobutenenitrile as a result of 2-aminothiophene ring-opening.[30] This reaction is in essence the reverse of the process of formation of 2-aminothiophene we are considering.

Because of the reasons specified above the reaction was first studied with fused thiophenes. Thus, it was demonstrated that 2-cyanobenzyl mercaptan occurred as a cyclic imine.[31]



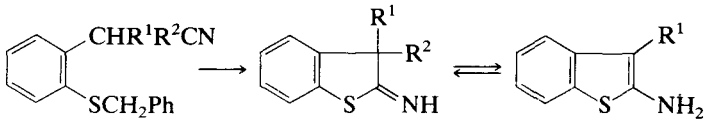
Later, the ring-chain tautomerism of fused iminothiolactones was studied by Stacy co-workers.[28,31–35]

The reactions mentioned are based on the preparation of 2-mercaptonitriles from the corresponding halides. The synthesis of thiouronium salts which undergo cyclization to give [c]-annelated systems[35] also appears to be a promising preparative



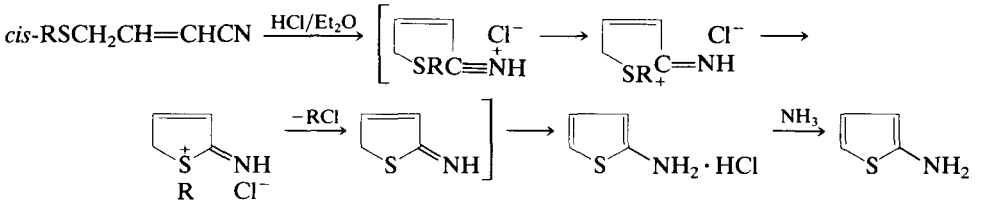
method.

Stacy *et al.*[28,35] described a procedure for the preparation of [b]-annelated 2-aminothiophenes including the cyclization of benzyl sulfide (**IV**) to 2-aminobenzo[b]thiophene (**VI**) or 2-iminobenzo[b]thiophene (**V**) under the action of anhydrous $AlCl_3$ or $AlBr_3$:



(**IV**) (**V**) (**VI**)

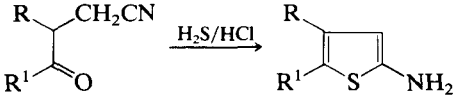
2-Aminothiophene formed from *cis*-γ-(benzylthio)crotononitrile whose *trans*-isomer gave γ-(benzylthio)-3-chlorobutyronitrile in 60% yield under similar conditions. The use of HCl as catalyst gives better results than that of $AlBr_3$.[28,29] The yield and quality of the 2-aminothiophene hydrochloride are improved substantially if *cis*-γ-(benzylthio)crotononitrile is used as starting material.



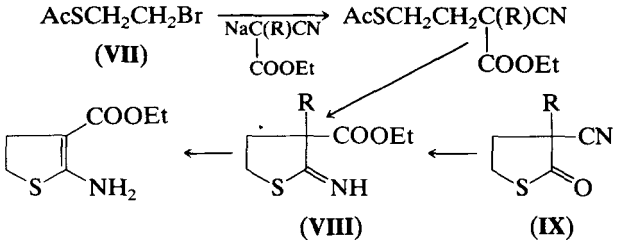
R = $PhCH_2$, Ph_2CH

The preparation of [b]- and [c]-annelated 2-aminothiophenes is described in the reviews.[17,23,27,36,37]

γ-Mercaptonitriles are produced not only from the corresponding halides but also by saturating methanolic solutions of γ-keto nitriles with hydrogen sulfide and hydrogen chloride. Like other acidic reagents HCl increases the electrophilic properties of the nitrile carbon and therefore the cyclization rate. This results in the production of 2-aminothiophenes as final reaction products.[38] This route was used to synthesize 2-amino-5-phenylthiophene and 2-amino-4,5,6,7-tetrahydrobenzo[b]-thiophene.

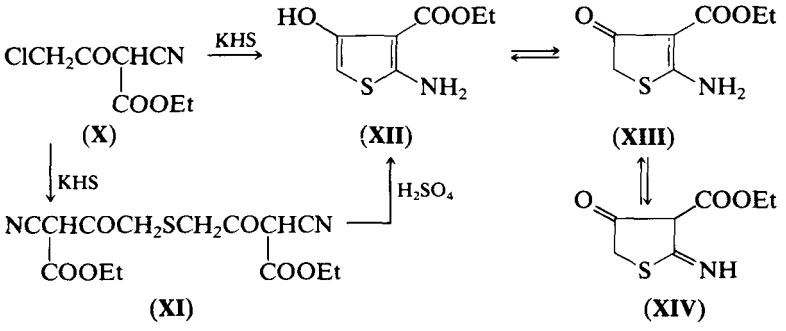


The ethyl 2-imino-4,5-dihydrothiophene-3-carboxylate (**VIII**) was isolated in an attempt to prepare a thiolactone from ethyl 2-cyano-4-mercaptobutenoate from 1-bromo-2-(acetylthio)ethane (**VII**) and sodium cyanoacetate.[39] It should be noted that cyanothiolactones (**IX**) readily undergo ring opening-ring closure to amino derivatives of dihydrothiophene under the action of sodium ethoxide (see the review[40]).



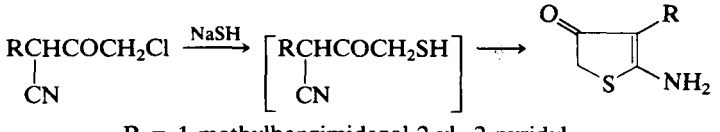
Ethyl 2-methyl-2-cyano-4-(acetylthio)butenoate undergoes a similar cyclization.[39]

Heating an aqueous solution of chloroacetylcyanoacetic ester (**X**) in the presence of potassium hydrogen sulfide gives ethyl 2-amino-4-hydroxythiophene-3-carboxylate (**XII**) in 46% yield and sulfide (**XI**).[41] According to proton NMR evidence the solution contains three isomers, **XII**, **XIII**, and **XIV**, the amino form (**XIII**) being the most stable one.[42]



Sulfide (**XI**) undergoes cyclization to aminothiophene (**XII**) in the presence of concentrated sulfuric acid.[41]

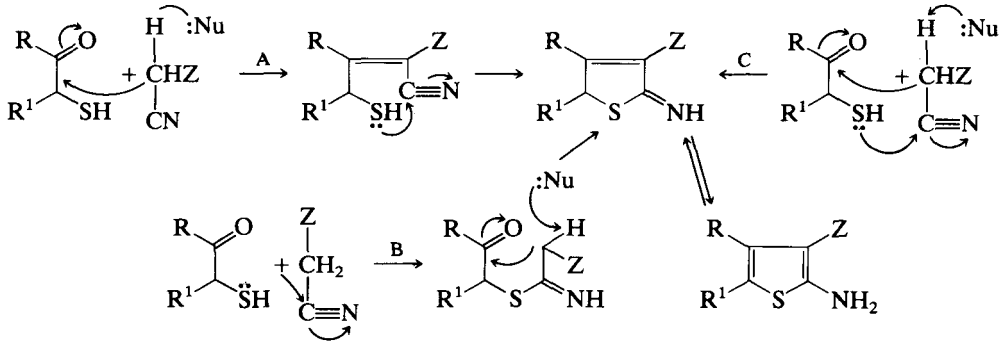
This approach was extended to chloroacetylheteroarylacetonitriles.[43]



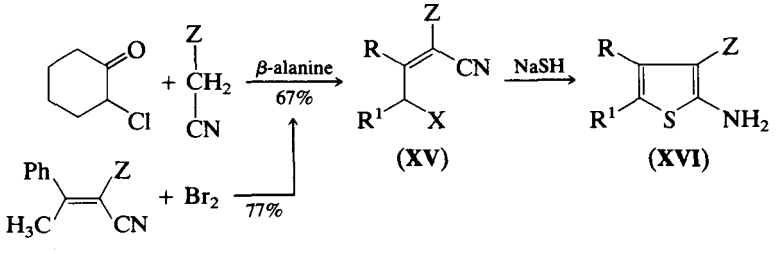
R = 1-methylbenzimidazol-2-yl, 2-pyridyl

The acylation of heteroarylacetonitriles by mercaptoacetic acid ester in the presence of sodium *t*-butoxide can serve as a route to 2-amino-3-heteroaryl-4(5*H*)-oxothiophenes used in the synthesis of physiologically active substances.[44]

Gewald suggested a convenient and promising procedure for the preparation of 2-aminothiophenes. He showed that the reaction of α-mercapto carbonyl compounds with nitriles containing an active methylene group in the presence of bases produced 2-aminothiophenes in satisfactory yields.[26,45,46] It is likely that the first step of the reaction is the condensation of a nitrile at the α-mercapto ketone carbonyl function (as in the Knoevenagel reaction) with the formation of a γ-mercaptonitrile structure convenient for cyclization (path A). The first step was also suggested to be the addition of an α-mercapto carbonyl derivative to the nitrile group (path B)[26] which readily goes at room temperature. Neither should the electrocyclic mechanism be ruled out (path C):



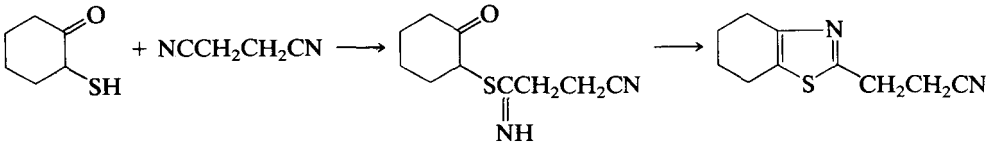
The structure of the 2-aminothiophenes (**XVI**) was proved by treating the halo derivatives (**XV**) with sodium hydrogen sulfide. Compounds (**XV**) were in their turn isolated from reactions of 2-chlorocyclohexanone with nitriles containing active methylene groups in the presence of β-alanine (other α-halo ketones do not undergo the Knoevenagel reaction), or they were obtained by direct bromination of ylidene derivatives of the nitriles according to[46]:



This procedure is, however, inferior to the Gewald reaction as a preparative route because the initial compounds are difficult of access.

Later, the reaction was extended to various γ-mercapto carbonyl derivatives.[47–52] The condensation is as a rule carried out in a polar solvent such as ethanol or DMF in the presence of an organic base (diethylamine, triethylamine, morpholine, piperidine, etc.). The reaction rate increases with the electron-acceptor properties of the substituent Z at the methylene group. Thus, mercapto ketones react with malononitrile so easily that the reaction goes in aqueous media and can be employed to

characterize the very labile mercaptoacetone.[53] Conversely, cyanoacetic acid and benzyl cyanide do not react with α-mercapto carbonyl compounds whereas 2-mercaptocyclohexanone undergoes addition to the nitrile group of succinonitrile under similar conditions to yield the corresponding thiazole as the final reaction product.[46]

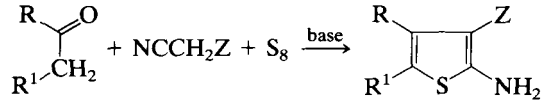


The reaction has certain other limitations, first of all because the starting compounds are unstable and difficult to prepare. For example, dimercaptoacetone and malononitrile yield bis(2-amino-3-cyano-4-thienylmethyl) disulfide under the reaction conditions in air[46]; this compound can, without isolation, be transformed to a number of other compounds.[54]

A number of modifications has been suggested to improve this reaction. 2,5-Dihydroxy-1,4-dithianes which are dimeric α-mercapto carbonyls have been successfully used to prepare substituted 2-aminothiophenes in yields amounting to 75 to 90%.[46,55–64] The procedure can be exemplified by the synthesis of 2-amino-3-carbamoylthiophene used as a diazo component in the production of disperse dyes.[45]

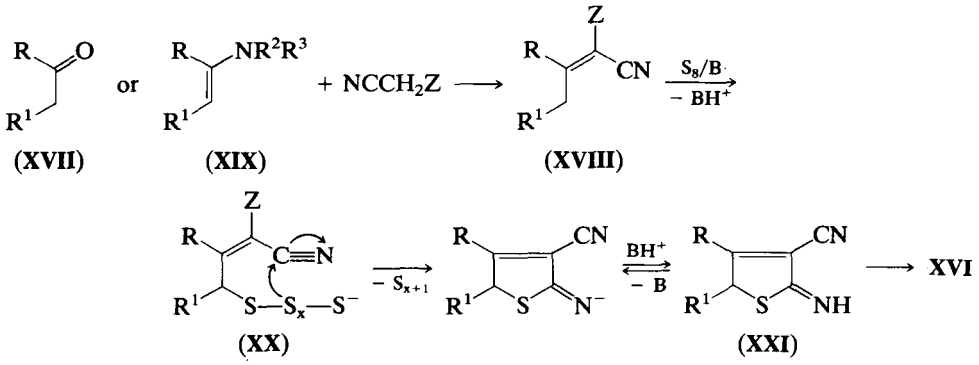
The technique was employed to obtain a number of 2-aminothiophenes unsubstituted at the 4- and 5-positions of the thiophene ring. The reaction was run with amides[56–59] and thioamides of cyanoacetic acid,[55] phenacyl cyanides,[61–63] and cyanoacetic acid.[56,57] Esters of mercaptoacetic acid react with nitriles containing an active methylene group in alcohol in the presence of diethylamine to give the corresponding 2-Z-methylenethiazolidinones-4 rather than their 2-amino-3-Z-4-hydroxythiophene isomers.[42]

A further considerable improvement of the Gewald reaction was the replacement of α-mercapto ketones by a mixture of a carbonyl compound and sulfur powder.[65,66] This technique gives 2-aminothiophenes in yields which are not only comparable with, but often exceed, those obtainable in the reactions described above. These reactions have been applied to carbonyl compounds like aldehydes,[66–73], ketones,[47–49,65,74–93] and 1,3-dicarbonyl compounds.[94–97] Nitriles such as malononitrile,[65,66,74,76,78–82,89,90–95] cyanoacetic esters,[66–68,71–74,76,78,81–85,89,90] cyanoacetamide and its *N*-substituted derivatives,[66,70,86–88] α-cyano ketones,[66,70,72,73,86–88] and heteroarylacetonitriles[77] can be used as the nitrile component in the reaction. Preferred solvents are ethanol and DMF. 2-Aminothiophenes unsubstituted at the heterocyclic ring position 4 have been prepared from aldehydes.[66–72].



Exceptions from the reaction pattern have been found for some simple carbonyl compounds. For example, acetaldehyde undergoes aldol condensation under the reaction conditions, and no corresponding 2-aminothiophene is formed. With acetone, the reaction goes further to give bis(2-amino-4-methyl-3-ethoxycarbonylthienyl-5) disulfide as the major product of the three-component condensation of acetone, sulfur, and cyanoacetic ester in ethanol in the presence of diethylamine or triethylamine. The reaction path includes oxidation by sulfur or air of the originally formed 2-amino-4-methyl-5-mercapto-3-ethoxycarbonylthiophene.[74] Under similar conditions, acetylacetone reacts with cyanoacetic acid ester and sulfur to give 2-amino-5-acetyl-4-methyl-3-methoxycarbonylthiophene, analogous with the nitrile of β-(2-amino-4-methyl-3-methoxycarbonylthienyl-5)crotonic acid.[66]

Carbonyl compound (**XVII**) can be thought to react first with the nitrile containing an active methylene group as in a Knoevenagel reaction to give the alkylidene derivative (**XVIII**) which then reacts with sulfur to produce the corresponding 2-aminothiophene (**XVI**). The observation that alkylidene derivatives of methylene-active nitriles (**XVIII**), isolated as individual substances, also react with sulphur to give 2-aminothiophenes[66,72,74,79,80,98–108] lends support to this reaction scheme. The yields of 2-aminothiophenes from the latter reaction are somewhat higher. The type of the interaction is determined by the reactivity of the methylene component, the structure of the initial aldehyde or ketone, the nature of the catalyst employed, and the solvent. The kinetic characteristics of the reaction were not studied, and the data available do not allow us to give preference of this technique over the one involving a preliminary sulfuration (thiolation) of carbonyl compounds or vice versa.



Certain points concerning the interaction of CH-acidic compounds with sulfur are discussed in Ref.[19] It should also be mentioned that initially enamine (**XIX**) may be formed because in most reactions organic bases are used as catalysts. Moreover, reactions of enamines (**XIX**) with methylene-active nitriles have been shown to give 2-aminothiophenes (**XVI**).[66,78] Reactions of both carbonyl compounds (**XVII**) and

enamines (**XIX**) involve γ-mercapto nitriles as intermediates. The possibility of their formation from γ-mercapto carbonyl compounds was already mentioned. The isolation of alkylidene derivatives (**XVIII**) or enamines (**XIX**) as synthetic procedure has no advantages over the three-component condensation of carbonyl compounds, methylene-active nitriles, and sulfur, except when the carbonyl component is an aliphatic-aromatic ketone of low reactivity such as acetophenone.

The high yields of substituted 2-aminothiophenes are indicative of the reaction being almost independent of the steric characteristics of the alkylidene derivatives of methylene-active nitriles (**XVIII**) which easily undergo isomerization in the presence of bases.[26,76,103]

The presence of electron-withdrawing substituents in the methylene-active intermediate is a necessary condition[26]; this condition is fulfilled by the use of starting nitriles containing an electron acceptor Z linked with the methylene group. The presence of such substituents also facilitates the Knoevenagel reaction. The most reactive methylene-active nitriles used were malononitrile and, in the order of decreasing reactivity, cyanoacetic acid ester and cyanoacetamide. Generally, thiolation mostly involves the methylene rather than the methyl group.[19,26] This is illustrated, e.g. by the preparation of 2-amino-3-Z-4,5-dimethylthiophenes from methyl ethyl ketone.[66] The presence of an electron-withdrawing substituent at the methylene group undergoing thiolation also facilitates the reaction.[103] It should also be borne in mind that electron-withdrawing substituents stabilize 2-aminothiophenes.

The Gewald reaction is limited by the dimerization of the alkylidene derivatives of methylene-active nitriles[26,27] which competes with the thiolation. This should be borne in mind, especially with aryl ketones having low reactivities which do not form

TABLE 1

Melting Points and Yields of 2-Aminothiophenes (XVI) Isolated from Various Reactions

R	R^1	Z	m.p., °C	Yield, % a	b	c	d
CH_3	CH_3	CN	141–142	70[46]	42[66]	41[66]	—
CH_3	CH_3	COOEt	91–92	—	39[66]	40[66] 55[99]	—
H	C_2H_5	COOEt	73	—	60[67] 75[66]	—	46[78]
H	COOEt	COOEt	107–108	—	32[66]	—	34[78]
$(CH_2)_4$	H	CN	147–148	70[46]	86[66] 61[79]	90[66]	—
$(CH_2)_4$	H	COOEt	115	80[46]	82[66]	91[66]	85[78]

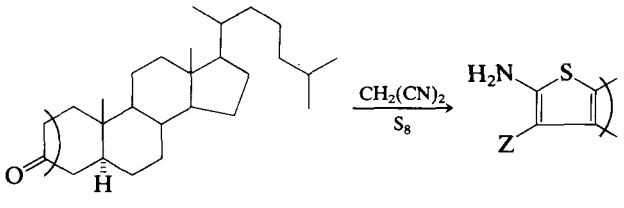
Footnote: [a] Condensation of mercapto carbonyl compounds with methylene-active nitriles.
[b] Three-component condensation of carbonyl compounds, methylene-active nitriles, and sulfur.
[c] Interaction of nitrile ylidene derivatives with sulfur.
[d] Condensation of enamines, methylene-active nitriles, and sulfur.

the corresponding 2-aminothiophenes, probably because of the dimerization. Aryl ethyl ketones were, however, found to react with malononitrile and sulfur in the presence of morpholine to give the corresponding 2-amino-3-cyanothiophenes.[81]

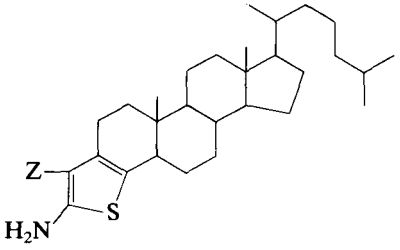
The reaction we are considering goes more easily with cyclic ketones such as cyclohexanone,[48,49,65,66,78,81–87] its substituted derivatives,[48,79,88–91] and fused systems incorporating cyclohexanone,[79,91,92] cyclopentanone[66] and the higher cycloalkanones,[82,89,93,103] and cycloalkylidene derivatives of methylene-active nitriles.[66,79,101,102,104]

Cyanoacetic acid hydrazide, cyclohexanone, and sulfur react to yield 3-cyclohexylideneamino-2,2-pentamethylene-5,6-tetramethylene-1,2-dihydrothieno[2,3-d]-pyrimidone-4, probably formed via the hydrazide of 2-aminothiophene-3-carboxylic acid. The latter compound can be isolated by subjecting the reaction products to acidic hydrolysis.[87]

Similar reactions leading to 2-aminothiophenes have been reported for more complex cyclic ketones such as bicyclo[2.2.1]heptanone-2,[109] steroids,[93,110,111] and 1,3,3a,4,9,9a-hexahydro-2-methyl-4,5-ethano-2*H*-benz[f]-isoindolone-10.[92] Thus cholestanone-3 (**XXII**) gives 2′-amino-3′-cyanocholest-2-eno[2,3-b]thiophene (**XXIII**).[110]



(**XXII**) (**XXIII**)

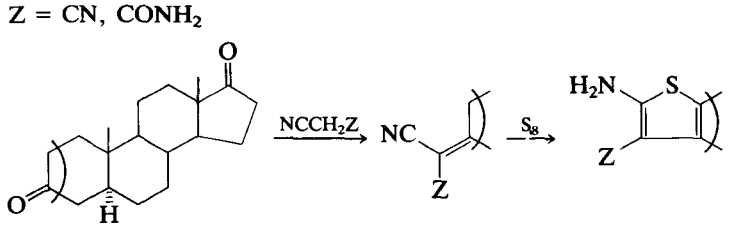


(**XXIV**)

The reaction is believed to involve the thiolation product (**XX**) as an intermediate. This intermediate undergoes cyclization to the imine (**XXI**) which isomerizes to produce a more stable amine (**XXIII**). Note that the final product was erroneously assigned the structure (**XXIV**) in Ref.[93]: the structure of the cholestenothiophene (**XXIII**) was proved by its synthesis from the 2-ethylxanthate of 3-cholestanol.[110] 3-Cholestanone-2-thiol and malononitrile can be used in this reaction instead of the corresponding ethylxanthate.

Androstane-3,17-dione also reacts with malononitrile or cyanoacetic ester and sulfur in the presence of morpholine. The reaction was shown to involve only the

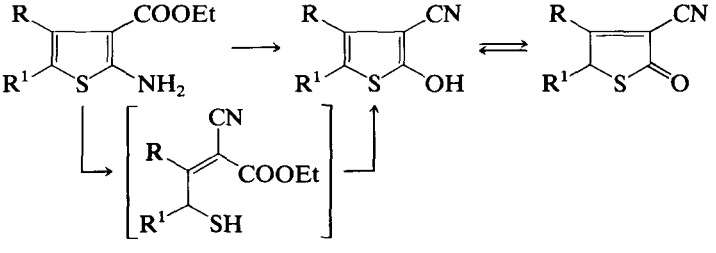
3-keto group of the steroid to give products (**XXVII**) identical with those obtained from the corresponding 3-ylidene derivatives (**XXVI**)[111]:



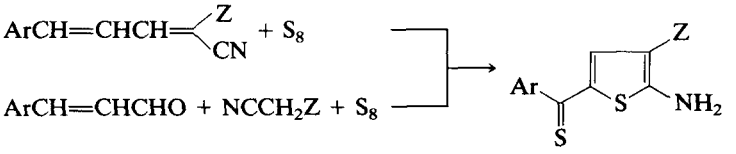
(**XXV**) (**XXVI**) (**XXVII**)

With a view towards preparing physiologically active substances and to broaden the scope of the Gewald reaction it was studied with heterocyclic ketones[89,112–128] and their ylidene derivatives.[115,116,120,128] The products obtained from these starting materials include 2-amino-3-Z-6,7-dihydro-4*H*-1,4-dithiepino[5,6-b]-thiophene,[128] 2-amino-5,5-dimethyl-4,5-dihydro-7*H*-pyrano[3,4-b]thiophene,[113–117] thiopyrano[3,4-b]thiophenes,[114–119] 4,5-dihydrothieno[2,3-b]thiophene,[112] 2-amino-6-R-3-Z-4,5,6,7-tetrahydrothieno[2,3-c]pyridines[119–127] including those based on quinuclidone-3,[126,127] and 2-amino-9-aza-3-cyanomethyleno[2,3-b]bicyclo[3.2.1]octane.[124] The initial heterocycloalkanones-4 are fairly easy to prepare by cycloaddition of hydrogen sulfide and ammonia or amines to chalcones. This circumstance and the observation that usually cyclic ketones form fused 2-aminothiophenes readily and in high yield make the reaction under consideration a promising synthetic route.

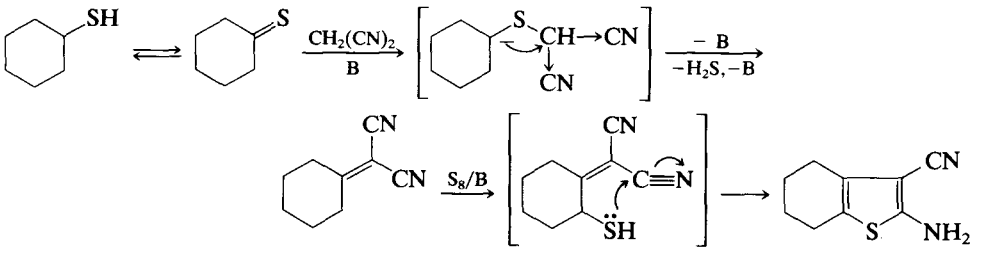
As mentioned organic bases are used as catalysts. Those employed most often are diethylamine, triethylamine, morpholine, piperidine, etc. The nature of the base is of considerable importance because the catalytic action depends on increasing the nucleophilic properties of the thiol group. For example, alkali metal alkoxides are known to be able to cause recyclization of 2-amino-3-alkoxycarbonylthiophenes to the corresponding 3-cyanothiolactones[129] which rules out the possibility of the formation of ylidene derivatives such as γ-mercaptonitriles.



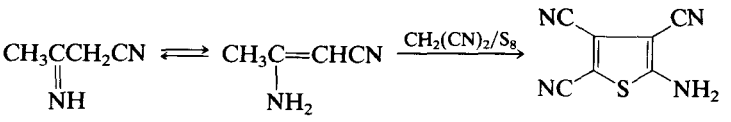
The interaction of 1-cyano-4-aryl-1,3-butadienes with sulfur powder in the presence of triethylamine provides a means of preparing 2-amino-3-Z-5-thioaroylthiophenes.[130,131] The reaction proceeds also with cinnamaldehyde and its derivatives, a methylene-active nitrile, and sulfur.



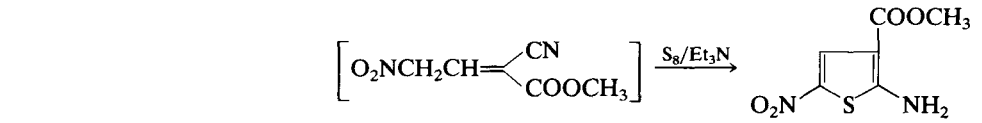
Cyclohexanethione[132] also reacts with malononitrile and sulfur in a similar way as carbonyl compounds. It is likely that in this reaction the thiocarbonyl sulfur atom is first attacked by the malononitrile anion. A further elimination of hydrogen sulfide results in the formation of cyclohexylidenemalononitrile which then produces 2-amino-4,5-tetramethylenethiophene following the usual scheme:



According to patent data[133] nitriles of β-aminocrotonic acids react likewise:

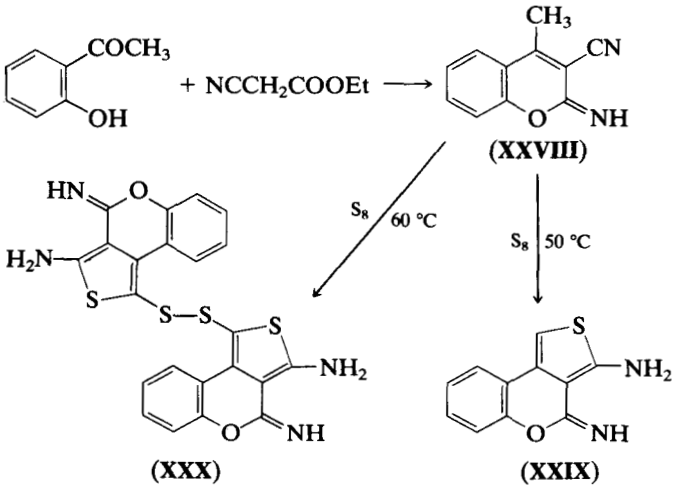


The interaction of 1-(*N*,*N*-dimethylamino)-2-nitroethylene and methyl cyanoacetate and sulfur may be regarded as a corresponding kind of transformation[134]



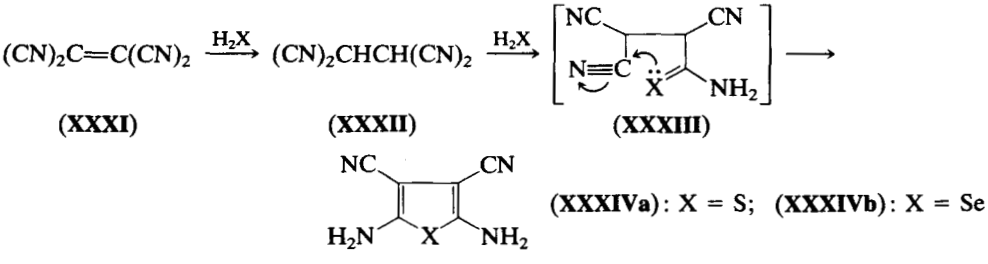
The examples discussed above show that both 3-keto and 3-thioxo or 3-imino derivatives of carbonyl compounds and nitriles interact with nitriles containing active methylene groups and sulfur to yield related 2-aminothiophenes.

The reaction between sulfur, cyanoacetic acid ester, and *o*-hydroxyacetophenone has been employed to prepare 2-aminothiophene fused with the coumarine fragment. Thiolation of 4-methyl-3-cyanocoumarin-2-imine (**XXVIII**) at the methyl group was proved experimentally[135]: depending on the conditions, either 3-amino-4-imino-4*H*-thieno-[3,4-c]benzopyrane (**XXIX**) (at 50 °C) or bis(3-amino-4-imino-4*H*-thieno-[3,4-c][1]benzopyran-1-yl) disulfide (**XXX**) (at 60 °C) were formed.



Nitriles containing less reactive methylene groups such as benzyl cyanide, cyanoacetamide, and succinonitrile cannot be used in this reaction.[135]

2,5-Diamino-3,4-dicyanothiophene (**XXXIV**) has been made by treating tetracyanoethylene (**XXXI**), 1,1,2,2-tetracyanoethane (**XXXII**), or certain other polycyanoethylenes with hydrogen sulfide.[136–144] It was shown that tetracyanoethylene underwent reduction to tetracyanoethane which then reacted with hydrogen sulfide.[137,140] The reaction was employed for preparative purposes[143].

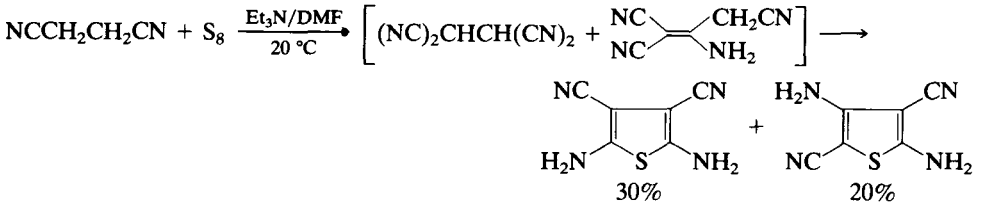


(**XXXIVa**): X = S; (**XXXIVb**): X = Se

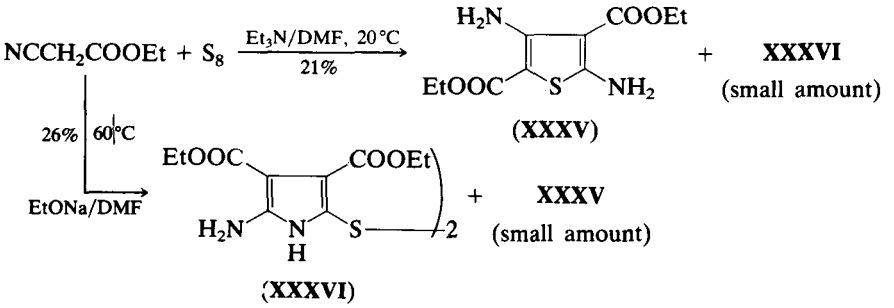
A systematic study of the interaction of tetracyanoethane (**XXXII**) with Group VIA element hydrides was carried out in Ref.[141]. The reaction was shown to be influenced by the acidity of H_2X (X = O, S, Se, Te) which should not exceed that of the starting compound (**XXXII**) being at the same time sufficient for providing the formation of intermediate (**XXXIII**) and its cyclization to the heterocyclic compounds (**XXXIV**) and (**XXXV**). This is why water ($K_a = 2 \cdot 10^{-16}$) does not react with nitrile (**XXXII**). Hydrogen telluride the acidity of which ($K_a = 2 \cdot 10^{-3}$) exceeds that of the starting compound (**XXXII**) also cannot be used in the reaction, whereas H_2S ($K_a = 9.1 \cdot 10^{-7}$) and H_2Se ($K_a = 1 \cdot 10^{-4}$) easily react with tetracyanoethane (**XXXII**) to yield 2,5-diamino-3,4,-dicyanothiophene (**XXXIVa**) and the corresponding selenophene (**XXXIVb**), respectively. The reaction readily goes in acetone or

pyridine at reduced temperature. It was extended to substituted 1,1,2-tricyanoethanes.[144]

The interaction of methylene-active nitriles and their dimers with elemental sulfur is another example of reactions of the type we are considering. Thus, malononitrile reacts with sulfur in the presence of triethylamine in DMF at room temperature[145] to give 2,5-diamino-3,4-dicyanothiophene (30%) and 2,4-diamino-3,5-dicyanothiophene (20%) as the major products. The reaction paths leading to the former and the latter products should involve tetracyanoethane (**XXXII**) and the dimer of malononitrile, respectively, as intermediates. The formation of the dimer was substantiated by synthesizing 2,4-diamino-3,5-dicyanothiophene from this compound as starting material in a yield of 85%.[145,146]



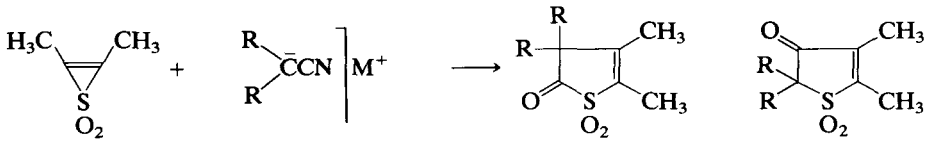
The interaction of cyanoacetic acid ester[145,147] and cyanoacetamide[145] with sulfur is a more complex process. It is so because they are less reactive than malononitrile. The resulting 2-aminothiophenes undergo further conversion under the reaction conditions. Thus cyanoacetic acid ester gives 2,4-diamino-3,5-diethoxycarbonylthiophene (**XXXV**) and bis (5-amino-3,4-diethoxycarbonylpyrrol-2-yl) disulfide (**XXXVI**)[145]. The ratio of the compounds (**XXXV**) and (**XXXVI**) depends on the synthesis and isolation conditions.



Cyanoacetamide gives 2-amino-5-mercapto-3,4-dicarbamoylpyrrole.[145]

Ring opening-ring closure of certain heterocyclic systems under the action of methylene-active nitriles can also be employed to prepare 2-aminothiophenes. Thus, thiiranes undergo the reaction to give products of the type of mercaptoethyl cyanoacetic acid ester which, without isolation, are converted to 2-aminodihydrothiophenes by cyclization.[149,151] If the reaction is run with cyanoacetic acid ester in methanol, reesterification can occur.[149] The work pertaining to this field is discussed in a review[152] and monographs.[153,154]

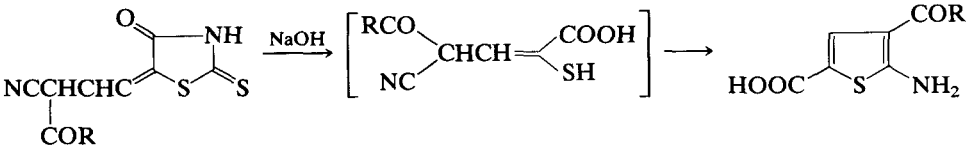
Note that 1,2-dimethylthiirene 1,1-dioxide (**XXXVII**) is an ambident electrophile; its reactions with α-metallated nitriles (**XXXVIIIa, b**) can yield 5-oxo-2,3-dimethyl-2-sulpholenes (**XXXIX**).[155,156] The reaction depends strongly upon the nucleophilic properties of the anion: **XXXVIIIa** attacks one of the carbon atoms, whereas **XXXVIIIb** first attacks the sulfur atom in the dioxide (**XXXVII**).



(**XXXVII**) (**XXXVIIIa**): R = CH_3; (**XXXVIIIb**): R = Ph (**XXXIX**)

Ring opening-ring closure of the cyanothiolactones (**IX**) has already been discussed.[39,40]

Ring opening-ring closure of substituted 5-alkylidenerhodanines in an alkaline medium results in 3-substituted 2-aminothiophene-5-carboxylic acids formed in 90% yield.[157]



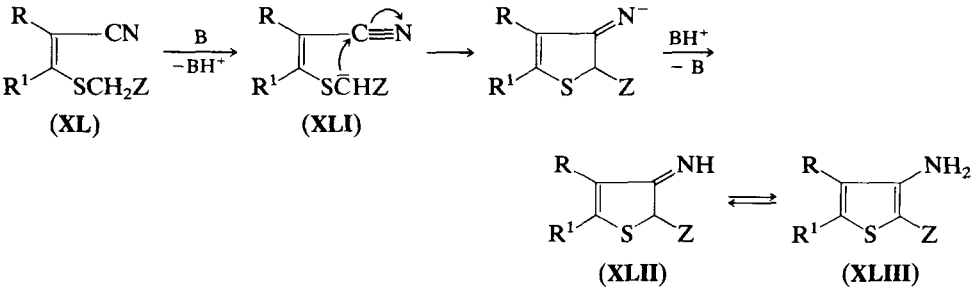
Certain points pertaining to the problem of intramolecular interactions in γ-hydroxy, γ-amino, and γ-mercapto nitriles are discussed by Valter in a review[158] and a monograph.[159]

III. SYNTHETIC ROUTES TO 3-AMINOTHIOPHENES

Various substituted 3-aminothiophenes are rather easy to prepare by the Thorpe reaction. As is known the term Thorpe reaction refers to the dimerization of nitriles to iminonitriles under the action of bases. From dinitriles cyclic β-amino(imino)nitriles are formed: such transformations are called the Thorpe-Ziegler reaction. The reaction has been extended to syntheses of various heterocyclic amines. We also include here numerous nitrile cyclization reactions (**I**, Y = an activated CH_2 group). The earlier work in this field is briefly discussed in Refs.[27,36,160–162]. However, at present there is no comprehensive account of the literature data on the synthesis of 3-aminothiophenes by the Thorpe reaction.

Rather numerous procedures for the preparation of 3-iminothiophenes (**XLII**) or 3-aminothiophenes (**XLIII**) are known to include intramolecular interaction between the methylene (methine) group (**XL** → **XLI**) and the nitrile function as the final reaction step.

Compounds with the (Z-methylthio)nitrile (**XLI**) structure readily undergo cyclization under the reaction conditions, and their preparation is in most cases impossible to

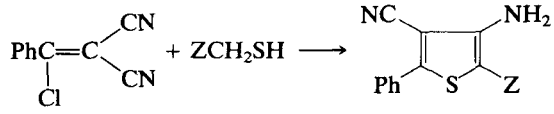


(XL) (XLI) (XLII) (XLIII)

carry out in practice. However, the possibility in principle of synthesizing these compounds cannot be ruled out. The procedures that may be used to this effect will be discussed below. It should be borne in mind that the compounds we are considering as a rule contain an activated methylene or methine group linked to a strong electron acceptor Z; for otherwise the cyclization is hindered or even blocked.

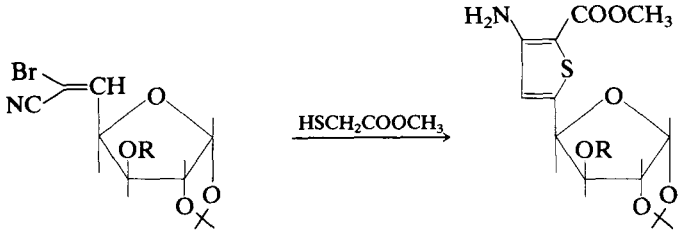
The synthesis of substituted 3-aminothiophenes and their fused derivatives by the Thorpe reaction has been studied more extensively than with the corresponding furans or pyrroles because the corresponding starting compounds are easier to obtain.

One of the principal routes to 3-aminothiophenes is the interaction of β-halo nitriles with mercaptans containing a methylene group activated by the presence of an electron acceptor Z. For example, α-chlorobenzylidenemalononitrile (**XLIV**) reacts with mercaptans (**XLV**) to yield substituted 3-amino-5-phenyl-4-cyanothiophenes (**XLVI**).[163]

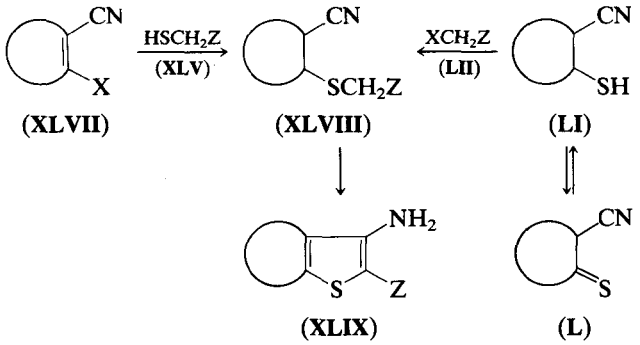


(XLIV) (XLV) (XLVI)

With CHO for Z in (**XLV**), the dimer of mercaptoacetaldehyde was used. The first reaction step is the addition of the mercaptan to the double bond of the halo nitrile rather than the replacement of the halogen, as follows from the observation that both β-[164–167] and γ-haloacrylonitriles[163,168] react to yield related 3-aminothiophenes. Thus, 2-acetyl-3-amino- and 3-amino-2-methoxycarbonylthiophenes have been isolated from the reaction of α-chloroacrylonitrile with the corresponding mercaptans.[164] 3-Amino-5-glycosylthiophenes[165] have been prepared likewise:



The reaction is of great importance for the synthesis of fused 3-aminothiophenes. The interaction then proceeds via nucleophilic substitution by a thiol group of the halogen atom attached to the ring (cf. the mechanism considered above). The reaction proceeds rather easily with vicinal halo nitriles containing a labile halogen atom because of the influence of the adjacent nitrile group. To sum up, the interaction of compounds (**XLVII**) with mercaptans (**XLV**) is one of the principal procedures for the preparation of fused 3-aminothiophenes (**XLIX**).

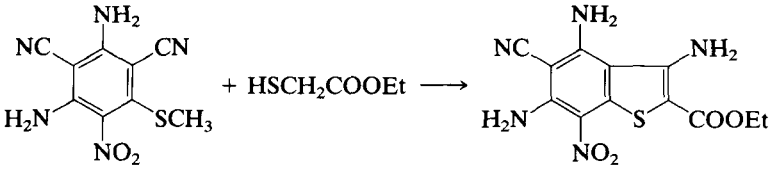


This technique has been employed to synthesize various 3-amino substituted fused thiophenes including 3-aminobenzo[b]thiophenes,[169–173] 3-aminothieno[2,3-c]pyrazoles,[174] 3-aminothieno[2,3-b]pyridine,[175–179] 3-aminothieno[2,3-c]pyridine,[179] 3-aminothieno[2,3-c]cinnolines,[180] 3-aminothieno[2,3-b]pyrazines,[175,181,182] 3-aminothieno[2,3-d]pyrimidines,[183,184] and 3-aminothieno[2,3-b]-1,6-[185] and -1,8-naphthyridines.[186]

The halogen lability can be increased and the reaction facilitated by the introduction of additional substituents into the starting halo nitrile (**XLIII**).[171,172] The transformation (**XLII**) → (**XLIX**) is effected using various catalysts including alkali metal alkoxides and hydroxides, potash, soda, and triethylamine; also alkali metal carbonates have found wide application.[174,176,180,181,183–186]. At the same time the choice of the catalyst is subject to certain limitations. For example sodium carbonate and triethylamine sometimes fail to induce the cyclization,[177] and the use of sodium ethoxide results in the formation of side products along with the desired compounds, 3-aminothieno[2,3-b]pyridines.[177]

o-Nitrobenzonitriles also react under the conditions specified,[187,188] first to exchange the nitro group or a thioglycolic acid ester residue,[189] amide,[175] or benzyl mercaptan[190] and then to undergo cyclization to 3-aminobenzo[b]thiophenes. The nitro group in *o*-nitrobenzonitriles, including 6-chloro derivatives, has been shown to be labile to a certain degree.[175,187–190]. This explains the possibility of replacing it with a thiol or alkylthio residue. It follows that the nitro group in *o*-nitrobenzonitriles can be ascribed a higher lability than the chlorine in *o*-chlorobenzonitriles. 2-(Benzylthio)benzonitrile can be oxidized to the corresponding sulfone which is converted to 3-amino-2-phenylbenzo[b]thiophene 1,1-dioxide in the presence of sodium methoxide.[190] It appears that *o*-(methylthio)benzonitriles can be introduced into the reaction. 3,4,6-Triamino-7-nitro-5-cyano-2-ethoxycarbonylbenzo[b]thio-

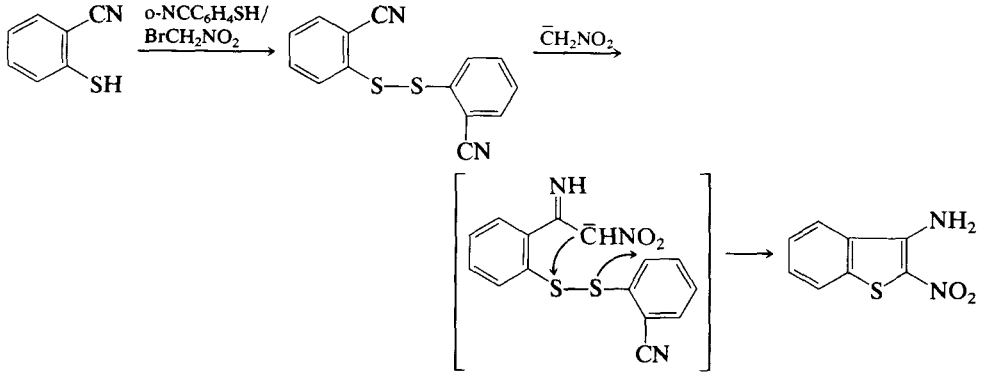
phene is prepared by this route[191]



A structure similar to those considered above and convenient for the cyclization can be produced by replacing the amino group in (*o*-aminophenyl)thioglycolic acid with a cyano group using the Sandmeyer process. The only reaction product was, however, 3-aminothionaphthene-2-carboxylic acid[192] also prepared from (*o*-cyanophenyl)thioglycolic acid by treatment with base.[161,162] When heated 3-aminothionaphthene-2-carboxylic acid readily undergoes decarboxylation to give 3-aminobenzo[b]-thiophene characterized as its *N*-acyl derivative.[161]

3-Aminothiophenes are easy to prepare by treating β-mercapto (**LI**) and β-thioxo nitriles (**L**), capable of a tautomeric transformation to thiols (**LI**), with α-halo derivatives of carbonyl compounds, nitriles, nitro compounds, and other substances containing an active methylene group (**LII**). The reaction has been employed to prepare a number of substituted 3-aminothiophenes, suggested for use as depressants acting on the central nervous system, from β-mercaptopropionic acid and α-chloro carbonyl compounds.[193]

The interaction of vicinal cyanothiolates with bromonitromethane has been studied.[194] It is supposed that a sulfenyl bromide and nitromethane anion are obtained in the initial step of the process to give nitromethane. The sulfenyl bromide reacts with the thiolate to rapidly give a disulfide. With *o*-cyanothiophenol, the produced diphenyl disulfide is attacked by the nitromethane anion at the CN group. The intermediate is then cyclized to give 3-aminobenzo[b]thiophene and to regenerate *o*-cyanothiophenol.



Support is given for this mechanism by the direct synthesis of 3-amino-2-nitrobenzo[b]thiophene from preformed diphenyl disulfide as well as from 2-(1-cyanoethylthio)benzonitrile and bromonitromethane in the presence of base.[194]

As the initial β-mercapto (**LI**) and β-thioxo nitriles (**L**) are easier to prepare than the corresponding halogenated (**XLVII**) or *o*-nitroarylnitriles the raction offers much promise as a preparative procedure. 2-Cyanothiophenes have been employed to prepare 3-aminobenzo[b]thiophenes.[194–197]

Alkylation of *o*-cyanothiophenol with bromoacetoacetic acid ester in the presence of NaOH leads to 3-aminobenzo[b]thenoyl-2-acetic acid ester which undergoes further cyclization to 4-hydroxy-1,2-dihydro[1]benzothieno[3,2-b]pyridine-2-one.[198]

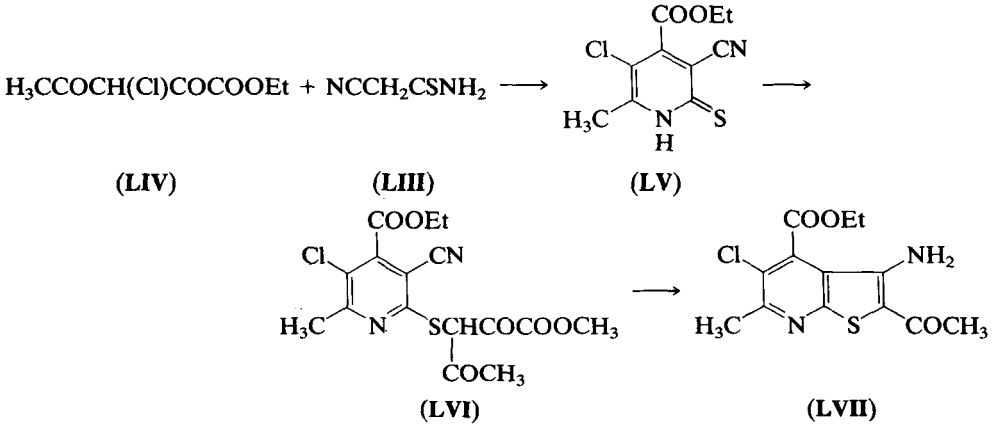
Far more frequently the synthesis of fused 3-aminothiophenes is carried out using 3-cyanazole- or -azine-2-thiones (**L**) the alkylation of which yields 2,3-, 3,4-, and 4,5-di(alkylthio)nitriles (**XLVIII**). Treating these products with a solution of an alkali metal hydroxide or alkoxide gives high yields of 3-aminothiophenes fused with pyrazole, isothiazole, pyridine, pyrimidine, and other heterocyclic systems. The ease of cyclization of the nitriles (**XLVIII**) depends on the nature of the substituent Z and decreases in the order.[199–201]

$$COAr > CN > COOR > CONH_2 > COOH > Ar$$

The nitriles (**XLVIII**) can be subjected to cyclization without isolating them from the reaction mixture.

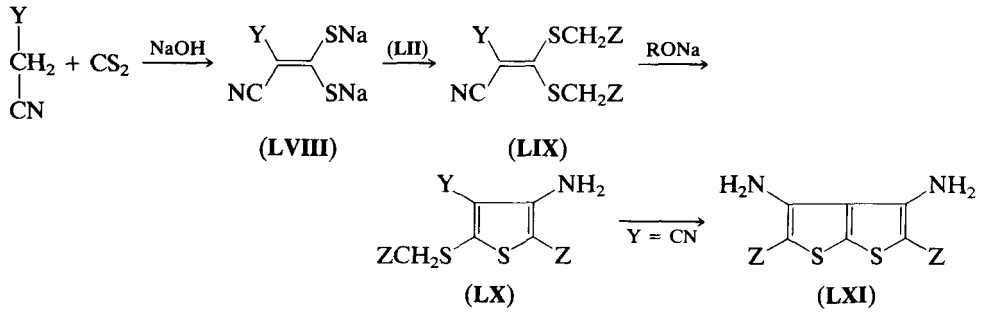
Alkylation of the appropriate heterocyclic cyano thiones (**L**) has been used in the preparation of 3-aminothieno[2,3-c]-[202–205] 3-aminothieno[3,2-d]-[204–207] and 3-aminothieno[3,2-c]-isothiazoles,[207] 3-aminothieno[2,3-b]pyridines,[199–201, 208–230] 5-aminothieno[2,3-d]pyrimidines[231–233] 3-aminothieno[2,3-b]pyrazines[234], 3-aminothieno[2,3-b]benzothiophenes,[235] and 3-aminothieno[2,3-b]thiochromones-4.[236,237]

The interaction of some keto halocarboxylic acids with cyanothioacetamide has been studied[219,220] to show that the reaction of thioamide (**LIII**) with acetylchloropyruvic ester (**LIV**) gives a high yield of 3-amino-2-acetyl-6-methyl-5-chloro-4-ethoxycarbonylthieno[2,3-b]pyridine (**LVII**). The reaction involves the pyridinethione (**LV**) and its *S*-alkylated derivative (**LVI**) as intermediates.

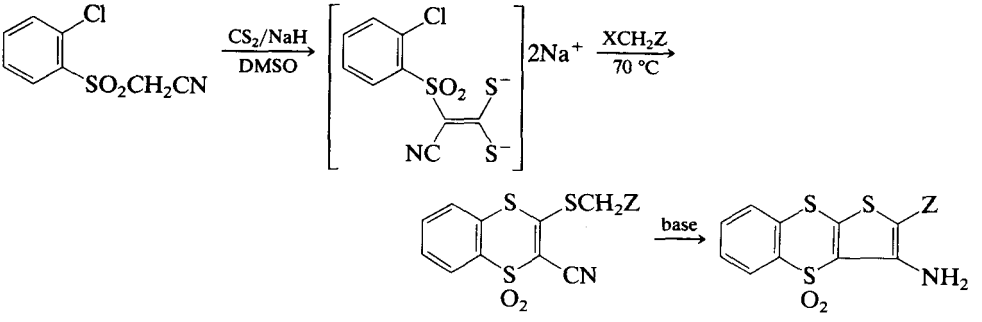


The alkylthio derivatives (**XLVIII**), isolated as such[27,173,182,190,199–207,210,212,217,224–232] can smoothly be transformed into fused 3-aminothiophenes under the action of bases or by thermal treatment.[212,235–237]

Another route to 3-aminothiophenes is based on the use of nitriles containing an active methylene group. Such nitriles react with carbon disulfide in the presence of alkali to give sodium or potassium 1-cyanoethylene-2,2-dithiolates (**LVIII**) which smoothly undergo alkylation by α-halocarbonyl derivatives or halides (**LII**) to yield 1-cyano-2,2-di(Z-methylthio)ethylenes (**LIX**). Sodium alkoxides and organic bases induce cyclization of these products to 3-aminothiophenes (**LX**). If the 3-aminothiophene (**LX**) contains a sufficiently active methylene group linked to the second substituent Z, and if Y stands for CN, compound (**LX**) can undergo Thorpe cyclization to form 3,4-diaminothieno[2,3-b]thiophenes (**LXI**).[238–240]

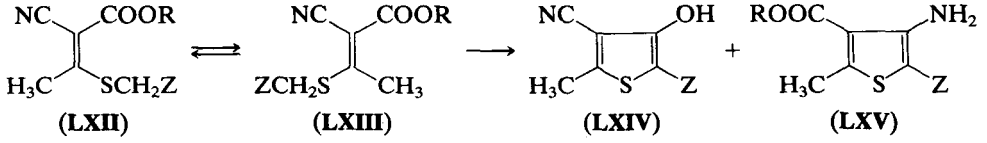


According to Ref.[239] the monoalkylation products of the salts (**LVIII**) do not form the corresponding thiophenes. It has also been noticed that 2-(4-bromobenzoyl)-3-amino-4-cyano-5-(4-bromophenacylthio)thiophene (**LX**, Y = CN, Z = 4-BrC_6H_4CO), prepared as described above, do not undergo the Thorpe reaction.[241] The same technique has been applied to prepare various substituted 3-aminothiophenes.[242–248] Instead, for example, 3-amino-2-methoxycarbonyl-thieno[3,2-b]-1,4-benzodithiin is obtained.[142]



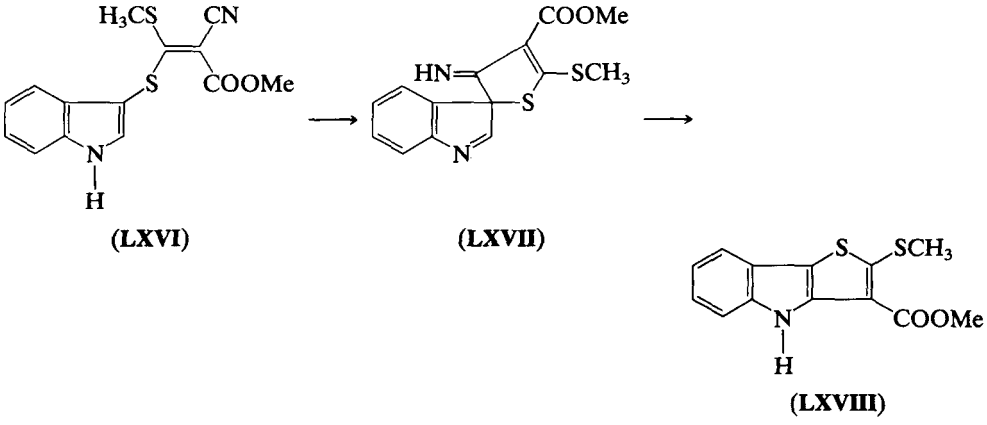
Nitriles (**LXII**) containing α-ester groups can be involved in two competing reactions at both groups simultaneously.[249,250] Irrespective of the geometric structure of the starting nitrile (**LXII**) ⇄ (**LXIII**)[249] a mixture of 3-hydroxythiophene (**LXIV**)

and 3-aminothiophene (**LXV**) results, with the 3-hydroxythiophene sometimes prevailing. Thus, heating the nitrile (**LXII**) in methanol in the presence of potash leads to a mixture of the thiophenes (**LXIV**) and (**LXV**) (R = Me, Z = COOMe) in yields of 43 and 31%, respectively.[250] The possibility of cyclization of nitriles (**LIX**, Y = CN, Z = H) involving the alkyl carbon atom under the action of lithium diisopropylamide should also be mentioned.[251]



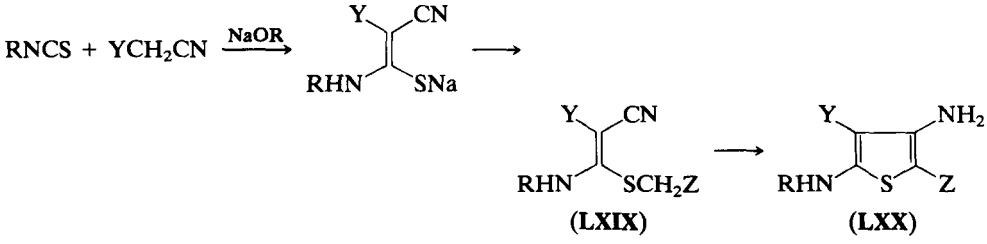
(**LXII**) (**LXIII**) (**LXIV**) (**LXV**)

Cyclization of (indolyl-3-thio)methylthiomethylenecyanoacetic ester (**LXVI**) in the presence of 10% hydrochloric acid under the action of short-term heating is an interesting example of the preparation of substituted 3-aminospirothiophenes (**LXVII**). Prolonged heating causes a rearrangement of the first formed iminospirothiophene (**LXVII**) to the thienoindole (**LXVIII**)[252].



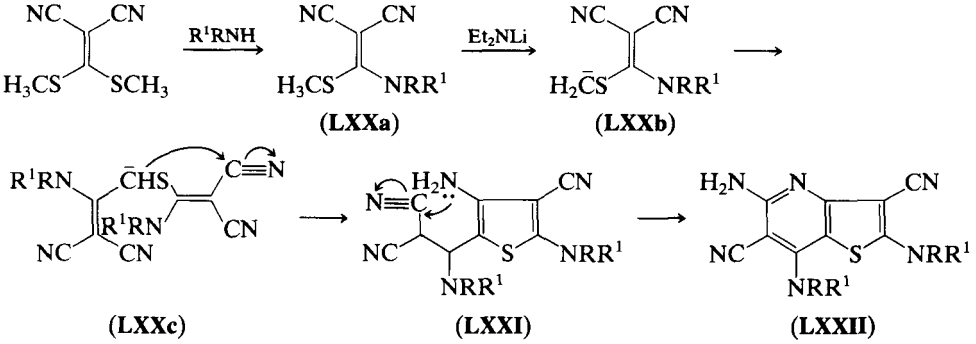
(**LXVI**) (**LXVII**) (**LXVIII**)

Ketene *N*,*S*-acetals (**LXIX**) can be made from isothiocyanates and methylene-active nitriles[238,242,253–256] or ketene *S*,*S*-acetals (**LIX**) and amines.[251,257] The acetals (**LXIX**) and (**LIX**), in the presence of base, form substituted 3,5-diaminothiophenes (**LXX**).[242,251,253–259]

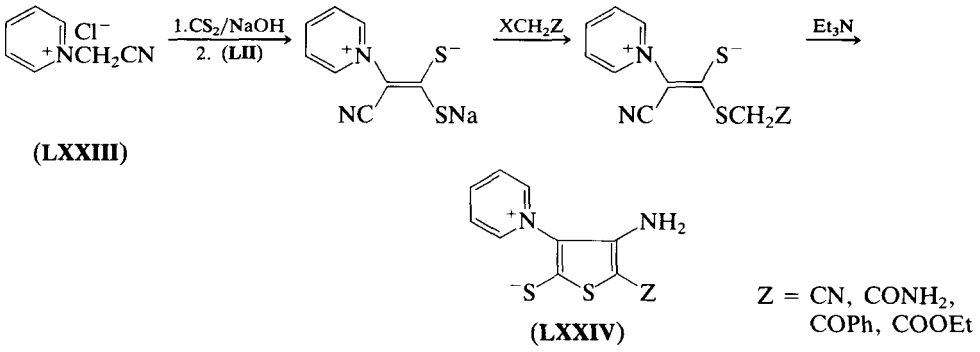


(**LXIX**) (**LXX**)

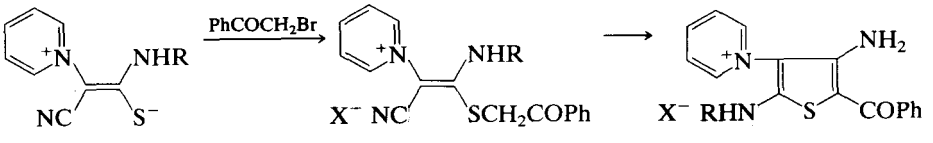
Compound (**LXIX**, R = Ph, Y = CN, Z = H) reacts analogously to give (**LXX**, R = Ph, Y = CN, Z = H). A quite different product was formed when (**LXXa**, $RR^1 = CH_2CH_2OCH_2CH_2$) was allowed to cyclize in the presence of lithium diisopropylamide. The carbanion (**LXXb**) reacts primarily with another molecule (**LXXa**) in an addition-elimination reaction to give the anion (**LXXc**). First at this stage the normal cyclization takes place to give thiophene (**LXXI**), which undergoes further ring closure to give (**LXXII**).[251]



The 3-aminothiophenes (**LXXIV**) can be prepared likewise, using 1-cyanomethylpyridinium salts as starting materials (**LXXIII**):[260,261]

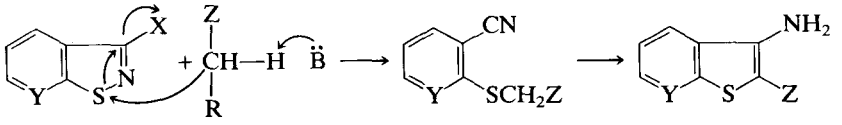


The products obtained by alkylation of 1-(2-amino-1-cyano-2-thio)ethene-pyridinium ylides with α-halo ketones are cyclized to 1-(4-amino-2-alkylamino-5-benzoylthiene-3)pyridinium salts.[262]



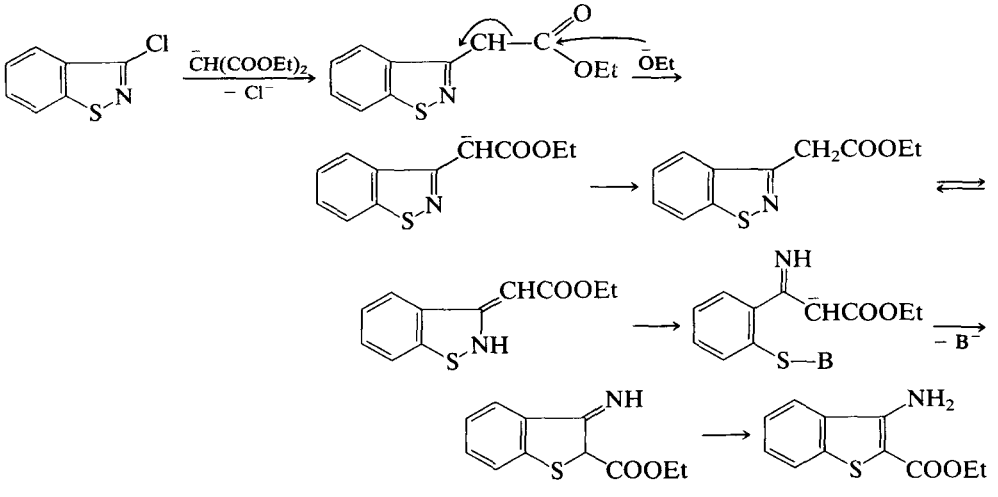
Hydroxy-,[263] alkoxy-,[250] and also mesyloxyacrylonitriles[264] react with mercaptans (**XLV**) to give 3-aminothiophene derivatives, e.g. 4-(β-D-ribofuranosyl)thiophenes.[264]

Another route to 3-aminothiophenes utilizes isothiazoles, thiazolines, and thioxolanes substituted with a leaving group. For example, 3-chloro-1,2-benzisothiazoles,[197,265,266] 2-alkyl-3-chloro-1,2-benzisothiazolium salts,[267,268] and 3-bromoisothiazolo[5,4-b]pyridines[269] undergo ring opening-ring closure under the action of carbonyl compounds (ketones, diketones, malonic ester) in the presence of base. The following mechanism of this reaction has been suggested.[266]



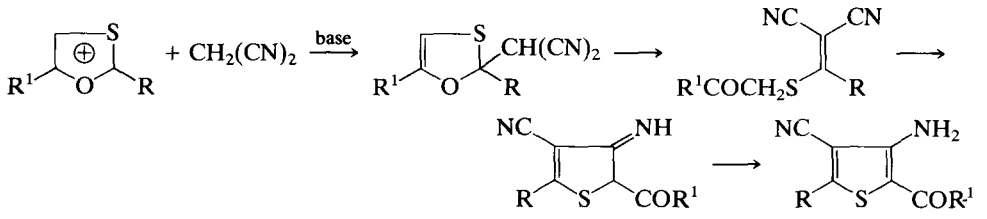
Y = CH, N: X = Cl, Br; R = H, CN, $COCH_3$, COPh, $CONH_2$

An alternative mechanism involves nucleophilic substitution of a halogen atom as the initial step. For example, the following scheme involves 3-chloro-1,2-benzisothiazole ring opening-ring closure in the presence of sodiomalonic ester.[197]



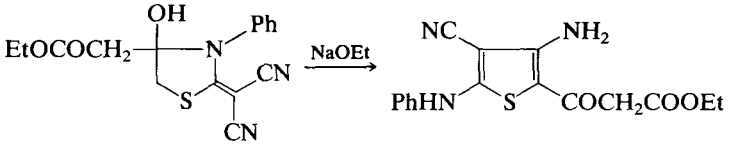
The formation of 3-aminobenzo[b]thiophenes was proven by their independent synthesis from *o*-mercaptobenzonitrile and the halo derivatives (**LII**).[197] The reaction often follows several paths. Thus 2-(thiocyanato)benzonitrile and bis(2-cyanophenyl) disulfide are formed along with 3-amino-2-acetylbenzo[b]thiophene in the presence of acetone and sodium cyanide.[265] These transformations are briefly discussed in a review.[266]

3-Aminothiophene derivatives have also been prepared by ring opening-ring closure of 1,3-oxathiolium salts with malononitrile effected by the action of bases.[270–274] Under the reaction conditions, the initial nucleophilic (malononitrile anion) attack at position 2 of the oxathiolium salt is followed by ring-opening with further intramolecular interaction of the methylene and nitrile groups.



The reaction takes another course when cyanoacetic acid ester is allowed to react with 1,3-oxathiazolium salts under these conditions. In the ring-closure the ester competes successfully with the nitrile for the carbanionic nucleophile to give a mixture of a 3-hydroxythiophene and a 3-aminothiophene.[271,273]

Similar intermediates occur in ring opening-ring closure reactions of 2-(cyano)-ethoxycarbonylmethylene-4-oxo-1,3-dithiole,[241] 2-dicyanomethylenethiazoline, and 2-dicyanomethylenethiazolinones.[255,275,276] The reaction of malononitrile with phenyl isothiocyanate in the presence of sodium ethoxide, followed by treatment of the reaction mixture with 4-bromoacetoacetic acid ester, gives a mixture of the thiazoline (**LXXV**) and the 3-aminothiophene (**LXXVI**). The action of sodium ethoxide on thiazoline (**LXXV**) transforms it into the thiophene (**LXXVI**).[255]

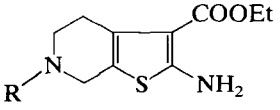


(**LXXV**) (**LXXVI**)

To sum up, the principal routes to 2-aminothiophenes are the cyclization of γ-mercaptonitriles and the three-component condensation of carbonyl compounds, nitriles containing an active methylene group, and sulfur (the Gewald reaction); the principal route to 3-aminothiophenes is the interaction of β-halo- or β-mercapto (thioxo) nitriles with mercapto or halo derivatives, respectively, of methylene-active nitriles.

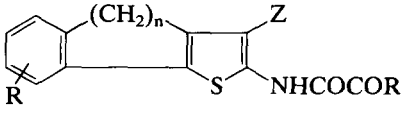
IV. PRACTICAL APPLICATIONS OF AMINO DERIVATIVES OF THE THIOPHENE SERIES

Amines of the thiophene series have found wide practical applications, and the scope of their applicability will increase with further development of their chemistry. 3-Aminothiophenes have been suggested as pharmaceuticals, e.g. Tinoridine (**LXXVII**, R = $PhCH_2$).[277]



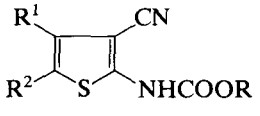
(**LXXVII**)

Derivatives of (**LXVII**) are useful as antiinflammatory agents, analgesics, and as remedies for diabetes mellitus.[278] A large number of aminothiophenes have been prepared with a view to synthesize physiologically active substances or intermediate products.[44,61,71,89,90,91,101,106,114–116,119,139,210,218,234,279–281] According to the literature and patent data 2-aminothiophenes and some of their *N*-substituted derivatives have antipyretic[120,121,126,172] and antiphlogistic effects.[69,70,101,122,124] The oxamic acid derivatives (**LXXVIII, LXXIX**) are used for the treatment of allergies.[279–280]



Z = CN, $CONH_2$, COOR

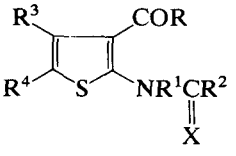
(LXXVIII)



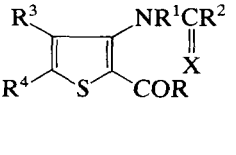
(LXXIX)

Certain aminothiophene derivatives can be used as bactericides[118] and antiviral drugs.[127] Fused 3-aminobenzo[b]thiophenes are inhibitors of thrombocytes.[169,170]. Fused 2-amino-[75] and 3-aminothiophenes have been tested as depressants of the central nervous system.[183,193] 2-Amino-3-cyano-4,7-methano-4,5,6,7-tetrahydrobenzo[b]-thiophene is used as a vasodilator.[109] Several aminothiophene derivatives show quite varied types of activity. 1,3,3a,4,9a-Hexahydro-2-methyl-4,9-ethano-2*H*-benzo[f]-isoindolone-10 has been suggested as an analgesic and antiviral substance and for diagnosing certain viral diseases in warm-blooded animals.[74]

Quite a number of 2- and 3-aminothiophene derivatives have been suggested as bactericides (**LXXX**, X = S)[281] and pesticides.[83] *N*-Substituted 2- (**LXXX**) and 3-aminothiophenes (**LXXXI**) are auxins.[80,81,84,105,282]



(LXXX)



(LXXXI)

X = O, S; R = AlkO, AlkNH: R^1,R^2 = H, Alk (or Cl, Br, and Alk containing CN as substituent), AlkS, AlkNH, Ar, etc., R^3,R^4 = H, Alk, Ar, Cl, Br, etc.

These substances stimulate the biosynthesis of ethylene when applied in 1% concentration, accelerate the ripening of tomatoes in 0.2% concentration, and stimulate the growth of soybeans, trees, wheat, and cotton plants in a concentration of 0.05%. Thiophenes prepared from cyclohexane, malononitrile, and sulfur facilitate the ripening of sugar cane in amounts of 1 to 4 kg per hectare.[81]

Benzothieno[3,2-d]-1,2,3-triazines made from 3-amino-2-cyanothiophenes have bactericidal activity and can be used for sterilization and disinfection as admixtures to soaps, detergents, and clarifying agents.[283] Thienylazo derivatives of cyanoacetic acid ester, acetoacetic acid ester, acetylacetone, and also pyrazolones prepared from these

substances exhibit pesticidal action.[284] Thieno[2,3-d]pyrimidines have been synthesized to study their pesticidal activity.[83] Short reviews on the use of thiophene derivatives as pesticides, dyes, and in veterinary practice have been published.[285–287]

Substituted 2- and 3-aminothiophenes are widely used as dyes and dyestuff intermediates[38,50,59,85,133,163,210,288–292].

The 2,5- and 2,4-diaminothiophenes may find application in the synthesis of polymers and in other fields of organic synthesis.

Several works on the synthesis of 2-[141,142,293] and 3-aminoselenophenes[294,295] using procedures similar to those described above have been published. In addition, it has been shown that thiophenes can be prepared by ring closure at the acetylene group[295–297] (cf. the cyclization of nitriles). Depending on the type of cyclization, 2-[295] and 3-methylthiophenes[297] can be prepared. Taking into consideration the data presented in this review, further fruitful development of this and other methods of synthesizing various thiophenes may be expected.

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