SYNTHETIC APPROACHES TO DIHYDROTHIOPHENES

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Abstract - *This review surveys available synthetic procedures for the preparation of dihydrothiophenes.*

INTRODUCTION

Thiophenes have been widely investigated and several reviews have been published on their chemistry.[1-4] The corresponding dihydro derivatives (thiolenes), however, have been widely neglected and only brief discussions of their chemistry are found in these reviews. Although general synthetic procedures are available for the preparation of dihydrothiophenes, these methods have not been reviewed except for a short section in a monograph.[5]

We intend to present a systematic review of synthetic routes to dihydrothiophenes, as well as describe some of their chemical and physical properties. The discussion will be divided as follows:

I. GENERAL ROUTES TO DIHYDROTHIOPHENES
   1. Reductive Methods
   2. Elimination Reactions
   3. Condensation Reactions
   4. Rearrangements

II. SYNTHESIS OF BIOTIN PRECURSORS

III. SYNTHESIS OF HALODIHYDROTHIOPHENES

IV. SYNTHESIS OF BICYCLIC DIHYDROTHIOPHENES

V. SPECTROSCOPIC STUDIES OF DIHYDROTHIOPHENES

I. GENERAL ROUTES TO DIHYDROTHIOPHENES

1. Reductive Methods

The first unambiguous preparation of an unsubstituted dihydrothiophene was effected by reduction of thiophene with sodium in liquid ammonia, using

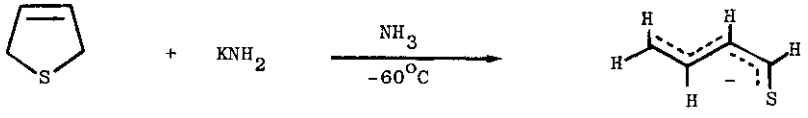
methanol as co-solvent and proton source.[6] A mixture of compounds resulted (Scheme 1), but the major product was 2,5-dihydrothiophene (1), isolated in 38% yield by distillation (bp 122°C). The isomeric 2,3-dihydrothiophene (2) was obtained in 18% yield (bp 112°C).

1 2

Scheme 1

A mixture of butenethiols comprising 23% of the reaction products was also isolated along with some butenes, and hydrogen sulfide. The structures of the dihydrothiophenes were confirmed by conversion to the corresponding known sulfones and mercuric complexes.[7]

Kloosterziel and co-workers reported the ring cleavage of 1 in the presence of potassium amide in liquid ammonia at -60°C, to afford anion 3.[8] The conditions employed by Birch and McAllan included methanol as a proton source. The alcohol could also act as a buffer and suppress any significant concentration of amide anion. Therefore, the mercaptans detected by these investigators were most likely the result of reductive cleavage, rather than base induced cleavage as observed by Kloosterziel (Scheme 2).



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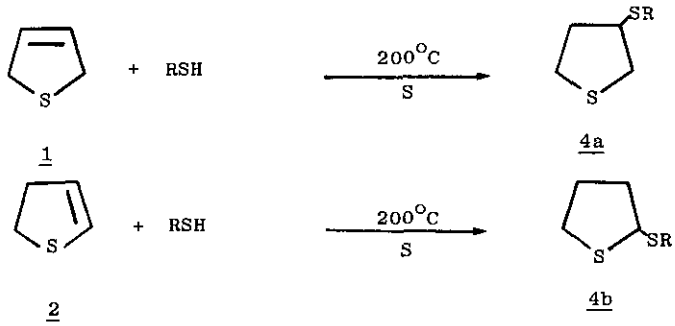
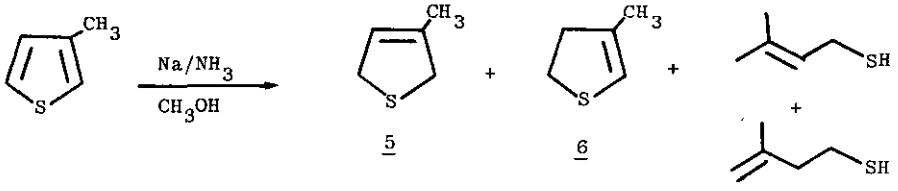
Scheme 2

The reactions of compounds 1 and 2 with alkyl mercaptans were also investigated.[9] When heated at 200°C with a mercaptan, in the presence of sulfur, 2,5-dihydrothiophene gave the corresponding 3-alkylthiotetrahydrothiophene (4a), while 2,3-dihydrothiophene afforded thioacetal 4b (Scheme 3).



Scheme 3

Reduction of alkylated thiophenes proceeded in an analogous manner[10] (Scheme 4).

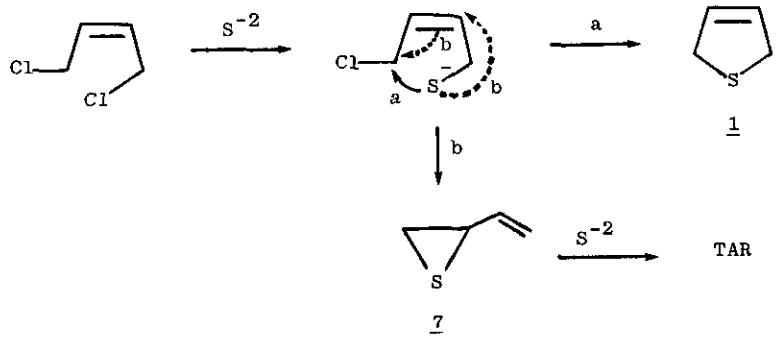


Scheme 4

3-Methylthiophene afforded the 2,5-dihydro derivative (5) in 43% yield, the 4,5-dihydro derivative (6) in 14% yield, and a mixture of unsaturated thiols in 10% yield. Detection of hydrogen sulfide indicated some reductive desulfurization, but the resulting alkenes or alkanes were not identified. Reduction of 2-methylthiophene produced only small amounts (9%) of the corresponding 2-methyldihydrothiophenes. A pentenethiol was the major product (45% yield). No dihydrothiophene resulted from reduction of 2,5-dimethylthiophene. A hexenethiol was isolated and converted to 2-hexanone on treatment with sodium hydroxide.

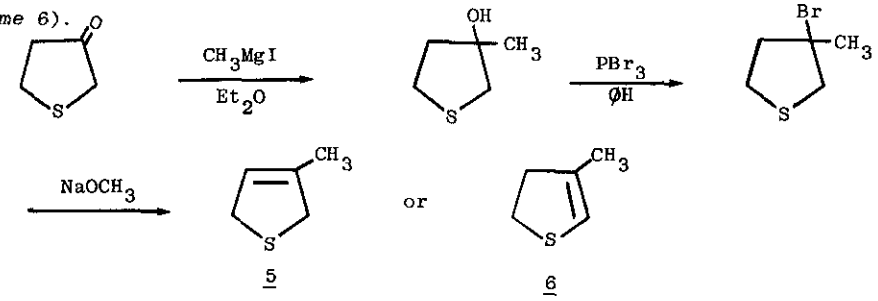
These investigations cast serious doubts on some earlier literature reports of dihydrothiophenes. In 1938, Slobodin investigated the reaction of 1,4-dibromo-2-butene with sodium sulfide, under various conditions.[11] Mixtures were obtained containing butadiene, rubber-like polymers, and a compound Slobodin indentified as 1. However, the boiling point reported for this compound, 103°-105°C, was considerably lower than that reported by Birch and McAllan,[6] who suggested that this lower boiling product was actually 3,4-epithio-1-butene (vinylthiirane) (7). Brandsma and co-workers prepared vinylthiirane by treating trans 1,4-dibromo-2-butene with sodium sulfide,

confirming the assignment proposed by Birch and co-workers.[12] The boiling point of the vinylthiirane (7), 55°C (110 mm), agreed with that of the product observed by Slobodin. Treatment of cis 1,4-dichloro-2-butene with sodium sulfide afforded a 2·1 mixture of 1 and 7[12] (Scheme 5). Dihydrothiophene 1 was purified by destroying the vinylthiirane with excess sulfide anion.



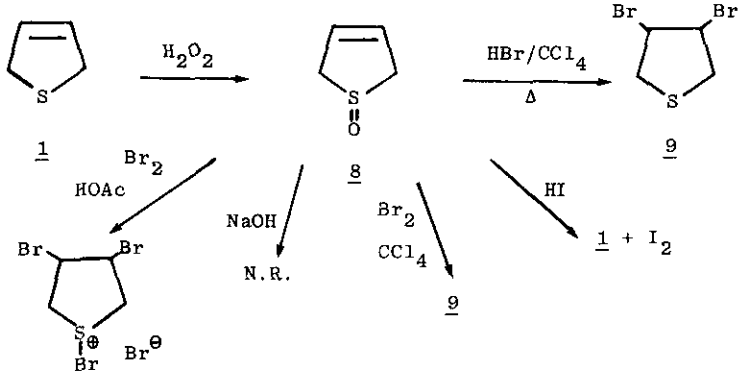
Scheme 5

The preparation of a 3-methyldihydrothiophene by Karrer and Kieso must also be questioned in light of Birch's investigations.[13] These authors treated 3-thiophanone with methylmagnesium iodide to produce the corresponding alcohol, which was then converted with phosphorus tribromide to 3-bromo-3-methyltetrahydrothiophene. *Dehydrobromination of this product* with sodium methoxide afforded a product, bp 108°-110°C, which they believed to be either the 3-methyl-4,5- (6) or 3-methyl-2,5-dihydrothiophene (5). However, when Birch and co-workers prepared these compounds and their known sulfone derivatives, they observed boiling points of 139°C and 147°C, respectively, for 6 and 5[10] (*Scheme 6*).



Scheme 6

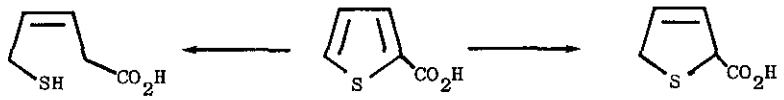
Birch and his group utilized sodium metal in their reductions, with methanol as the proton source. Krug and Tocker investigated the use of both lithium and sodium in conjunction with a variety of ammonium salts as the proton source.[14] When they employed ammonium sulfate or ammonium chloride with either lithium or sodium, or ammonium bromide with lithium, the products were primarily polymers, mercaptans, and hydrogen sulfide. The reduction of thiophene with sodium and ammonium bromide produced a 53% yield of 2,3- and 2,5-dihydrothiophenes. Destruction of the 2,3-dihydrothiophene with 30% sulfuric acid afforded 1 in purified form. Reaction of 1 with hydrogen peroxide yielded the corresponding sulfoxide (8).[15] Reactions of 8 are illustrated in Scheme 7.



Scheme 7

A few of the other dihydrothiophenes reported in the literature have been prepared by reductive methods. Conversion of the tosylhydrazone of 3-keto-thiophane to a 65:35 mixture of 2 and 1 was accomplished with sodium metal in ethylene glycol.[16] Russian investigators electrochemically reduced thiophene-2-carboxylic acid and its 5-methyl, 4-methyl, and 4,5-dimethyl derivatives to obtain the corresponding 2,5-dihydrothiophene-2-carboxylic acids.[17,18] Yields were best (75-90%) in 2M lithium hydroxide; potassium or sodium hydroxide afforded poorer results.

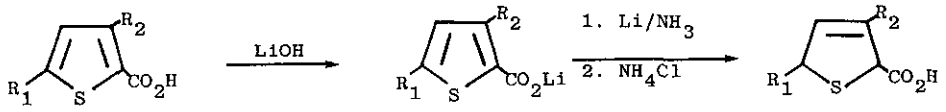
Gol'dfarb and co-workers reported on the Birch reduction of thiophene-2-carboxylic acid.[19] Among the products formed were 2,5-dihydrothiophene-2-carboxylic acid (10) and cis 5-mercapto-3-pentenoic acid (11). The relative amounts of these compounds depended on the reaction conditions (Scheme 8).



11 10

Scheme 8

Similar results were reported independently by Blenderman and Joullié.[20] These investigators further observed that the formation of acyclic products could be prevented by employing the lithium carboxylate salt instead of the free acid. Therefore, the synthesis of some substituted 2,5-dihydrothiophenes (10a,b) was effected in good yields (75-90%) via the lithium/ammonia reduction of the lithium carboxylate salts[21] (Scheme 9).

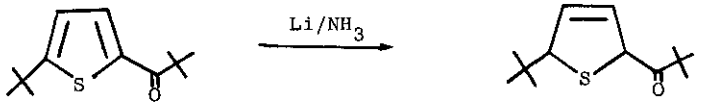


10a,b

a. R_1=H, R_2=Me
b. R_1=Me, R_2=H

Scheme 9

Russian investigators have also reduced thiophenes using triethylsilane[22] or zinc in trifluoroacetic acid[23], the latter reagents being superior. Alkyl substituted thiophenes proved to be the best substrates. A Japanese group has used the Birch reduction in the course of a thiepin synthesis.[24] Product 12 reportedly contained about 5% of the corresponding 2,3- and 4,5-dihydro isomers (Scheme 10).



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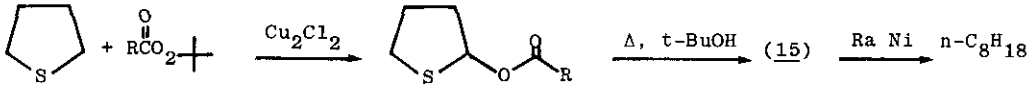
Scheme 10

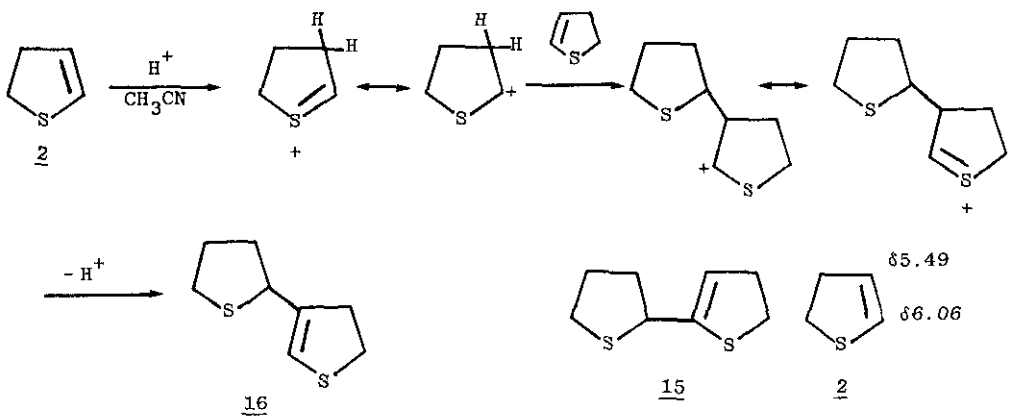
2. Elimination Reactions

The Birch reduction is not well suited for the preparation of 2, as the 2,3- isomer is only a minor product of the reaction. Sosnovsky developed the acyloxylation of tetrahydrothiophene (13) with tert-butyl-peracetate or tert-butylperbenzoate to afford the tetrahydrothienyl acetate (14a) or benzoate (14b).[25,26] When 14b was heated to 110°C for two hours, 2 was obtained in 80% yield, along with benzoic acid. In contrast, heating 14b in tert-butyl alcohol for 100 hours converted it to a species identified from its molecular weight as a dimer of dihydrothiophene (15), which was not characterized further (Scheme 11).



Scheme 11

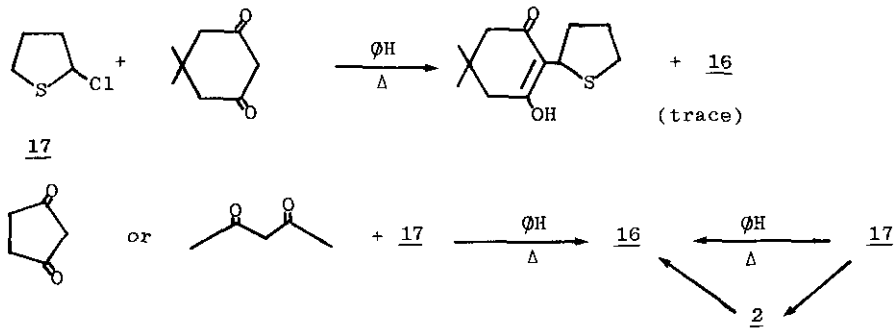
Lawesson and Berglund concurrently conducted similar investigations and reported identical results.[27,28] They desulfurized the dimer with Raney nickel and claimed to have identified n-octane as a product by gas chromatography. They postulated, as a result, that the product was a 2,2' dimer (15). However, the poorly resolved 40 MHz NMR spectrum of the dimer did not appear to support the assigned structure (15). A broad singlet, due to the olefinic proton, occurred downfield (no δ values given). A poorly resolved, but definite, triplet further upfield was probably due to the methylene group adjacent to the sulfur in the dihydrothiophene ring. The lack of splitting in the olefinic resonance was especially puzzling and contradictory. Studies carried out by two other groups have shown that the dimer was not a 2,2' isomer as suggested by Lawesson, but a 3,2' isomer. Cohen and Steele, while investigating the use of 2 as protecting group for alcohols, obtained the same dimer and showed its structure to be 16.[29] A reasonable mechanism for this dimerization is based on the polarization of thioenol ethers (Scheme 12).



2 16 15 2

Scheme 12

Cox and Owen, examining NMR data of various cyclic hemithioketals, found that the resonance of the olefinic proton of 16 experienced only long range splitting.[30] Furthermore, the chemical shift of the olefinic proton (δ.5.92) is closer to that of the 2-proton (δ6.06) than the 3-proton (δ 5.49) in 2. Treatment of 2-chlorotetrahydrothiophene (17) with several 1,3-diones led unexpectedly to the formation of 16.[31] Under the same conditions, but with no dione present, 17 also gave 16. Presumably, 17 is converted to 2, which reacts further to give 16 (Scheme 13).



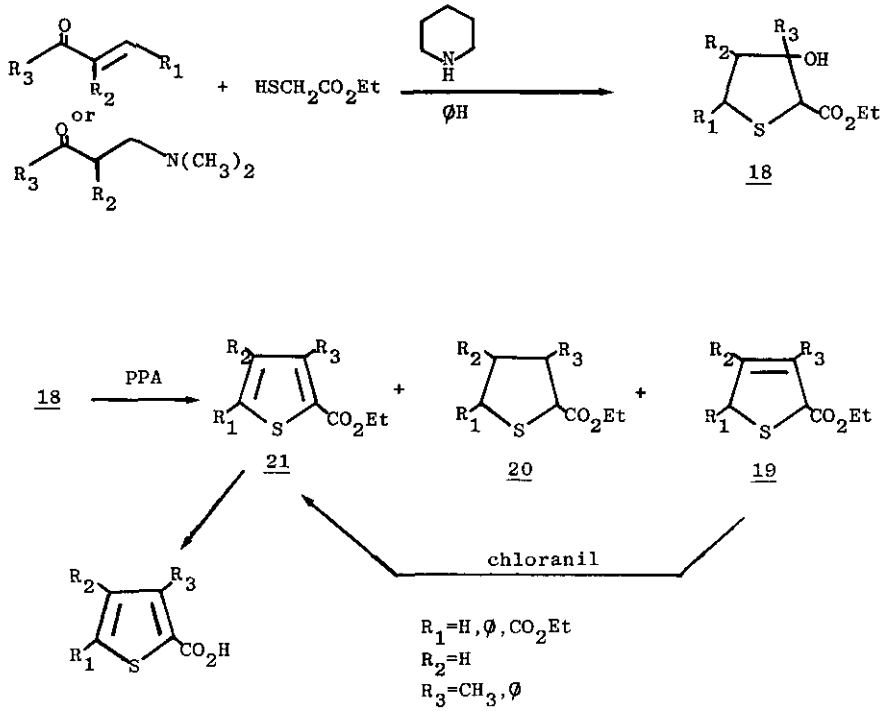
Scheme 13

3. Condensation Reactions

Examination of the literature reveals that ring closures are the best method for preparing substituted dihydrothiophenes. There are two general approaches to cyclization depending on whether the formation of the sulfur-carbon bond occurs as the first or last step. There are several variations on both

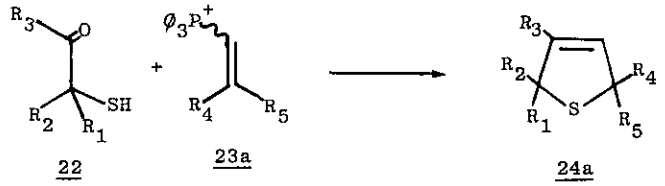
strategies.

Tilak et al. developed the condensation of thioglycolates with either α,β-unsaturated ketones or β-dimethylaminoketones to produce hydroxytetrahydrothiophenes (18) which dehydrated in polyphosphoric acid to 2,5-dihydrothiophenes (19)[32,33] (Scheme 14).

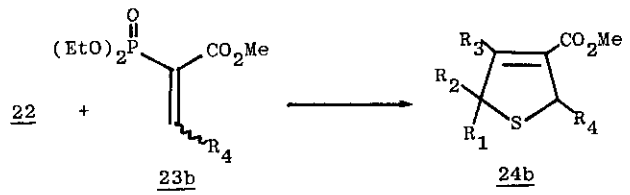


Scheme 14

Disproportionation products 20 and 21 were observed in some cases. This side reaction was not considered a problem as the desired products were thiophenes rather than dihydrothiophenes. The 2,5-dihydrothiophene-2-carboxylate ester (19) did not disproportionate when both R_1 and R_3 were large groups: R_1=R_3=Ø and R_2=H_1 or R_1=CO_2Et, R_2=H and R_3=Ø. This behavior suggested that large groups hindered hydride transfer. When these groups (R_1 or R_3) were smaller, eg. hydrogen or methyl, all three products (19, 20, 21) were obtained. One of the more fully investigated synthetic methods for dihydrothiophenes involves cyclization of α-mercapto aldehydes or ketones (22) with vinyl Wittig or Wittig-Horner reagents (23a,b) (Scheme 15).



22 23a 24a



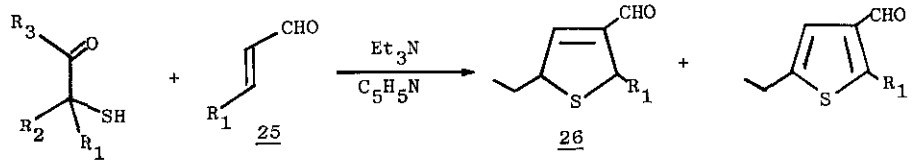
22 23b 24b

R_1=H,Me
R_2=H,Me,∅
R_3=Me,isopropyl
R_2R_3= $-(CH_2)_4-$

Scheme 15

McIntosh and co-workers prepared several substituted 2,5-dihydrothiophenes (24a,b) by this procedure. Many of the resulting dihydrothiophenes were oxidized to the corresponding sulfones and then converted to 1,3-dienes via elimination of sulfur dioxide.[34-38] Use of Wittig-Horner reagents allowed the introduction of an ester group on the dihydrothiophene.[39-40]

α-Mercaptoaldehydes (22) also add to α,β-unsaturated aldehydes to give 2,5-dihydrothiophene-3-carboxyaldehydes (26) as the major products along with some of the corresponding aromatic products (Scheme 16).[41]

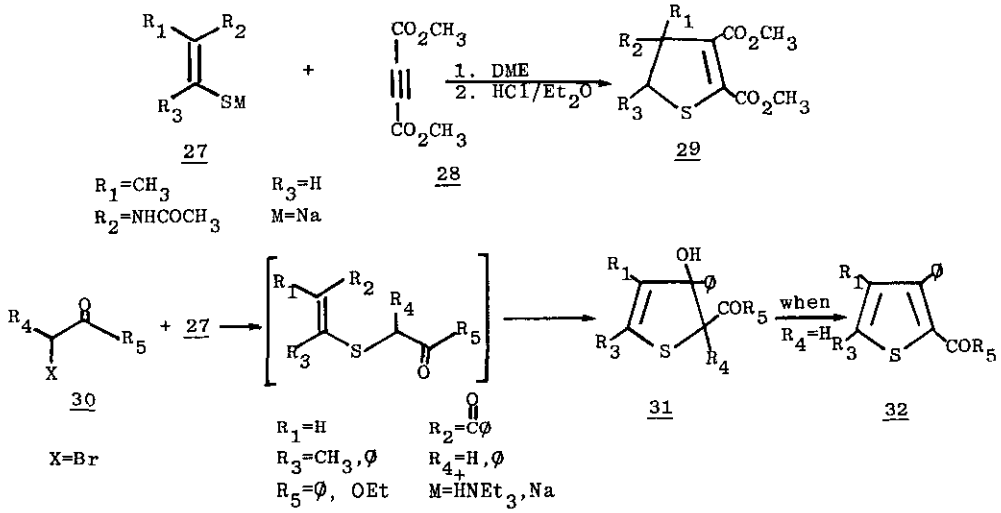


25 26

R_1=H,R_2=Et,R_3=H R_1=H,Me

Scheme 16

These substituted dihydrothiophenes (26) are not available from the previously reported reactions of vinylphosphonium salts as they would require the use of the unknown α-formyl vinylphosphonium salts or a 3-mercapto-2-ketoaldehyde. Another example involving initial carbon-sulfur bond formation includes the condensation of thioenolates (27) with 1,2-dicarbomethoxyacetylene (28) to afford substituted dimethyl 4,5-dihydrothiophene-2,3-dicarboxylates (29).[42] Cyclization of thioenolates with α-bromoketones and esters (30 X=Br) gives 2,3-dihydro-3-hydroxythiophenes (31), which readily dehydrate to to thiophenes (32) if the carbon adjacent to the hydroxy carbon is secondary.[43] A different approach involves the synthesis of 3-amino-4,5-dihydrothiophene (34) by the cyclization of β-mercaptonitriles (33) with chloromethyl aryl or alkyl ketones (30 X=Cl).[44] The dihydrothiophenes are readily oxidized with elemental sulfur to aminothiophenes (35). These reactions are summarized in Scheme 17.



27 $R_1=CH_3$ $R_2=NHCOCH_3$ $R_3=H$ M=Na

28

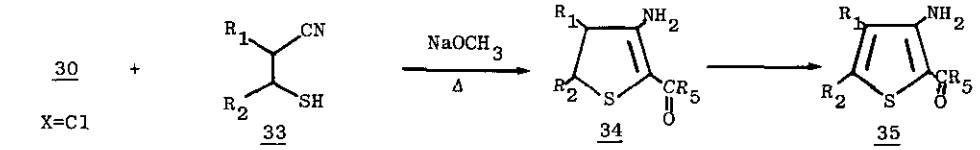
29

30 X=Br

31

32

$R_1=H$ $R_3=CH_3,\phi$ $R_5=\phi$, OEt $R_2=C\phi$ $R_4=H,\phi$ M=$HNEt_3$,Na



30 X=Cl

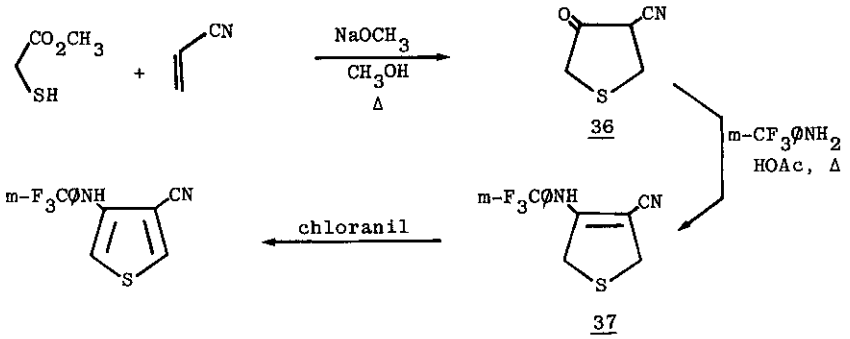
33 $R_1=H,CH_3$ $R_2=H,CH_3,\phi$

34 $R_5=CH_3,\phi$, p-Clϕ, C_4H_3S

35

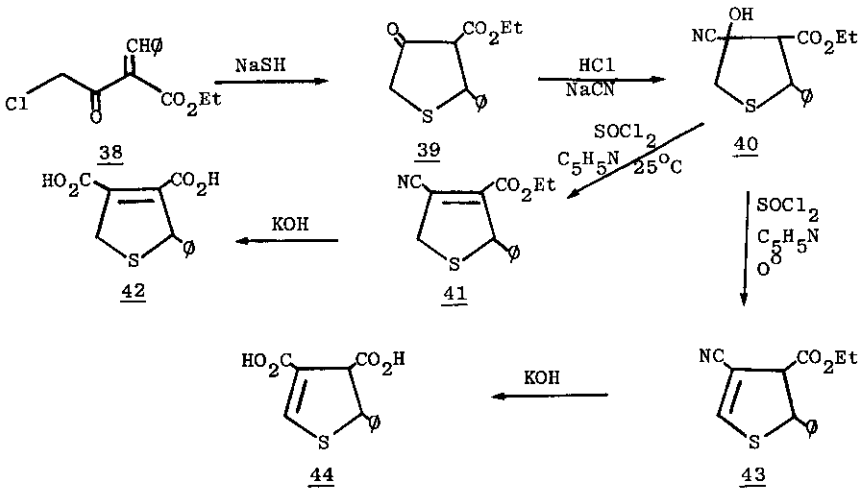
Scheme 17

Another aminothiophene synthesis involves condensation of methyl thioglycolate with acrylonitrile to produce 3-keto-4-cyanotetrahydrothiophene (36). Reaction of 36 with a substituted aniline affords enamine 37, a 2,5-dihydrothiophene derivative.[45] Oxidation of 37 with chloranil gives the corresponding thiophene (Scheme 18).



Scheme 18

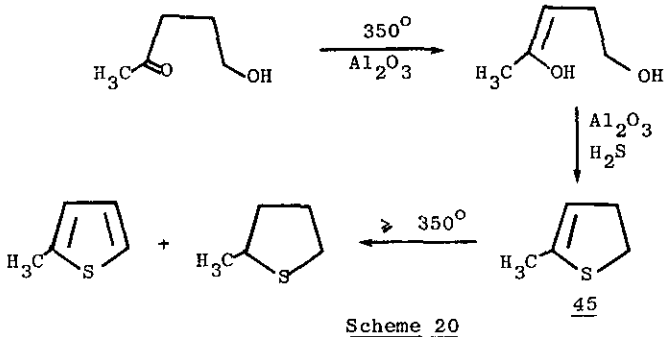
An alternative approach involves reaction of hydrogen sulfide or one of its alkali metal salts, usually sodium sulfide or bisulfide, with appropriately substituted Michael acceptors. An early example of this method is the synthesis of both 2,5-and 2,3-dihydrothiophenes via a common 3-ketotetrahydrothiophene[46] (Scheme 19).



Scheme 19

The assignment of structures 41 and 43 was based on the ultraviolet spectra of these compounds. Compound 41 showed the more intense absorption at 280 nm, consistent with the increased conjugation of this system.

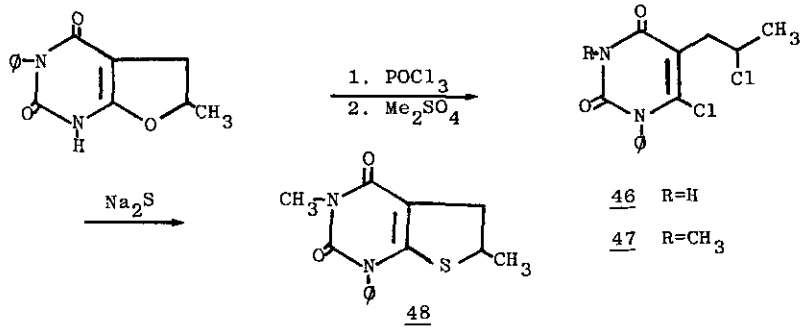
The formation of 39 arises via a Michael addition of sulfide ion to 38 followed by a nucleophilic displacement of the chloro group three carbons away. A variation of this "1,4-addition" methodology is illustrated with the synthesis of 2-methyl-4,5-dihydrothiophene (45), prepared by passing hydrogen sulfide over 5-hydroxyl-2-pentanone on alumina at 325°C.[47] At or above 350°C the products were the corresponding thiophene and tetrahydrothiophene (Scheme 20).



45

Scheme 20

1,4-Diketones have been converted to mixtures of thiophenes, dihydrothiophenes, and tetrahydrothiophenes by treatment with hydrogen sulfide.[48,49] Dichloro and dibromo compounds have also been used as precursors for dihydrothiophenes, and were, in fact, among the earliest materials used for this purpose[11,12,50] (Scheme 21).



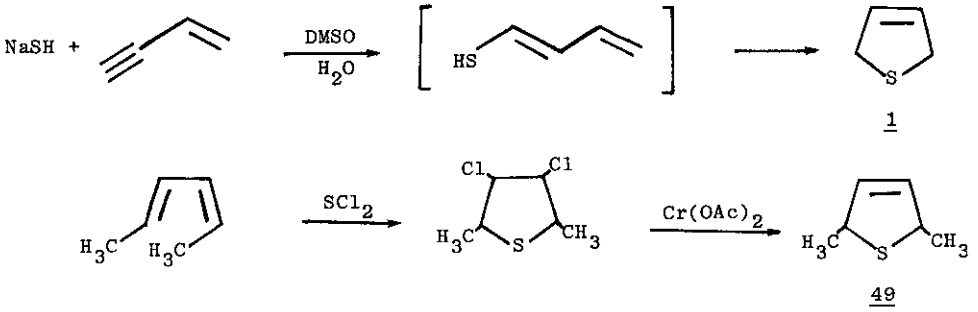
46 R=H

47 R=CH_3

48

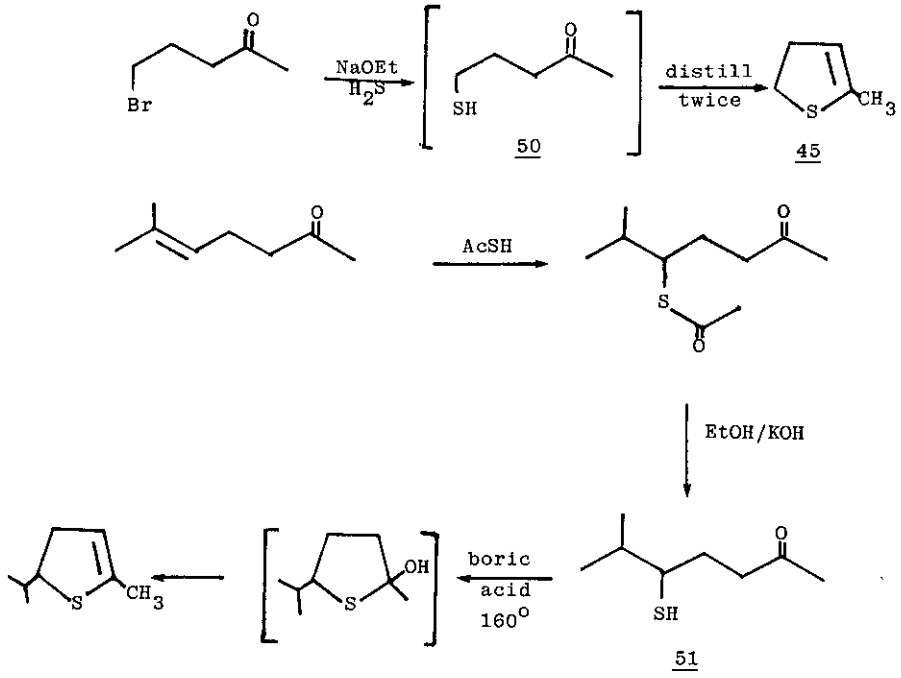
Scheme 21

Other precursors to dihydrothiophenes include vinyl acetylene[51] and 2,4-hexadiene[52] (Scheme 22).



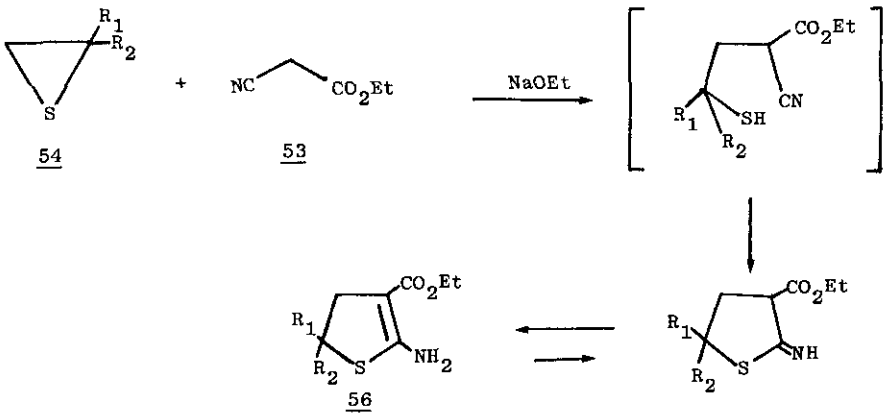
Scheme 22

γ-Mercapto ketones, (50,51) generated from γ-haloketones[53] or γ,δ-unsaturated ketones[54,55] via reaction with sulfur nucleophiles, also serve as dihydrothiophene precursors (Scheme 23).



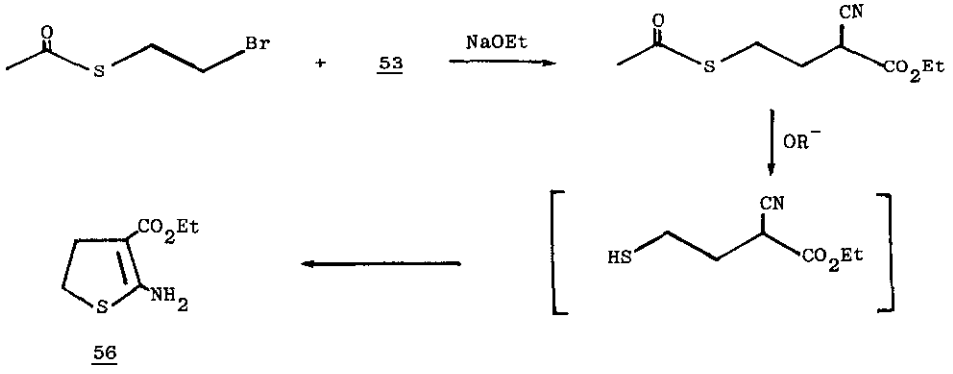
Scheme 23

Several 2-amino-4,5-dihydrothiophenes (56) have been prepared by the reaction of ethyl cyanoacetate (53) with substituted episulfides (54) (Scheme 24).



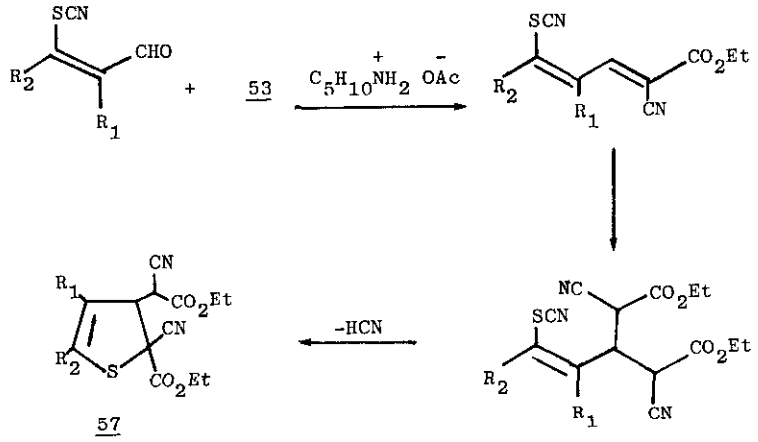
Scheme 24

This reaction was originally carried out with compounds in which R_1 and R_2 were hydrogen or methyl, and was later applied to substances containing bulkier substituents such as N-piperidino or N-morpholino groups.[56,57] Malononitrile has been used in a similar condensation.[58] Another variation of this method involves the reaction of 53 and β-bromoethyl thioacetate.[59,60] Condensation of these compounds followed by *in situ* hydrolysis of the thioester formed an intermediate similar to that obtained from the episulfide (54). Ring closure yielded 56 where R_1=R_2=H (Scheme 25).



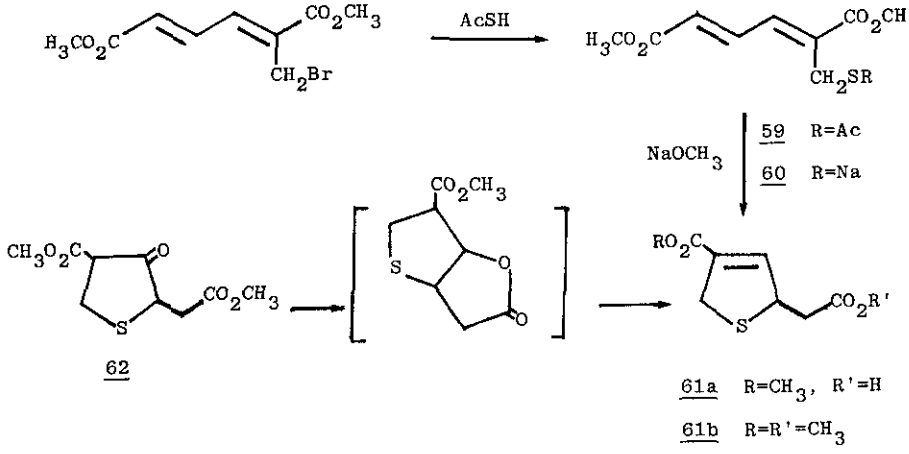
Scheme 25

An unusual cyclization affording a substituted 2,3-dihydrothiophene (57) involves condensation of an unsaturated thiocyanate with two equivalents of ethyl cyanoacetate (53)[61] (Scheme 26).



Scheme 26

Stotter and co-workers developed a general procedure for the preparation of 2,5-dihydrothiophenes which is also applicable to the synthesis of 2,5-dihydrofurans and 2,5-dihydropyrroles.[62] Treatment of dimethyl 2-bromomethyl-2,4-hexadienoate (58) with thiolacetic acid afforded the corresponding 2-acetyl thiomethyl compound (59). Removal of the acetyl group with sodium methoxide gave the mercaptide intermediate (60) which was then converted in situ to dihydrothiophene 61 (Scheme 27).

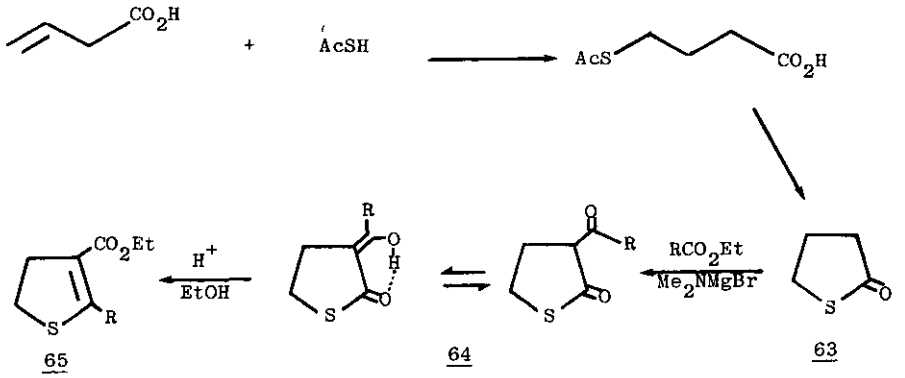


Scheme 27

Stotter and Stork also prepared dihydrothiophene 61 via a different cyclization procedure.[63] Condensation of methyl 3-mercaptopropionate with dimethyl maleate afforded ketoester 62. Compound 62 was reduced in methanol with an excess of morpholine-borane at ambient temperatures followed by an immediate treatment with sodium methoxide. Acidic work-up afforded 2,5-dihydro-4-carbomethoxy-2-thiopheneacetic acid (61a). Esterification of 61a gave 62b in 49% yield from 62. The diester (62b) was useful in the synthesis of trans-fused bicyclic systems (Scheme 27).

4. Rearrangements

Rearrangements have been used as another synthetic approach to dihydrothiophenes. The acid catalyzed rearrangements of substituted γ-thiolactones, for example, are well documented. Korte employed this route to prepare several substituted dihydrothiophenes as shown in Scheme 28.[64-66]

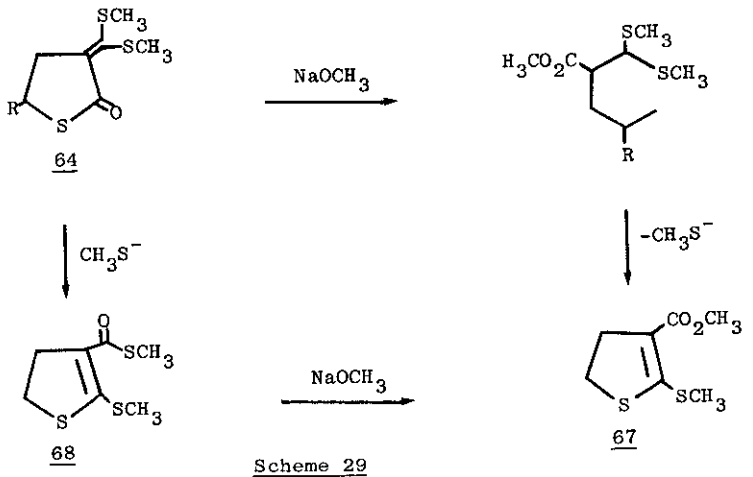


65 64 63

Scheme 28

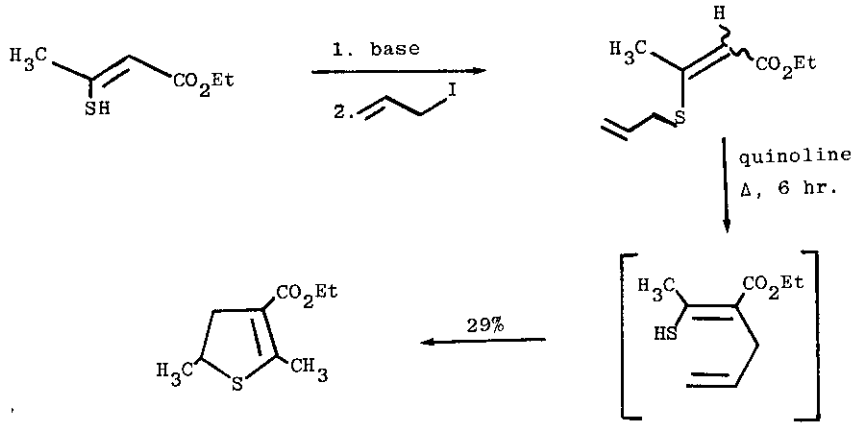
Best yields were obtained when R was an ethoxycarbonyl group. When R was hydrogen or a methyl group, yields were generally lower. The catalysts employed included hydrogen chloride in alcohol, concentrated aqueous hydrogen chloride, and Dowex 50 or Duolite C20 in the acid form. The ethoxycarbonyl group could readily be converted to an amide by reaction of the acyl thiolactone (64) with an amine prior to the rearrangement.[67] Ethyl 2-methyl-4,5-dihydrothiophene-3-carboxylate (65 R=CH_3) was easily converted to the 2-bromomethyl compound with bromine.[68] Similar thiolactones have been transformed to the corresponding dihydrothiophenes by other investigators. Condensation of 63 with carbon disulfide followed by treatment of the resulting product

with methyl iodide gave 66, which rearranged in basic solution as shown in Scheme 29.[69]



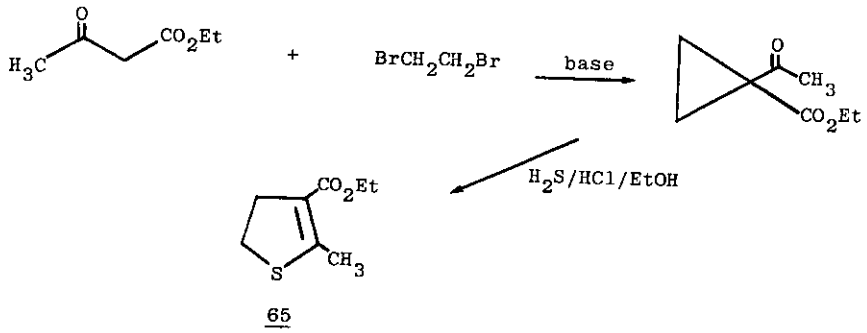
Scheme 29

Duus and Lawesson,[70] studied the rearrangement of thioacyl analogs of 64 to dihydrothiophenes 65 under acid conditions, work closely related to that of Korte.[64-66] Lawesson also reported an interesting Claisen rearrangement which led to the 5-substituted homolog of 65[71] (Scheme 30).



Scheme 30

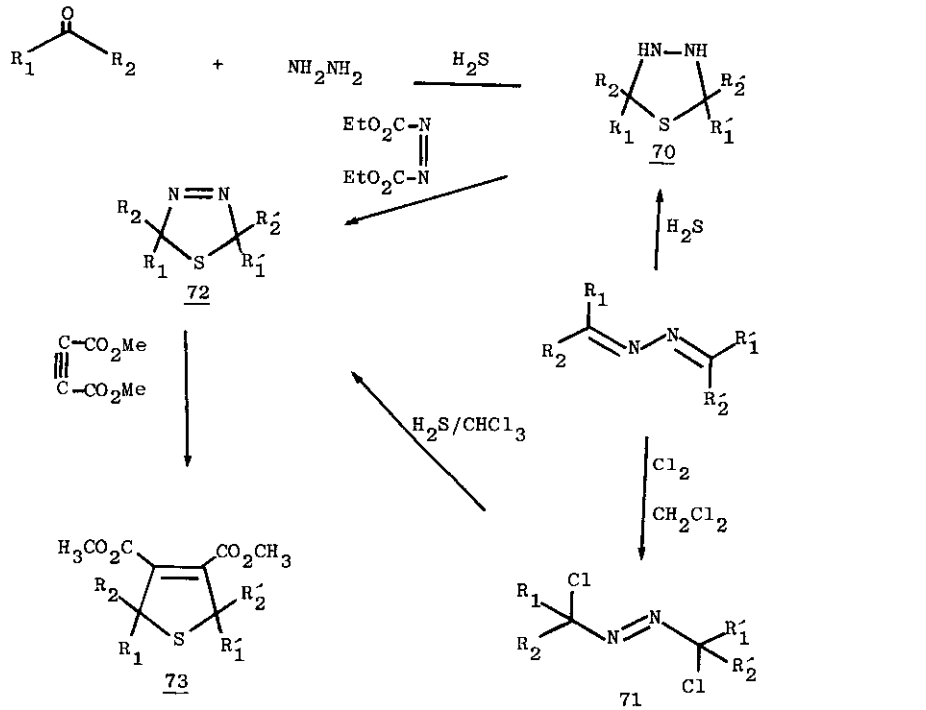
Cyclopropyl ketones have been converted to 4,5-dihydrothiophenes under acid conditions[72] (Scheme 31).



65

Scheme 31

Kellogg and co-workers have prepared several highly substituted 2,5-dihydrothiophenes by rearrangement processes[73,74] (Scheme 32).



70 R_1=H R_2=Et
R_1'=H R_2'=t-Bu

71 R_1=R_2=CH_3, Et, $(CH_2)_6$, $(CH_2)_2CH(t\text{-}Bu)(CH_2)_2$
R_1'=t-Bu R_2'=CH_3

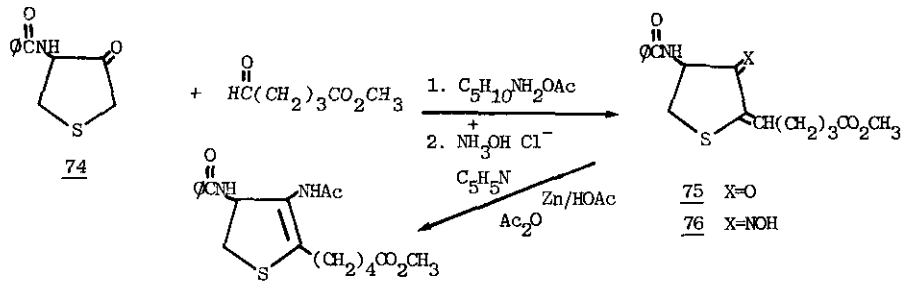
Scheme 32

These investigators were interested in the preparation and reactions of thiocarbonyl ylides, which are generated on heating thiadiazolines (72). The most successful general method proceeded via chlorinated azine 71. In situ reaction of the dipolarophile dimethyl acetylenedicarboxylate with the thiocarbonyl ylides generated from 72 afforded dihydrothiophenes (73). Where R_1=H and R_2=Et, the cis/trans ratio was observed to be 20.80. Upon photochemical decomposition, the dihydrothiophenes (73) afforded mixtures of isomeric dienes.[75-77]

II. SYNTHESIS OF BIOTIN PRECURSORS

Much of the progress in dihydrothiophene chemistry resulted from interest in biotin during the late forties. It is not the purpose of this review to discuss the various biotin syntheses that have been developed in recent years. Only the methodology which relates to dihydrothiophenes will be examined. Ring closures have been the route of choice to biotin. In contrast with the majority of cyclizations previously discussed, these ring closures initially afford ketotetrahydrothiophenes rather than dihydrothiophenes.

Harris and co-workers obtained 74 via a Dieckmann condensation and decarboxylation. This compound was then converted to 4,5-dihydrothiophene (77) and ultimately dl-biotin in three additional steps[78] (Scheme 33).

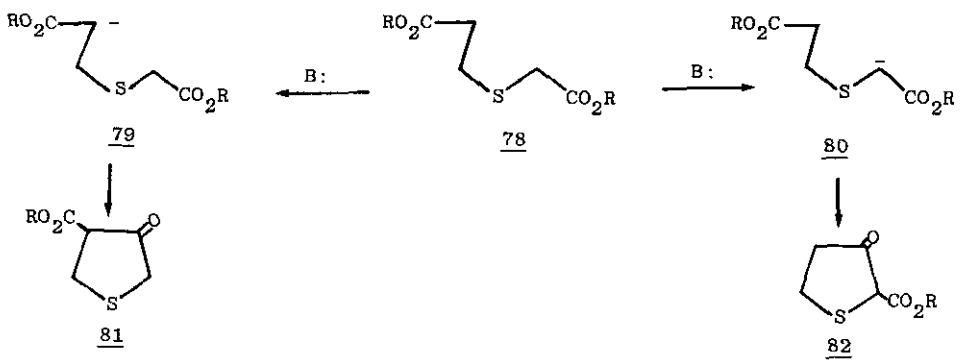


Scheme 33

Also formed was an isomer of 77, later determined to possess an exocyclic double bond, in which the amide functions had a trans relationship.[79] Very similar compounds were subsequently reported by Russian workers using analogous routes.[80-82]

Ketoester 81 played an important role in investigations leading to biotin. Woodward and Eastman, for example, systematically studied the cyclization

of 78 to 81 and 82[83] (Scheme 34).

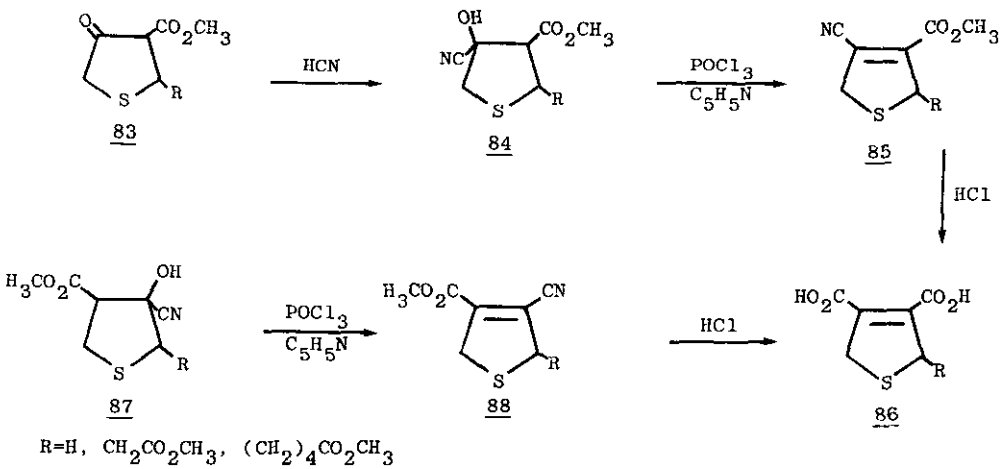


Scheme 34

At ambient temperatures, sodium methoxide in ether favored formation of the kinetic anion, 80, which then led to 82. The same base in refluxing toluene afforded 81 via the thermodynamically favored anion, 79.

Homologs of keto-ester 81 have been utilized to prepare compounds other than biotin (see Schemes 19 and 40). Spectroscopic studies of 81 showed that this compound existed mostly in its enol form, while 82 existed preferentially in the keto form.[84,85]

In a series of publications dealing with the synthesis of biotin, Baker and co-workers developed a route to a dihydrothiophene-3,4-dicarboxylic acid (86) (Scheme 35).[86-89]

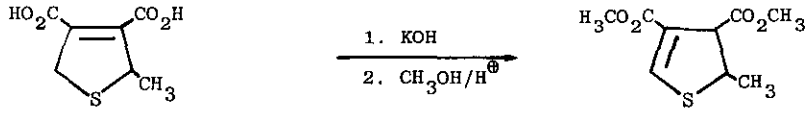


R=H, $CH_2CO_2CH_3$, $(CH_2)_4CO_2CH_3$

Scheme 35

These authors demonstrated, via comparisons of the ultraviolet spectra of known compounds, that the olefinic function in these dihydrothiophenes was in the 3,4 position, thereby characterizing the 2,5-dihydrothiophene ring.[90] The order of the dehydration and hydrolysis steps could be reversed without changing the outcome of these reactions. Where R ≠ H, the precursor of 87 was isomeric with 83.

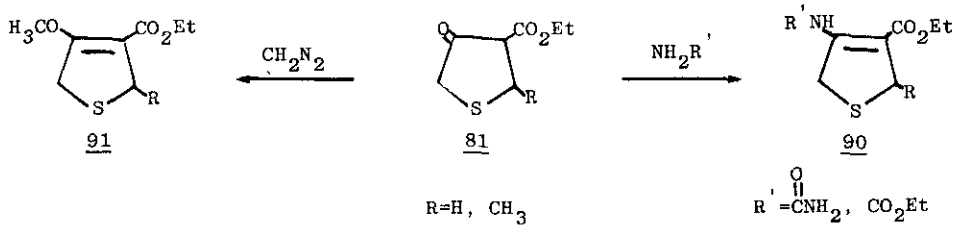
Takaya and co-workers prepared a number of interesting dihydrothiophenes during their synthetic investigations of biotin.[91-93] Using the procedure of Baker et al.,[86-89] they prepared 85 (R=H) and 86 ($R=CH_3$) as well as the dimethyl ester of 86. Treatment of 86 with sodium hydroxide converted it to the 2,3-dihydro isomer (89), a reaction[91] also observed but not as well documented by Baker[90] (Scheme 36).



86 89

Scheme 36

The NMR spectrum of 89 was reported to show a vinylic proton at δ 7.3. Reaction of 81 with urea or ethyl carbamate yielded an amino-substituted dihydrothiophene (90), while 81 and diazomethane afforded the methyl vinyl ether (91)[91,92] (Scheme 37).



91 81 90

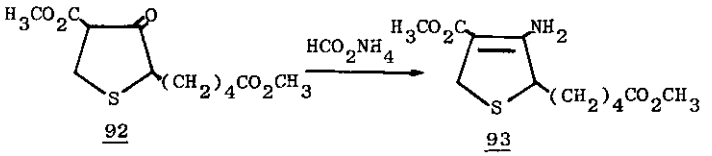
R=H, CH_3 $R'=CNH_2$, CO_2Et

Scheme 37

The behavior of compounds 85, 86, 89, 90, and 91 toward oxidation was investigated.[92] With hydrogen peroxide/acetic acid, dihydrothiophenes with two electron withdrawing groups (85, 86, 89) were oxidized to the corresponding thiophenes. Perbenzoic acid in chloroform afforded the sulfone derivatives instead. In contrast, dihydrothiophenes with one electron withdrawing and one electron donating group (90, 91) gave sulfones with either oxidizing

agent. Iodosobenzene was found to give only thiophenes, with no sulfone formation.[93]

Confalone and co-workers[94] prepared enamine 93 from keto-ester 92 (Scheme 38).

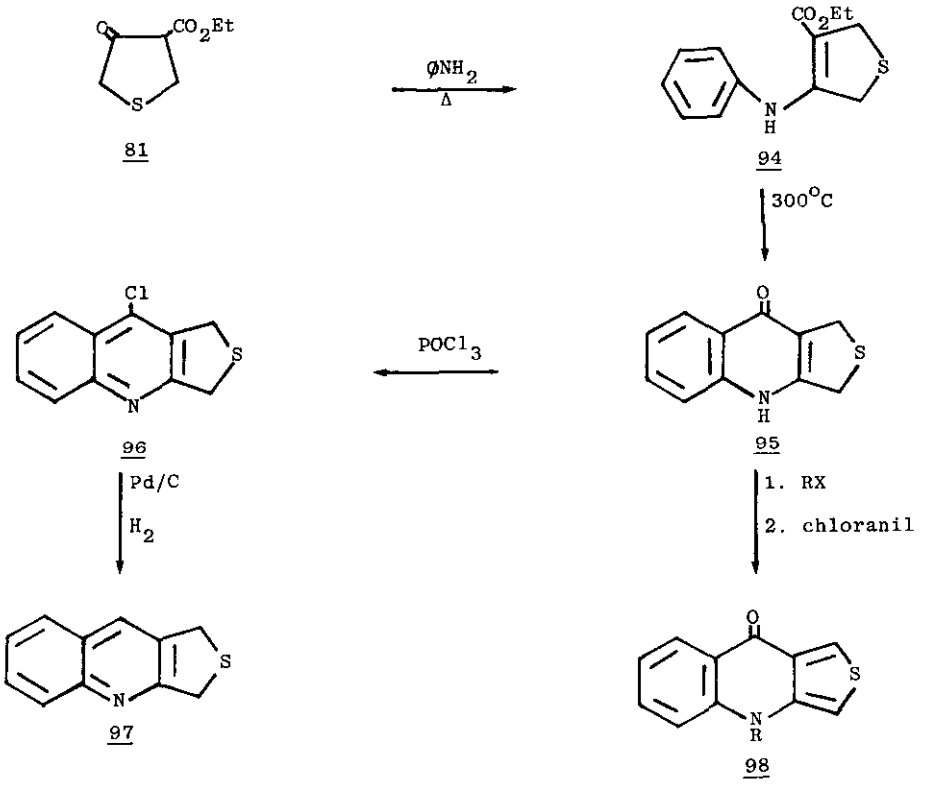


92 93

Scheme 38

Compound 93 was then converted to biotin.

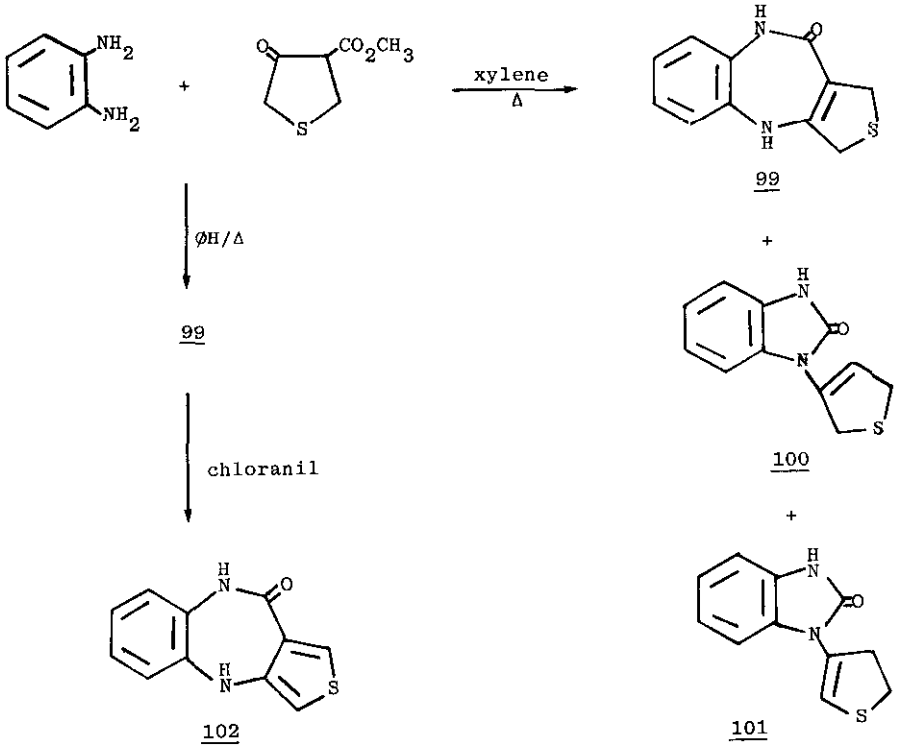
Several investigators have studied the preparation of bicyclic and polycyclic compounds from 81 and aromatic amines. Reaction of 81 with aniline afforded the expected enamine 94 which could be cyclized and further aromatized as shown in Scheme 39.[95]



81 94 95 96 97 98

Scheme 39

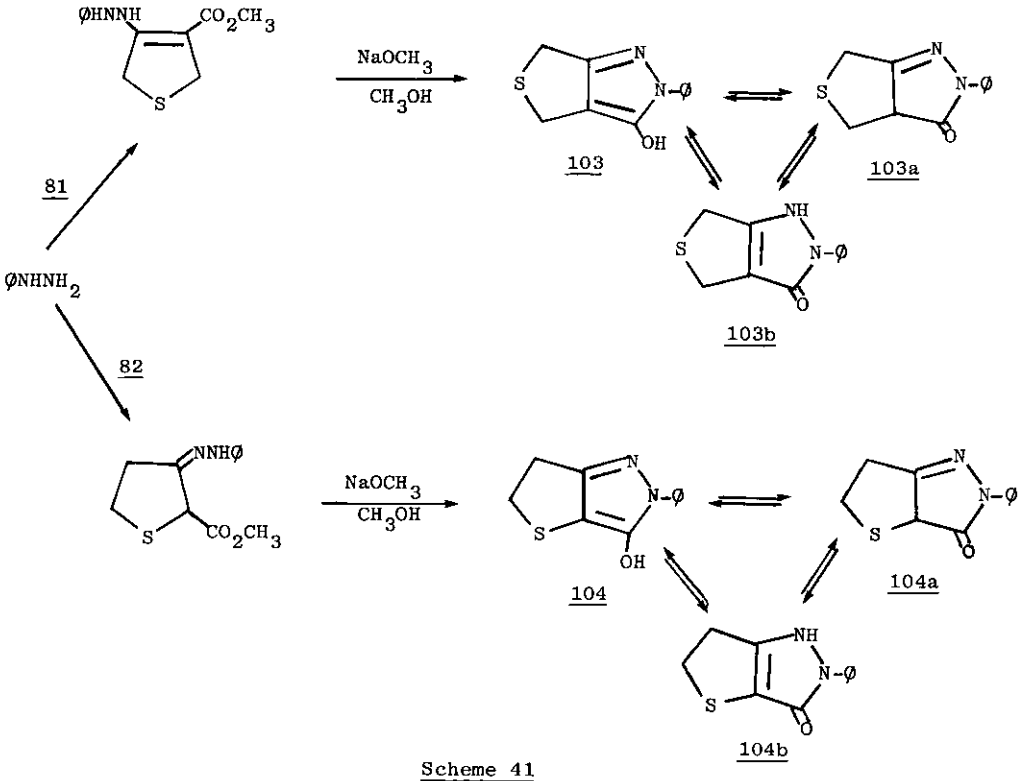
These reactions were explored further by Hromatka. When 94 was oxidized with chloranil to the thiophene, ring closure was no longer possible. Alkylation could be achieved at either the oxygen of 95 ($NaOCH_3$/DMF, RX=TsCl, $ClCO_2Et$) or both the oxygen and nitrogen ($NaOCH_3$/DMF, RX=CH_3Cl, $Cl(CH_2)_3CO_2Et$). The N-alkyl products were purified by fractional crystallization and could be further oxidized to the thiophene derivatives (98).[96] Condensation of 81 with o-aminoaniline had variable results, depending upon the reaction temperature[97] (Scheme 40).



Scheme 40

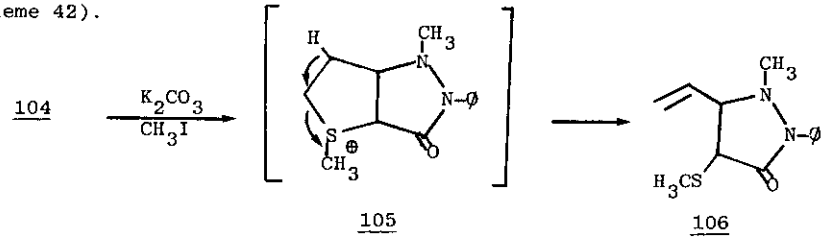
Introduction of hydrogen chloride in xylene caused the formation of 100 as the sole product. On further heating with p-toluenesulfonic acid 100 was isomerized to 101.[98] Press and Safir, during the course of their investigations on 4H-thienobenzodiazepins, prepared several compounds similar to 99.[99] Press and Safir also examined the reaction of 81 with other aromatic nucleophiles. Use of o-aminophenol led to the o-hydroxy analog of 94, which could not be induced to form the lactone analog of 99.[100] Interesting

tautomeric products resulted from other work in Safir's laboratory regarding reactions of 81 and 82 with phenylhydrazine[101] (Scheme 41).



Scheme 41

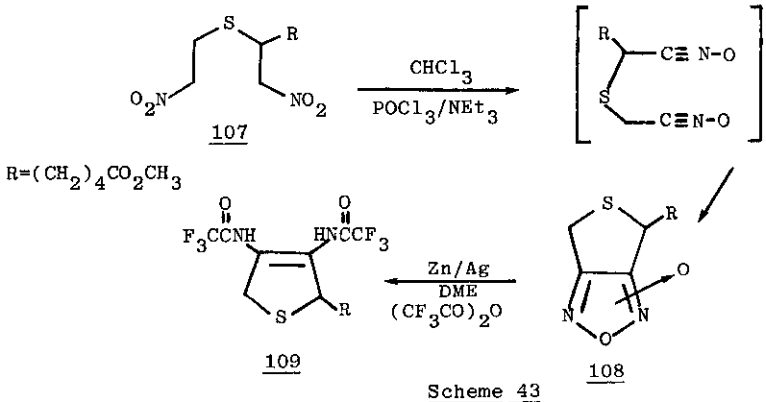
The enol forms (103, 104) were observed in the solid state, while the non-conjugated keto forms (103a, 104a) were observed in dilute chloroform solution. The conjugated keto forms were not detected. However, alkylation of 103 with alkyl iodides and potassium carbonate in acetone resulted in reaction at oxygen, nitrogen, and carbon. Isomeric compound 104 behaved rather differently, giving an acyclic product (106) via a sulfonium intermediate (Scheme 42).



Scheme 42

Finally, 81 and some O-alkylated or acylated derivatives of its tautomeric form have been converted to the corresponding substituted thiophene with sulfuryl chloride.[102,103]

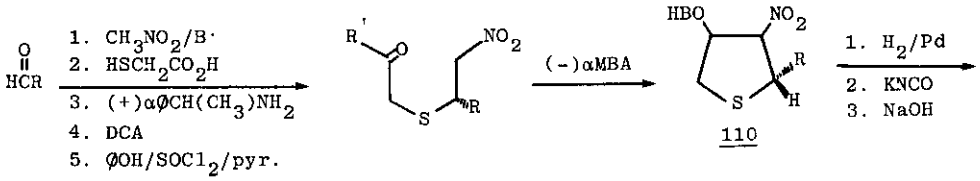
Two other approaches to biotin utilizing dihydrothiophenes also deserve mention. Marx and co-workers recently converted 107, prepared via aldol and Michael type reactions, to a dihydrothiophene which was transformed into dl-biotin in three steps[104] (Scheme 43).



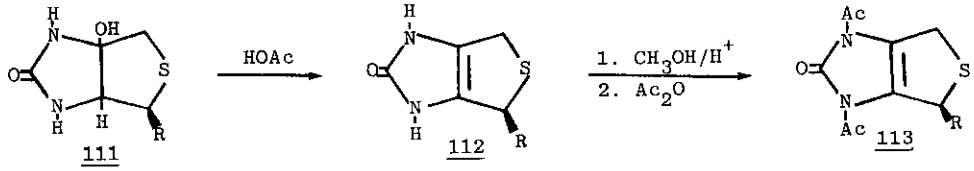
107 108 109

Scheme 43

A minor product formed along with 109 was the corresponding thiophene. The second approach first produced the imide ring of biotin with potassium isocyanate and then generated the 2,5-dihydrothiophene, which, in turn, was stereospecifically reduced to d-biotin. The d and l isomers were separated in an earlier step[105] (Scheme 44).



110

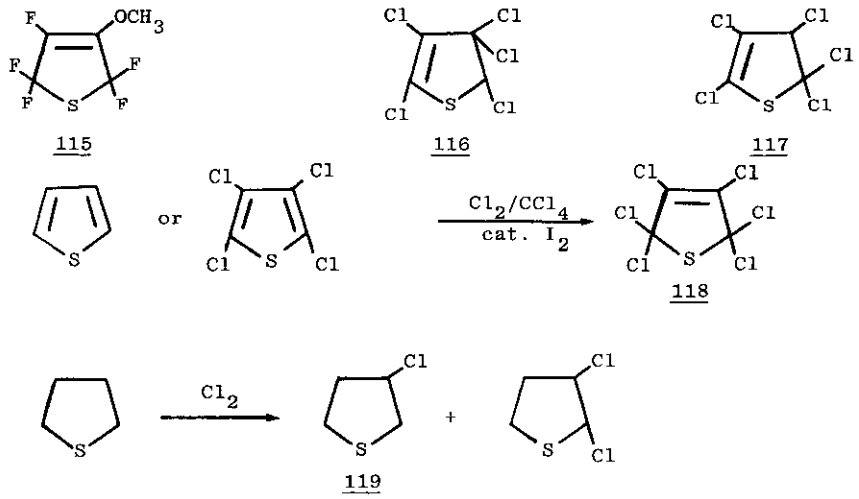


111 112 113

Scheme 44

III. SYNTHESIS OF HALODIHYDROTHIOPHENES

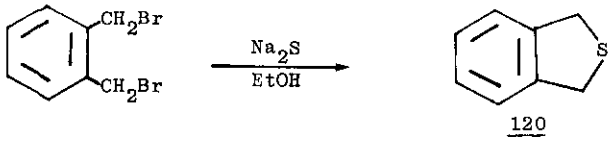
Syntheses of halodihydrothiophenes have involved a number of methods besides direct halogenation. Perfluoro-2,5-dihydrothiophene resulted from the treatment of perfluorocyclobutene with sulfur under heat and pressure.[106] Treatment of tetrachlorothiophene with silver difluoride or potassium tetrafluorocobaltate (PTFC) yielded 3,4-dichloro-2,2,5,5-tetrafluoro-2,5-dihydrothiophene. Thiophene with PTFC gave a mixture of products whose major constituent was 2,2,5,5-tetrafluoro-2,5-dihydrothiophene. Penta- and hexafluorodihydrothiophenes were also formed, along with fluorotetrahydrothiophene.[107] Reaction of these fluorodihydrothiophenes with sodium methoxide gave methoxyfluorodihydrothiophenes such as 115[108] (Scheme 45). A trace amount of perfluoro-2,5-dihydrothiophene was also formed on exposure of perfluorobutadiene and sulfur dioxide to ultraviolet light.[109] An early investigation of the direct chlorination of thiophene or 2-thiophenecarboxylic acid in acetic acid characterized the product as a pentachlorodihydrothiophene having structure 116 or 117[110] (Scheme 45). More recently, perchloro-2,5-dihydrothiophene (118) was found to be the product of direct chlorination of either thiophene or tetrachlorothiophene in carbon tetrachloride using iodine as catalyst.[111,112] 3-Chloro-4,5-dihydrothiophene (119) was formed along with 2,3-dichlorotetrahydrothiophene in the direct chlorination of tetrahydrothiophene[113] (Scheme 45).



Scheme 45

IV. SYNTHESIS OF BICYCLIC DIHYDROTHIOPHENES

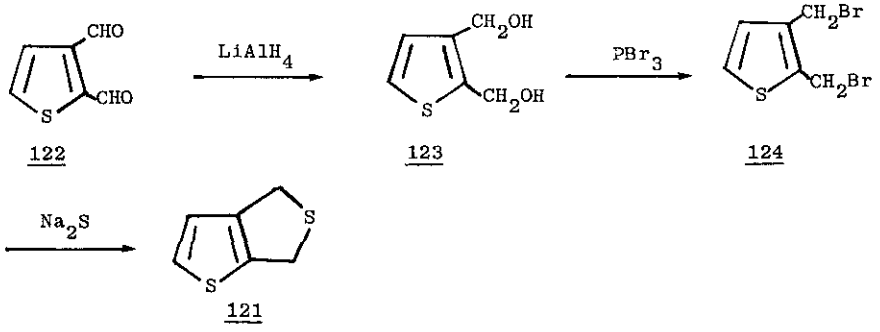
A few condensed dihydrothiophenes were discussed earlier; a number of additional examples will be given here. A very early investigation by Leser reported the preparation of benzo[c,2,5]dihydrothiophene (120) from α,α'-dibromo-o-xylene[114] (Scheme 47).



120

Scheme 46

This author also commented upon the relationship between thiophene and dihydrothiophene, at that time unknown, as compared to benzene and dihydrobenzene. Many years later, Cava utilized this reaction to prepare benzocyclobutene. Compound 120 was oxidized to the sulfone which, upon loss of sulfur dioxide, gave a mixture of compounds containing benzocyclobutene.[115] MacDowell and Patrick synthesized 4,6-dihydrothieno[3,4-b]thiophene (121) to investigate the strain in the aromatic portion of the molecule.[116] Reduction of dialdehyde 122 afforded dialcohol 123. Conversion of 123 to the bis bromomethylthiophene 124 followed by reaction with sodium sulfide gave 121 in 18% overall yield (Scheme 47).



122 123 124

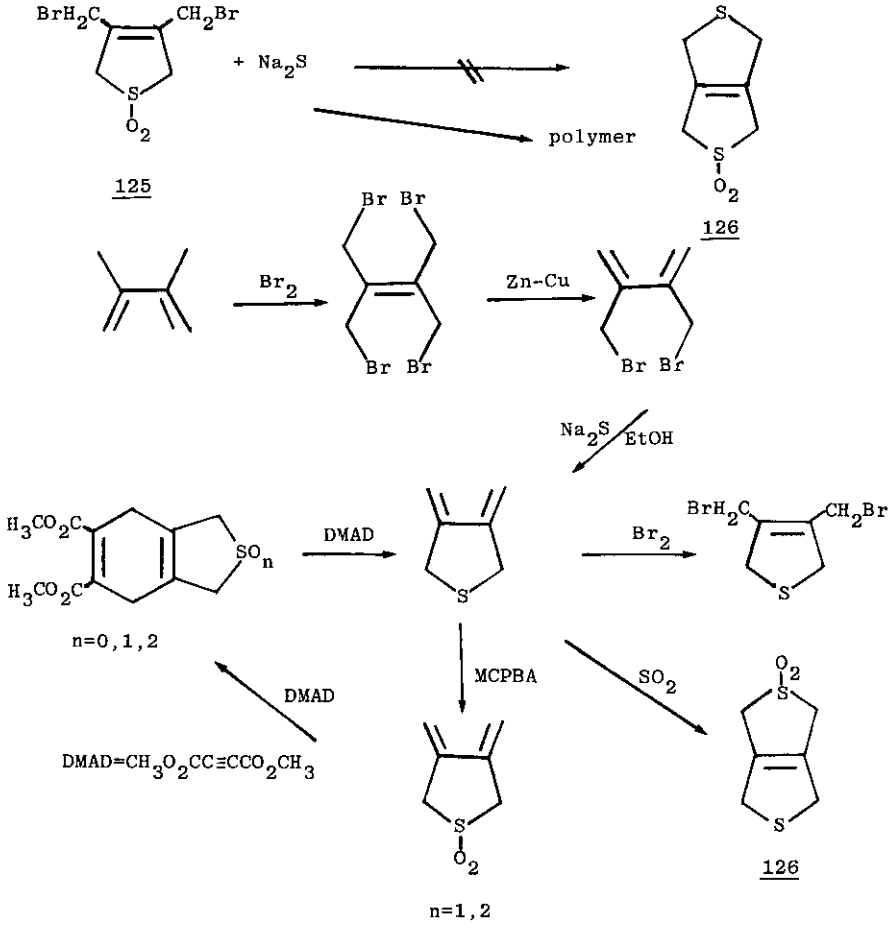
121

Scheme 47

The NMR spectrum of 121 was compared to that of the unstrained 2,3-bisethylthiomethylthiophene. Differences in the chemical shifts of the corresponding C_1 and C_2 protons were too small to be attributed to a decrease in aromaticity in the bicyclic molecule 121.[116]

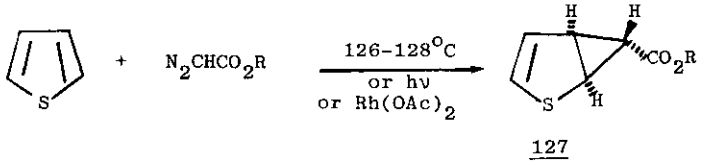
The interesting sulfide/sulfone 126 could not be prepared from 125,[117] but

was later made by a related route[118,119] (Scheme 48).



Scheme 48

Reaction between thiophene and ethyl diazoacetate under both thermal and photochemical conditions yielded the bicyclic compound 127 (R=Et), ethyl 2-thiabicyclo[3.1.0]hex-3-ene-6-carboxylate[120,121] (Scheme 49).



Scheme 49

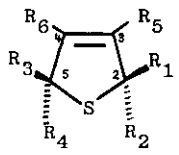
The isolated yield of 129 (20%) was recently improved more than threefold by the use of a rhodium (II) catalyst, and the n-butyl rather than ethyl diazo ester.[122] The exo-stereochemistry was deduced from the small trans coupling constant (3.2 Hz) for the cyclopropane protons,[122] observed in the carboxylic acid (127, R=H) obtained on basic hydrolysis of the ester. Diazomethane reacts in a similar manner to afford the parent bicyclic compound.[123]

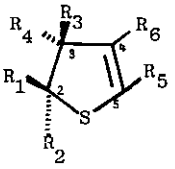
V. SPECTROSCOPIC STUDIES OF DIHYDROTHIOPHENES

Detailed spectroscopic studies have been carried out on simple dihydrothiophenes. The ultraviolet spectra of 2,3-dihydrothiophene and 2,5-dihydrothiophene were reported to show absorption maxima at 236 and 262 nm and at 211 and 232 nm, respectively, but no ε_{max} values were given.[124]

Investigations of the near infrared spectral characteristics of dihydrothiophenes showed that the 2,5-dihydro isomer is planar.[125,126] However, the 2,3-dihydro isomer has a nonplanar ring.[125] A detailed analysis of the infrared spectrum of 2,5-dihydrothiophene revealed C_{2v} symmetry, supporting a planar ring.[127]

Nuclear magnetic resonance data comprises the largest body of spectral information available on dihydrothiophenes. Chemical shift values and to a lesser extent coupling constants have been determined for a variety of substituted dihydrothiophenes. ^{13}C chemical shifts of several dihydrothiophenes have also been determined. These values are listed in Tables I and II. Originally, coupling constants $J_{1,3}$ and $J_{1,4}$ for compound 1a had been assigned differently from the assignment shown in Table I.[128] However, investigations of similarly substituted 2,5-dihydrofurans[129,130] and 2,5-dihydropyrroles[135] have shown that the coupling constants ($J_{1,4}$) of trans substituted compounds are always larger than those of cis derivatives. Thus, the present assignments are consistent with those made for 2,5-dihydrofurans and 2,5-dihydropyrroles. The following structures refer to the compounds listed in Tables I and II.





1a R_{1-6}=H

1b R_2=R_4=R_6=H R_1=R=R_5=CH_3

1c $R_{1-4,6}$=H R_5=CO_2CH_3

1d R_1=CO_2H R_{2-6}=H

1e R_1=CO_2H R_3=CH_3 $R_{2,4-6}$=H

1f R_1=CO_2H R_4=CH_3 $R_{2,3,5,6}$=H

1g R_1=CO_2H R_5=CH_3 $R_{2-4,6}$=H

2a R_{1-6}=H

2b R_5=CH_3 $R_{1-4,6}$=H

2c R_5=NH_2 R_6=$CO_2CH_2CH_3$ R_{1-4}=H

2d $R_{1,6}$=H R_2=2BI R_3=OH R_4=CH_3 R_5=Ø

2e $R_{1,6}$=H R_2=2BI R_3=CH_3 R_4=OH R_5=Ø

2f R_{1-4}=H R_5=2BI R_6=CH_3

2g R_5=CO_2H $R_{1-4,6}$=H

2h R_5=CO_2H R_6=CH_3 R_{1-4}=H

2BI =

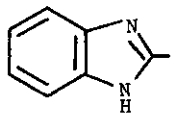


Table I ^{1}H NMR Chemical Shifts and Coupling Constants

Compound	δR_1	δR_2	δR_3	δR_4	δR_5	δR_6	$J_{1,3}$	$J_{1,4}$	$J_{1,5}$	$J_{1,6}$	$J_{2,3}$	$J_{2,4}$	$J_{2,5}$	$J_{2,6}$	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
1a[a]	3 67	3 67	3 67	3 67	5 81	5 81														
1a[b]	3 6644	.	.	.	.	5 7938	3 24	6.60	2 52	-2 36	6 80	3 24	2.52	-2 36	-	-2 36	2 52	-2.36	2 52	6.31
1d[c]	10 02	4 77	3 82	3 82	5 91	5 91														
1e[d,c]	11 65	4 75	1 46	4 36	5 96	5 76	-	-	-	-	-	2 25	1 7	2.6	6 9	-	-	2	1 6	6 0
1f[d,c]	11.39	4 86	1 45	4 47	5 94	5 76	-	-	-	-	5.1	-	1 8	2 2	6 7	2 0	2 1	-	-	6 5
1g[d]	10 76	4 52	3 78	3 78	1.87	5.73														
2a[a]	3.08	3 08	2.62	2.62	6.06	5.48	9 2	9.2	-	-	9 2	9.2	-	-	-	2 2	2 5	2 2	2 5	6 1
2a[e]	-	-	-	-	-	-	9.99	7 53	-	-	7 53	9 99	-	-	-	-2 23	2 78	-2 23	2 78	5 98
2b[e]	-	-	-	-	-	-	9.37	7.34	-	-	7.34	9 37	-	-	-	1 28	2 55	1 28	2 55	-1 49
2c[f]	3 1	3.1	3 1	3 1	6.05	1 27(CH_3) 4 16(CH_2)														
2d[g]	5 10	-	-	1.20	7 41	6 20														
2e[g]	5 20	-	-	1.65	7.41	6.30														
2f[g]	3 16	3.16	3 16	3.16	7 41	2.30														
2g[c]	3 31	3.31	2 95	2 95	10 22	6.59	8.5	8 5	-	-	8 5	8 5	-	-	-	-	3 0	-	3 0	-
2h[c]	3 15	3 15	3.15	3.15	10.50	2 23														

a. Ref 131 b Ref 128 c. unpublished results d Ref. 21 e. Ref. 132 f Ref 60 g Ref 134

Table II ^{13}C NMR Chemical Shifts

Compound	δC-2	δC-3	δC-4	δC-5	δ2-CH_3	δ3-CH_3	δ4-CH_3	δ5-CH_3	δ2-C=O	δ3-C=O
1a[a]	39.1	128.8	128.8	39.1	-	-	-	-	-	-
1b[a]	52.0	141.3	129.1	47.7	25.4	14.8	-	28.8	-	-
1c[a]	(37.2)[e]	135.6	140.8	(39.0)[e]	-	51.8	-	-	-	164.2
1d[b]	55.5	126.9	132.3	39.5	-	-	-	-	177.8	-
1e[b]	55.5	125.1	138.4	50.7	-	-	-	23.9	177.9	-
1f[b]	56.1	125.6	138.5	50.4	-	-	-	23.0	175.2	-
1g[c]	57.7	136.3	127.4	38.6	-	15.5	-	-	177.9	-
2d[d]	58.8	88.8	130.0	130.7	-	24.5	-	-	-	-
2e[d]	57.0	86.3	130.4	130.7	-	28.6	-	-	-	-
2f[d]	45.2	31.3	123.3	137.2	-	-	18.0	-	-	-
2g[b]	136.8	134.9	(37.1)[e]	(32.8)[e]	-	-	-	-	163.8	-

a. Ref. 133 b. unpublished results c. Ref. 21 d. Ref. 134 e. values in parentheses may be interchanged

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