THIOPHENE AND ITS DERIVATIVES

Part Three

This is the Forty-Fourth Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

THIOPHENE AND ITS DERIVATIVES

Part Three

Edited by

Salo Gronowitz

University of Lund
Lund, Sweden

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible, new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

In 1952, in the first volume of *The Chemistry of Heterocyclic Compounds*, Howard D. Hartough described the state of research on the chemistry of thiophene and its derivatives up to 1950. Selenophene and tellurophene were also included in this monograph which, except for two chapters, was written by Hartough alone. When this book was written, the explosive development triggered by the commercial process for thiophene from butane and sulfur, developed by Socony-Vacuum Oil Company in the 1940s, had just begun. The enormous amount of work carried out on this important aromatic five-membered heterocycle since 1950 makes it of course impossible for one person to cover all aspects, and an able group of specialists were assembled from all over the world to treat the entire field. This makes some minor overlaps between chapters unavoidable, but I think it is important to treat some topics from different angles of approach.

Because of the wealth of results and the rather large number of contributors, these volumes are not as strictly organized as some previous volumes in this series, but can be considered as a collection of topics on thiophene chemistry. Together, however, it is my hope that these chapters give as comprehensive a description as possible of the chemistry of thiophene and its monocyclic derivatives, based on the literature from 1950 to 1982. References to previous results, treated in Hartough's book, are also given when necessary.

The chapters fall in two categories: (1) those that treat syntheses, properties, and reactions of thiophenes, and (2) those that treat systematically functionalized simple thiophenes, such as alkylthiophenes, halothiophenes, aminothiophenes, thiophenecarboxylic acids, and so on. The latter chapters, as is customary in the Weissberger–Taylor series, contain tables of compounds with their physical properties, which should be very useful for all synthetic chemists. Part 1 of these volumes contains only chapters in category 1 and starts with a treatise on the preparation of thiophenes by ring-closure reactions and from other ring systems. It is followed by a chapter on theoretical calculations. Then, in two chapters, naturally occurring thiophenes in plants and in petroleum, shale oil, and coals are treated. The topic of the next chapter is the important field of pharmacologically active compounds. The synthetic use of thiophene derivatives for the synthesis of aliphatic compounds by desulfurization follows. Two chapters treat thiophenes modified at the sulfur, namely thiophene-1,1-dioxides and thiophene-1-oxides, and *S*-alkylation of thiophenes. In the last three chapters, the discussion on different reactivities of thiophenes starts with radical reactions of thiophenes, cycloaddition reactions, and photochemical reactions.

Part 2 of this four-part volume begins with a treatment of the important field of electrophilic aromatic substitution of thiophenes, followed by systematic treatment of four classes of functionalized thiophenes, namely the alkyl-, halo-, nitro- and aminothiophenes.

The first two chapters of Part 3 of this volume treat the chemistry of thiophene derivatives containing thiophene-to-oxygen bonds and thiophene-to-sulfur bonds, respectively, and the remaining chapters cover formyl and acyl derivatives of thiophene, thiophenecarboxylic acids, and thenyl derivatives.

In part 4, nucleophilic aromatic substitution of thiophenes, physical properties of thiophenes, metal derivatives of thiophenes as well as thienyl ethenes, thienyl acetylenes and aryl- and heteroarylthiophenes will be examined.

I wish to thank all the distinguished scientists who contributed chapters to these volumes for their splendid cooperation and my secretary Ann Nordlund for her invaluable help. I am also indebted to Dr. Robert E. Carter for correcting my chapter and those of some of the other authors whose native tongue is not English.

SALO GRONOWITZ

Lund, Sweden
January 1986

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THIOPHENE AND ITS DERIVATIVES

Part Three

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THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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CHAPTER I

Syntheses, Physical Properties, and Reactions of Compounds Containing Thiophene—Oxygen Bonds

SALO GRONOWITZ and ANNA-BRITTA HORNFELDT

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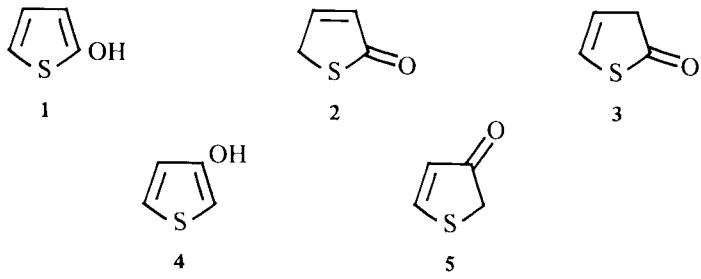
I. INTRODUCTION

This chapter treats the 2- and 3-hydroxythiophenes, their alkyl and aryl ethers, their esters, the acyloxythiophenes, as well as other thiophene derivatives containing thiophene-oxygen bonds.

The chemistry of the hydroxythiophene systems, which only recently has been studied in detail, differs very much from that of the analogous phenols. Hydroxythiophenes are often very unstable air-sensitive, and acid-sensitive compounds, which decompose easily. They also show characteristic tautomeric properties. Thus 2-hydroxythiophene could in principle exist in the three tautomeric forms **1** to **3** (Scheme 1). The unsaturated thiolactone forms **2** and **3** are also called 3-thiolen-2-one and 4-thiolen-2-one, respectively. In another nomenclature, which has been used in the literature, **2** and **3** are called 2,5-dihydro-2-oxothiophene and 2,3-dihydro-5-oxothiophene. In *Chemical Abstracts* they are found under 2(5H)-thiophenone and 2(3H)-thiophenone, respectively. In analogy with the corresponding furan derivatives they have also been called α,β-thiobutenolide (**2**) and



Scheme 1

β,γ-thiobutenolide (**3**). In substituted derivatives, depending on the nature and position of the substituents, the form **1**, **2**, or **3** can be the most stable. 3-Hydroxythiophene (**4**) can also exist in the keto form (**5**), which is called 4-thiolen-3-one, or 3(2H)-thiophenone. The position of the tautomeric equilibrium is greatly influenced by solvent effects.

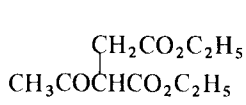
II. PREPARATION OF HYDROXYTHIOPHENES

1. Preparation of 2-Hydroxythiophenes through Ring-Closure Reactions

In this section on synthesis the compounds are called 2-hydroxythiophenes regardless of their true tautomeric structure. Only a few ring-closure reactions leading to 2-hydroxythiophenes are known.

A. $C_4 + S$ Methods

5-Methyl-2-hydroxythiophene was prepared as early as 1886 by Kues and Paal[1] through the reaction of levulinic acid with P_4S_{10}. Steinkopf and Thormann[2] realized that two tautomeric forms of 5-methyl-2-hydroxythiophenes could be obtained, but made an erroneous structure assignment. Correct structure assignments were made in 1960 by the use of NMR.[3] 5-Aryl-2-hydroxythiophenes have also been prepared by this method.[7] The reaction of aliphatic γ-oxo esters with H_2S/HCl gave a mixture of tautomers of the 5-alkyl-2-hydroxythiophene system and 5-alkyl-5-mercapto-thiolan-2-ones, which upon refluxing in pyridine could be transformed to the tautomers of 5-alkyl-2-hydroxythiophenes[4] (cf. Part 1, Chapter I, Section II.E). 5-Methyl-2-hydroxythiophene has also been prepared in low yield through the reaction of the acid chloride of pentyne-4-carboxylic acid with KSH and H_2S in pyridine.[5] The reaction of **6** with H_2S/HCl gives the 2-hydroxy-4-carbethoxy-5-methylthiophene (**7**) in 54% yield[6] (see also Part 1, Chapter I, Section II.3) (Scheme 2). The reaction of 3-bromomethyl-3-(2-furyl)-2-propenoic acid with thiourea gave 4-(2-furyl)-3-thiolen-2-one.[8]



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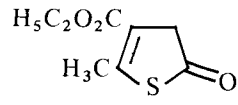

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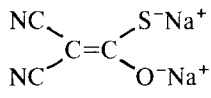
Scheme 2

B. C_3S + C Methods

Condensation of crude carbonyl sulfide with malonitrile and alkylation of the intermediate (**8**) with phenacyl bromide gives 4-amino-2-hydroxythiophene (**9**) in 64% yield[9] (Scheme 3).



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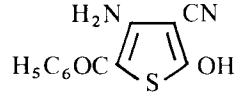


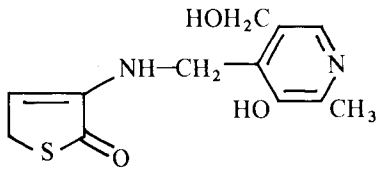
9

Scheme 3

C. Other Ring Systems

The reaction of bromocysteine thiolactone hydrochloride with pyridoxal in ethanol gave the 3-amino-2-hydroxthiophene derivative **10**[10] (Scheme 4). Bromination of the thiolactones (**11**), followed by dehydrobromination with triethylamine, was used for the preparation of 2-hydroxythiophene and 3-ethyl-2-hydroxythiophene (**12**).[11] The reaction of **13** with NaSH and hydrogen chloride, followed by an aromatic aldehyde, gave **14** directly,[12] which can also be prepared by the acid-catalyzed condensation of 2-hydroxythiophenes with aldehydes (Scheme 5). Compound **13** was prepared by the treatment of 4-aryl-4-oxybutanoic acids with acetic anhydride and sulfuric acid.

Treatment of dichloromaleic thioanhydride with acetic anhydride, followed by



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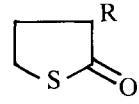
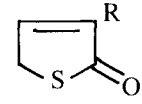


R = H, C_2H_5

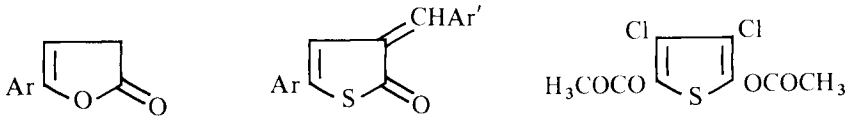
11



R = H, C_2H_5

12

Scheme 4

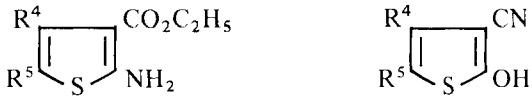


13 14 15

$Ar = C_6H_5$ $Ar' = 4\text{-}ClC_6H_4$
$Ar = 3,4\text{-}(CH_3)_2\text{-}C_6H_3$ $Ar' = 2,4\text{-}Cl_2C_6H_3$

Scheme 5

heating with powdered zinc, gave the acetoxy derivatives of 2,5-dihydroxythiophene (**15**).[13] The reaction of 4-chloromethyl-4-methyl-azetidin-2-one with sodium hydrogen sulfide gave 4-methyl-2-hydroxythiophene in 40% yield.[14] The azetidinone was obtained through the cycloaddition of methallyl chloride to chlorosulfonyl isocyanate, followed by splitting off the sulfonyl chloride group. The reaction of **16** with sodium ethoxide in refluxing ethanol gave the 3-cyano-2-hydroxythiophenes (**17**)[15] (Scheme 6).



16 17

$R^4 = C_6H_5$,	$R^5 = H$	66%
$R^4 = CH_3$,	$R^5 = H$	59%
$R^4 = CH_3$,	$R^5 = CO_2C_2H_5$	76%
$R^4 = CH_3$,	$R^5 = COCH_3$	55%

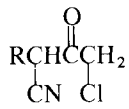
Scheme 6

2. Preparation of 3-Hydroxythiophenes through Ring-Closure Reactions

In this section on synthesis the compounds are called 3-hydroxythiophenes, regardless of their true tautomeric structure, although the most stable tautomeric forms are usually indicated in the formulas. Ring-closure reactions are in many cases the best routes for the preparation of mono- or disubstituted 3-hydroxythiophenes.

A. $C_4 + S$ Methods

This approach has been used for the preparation of some 2-amino-4-hydroxythiophenes (**19**) through the reaction of **18** with NaSH[16] (Scheme 7). Another example is the reaction of α,α'-dibromo-1,2-diketones (**20**) with sodium sulfide to give the 3,4-dihydroxythiophene (**21**)[17] (Scheme 8). A somewhat modified approach starts



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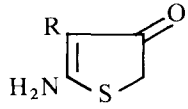

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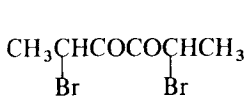
R = 1-H_3C–2-benzimidazolyl
R = 2-pyridyl

Scheme 7



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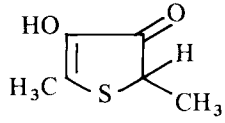


21

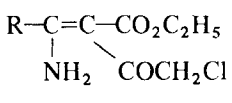
Scheme 8

from the ditosylate of 3-hexyne-2,5-diol, which was oxidized with potassium permanganate to hexane-3,4-dione-2,5-diol ditosylate, which upon reaction with sodium sulfide gave **21**.[18]

The classical Benary reaction,[19] which consists of the reaction of **22** with sodium hydrogen sulfide in ethanol, has been used repeatedly for the preparation of 5-substituted 3-hydroxy-4-thiophenecarboxylic acid derivatives **(23)**[20–24] (Scheme 9).

The reaction of tetraketones **(24)** with sulfur dichloride gave 2,5-diacyl-3,4-hydroxythiophenes **(25)**[25] (Scheme 10).

The reaction of the diacetylenic ketones **(26)** with thiourea gave by way of **27** the condensation product of 2-phenyl-4-hydroxythiophene with benzaldehyde **(28)**, which was also prepared from 2-phenyl-4-hydroxythiophene and benzaldehyde[26] (Scheme 11). Michael addition of ethyl acetoacetate to **28** led to thiophene **(29)**. In acidified methanol **28** gave most probably **30**, which might have been formed by reverse aldol condensation to give 2-phenyl-4-hydroxythiophene, which then condensed with **28** to give **30**.[26,27]



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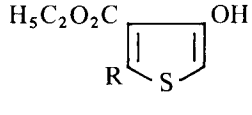
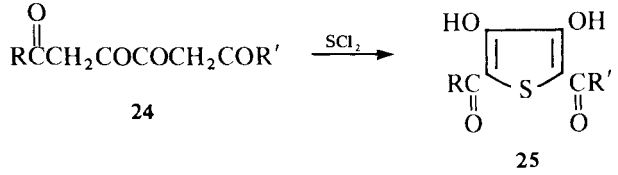


23

R = H, CH_3, C_6H_5

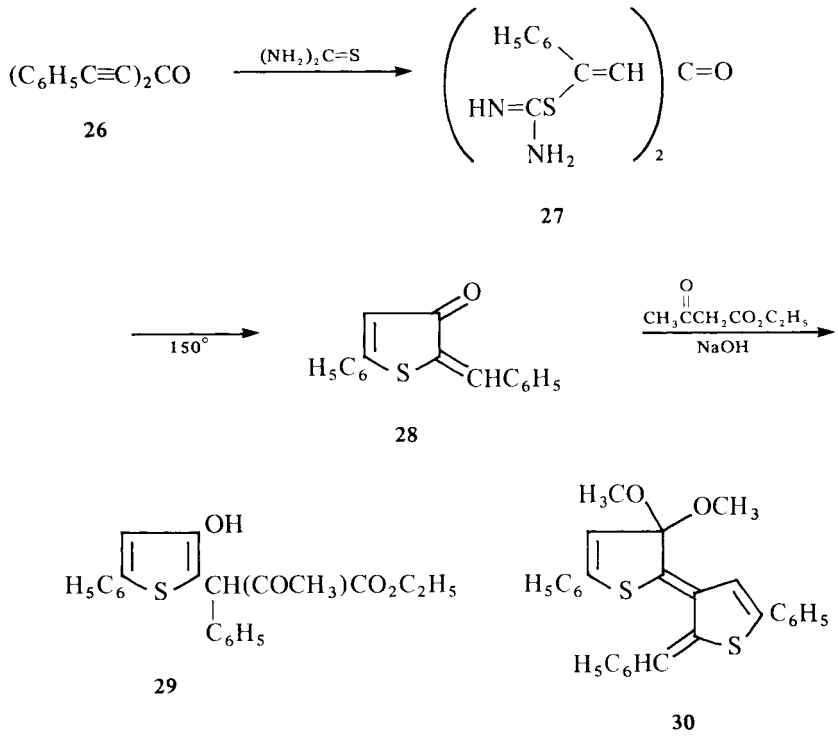
Scheme 9



24 25

$R = R' = C_6H_5CO$	33%
$R = COCH_3$, $R' = C_6H_5CO$	33%
$R = R' = COCH_3$	26%
$R = R' =$ isovaleryl	20%
$R = R' =$ pivaloyl	40%

Scheme 10

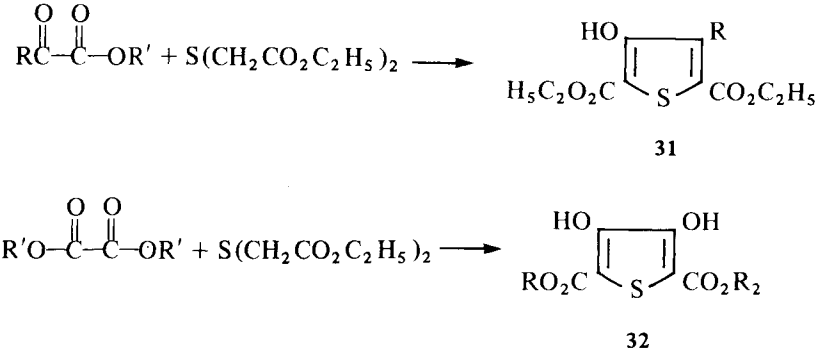


26 27 28 29 30

Scheme 11

B. C_2 + CSC Methods

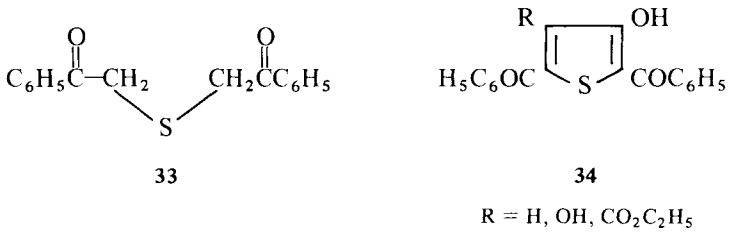
The Hinsberg reaction[28] has been extensively used for the preparation of 3-hydroxythiophenes (**31**), and especially 3,4-dihydroxythiophenes through the reaction of diethylthiodiacetate with α-keto esters[29] and diethyl oxalate[20,30–36],



Scheme 12

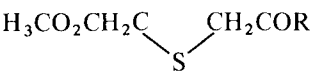
respectively (Scheme 12). It has been claimed that 3,4-dihydroxythiophene is obtained as yellow needles in 82% yield upon heating 3,4-dihydroxy-2,5-thiophenedicarboxylic acid at 120°C/3 mm Hg.[34] In these cases the mechanism is most probably a normal Dieckman reaction,[29,35] since 2,5-diesters are obtained. In the reaction with α-diketones, monoesters of the 2,5-thiophenedicarboxylic acids and a Stobbe-type mechanism are indicated (cf. Part 1, Chapter I, Section II.2).

The reaction of the diketo sulfide (**33**) with butyl glyoxylate, diethyl mesoxalate, and dibutyl oxalate gave **34** (R = H), **34** (R = OH), and **34** ($R = CO_2C_2H_5$) in 50%, 36%, and 25% yields[273] (Scheme 13).



Scheme 13

Mixed sulfides such as **35** have been reacted with glyoxylates, mesoxalates, and oxalates to give 3-hydroxythiophenes and 3,4-dihydroxythiophenes.[273–276] The reaction is regiospecific, and **35** ($R = C_6H_5$) gave only **36** (R = H) and **36** ($R = CH_3$) with butyl glyoxylate and ethyl pyruvate, respectively. Similarly, **35** ($R = CH_3$) gave only **37**. The reaction of **35** ($R = (H_3C)_3CH_2\overset{O}{\overset{\|}{C}}$) with diethyl oxalate gave **38**.[275] The complex sulfide **39** gave **40** with butyl glyoxalate[276] (Scheme 14). For additional details about the Hinsberg reaction, see Part 1, Chapter I, Section II.A and Table I-15 in that chapter, and the four dissertations from the University of Erlangen.



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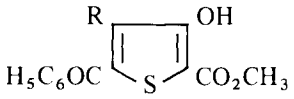
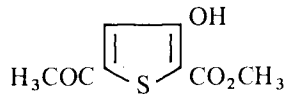


36

R = H, CH_3



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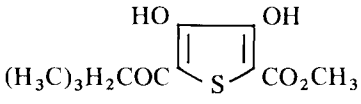

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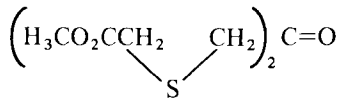

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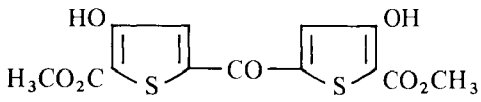


40

Scheme 14

C. $C_2S + C_2$ Methods

There are only a few examples of this approach to the synthesis of 3-hydroxythiophenes. Thus a Russian patent describes the preparation of 2-amino-4-hydroxythiophenes (**42**) through the reaction of an arylacetonitrile (**41**) with esters of thioglycolic acid in a refluxing organic solvent such as pyridine or *t*-butyl alcohol in the presence of an alkali metal alkoxide[37] (Scheme 15).

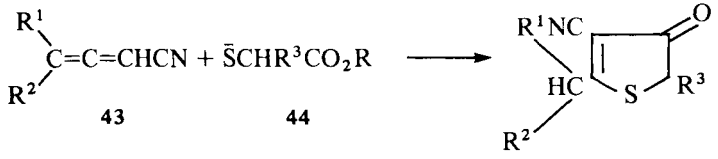
The reaction of 2,3-dienonitriles (**43**) with mercaptoacetates (**44**) gave 4-cyano-3-hydroxythiophenes in 65 to 90% yield[38] (Scheme 16).

41

42

Ar = C_6H_5, *p*-anisyl, 2-pyridyl, 2-quinolyl, 2-benzimidazolyl, and 1-methyl-2-benzimidazolyl

Scheme 15



43 44 45

$R^1 = R^2 = CH_3$,	$R^3 = H$	89%
$R^1 = CH_3$, $R^2 = C_2H_5$	$R^3 = H$	90%
$R^1 = R^2 = R^3 = CH_3$		65%
$R^1 = CH_3$, $R^2 = C_2H_5$,	$R^3 = CH_3$	75%
$R^1 = CH_3$, $R^2 = C_2H_5$,	$R^3 = CH_2CH_2CO_2C_2H_5$	75%

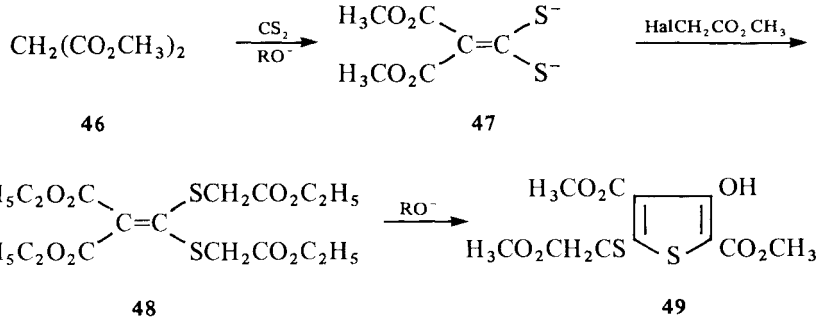
Scheme 16

D. $C_3S + C$ Methods

The Gompper reaction (see Part 1, Chapter I, Section II.4.A), which consists of the condensation of active methylene compounds with carbon disulfide, followed by alkylation of the intermediate enethiolates (**47**) with α-halogenacetic acid to **48** and ring closure, leads to 3-hydroxythiophenes (**49**) when malonate (**46**) is used as the active methylene compound[39,40] (Scheme 17).

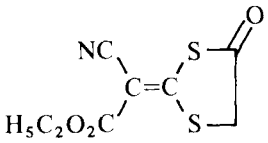
If cyanoacetate is used as active methylene compound, both 3-amino- and 3-hydroxythiophenes can be formed, as observed in the reaction of **50** with methyl iodide and sodium methoxide, which gave a mixture of **51** and **52**[41] (Scheme 18).

S-Alkylation of dimethyl monothione malonate (**53**) with α-haloesters or α-haloketones to give **54**, followed by base treatment, leads to 5-methoxy-3-hydroxythiophenes (**55**)[42] (Scheme 19). Treatment of **53** with morpholine gave the corresponding thioamide, which was alkylated with ethyl chloroacetate and then ring closed to **56**. Enethiols prepared from β-ketoesters (**57**) have been *S*-methylated to give **58**, which upon treatment with sodium ethoxide ring closed to the 3-hydroxy-2-cyanothiophenes (**59**). Alkylation of **57** with benzyl chloride followed



46 47 48 49

Scheme 17



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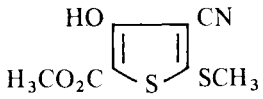

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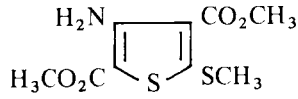

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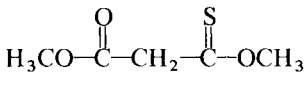
Scheme 18



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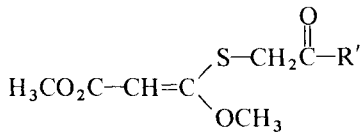

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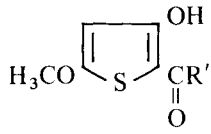
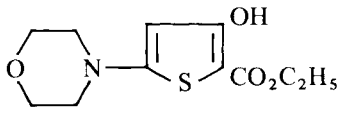


55

$R' = OCH_3, OC_2H_5, C_6H_5$



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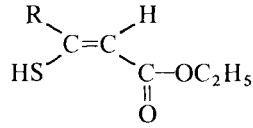

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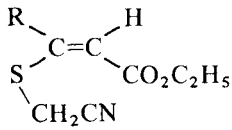

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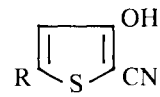


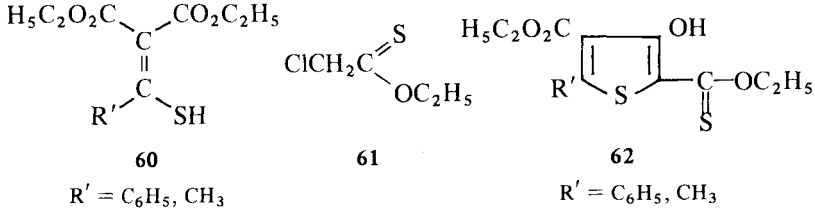
59

$R = CH_3$	78%
$R = CH(CH_3)_2$	57%
$R = C(CH_3)_3$	32%
$R = C_6H_5$	50%

Scheme 19

by treatment with potassium *t*-butoxide, or alternatively with ethyl 2-bromophenylacetate and treatment with aqueous sodium hydroxide, gave 2-phenyl-5-methyl-3-hydroxythiophene.[43]

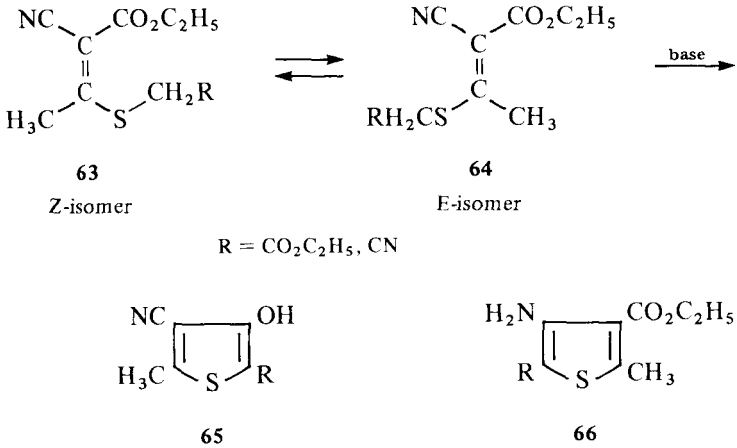
The condensation of malonic acid derivatives with esters of thione or dithio acids in the presence of potassium alkoxides gave **60**, which upon reaction with **61** gave the 3-hydroxy-2-thiophene ester **62**[44] (Scheme 20).



60 $R' = C_6H_5, CH_3$ **61** **62** $R' = C_6H_5, CH_3$

Scheme 20

Condensation of ethyl cyanoacetate with ethyl dithioacetate or thione acetate, followed by alkylation with ethyl α-haloacetate or α-haloacetonitrile, gives **63**, which is in equilibrium with **64**. Upon treatment with base **65** and **66** were formed. The proportions of **65** and **66** depended both on the nature of the substituent R and on the base and were independent of the proportions of **63** and **64** in equilibrium. Thus for $R = CO_2C_2H_5$ the E to Z ratio, **64** to **63**, was 8:92, and cyclization with sodium hydride in benzene gave 80% of **65** and 13% of **66**. On the other hand, triethylamine in benzene gave 32% of **65** and 35% of **66**. 2,3,4,6,7,8-Hexahydropyrrole[1,2-a]pyrimidine(HHP) in benzene, which is a system not prone to cause rearrangement, also gives 82% of **65** derived from the predominant Z-isomer and 10% of **66**. When R = CN, only the Z-isomer **63** can be observed with NMR. In spite of this, 95% of **66** (R = CN) is obtained on treatment with triethylamine, and 3% of **65** (R = CN). Thus the nondetectable E-isomer (**64**) ring-closes much faster than the Z-isomer, and isomerization of **63** to **64** must be very fast. When HPP in



63 Z-isomer **64** E-isomer

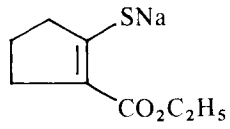
$R = CO_2C_2H_5, CN$

65 **66**

Scheme 21

benzene was used, 33% of **65** and 36% of **66** was obtained. The hydroxythiophenes were easily separated from the aminothiophenes by extraction of the benzene phase with water followed by acidification[45] (Scheme 21).

The $C_3S + C$ modification of the Fiesselmann reaction is a useful method for the preparation of 3-hydroxy-2-carbonyl-substituted thiophenes. Thus the sodium salt of thiocyclopentanonecarboxylic acid (**67**) prepared from the β-ketoester, hydrogen chloride, and hydrogen sulfide were reacted with various α-halocarbonyl derivatives to yield sulfides (**68**), which, in most cases without isolation, ring closed to the hydroxythiophene (**69**) on treatment with alkoxides.[275] It was shown that the product from the reaction with ethyl chloroacetate has the structure **69** ($R = OC_2H_5$) and not **70**, as previously claimed[222] (Scheme 22). In the same way,



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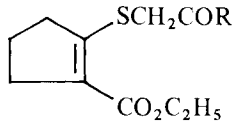

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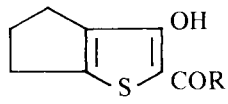
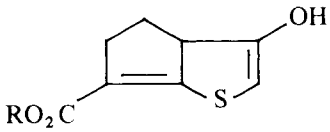


69

$R = OC_2H_5, C_6H_5, CH_3$



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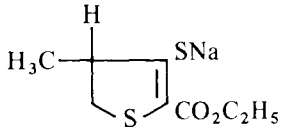

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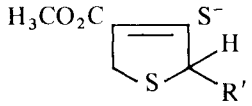
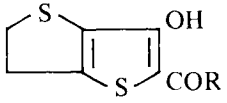


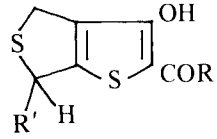
72

$R' = CH_3, C_6H_5$



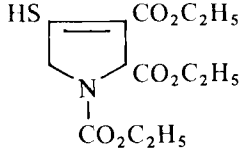
73

$R = OC_2H_5, CH_3, C_6H_5$



74

$R = OCH_3, C_6H_5, CH_3$
$R' = CH_3, C_6H_5$



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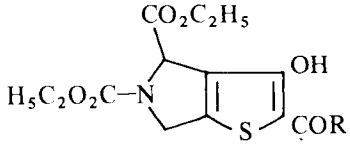


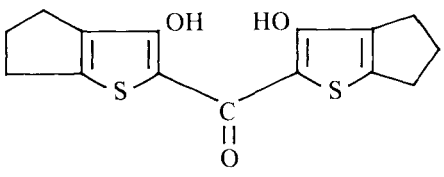
76

$R = OC_2H_5, CH_3, C_6H_5$

Scheme 22

71 and **72** were alkylated with α-halocarbonyl compounds and the intermediate sulfides ring closed to **73**[275] and **74**.[278]

The analogous reaction of **75** gave **76**.[279] Thiolates such as **67**, **71**, and **72** were also reacted with α,α-dichloroacetone and upon treatment with ethoxide gave **77**,[275] **78**, and **79**[278] (Scheme 23). For more details see Part 1, Chapter I, Section 4.C and Table I-26 of that chapter.



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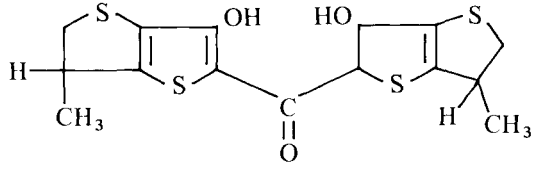

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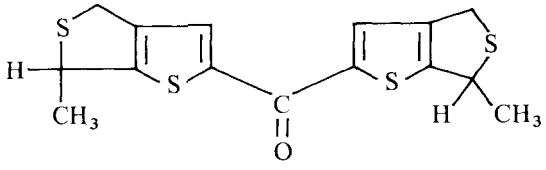

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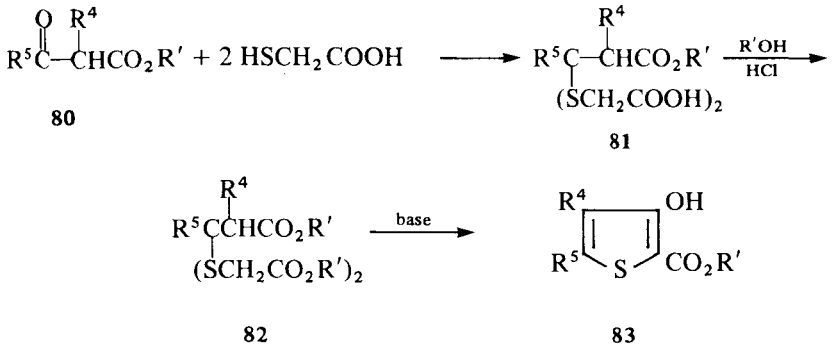
Scheme 23

E. C_3 + *CS Methods*

The most important method for the preparation of 3-hydroxy-2-carbonyl-substituted thiophene derivatives is due to Fiesselmann, and consists of the reaction of β-keto-esters **80** with 2 eq. of anhydrous or 80% thioglycolic acid in the presence of hydrogen chloride, which quantitatively gives the thioacetals (**81**), which are esterified in high yield to **82**. On treatment of **82** with alcoholic potassium hydroxide or alcoholate, 5-, as well as 4,5-substituted 3-hydroxy-2-thiophenecarboxylates are obtained[46–51] (Scheme 24).

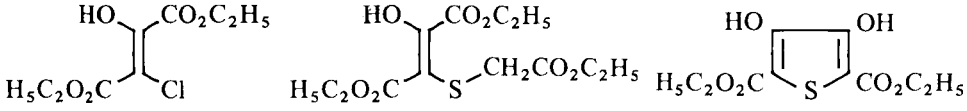
Many β-ketoesters functionalized in the 3-(α)-position with an acetoxy[150] alkylthio, arylthio, or phenacetylamino group[253] can be transformed to thioacetals by the foregoing methodology, and with alkoxides ring closed to 3,4-dihydroxy-2-thiophenecarboxylates, 4-alkylthio- and 4-arylthio-3-hydroxy-2-thiophene-carboxylates, and 4-amino-3-hydroxy-2-thiophenecarboxylates. An alternative to the Hinsberg synthesis of diethyl 3,4-dihydroxy-2,5-thiophenedicarboxylate is the reaction of diethyl chlorooxaloacetate (**84**) with ethyl thioglycolate in pyridine to give **85**, which on treatment with sodium ethoxide in ethanol gave **86** in 33% yield[274] (Scheme 25). For more details, see Part 1, Chapter I, Section 5.A.c, and especially Table I-29 in that chapter. Much of this work has only been published in dissertations at the University of Erlangen.

In another version of the Fiesselmann synthesis, esters of α,β-dihalocarboxylic



80 81 82 83

Scheme 24

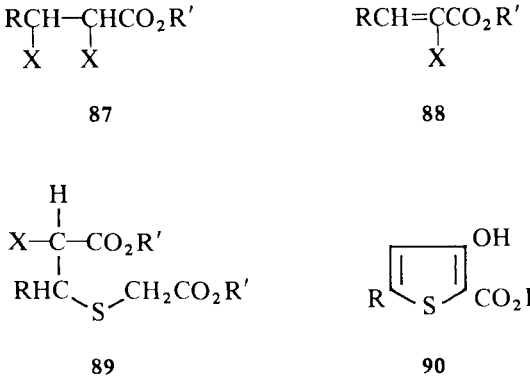


84 85 86

Scheme 25

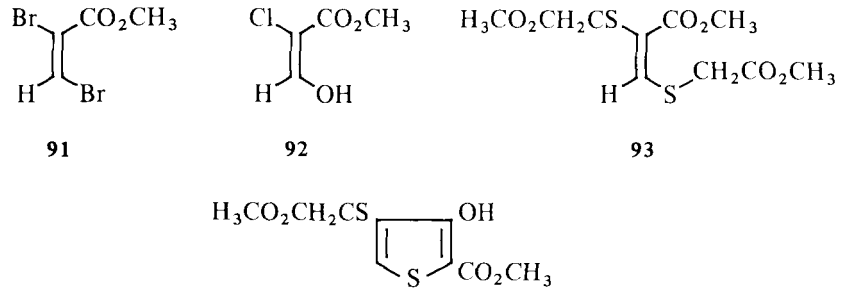
acids (**87**) or α-halo-α,β-unsaturated acids (**88**) are used instead of β-ketoesters in the reaction with thioglycolates in the presence of 2*N* methanolic potassium hydroxide to give **90** (Scheme 26). The reaction of **87** proceeds by way of **88** and **89**, and under different conditions both **88** and **89** could be isolated and separately ring closed with the same high yield to **90**.[52–54,250,277]

Both **91** and **92** react with methyl thioglycolate to give **93**, which ring closes to **94** even upon shaking with dilute sodium hydroxide solution[274] (Scheme 27). For



87 88 89 90

Scheme 26



91 **92** **93**

94

Scheme 27

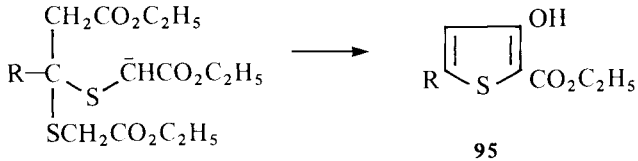
more details see Part 1, Chapter I, Section 5.A.d and Tables I-30 and I-31 of that Chapter.

In the first version of the Fiesselmann reaction, esters of acetylenic carboxylic acids were used, and from dimethyl acetylene dicarboxylate and thioglycolate with a suspension of sodium methoxide in benzene or with alcoholic potassium hydroxide, dimethyl 3-hydroxy-2,5-thiophenedicarboxylate was obtained in high yield.[55–60] However, it was also originally claimed that esters of phenylpropiolic acid and alkylpropiolic acid reacted similarly to give 3-hydroxy-2-thiophenecarboxylates.[20,57,58,61] Recent results indicate, however, that the reaction of esters of arylpropiolic acid leads to mixtures of 5-aryl-3-hydroxy-2-thiophenecarboxylates (**95**) and 5-aryl-3-hydroxy-4-thiophenecarboxylates (**96**) in which the latter often predominate. Compounds (**95**) are thus formed by Dieckman condensation of the carbanion (**97**), while (**96**) is formed either from the carbanion (**98**) or the vinyl carbanion (**99**)[50,51,62] (Scheme 28). The amounts of **95** and **96** can be influenced by reaction conditions.[63] For more details see Part 1, Chapter I, Section 5.B and Table I-28 of that chapter.

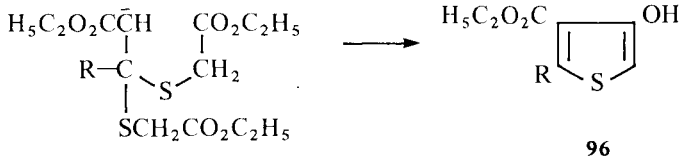
Hydroxythiophenes have also been obtained in other modifications of the Fiesselmann reaction. In the reaction of **100** with thioglycolates, both the 3-hydroxythiophene (**101**) and the 3-aminothiophene (**102**) are formed in approximately equal amounts.[159] When R^5 was isopropyl, **102a** was obtained as a by-product, in addition to **101**. When $R^5 = C_6H_5$, dealkylation of **100**, along with the formation of **101**, was observed (Scheme 29).

Another example of when the Fiesselmann reaction leads to mixtures of different thiophene derivatives is the reaction of the ethoxymethylene derivative of methyl acetoacetate, which on reaction with thioglycolate gives two isomeric thioesters, **103** and **104**, and ring closure leads to a mixture of **105** and **106**[146] (Scheme 30).

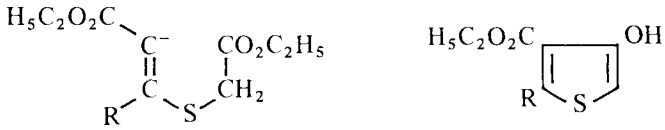
Similarly, the ethoxymethylene derivative of ethyl benzoyl acetate (**107**) gave about equal amounts of (**108**) and (**109**) after reaction with alkyl thioglycolates and treatment with sodium methylate in ether (Scheme 31). On treatment with 2*N* methanolic potassium hydroxide, only aldol condensation to **109** occurred.[283]



97 95

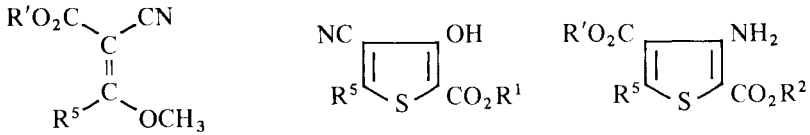


98 96



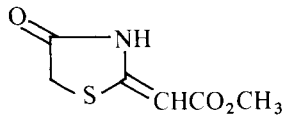
99 96

Scheme 28



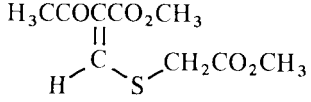
100 101 102

$R^5 = CH_3, C_2H_5, CH(CH_3)_2, C_6H_5$



102a

Scheme 29



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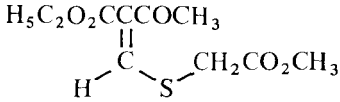

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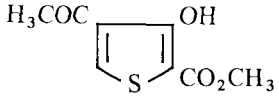

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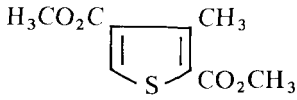
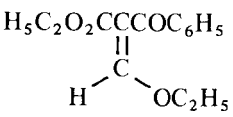


106

Scheme 30



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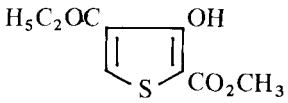

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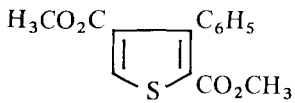


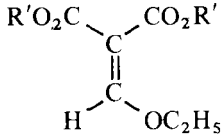
109

Scheme 31

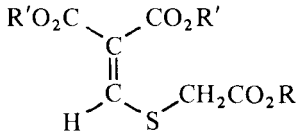
In the reaction of the ethoxy methylene derivative of malonates (**110**), of course only the esters of 3-hydroxy-2,4-thiophenedicarboxylic acids (**112**) were obtained by way of the unsaturated sulfide **111**[64] (Scheme 32).

The difficulty in predicting the type of ring closure that will occur is amply illustrated by the fact that, whereas **113** ($R = C_6H_5$) upon reaction with thioglycolate and ring closure only gives Dieckmann cyclization yielding **114** in 71% yield, **113** ($R = CH_3$) only gives aldol condensation, and **115** is obtained in 70% yield[70] (Scheme 33).

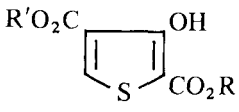
3-Acetoxy-substituted acetylacetone (**116**) has been transformed to **117** by



110

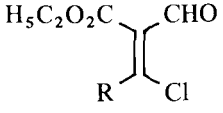


111

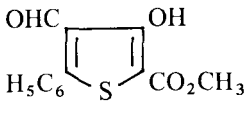


112

Scheme 32



113



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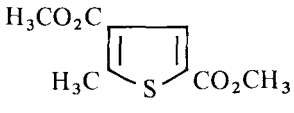


115

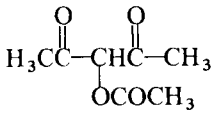
Scheme 33

hydrogen chloride-catalyzed reaction with thioglycolic acid followed by esterification, which on treatment with base gave **118**[253] (Scheme 34).

The reaction of **119** with methyl thioglycolate followed by ring closure gave **120** in only 5% yield[253] (Scheme 35).

α-Mercaptocarbonyl derivatives other than thioglycolates can also be used in the Fiesselmann reaction, and especially α-mercapto aldehydes and α-mercapto ketones, which exist in equilibrium with their stable 2,5-dihydroxy-1,4-dithiane forms, have been shown to be useful. Thus α-mercaptoacetone, α-mercapto acetaldehyde, and phenacyl mercaptan have been reacted with dimethyl acetylene dicarboxylate, methyl propiolate, and methyl phenylpropiolate,[273] or with α,β-dihalo esters and α-halo-α,β-unsaturated esters,[53] or with β-halo-α,β-unsaturated esters,[275] to give 2-acyl-3-hydroxythiophenes (cf. Part 1, Chapter I). The reaction between α,α′-dimercapto acetone (**121**) and propiolic acid derivatives (**122**) gave **123** on cyclization with sodium methoxide[273] (Scheme 35).

The naturally occurring thiophene (**125**) was prepared from **124** and mercapto acetone[66] (Scheme 36). For more details, see Part 1, Chapter I, Section 5.I and Table I-39 in that chapter.



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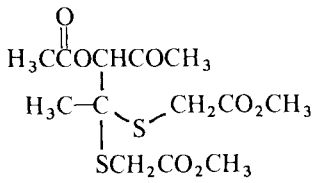

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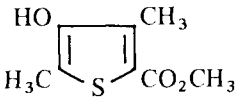
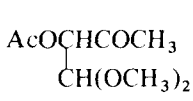


118

Scheme 34



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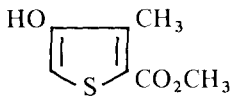

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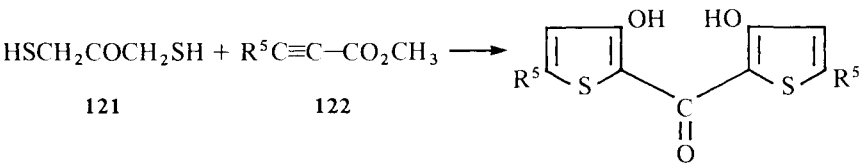
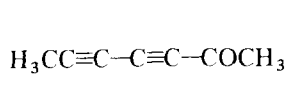
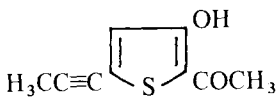


121 **122** **123**

Scheme 35



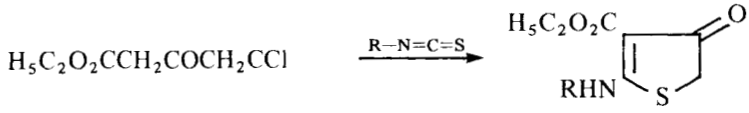
124



125

Scheme 36

Another C_3 + CS approach to 3-hydroxythiophenes is the reaction of phenylisothiocyanate or 2-isothiocyanovinyl acetate with γ-chloroaceto acetate (**126**) in the presence of sodium hydride, giving 2-amino-4-hydroxythiophenes, which exist in the tautomeric keto form **127**.[67,68] In a recent modification, amides of γ-bromoacetoacetic acids were used instead of (**126**)[287] (Scheme 37).



126

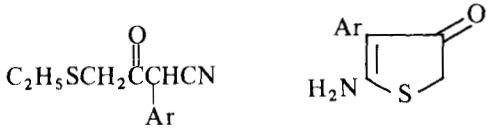
R = C_6H_5, $CH_3CO_2CH{=}CH$

127

Scheme 37

F. 3-Hydroxythiophenes through Ring Closure of C_4S Compounds

Treatment of **128** with 90% sulfuric acid for a few minutes leads to 2-amino-4-hydroxythiophenes (**129**)[69] (Scheme 38).



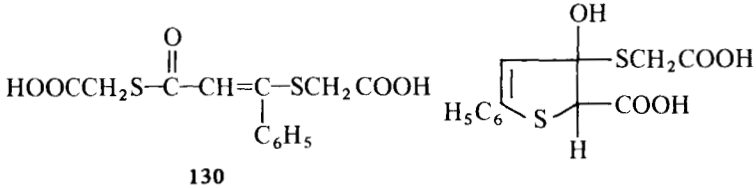
128 **129**

Ar = C_6H_5, p-ClC_6H_4

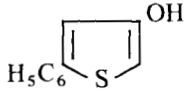
Scheme 38

G. 3-Hydroxythiophenes through Ring Closure of C_3SC Compounds

Some reactions of this type have already been treated in Section II.2.D. Treatment of **130** with acetic anhydride and sodium acetate gave the acetate of **132**, probably by way of **131**[7] (Scheme 39).



130 **131**



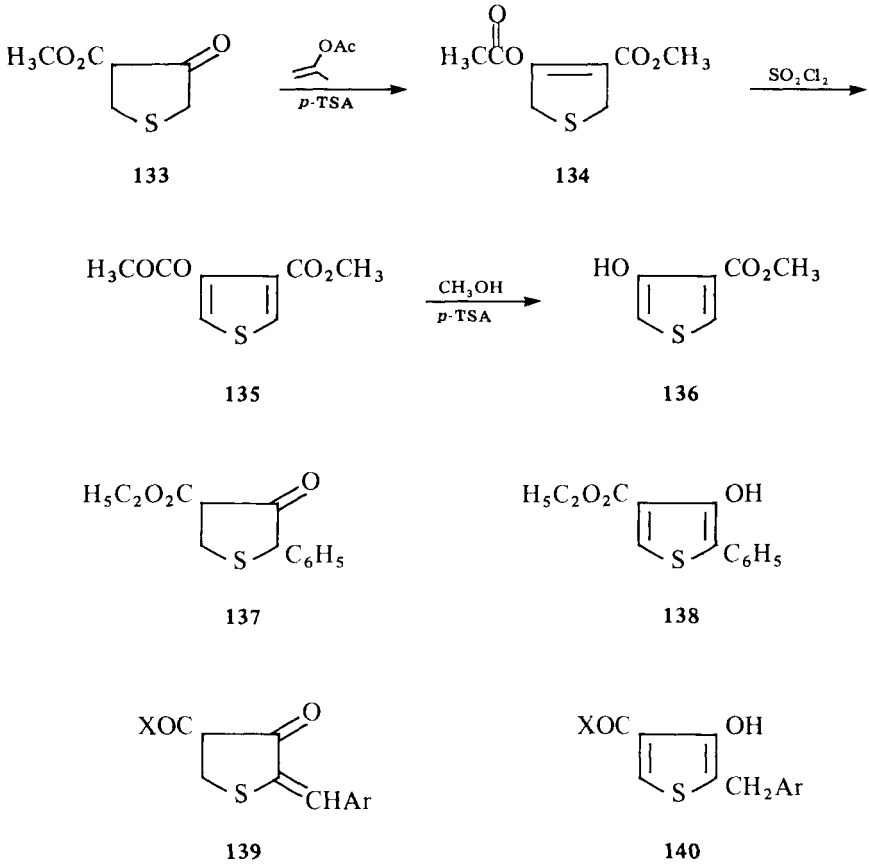
132

Scheme 39

H. 3-Hydroxythiophenes from 3-Oxotetrahydrothiophenes

Direct aromatization of 3-oxotetrahydrothiophenes to 3-hydroxythiophenes has been achieved by careful reaction with bromine,[250,276,279] or more conveniently with sulfuryl chloride.[71] In some cases the 3-oxotetrahydroxythiophene (**133**) was first converted to the enol acetate (**134**), before aromatization with sulfuryl chloride to give **135**, which was hydrolyzed to **136**.[72] Instead of enol acetates, enol methyl ethers and enol methyl sulfonates can also be used.[71,72] Treatment of 2- or 4-acyl-3-oxotetrahydrothiophenes with sulfur in DMF gave 2-acyl- or 4-acyl-3-hydroxythiophenes.[65] Hydrogen peroxide (40%) has also been used for the aromatization of **137** to **138** in 90% yield.[73]

Condensation of 4-carbomethoxy-3-oxotetrahydrothiophenes with aromatic aldehydes gave **139** (X = OCH_3). On treatment with an arylamine in boiling xylene, these compounds gave the corresponding anilides **139** (X = NHAr), which upon base- or acid-catalyzed isomerization gave **140** (X = NHAr). Treatment of **139** (X = OCH_3) with strong acid gave **140** (X = OCH_3)[74] (Scheme 40). Treatment of



133 **134** **135** **136** **137** **138** **139** **140**

Scheme 40

141 with mercuric chloride and piperidine in DMF gave a 46% yield of **142**, which was hydrolyzed to an unstable 3-hydroxythiophene.[75]

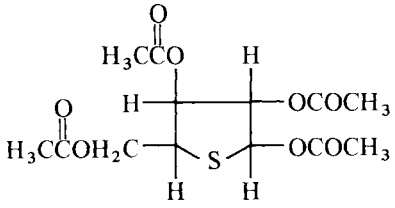
Pyrolysis of the Mannich bases **143** and **144** gives directly **145** in very low yield[76] (Scheme 41). It was used as evidence that 3-oxotetrahydrothiophene is aminomethylated in the 4-position.[76]

I. 3-Hydroxythiophenes from Other Heterocyclic Compounds

The classical method of Friedländer and Kielbasinski[77] has been used to prepare some 3-hydroxythiophenes (**147**) from the corresponding 1,2-dithiol-3-ones (**146**) and ethyl chloroacetate in low yields[78,79] (Scheme 42). (See also Ref. 70).

The reaction of **148** with active methylene compounds of type **149** gave **150**.[80–83] For more details see Part 1, Chapter I, Section VI.B.

Cycloaddition between phenyl azide and **151** gives after isomerization **152**, which on heating yields the 3-hydroxy-4-anilinomethylthiophene system **153**[84] (Scheme 43).



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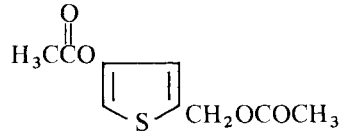

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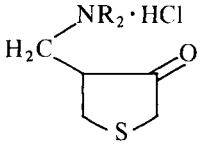

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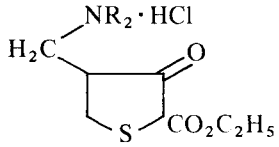

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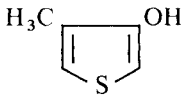
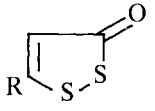


145

Scheme 41



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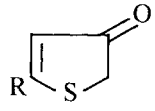
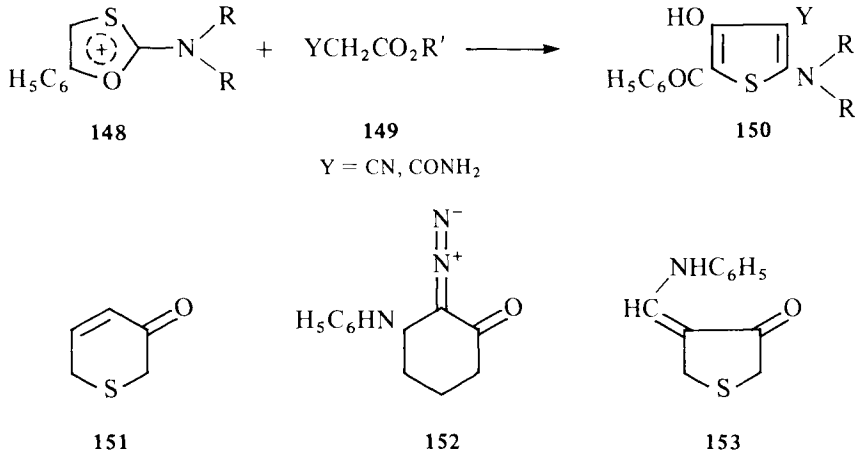


147

R = $(CH_3)_3C$, C_6H_5, *p*-$CH_3OC_6H_4$

Scheme 42



Scheme 43

3. Hydroxythiophenes by Way of Thiophene Metal Derivatives

The two most important preparation methods, in particular for monosubstituted hydroxythiophenes, are the reaction of thienyllithium derivatives with alkyl borate followed by oxidation of the thiopheneboronic acids by hydrogen peroxide, and the reaction of thiophenemagnesium derivatives with *t*-butylperbenzoate followed by dealkylation of the *t*-butyl ethers with acid. The dealkylation of alkoxythiophenes prepared by other means has also been used for the syntheses of hydroxythiophenes. However, direct oxidation of thiophene metal derivatives has been used in some cases.

A. Hydroxythiophenes from Grignard and Thienyllithium Reagents

2-Hydroxythiophene was first prepared in 25% yield through the reaction of 2-bromothiophene and isopropyl bromide with magnesium followed by oxygen. 2,2′-Bithienyl (29%) was also obtained. When the oxidation was carried out in the absence of isopropylmagnesium bromide only 2,2′-bithienyl was isolated.[85,86] This method was also used for the preparation of 5-phenyl-2-hydroxythiophene.[7] Oxidation of 2-thienyllithium or 2-thiophenemagnesium bromide with 1,2,3,4-tetrahydro-1-naphthyl hydrogen peroxide gave even lower yields of 2-hydroxythiophenes.[87]

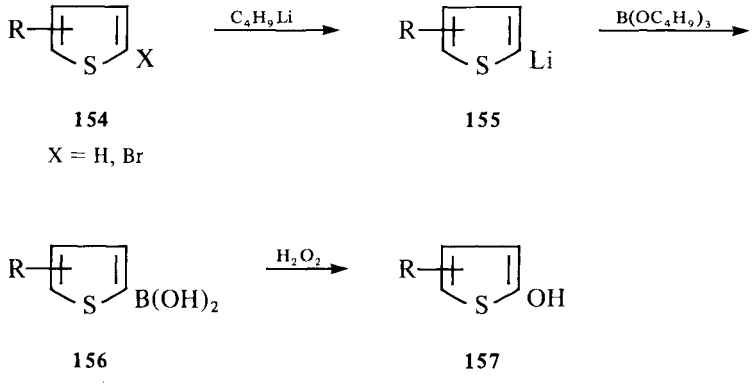
Formation of 3-thiophenemagnesium bromide according to the entrainment method and oxidation of its mixture with isopropylmagnesium bromide with oxygen gave the highly unstable 3-hydroxythiophene in 5% yield.[88] These methods for the preparation of hydroxythiophenes are only of historical interest.

B. Hydroxythiophenes from Thiopheneboronic Acids

The reaction of 3-methyl-2-thiophenemagnesium bromide and 4-methyl-2-thiophenemagnesium bromide with butyl borate gave the corresponding boronic acid, which without purification was oxidized with 10% hydrogen peroxide to 3- and 4-methyl-2-hydroxythiophene.[89] However, in most cases it is more convenient to use the corresponding 2-thienyllithium derivatives (**155**), which are easily available by metalation of thiophenes or halogen-metal exchange of halothiophenes (**154**). Reaction with butyl borate followed by hydrolysis gives the thiopheneboronic acids (**156**), which usually without purification are oxidized to the 2-hydroxythiophene system (**157**) with 10% hydrogen peroxide solution (Scheme 44). If deboronation upon hydrolysis is fast, the ester can be oxidized directly,[90] and also when the boronic ester is difficult to hydrolyze.[91] In this way 2-hydroxythiophene,[92] 5-alkyl-2-hydroxythiophenes,[92-94] 4-alkyl-2-hydroxythiophenes,[92,95] 5-halo-2-hydroxythiophenes,[92,96] as well as 3-bromo- and 3-methoxy-2-hydroxythiophene,[92] have been prepared. Attempts to prepare the 5-methoxy-2-hydroxythiophene system by oxidation of 5-methoxy-2-thiopheneboronic acid failed, and a low yield of methyl hydrogen succinate was isolated.[92]

4-Methyl-2-hydroxythiophene was prepared in a one-pot procedure from 2,4-dibromothiophene by reaction with ethyllithium, butyl borate, ethyllithium, and dimethyl sulfate in sequence, followed by hydrogen peroxide oxidation of the boronic acid.[97] In a later modification of this procedure 5-alkyl-2-thienyllithium derivatives were reacted with methyl borate to favor formation of trisubstituted boron, or at least disubstituted rather than monosubstituted boron, as in the preparation of boronic acid. After hydrolysis the two-phase systems were oxidized with H_2O_2 without isolation of any thienylboron compounds.[98] The tautomeric structures of the 2-hydroxythiophene systems mentioned are discussed in Section III.

3-Hydroxythiophene systems were prepared in an analogous way. However,



154

X = H, Br

155

156

157

Scheme 44

owing to the tendency of 3-thienyllithium derivatives to rearrange to more stable 2-thienyllithium derivatives or to undergo ring-opening reactions, halogen–metal exchange and reaction with the borates must be carried out at $-70°C$. In this way 2-alkyl-3-hydroxythiophenes,[99] various 2,5-dialkyl-3-hydroxythiophenes,[78,91,99] and 2-methyl-5-phenyl-3-hydroxythiophene[100] were prepared.

2-Formyl-3-thiopheneboronic acid, easily prepared from 2,3-dibromothiophene, could be oxidized with 10% hydrogen peroxide to 3-hydroxy-2-thiophene aldehyde, and from 2-carboxy-3-thiophenecarboxylic acid, 3-hydroxy-2-thiophenecarboxylic acid was obtained in 62% yield.[101]

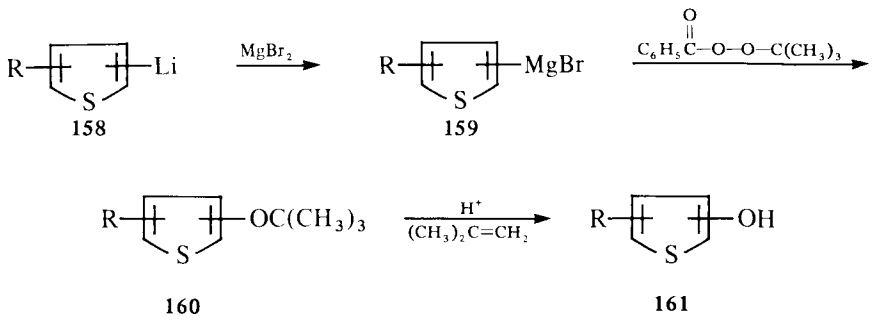
From 4-formyl-3-thiopheneboronic acid, the highly unstable 4-hydroxy-3-thiophene aldehyde, only characterized by its NMR spectrum, was obtained. Upon attempted oxidation of 3-formyl-2-thiopheneboronic acid, Baeyer-Villiger oxidation apparently also occurred, as 2,3-dihydroxythiophene (in the tautomeric form 3-hydroxy-3-thiolen-2-one) was obtained in low yield.[101]

The oxidation of thiopheneboronic acids is a generally useful method for the preparation of hydroxythiophenes. Its limitations are, of course, that functional groups that react rapidly with alkyllithium derivatives cannot be present. Furthermore, in a few cases with strongly electron-donating groups present, hydrolytic cleavage of the thiophene–boron bond can compete with the oxidation, thus diminishing the yield of the hydroxythiophenes.

C. Hydroxythiophenes from t-Butoxythiophenes

Another approach introduced by Lawesson, using thiophene, magnesium **(159)**, and lithium derivatives **(158)**, is their reaction with *t*-butylperbenzoate to give *t*-butoxythiophenes **(160)**, which on treatment with catalytic amounts of a strong acid, such as *p*-toluenesulfonic acid, are dealkylated to hydroxythiophenes **(161)** (Scheme 45).

Grignard reagents give much better yields of *t*-butoxythiophenes than thienyllithium derivatives. Thus when Grignard reagents cannot be obtained from a halothiophene and magnesium, the corresponding lithium compounds are transformed to the magnesium derivatives through reaction with anhydrous magnesium bromide.



Scheme 45

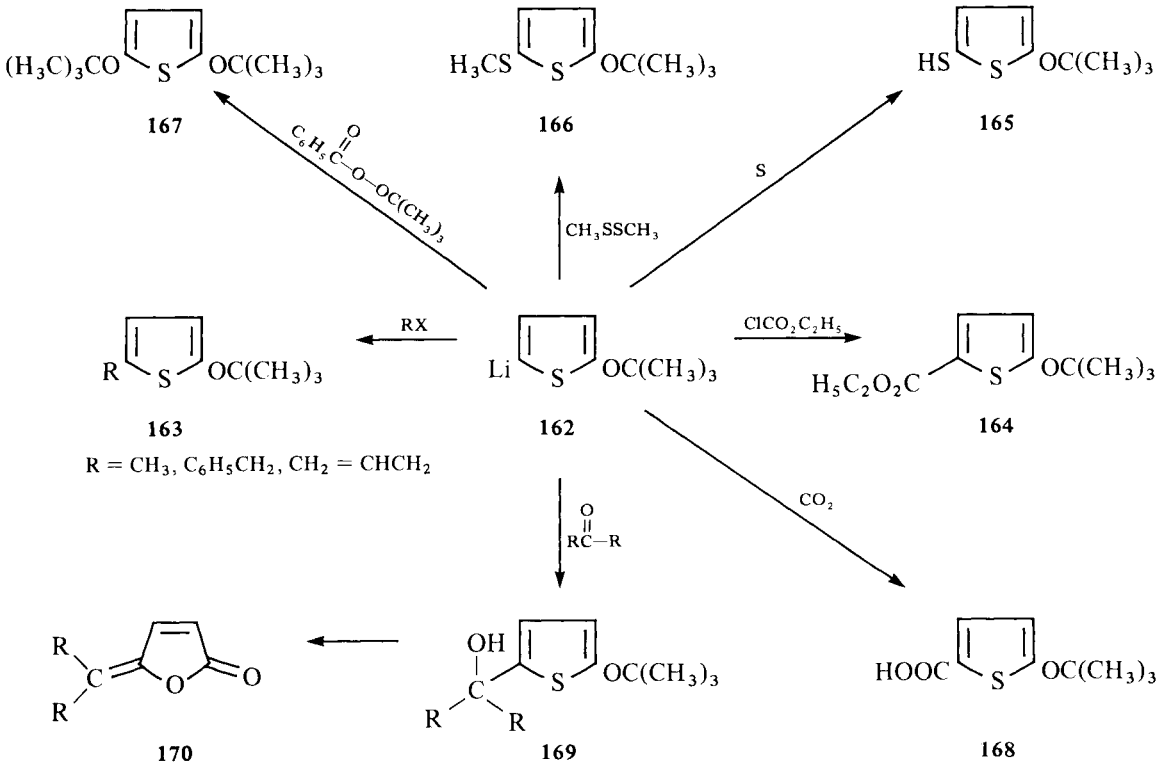
2-*t*-Butoxythiophene was prepared from the Grignard reagent derived from 2-bromothiophene in 70 to 76% yield on reaction with *t*-butylperbenzoate, and on dialkylation 2-hydroxythiophene was obtained in 89 to 94% yield.[102,103] 2-*t*-Butoxythiophene can be metalated with butyllithium to the 5-lithium derivative (**162**), which was transformed to various 5-substituted 2-*t*-butoxythiophenes such as 5-alkyl- (**163**), 5-carboethoxy- (**164**), 5-mercapto- (**165**), 5-methylthio- (**166**), 5-*t*-butoxy- (**167**), and 5-carboxy-2-*t*-butoxythiophene (**168**)[104] (Scheme 46). Upon dealkylation the corresponding hydroxythiophenes were obtained. Reaction of **162** with ketones gave the carbinols (**169**), which however could not be obtained in a pure state, and upon dealkylation gave **170**.[104,105]

The highly unstable 5-bromo-2-hydroxythiophene[106] was prepared from 5-bromo-2-*t*-butoxythiophene,[104] obtained by way of 5-bromo-2-thienyllithium. On storage of 5-bromo-2-hydroxythiophene in the liquid state at $-20°C$, it underwent allylic rearrangement to the 3-bromo-2-hydroxythiophene system.[106] 5-Chloro-2-hydroxythiophene has been prepared by metalation of 2-chlorothiophene with butyllithium, followed by magnesium bromide and *t*-butylperbenzoate and dealkylation.[106] Treatment of 3-bromo-2-*t*-butoxythiophene with boron trifluoride etherate at 0°C gave 3-bromo-3-thiolen-2-one in 80% yield.[119] Dealkylation of 3-*t*-butoxythiophene[107] only led to tar formation.[108] However, the selective metalation of 3-*t*-butoxythiophene in the 2-position made **171** an excellent starting material for the preparation of many 3-hydroxythiophenes, as indicated in Scheme 47. Its reaction with ethyl chloroformate and with magnesium bromide, followed by acetic anhydride, gave **172** and **173**, respectively. On dealkylation, **174** and **175** were obtained in high yield. Reaction of **171** with dimethyl sulfate gave **176**, which was metalated in the free α-position to give **177**. On reaction with ethyl chloroformate and dealkylation **179** was obtained by way of **178**. Reaction of **171** with *t*-butylperbenzoate gave 2,3-di-*t*-butoxythiophene (**180**), which was metalated to **181** and carbethoxylated to **182**. Compound **182** was then dealkylated to the rather unstable 2-hydroxy derivative **183**.[108]

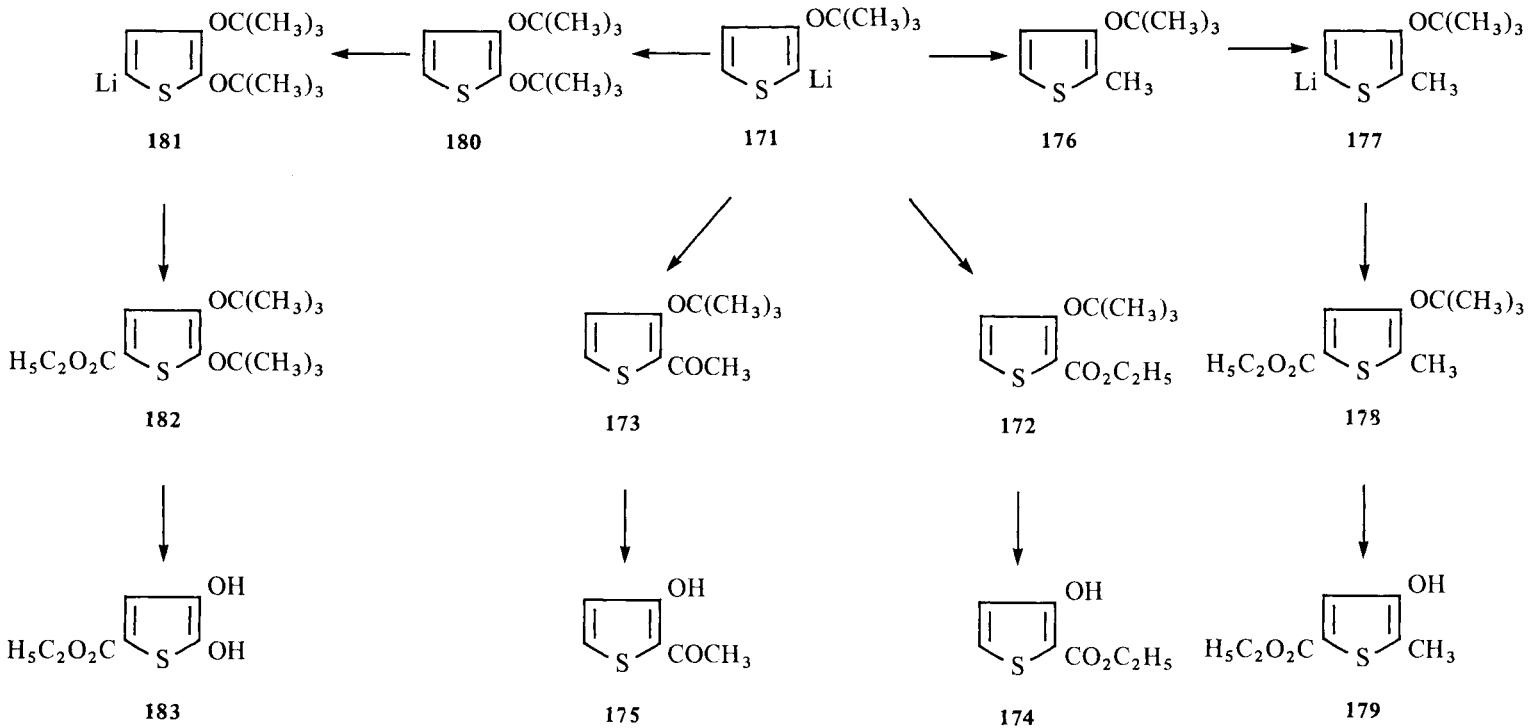
4-Substituted 3-hydroxythiophenes were prepared from 3,4-dibromothiophene by halogen–metal exchange at $-70°C$, followed by reaction with magnesium bromide and *t*-butylperbenzoate to give **184**. Upon renewed halogen–metal exchange and reaction with magnesium bromide and acetic anhydride **184** gave **185**, which in the usual way with catalytic amounts of *p*-toluenesulfonic acid was dealkylated to **186**[108] (Scheme 48).

Another example of this approach to the synthesis of orthocarbonyl-substituted hydroxythiophenes is shown in Scheme 48. By means of halogen–metal exchange with butyllithium followed by reaction with magnesium bromide and *t*-butylperbenzoate, 2,3-dibromothiophene is transformed to **187**, which upon halogen–metal exchange at $-70°C$ followed by reaction with $MgBr_2$ and acetic anhydride yields **188a**. Reaction of the lithium intermediate with ethyl chloroformate gives **189a**. Dealkylation of **188a** and **189a** gives **188b** and **189b** in very good yields.[109]

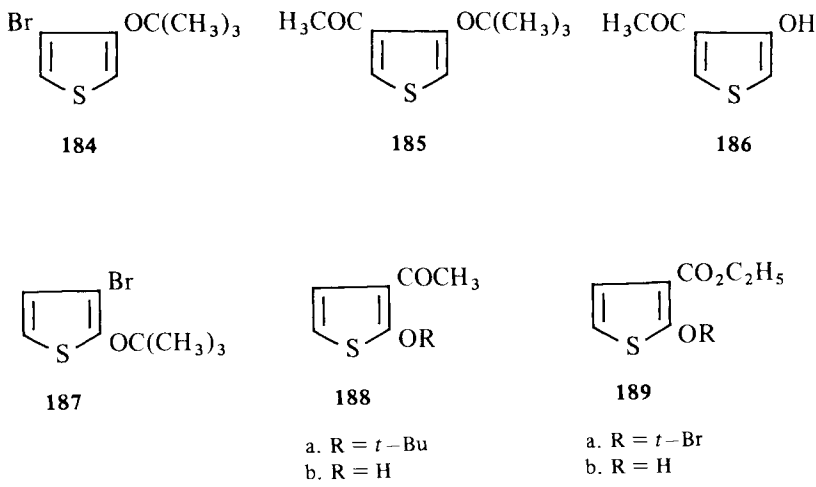
The approach by way of *t*-butoxythiophenes is also useful for the preparation of dihydroxythiophene systems. Thus **180** has been dealkylated to 2,3-dihydroxythiophene, which exists as **190**. From **182**, on dealkylation, **191** was prepared.


(H3C)3CO
S
OC(CH3)3
167
H3CS
166
HS
165
C6H5C(=O)–O–OC(CH3)3
CH3SSCH3
S
RX
ClCO2C2H5
R
163
Li
162
H5C2O2C
164
R = CH3, C6H5CH2, CH2 = CHCH2
RC(=O)–R
CO2
OH
HOOC
R
O
170
169
168

Scheme 46


OC(CH3)3
Li
S
OC(CH3)3
181
180
171
176
177
H5C2O2C
182
COCH3
173
CO2C2H5
172
CH3
178
OH
183
175
174
179

Scheme 47

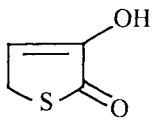


Scheme 48

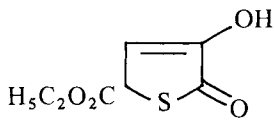
Reaction of **181** with dimethyl sulfate followed by dealkylation gave **192.**[110] Other substituted 2,3-dihydroxythiophenes were prepared from **184**, which by halogen–metal exchange and reaction with dimethyl sulfate was transformed to **193**. Metalation of **193** with butyllithium occurs in the 2-position, and reaction with magnesium bromide and *t*-butylperbenzoate gives **194**, which on dealkylation gives **195** in 32% yield.[110] An alternative route to **194** appears to be the reaction of 2,3,4-tribromothiophene, which under different conditions yields **196** and **197** as unstable noncharacterized products. Halogen–metal exchange of **197** followed by reaction with dimethyl sulfate is claimed to give **194**, identical with that described previously. Dealkylation of **197** is claimed to give the 4-bromo-2,3-hydroxythiophene existing as the dioxo derivative **198**. However, the experimental evidence is very weak[110] (Scheme 49).

An approach similar to that used for the 2,3-dihydroxythiophene system can also be applied to 3,4-dihydroxythiophenes. Starting from **184**, halogen–metal exchange and reaction with $MgBr_2$ and *t*-butylperbenzoate gave **199**, which was dealkylated to **200**. Metalation of **199** followed by reaction with dimethyl sulfate gave **201**, which was dealkylated to **202**. Furthermore, **201** was converted to **203** by the same reaction sequence[110] (Scheme 50). 3,4-Dihydroxythiophenes are of course also easily obtained by way of the Hinsberg reaction (compare Section II.2.B). 2,4-Dihydroxythiophenes are usually prepared by the Benary reaction (see Section II.2.A). However, the *t*-butoxy approach can also be used.

Starting from 2,4-dibromo- or 2,4-dibromo-5-methylthiophene (**204**), first **205** and then **206** were prepared in the usual way. Dealkylation of **206** then gave **207.**[110] Bromination of **207** gave **208** in quantitative yields (Scheme 51).[110] The 4-mercapto-2-hydroxythiophene system was prepared starting from 2,4-dibromothiophene by first introducing the *t*-butoxy group followed by halogen–metal exchange reaction with sulfur and dealkylation.[111]



190



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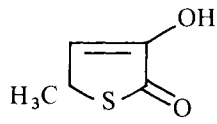

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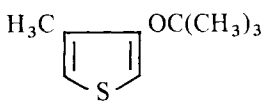
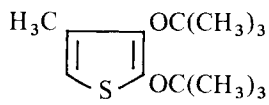


193



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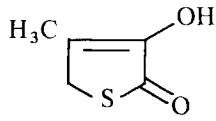

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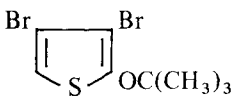

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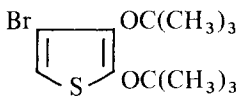

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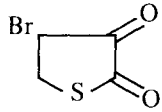
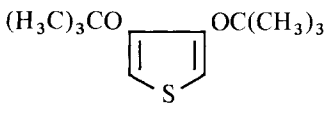
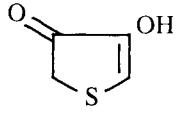


198

Scheme 49



199



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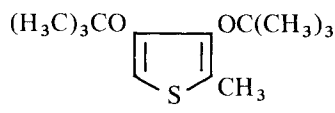

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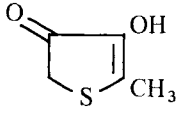

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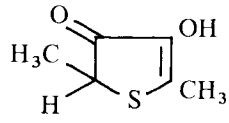
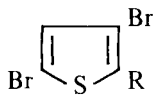


203

Scheme 50

Attempts have been made to prepare some 2,5-dihydroxythiophenes by way of *t*-butoxy derivatives. However, compound **209**, easily obtained from 2,3,5-tribromothiophene, gave both isobutylene and HBr-elimination upon heating with *p*-toluenesulfonic acid, yielding thiomalic anhydride **210**. On the other hand, **211**, prepared from **209** by halogen–metal exchange and reaction with dimethyl sulfate, gave the 2,5-dihydroxythiophene as the dioxo form **212**[110] (Scheme 52).



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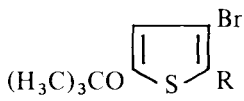

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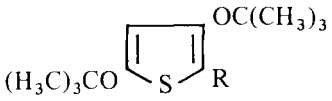
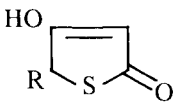


206

R = H, CH_3



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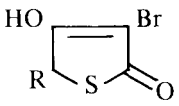
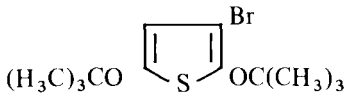


208

Scheme 51



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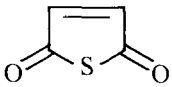

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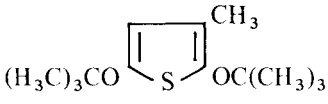
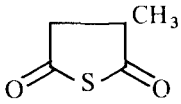


211

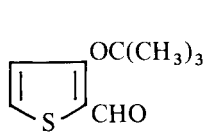


212

Scheme 52

The dealkylation of *t*-butoxythiophenes has often been applied in connection with the synthesis of bicyclic oxygen heterocycles. Thus metalation of 3-*t*-butoxythiophene followed by reaction with DMF gave **213**, which on Claisen-Schmidt reaction with aryl methyl ketones gave **214**. Dealkylation on treatment of **214** with trifluoroacetic acid gave **215**, which was ring closed to **216** with hydrogen chloride–perchloric acid.[112] Compound **213** was dealkylated with *p*-toluenesulfonic acid to 3-hydroxy-2-thiophene aldehyde. Attempts to condense it with methyl aryl ketones failed. Attempts to prepare 2-hydroxy-3-thiophene aldehyde and 4-hydroxy-3-thiophene aldehyde by dealkylation of 2-*t*-butoxy-3-thiophene aldehyde and 4-*t*-butoxy-3-thiophene aldehyde failed.[112]

Condensation of **213** with malonitrile and ethyl cyano acetate gave **217**, which could be dealkylated to **218**, which could be further transformed to **219**[113,114] (Scheme 53). A one-pot procedure for the preparation of 3-*t*-butoxy-2,5-diformylthiophene from 3-*t*-butoxythiophene has been worked out, and, on dealkylation, **220** was obtained.[115] Similarly, from 3,4-di-*t*-butoxy-2,5-diformylthiophene, **221** was prepared.[115]



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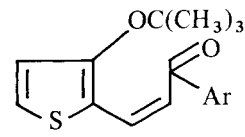

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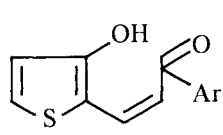

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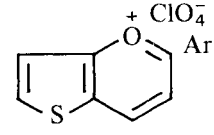

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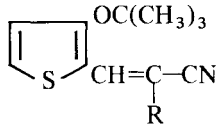

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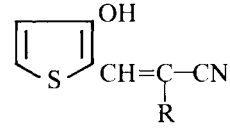

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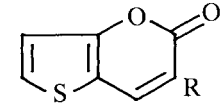


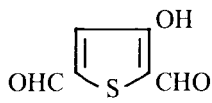
219

R = CN, $CO_2C_2H_5$

Scheme 53

Both 3-hydroxy-2-thiophene aldehydes could be condensed with aryl acetic acids using triethylamine and acetic anhydride to give **222** and **223**, respectively[115] (Scheme 54).

Theoretically interesting systems such as **224**,[116] **225**,[117] and **226**[118] have been prepared by dealkylation of the corresponding *t*-butoxy derivatives (Scheme 55). Boron trifluoride etherate has been used for the dealkylation of 4-bromo-3-*t*-butoxythiophene to give 3-bromo-4-hydroxythiophene.[119]



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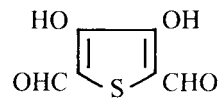

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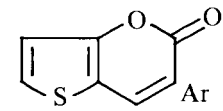

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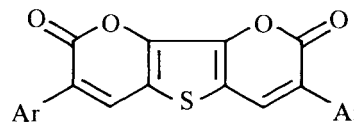
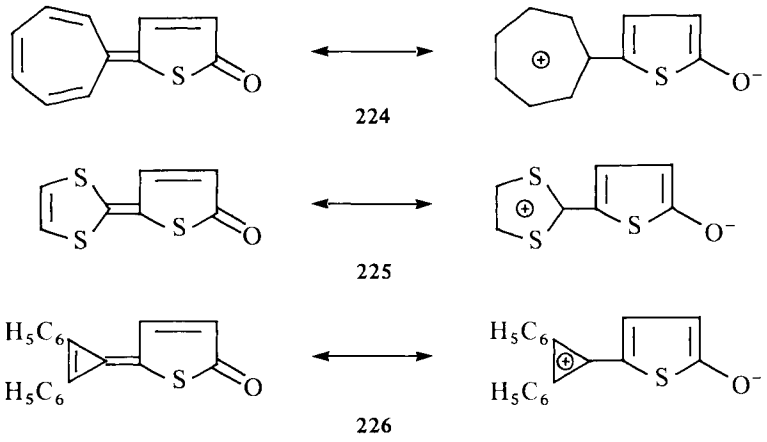


223

Scheme 54



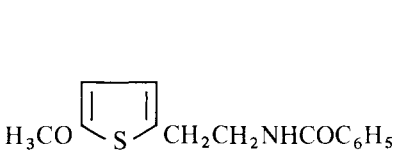
Scheme 55

D. Hydroxythiophenes from Other Alkoxythiophenes

Alkoxythiophenes can be prepared by direct ring-closure reactions, and especially also by nucleophilic aromatic substitution (see Sections VII.1.C and D). Dealkylation of alkoxythiophenes therefore offers in certain cases a preparatively useful route to hydroxythiophenes. The ease of demethylation of 2-methoxythiophenes was found unintentionally. On attempted cyclization of **227** with phosphorous oxychloride **228** was obtained. Demethylation also occurred when an attempt was made to apply the Eschweiler-Clarc reaction to 2-(2-methoxy-2-thienyl)ethylamine, which yielded **229**.[120] Dealkylation also occurred on attempted Vilsmeyer formylation (treatment with DMF and $POCl_3$, at 50 to 70°C) of 5-alkyl-2-alkoxythiophenes **(230)** prepared from the corresponding iodo derivatives. Treatment of **(231**, R = CH_3) with 5% sodium hydroxide solution gave an 80% yield of **232**[121] (Scheme 56).

Heating of 3-methoxy-2-carbonylthiophenes such as 3-methoxy-2-thiophene aldehyde and 2-acetyl-3-methoxythiophene with pyridine hydrochloride gives the corresponding 3-hydroxythiophene derivatives in 80 to 90% yield.[122,123] From 3-methoxy-2-cyanothiophene, 2-cyano-3-hydroxythiophene has been prepared by the same method.[124,125] This approach has also been used for the preparation of more complex condensed systems. Thus Friedel-Crafts substitution of 3-methoxythiophene with cinnamic acid chloride catalyzed by $SnCl_4$ yields **233**. Addition of bromine then gives **234**, which on heating with pyridine hydrochloride gives thiophene analogues of flavones **(235)**[126] (Scheme 57). This approach was recently used for the preparation of some thiophene analogues of antiviral 4′,6-dichloroflavans.[288]

Acylation of 3,4-dimethoxythiophene with one equivalent of cinnamoyl chloride gave **236**, which after bromination and heating with pyridine hydrochloride gave **237**. Mercuration of **236**, followed by Friedel-Crafts acylation, led to simultaneous



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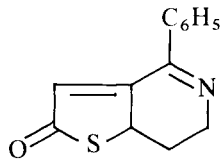

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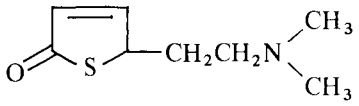

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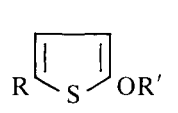

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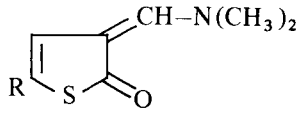

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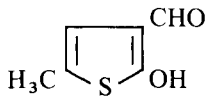
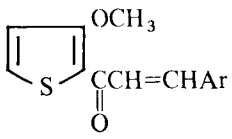


232

R = C_2H_5, R′ = CH_3
R = R′ = CH_3
R = R′ = C_6H_5

Scheme 56



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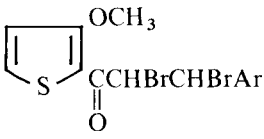

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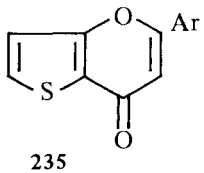


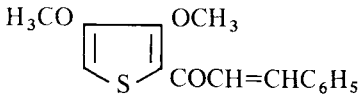
235

Scheme 57

demethylation, yielding **238**, which as described before was ring closed to **239**.[126] Friedel-Crafts acylation of 3-methoxythiophene with orthoanisoyl chloride and 3-methoxy-2-thiophenecarbonyl chloride gave **240** and **241**, respectively. Heating with pyridine hydrochloride then gave **242** and **243**.

Similar reaction sequences, starting from 3,4-dimethoxythiophene, were used for the preparation of **244** and **245** (Scheme 58).

From **246** and anisoyl chloride, **247** was prepared and ring closed to **248**.[126] Compounds such as **235** are very useful for the preparation of a variety of 3-hydroxythiophenes. Reaction with sodium ethoxide in ethanol gave **249**, and with ethyl amine **249a** was obtained. The reaction with thiourea gave **249b** with hydrazines **249c**, and with hydroxylamine **249d** was obtained. Finally, *p*-hydroxyphenylamidine and **235** yielded **249e**[127] (Scheme 59). Further examples are the



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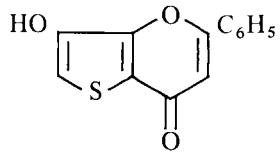

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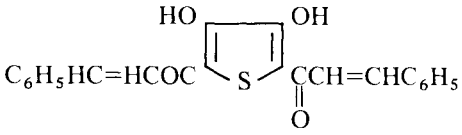

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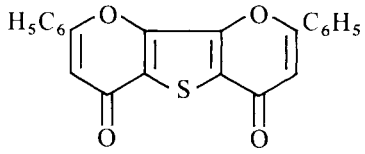

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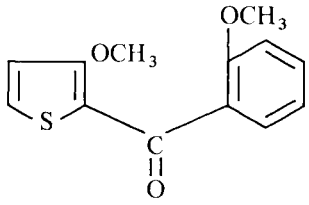

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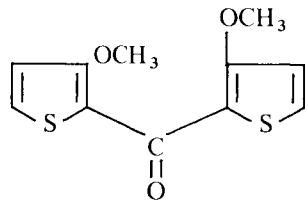

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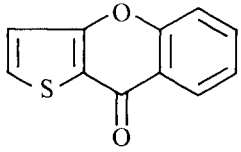

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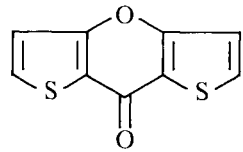

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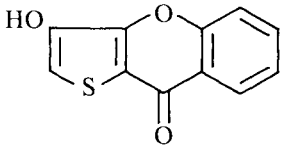

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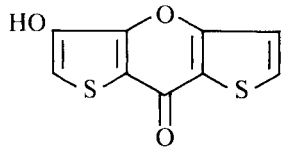

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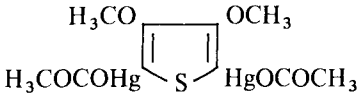
Scheme 58



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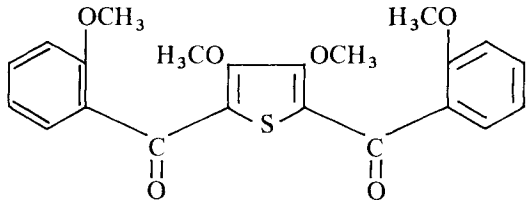

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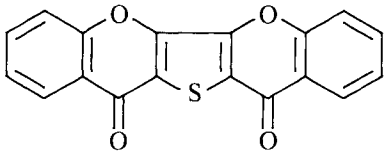

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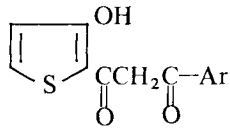

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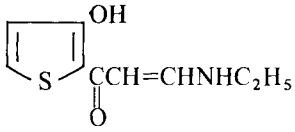

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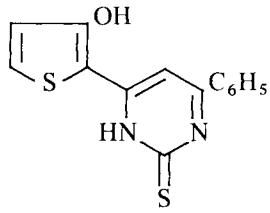

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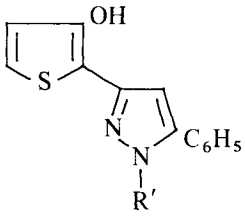

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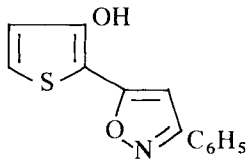

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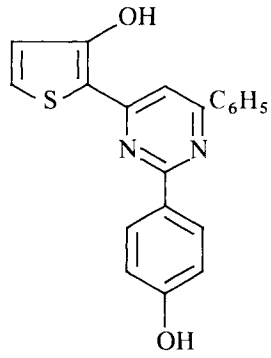


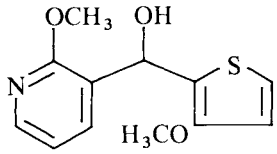
249e

Scheme 59

syntheses of some other xanthones. 3-Methoxy-2-thiophene aldehyde and ortho-methoxypyridyllithium derivatives gave **250** and **251**, which were oxidized to the corresponding ketones and then by treatment with pyridine hydrochloride transformed to **252** and **253**.[128]

Another example of the use of pyridine hydrochloride for dealkylation is the transformation of **254** to **255**[129] (Scheme 60).

Another useful method for the dealkylation of alkoxythiophenes is treatment with boron tribromide in methylene chloride. In this way, 4-ethoxy-3-thiophenecarboxylic acid was transformed to 4-hydroxy-3-thiophenecarboxylic acid, and **256**



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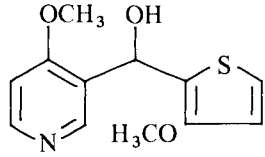

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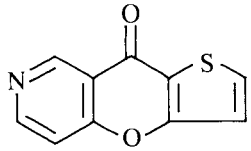

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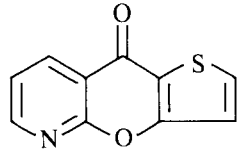

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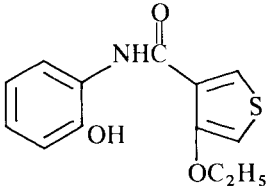

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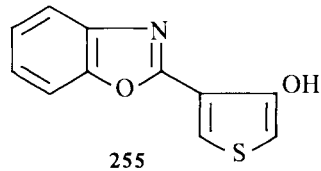

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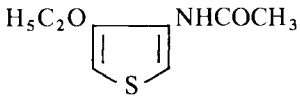

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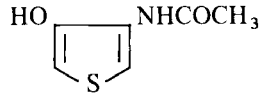


257

Scheme 60

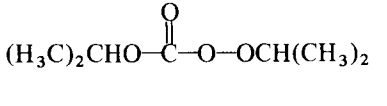
to **257**[72] (Scheme 60). Some other recent examples, describing the use of boron tribromide for demethylation are given in Reference 289, where it was clearly demonstrated that a thiophenic methoxy group is selectively demethylated before a benzenic methoxy group.

Esters derived from hydroxythiophenes can also be used for the preparation of hydroxythiophenes if they have been obtained from other starting materials. Thus 3-acetoxy-4-carbomethoxythiophene was transformed to 5-acetyl-4-hydroxy-3-thiophenecarboxylic acid in 70% yield by treatment with lithium iodide, sodium cyanide, and DMF.[72]

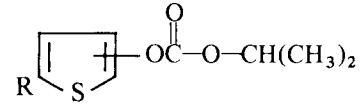
F. Various Methods for the Preparation of Hydroxythiophenes

Direct nucleophilic aromatic substitution of activated halothiophenes has been used in a few cases for the preparation of hydroxythiophenes. Thus the reaction of 2-chloro-3,5-dinitrothiophene and 2-acetyl-4-nitro-5-chlorothiophene with sodium formate in anhydrous methanol, followed by acidification, gave 2,4-dinitro-5-hydroxythiophene and 3-nitro-5-acetyl-2-hydroxythiophene, respectively.[130] Direct replacement of nuclear hydrogen of thiophenes by an oxygen function has been noted in a few cases. Thus decomposition of 2-thenoyl peroxide in thiophene gave 2-thienyl-2-thenoate in 30% yield. Benzoyl peroxide afforded 2-thienyl benzoate in 15% yield,[131] and 3-thenoyl peroxide produced 13% of 2-thienyl-3-thenoate.[132] The most important route for direct oxygenation is the reaction of thiophenes with diisopropyl peroxydicarbonate (IPP; **258**) in acetonitrile in the presence of cupric chloride to give thienyl isopropylcarbonates **259** and **260**[132] (Scheme 61).

In the reaction with thiophene the best yield was obtained when a thiophene: IPP: cupric chloride ratio of 10:1:0.3 in acetonitrile at 60°C was used. A 67%

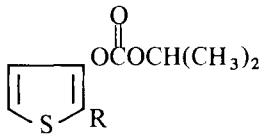


258

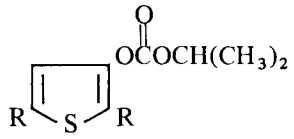


259

R = H, CH_3, Cl, Br



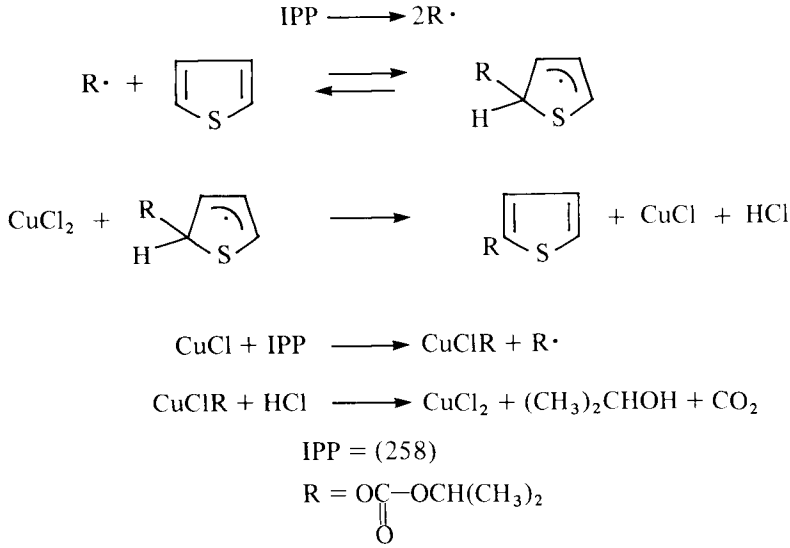
260



261

Scheme 61

yield of 2-thienyl isopropylcarbonate (**259**, R = H) and 3% of the 3-isomer (**260**, R = H), along with small amounts of 5-chloro-2-thienyl isopropylcarbonate (**259**, R = Cl), 2,2′-bithienyl 2,5-dihydroxythiophene bis(isopropyl)carbonate, and 2-isopropoxy-5-chlorothiophene, were obtained. Decomposition of IPP in thiophene and acetonitrile in the absence of cupric chloride gave only 17% of **259** (R = H), no **260** (R = H), but significant amounts of 2,2′- (9%), 2,3′- (6.5%), and 3,3′-bithienyl (0.7%) were obtained. In the reaction with 2-methylthiophene, **259** ($R = CH_3$) and **260** ($R = CH_3$) were obtained in a 65:35 ratio in the cupric chloride catalyzed reaction. 2-Chlorothiophene reacted more selectively, and only **259** (R = Cl) was obtained in 74% yield. When cupric chloride was omitted the yield was lower, and **259** (R = H) was also formed as a minor product. The ratio between **259** (R = Cl) and **259** (R = H) was 11:1. 2-Bromothiophene behaved similarly and gave in the catalyzed reaction 57% of **259** (R = Br). In the non-catalyzed reaction, small amounts of **259** (R = H) were also formed. In the reaction of 2,5-dichlorothiophene the effect of the catalyst is more noticeable. In the presence of $CuCl_2$, **259** (R = Cl) and **261** (R = Cl) are formed in the ratio of approximately 1:1, whereas in the absence of $CuCl_2$ the proportions were 16:1. 2,5-Dibromothiophene also gave a 1:1 ratio of **259** (R = Br) and **261** (R = Br), whereas in the absence of $CuCl_2$ a 1:1 ratio was observed. A radical chain reaction mechanism has been suggested for this oxygenation reaction, as shown in Scheme 62. The carbonate esters **259** to **261** were dealkylated to the corresponding hydroxythiophenes in good to fair yields by treatment with aluminium chloride in *m*-xylene.[132] The main drawback for preparative purposes is of course the need for the thiophene substrate to be used in excess.



Scheme 62

On treatment of 2-chlorothiophene with Amberlyst 15 or 100% orthophosphoric acid, a complex dimer mixture is formed in which 4-(2-thienyl)-2-hydroxythiophene (as the 3-thiolen-2-one form) was a minor constitutent.[133] γ-Irradiation of a thiophene–water mixture gave 2-hydroxythiophene.[148,284–286] Thermolysis of 3-azidothiophene in a mixture of polyphosphoric acid and acetic acid gave a 64% yield of 3-acetamido-3-thiolen-2-one.[134] 3-Thiolen-2-ones are collected in Table 1, 4-thiolen-2-ones in Table 2, 3-hydroxythiophenes in Table 3 and 4-thiolen-3-ones in Table 4.

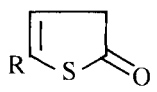
III. TAUTOMERISM OF HYDROXYTHIOPHENES

1. Alkyl-, Aryl-, and Halo-Substituted 2-Hydroxythiophenes

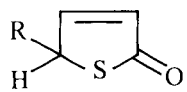
By a now classical use of NMR spectroscopy, it was shown that the two forms of 5-methyl-2-hydroxythiophene that previously had been erroneously assigned in the literature[1,2] were 5-methyl-4-thiolen-2-one **262** (R = CH_3), which is the lower-boiling isomer, and 5-methyl-3-thiolen-2-one **263** (R = CH_3)[3] and not **263** (R = CH_3) and **264** (R = CH_3), respectively[2] (Scheme 63).

The availability of NMR spectroscopy then led to a detailed investigation of the tautomeric equilibria and the rate and mechanism of tautomerization. For a review see Reference 139. Tautomerization in the 5-alkyl-2-hydroxythiophene series is rather slow, and the 4-thiolen-2-one and 3-thiolen-2-one can be separated by fractional distillation. Preparatively, the thermodynamically less stable 4-thiolen-2-one is formed predominantly upon careful acidification at low temperature of a solution of the carbanion common for the 4- and 3-thiolen-2-one forms. If the 3-thiolen-2-one form is desired, the 4-thiolen-2-one form is isomerized under base or acid catalysis.[3,93] In the determination of tautomeric equilibria, triethylamine or traces of hydrogen chloride were used, and the equilibria were reached from both sides. Different solvents were used, and the percentages of 4-thiolen-2-one are given in Table 5[93] (compare also Reference 104).

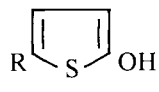
The greater thermodynamic stability of **263** (R = alkyl) is of course due to stabilization of this form by conjugation between the double bond and the carbonyl group, whereas **262** (R = alkyl) is only stabilized by hyperconjugation between the alkyl group and the double bond. When this stabilization is absent, as in the parent compound, **262** (R = H) could not be isolated, and the equilibrium lies completely toward the conjugated form **263** (R = H).[3,104] As can be seen from



262



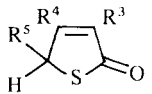
263



264

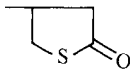
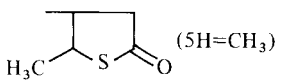
Scheme 63

TABLE 1. 3-THIOLEN-2-ONES



C_n	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
4	H	Br	H		65–68	27	92
	H	H	Br	60–65/0.1		90	106
	Br	H	H	110–113/10	81–82	21	92
	Br	OH	H		33	100	110
	H	H	Cl	97–98/12		38	96
	H	H	F	80–82/30		83	96
	H	H	H	89–91/10		28	3
	H	SH	H	118–121/1	53–54.5		111
	H	OH	H		115–116	77	110
	OH	H	H	120–125/12		93	110
5	Br	OH	CH_3		Oil	100	110
	H	H	CH_3	89–91/13			3
	H	CH_3	H	69–70/0.9		75	97
	CH_3	H	H	96–98/8		43	89
	H	H	SCH_3	70–72/0.1		63	104
	H	OH	CH_3		Oil	72	110
	OCH_3	H	H		49–50	24	92
	OH	CH_3	H	85/0.5	32	38	110
	OH	H	CH_3	80/0.5		90	110
	H	OCH_3	H		85–86	33	292
	Br	OCH_3	H		119–120	29	292
	Cl	OCH_3	H		81–82	48	292
6	$NHCOCH_3$	H	H		153–155	64	134
	C_2H_5	H	H	101/9			164
	H	CH_3	CH_3	68–69/0.9		65	97
	CH_3	H	CH_3	86–87/9		53	94

TABLE 1. (*Continued*)

C_n	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
7	H	H	$CH_2CH{=}CH_2$	50–57/0.1		91	104
	$CH_2CH{=}CH_2$	H	H	124/14			164
	H	H	$(CH_2)_2CHO$			38	168
	H	H	$(CH_2)_2CH_3$	90–100/9		50	93
	$CH(CH_3)_3$	H	H	112/12			164
8	H	2-Thienyl	H		165–166		133
	H	2-Furyl	H		103–105	61.6	8
	CN	CH_3	$COCH_3$		211–215	55	15
	H	H		185/0.5		23	192
	H	CH_3	$CO_2C_2H_5$		86–90	76	15
	$CH(CH_3)CH{=}CH_2$	H	H	90/0.4			164
	$CH_2CH{=}CH{-}CH_3$	H	H	90/0.4			164
	$CH_2CO_2C_2H_5$	H	H	126/0.5			164
	H	H	$(CH_2)_3CH_3$	130/8		50	93
	$C(CH_3)_3$	H	H	74–76/1.4		83	95
	H	H	$C(CH_3)_3$		31.5–32.5	50	93
	H	S–$C(CH_3)_3$	H		53–54	65	111
	H	H	$(CH_2)_2N(CH_3)_2$	85–86/0.4	40.5–41.5		120
9	1-Cyclopentenyl	H	H	85–115/0.3		50	105
	$C(C_2H_5){=}CHCH_3$	H	H	80–82/0.2		65	105
10	3-Thienyl-5-CH_3	H	CH_3		77–78		90
	H	H	3-Cyclohexanone			83	168
	H	H			104–105		192

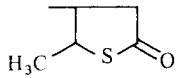
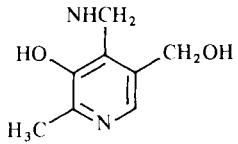
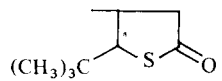
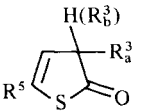
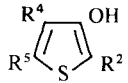
		H	CH_3		Oil		192
11	CN	C_6H_5	H		110–113	66	15
	H	H	$CH_2C_6H_5$	130–132/0.3		91	104
	$CH_2C_6H_5$	H	H	150/0.4			164
12	H	OH	$CH_2C_6H_5$ (5H = CH_3)		119–120		219
		H	H		172–175 (decomp.)		10
13	$C(C_6H_5)$=$CHCH_3$	H	H	138–160/0.5		96	105
	C_2H_5	OH	CH=$C(CH_3)$–CH=CH_2 (5H = C_2H_5)		92		218
14	$COCH_3$	OH	$CH_2C_6H_5$ (5H = CH_3)		163–164		219
	C_2H_5	OH	$CH_2C_6H_5$ (5H = CH_3)		107–108		219
16	3-Thienyl-5-$C(CH_3)_3$		$C(CH_3)_3$		93–94		90
		H	$C(CH_3)_3$		95–97 119–121	53	192
18	C_6H_5	OH	$CH_2C_6H_5$ (5H = CH_3)		128–129		219

TABLE 2. 4-THIOLEN-2-ONES



C_n	R^3_a	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
4	NO_2	NO_2		100		130
	H	F	40/10	30		96
5	H	CH_3	65–66/13			3
6	H	C_2H_5	82–83/11		59	93
7	H	$CH(CH_3)_2$	101–103/10		30	93
	H	$(CH_2)_2CH_3$	96/13		75	93
8	H	2-Thienyl		81–82	66	93
	H	$C(CH_3)_3$	98–100/8		64	93
	H	$(CH_2)_3CH_3$	118–119/10		64	93
9	$C(CH_3)_3$ $R^3_b = CH_3$	H		67–68		95
10	H	C_6H_5		81.5–81.8	30	7
11	H	C_6H_4–4-CH_3		95–97	23	184
19	$CH_2C_6H_5$ $R^3_b = CH_2C_6H_5$	CH_3	232–238/8	135.5–136		94

TABLE 3. 3-HYDROXYTHIOPHENES



C_n	R^2	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
4	H	H	H	38–39/0.01			88
	H	OH	H		90–91	82	34
5	CN	H	H		116	60	53
	H	CN	H		40–43	80	71
	CHO	H	H		86	10	53
	$CONH_2$	H	H		191	45	53
	CH_3	H	H	92–98/12		49	99
	H	CH_3	H	56–58/0.1		6	76
	H	H	CH_3	53/0.1		40.3	61
	CH_3	OH	H		157	31	253
6	CHO	H	CO_2H		216		273
	CN	H	CH_3		137	78	43
	CO_2CH_3	H	NO_2		61		53
	$COCH_3$	H	H		50–51	40	273
	H	H	$COCH_3$		118	80	274
	H	H	$COCH_3$		118	80	274
	CHO	H	CH_3		95	50	53
	H	H	CO_2CH_3		89.5	71.7	61
	CO_2CH_3	H	H		44	80	53
	CH_3	H	CO_2H		219	60	53
	CO_2H	H	CH_3		95–98 (decomp.)	34.7	61
	H	SCH_2CO_2H	H		105		253
	$CONH_2$	H	CH_3		220	60	53
	H	$NHCOCH_3$	H		148.5–149	41	72

TABLE 3. *(Continued)*

C_n	R^2	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	CH_3	H	CH_3	94–95/11		32	156
	CH_3	OH	CH_3			50	110
7	CN	CN	CH_3		180–185 (decomp.)		45
	CN	H	CO_2CH_3		183	70	53
	CO_2CH_3	OH	CN		210 (decomp.)	70	276
	$COCH_3$	H	CO_2H		216–217		273
	CO_2H	H	$COCH_3$		135 (decomp.)	74	274
	CHO	H	CO_2CH_3		163	52	53
	CO_2H	OH	$COCH_3$		150 (decomp.)	70	274
	CO_2CH_3	H	CO_2H		191	80	274
	$CONH_2$	H	CO_2CH_3		205	70	53
	$COCH_3$	H	CH_3		73–74	15	273
	$COCH_3$	CH_3	H		36–37	25	65
	2,4-Dinitrophenylhydrazone				261–262		65
	CH_3	CH_3	CO_2H		208	90	253
	H	CH_3	CO_2CH_3		115	5	253
	CH_3	H	CO_2CH_3		136	70	53
	CO_2CH_3	SH	CH_3		47	50	253
	CO_2CH_3	OH	CH_3		113	42	253
	H	OH	$(CH_2)_2CO_2H$		194–197		280
	C_2H_5	H	CH_3	62–67/1.2		89	156
	CH_3	H	C_2H_5	108–11/14		29	156
8	CO_2CH_3	CH_3	CN		93	31	276
	$COCH_3$	H	CO_2CH_3		113	77	273
	CO_2CH_3	H	$COCH_3$		167	41	274
	CO_2CH_3	H	CO_2CH_3		111	78	274
	$CO_2C_2H_5$	H	CO_2H		171	45	274
	CO_2CH_3	OH	$COCH_3$		136	30	274

	CO_2CH_3	SCH_2CO_2H		H		140	68	274
	CN	H		$CH(CH_3)_2$		67–68	57	43
	H	CN		$CH(CH_3)_2$	130/0.5		89	38
	$CONH_2$		$-(CH_2)_3-$			195–205 (decomp.)	64	275
	$CO_2C_2H_5$	CH_3		H		40	50	65
	Phenylhydrazone					246		65
	CH_3	CH_3		CO_2CH_3		134	39	253
	CO_2CH_3	CH_3		CH_3		52	78.5	48
	H	H		$CH_2CO_2CH_3$	96/5			281
	CH_3	H		$CH(CH_3)_2$	116–119/15		13	156
9	$COCH_3$		$-(CH_2)_3-$			51	58	275
	2,4-Dinitrophenylhydrazone					255–260		275
	CO_2CH_3		$-(CH_2)_3-$			78–78.5	85.3	48
	$CO_2C_2H_5$	SCH_2CO_2H		H		106	48	274
	CO_2CH_3	$SCH_2CO_2CH_3$		H		80	65	274
	CH_3	CN		$CH(CH_3)_2$	111/0.1		65	38
	H	CN		$CH(CH_3)C_2H_5$	134/0.5		90	38
	CN	H		$C(CH_3)_3$		95–96	32	43
	$CONH_2$		$-(CH_2)_4-$			186–188	85	275
	CO_2CH_3	C_2H_5		CH_3		43–44	81.3	48
	$CO_2C_2H_5$	CH_3		CH_3		50	80.5	48
	CH_3	H		$CH_2CO_2C_2H_5$	104/5			281
	H	H		$CH(CH_3)CO_2C_2H_5$	116/5	53		281
	CO_2CH_3	SC_2H_5		CH_3	110/0.2		74	253
	$(CH_2)_4CO_2H$	OH		H		183		282
	$C(CH_3)_3$	H		CH_3	68–72/1.3		33	156
	CH_3	H		$C(CH_3)_3$	118–122/10		41	156
10	NO	H		C_6H_5		215–216		209
	NO_2	H		C_6H_5		101		79
	H	H		C_6H_5		78	59	7
	NH_2	H		C_6H_5		> 300		79
	$COCH_3$		$-CH(CO_2CH_3)SCH_2-$			121	66	275
	2,4-Dinitrophenylhydrazone					220		275

TABLE 3. (*Continued*)

C_n	R^2	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	$COCH_3$	$-(CH_2)_4-$			47	73	275
	2,4-Dinitrophenylhydrazone				243–246		275
	$CO_2C_2H_5$	$-(CH_2)_3-$			51	86.7	48
	CO_2CH_3	$-(CH_2)_4-$			64.5	80	275
	$CO_2C_2H_5$	H	$CO_2C_2H_5$		69	79.9	61
	CH_3	CN	$CH(CH_3)C_2H_5$	121/0.3		75	38
	$CO_2C_2H_5$	C_2H_5	CH_3	97–98/0.8		73.4	48
11	CN	H	C_6H_5		182–184	50	43
	COC_6H_5	H	H		62	55	53
	2,4-Dinitrophenylhydrazone				247–250		275
	CHO	H	C_6H_5		155–156	20	273
	CO_2H	H	C_6H_5		120–121	10.2	61
	H	CO_2H	C_6H_5		170 (decomp.)	59	276
	CO_2H	C_6H_5	H		133	86.5	274
	CO_2H	OH	C_6H_5		175–177	85	150
	C_6H_5	H	CH_3	118–122/0.8		78	100
	CH_3	H	C_6H_5	136–138/0.3		48	100
	H	$CH_2NH-C_6H_5$	H		198–200		84
	$CO_2C_2H_5$	$-(CH_2)_4-$			34–34.5	76	48
	$COC(CH_3)_3$	OH	CO_2CH_3		92–93	35	275
	CO_2CH_3	$S(CH_2)_3CH_3$	CH_3	123/0.2	22	81	253
12	COC_6H_5	H	CO_2H		204–205		273
	CO_2H	H	COC_6H_5		140		273
	H	CO_2H	COC_6H_5		140 (decomp.)	84	276
	2,4-Dinitrophenylhydrazone				220–223	66	276
	$CO_2C_6H_5$	CH_3	H		57–58	50	65
	2,4-Dinitrophenylhydrazone				220		65
	$COCH_3$	H	C_6H_5		97–98	25	273
	$COCH_3$	H	CH_3		58.5	52	275

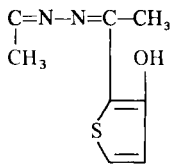
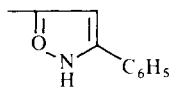
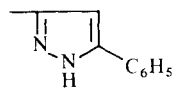
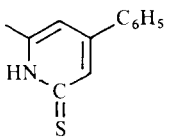
	CO_2CH_3	H		C_6H_5		97–98	88	48
	CO_2CH_3	C_6H_5		H		82	73	274
	CO_2CH_3	OH		C_6H_5		146–147	78	150
	$NHCOCH_3$	H		C_6H_5		146–147	75	209
		H		H		199		273
	$CO_2C_2H_5$	$SCH_2CO_2C_2H_5$		CO_2H		116	7	274
	$CH_2CO_2C_2H_5$	CN		$CH(CH_3)C_2H_5$	155/0.1		75	38
	$COC(CH_3)_3$		$-(CH_2)_3-$			90	87	275
13		H		H		200	62	127
		H		H		147	57	127
	CO_2CH_3	COC_6H_5		H		112	34	146
	COC_6H_5	H		CO_2CH_3		102	78	273
	CO_2CH_3	H		COC_6H_5		125–127	30	273
	CO_2CH_3	CHO		C_6H_5		86–89	71	70
	2,4-Dinitrophenylhydrazone					230–232		70
	CO-2-Thienyl-5-CO_2CH_2	H		CO_2CH_3		257	49	273
	$CO_2C_2H_5$	H		C_6H_5		68	91	48
	CO_2CH_3	$S \cdot C_6H_5$		CH_3		107	85	253
14		H		H		205	16	127

TABLE 3. (*Continued*)

C_n	R^2	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	CH=N–N=CH | 2-Thienyl-5-CO_2CH_3	H	CO_2CH_3		278–279		273
	COC_6H_5	–$(CH_2)_3$–			83	84	275
	2,4-Dinitrophenylhydrazone				241–244		275
	CO_2CH_3	CO_2CH_3	C_6H_5		79	85	276
	$CO_2C_2H_5$	H	COC_6H_5		71	52	276
	2,4-Dinitrophenylhydrazone				163		276
	CO_2CH_3	CH_3	COC_6H_5		85	31	276
	CO_2CH_3	SC_2H_5	C_6H_5		87	54	253
	C=N–N=C– | | CH_3 CH_3 -2-Thienyl-5-CH_3	H	CH_3		234–235		273
15	CO_2CH_3	CO_2CH_3	COC_6H_5		94	58	276
	2,4-Dinitrophenylhydrazone				212–215	47	276
	$CO_2C_2H_5$	C–CH_3 ‖ 2,4-Dinitrophenylhydrazone	H		213–214		146
	COC_6H_5	–$(CH_2)_4$–			133–134	68	275
	CO_2CH_3	$NHCOCH_2C_6H_5$	CH_3		202	40	253
16	C=N–N=C– | | CH_3 CH_3 -2-Thienyl-5-CO_2CH_3	H	CO_2CH_3		287–288		273
	CO_2CH_3	$S(CH_2)_3CH_3$	C_6H_5		94	47	253
	CO_2CH_3	–S–$(CH_2)_2$–S– -3-Thienyl-2- –CH_3-4-OH– -5-CO_2CH_3	CH_3		170	49	253
17	COC_6H_5	H	C_6H_5		123–124	41	275

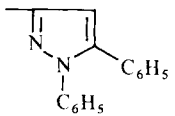
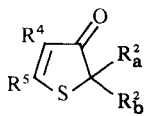
	H	C—C_6H_5 ‖ 2,4-Dinitrophenylhydrazone		208–209		146
18	COC_6H_5	H	COC_6H_5	136–137		273
	COC_6H_5	OH	COC_6H_5	184–186	25	273
	CO_2CH_3	SC_6H_5	C_6H_5	101	46	253
	CO_2CH_3	—S—$(CH_2)_4$—S— -3-Thienyl-2- —CH_3-4-OH-5- —CO_2CH_3	CH_3	141	78	253
19		H	H	198	50	127
20	4-Pyrimidyl- -2,6-C_6H_5	H	H	> 300	43	127
	COC_6H_5	$CO_2C_2H_5$	COC_6H_5	123	36	273
	CO_2CH_3	CH_2	C—C_6H_5 ‖ 2,4-Dinitrophenylhydrazone	240–242	68	276
21	CO-2-Thienyl- -3-OH-5-C_6H_5			236–238	32	273
22	CH=N—N=CH— -2-Thienyl- 3-OH-5-C_6H_5	H	C_6H_5	280		273
23	CH—C_6H_5 | $CH(COCH_3)CO_2C_2H_5$	H	C_6H_5	136–138		27
24	C=N—N=C— | | CH_3 CH_3 2-Thienyl- -3-OH-5-C_6H_5	H	C_6H_5	316		273

TABLE 4. 4-THIOLEN-3-ONES



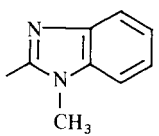
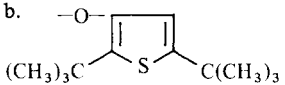
C_n	R^2_a	R^2_b	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	H	H	H	OCH_3		84–85	56	292
	H	H	Br	OCH_3		140	63	292
	H	H	Cl	OCH_3		118–120	37	292
6	CH_3	H	H	CO_2H		198		53
	2,4-Dinitrophenylhydrazone					> 280 (decomp.)		53
	CH_3	CH_3	H	H	78–80/12		38	170
	H	H	H	OC_2H_5		57–58	48	292
9	H	H	2-Pyridyl	H		182–183	73	16
10	H	H	C_6H_4-4-Cl	NH_2		210–211		69
	H	H	C_6H_5	NH_2		204		69
	H	H	H	NHC_6H_5		185–186	76	67
11	H	H	H	C_6H_4-4-OCH_3			14	78
12	H	H		NH_2		256–257	67	16
	$C(CH_3)_3$	H	H	$C(CH_3)_3$	130/13			91
24	a. $C(CH_3)_3$		H	$C(CH_3)_3$				
	b. 					152–154		91

TABLE 5. PERCENTAGE 4-THIOLEN-2-ONE AT EQUILIBRIUM IN DIFFERENT SOLVENTS

Compound	Carbon Tetrachloride[a]	Cyclohexane	Acetone	Nitromethane
5-Methyl-4-thiolen-2-one	18.5	19.0	13.0	6.0
5-Methyl-3-thiolen-2-one	18.5	19.5	12.0	10.0
5-Ethyl-4-thiolen-2-one	12.0	12.5	9.0	7.0
5-Ethyl-3-thiolen-2-one	15.0	13.0	8.5	7.0
5-Isopropyl-4-thiolen-2-one	–	11.5	–	–
5-*tert*-Butyl-4-thiolen-2-one	8.0	8.5	5.0	5.0
5-*tert*-Butyl-3-thiolen-2-one	9.5	8.0	7.0	5.0
5-*n*-Propyl-4-thiolen-2-one	18.0	19.0	15.0	13.5
5-*n*-Propyl-3-thiolen-2-one	19.0	18.5	13.0	14.5
5-*n*-Butyl-4-thiolen-2-one	18.0	18.5	14.0	14.0
5-*n*-Butyl-3-thiolen-2-one	19.5	19.0	13.0	15.5

[a]In carbon tetrachloride solution, only the acid-catalyzed equilibrium composition has been determined, as carbon tetrachloride contains hydrogen chloride leading to salt formation with the triethylamine used in the basic catalysis.

Table 5, the percentage of **262** in equilibrium diminishes with the polarity of the solvent. This is due to the lower polarity of **262**. The dipole moments of **262** ($R = CH_3$) and **262** ($R = C(CH_3)_3$) are 3.7 D and 3.8 D, whereas those for **253** ($R = CH_3$ and $R = C(CH_3)_3$) were both 4.4 D in cyclohexane.[135]

Both **262** ($R = CH_2CH{=}CH_2$) and **263** ($R = CH_2CH{=}CH_2$) could be isolated. The equlibrium mixture consisted of 15% of the 4-thiolen-2-one and 85% of the 3-thiolen-2-one form.[104] In the 5-benzyl case and the 5-methylthio case, tautomerization was so fast that **262** could not be obtained upon acidification of a solution of the carbanion. The observed equilibria contained 30% of **262** and 70% of **263** in the benzyl case and 15% of **262** and 85% of **263** in the 5-methylthio-2-hydroxythiophene system.[104]

5-Aryl-substituted 2-hydroxythiophenes are more air sensitive than the corresponding alkyl derivatives. However, on oxidation of 5-phenyl-2-thiopheneboronic acid, crystalline **262** ($R = C_6H_5$) is formed, according to its NMR spectrum in CCl_4.[93] However, in methanol solution, 25 to 30% of the hydroxy form **264** ($R = C_6H_5$) is present, as is shown by comparison with the coupling constants and chemical shifts of 5-phenyl-2-methoxythiophene. The even more sensitive 5-(2-thienyl)-4-thiolen-2-one **262** (R = 2-thienyl) behaved similarly. The only tautomer observed in the 4-(2-furyl)-2-hydroxythiophene system is 4-(2-furyl)-3-thiolen-2-one.[8] The 5-chloro-2-hydroxythiophene system was rather unstable, and **262** (R = Cl) could not be isolated as it rapidly tautomerized. The NMR spectrum of a freshly distilled product in acetone showed the presence of about equal amounts of **262** (R = Cl) and **263** (R = Cl). After a few hours only the NMR spectrum of **263** (R = Cl) was observed.[96,106] In the case of the 5-fluoro-2-hydroxythiophene system, both **262** (R = F) and **263** (R = F) could be isolated in the usual way, and the rate of tautomerization was approximately the same as for **262** ($R = CH_3$), but activation parameters were quite different.[96] The 5-bromo-2-hydroxythiophene system could not be prepared by oxidation of 5-bromo-2-thiopheneboronic acid.[92] It was, however, obtained by dealkylation of 5-bromo-2-*t*-butoxythiophene and exists as the very labile **263** (R = Br), according to its NMR spectrum.[106] The only isolable tautomeric form of the 3-methyl-, 3-bromo-, and 3-methoxy-2-hydroxythiophene system was the 3-thiolen-2-one form. This was also true in the 4-bromo- and 4-methyl-2-hydroxythiophene case. The stability of the 3- and 4-substituted 3-thiolen-2-ones is quite understandable, as in this form both the C=O group and the substituent can conjugate with the double bond.[89,92]

The tautomeric rearrangement of **262** ($R = CH_3$) and **262** ($R = C(CH_3)_3$) has been studied at different temperatures. The kinetics clearly indicate that in methanol solution with pyridine as base the isomerizations are first order in substrate and first order in base. The tautomerization follows a two-stage mechanism and obeys both parts of the Hughes-Ingold rule.[136] In addition, the catalytic effect of various pyridine bases on the tautomeric rearrangement of **262** ($R = CH_3$) to **263** ($R = CH_3$) in methanol at various temperatures has been measured, and the activation parameters for the reaction, which follows a general base catalysis pattern, have been calculated. When the various catalytic constants of the pyridines were plotted against their pK_a values, a straight line with a slope of

0.58 was obtained for the 4-substituted pyridines. The α-substituted pyridines, on the other hand, showed deviations in the Brønsted diagrams, which were functions of the steric conditions.[135] Additional support for a two-step mechanism for the tautomerization of **262** ($R = CH_3$) to **263** ($R = CH_3$) was obtained by a study of hydrogen–deuterium exchange at the 3-position of **262** ($R = CH_3$) in deuteriomethanol, using low concentrations of pyridine at various temperatures. A comparison with ethyl acetoacetate, whose keto form has a pK_a value a few units higher than that of **262** ($R = CH_3$),[137] shows that hydrogen exchange in the latter occurs more rapidly. The difference, however, is of such an order of magnitude as is reconcilable with the relation between the kinetic and thermodynamic acidity of similar systems. This means that **262** are *pseudo* acids of the acetoacetate type and that hydrogen exchange takes place by way of the common anion.[138] The rates, enthalpies, free energies, and entropies of activiation for deuterium exchange[138] and isomerization[136] at 18°C catalyzed by pyridine are given in Table 6. The profile of free-activation energy *versus* reaction coordinate for the tautomerization of **262** ($R = CH_3$) to **263** ($R = CH_3$) is shown in Figure 1.[139]

The rates of tautomerization of **262** ($R = CH_3$) and **262** ($R = C(CH_3)_3$) have been compared with those of their oxygen analogues 5-methyl- and 5-*t*-butyl-β,γ-butenolide. In benzene solution the butenolides tautomerized 1000 to 10,000 times more slowly than the thiobutenolides. The observations were interpreted in terms of *d*-orbital effects of the sulfur atom.[140] A review of the tautomeric properties of hydroxythiophenes has been published.[139]

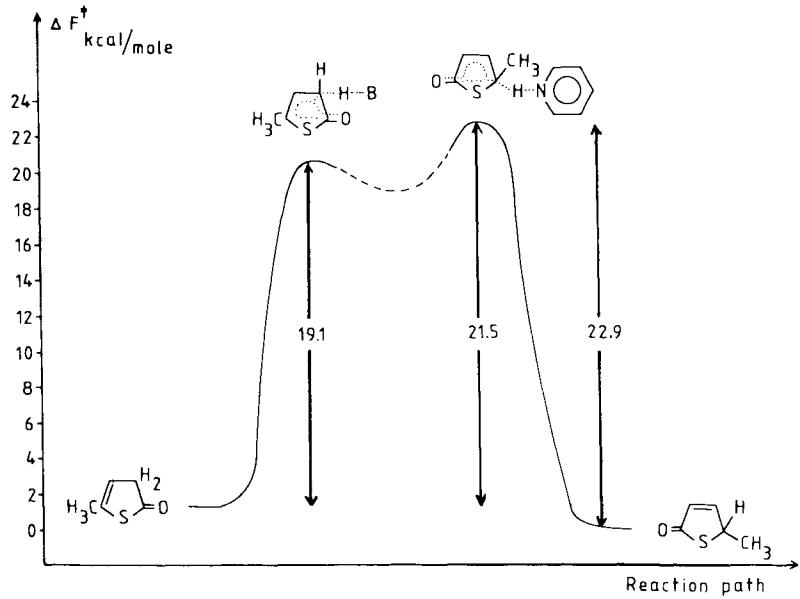


Figure 1. The profile of free-activation energy *versus* reaction coordinate for the carbon–carbon tautomerization of the 5-methyl-2-hydroxythiophene system.

TABLE 6. RATES, ENTHALPIES, FREE ENERGIES, AND ENTROPIES OF ACTIVATION FOR THE ISOMERIZATION AND DEUTERIUM EXCHANGE OF 5-METHYLTHIOLEN-2-ONE IN METHANOL CATALYZED BY PYRIDINE AT 18° C

Reaction	Base Concentration (mole/l)	$k:10^3$ (per min)	$\Delta H^{\ddagger}$ (kcal/mole)	$\Delta G^{\ddagger}$ (kcal/mole)	$\Delta S^{\ddagger}$ (cal/(mole)(deg))
Deuterium exchange	0.001	23	7.0	21.6	−50.1
Deuterium exchange	0.2	1835	7.0	19.1	−41.4
Isomerization A → B	0.2	25.3	10.9	21.5	−36.5
Isomerization B → A	0.2	2.2	12.5	22.9	−35.9

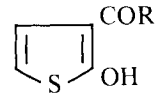
The determination of appearance potentials (AP) and ionization potentials (IP) can be used for structural analysis of gaseous molecules in the mass spectrometer. Therefore IP:s for tautomeric alkyl 2-hydroxythiophenes have been analyzed by comparison with IP data derived from either tautomeric form. The enol form (**264**) could not be detected. Both **262** and **263** were observed, and, as in solution, the latter was the major isomer. The ratios depended on the position of the alkyl substituent. Investigation of the analogous hydroxyfuran and hydroxythiophene systems was also carried out.[141] Attempts to determine the tautomeric equilibrium of the 2-hydroxythiophene system by paper chromatography gave erroneous results.[142]

2. Carbonyl-Substituted 2-Hydroxythiophenes

Investigations by NMR and IR spectroscopy indicate that 2-hydroxy-3-carbonyl-substituted thiophenes such as **265** exist exclusively in the hydroxy form, probably due to chelation.[143] On the other hand, when the carbethoxy group is in the 5-position, an equilibrium mixture containing 85% of **266** and 15% of **267** was obtained.[104]

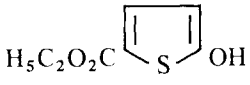
NMR investigations indicate that 2-hydroxy-3-thiophenealdimines, for which several tautomeric forms (**268** to **270**) are possible, exist in solution and in the molten state mainly as *N*-substituted 5-alkyl-3-aminomethylene-4-thiolen-2-ones (**269**), in contrast to 2-hydroxy-3-carbonyl derivatives. In sufficiently polar solvents such as DMSO the intramolecular hydrogen bond breaks[144] (Scheme 64).

The hindered rotation about the C—N bond in compounds of type **269** and also in dialkylamino derivatives in which hydrogen bonding is not possible has been investigated by dynamic NMR.[145]

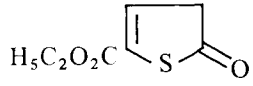


265

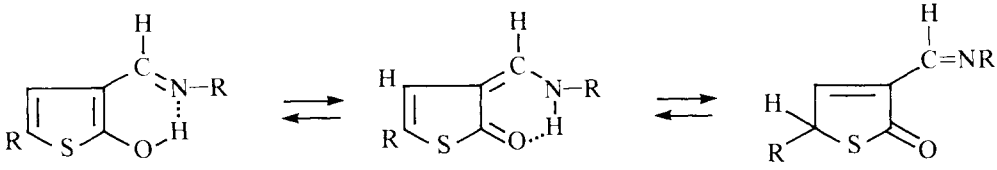
$R = CH_3$
$R = OC_2H_5$



266



267

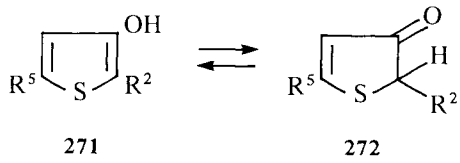


268 **269** **270**

Scheme 64

3. Alkyl-Substituted 3-Hydroxythiophenes

The simple 3-hydroxythiophenes are even more unstable and air sensitive than the corresponding 2-hydroxythiophenes, and 3-hydroxythiophene has not been obtained in pure form, but spectral data have indicated that it is a mixture of the hydroxy form **271** ($R^2 = R^5 = H$) and the keto form **272** ($R^2 = R^5 = H$)[131] (Scheme 65).



271 **272**

Scheme 65

Of the three monomethyl derivatives, only **271** ($R = Me$; $R^5 = H$) was stable enough to be obtained in pure form, and the tautomeric equilibrium composition, which was 80% of **271** and 20% of **272**, was determined. The equilibrium composition in the 2-*t*-butyl-3-hydroxythiophene system was 55% of **271** and 45% of **272**.[99]

2,5-Dialkyl-3-hydroxythiophenes were more stable,[99] and a detailed investigation on their tautomerism has been carried out.[100,147] Ultraviolet-spectroscopic techniques could be used, in addition to NMR, for the determination of the tautomeric equilibrium. For instance, by comparing the UV spectrum of the tautomeric mixture of the 2,5-dimethyl-3-hydroxythiophene system with those for 3-methoxy-2,5-dimethylthiophene and 2,2,5-trimethyl-4-thiolen-2-one, the oxo–enol equilibrium constant in cyclohexane solution was found to be 2.61. Using the same technique, the constants were determined in the analogous furan and selenophene systems and found to be 1.24 and 8.53, respectively. In methanol solution, the oxo–enol equilibrium constants for the 2,5-dimethyl-3-hydroxyfuran–thiophene and –selenophene systems were found to be 1.37×10^4, 1.21, and 2.20×10^2, clearly reflecting the higher aromaticity of thiophene compared to furan and selenophene.[100] However, in all cases, tautomerism was fast, and the different tautomeric forms could not be separated. Thus the tautomeric equilibrium mixture was observed. The tautomeric proportions in carbon disulfide solution at 31°C for some 2,5-dialkyl-3-hydroxythiophene systems are given in Table 7. The equilibrium constants for the 2,5-dimethyl-3-hydroxythiophene system in various solvents are given in Table 8.[156] The 2,5-dichloro-3-hydroxythiophene system was found by NMR to exist in equal amounts of **271** and **272**.[132] The tautomeric equilibria were also determined for **271** $\rightleftharpoons$ **272**, where $R^5 = C_6H_5$, $R^2 = CH_3$, and where $R^5 = CH_3$ and $R^2 = C_6H_5$. K was found to be 0.67 and 0.35, respectively[100] (see also Reference 43). Some 3-hydroxythiophene systems with various aromatic heterocyclic rings, such as oxazoles, pyrazoles, or pyrimidines in the 2-position, seem to exist in the hydroxy forms.[127] Ionization potentials were also used for the determination of tautomeric equilibria in the gas phase of 2,5-dialkyl-3-hydroxy-

TABLE 7. TAUTOMERIC PROPORTIONS AND TAUTOMERIC EQUILIBRIA IN CARBON DISULFIDE SOLUTION AT 31° FOR SOME 2,5-DIALKYL-3-HYDROXYTHIOPHENE SYSTEMS

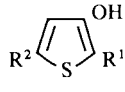
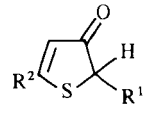
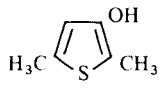
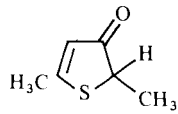
R^1	R^2			K (keto/enol)
CH_3	CH_3	32	68	2.13
CH_3	C_2H_5	35	65	1.86
CH_3	$CH(CH_3)_2$	39	61	1.56
CH_3	$C(CH_3)_3$	43	57	1.33
C_2H_5	CH_3	29	71	2.45
$C(CH_3)_3$	CH_3	26	74	2.85

TABLE 8. EQUILIBRIUM CONSTANTS FOR THE 2,5-DIMETHYL-3-HYDROXYTHIOPHENE SYSTEM IN VARIOUS SOLVENTS

Solvent	Dipole Moment			K (keto/enol)
–	–	36	64	1.78
Cyclohexane	0	33	67	2.03
Carbon disulfide	0	32	68	2.13
Chloroform	1.15	11	89	8.09
Acetone	1.66	49	51	1.04
Nitromethane	3.17	18	82	4.56

thiophenes and the analogous furans and selenophenes. The isomer ratio depended on the substituents, the nature of the heteroatom, and also on the relative evaporation rates from rapidly equilibrating samples.[149] 2-Amino-4-hydroxythiophenes exist in the oxo form, according to NMR.[16]

4. Carbonyl-Substituted 3-Hydroxythiophenes

From investigations of the NMR and infrared (IR) spectra of a large number of carbalkoxy- and acetyl-substituted 3-hydroxythiophenes, it was claimed that they all existed in the hydroxy form independent of the position of the carbonyl-containing group.[42] However, in connection with complex chemical investigations of the thiophene analogues of salicylic acid, it was concluded that 3-hydroxy-4-carbethoxythiophenes consist of a tautomeric mixture of both forms. The conclusion was based on the effect on acidity of substituents in the 5-position.[151] 3-Hydroxy-2-cyanothiophenes also appear to exist exclusively in the hydroxy form.[43] On the other hand, 3-hydroxy-4-cyanothiophenes, such as 5-isopropyl-3-

hydroxy-4-cyanothiophene, exist as a tautomeric mixture containing 40% enol and 60% keto form.[38] For the very unstable 3-hydroxy-4-thiophene aldehyde, only the hydroxy form was observed.[101]

5. Dihydroxythiophenes

2,5-Dihydroxythiophene is claimed to exist completely in the dioxo form.[104] The 2,3-dihydroxythiophenes exist exclusively as 3-hydroxy-3-thiolen-2-ones, as shown by NMR and IR.[110] It could not be decided from NMR or IR spectra if the stable tautomeric form of **273** was **274** or **275**.[108]

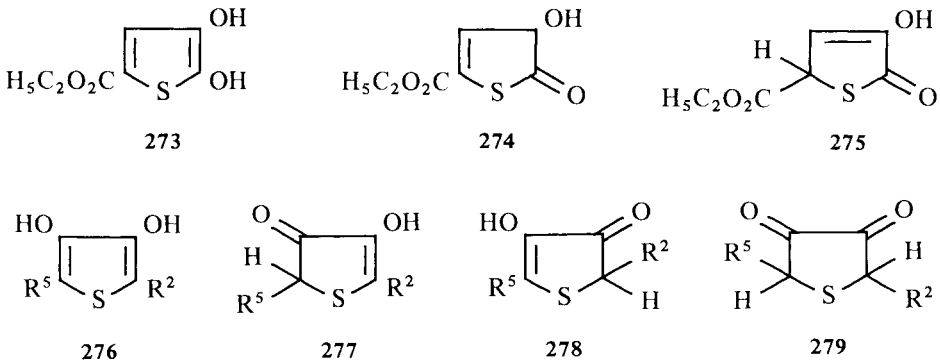
It was shown that 2,4-dihydroxythiophenes, also called thiotetronic acids, exist as 4-hydro-3-thiolen-2-ones.[110] However, it has been claimed that the dioxo form is the sole form in the solid state, and the predominant form in ether or dioxane solution, as shown by IR spectroscopy, and that in trifluoroacetic acid only the enol form exists.[152] For 3,4-dihydroxythiophenes, four tautomeric forms (**276** to **279**) are theoretically possible (Scheme 66).

If $R^2 = R^5 = H$ or CH_3, only tautomer (**277**) (equal to **278**) was observed. If $R^2 = H$, $R^5 = CH_3$, **278** was the stable tautomer, whereas if R^2 and R^5 are ethoxycarbonyl groups, only the dihydroxy form **276** was observed.[110]

IV. PHYSICAL PROPERTIES OF THE HYDROXYTHIOPHENE SYSTEMS

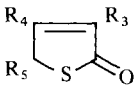
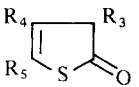
1. Ultraviolet Spectra of the Hydroxythiophene Systems

The UV spectra of some 2-hydroxythiophenes existing in the 3-thiolen-2-one and 4-thiolen-2-one forms are given in Table 9, where 2,4- and 2,3-dihydroxythiophenes existing in the 3-thiolen-2-one form are also collected. 3-Thiolen-2-one and its 3- and 4-substituted derivatives show a band at 220 nm, which is substituent



Scheme 66

TABLE 9. ULTRAVIOLET DATA OF 2-HYDROXYTHIOPHENE SYSTEMS IN ETHANOL SOLUTIONS, λ_{max} (nm), log ϵ

Substituent	 λ_{max}	log ϵ	 λ_{max}	log ϵ	Reference
	220	(3.79)	263(3.34)		86, 93, 154
R_3 = Me	223	(3.84)	260(3.36)		92
R_4 = Br	235	(4.02)	268(3.32)		92
R_3 = Br	238	(3.75)	265(3.33)		92
R_3 = OMe	245	(3.90)	268(3.29)		92
R_5 = Me	265	(3.36)		268(3.11)	93
	216(3.82)	265(3.34)		216(3.80), 266(3.31)	155
$R_5 = C_3H_7$	265	(3.46)		268(3.18)	93
$R_5 = C_4H_9$	265	(3.41)		268(3.31)	93
$R_5 = i\text{-}C_3H_7$	265	(3.29)		268(3.37)	93
$R_5 = t$-Bu	278	(3.36)		270(3.33)	93
	220(3.83)	268(3.39)		219(3.80), 268(3.39)	
$R_5 = CH_2CH{=}CH_2$	220	(3.6)	268	(3.2)	104
R_4 = OH	232(4.0)	263(3.6)			110
	284(3.6)	350(2.9)			
R_4 = OH, $R_5 = CH_3$	233(4.0)	262(3.4)			110
	286(3.4)	356(2.9)			
$R_3 = CO_2Et$, R_4 = OH	232(4.1)	245(4.2)			110
	267(3.9)				
$R_3 = CO_2Et$, R_4 = OH, $R_5 = CH_3$	233(4.2)	246(4.1)			
	268(3.8)				
R_3 = OH	248(3.9)	246(4.1)			
R_3 = OMe	244(3.9)	268(3.3)			
R_3 = OH, R_5 = Me	247(3.9)	264(sh)			110
R_3 = OH, R_4 = Me	249(3.9)	266(sh)			

dependent, while a second band at 265 nm is not affected by the substituents.[92] The 5-alkyl-3-thiolen-2-one form also shows two bands, one around or below 220 nm, which was not reached in the first measurement,[93] and a second peak at 265 to 270 nm.[137] Clear assignments of these bands to definite transitions have not been made.[137] As mentioned previously, simple alkyl 3-hydroxythiophenes exist as a tautomeric equilibrium of **271** and **272**. In Figure 2 the UV spectrum of the tautomeric mixture of the 2,5-dimethyl-3-hydroxythiophene system is compared with those of the locked methylation products, 2,5-dimethyl-3-methoxythiophene and 2,2,5-trimethyl-4-thiolen-3-one.[100,153]

The UV spectra of some cyano-substituted 3-hydroxythiophenes are given in Table 10. No differences were observed on changing the solvent from hexane to ethanol, and the spectra of the methoxy derivatives were the same as those of the hydroxy derivatives.

As previously mentioned, 3,4-dihydroxythiophene exists in forms such as **277** and **278**, and the UV spectra for some derivatives are given in Table 11. The UV spectrum of **276** ($R^2 = R^5 = CO_2Et$), which exists in the dihydroxy form, shows the following spectrum: λ_{max} nm (log ϵ) 287(4.3), 295(4.3), 326(3.8).[31,33,110] UV spectroscopy has been used for determination of acidity constants (see Section IV.5).

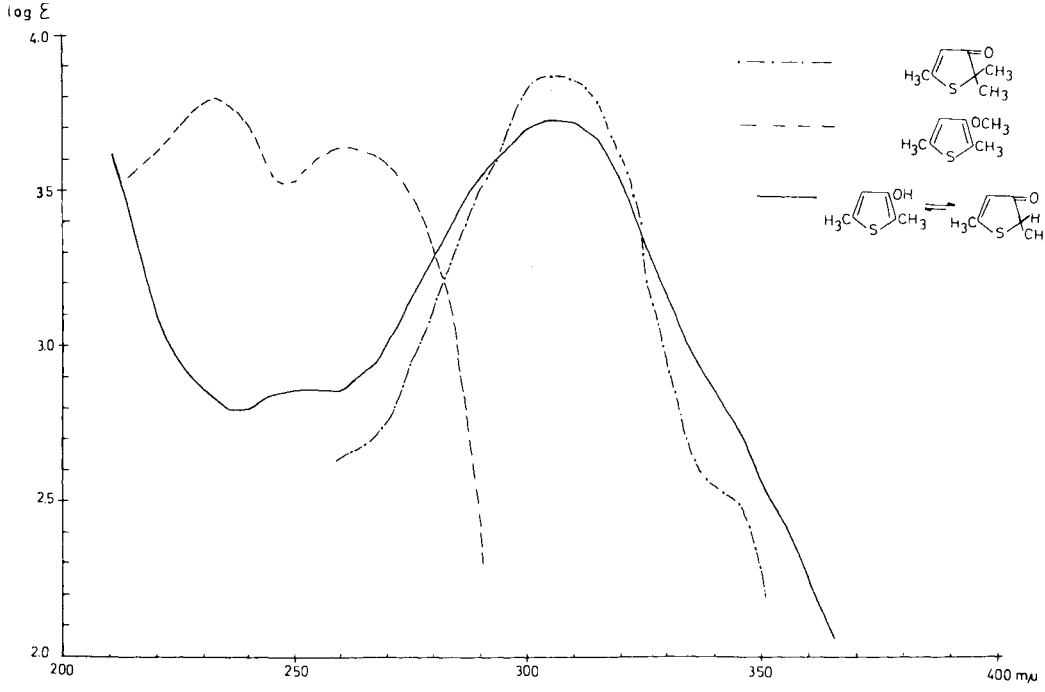
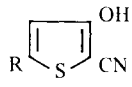


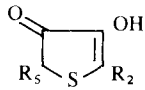
Figure 2. Ultraviolet spectra of the 2,5-dimethyl-3-hydroxythiophene system, 2,5-dimethyl-3-methoxythiophene and 2,2,5-trimethyl-4-thiolen-2-one in cyclohexane solution at 25°C.

TABLE 10. UV SPECTRA OF SOME 3-HYDROXY-2-CYANOTHIOPHENES



Solvent	Hexane		EtOH		
	λ_{max}	log ϵ	λ_{max}	log ϵ	Reference
R = CH_3	257	(4.08)	257	(4.04)	43
R = *i*-C_3H_7	258	(4.08)	258	(4.07)	43
R = *t*-C_4H_9	257	(4.09)	258	(4.08)	43
R = C_6H_5	283	(4.10)	283	(4.20)	43

TABLE 11. UV SPECTRA OF SOME 3,4-DIHYDROXYTHIOPHENE SYSTEMS, λ_{max} (in nm), log ϵ



Substituent		Reference
$R_2 = R_5 = H$	335(sh)	110
$R_2 = CH_3$, $R_5 = H$	255(3.0), 343(3.8)	110
$R_2 = R_5 = CH_3$	254(3.0), 342(3.8)	110
$R_2 = CO_2C_2H_5$, $R_5 = H$	290(4.0), 297(4.0)	110
	328(3.8), 342(sh)	110

2. Infrared Spectra of the Hydroxythiophene Systems

IR spectra have mainly been investigated in connection with the determination of tautomeric structures and of chelation in hydroxythiophenes containing orthocarbonyl substituents. The carbonyl absorptions of 5-substituted 3-thiolen-2-ones occur in the interval 1695 to 1670 cm^{-1}, and for the 4-thiolen-2-ones at 1750 to 1730 cm^{-1}. Both these intervals have rather large shifts toward lower frequencies compared with the corresponding oxygen analogues, which absorb between 1740 and 1760 cm^{-1}.[93] The 3- and 4-substituted 2-hydroxythiophene systems, which can be isolated only in the thermodynamically stable 3-thiolen-2-one form, also have their carbonyl absorption in the same interval as the 5-substituted 3-thiolen-2-ones.[92] The carbonyl-stretching frequencies of the two thiolactone forms of the 5-chloro- and 5-fluoro-2-hydroxythiophene systems occur within different intervals, but the bands are displaced toward each other.[96] There are also other very useful bands which can be used to establish the mutual purity of isomers. Thus, all 4-thiolen-2-ones have a comparatively strong band at 985 to 971 cm^{-1}, whereas the 3-thiolen-2-ones have a band in the 805 to 970 cm^{-1} region.[93] In all these alkyl hydroxythiophene systems no OH stretching is observed.

The 3-hydroxythiophene system and its simple alkyl derivatives show, as

expected, both an OH-stretching band at 3300 to 3600 cm^{-1}, depending upon solvent and hydrogen-bonding situation, and a carbonyl-stretching band at 1655 to 1680 cm^{-1}.[88,100,156]

The 2-hydroxy-5-carbethoxythiophene system, which exists, as mentioned previously, as a mixture of two tautomeric forms, shows a broad band at 3500 to 3050 cm^{-1} in the liquid state, and in the C=O-stretching region two bands at 1650 cm^{-1} and 1710 cm^{-1}. Changes in the IR spectrum in these regions upon dilution in carbon tetrachloride were discussed in terms of hydrogen bonding.[104] Orthocarbonyl-substituted hydroxythiophenes all show OH-stretching in the 2900 to 3300 cm^{-1} region.[143] The C=O-stretching frequencies of the carbonyl groups often fall in the same region as those expected for the 3-oxo form. The 3-hydroxy-2-cyanothiophenes showed a strong band at 3130 to 3190 cm^{-1} and a weaker band at 3570 to 3850 cm^{-1}, which were ascribed to chelated and free hydroxyl groups.[43]

The IR spectrum of the 2,3-dihydroxythiophene system is also in accordance with its existence as 3-hydroxy-3-thiolen-2-one. A broad band is observed at 3320 cm^{-1}, and C=O- and C=C-stretching bands around 1680 cm^{-1} and 1645 cm^{-1}, respectively.[110] The 2,4-dihydroxythiophene systems existing as 4-hydroxy-3-thiolen-2-ones show similar bands.[110] Finally, the 3,4-dihydroxythiophene systems show OH-stretching at 3300 to 3400 cm^{-1} and C=O- and C=C-stretching at 1670 and 1645 cm^{-1}.[110]

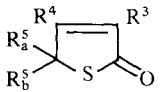
3. NMR Spectra of the Hydroxythiophene Systems

The ^1H NMR spectra have been of utmost importance for the understanding of the tautomerism of hydroxythiophenes. Even 40 MHz spectra of the 3- and 4-thiolen-2-one were generally first order, and couplings to the side-chain could also be resolved. Long-range couplings (2.5 Hz) over five bonds were observed in 5-alkyl-4-thiolen-2-ones.[93] This coupling is considerably larger than for 3-methyl-3-thiolen-2-one.[92] In 5-ethyl- and 5-*n*-propyl-3-thiolen-2-one the couplings of the 5-hydrogen to the α-hydrogens in the side-chain have different magnitudes due to their prochiral nature.[93]

In 3-thiolen-2-one the coupling constants (~6.1 Hz) between the 3- and 4-hydrogens are larger than J_{34} in thiophenes,[93] which in 5-nitro-2-hydroxythiophene was 4.1 Hz.[157] The NMR spectra of 5-bromo- and 5-chloro-3-thiolen-2-one have been analyzed in detail.[106] Shifts and coupling constants of the various tautomers of the 2-hydroxythiophene system have been collected in Tables 12 and 13. The spin-spin couplings of 13 Hz between H^1 and H^2 and of 92.5 to 92.8 Hz between H^1 and N^{15} were used as evidence that **281** was the stable tautomer in the system **280** to **282**[158] (Scheme 67).

The orthocarbonyl-substituted derivatives, which exist in the hydroxy form, generally show shifts and coupling constants expected for thiophenes, except for the J_{45}-coupling in 3-acetyl-2-hydroxythiophene and 3-carboethoxy-2-hydroxythiophene, which are unexpectedly large, 6.7 and 6.0 Hz, respectively.[143] Shifts and coupling constants for various 3-hydroxythiophene systems are given in Tables 14 and 15; see also Reference 159.

TABLE 12. ^{1}H NMR SHIFTS AND COUPLING CONSTANTS OF 3-THIOLEN-2-ONES

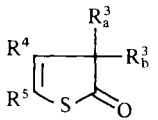


R^3	R^4	R^5_b	δR^3	δR^4	δR^5_a	δR^5_b	J_{34}Hz	J_{35}Hz	J_{45}Hz	Solvent	Reference
H	Br	H	6.65		4.51	4.51		1.8		Cyclohexane	92
H	H	Br	6.37	7.61	6.34		6.1	1.2	2.9	CCl_4	106
			5.68	6.66	5.51		5.8	1.1	3.0	C_6D_6	106
Br	H	H		7.99	4.75	4.75			3.1	Cyclohexane	92
Br	OH	H		~8	3.39	3.39				$(CD_3)_2SO$	110
H	H	Cl	6.48	7.76	6.61		5.95	1.20	2.90	$(CH_3)_2CO$	96
			6.37	7.51	6.37		6.0	1.3	2.8	CCl_4	106
H	H	F	7.71	4.45	7.17		6.14	−0.80	2.77	$(CH_3)_2CO$	96
			$\delta_F = 0.72$ ppm upfield C_6F_6; $J_{F-H_3} = -2.07$ Hz; $J_{F-H_4} = 4.06$ Hz; $J_{F-H_5} = 52.49$ Hz								
H	H	H	6.47	7.84	4.29	4.29	5.90	2.00	2.80	Cyclohexane	92
H	OH	H	5.37	~9	4.00	4.00				$(CD_3)_2SO$	110
OH	H	H	~6.52	6.40	3.87	3.87				$CDCl_3$	110
Br	OH	CH_3		7.3	3.63	1.39				$(CD_3)_2SO$	110
H	H	CH_3	6.12	7.40	4.48		6.0	2.0	2.7	CCl_4	93
H	CH_3	H	6.05	2.22			1.50	1.50	0.75	$CDCl_3$	97
CH_3	H	H	1.93	7.30			1.5	1.9	3.0	$CDCl_3$-Cyclohexane	89
H	H	SCH_3	6.18	7.23	5.43	1.96	5.9	1.8	2.8		104
H	OH	CH_3	5.29	~7	4.29	1.51				$(CD_3)_2SO$	110
OCH_3	H	H	3.76	6.59	3.94	3.94			2.5	Cyclohexane	92
OH	CH_3	H	6.20	2.10	3.89	3.89				$CDCl_3$	110
OH	H	CH_3	6.32	6.10	4.10	1.55				$CDCl_3$	110
$NHCOCH_3$	H	H		7.89	4.03	4.03			3.1	$CDCl_3$	134
C_2H_5	H	H	2.33(CH_2)	7.25	3.97	3.97	1.5	2.0	2.9	$CDCl_3$	164
H	CH_3	CH_3	5.95	2.14	4.32	1.58	1.4		0.7	$CDCl_3$	97
CH_3	H	CH_3	1.83	7.27	4.41	1.57	1.4	2.0	3.0	$CDCl_3$	94

TABLE 12. (*Continued*)

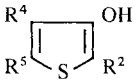
R^3	R^4	R^5_b	δR^3	δR^4	δR^5_a	δR^5_b	J_{34}Hz	J_{35}Hz	J_{45}Hz	Solvent	Reference
H	H	CH_2—CH=CH_2	6.15	7.40	4.45		6.0	2.0	2.6		104
CH_2—CH=CH_2	H	H	3.00(CH_2)	7.23	3.96	3.96	1.4	1.9	2.8		164
H	H	$(CH_2)_2OH$	6.1	7.3							168
H	H	$(CH_2)_2CH_3$	6.10	7.42	4.39		6.1	2.0	2.5	Cyclohexane	93
$CH(CH_3)_2$	H	H	2.67(CH)	7.14	3.93	3.93	1.2	1.4	2.9		164
H	2-Thienyl	H	6.49		4.39	4.39		1.50			133
$CH(CH_3)CH=CH_2$	H	H	3.3(CH)	7.16	2.94	2.94	1.0	1.2	3.0		164
$CH_2CH=CH-CH_3$	H	H	2.93(CH_2)	7.16	3.93	3.93	1.5	2.0	2.9		164
$CH_2CO_2C_2H_5$	H	H	3.34(CH_2)	7.53	4.06	4.06	1.2	1.5	2.8		164
H	H	$(CH_2)_3CH_3$	6.21	7.50	4.42		6.3	2.0	2.8	Cyclohexane	93
$C(CH_3)_3$	H	H	1.22	7.19	3.88	3.88			2.90	$CDCl_3$	95
H	H	$C(CH_3)_3$	6.15	7.43	4.27		6.1	2.1	2.5	Cyclohexane	93
H	$SC(CH_3)_3$	H	6.02	1.45	3.91	3.91		1.5		CCl_4	111
1-Cyclopentenyl	H	H		7.20	4.01	4.01			3.0		105
3-(2-Pentenyl)	H	H		7.24	3.94	3.94			3.0		105
5-Methyl-3-thienyl	H	CH_3		7.35	4.40	1.57			3.05	$CDCl_3$	90
H	H	3-Cyclohexanone	6.3	7.5						$CDCl_3$	168
H	H	$CH_2C_6H_5$	6.07	7.23	4.52		3.0	1.9	2.5		104
$CH_2C_6H_5$	H	H	3.56(CH_2)	6.94	3.83	3.83	1.5	1.8	2.8		164
		E		6.80	3.82	3.82			3.0		
3-Phenyl-2-propene	H	H									105
		Z		7.20	3.87	3.87			3.0		
5-*t*-butyl-3-thienyl	H	$C(CH_3)_3$		7.50	4.25				3.0	$CDCl_3$	90

TABLE 13. ^{1}H NMR SHIFTS AND COUPLING CONSTANTS OF 4-THIOLEN-2-ONES



R^3_a	R^3_b	R^5	δR^3_a	δR^3_b	δR^4	δR^5	J_{34}Hz	J_{35}Hz	J_{45}Hz	Solvent	Reference
H	H	F	3.71	3.71	5.41		2.85	6.40	8.70	$(CH_3)_2CO$	96
(δF = 55.15 ppm downfield from C_6F_6)											
H	H	CH_3	3.34	3.34	5.45		2.60	2.60	1.60	CCl_4	93
H	H	SCH_3	3.45	3.45	5.60	2.38	2.8				104
H	H	C_2H_5	3.27	3.27	5.43		2.50	2.50	1.50	CCl_4	93
H	H	$CH_2CH{=}CH_2$	3.32	3.32	5.48		2.5				104
H	H	$CH(CH_3)_2$	3.33	3.33	5.49		2.80	1.90	1.40	CCl_4	93
H	H	$(CH_2)_2CH_3$	3.25	3.25	5.42		2.60	2.10	1.50	CCl_4	93
H	H	2-Thienyl	3.56	3.56	5.97			3.0		CCl_4	93
H	H	$C(CH_3)_3$	3.31	3.31	5.43		2.80			CCl_4	93
H	H	$(CH_2)_3CH_3$	3.37	3.37	5.55		2.80	2.00	1.40	CCl_4	93
$-(CH_2)_4-$		H			6.65	6.30			7.5	$CDCl_3$	105
$-C(C_2H_5)_2-$		H			6.60	6.50			7.5	$CDCl_3$	105
CH_3	$C(CH_3)_3$	H	1.20	1.01	5.91	6.60			7.80	$CDCl_3$	95
H	H	$CH_2C_6H_5$	3.23	3.23	5.35		2.4				104
H	H	C_6H_4-4-CH_3	3.65	3.65	6.06		3.0				184
C_6H_5 C_2H_5 $\diagdown$ $\diagup$ $-C-$		H			6.53	6.35			7.5	$CDCl_3$	105
$CH_2C_6H_5$	$CH_2C_6H_5$	CH_3			5.44	1.82			1.60	$CDCl_3$	94

TABLE 14. ^{1}H NMR SHIFTS AND COUPLING CONSTANTS OF 3-HYDROXYTHIOPHENES



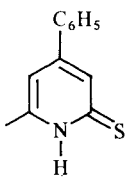
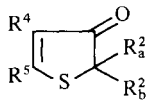
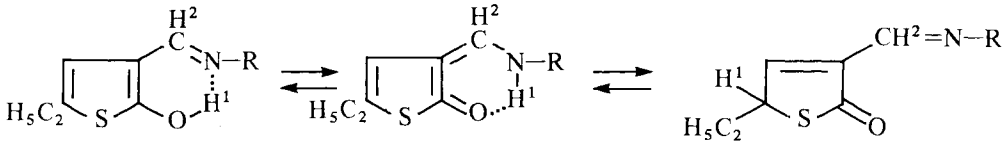
R^2	R^4	R^5	δR^2	δOH	δR^4	δR^5	J_{45}Hz	Solvent	Reference
CH_3	H	H	2.15	6.21	6.43	6.72	5.5	CS_2	99
CN	H	CH_3		8.88				$(CD_3)_2CO$	43
H	$NHCOCH_3$	H	6.18		2.11	7.31			72
CH_3	H	CH_3	2.09	6.65	6.15	2.25		CS_2	99
C_2H_5	H	CH_3		7.04	6.18	1.91	1.1	CS_2	156
CH_3	H	C_2H_5	2.11	6.49	6.20	2.61 (CH_2)	0.7	CS_2	156
CN	H	$CH(CH_3)_2$		8.22				$CDCl_3$	43
$C(CH_3)_3$	H	H	1.32	6.37	6.45	6.65	5.5	CS_2	99
CH_3	H	$CH(CH_3)_2$	2.12	6.37	6.20	2.85 (CH)	0.7	CS_2	156
				7.68				CS_2	
CN	H	$C(CH_3)_3$		8.13				$CDCl_3$	43
$C(CH_3)_3$	H	CH_3	1.16		6.19	2.34	1.1	CS_2	156
CH_3	H	$C(CH_3)_3$	2.10		6.23	1.21		CS_2	156
C_6H_5	H	CH_3		5.52				$CDCl_3$	43
3-Phenyl-5-oxazolyl	H	H			6.90	7.25	5.30	$(CD_3)_2SO$	127
5-Phenyl-3-pyrazolyl	H	H			6.95	7.40	5.30	$CDCl_3$	127
	H	H			6.80	7.50	5.40	$CDCl_3$	127
1,5-Diphenyl-3-pyrazolyl	H	H			7.00	7.45	5.30	$(CD_3)_2SO$	127
2,6-Diphenyl-4-pyrimidyl	H	H			6.70	7.60	5.40	$CDCl_3$	127
$CH(C_6H_5)CHCO_2C_2H_5$	H	C_6H_5		3.95	6.88	~7.27		$CDCl_3$	27

TABLE 15. ^{1}H NMR SHIFTS AND COUPLING CONSTANTS IN 4-THIOLEN-3-ONES



R^2_a	R^2_b	R^4	R^5	δR^2_a	δR^2_b	δR^4	δR^5	J_{25}Hz	J_{45}Hz	Solvent	Reference
H	CH_3	H	H	4.53	1.46	6.07	8.28		6.0	CS_2	99
H	H	OH	CH_3	3.7	3.7	5.9	2.10				110
H	CH_3	H	CH_3	3.68	1.44	5.85	2.33			CS_2	99
H	CH_3	OH	CH_3	3.6	1.40	5.9	2.10				110
H	C_2H_5	H	CH_3	3.67		5.84	1.96	0.8	1.2	CS_2	156
H	CH_3	H	C_2H_5	3.64	1.45	5.27	2.61 (CH_2)	0.6	1.1	CS_2	156
H	CH_3	H	$CH(CH_3)_2$	3.58	1.44	5.85	2.85 (CH)		0.8	CS_2	156
H	$C(CH_3)_3$	H	CH_3	3.49	1.04	5.80	2.27	0.6	1.1	CS_2	156
H	CH_3	H	$C(CH_3)_3$	3.61	1.44	5.90	1.26			CS_2	156
H	H	H	NHC_6H_5	3.7	3.7	5.5				$CDCl_3$	67
H	C_6H_5	H	CH_3	4.76	7.2–7.5	5.90		0.9		$CDCl_3$	43
H	$C(CH_3)_3$	H	$C(CH_3)_3$	3.50	1.10	5.95	1.32			$CDCl_3$	91
$C(CH_3)_3$	*o*-2,5-di-t.-Butyl-3-thienyl	H	$C(CH_3)_3$	1.2		6.31	1.22			$CDCl_3$	91



280 281 282

Scheme 67

4. Mass Spectra of the Hydroxythiophene Systems

The mass spectra of a number of hydroxythiophenes existing as such or in the thiolactone forms have been discussed. These compounds fragment in a well-defined manner on electron impact. In compounds containing adjacent OH and CO_2R substituents, base peaks, or very prominent peaks, corresponding to M-ROH ions are observed.[160] Ionization potentials for 2-hydroxythiophene systems[141] and 3-hydroxythiophene systems[149] have been determined.

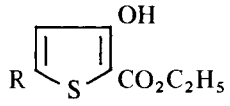
5. Acid Dissociation Constants of Hydroxythiophenes

The apparent pK_a values for the 5-methyl- and *t*-butyl-2-hydroxythiophene system were determined by UV spectrophotometric and potentiometric titration methods, and the individual pK_a values for the 3-thiolen-2-one and 4-thiolen-2-one forms were calculated. From the values given in Table 16 it can be seen that the C—H acidities of these compounds are of the same magnitude as the OH acidities of the corresponding phenols.[137] The apparent pK_a value of the 2,5-dimethyl-3-hydroxythiophene system was found by potentiometric titration to be 10.79 and was compared with those of the corresponding furans and selenophenes.[156] The pK_a values for a number of 2-substituted 3-hydroxythiophenes such as 2-formyl-, 2-cyano-, 2-acetyl-, 2-carbamoyl-, 2-(2-pyrimidyl)-, and 2-(2-tetrazolyl)-3-hydroxythiophene, in water–dimethyl sulfoxide, have been determined by potentiometric titration and extrapolated to zero ionic strength. Each 3-hydroxythiophene was more acidic than its benzene analogue, but the substituent effects are different in the two series. On the other hand, a linear correlation between the pK_a values of 2-substituted 3-hydroxythiophenes and the pK_a values of 4-substituted phenols in water was observed.[125] The acidity constants of the hydroxy systems **283** and **284** have been determined by the UV spectroscopic technique in 10% aqueous dioxane.[151] The stability constants of their complexes with some divalent metal ions were determined, and the stability of the chelates of **283** was greater than that of the corresponding chelates of **284**[151,161] (Scheme 68).

The acidity constants of 2-acetyl- and 4-acetyl-3-hydroxythiophene have been determined both by UV spectrophotometry and by potentiometric titration. Again the complexes of the 3-hydroxy-2-carbonyl system showed higher stability, in spite

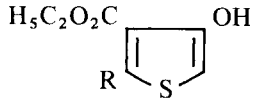
TABLE 16. APPARENT AND INDIVIDUAL pK_a-VALUES OBTAINED BY UV-SPECTROPHOTOMETRIC AND POTENTIOMETRIC TITRATION METHODS

Compound	UV-Spectrophotometric Buffers	$pK_{a\ app}$	pK_a (α, β)	pK_a (β, γ)
5-Methyl-thiolen-2-one	$Na_2B_4O_7$ + NaOH	10.28 ± 0.08	10.26	8.84
5-Methyl-thiolen-2-one	$NaHCO_3$ + NaOH	10.09 ± 0.05	10.07	8.65
5-*t*-Butyl-thiolen-2-one	$Na_2B_4O_7$ + NaOH	10.53 ± 0.05	10.52	9.03
5-*t*-Butyl-thiolen-2-one	$NaHCO_3$ + NaOH	10.44 ± 0.03	10.43	8.94
5-Methyl-thiolen-2-one	Potentiometric	10.18 ± 0.03	10.16	8.75
5-*t*-Butyl-thiolen-2-one	Potentiometric	10.53 ± 0.08	10.52	9.03



283

R = H, CH_3, C_6H_5
p-biphenylyl,
α-naphthyl



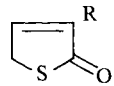
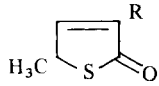
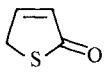
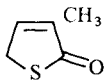
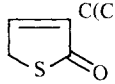
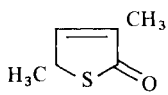
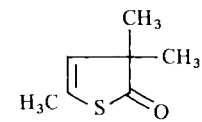
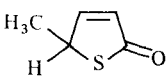
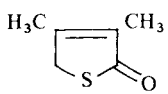
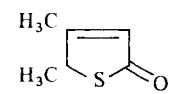
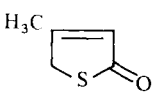
284

R = H, CH_3, C_6H_5

Scheme 68

of the lower basicity, due to the quasi-aromatic nature of the chelate ring.[162] The catalytic properties in H_2O_2 decomposition of the Cu^{2+} chelates of 2-acetyl-3-hydroxythiophene and 3-acetyl-4-hydroxythiophene have also been investigated and related to the bond orders of the 2,3- and 3,4-carbon bond of the ring.[163]

TABLE 17. ALKYLATION OF 3-THIOLEN-2-ONES, 3-METHYL-, AND 3-*t*-BUTYL-3-EXTRACTION METHOD WITH METHYL IODIDE AND DIMETHYL

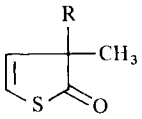
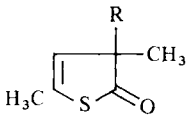
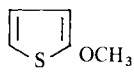
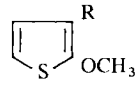
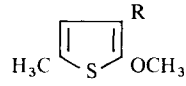
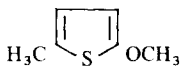
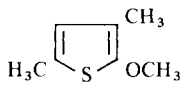
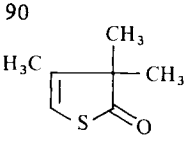
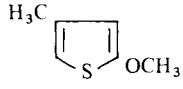
			Products and Relative Yields	
Substrate	Reagent	Yield (%)		
	CH_3I	53 R=CH_3	59.0	4.5
	$(CH_3O)_2SO_2$	87	3.6	–
	CH_3I	64 R=CH_3	9	6
	$(CH_3O)_2SO_2$	74	6	–
	CH_3I	72 R=$C(CH_3)_3$	23	15
	$(CH_3O)_2SO_2$	78	15	–
				
	CH_3I	53	86	2
	$(CH_3O)_2SO_2$	89	4	2
				
	CH_3I	49	84	3

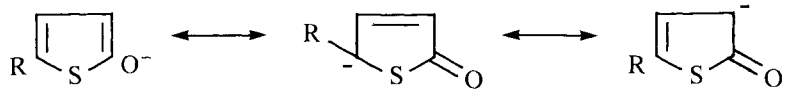
V. REACTIONS OF THE HYDROXYTHIOPHENE SYSTEMS

1. Alkylation of 2-Hydroxythiophene Systems

The noncarbonyl-substituted hydroxythiophenes give a trident carbanion (**285** to **287**) under basic conditions. Depending on the reaction conditions and the electrophile used, this carbanion can be alkylated in various positions (Scheme 69). Methylation of the sodium salt of 5-methyl-2-hydroxythiophene with excess methyl iodide occurs in low yield (18%), predominantly in the 3-position, yielding the 3,5-dimethyl-3-hydroxythiophene system. Some dialkylation of the 3-position is also observed.[94] Similar results were obtained upon reaction with allyl bromide and benzyl bromide, although the yields were somewhat better, namely, 33% and 28%, respectively.[94]

THIOLEN-2-ONE, 4-METHYL-, AND 5-METHYL-3-THIOLEN-2-ONE BY THE ION-PAIR SULFATE

Products and Relative Yields				
				
8.7	1.3	21.6	3.9	1.0
–	–	94.0	2.4	–
55	2	–	28	–
4	–	–	90	–
12	4	37	9	–
–	–	–	85	–
				
12	–			
90	4			
				
4	9			



285 286 287

Scheme 69

The low yields are most probably due to ring opening under these conditions. Use of the harder electrophile, dimethyl sulfate, gave 2,5-dimethyl-3-methoxythiophene and the 3,5-dimethyl-3-hydroxythiophene system in a 2:1 ratio.[94] Much higher overall yields and better selectivity were obtained using the ion-pair extraction method in the methylation, as shown in Table 17 for the methylation of 2-thiolen-3-one and some alkylated derivatives.[95,97] The soft electrophile methyl iodide predominantly gives methylation of the 3-carbon. Only by using the bulky *t*-butyl group in the 3-position can some increased alkylation in the 5-position be observed, and *O*-alkylation is also increased in comparison with the 3-methyl-3-thiolen-2-one system.[95] Almost exclusive *O*-methylation is observed when the hard electrophile dimethyl sulfate is used.

Thallium salts of the hydroxythiophene system have also been successfully alkylated.[164–166] The methylation of the 5-methyl-2-hydroxythiophene system with methyl iodide seems to be less selective than the ion-pair extraction method, since the O/C alkylated ratio was 1:2.[165] Solvent effects on the ethylation of the thallium(I) salts of 3-thiolen-2-one have been investigated (Table 18).[164] It is interesting to note that in ethanol no *O*-methylation occurred, although the O/C ratio was increased with increasing polarity of aprotic solvents. Alkylation of the thallium salts of 3-thiolen-2-one with isopropyl iodide, benzyl halides, allyl- and crotonyl halides leads to complex product mixtures. Increased steric demands of the electrophile gave, as expected, an increased O/C ratio for $CH_3 < C_2H_5 < CH(CH_3)_2$. Benzyl bromide leads to high *C*-alkylation in the 3-position (O/C = 0.1).[164]

The ion-pair extraction method was used to alkylate 3-thiolen-2-one with α-halocarboxylates to prepare α-(2-thienyloxy) fatty acid esters of interest as potential hypolipidemic agents.[167]

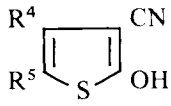
5-Phenyl-2-hydroxythiophene gave only a 39% yield of the methoxy derivative on methylation with dimethyl sulfate and sodium hydroxide. Attempts with diazomethane or methyl iodide were unsuccessful.[7]

TABLE 18. SOLVENT EFFECTS ON ETHYLATION OF THE THALLIUM(I) SALT OF 3-THIOLEN-2-ONE (IN %)

	Solvent			
Products	$(CH_3)_2NCHO$	CH_3CN	Petroleum Ether	C_2H_5OH
O/C-ratio	1.25	0.46	0.20	0
O-Ethyl	50	24	13	0
3-Ethyl	40	52	65	64
3,3-Diethyl	2	3	1	4
3,5-Diethyl	2	4	5	8
3,3,5-Triethyl	2	3	2	4
3-Thiolen-2-one	4	14	14	20

The reaction of 3-thiolen-2-one with trimethylsilyl chloride and trimethylsilyl diethylamide gave a 65% yield of 2-(trimethylsiloxy)thiophene.[168]

Alkylation of 2-hydroxy-3-cyanothiophene systems (**288**) occurs exclusively on the oxygen, giving the 2-methoxy derivative with methyl iodide in methanol sodium methoxide.[15] With α-bromocarbonyl compounds the corresponding ethers (**289**) are formed, which upon treatment with base were ring closed to thienofurans (**290**)[169] (Scheme 70).



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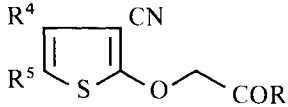

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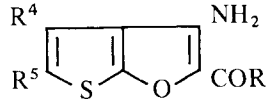
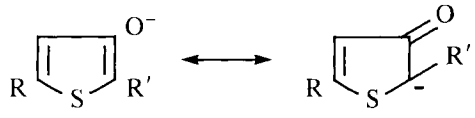


290

Scheme 70

2. Alkylation of the 3-Hydroxythiophene Systems

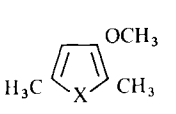
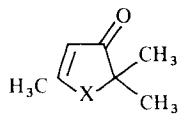
The anions of simple alkyl-3-hydroxythiophenes (**291** to **292**) show pronounced ambident character (Scheme 71). Alkylation of 2,5-dimethyl-3-hydroxythiophene system by the ion-pair extraction method has been compared with that of the corresponding furan and selenophene systems. The results are given in Table 19. The hard electrophile dimethyl sulfate gives predominantly *O*-alkylation with the



291 **292**

Scheme 71

TABLE 19. METHYLATION OF 2,5-DIMETHYL-3-HYDROXYFURAN, -THIOPHENE, AND -SELENOPHENE SYSTEMS WITH METHYL IODIDE AND DIMETHYL SULFATE BY THE ION-PAIR EXTRACTION METHOD

			Products and Relative Yields	
Substrate	Reagent	Yield (%)		
2,5-Dimethyl-	CH_3I	37	2	98
-3-hydroxyfuran	$(CH_3O)_2SO_2$	[a]	54	46
2,5-Dimethyl-	CH_3I	66	35	65
-3-hydroxythiophene	$(CH_3O)_2SO_2$	91	90	10
2,5-Dimethyl-	CH_3I	53	15	85
-3-hydroxyselenophene	$(CH_3O)_2SO_2$	53	93	7

[a] The product contained $(CH_3O)SO_2$.

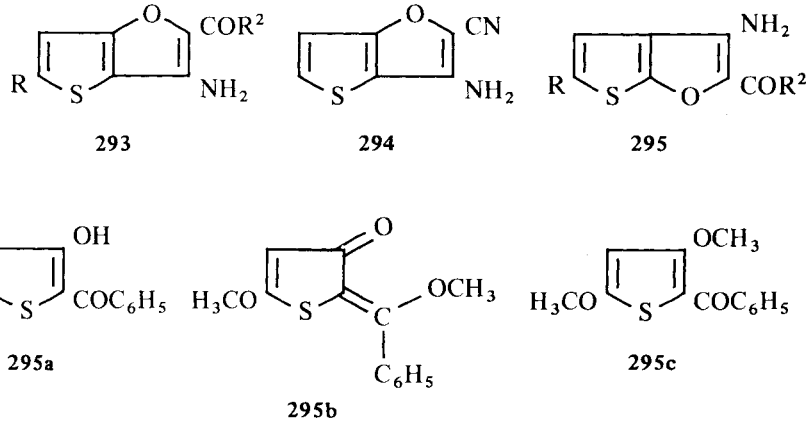
thiophene and selenophene system, whereas the less aromatic furan system gives about equal amounts of *O*- and *C*-alkylation.[100] The soft methyl iodide gives almost exclusively *C*-alkylation with furan; the thiophene system gives 65% *C*-alkylation and 35% *O*-alkylation. Alkylation of 2-*t*-butyl-5-methyl-3-hydroxythiophene with methyl iodide occurred only at the oxygen due to steric hindrance, giving a 33% yield of 2-*t*-butyl-3-methoxy-5-methylthiophene.[100] 2-Phenyl-4-hydroxythiophene gives *O*-methylation with dimethyl sulfate.[7] The photochemistry of 2,2-dimethyl-3(2H)-thiophenone has been studied.[170]

3. Alkylation of Orthocarbonyl-Substituted 3-Hydroxythiophenes

Orthocarbonyl-substituted 3-hydroxythiophene systems are exclusively alkylated on oxygen. Methoxy derivatives have been obtained using dimethyl sulfate and sodium hydroxide,[43,66,171] or sodium carbonate,[55] diazomethane,[38,42,58,74] and even by reaction with methanol and *p*-toluenesulfonic acid.[72] Ethylation has been achieved through reaction with triethyloxonium fluoroborate[44] or with ethanol and *p*-toluenesulfonic acid.[72] Sodium salts have been allylated through the reaction with allyl bromide in anhydrous DMF[172] and reacted with epichlorohydrine to give the 2,3-epoxy-1-oxypropane derivative.[173] *O*-Alkylation of 3-hydroxy-2-cyano-substituted thiophenes followed by Thorpe-Ziegler cyclization was used for the synthesis of **293** and **294**[124,174] (Scheme 72). Compound **295** was obtained analogously from 2-hydroxy-3-cyanothiophenes.[169]

Reaction of **295a** with diazomethane was exceptional in giving a mixture of **295b** (62%) and the expected **295c** in 15% yield.[42]

3,4-Dihydroxy-2,5-carbonyl-substituted thiophenes, easily available through the Hinsberg reaction, have been methylated by diazomethane.[32,72,175] The disodium salt was benzylated with benzyl chloride in DMF[35] and ethylated with diethyl



Scheme 72

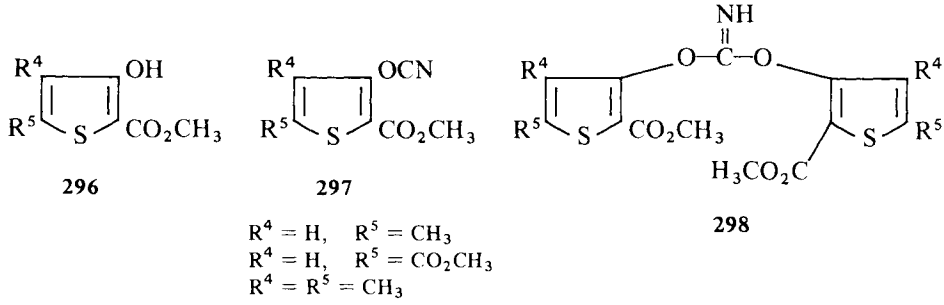
sulfate.[34] The methylene dioxy derivatives were obtained on reaction with bromochloromethane and potassium carbonate in DMF.[36] 3,4-Ethylenedioxythiophenes have also been prepared.[34,176] Methyl 3-hydroxy-5-methyl-2-thiophenecarboxylate was alkylated with chloroacetaldehyde diethyl acetal in DMF using sodium hydride as base and the product further transformed to 5-[(5-methyl-3-thienyl)oxy]-2-(1H)-pyrimidone which is of pharmaceutical interest.[290] Methyl 3-hydroxy-2-thiophenecarboxylate and its 4-chloro, 4-bromo, and 4,5-bromo derivatives were alkylated with methyl chloroacetate in DMSO in the presence of potassium *t*-butoxide at 90–100° or by methyl bromoacetate in boiling ethyl methyl ketone in the presence of potassium carbonate[291] and further transformed to 3-thienyloxy-acetic acids, which were chlorinated and brominated. The compounds which were prepared are given in Table 29.

4. Acylation of Hydroxythiophenes

Owing to the hard nature of acyl chlorides and acyl anhydrides, *O*-acylation has always been observed, even with hydroxythiophene systems which upon alkylation give large amounts of *C*-alkylation. Reaction with acyl chlorides has often been used for characterization of the labile hydroxythiophenes. Reaction with acetic anhydride and sodium hydroxide or sodium acetate,[32,85,89] with pyridine,[119] or triethylamine,[15] or in the presence of catalytic amounts of sulfuric acid or *p*-toluenesulfonic acid,[72,177,178] has been used for the preparation of acetoxythiophenes. Acetyl chloride has also often been used.[30,58,91–93,95,96,100,156,179]

Other esters that have been prepared in similar ways are benzoates,[85,88,92] 2,4-dinitrobenzoates,[88] carbamates,[38,88,180] methacrylates,[98] and malonates.[181] The formation of **219** from **218** is one example of the intramolecular esterification of a hydroxythiophene[112,115,122,123] that has been extensively investigated.

Reactions of 3-hydroxy-2-carbomethoxythiophenes (**296**) with cyanogen bromide in acetone in the presence of triethylamine at −10 to 15°C gave the cyanates (**297**). At higher temperatures the iminocarbonates (**298**) were also formed[182] (Scheme 73).

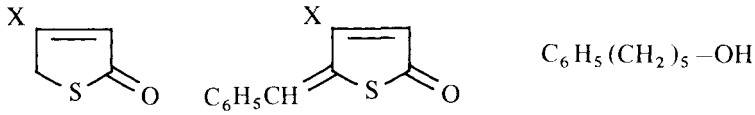


$R^4 = H, \quad R^5 = CH_3$
$R^4 = H, \quad R^5 = CO_2CH_3$
$R^4 = R^5 = CH_3$

Scheme 73

5. Condensation of Hydroxythiophene Systems with Carbonyl Compounds

2-Hydroxythiophene systems with active methylene groups in their unsaturated thiolactone tautomers can be condensed with aromatic aldehydes such as benzaldehyde, or ketones such as acetone, generally using acidic conditions (hydrogen chloride). In 2-hydroxythiophene itself and in 4-substituted 2-hydroxythiophene the active methylene group is in the 3-position of the 4-thiolen-2-one form and in the 5-position of the 3-thiolen-2-one. It was shown that condensation of **299** occurs exclusively in the 5-position to give **300**, as Raney-nickel desulfurization and reduction with sodium borohydride gave **301**[85,92] (Scheme 74).

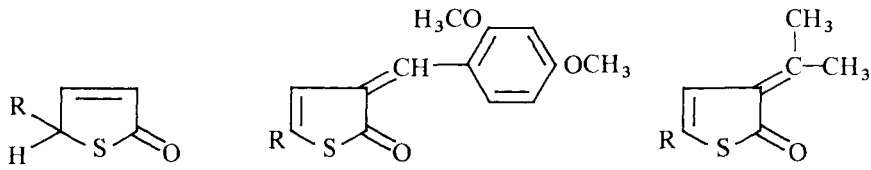


299 **300** **301**

X = H, Br

Scheme 74

This is in contrast to *C*-alkylation which, as discussed previously, occurs in the 3-position. 5-Substituted 2-hydroxythiophenes (**302**) can only react in the 3-position and, with piperonal as aldehyde crystalline condensation products (**303**), were also obtained with the longer chain substituents.[93] From 5-fluoro- and 5-chloro-4-thiolen-2-one, the 3-benzylidene derivatives were prepared.[96] With acetone, **302** (R = CH_3) gave the easily polymerized condensation product **304**[93] (Scheme 75).

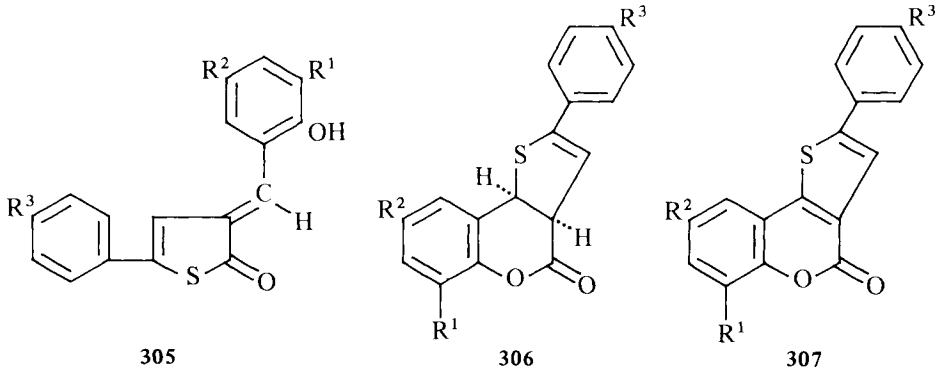


302 **303** **304**

R = CH_3, C_2H_5, C_3H_7, C_4H_9, *t*-C_4H_9

Scheme 75

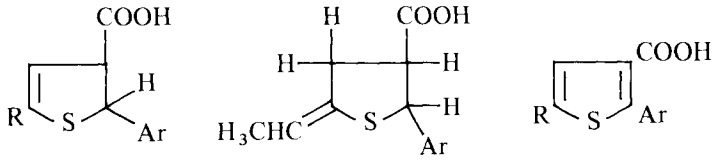
3-Substituted 2-hydroxythiophenes such as 3-methyl-2-hydroxythiophene can only react in the 5-position with benzaldehyde to give 5-benzylidene-3-methyl-3-thiolen-2-one.[89] From 2-hydroxy-3-cyanothiophenes, with a free 5-position, 5-arylidene-3-thiolen-2-ones were easily prepared by refluxing a mixture of the aldehyde and 2-hydroxy-3-cyanothiophene in propanol.[15] 5-Ethyl- and 5-aryl-substituted 2-hydroxythiophene systems have been condensed with salicylic aldehydes to give **305**,[183,184] which upon treatment with triethylamine gave a salicylidene–thiolactone rearrangement to yield **307** by way of **306** (Scheme 76).



305 306 307

Scheme 76

Treatment of compounds of type **303** with potassium hydroxide in methanol leads also to rearrangement, giving mixtures of **308**, **309**, and **310** depending on substituents. Thus **310a** and **310c** were obtained in 24 and 84% yields, respectively, while in the other cases mixtures of **308** and **309** were isolated[185] (Scheme 77).

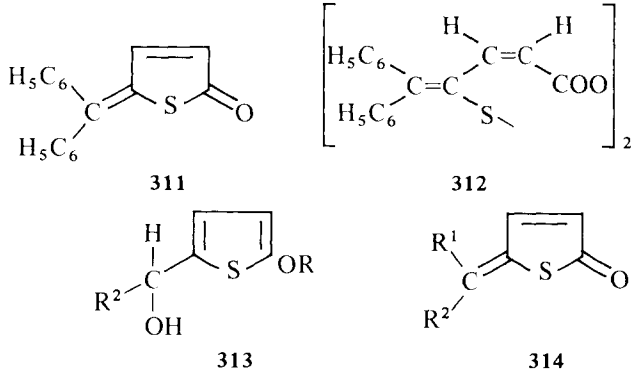


308 309 310

a. R = 4-$CH_3C_6H_4$, Ar = C_6H_5
b. R = 4-$CH_3C_6H_4$, Ar = 3-CH_3O-4-OH-C_6H_3
c. R = C_6H_5, Ar = 4-ClC_6H_4
d. R = CH_3CH_2, Ar = 4-ClC_6H_4
e. R = CH_3CH_2

Scheme 77

Treatment of **311** with 0.1 *N* potassium hydroxide solution at room temperature for five days gave the *cis* form **312** in 71% yield. When **311** was refluxed with aqueous 2*N* potassium hydroxide for 24 hours, the *trans* form corresponding to **312** was obtained in 37% yield[186] (Scheme 78).



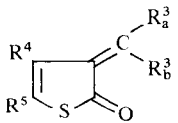
311 312

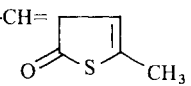
313 314

R = CH_3, *t*-Bu

Scheme 78

TABLE 20. CONDENSATION PRODUCTS OF 4-THIOLEN-2-ONES



C_n	R^3_a	R^3_b	R^5	Melting Point (°C)	Yield (%)	Reference
8	CH_3	CH_3	CH_3	59–62	48	93
11	C_6H_5		Cl	79–80	34.5	96
	C_6H_5		F	67–69	100	96
	C_6H_5		H	62	53	105
12	C_6H_5		CH_3	85–86	57	2
	C_6H_4–4-Cl		C_2H_5	67–68	32	185
	NHC_6H_5		CH_3	159–160	52	212
	NHC_6H_{11}		CH_3	152.5–153.5	65	212
13	C_6H_4–4-CHO		CH_3	167–168		2
	C_6H_5–3-OCH_2O-4		CH_3	136–137	100	93
	C_6H_3–2-OH-5-Cl		C_2H_5	164–165	81	183
	C_6H_4–4-OCH_3		CH_3	98		5
	C_6H_4–2-OH		C_2H_5	154–156	80	183
	NHC_6H_5		C_2H_5	99–100	43	121
	$NHCH_2C_6H_5$		CH_3	125–125.5	70	212
	$N(CH_3)C_6H_5$		CH_3	105–106	37	121
	NHC_6H_{11}		C_2H_5	136–137	80	212
14	C_6H_3–3-OCH_2O-4		C_2H_5	99–102	86	185
	C_6H_3–2-OH–3-OCH_3		H	126–128	56	183
	$N(CH_3)C_6H_5$		C_2H_5	77–78	53	121
	$NHCH_2C_6H_5$		C_2H_5	96–97	67	212
15	C_6H_3–3-OCH_2O-4		$(CH_2)_2CH_3$	95–96	48	93
16	2-Thienyl-3,4-dibromo-5-CH= 		CH_3	232–234		2

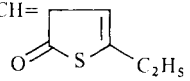
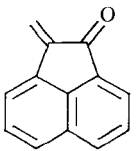
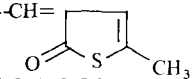
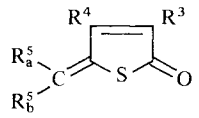
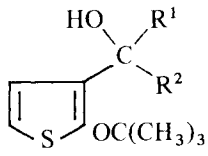
	C_6H_5	C_6H_5	H	103	54	105
	C_6H_4–3-OCH_2O-4		$(CH_2)_3CH_3$	57–58	80	93
	C_6H_4–3-OCH_2O-4		$C(CH_3)_3$	83–84	61	93
	$NH(CH_2)_2NH$–CH= 		C_2H_5	231–232	67	212
17			CH_3	164		2
	C_6H_4–4-Cl		C_6H_5	166–168	76	185
	C_6H_3–2-OH–5-Cl		C_6H_5	204–206	53	184
	C_6H_5		C_6H_5	64.5–65		7
	C_6H_4–2-OH		C_6H_5	172–173	89	184
	α-Naphthyl–2-OH		C_2H_5	165–167	85	183
	NH-β-naphthyl		C_2H_5	164–165	50	212
18	C_6H_5		C_6H_4-4-CH_3	119–120	46	185
	C_6H_4–2-OH		C_6H_4-4-CH_3	184–186	28	184
	C_6H_4–4-CH= 		CH_3	277–279		2
	C_6H_3–2-OH–3-OCH_3		C_6H_5	160–162	83	184
19	C_6H_3–2,4-Cl		C_6H_3-3,4-CH_3	171.5–173	12	12
	C_6H_5–3-OCH_3–4-OH		C_6H_4-4-CH_3	165–166	35	185

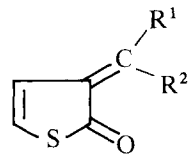
TABLE 21. CONDENSATION PRODUCTS OF 3-THIOLEN-2-ONES



C_n	R^3	R^4	R^5_a	R^5_b	Melting Point (°C)	Yield (%)	Reference
6	H	H	H	CH_3	47–49	57	104
7	H	H	–S–CH=CH–S–		187–188	32	117
	H	H	CH_3	CH_3	61.5–63	82	104
8	H	H	H	$(CH_2)_2CH_3$		46	168
9	H	H	$-(CH_2)_4-$		121.5–122.5	80	104
11	H	Br	H	C_6H_5	76–77	88	92
	Br	H	H	C_6H_5	137–138	80	92
	H	H	H	C_6H_5	97–98	80	92
	H	H	–C=C–C=C–C=C–		90–91	79	116
	H	H	$-(CH_2)_6-$		33–34	45	116
15	CN	CH_3	H	CH=CH–C_6H_5	200–205	85	15
	CN	CH_3	H	C_6H_4-4-$N(CH_3)_2$	210–214	80	15
17	H	H	C_6H_5	C_6H_5	111.5–112.0	72	187
18	CN	C_6H_5	H	C_6H_5	164	72	15
19	H	H	–C(C_6H_5)=C(C_6H_5)–		164–166	54	118
	C_6H_5	OH	CO_2CH_3	C_6H_5	173–175	84	220
20	CN	C_6H_5	H	CH=CHC_6H_5	183–185	80	15
	CN	C_6H_5	H	$C_6H_4N(CH_3)_2$	203	90	15



315



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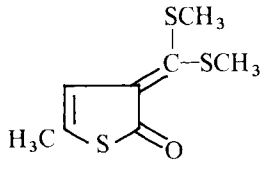

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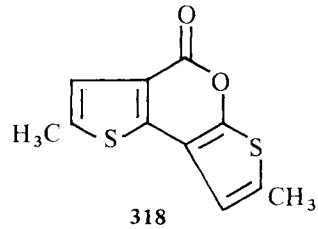
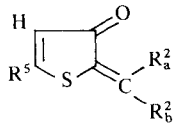


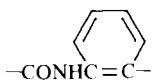
318

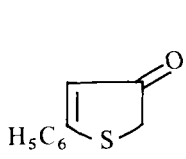
Scheme 79

It should perhaps be mentioned here that **311** and other compounds which might be obtained through the condensation of 3-thiolen-2-one with carbonyl compounds can alternatively be prepared by reacting 2-methoxythiophenes or 2-*t*-butoxythiophenes with butyllithium followed by a carbonyl compound to give **313**, which upon heating with catalytic amounts of acid gives **314**.[104,105,187] This route is of course especially useful for the preparation of **316** from **315**[105] (Scheme 79). The reaction of the ambient ion of the 5-methyl-2-hydroxythiophene system with carbon disulfide and methyl iodide, in addition to a 50% yield of the expected

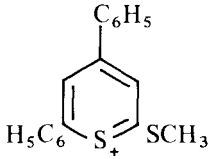
TABLE 22. CONDENSATION PRODUCTS OF 4-THIOLEN-3-ONES



C_n	R^2_a	R^2_b	R^5	Melting Point (°C)	Yield (%)	Reference
11	H	C_6H_4–4-Cl	H	141–142	44.9	61
	H	C_6H_5	H	100–101	56.6	61
12	H	C_6H_5	CO_2H	216–232	68.9	61
	H	C_6H_5	CH_3	97	58.7	61
	H	C_6H_4–4-OCH_3	H	141	61.1	61
13	H	CH=CH–C_6H_5	H	136	87.1	61
	H	C_6H_4–4-OCH_3	CO_2H	218–232	24.4	61
	H	C_6H_4–4-OCH_3	CH_3	113.5	43	61
	H	C_6H_3–3,4-OCH_3	H	94	40.2	61
	H	C_6H_4–4-$N(CH_3)_2$	H	187 (decomp.)	57.6	61
14	H	CH=CH–C_6H_5	CO_2H	218 (decomp.)	58.1	61
	H	C_6H_3–3,4-OCH_3	CO_2H	221–222	27.4	61
	H	C_6H_4–4-$N(CH_3)_2$	CO_2H	218 (decomp.)	39.9	61
	H	C_6H_3–3,4-OCH_3	CH_3	127	61.0	61
	H	C_6H_4–4-$N(CH_3)_2$	CH_3	183	57.1	61
15	–S–S–C(C$(CH_3)_3$)=CH–		$C(CH_3)_3$	97	68	78
17	H	C_6H_5	C_6H_5	142–144	52	27
	–S–S–C(C$(CH_3)_3$)=CH–		C_6H_4-4-Cl	196	76	78
18			C_6H_5	281 (decomp.)		77
	H	C_6H_4-4-OCH_3	C_6H_5	161.5	88.4	61
	–S–S–C(C_6H_4-4-OCH_3)=CH–		$C(CH_3)_3$	167	27	78
	–S–S–C(C$(CH_3)_3$)=CH–		C_6H_4-4-OCH_3	150	27	78
19	–S–S–C(C_6H_5)=CH–		C_6H_5	206	34	78
	H	C_6H_5-3,4-OCH_3	C_6H_5	147–148	86.3	61
	H	C_6H_4-4-$N(CH_3)_2$	H	158–159	97.7	61
21	–S–S–C(C_6H_4-4-OCH_3)=CH–		C_6H_4-4-OCH_3	208	72	78
27	–S–C(C_6H_5)=CH–C-(C_6H_5)=CH–		C_6H_5	206		190



319



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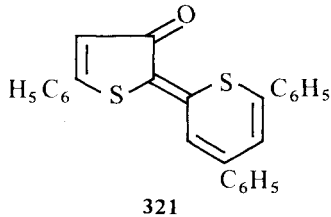


321

Scheme 80

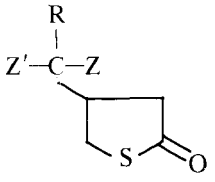
317, gave **318** in 36% yield. Its structure was proven by X-ray crystallography[189] (see also Reference 4).

Condensation of **319**, one of the few 3-hydroxythiophenes unsubstituted in the 2-position, has been carried out with benzaldehyde,[7] and with **320** in pyridine solution **321** was obtained[190] (Scheme 80 and Tables 20–22).

6. Michael Additions of the 2-Hydroxythiophene System

The 3-thiolen-2-one form of the 2-hydroxythiophene system can act as an acceptor in the Michael reaction, but complications are observed due to ring opening. Using sodium ethoxide in absolute ethanol as base, the anions of various active methylene derivatives were added to 3-thiolen-2-one to give adducts of type **322** in 23 to 63% yield[191] (Scheme 81).

Sulfur analogues of pilocarpin (**323**) have been obtained by the addition of the anion from 4-methylpyrimidine, formed on treatment with sodamide in ether, to



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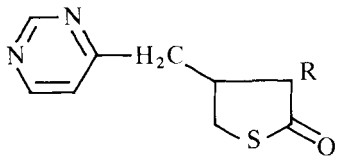
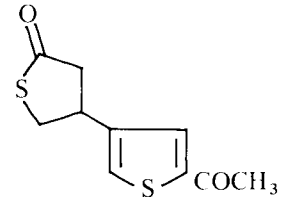


323

		Yield (%)
$Z = Z' = CO_2C_2H_5$	R = H	63
$Z = Z' = COCH_3$	R = H	31
$Z = COCH_3$, $Z' = CO_2C_2H_5$	R = H	63
$Z = COCH_3$, $Z' = CO_2C_2H_5$	R = allyl	36
$Z = Z' = CO_2C_2H_5$,	$R = C_4H_9$	41
$Z = CN$, $Z' = CO_2C_2H_5$	R = H	23

Scheme 81



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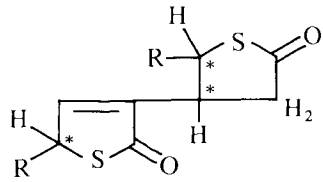

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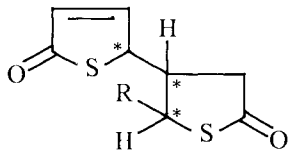


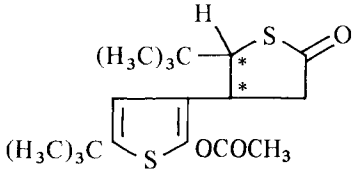
326

Scheme 82

3-thiolen-2-ones.[11] A rather curious example of a Michael-type reaction is the formation of **324** in 10% yield in the attempted acetylation of 2-methoxythiophene in benzene at 0°C using tin tetrachloride as a catalyst. Apparently demethylation to 3-thiolen-2-one occurred, followed by nucleophilic addition of 2-methoxy-5-acetylthiophene[119] (Scheme 82).

It is clear that the trident anion (Scheme 69) of the 2-hydroxythiophene system could act as a donor in the Michael reaction and the 3-thiolen-2-one form as an acceptor, leading to dimerization products. With the 5-methyl- and 5-*t*-butyl-2-hydroxythiophene system, dimerization was best carried out by allowing the reaction to proceed for 20–30 minutes at 0°C in ethanol containing catalytic amounts of ethoxide. The Michael adduct from 2-hydroxythiophene itself was best obtained by pouring the cold solution of the sodium salt into ice-cooled solution of the freshly acidified acceptor.

In these dimerizations a complex mixture of products can be expected, as three asymmetric carbons are formed and two positional isomers are possible depending on whether the anion adds with its 3- or 5-carbon. In the *t*-butyl case only **325** (R = *t*-butyl) was obtained in two of the four possible diastereomeric forms, which could be separated. Both forms gave the same acetate (**327**), showing that the two diastereomers have different configurations at carbon 5. In the methyl case the ambient anion attacked both with its 3- and 5-carbon, giving a mixture of **325** (R = CH_3) and **326** (R = CH_3) in about equal amounts, which were separated by chromatography. Dimerization of 2-hydroxythiophene occurred only by attack at the 5-carbon, giving a mixture of **326** (R = H) and its tautomeric form (**328**).[192]



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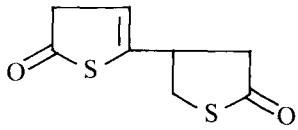

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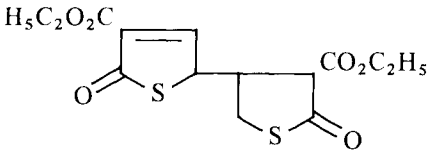

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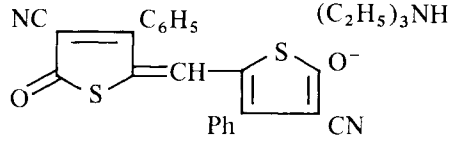


329b

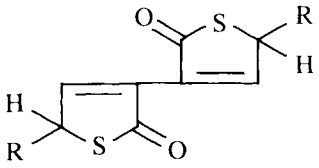
Scheme 83

The dimer **329** was formed spontaneously from the 3-carbethoxy-2-hydroxythiophene system at room temperature or under the influence of trifluoroacetic acid[143] (Scheme 83). Condensation of 2-cyano-3-hydroxythiophenes with ethyl orthoformate in toluene and triethylamine, followed by acetic anhydride, gave **329b** in good yield.[15]

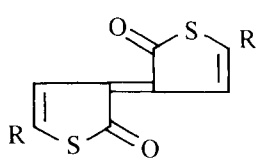
7. Oxidative Coupling Reactions of Hydroxythiophene Systems

The hydroxythiophene systems, are mentioned previously, as very air sensitive, and upon exposure rapidly discolor and polymerize. In the preparation of the 5-*t*-butyl- and 5-methyl 2-hydroxythiophene system, crystalline by-products were isolated. From IR and NMR data, structure **330** was suggested and proven by synthesis of authentic samples from 5,5′-di-*t*-butyl-3,3′-bithienyl and 5,5-dimethyl-3,3′-bithienyl, by the boronic acid method. Oxidative coupling of 5-*t*-butyl-2-hydroxythiophene could be achieved with potassium ferricyanide or chloranil to give the indigoid compound **331** in high yield, and **331** ($R = C_6H_5$) is obtained as a by-product in the preparation of 5-phenyl-2-hydroxythiophene.[4] Its formation does not proceed by **330** ($R = C(CH_3)_3$) or its tautomeric form, as it was recovered quantitatively upon attempted oxidation with potassium ferricyanide.[90] The products of the oxidation of the 5-methyl-2-hydroxythiophene system were not well defined.[90] 2-Hydroxy-3-cyanothiophenes can be oxidatively coupled in the 5-position with $FeCl_3$ to give **332**.[15]

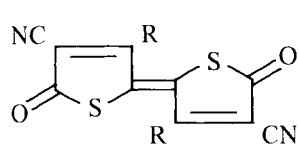
3-Hydroxythiophenes with a free 2-position are easily oxidized by air or $FeCl_3$ to indigoid derivatives **333**.[7,85] The carbonyl bands and light absorption of these compounds have been discussed.[193]



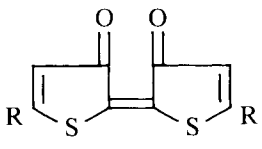
330
R = CH_3, $C(CH_3)_3$



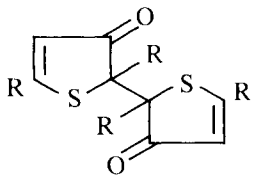
331
R = $C(CH_3)_3$, C_6H_5



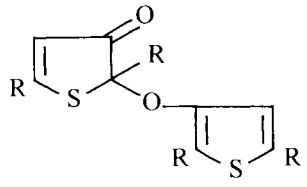
332



333
R = H, CH_3, C_6H_5



334

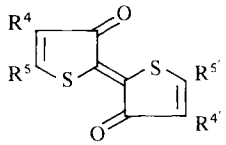


335

Scheme 84

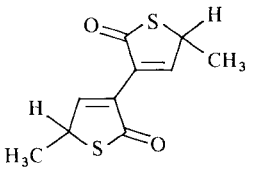
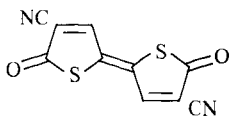
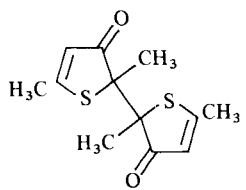
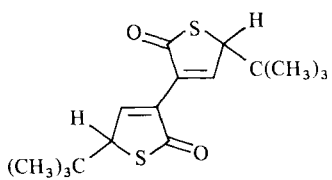
When the 2,5-dimethyl-3-hydroxythiophene system was treated with potassium ferricyanide, the *racemic* and *meso* forms of **334** (R = CH_3) were obtained and separated by chromatography. The crystalline form, which is probably the *meso* form, was also obtained upon prolonged reaction with hydrogen peroxide in connection with the preparation of the 3-hydroxy derivative from the boronic acid. The 2,5-di-*t*-butyl-3-hydroxythiophene system behaved differently upon oxidation. On hydrogen peroxide oxidation, or on exposure to air, **335** (R = $C(CH_3)_3$) was obtained[91] (Scheme 84; Tables 23 and 24).

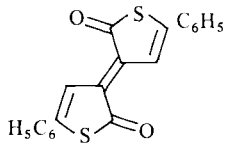
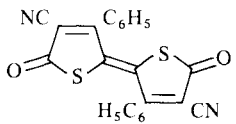
TABLE 23. OXIDATIVE COUPLING PRODUCTS OF 4-THIOLEN-3-ONE SYSTEMS

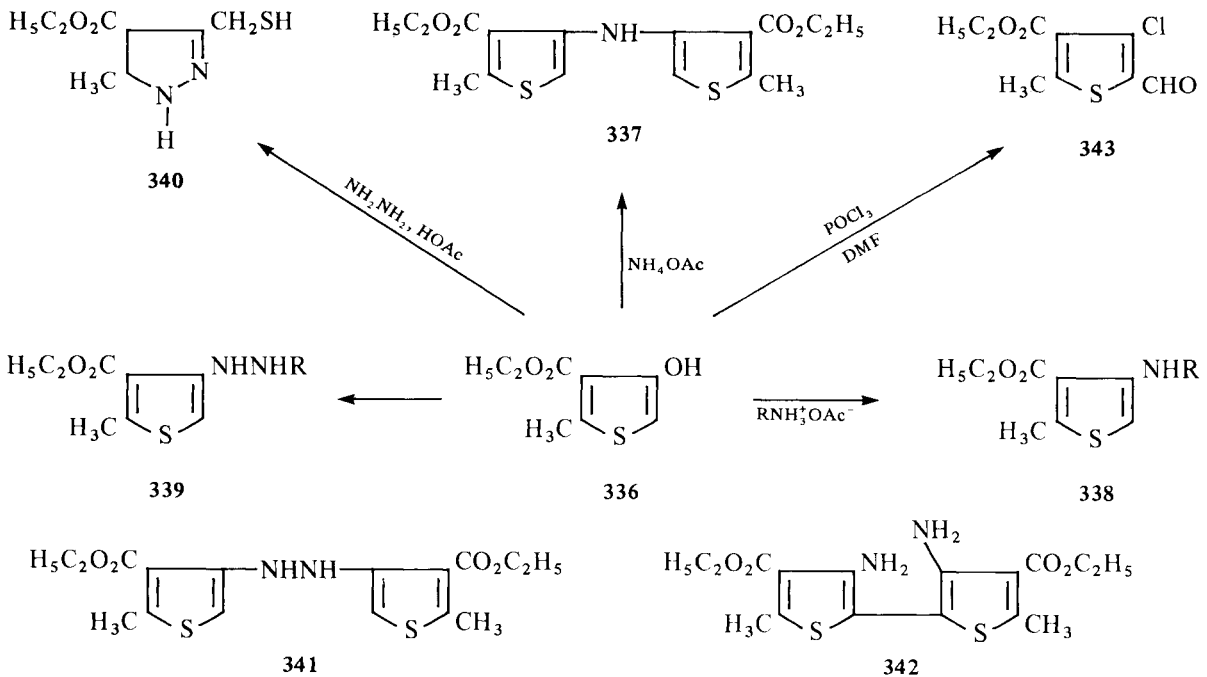


C_n	R^4	R^5	$R^{4'}$	$R^{5'}$	Melting Point (°C)	Yield (%)	Reference
8	H	H	H	H	200	61.1	61
10	H	CO_2H	H	CO_2H	>320	21.1	61
	H	CH_3	H	CH_3	188–190		2
12	H	CO_2CH_3	H	CO_2CH_3	27.3	72.6	61
16	H	$C(CH_3)_3$	H	$C(CH_3)_3$	198–199	78	90
20	C_6H_5	H	C_6H_5	H	285	66	274
22	C_6H_5	CO_2H	C_6H_5	CO_2H	264	68	276
	OCH_3	C_6H_5	OCH_3	C_6H_5	288–290	61	150
24	CO_2H	COC_6H_5	CO_2H	COC_6H_5	>320	61	276

TABLE 24. MISCELLANEOUS OXIDATIVE COUPLING PRODUCTS OF THIOLENONES

		Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
			165–168	17	90
			>360	60	15
	Two diastereomers	80–85/0.1	195–196	32	91
			219–220	15	90

	309–310	10	4
	>360	65	15


$H_5C_2O_2C$
CH_2SH
H_3C
N
N
H
340
$H_5C_2O_2C$
NH
$CO_2C_2H_5$
H_3C
S
S
CH_3
337
$H_5C_2O_2C$
Cl
H_3C
S
CHO
343
NH_2NH_2, HOAc
NH_4OAc
$POCl_3$
DMF
$H_5C_2O_2C$
NHNHR
H_3C
S
339
$H_5C_2O_2C$
OH
H_3C
S
336
$RNH_3^+OAc^-$
$H_5C_2O_2C$
NHR
H_3C
S
338
$H_5C_2O_2C$
NHNH
$CO_2C_2H_5$
H_3C
S
S
CH_3
341
NH_2
$H_5C_2O_2C$
NH_2
$CO_2C_2H_5$
H_3C
S
S
CH_3
342

Scheme 85

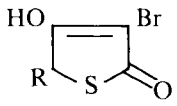
8. Substitution of the Hydroxy Group in Hydroxythiophenes

Reaction of orthocarbonyl-substituted hydroxythiophenes, such as **336**, with ammonium acetate gave **337**.[194] Reaction of **336** with alkyl ammonium acetates gave **338** (R = alkyl). To obtain arylamino derivatives, the reaction had to be carried out in the presence of iodine.[195,196] The reaction of **336** with phenyl hydrazine,[21,197] *N*,*N*-dimethylhydrazine,[197] and especially with acyl-substituted hydrazines, gives stable thienyl hydrazines **339**.[198] The preliminary report that **339** (R = H) is formed upon reaction of **336** with hydrazine acetate[194] was later shown to be erroneous. Instead, **340** is formed by way of an interesting ring opening reaction.[197] Reaction of **336** with **339** (R = CHO) gives by way of benzidine rearrangement of the nonisolable intermediate **341** the bithienyl **342** in 41% yield.[199] Attempted Vilsmeyer formylation of **336** gave simultaneously exchange of the OH for chlorine, giving **343**[200] (Scheme 85).

The reaction of noncarbonyl-substituted 2-hydroxythiophenes, such as 3-thiolen-2-one and 5-methyl-3-thiolen-2-one, with HMPA at 220°C gave very low yields of the corresponding dimethylaminothiophenes.[201] The oxo form of the 3-hydroxythiophene system in simple systems also gives some of the normal carbonyl reactions, for instance, hydrazone formation.[79]

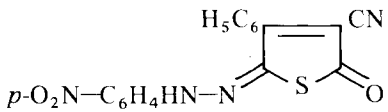
9. Electrophilic Substitution of Hydroxythiophenes

Hydroxythiophenes show very high reactivity in electrophilic aromatic substitution. However, owing to their instability, it is very difficult to obtain well-defined reaction products. Hurd and Kreuz showed as early as 1950 that 2-hydroxythiophene could be coupled to phenyldiazonium salts to give the 5-phenylazo-2-hydroxythiophene system.[85] They failed to obtain well-defined products from bromination.[85] Bromination of 2,4-dihydroxythiophene gave quantitative yields of **344**.[110] More

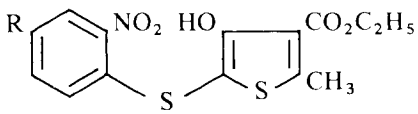


344

R = H, CH_3

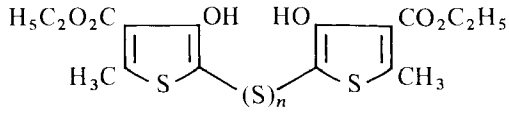


345



346

R = H, Cl, Br, $CO_2C_2H_5$



347

Scheme 86

positive results have been obtained with the somewhat less reactive carbonyl-substituted derivatives. Thus condensation of 3-cyano-4-phenyl-2-hydroxythiophenes with *p*-nitrophenyldiazonium salts gave **345**[15] (Scheme 86).

Nitration of **336** gave 3-ethoxycarbonyl-4-hydroxy-2-methyl-5-nitrothiophene in 59% yield.[202] The reaction of **336** with arenesulfenyl chlorides led to **346** in 80 to 98% yield.[189,203] Reaction of **336** with sulfur dichloride and sulfur monochloride was used for the preparation of **347** ($n = 1$) and **347** ($n = 2$).[204,205] 2-Phenyl-4-hydroxythiophene has been both nitrosated and nitrated in the 5-position.[79] Methyl-3-hydroxy-2-thiophenecarboxylate gave a mixture of predominantly methyl 4-nitro- and 5-nitro-3-hydroxy-2-thiophenecarboxylate.[206]

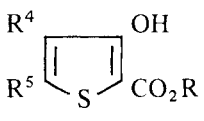
10. Various Reactions of Hydroxythiophenes

3-Hydroxy-2-carbethoxythiophenes (**348**) react with P_4S_{10} in xylene to give mixtures of **349** and **350**[50,51,207,208] (Scheme 87). Treatment of **351** with P_4S_{10} gave **352**.[209]

3-Thiolen-2-one has recently been shown to be useful as a dienophile and has been reacted with dienes, such as 2,3-dimethyl-1,3-butadiene, 1,3-cyclohexadiene, and cyclopentadiene, to give **353**, **354**, and **355**, respectively[210] (Scheme 88). The reaction of **356** with primary and secondary amines occurs at the formyl group to give **357**.

It was shown by NMR, IR, and UV spectra that the monosubstituted aminomethylene derivatives exist in the *cis* enamine form stabilized by an intramolecular hydrogen bond, whereas the disubstituted form exists in the *trans* form.[211] The amino group of **357** can be exchanged for other amines, which were characterized as copper chelates.[212] The reaction of **358** with ethyl phenyl thiomalonate gave **359** (Scheme 89).

The base-induced photolysis of the 3-acetyl derivative of the 2,4-dihydroxythiophene system (3-acetylthiotetronic acid) **360** leads to **361** and **362**, owing to reductive cleavage or two types of fragmentation with carbon-skeleton rearrange-



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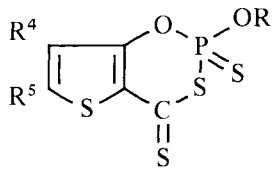
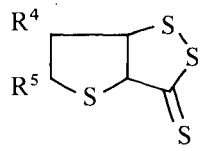


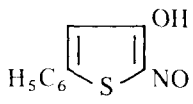
349

$R^4 = R^5 = H$
$R^4 = H, \quad R^5 = CH_3$
$R^4 = R^5 = CH_3$
$R^4 = C_2H_5, \quad R^5 = CH_3$
$R^4 = H, \quad R^5 = C_6H_5$
$R^4 = R^5 = -(CH_2)_3-$

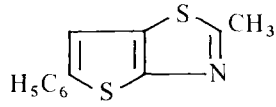


350

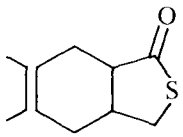
Scheme 87



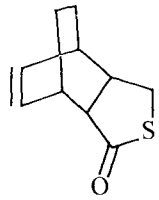
351



352



353



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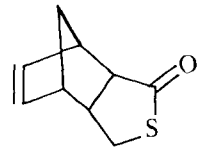
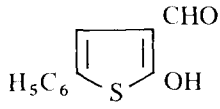
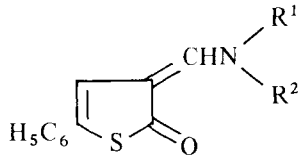


355

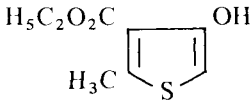
Scheme 88



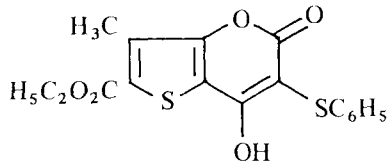
356



357



358

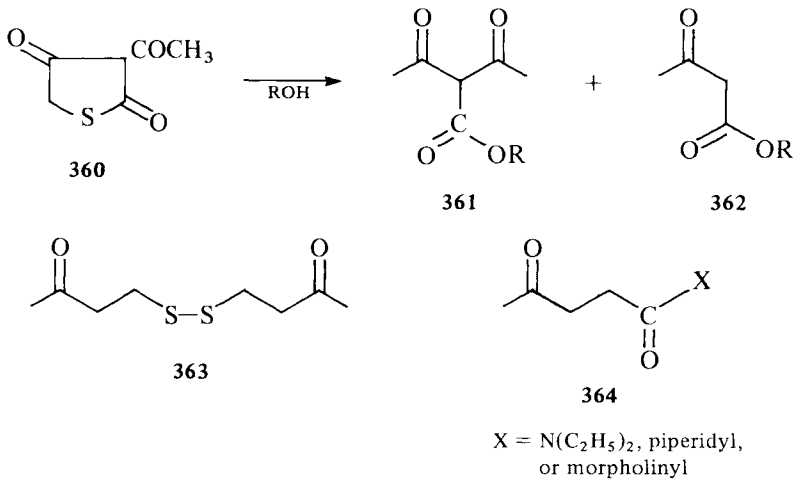


359

Scheme 89

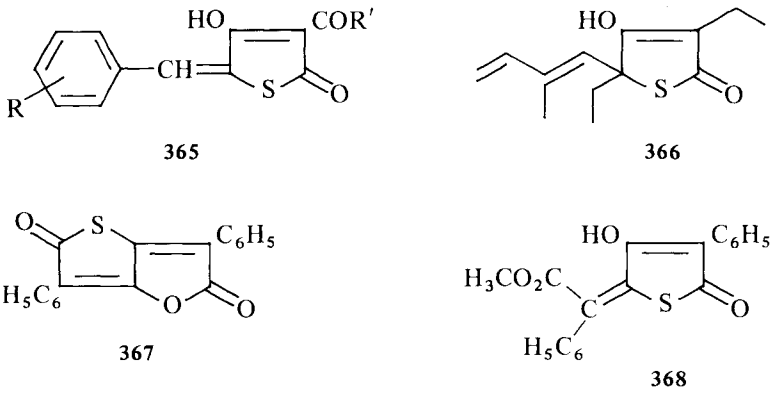
ment. This depends on irradiation conditions, leading in pyridine to **363** and the corresponding mercaptan, whereas in water-containing amines, mainly **364** was obtained[213] (Scheme 90).

Other derivatives of the 2,4-dihydroxythiophene system, such as **365**, which are aldol condensation products of 2,4-dihydroxy-3-acetylthiophene, have been investigated in detail because of their cytotoxic and antiallergic properties.[214–217] Recently a new antibacterial compound called thiotetromycin was isolated from *Streptomyces*, Sp. OM-674, and is an alkylated 2,4-dihydroxythiophene.[218,219] Another derivative of the 2,4-dihydroxythiophene system, thiovulpinic acid (**368**), of interest as an antiinflammatory agent, was prepared by the reaction of **367** with sodium methoxide in methanol[220] (Scheme 91).



360 361 362 363 364

Scheme 90



365 366 367 368

Scheme 91

A recent elegant synthesis of mono- and dialkyl ethers of 2,4-dihydroxythiophene consists in the reaction of methyl 3-hydroxy-2-thiophenecarboxylate or methyl 4-bromo-3-hydroxy-2-thiophenecarboxylate with sulfuryl chloride in chloroform giving methyl 2-chloro-3-oxo-2,3-dihydrothiophene-2-carboxylate and methyl 4-bromo-2-chloro-3-oxo-2,3-dihydroxythiophene-2-carboxylate, respectively. These products are α,β-unsaturated ketones sensitive to base. On the other hand, treatment with 3 M hydrochloric acid at room temperature caused both decarboxylation and partial dealkylation leading to mixtures of 5-alkoxythiophen-3(2H)ones and 4-alkoxythiophen-2(5H)ones, which could be separated.[292]

VI. ACYLOXYTHIOPHENES

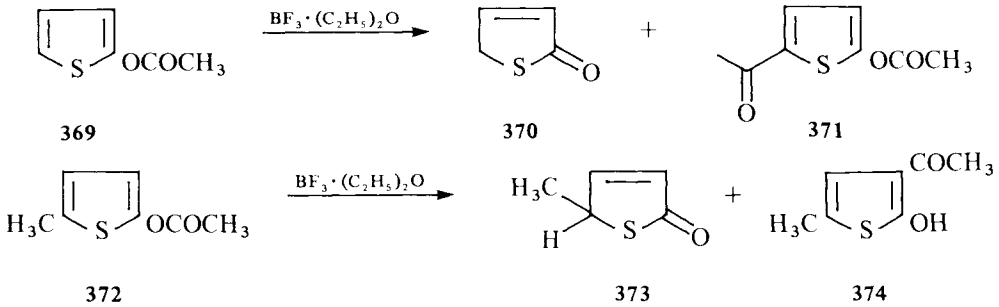
1. Preparation of Acyloxythiophenes

The most generally used method for the preparation of acyloxythiophenes is the reaction of hydroxythiophenes with acyl chlorides or acyl anhydrides under conditions discussed in Section V.1.[15,58,64,72,85,88-93,95,96,98,134,156,164,171,176,177,181,192] The compounds that have been prepared are given in Tables 25 and 26, together with their physical data.

Direct acyloxylation of thiophenes has not been very successful. The only preparatively useful method is probably the reaction of some simple thiophenes with diisopropylperoxydicarbonate in acetonitrile in the presence of cupric chloride catalyst, which gives thienyl isopropylcarbonates in 41 to 74% yield.[132] Refluxing 3-azidothiophene with acetic anhydride gave a 52% yield of 3-diacetyl-amino-2-acetoxythiophene.[134] 4-Acetoxy-3-carbomethoxythiophene has been prepared by the aromatization of methyl 2,5-dihydro-4-acetoxy-3-thiophenecarboxylate with sulfuryl chloride in methylene chloride.[72]

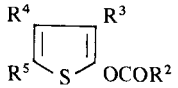
2. Reaction of Acyloxythiophenes

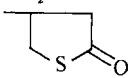
The reaction of acyloxythiophenes has been very little studied. For the most part they were prepared to characterize the unstable hydroxythiophenes. They are also very easily hydrolyzed back to the hydroxythiophene system. Thienyl methacrylates have been homo- and copolymerized.[98] The reaction of 2-acetoxythiophene (**369**) with boron trifluoride etherate gave a mixture of **370** and **371**. Similarly, **372** led to **373** and **374**. The reaction probably occurs by an intermolecular electrophilic attack of the carbonyl carbon on the most reactive thiophenic position[221] (Scheme 92). Acylation of 3-bromo-2-acetoxythiophene with acetyl chloride in benzene using $SnCl_4$ as catalyst gave a 60% yield of 2-acetyl-4-bromo-5-acetoxythiophene, which could be converted to 2-acetyl-4-bromo-5-methoxythiophene by hydrolysis with 1% potassium carbonate solution, followed by methylation with diazomethane.[119]



Scheme 92

TABLE 25. ESTERS OF THE 2-HYDROXYTHIOPHENE SYSTEM



C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
6	CH_3	H	H	Br	92–96/2.5			157
	CH_3	H	Br	H		40–41		92
	CH_3	Br	H	H	122–124/22			92
	CH_3	H	H	Cl	110/18		56	96
	CH_3	H	H	NO_2		38–39		157
	CH_3	H	H	H	96/25		56	85
7	CH_3	H	H	CH_3	208–212			1
8	CH_3	Cl	Cl	$OCOCH_3$		125–127		13
	$C(CH_3)=CH_2$	H	H	H	74–75/2.4		68	98
	CH_3	H	H	C_2H_5	108/15		65	93
	$N(CH_3)_2$	H	H	CH_3	89–90/0.03			180
9	2-Thienyl	H	H	H		54		131
	$C(CH_3)=CH_2$	H	H	CH_3	99/0.4		63	98
	CH_3	H	H	$(CH_2)_2CH_3$	123/14		74	93
	$CH(CH_3)_2$	H	H	CH_3	80/1.0			132
10	2-Thienyl	H	H	CO_2H		195		131
	CH_3	H	H			76–77	62	192
	CH_3	$N(COCH_3)_2$	H	H	118–120/1		52	134
	$C(CH_3)=CH_2$	H	H	C_2H_5	103/3.1		76	98
	CH_3	$C(CH_3)_3$	H	H	86–89/2		53	95
	CH_3	H	H	$(CH_2)_3CH_3$	142–143/11		53	93
	CH_3	H	H	$C(CH_3)_3$	127/10		55	93
11	C_6H_5	H	H	H		44–45		85
	2-Thienyl	H	H	CO_2CH_3		131–132		131
	CH_3	$C(CH_3)_3$	H	CH_3	95–97/2		43	95

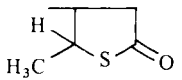
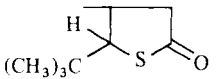
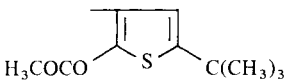
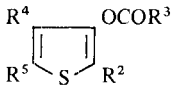
12	C_6H_3–3,5-NO_2	CH_3	H	H	172–173		92
	C_6H_5	H	H	CH_3	47.0–47.5		2
	CH_3	H	H	C_6H_5	55–57	77	7
	C_6H_5	OCH_3	H	H	34–36		92
	CH_3		H	CH_3	91–93	42	192
13	CH_3	CN	C_6H_5	H	74–76	82	15
18	CH_3		H	$C(CH_3)_3$	112–113	80	192
20	CH_3		H	$C(CH_3)_3$	162–165		90

TABLE 26. ESTERS OF THE 3-HYDROXYTHIOPHENE SYSTEM



C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
7	CO_2H	CH_3	H	H		110–111	91.3	61
	H	CH_3	H	CH_3	59/0.3		80	61
	CH_3	CH_3	H	H	86/10			99
8	CO_2H	CH_3	H	CH_3	95/0.2		75	61
	CH_3	CH_3	H	CH_3	108–110/15		82	156
9	CH_3	CH_3	H	C_2H_5	112–114/15		81	156
	C_2H_5	CH_3	H	CH_3	103–105/9		77	156
10	CO_2CH_3	CH_3	H	CO_2CH_3		74	70	274
	H	$NHCH_3$	CN	$CH(CH_3)_2$		46	26	38
	$CH(CH_3)_2$	CH_3	H	CH_3	118–120/14		36	156
	CH_3	CH_3	H	$CH(CH_3)_2$	122–123/12		25	156
11	H	C_6H_3-3,5-NO_2	H	H		150		88
	H	C_6H_5	H	H		40		88
	H	NHC_6H_5	H	H		120		88
	H	$N(CH_3)_2$	CN	$CH(CH_3)_2$	132–133/0.5		71	38
	$C(CH_3)_3$	CH_3	H	CH_3	121–123/10		57	156
	CH_3	CH_3	H	$C(CH_3)_3$	116–118/10		68	156
12	H	C_6H_5	H	CO_2H		169	60.4	61
	CO_2H	C_6H_5	H	H		152–153	84.6	61
	H	C_6H_5	H	CH_3		67–68	41.2	61
	H	CH_3	H	C_6H_5		72–75		7
	H	$N(CH_3)_2$	CN	$CH(CH_3)_2$	126–127/0.1		55	38
13	H	C_6H_5	H	CO_2CH_3		61–62	76.3	61
	CO_2H	C_6H_5	H	CH_3		147–148	64.8	61
	C_6H_5	CH_3	H	CH_3	142–144/1.5		77	100
	CH_3	CH_3	H	C_6H_5	128–130/0.8	60–61	81	100

	CH_3	$N(CH_3)_2$	CN	$CH(CH_3)_2$	197/13		62	38
14	CO_2CH_3	CH_3	C_6H_5	H		42	91	274
	$C(CH_3)_2$	CH_3	H	$C(CH_3)_3$	110/11		70	91
15	CO_2CH_3	C_6H_5	H	CO_2CH_3		120	68	274
	$CONH_2$	C_6H_5	$-(CH_2)_3-$			197–204 (decomp.)		275
16	CO_2CH_3	CH_3	$OCOCH_3$	C_6H_5		84–85	78	150
	$CONH_2$	C_6H_5	$-(CH_2)_4-$			160–162		275
18	COC_6H_5	C_6H_5	H	H		64		275
	CO_2H	C_6H_5	H	C_6H_5		162.5	55.5	61
19	COC_6H_5	C_6H_5	H	CH_3		53		275
	CO_2CH_3	C_6H_5	C_6H_5	H		143	73	274
21	CO_2CH_3	C_6H_5	CO_2CH_3	C_6H_5		130		276
24	COC_6H_5	C_6H_5	H	C_6H_5		99–100		275
	2-Thienyl-3-$OCOCH_3$-4-C_6H_5	CH_3	C_6H_5	H		227	69	274

VII. ALKOXY- AND ARYLOXYTHIOPHENES

1. Preparation of Alkoxy- and Aryloxythiophenes

A. Preparation from Hydroxythiophene Systems

The alkylation of hydroxythiophenes has been discussed in detail in Section V.1. If they have orthocarbonyl groups, *O*-alkylation is preferred. In other cases, hard electrophiles must be used to obtain predominantly *O*-alkylation, and best yields are obtained using the ion-pair extraction method. If the hydroxythiophenes are easily available, which is the case with many orthocarbonyl-substituted hydroxythiophenes, the alkylation reaction is the most convenient method for the preparation of the alkoxythiophenes. Compounds prepared by this method are given together with physical data in Tables 27 and 28.

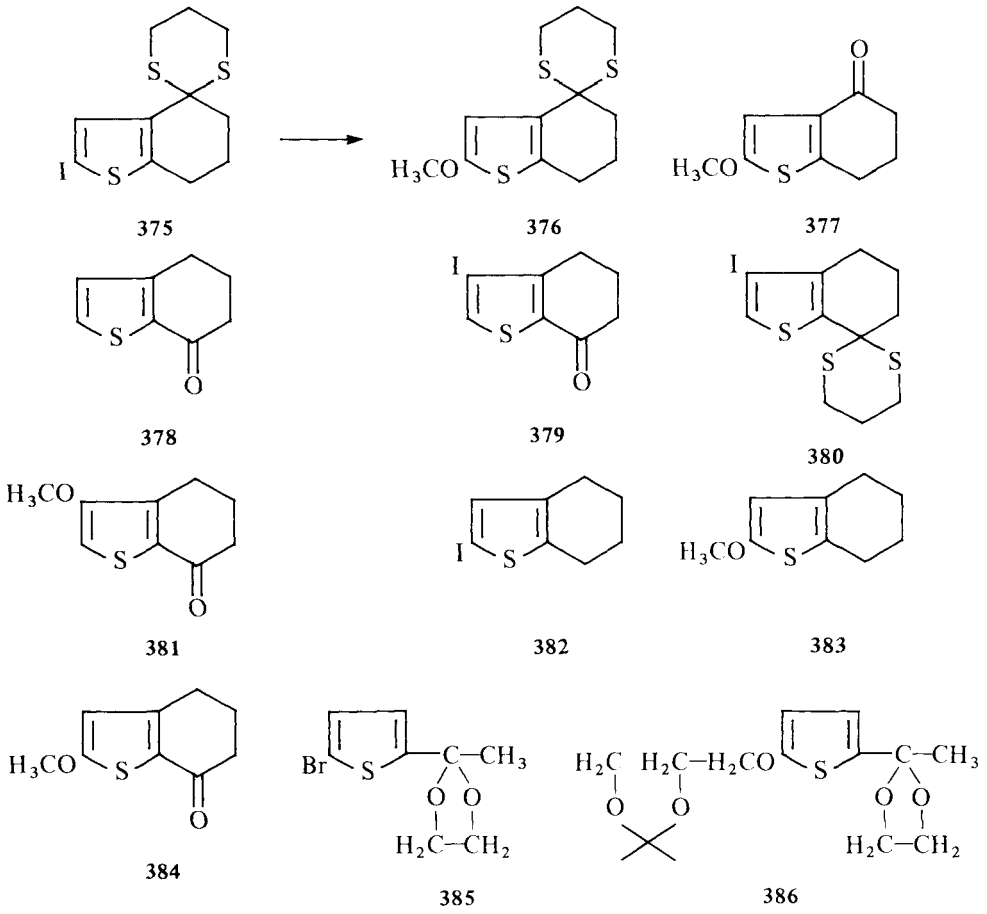
B. Preparation of Alkoxythiophenes from Thienyllithium and Thienylmagnesium Derivatives

The reaction of thiophenemagnesium derivatives with *t*-butylperbenzoate, introduced by Lawesson, has extensively been used for the preparation of *t*-butoxythiophenes.[102-108,110-112,115-118,122,123,143,166,191] The thiophenemagnesium derivatives are prepared directly from halothiophenes and magnesium or through the reaction of thienyllithium derivatives with magnesium bromide. The *t*-butoxythiophenes prepared in this way, together with some physical data, are given in Tables 27 and 28. They have been used mostly as precursors to hydroxythiophene systems.

C. Preparation of Alkoxythiophenes by Copper-Promoted Nucleophilic Aromatic Substitution of Halothiophenes

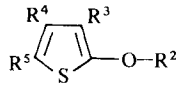
A convenient method introduced by Sicé for the preparation of 2-methoxythiophene is the reaction of 2-iodothiophene with sodium methoxide in anhydrous methanol in the presence of powdered cupric oxide. The reaction is slow and requires 30 hours of reflux. Instead of 2-iodothiophene, 2-bromothiophene can be used if a catalytic amount of sodium iodide is added to the reaction mixture and longer reaction times are used[223] (see also References 224 and 225). Using this technique, 3-methoxythiophene was obtained from 3-bromothiophene.[226] Other alkoxides can also be used, and in this way 2-ethoxy- and 2-*n*-propoxythiophene were obtained in 34% yield from 2-iodothiophene. The yields of *n*-butoxy- and *n*-amyloxythiophenes were only 13 to 16%.[225,227] From 2-methyl-5-iodothiophene and 2-ethyl-5-iodothiophene, 2-methyl-5-methoxy- and 2-ethyl-5-methoxythiophene were obtained in 67 and 74% yields, respectively. Again, the yield of 2-ethyl-5-ethoxythiophene from 2-ethyl-5-iodothiophene was lower (39%).[121] The reactions

often do not go to completion, and difficulties can occur in the separation of the methoxythiophenes from the starting halothiophenes by fractional distillation. In such cases the halothiophenes can be removed by reaction with magnesium or butyllithium followed by hydrolysis. Carbonyl-substituted halothiophenes usually can not be transformed to methoxy derivatives because of complicating condensation reactions, so the carbonyl group must first be protected by acetal formation, as shown by the reaction of **375** with sodium methoxide and cupric oxide in THF to give **376**, which upon hydrolysis gave **377**. Similarly, **380** prepared by iodination of **378** to **379**, followed by thioacetylation, gave **381** after substitution and deprotection. That iodination of **378** had occurred in the 3-position was indirectly proven by preparation of **383** from **382** followed by oxidation to **384** with CrO_3 in pyridine.[228] Reaction of **385** with 2,3-*O*-isopropylidene glycerol and sodium in the presence of cupric oxide and sodium iodide gave **386**.[229] This reaction was also carried out with 2-bromothiophene and 2-methyl-4-bromothiophene in addition to **385**[230] (Scheme 93).

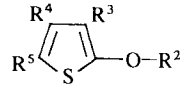


Scheme 93

TABLE 27. 2-THIOPHENE ETHERS

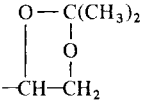


C_n	R^2	R^3	R^4
5	CH_3	F	F
	CH_3	H	Br
	CH_3	Br	H
	CH_3	Br	H
	CH_3	NO_2	H
	CH_3	H	H
	CH_3	Br	H
	CH_3	H	H
	CH_3	H	H
	CH_3	NO_2	H
	CH_3	H	H
	CH_3	H	H
6	CH_3	Cl	Cl
	C_2H_5	NO_2	H
	CH_3	H	Br
	CH_3	Cl	OCH_3
	CH_3	Br	H
	CH_3	H	OCH_3
	CH_3	Cl	H
	C_2H_5	H	Br
	CH_3	Br	OCH_3
	C_2H_5	NO_2	H
	CH_3	NO_2	H
	C_2H_5	H	H
	CH_3	H	H
	CH_3	H	H
7	CH_3	H	H
	$CH_2CH{=}CH_2$	NO_2	H
	CH_3	H	H
	$CH_2CH{-}CH_2$	H	H
	CH_3	Br	CH_3
	CH_3	H	H
	CH_3	H	H
	C_2H_5	H	H
	$(CH_2)_2CH_3$	H	H
	CH_3	H	H
	CH_3	CH_3	H
	$CH_2CH(OH)CH_2OH$	H	H
	CH_3	H	H
	$Si(CH_3)_3$	H	H
8	CH_3	H	H
	Oxime		
	$C(CH_3)_3$	Br	H



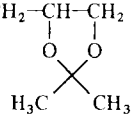
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
F		Oil		236
Cl	116–119/12		68	265
Cl	104–106/5		75	265
Br	94–95/2.5		83	252
NO_2		138–139	55	130
Br	92–93/19		62	223
H	56–58/1.5		90	252
Cl	83–86/48		84	233, 289
NO_2		61–63		223
H		97–98	65	252
H	74–75/50		80	223
CN	122/14	12	75	224
OCH_3	121–125/0.5		60	266
NO_2		94–95		130
CH_3	57–61/0.7		32	264
H		60–62	78	292
CH_3	115–117/20		34	264
H	115/30		90	292
OCH_3	114–119/12		77	266
H	93/10			289
H		98–100	92	292
H		96.5–97.5		130
SO_2CH_3		178		268
H	64/18		34	225
CH_3	58–60/12		54	264
CH_2OH	84/0.7		75	223
CH_2CN	110–113/2		68	256
H		55–56		283
$CH{=}CHNO_2$		120.6–130.0		120
H			78	230
OCH_3		Oil	89	232
$C(OCH_3){=}NH \cdot HCl$		179	80	224
C_2H_5	112/65		74	121
CH_3	120/6			281
H	93–96/30		34	225
$(CH_2)_2OH$	87–89/0.3			120
OCH_3	105/22		30	232
H	174–175/0.5		82	232
$(CH_2)_2NH_2$	77–88/0.3		60	120
H	23/0.03		66	210
$CH_2{-}\overset{\overset{S}{\|}}{C}{-}CO_2H$		191–193		256
		143–145	55	256
Br	90–91/0.3		95	110

TABLE 27. (*Continued*)

C_n	R^2	R^3	R^4
	CH_3	H	H
	$CH_2CO_2C_2H_5$	H	H
	$C(CH_3)_3$	H	H
	$C(CH_3)_3$	Br	H
	$C(CH_3)_3$	H	H
	CH_3	H	H
	CH_3	H	H
	CH_3	H	H
	$C(CH_3)_3$	H	H
	C_2H_5	H	H
	$(CH_2)_3CH_3$	H	H
	C_2H_5	H	H
	CH_3	H	H
	CH_3	H	H
9	$(CH_2)_4CH_3$	H	H
	CH_3	H	$-(CH_2)_4-$
	$(CH_2)_2CO_2C_2H_5$	H	H
	$C(CH_3)_3$	Br	H
	CH_3	H	H
	CH_3	Br	H
	CH_3	$C(CH_3)_3$	H
	$C(CH_3)_3$	H	H
	$C(CH_3)_3$	CH_2OH	H
	CH_3	H	H
10	C_6H_5	Cl	Cl
	C_6H_5	Cl	Cl
	C_6H_5	NO_2	H
	$CH(CH_3)CH_2CO_2C_2H_5$	H	H
	$CH(CH_3)CH_2CO_2C_2H_5$	H	H
		H	H
	CH_3	H	H
	CH_3	CH_2OH	H
	$CH_2CH(OH)CH_2NHCH(CH_3)_2$	H	H
	CH_3	H	H
11	CH_3	H	H
	$C(CH_3)_3$	H	H
	$C(CH_3)_3$	$C(CH_3)=CH_2$	H
	CH_3	H	H
	$C(CH_3)_3$	$C(OH)(CH_3)_2$	H
	$CH_2CH(OH)CH_2NHC(CH_3)_3$	H	H
12	CH_3	CN	C_6H_5
	CH_3	H	H
	CH_3	H	Br

R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
CH_2—CH=CH_2	93/17			223
H			12	167
Br	52–53/0.08		79	104
H	50–52/0.1		64	143
Cl	37–38/0.1		72	106, 289
$(CH_2)_2NHCOH$	145–155/0.4		72	120
$C(OC_2H_5)$=NH	152/12		70	224
$C(OC_2H_5)$=NH · HCl		160	86	224
H	64–66/13		76	102
C_2H_5	110/40		39	121
H	40–43/0.6		40	225
OC_2H_5	52/0.25		18	289
$CH_2N(CH_3)_2$	106/15		74	260
$(CH_2)_2NHCH_3$	78–80/1			120
H	57–61/0.6		52	225
	82–83/0.6		85	228
H			9	167
CH_3	59–63/0.13		67	110
$(CH_2)_2NHCOCH_3$	151–154/0.5			120
$CH(OH)CH_2N(CH_3)_2$		Oil	67	262
H	80–81/10		51	95
CH_3	77–78/7		87	104
H	83–84/0.5		75	262
$(CH_2)_2N(CH_3)_2$	83–84/1.0		40	262
Cl		14	72	235
H		36	91	235
NO_2		151.5–152.5		130
Cl			86	167
H			9	167
H	149–150/21		72	230
CH_2-*N*-morpholino	168/17		89	260
$(CH_2)_2N(CH_3)_2$			67	262
H		79–80	67	230
$(CH_2)_2N(CH_3)_3I$		212–213	70	120
C_6H_5	135–136/1		39	7
CH_2—CH=CH_2	61–63/0.2		86	104
H			21	105
CH_2-*N*-morpholino	163/19		77	260
H	68–71/0.3		19	105
H		93–94	63	230
H		91–93	40	15
$C(NH_2)$=CNHC$_6H_5SO_3H$		180	95	224
CH—CH_2—Br | O—O			87	119

TABLE 27. *(Continued)*

C_n	R^2	R^3	R^4
	$C(CH_3)_3$	Br	H
	$C(CH_3)_3$	Br	H
	$C(CH_3)_3$	CH_3 | $C-CH_2CH_3$ | OH	H
	$C(CH_3)_3$	H	H
	$C(CH_3)_3$	H	$OC(CH_3)_3$
	$C(CH_3)_3$	$OC(CH_3)_3$	H
13	$C_6H_4-2-CO_2C_2H_5$	H	H
	$C(CH_3)_3$	$C(C_2H_5)CHCH_3$	H
	$C(CH_3)_3$	CH_3	H
	$C(CH_3)_3$	$OC(CH_3)_3$	CH_3
	$C(CH_3)_3$	$C(OH)(C_2H_5)_2$	H
	$C(CH_3)_3$	CH_2OH	H
14	$CHCOC_6H_5$	CN	CH_3
	CH_2COCH_3	CN	C_6H_5
	CH_3	H	H
		H	H
	$C(CH_3)_3$	OH | $CCH_2CH(CH_3)_2$ | CH_3	H
15	$CH_2CO_2C_2H_5$	CN	C_6H_5
	$C(CH_3)_3$	H	H
	$C(CH_3)_3$	$CH(OH)C_6H_5$	H
16	C_6H_4-4-Br	NO_2	OC_6H_4-4-Br
	C_6H_4-4-Cl	NO_2	OC_6H_4-4-Cl
	C_6H_5	NO_2	OC_6H_5
	$C(CH_3)_3$	$OC(CH_3)_3$	H
17	$C(CH_3)_3$	$C(C_6H_5)=CHCH_3$	H
	$C(CH_3)_3$	OH | $C-C_6H_5$ | C_2H_5	H
	$CH_2-CH(OH)CH_2NH-$ $-(CH_2)_2C_6H_3-3,4-OCH_3$	H	H
18	$C_6H_4-2-CH_3$	NO_2	$OC_6H_4-2-CH_3$
	$C_6H_4-4-CH_3$	NO_2	$OC_6H_4-4-CH_3$
19	$CH_2COC_6H_4-4-Br$	CN	C_6H_5
	$CH_2COC_6H_5$	CN	C_6H_5

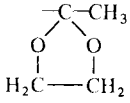
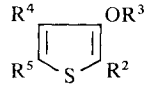
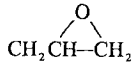
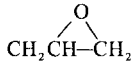
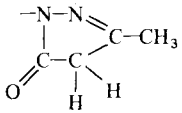
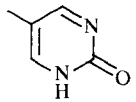
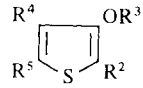
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
$OC(CH_3)_3$	62–64/0.1		90	247
$(CH_2)_2N(CH_3)_2$	90–95/0.01		21	262
H	91–93/0.2		70	105
$OC(CH_3)_3$	74–76/0.2	38.0–39.5	78	104
H	55–57/0.1		60	110
H	51–53/0.1		70	108
H	110/0.07		8	234
H			22	105
$OC(CH_3)_3$	62–64/10		91	110
H	73–75/0.2		79	110
H	84–85/0.2		62	105
$(CH_2)_2N(CH_3)_2$			30	262
H		100–103	69	174
H		112–113	52	174
$(CH_2)_2NHCOC_6H_5$		68.4–69	82	120
	148–151/0.5		65	229
H	81–82/0.2		84	105
H		56–59	21	174
$CH_2C_6H_5$	112–114/0.08		73	104
H	139–141		82	105
NO_2		173		244
NO_2		158		244
NO_2		117		244
$(CH_2)_2N(CH_3)_2$	80–87/0.01		13	262
H			9	105
H	134–138/0.3		48	105
H		108–109	60	230
NO_2		137		244
NO_2		175		244
H		201–204	50	174
H		149–150	75	174

TABLE 28. 3-THIOPHENE ETHERS

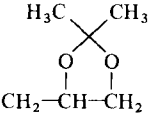
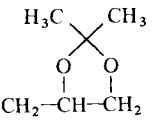


C_n	R^2	R^3	R^4
5	H	CH_3	H
6	NO_2	CH_3	OCH_3
	$CONH_2$	CH_3	H
	NO_2	CH_3	CH_3
	H	CH_3	H
	CH_3	CH_3	H
	H	CH_3	OCH_3
	H	C_2H_5	NH_2
7	CH_2CN	CH_3	H
	CN	CH_3	H
	NO_2	CH_2—CH=CH_2	H
	H		H
	CH_3	CH_3	H
	H	C_2H_5	NHCHO
	CH_3	CH_3	H
	H	$CH_2CH(OH)CH_2OH$	H
8	CH_2CSCO_2H Oxime		H
	H		H
	CH_3	CH_3	CH_3
	CH_3	CH_3	H
	CO_2CH_3	CH_3	H
	CO_2H	CH_3	OCH_3
	H	C_2H_5	$NHCOCH_3$
	H	$C(CH_3)_3$	H
	H	$CH_2CH(OH)CH_2OH$	H
	$CH_2N(CH_3)_2$	CH_3	H
9	CN	CH_2COCH_3	H
	CO_2CH_3	CH_3	OCH_3
	H		OCH_3
	CO_2H	CH_3	$-(CH_2)_3-$
	H		H
	CN	CH_3	H
	H	CH_3	CN
	CH_3	CH_3	CH_3
	CO_2H	CH_3	SC_2H_5
	CO_2CH_3	CH_3	OCH_3



R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H	80–82/6.5		81	226
NO_2		116.5–117.2	46.2	32
H		152	85	53
H		57		242
CH_3	66/12		54.6	61
H	70/20		51	53
H	110/17		87.5	32
H	69/0.4		98	72
H	112–114/2.2		60	256
CH_3		32–33	64	43
H		66.5–67		283
H			74	230
CO_2H		180	85	53
H	117/0.08	112–113	82	72
CH_3	68–72/13		53	100
H		65–66	84	230
H		212–214		256
		121–123	82	256
CH_3			81	230
CO_2H		161	90	253
CO_2CH_3		56	85	53
CH_3		69	85.9	61
CH_3		124	95	253
H		104	55	72
H	74–76/15		70	107
CH_3		82–83	78	230
H	103/14		69	260
CH_3		84–85	89	174
CN		85	70	276
H		142–147	25	231
		173	76	48
CH_3		162–164	27	290
$CH(CH_3)_2$			65	43
$CH(CH_3)_2$	100–102/0.4		80	38
CO_2CH_3		Oil	90	253
CH_3		113	91	253
CH_3		Oil	90	253

TABLE 28. (*Continued*)

C_n	R^2	R^3	R^4
	H	C_2H_5	$NHCO_2C_2H_5$
10	H	C_6H_5	H
	CN	$CH_2CO_2C_2H_5$	H
	CO_2CH_3	CH_3	$-(CH_2)_3-$
	CN	CH_3	H
	H	Cyclohexyl	H
	H	C_2H_5	H
	H		H
	CO_2CH_3	CH_3	SC_2H_5
	CH_2-*N*-morpholino	CH_3	H
	H	CH_3	H
	H	CH_3	H
	$C(CH_3)_3$	CH_3	H
	H	$CH_2CH(OH)CH_2NHCH(CH_3)_2$	H
	$CH_2NH(CH_3)_2I$	CH_3	OCH_3
11	H	CH_3	H
	H	C_6H_4-4-CH_3	H
	$CO_2C_2H_5$	CH_3	$-(CH_2)_3-$
	H		H
	CO_2H	CH_3	$S(CH_2)_3CH_3$
	CH_2-N-morpholino	CH_3	H
	H	$CH_2CH(OH)CH_2NHC(CH_3)_3$	H
	H	$CH_2CH(OH)CH_2NHCH(CH_3)_2$	H
	H	$CH_2CH(OC_2H_5)_2$	H
12	C_6H_5	CH_3	CH_2Cl
	H	C_6H_3–2-$NHCH_3$-4-Cl	CH_2OH
	$CH{=}C(CH)_2$	$C(CH_3)_3$	H
	C_6H_5	CH_3	H
	H	C_6H_3–2,4-CH_3	H
	C_6H_5	CH_3	CH_2OH
	H	C_6H_2–2-$NHCH_3$	CH_2OH
	H	C_2H_5	NH-3-thienyl–4-OC_2H_5
	CO_2CH_3	CH_3	$S(CH_2)_3CH_3$
	$CH(O{-}Si(CH_3)_3)-CH_2Br$	CH_3	OCH_3
	H	$C(CH_3)_3$	$OC(CH_3)_3$
	H	$CH_2CH(OH)CH_2NHC(CH_3)_3$	H
13	H	$C_6H_4NHCH_3 \cdot HCl$	CH_2OCH_3

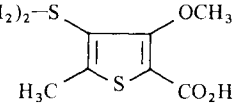
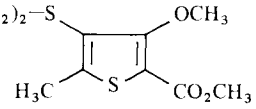
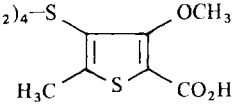
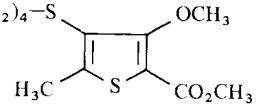
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H		62.5–63	86	72
H	110/0.05		50	234
CH_3		52–54	75	174
		62–63	88	48
$C(CH_3)_3$		Oil	79	43
H	119–123/16		23	246
$CH_2CO_2C_2H_5$	102/5			281
H		46–47	61	230
CH_3		Oil	92	253
H	160/15		80	260
$NHCO_2C(CH_3)_3$		116–118	64	231
$N(NH_2)CO_2C(CH_3)_3$		78–80	77	231
CH_3	75–78/14		33	100
H		94–95	71	230
H		159–162	66	260
C_6H_5	141–142/3		60	7
H	110/0.05		86	234
		71	91.6	48
CH_3	101–103/0.2		64	230
CH_3		119	66	253
H	164–166/22		73	260
H		90–91	66	230
CH_3		94–95	68	230
CH_3	140/0.5		98	290
H	138/0.1		76	73
H		92–93	42	272
H		158	80	123
CH_3			92	43
H	108/0.1		18	234
H	139–141/0.1		72	73
H		70–71	20	272
H		131–133	60	72
CH_3		Oil	95	253
H			60	119
H	70–71/0.2		66	110
CH_3		75–76	64	230
H		125–127	30	272

TABLE 28. *(Continued)*

C_n	R^2	R^3	R^4
	CO_2H	CH_3	CO_2H
	H	C_6H_3–2-$CO_2C_2H_5$–4-Cl	H
	C_6H_5	CH_3	CH_2CN
	CO_2CH_3	CH_3	H
	CO_2H	CH_3	OCH_3
	CO_2H	CH_3	SC_6H_5
	H	C_6H_3–2-$NHCH_3$–4-CH_3	CH_2OH
	H	C_6H_3–2-$NHCH_3HCl$–5-CH_3	CH_2OH
	H	C_2H_5	NHCONH–3-thienyl–4-OC_2H_5
	H	CH_3	H
	H	$CH_2CH(OH)CH_2$-NH–$CH(CH_3)_2 \cdot HCl$	$-(CH_2)_3-$
	CH_3	$C(CH_3)_3$	$OC(CH_3)_3$
	CH_3	$C(CH_3)_3$	H
14	CN	$CH_2COC_6H_5$	H
	CN	CH_2COCH_3	H
	C_6H_5	CH_3	$CH(CO_2H)=CH_2$
	CO_2H	CH_3	SC_2H_5
	CO_2CH_3	CH_3	SC_6H_5
	CO_2CH_3	CH_3	OCH_3
	H	C_6H_3–2-$CO_2C_2H_5$–4-OCH_3	H
	H	CH_3	$NHCOCH_2C_6H_5$
	$CH=C(CN)CO_2C_2H_5$	$C(CH_3)_3$	H
	H	$CH_2CH(OH)CH_2NHC(CH_3)_3 \cdot HCl$	$-(CH_2)_3-$
	H	$CH_2CH(OH)CH_2NHC(CH_3)_3 \cdot HCl$	$-(CH_2)_4-$
	CH_3	$C(CH_3)_3$	$OC(CH_3)_3$
15	CN	$CH_2CO_2C_2H_5$	H
	CO_2CH_3	CH_3	CO_2CH_3
	CO_2H	CH_3	$NHCOCH_2C_6H_5$
	CH=CHCO–2-thienyl	$C(CH_3)_3$	H
	C_6H_5	CH_3	$CH_2CO_2C_2H_5$
	CH=CHCO–2-furyl	$C(CH_3)_3$	H
	CO_2CH_3	CH_3	SC_2H_5
	CH=CHCO–2-pyrryl	$C(CH_3)_3$	H
	H	CH_3	H
	H	$CH_2CH(OH)CH_2-NHC(CH_3)_3 \cdot HCl$	$-(CH_2)_4-$
16	C_6H_5	CH_3	$C(CO_2C_2H_5)=CH_2$
	CH=CHCO–4-pyridyl	$C(CH_3)_3$	H
	CH=CHCO–3-pyridyl	$C(CH_3)_3$	H
	CH=CHCO–2-pyridyl	$C(CH_3)_3$	H

R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
C_6H_5		200	88	276
H	146/0.85		9	234
H	146/0.1		95	73
C_6H_5		114–115	78.5	61
C_6H_5		135–137	88	150
CH_3		131	82	253
H		57–58	17	272
H		150–151	16	272
H		298–299	80	72
$-N(CO_2C(CH_3)_3)-N=C(CH_3)_2$			60	231
		149–150	67	173
H	69–70/0.14		91	110
$OC(CH_3)_3$	57–58/0.12		92	110
CH_3		100–102	94	174
C_6H_5		139–141	82	174
H		124.5–126	72	73
C_6H_5		189	76	253
CH_3		Oil	96	253
C_6H_5		55–57	95	150
H	158/0.5		16	234
CH_3		136	70	253
H		78	86	123
		164–165	65	173
		138–139	75	173
CH_3	90/0.3		81	110
C_6H_5		96–99	64	174
C_6H_5		85	86	276
CH_3		181	83	253
H		90	50	112
H	158–160/0.2		88	73
H		110	50	112
C_6H_5		47	90	253
H		107	30	112
$N(CO_2C(CH_3)_3)-NH-C(CH_3)=CHCO_2CH_3$		109–112	74	231
		159–160	77	173
H	138/0.1	45–46	80	73
H		98	25	112
H		79	40	112
H		93	65	112

TABLE 28. (*Continued*)

C_n	R^2	R^3	R^4
	CO_2CH_3	CH_3	$NHCOCH_2C_6H_5$
	C_6H_5	CH_3	$CH(CH_3)CO_2H$
	CO_2H	CH_3	$S(CH_2)_3CH_3$
			
	CO_2H	CH_3	
17	$CH{=}C(CN)C_6H_5$	$C(CH_3)_3$	H
	$CH{=}CHCOC_6H_5$	$C(CH_3)_3$	H
	CO_2CH_3	CH_3	$S(CH_2)_3CH_3$
	H	$CH_2CH(OH)CH_2NH{-}CH_2CH_2C_6H_3{-}3,4\text{-}OCH_3$	H
18	CO_2H	CH_3	SC_6H_5
			
	CO_2CH_3	CH_3	
			
	CO_2H	CH_3	
	H	$CH_2CH(OH)CH_2{-}NH{-}(CH_2)_2C_6H_3{-}3,4\text{-}OCH_3$	H
19	CN	$CH_2COC_6H_5$	H
	CO_2CH_3	CH_3	SC_6H_5
			
20	CO_2CH_2	CH_3	
	H	$CH_2CH(OH)CH_2NH\cdot HCl{-}(CH_2)_2C_6H_3{-}3,4\text{-}OCH_3$	$-(CH_2)_3-$
	H	$CH_2CH(OH)CH_2NH\cdot HCl{-}(CH_2)_2C_6H_3{-}3,4\text{-}OCH_3$	$-(CH_2)_4-$

The reaction of methyl 4-bromo-2-thiophenecarboxylate with sodium hydride and methanol in dioxane gave methyl 4-methoxy-2-thiophenecarboxylate in 58% yield.[231]

The reaction of 2,5-diiodo-3-methylthiophene with sodium methoxide in methanol in the presence of cupric oxide gave a 30% yield of 3-methyl-2,5-dimethoxythiophene after four days of reflux. The small amounts of iodo-methoxy-3-methylthiophene that were present in the crude product were removed by reaction with butyllithium and carbon dioxide.[232]

Complications due to halogen dance occur in certain cases. Thus 3-bromo-2-iodothiophene, 4-bromo-2-iodothiophene, and 3-bromo-4-iodothiophene all gave 4-bromo-2-methoxythiophene in low yield upon reaction with sodium methoxide

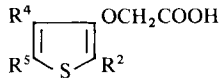
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
CH_3		156	94	253
H	156–158/0.1		91	73
C_6H_5		191	81	253
CH_3		207	71	253
H		91	90	123
H		90	65	112
C_6H_5		48	92	253
H		113–114	59	230
C_6H_5		198	69	253
CH_3		121	87	253
CH_3		197	55	253
CH_3		104–105	61	230
C_6H_5		157–158	81	174
C_6H_5		61	95	253
CH_3		Oil	90	253
		111–112	63	173
		141–142	81	173

in methanol in the presence of cupric oxide. The other main products were 2- and 3-bromothiophene. In the reaction of 2-chloro-5-iodothiophene about 20% of 2-chloro-5-methoxythiophene was formed.[233]

The reaction of 2,4-dibromothiophene with sodium ethylate in a mixture of ethyl alcohol dioxane led to a mixture of 2,4-diethoxythiophene, 4-bromo-2-ethoxythiophene, and 2-bromo-4-ethoxythiophene. Treatment of the product mixture with butyllithium and water transformed the two latter compounds to 2- and 3-ethoxythiophene, which facilitated the isolation of the desired 2,4-diethoxythiophene in 14% yield.

Copper-promoted substitution of 5-chloro-2-iodothiophene with sodium methoxide in methanol has later been claimed to give a 55% yield of 5-chloro-2-

TABLE 29. 3-THIENYLOXYACETIC ACIDS[291]



C_n	R^2	R^4	R^5	Melting Point (°C)	Yield (%)
6	H	H	H	112–114	68
	H	Cl	H	119–120	71
	H	H	Cl	117–119	70
	H	Cl	Cl	152–154	67
	H	Br	H	107–108	76
	H	Br	Br	154–156	73
	Cl	H	H	94–96	60
	Cl	Cl	H	93–94	88
	Cl	H	Cl	89–90	67
	Cl	Cl	Cl	112.5–113.5	61
	Br	H	H	114–116	58
	Br	H	Br	108–110	63
	Br	Br	H	119–120	59
	Br	Br	Br	156–157	77

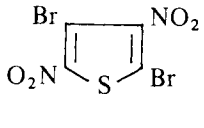
methoxythiophene, which also was prepared in 30% yield by metalation of 2-methoxythiophene with butyllithium followed by reaction with carbon tetrachloride. Similarly, 5-chloro-2-*t*-butoxythiophene was obtained from 2-*t*-butoxythiophene.[289]

Phenolates can also be used in these substitution reactions, if more forcing reaction conditions are used. Thus refluxing a mixture of 3-bromothiophene with *p*-cresol, copper bronze, and anhydrous potassium carbonate for seven days gave 3-(*p*-tolyloxy)thiophene in 86% yield. Phenol itself and other substituted phenols have also been used.[234] The reaction of tetrachlorothiophene with sodium phenolate in DMF at 150°C for five hours gave a 72% yield of 2-phenoxy-3,4,5-trichlorothiophene.[235]

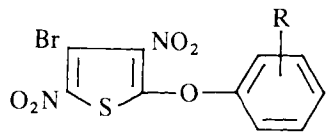
The reaction of tetrafluorothiophene with sodium methoxide in methanol in the absence of cupric oxide gave 3,4,5-trifluoro-2-methoxythiophene after 45 hours of reflux.[236] Treatment of 3H,4H-tetrafluoro-3-thiolen-2-one with sodium methoxide, followed by reaction with molten potassium hydroxide, gave 3-methoxy-2,5-difluorothiophene.[236] By a similar process 2,3,5-trifluoro-4-methoxythiophene was prepared.[237] Alkoxythiophenes prepared by the foregoing methods and their physical data are given in Tables 27 and 28.

D. Preparation of Alkoxythiophenes by Nucleophilic Substitution of Activated Thiophenes

Reactive dinitrohalothiophenes or nitrocarbonyl-substituted halothiophenes react smoothly with alkoxide or phenolate to give the corresponding alkoxy- and



387



388

R = H, O—CH_3, *p*-CH_3, *p*-Cl, *p*-Br

Scheme 94

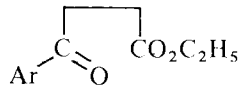
phenoxythiophenes. Thus from 2-chloro-3,5-dinitrothiophene, 2-methoxy-, 2-ethoxy-, and 2-phenoxy-3,5-dinitrothiophenes were prepared using the corresponding alcohol and potassium hydroxide, mostly in high yields. In some cases by-products were observed. Alkoxy and phenoxy derivatives were also prepared from 2-chloro-3-nitrothiophene and 4-nitro-5-chloro-2-acetothienone.[130,238,239] Other examples are the preparation of methyl 2-methoxy-3-nitro-5-thiophenecarboxylate from the 2-bromo derivative,[240] 3-methoxy-2-nitro- and 3-methoxy-4-methyl-2-nitrothiophene from the corresponding 3-bromo derivatives,[241,242] and 3-cyano-2-methoxy-5-nitrothiophene from 2-bromo-3-cyano-5-nitrothiophene.[243]

Reaction of **387** with various phenolates gave **388**[244] (Scheme 94). The reaction of 2,3-dinitrothiophene with sodium methoxide apparently gives a mixture of 3-nitro-2-methoxy- and 2-nitro-3-methoxythiophene.[241] The reaction of 5-*t*-butylsulfonyl-2,4-diformylthiophene with sodium alkoxides has been used for the preparation of 5-alkoxy-2,4-diformylthiophenes.[245]

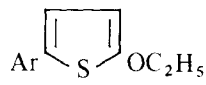
E. Various Preparations of Alkoxy- and Phenoxythiophenes

The reaction of di-(3-thienyl)iodonium chloride, prepared from 3-thienyllithium and *trans*-chlorovinyl iodosodichloride, with phenol and sodium hydroxide in refluxing water gave a 23% yield of 3-phenoxythiophene. With the sodium salt of 1-hexanol in the presence of anhydrous copper sulfate, 3-hexyloxythiophene was obtained in 23% yield.[246]

Aromatic γ-oxo esters (**389**) gave 5-aryl-2-ethoxythiophenes directly on reaction with hydrogen sulfide and hydrogen chloride (**390**)[4] (Scheme 95).



389



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Scheme 95

2. Reactions of Alkoxythiophenes

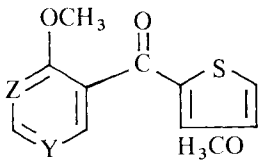
A. Reactions with Cleavages of the O-Alkyl Bond

The various cleavages of alkoxythiophenes to hydroxythiophene systems using acidic catalyst were discussed in detail in Section II.3.C. 3-Bromo-2,5-di-*t*-butoxythiophene yields thiomaleic anhydride on heating with *p*-toluenesulfonic acid.[247] This easy dealkylation has often been utilized to prepare condensed systems without isolation of the hydroxy intermediates. Thus **234** gave **235** (Scheme 57),[126,248] and from **240** and **241**, the xanthone analogues **242** and **243** (Scheme 58) were formed.[126] A related example is the formation of **392** from **391**;[128] compare also Schemes 59 and 60 (Scheme 96).

Whereas the reaction of **254** with pyridine hydrochloride gave **255** (Scheme 60), the reaction of **393** and **394** with triethylamine in benzene gave **395** (Scheme 97).

Acidification of compounds of type **396** gives **397** directly. Such compounds (**396**) are easily obtained by the reaction of 2-alkoxy-5-thienyllithium derivatives with aldehydes or ketones.[104,105,249,251] Similarly, from 2-*t*-butoxy-3-thienyllithium derivatives and aldehydes or ketones **398** is obtained upon acidification[105] (Scheme 98).

Reaction of 2-alkyl-5-methoxythiophene with Vilsmeyer reagent at 50–70°C



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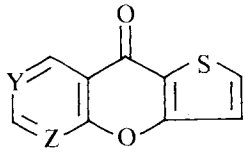
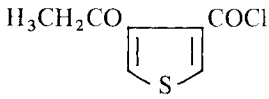


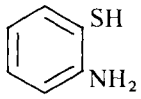
392

Y = CH, Z = N
Y = N, Z = CH

Scheme 96



393



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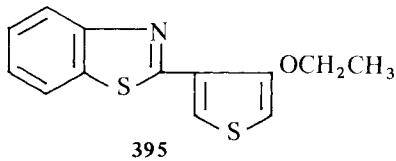

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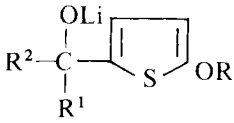
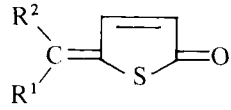
Scheme 97

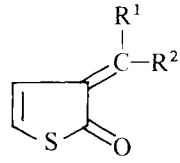


396

$R = CH_3, C(CH_3)_3$

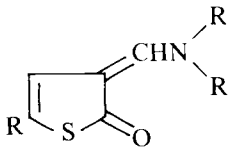


397

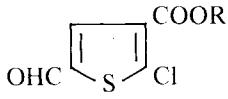


398

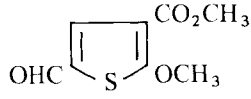
Scheme 98



399



400



401

Scheme 99

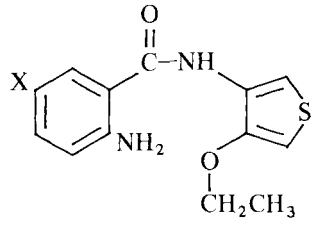
leads to dealkylation giving **399**, whereas at 20°C normal formylation occurred in the 3-position.[121] 2-Methoxy-3-thiophenecarboxylic acid gave **400** (R = H) or **400** (R = CH_3) with the Vilsmeyer reagent (by way of the acid chloride), depending upon the work-up, while methyl 2-methoxy-3-thiophenecarboxylate behaved as expected, giving **401**[252] (Scheme 99).

B. Reactions with Cleavages of the O-Thiophene Bond

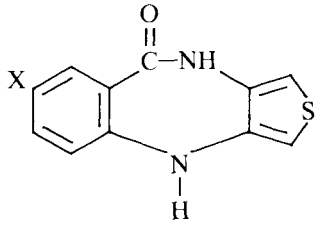
There are several reactions in which the alkoxy group is substituted for another group. Thus heating **402** with polyphosphoric acid gave **403**.

An interesting bromine migration occurred on heating **404** (X = Br) with polyphosphoric acid, as **406** was obtained, which was also the product on heating **405** in polyphosphoric acid. No such halogen migration occurred with **404** (X = Cl), and **407** was the product[254] (Scheme 100).

3- and 2-methoxythiophene reacted with tetracyanoethylene oxide to give 3-methoxy-2-thenyl cyanide and 5-methoxy-2-thenoyl cyanide, respectively, in low yields. It was suggested that the products were formed by reaction with carbonyl cyanide formed in the first step of the reaction.[255] In an attempted Hoesch reaction between **408** and phloroglucinol, **409** was formed in 38% yield[256] (Scheme 101).

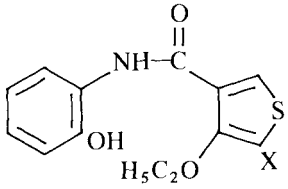


402



403

X = H, F, Cl



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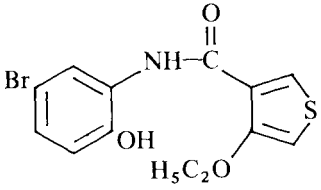

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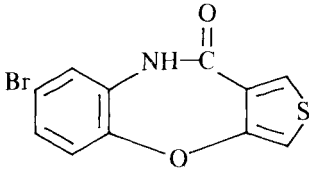

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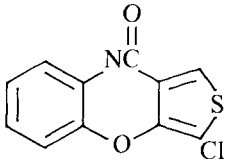
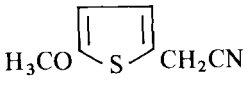
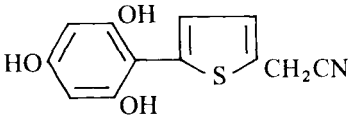


407

Scheme 100



408



409

Scheme 101

C. Electrophilic Substitution of Alkoxythiophenes

The acid sensitivity of the alkoxy group in thiophenes makes electrophilic substitution somewhat problematic. However, Sicé, as early as 1953 managed to acetylate 2-methoxythiophene in CS_2 at $-20°C$ using $SnCl_4$ as a catalyst, with a yield of 16%, and to nitrate it with acetyl nitrate at the same temperature. Owing to the

strong *o-p*-directing effect of the methoxy group, appreciable amounts of the 3-isomer were obtained together with the 5-isomer, especially in the nitration (36% 5-isomer and 24% yield of the 3-isomer).[223] Somewhat better yields were obtained when the acetylation was carried out at $-70°C$.[257]

Friedel-Crafts acylation of 3-methoxythiophene and 3,4-dimethoxythiophene under mixed conditions with $SnCl_4$ as catalyst could be achieved with substituted cinnamic acid chlorides without dealkylation. 5-Chloro-2-methoxythiophene was under these conditions selectively acylated in the 3-position.[289]

Bromination with NBS in carbon tetrachloride went more smoothly, and a 62% yield of 5-bromo-2-methoxythiophene was obtained.[223] Using two equivalents of NBS gave an 82% yield of 3,5-dibromo-2-methoxythiophene, which upon treatment with one equivalent of butyllithium and methanol gave 3-bromo-2-methoxythiophene.[252] A detailed investigation of the isomer distribution in the nitration of 2-methoxythiophene[258] and in the acetylation of 2- and 3-methoxythiophene[259] was subsequently carried out.

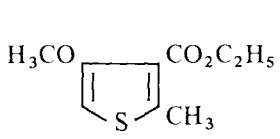
Vilsmeyer formylation of several alkoxythiophenes using $POCl_3$ and *N*-methylformanilide at room temperature gave the 5-formyl derivatives in 40 to 63% yield.[225] Reaction of 2- or 3-methoxythiophene with formaldehyde and dimethylamine, piperidine, or morpholine under the conditions previously used for indole gave good yields of the Mannich bases.[260]

General acid catalysis has been demonstrated in the protodetritiation of 5-methoxy-2-tritiothiophene.[261]

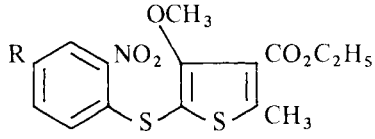
The reaction of **410** with aromatic sulfenyl chlorides gave **411**[171] (Scheme 102).

D. Metalation of Alkoxythiophenes

Owing to the acid sensitivity and selectivity in electrophilic substitution of alkoxythiophenes, metalation of 2-alkoxythiophenes with organolithium compounds, which occurs selectively in the 5-position, followed by reactions with electrophiles, has been extensively used for the preparation of 5-substituted 2-methoxythiophenes. In this way 5-methoxy-2-thiophene aldehyde, 2-methoxy- and 5-allyl-2-methoxythiophene,[223] 2,3-di-*t*-butoxy-5-thiophenecarboxylic acid,[108] and many other 5-substituted thiophenes have been prepared. It was found that the reaction



410



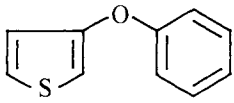
411

R = H, Cl, Br, $CO_2C_2H_5$

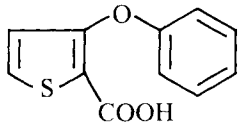
Scheme 102

between 5-alkoxy-2-thienyllithium derivatives and 1-chloro-2-dimethylaminoethane gave good yields of 2-alkoxy-5-(2-dimethylaminomethyl)thiophenes, whereas most other thienyllithium derivatives gave low yields. The reason for this was discussed.[262] With 3-alkoxythiophenes, metalation occurs predominantly in the 2-position, due to heteroatom-facilitated metalation.[107,115,226] However, a more careful investigation using GLC analysis showed that butyllithium in ether gave 87% 2-lithium and 13% of the 3-lithium derivative, determined as the methyl compounds after reaction with dimethyl sulfate. Metalation with lithium diisopropylamide was much more selective, giving the 2-lithium- and 5-lithium derivative in the ratio 99:1.[263] Metalation of **412** with one equivalent of phenyllithium in ether followed by reaction with carbon dioxide gave **413** and **414** in the ratio 98.3:1.7. Reaction with two equivalents of butyllithium followed by carbon dioxide gave **413** and **415** in the ratio 60:40[234] (Scheme 103).

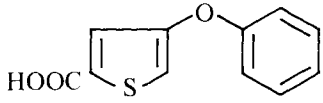
Methoxy groups also have curious effects on the ring opening of 3-thienyllithium derivatives. Thus 5-methyl-2-methoxy-3-thienyllithium, prepared through halogen–metal exchange of the 3-bromo derivative, is stable.[264] On the other hand, the reaction of 2-chloro-5-methoxythiophene with butyllithium at room temperature, or with 5-chloro-3-bromo-2-methoxythiophene at −70°C, gave **416** (R = Cl),



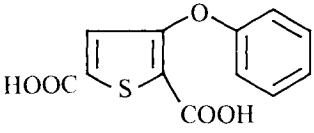
412



413

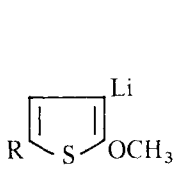


414



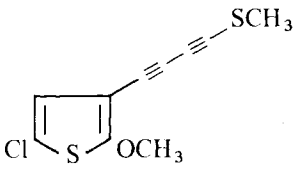
415

Scheme 103

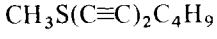


416

R = Cl
R = OCH_3



417



418

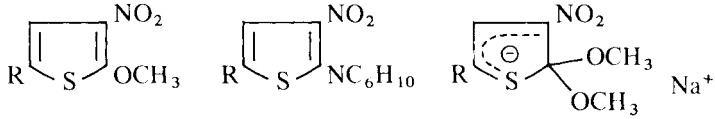
Scheme 104

which at room temperature ring opened and upon methylation with dimethyl sulfate gave **417** in 20% yield.

A reaction path for the formation of **417** was suggested.[265] Similarly, 2,5-dimethoxythiophene gave **416** ($R = OCH_3$) upon metalation with butyllithium, which rapidly ring opened to give **418** in 45% yield.[232] 3,4-Dichloro-2,5-dimethoxythiophene gave dibutyl and diphenyl sulfide upon reaction with butyllithium and phenyllithium, respectively, which was interpreted mechanistically as an attack by the organolithium reagent on the sulfur atom of the thiophene ring[266] (Scheme 104).

E. Reactions of Methoxythiophenes with Nucleophiles

The kinetics of piperidino substitution of **419** leading to **420** have been studied in methanol as a function of piperidine and methoxide ion concentrations. The reactions are catalyzed by both piperidine and methoxide. Evidence was given that the departure of the methoxide group is generally acid-catalyzed, indicating a specific base-general acid mechanism for base catalysis.[240] Similarly, mechanistic investigation of the reaction of **419** ($R = H$) with various cyclic secondary amines in methanol and benzene has been carried out.[267] The rate and equilibrium constants of the Meisenheimer adducts **421** from **419** and sodium methoxide in methanol have been determined, and factors determining the stability were discussed[268] (Scheme 105).



419 **420** **421**

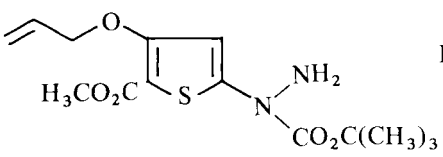
$R = H, CO_2CH_3, COCH_3$

Scheme 105

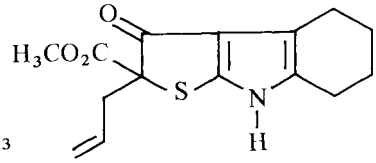
An NMR investigation of the behaviour of **419** ($R = H$) toward sodium methoxide has also been reported.[269] The rate and equilibrium constants for the formation of Meisenheimer adducts from 3-cyano-2-methoxy-5-nitro- and 5-cyano-2-methoxy-3-nitrothiophene have also been determined.[243]

F. Various Reactions of Alkoxythiophenes

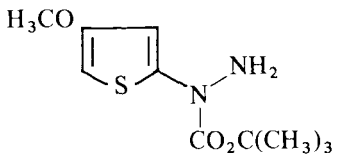
The use of **422** in an attempted Fischer indole cyclization with cyclohexanone and HCl led simultaneously to rearrangement of the allyl group to give **423**.[172] Another complication occurred in the attempted Fischer reaction of **424**, which gave **425**[231] (Scheme 106).



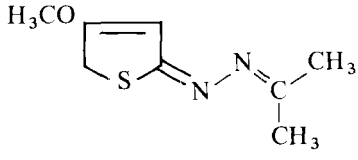
422



423



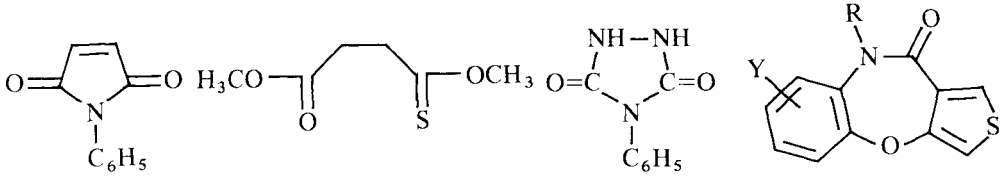
424



425

Scheme 106

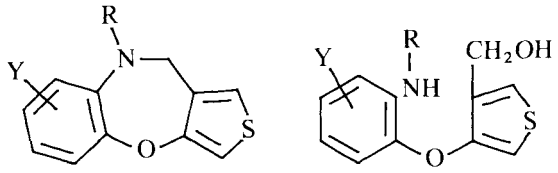
2,5-Dimethoxythiophene reacted with **426** in methanol to give **427** and **428** after hydrolysis.[270] Diethyl 3,4-methylenedioxy-2,5-thiophenedicarboxylate has been converted to symmetrically and unsymmetrically substituted thiophene derivatives[271] (Scheme 107).



426 427 428 429

Scheme 107

Reduction of **429** with lithium aluminum hydride gave ring opened products **431**, in addition to the expected **430**[272] (Scheme 108).



430 431

Scheme 108

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CHAPTER II

Syntheses, Physical Properties, and Reactions of Compounds Containing Thiophene–Sulfur Bonds

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I. INTRODUCTION

This chapter treats all classes of compounds with a thiophene–sulfur bond. Thus the preparation, physical properties, and reactions of thiophenethiols, alkyl and aryl thiophenesulfides, thiophenesulfonium salts, thiophenedisulfides, thiocyanothiophenes, alkyl and aryl thienylsulfones, thiophenesulfonic acids, and thiophenesulfonic acids and their derivatives are discussed. Compounds containing thiophene–selenium and thiophene–tellurium bonds are also treated. The characterized compounds are tabulated together with their physical data.

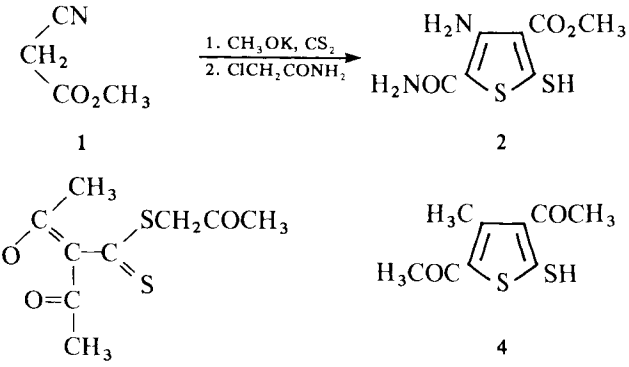
II. THIOPHENETHIOLS

1. Introduction

Thiophenethiols have mainly been prepared by the following methods: (1) ring closure of aliphatic compounds; (2) introduction of the thiophene–sulfur bond into appropriate thiophene derivatives; and (3) by modification of thiophenes already containing the thiophene–sulfur bond, such as thiophenesulfonyl chlorides or alkylthiothiophenes.

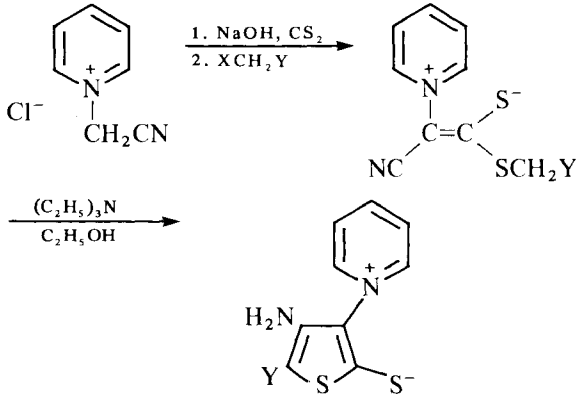
2. Syntheses of 2-Thiophenethiols

2-Thiophenethiol and 5-methyl-2-thiophenethiol were obtained as by-products in the ring closure of succinic acid[1] and levulinic acid[2] with phosphorus penta-



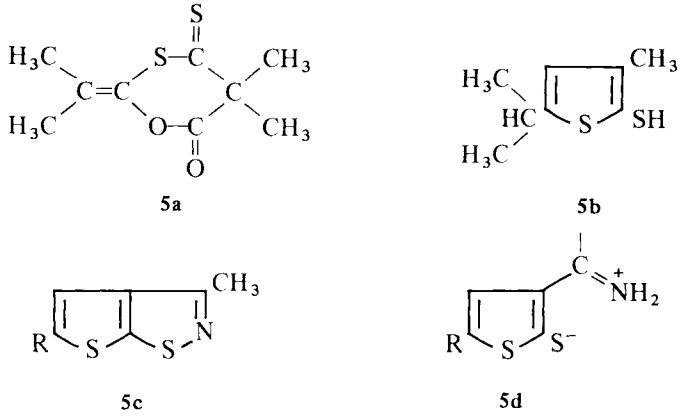
1 2 3 4

Scheme 1



Y = CN, $CONH_2$, $CO_2C_2H_5$, COPh

5



5a 5b 5c 5d

R = $CO_2C_2H_5$, H, NO_2

Scheme 2

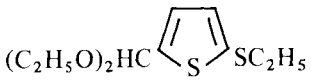
sulfide. There are also some ring-closure reactions that lead to highly substituted 2-thiophenethiols as the main products. The Gompper reaction (for review, see Part 1, Chapter I.4.A) has been used for the preparation of the 3-amino-2-thiophenethiol (**2**),[3] and from **3**, the diacetyl-2-thiophenethiol (**4**) has been obtained.[4] The Gompper reaction was also used for the preparation of the interesting zwitterionic thiolates (**5**) shown in Scheme 2.[5] Both the Gompper reaction and other cyclization reactions are, however, of much greater importance for the direct synthesis of 2-alkylthiothiophenes (see following material). The reaction of sodium phenyl dithioacetate with phenacyl bromide in boiling ethanol gives 3,4-diphenylthiophene-2-thiol.[85]

Reaction of dimethylketene with CS_2 gives **5a**, which upon heating in refluxing toluene gives **5b** in 40% yield.[86] A recent interesting reaction leading to thiophenethiols is ring opening of **5c** on treatment with hypophosphorous acid to give **5d**, which could be transformed to 3-acetyl derivatives or alkylated on the sulfur.[266] Ring closures that lead to 2-thiophenethiolates, which were further transformed to thioethers or disulfides before isolation, are treated in the appropriate sections.

2-Thiophenethiols have also been prepared by the reduction of 2-thiophenesulfonyl chlorides with zinc dust[6,7] or lithium aluminium hydride.[8] However, the most common and convenient method consists of the reaction of the Grignard reagents from 2-bromo- or 2-iodothiophenes with sulfur[2,7,9] or the reaction of 2-thienyllithia with sulfur.[9–16,254] The obtained 2-thienyllithia are obtained by direct metalation of thiophenes or by halogen–metal exchange with alkyllithia. A detailed procedure for the preparation of 2-thiophenethiol has appeared in *Organic Synthesis*.[17] Recently the reaction of 2-thienyllithium with tetraisopropyl thiuramdisulfide has been used for the preparation of highly crystalline and readily purified *S*-(2-thienyl)-*N,N*-diisopropyldithiocarbamate in 96% yield, which upon alkaline hydrolysis yields 2-thiophenethiol.[250]

2-Chloro-, 2,5-dichloro-, and 5-ethyl-2-chlorothiophene give the corresponding 2-thiophenethiols on reactions with hydrogen sulfide.[18]

A method for the preparation of 2-thiophenethiols, which has extensively been used by Gol'dfarb et al.,[19–28] is the dealkylation of alkylthiothiophenes with sodium in liquid ammonia.[19] In this way 2,5-thiophenedithiol was prepared from 2,5-diethylthiothiophene.[11] The use of two equivalents of sodium on **6** gave the



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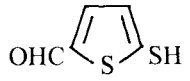

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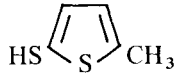

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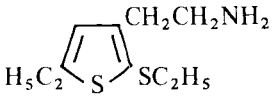

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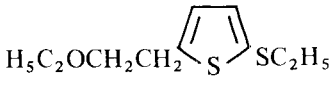

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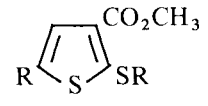

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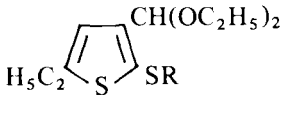
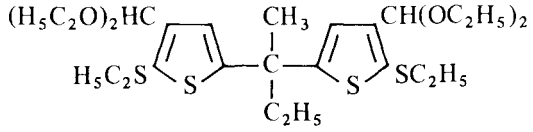
Scheme 3



R = C_2H_5, $C_6H_5CH_2$

12



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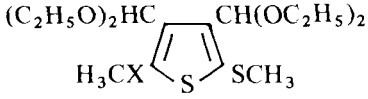
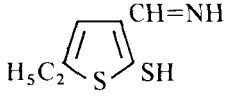


X = O,S

14



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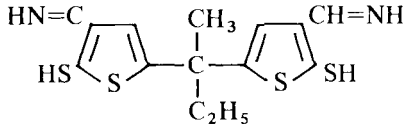

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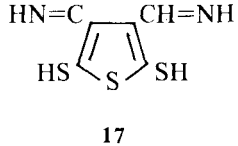

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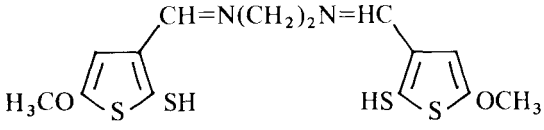


18

Scheme 4

aldehyde **7**, whereas six equivalents gave **8**.[20] Also compounds such as **9**,[21] **10**,[22] and **11**[23] could be smoothly dealkylated. From **11**, the amide was obtained (Scheme 3).

Especially interesting is the dealkylation of acetal-protected orthoformyl alkylthiothiophenes such as **12**[20,24–27] **13** and **14**,[28] which leads to the aldimines (**15**), (**16**), and (**17**), which upon reaction with primary amines could be converted to more stable and better characterized Schiff's bases.[22,25,28,30,31] Thus the reaction of **14**, X = O with sodium and liquid ammonia followed by ethylene diamine gave **18**[32] (Scheme 4).

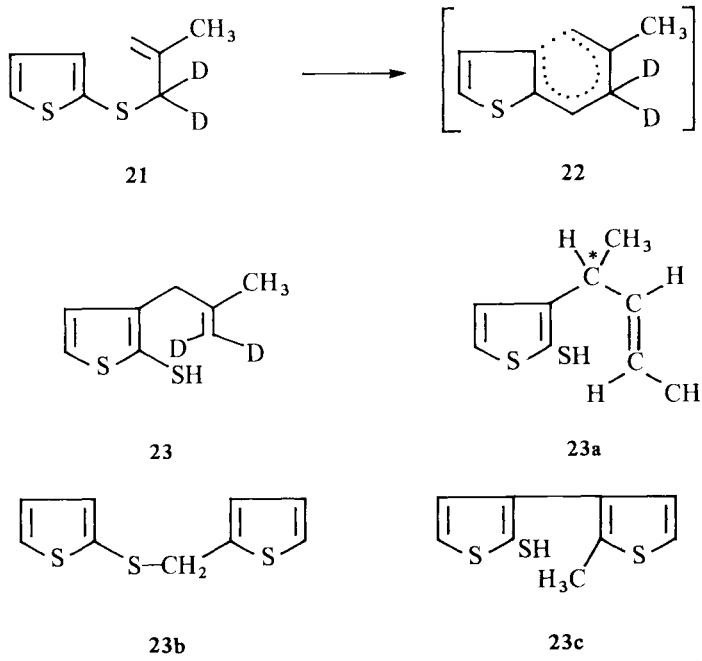
Another route to 2-thiophenethiols (**20**) is the thio-Claisen rearrangement of allyl 2-thienylsulfides (**19**) (Scheme 5)[33,34] which takes place on heating without solvent or in *N,N*-dimethylaniline, triethylamine, or pyridine in the temperature range 100 to 180°C.

In the rearrangements of allyl thienyl sulfides, the thiols can be isolated as such, if the right conditions are used. This is in contrast to the rearrangement of allyl phenyl sulfides in *S*-methyl derivatives.[35] Using deuterium-labeled allyl thienyl sulfide (**21**), it was demonstrated that the reaction takes place by way of inversion

19 20

a. X = Cl, Y = H
b. X = H, Y = Cl
c. X = H, Y = H
d. X = OCH_3, Y = H
e. X = CH_3, Y = H
f. X = SCH_3, Y = H
g. X = Br Y = H

Scheme 5

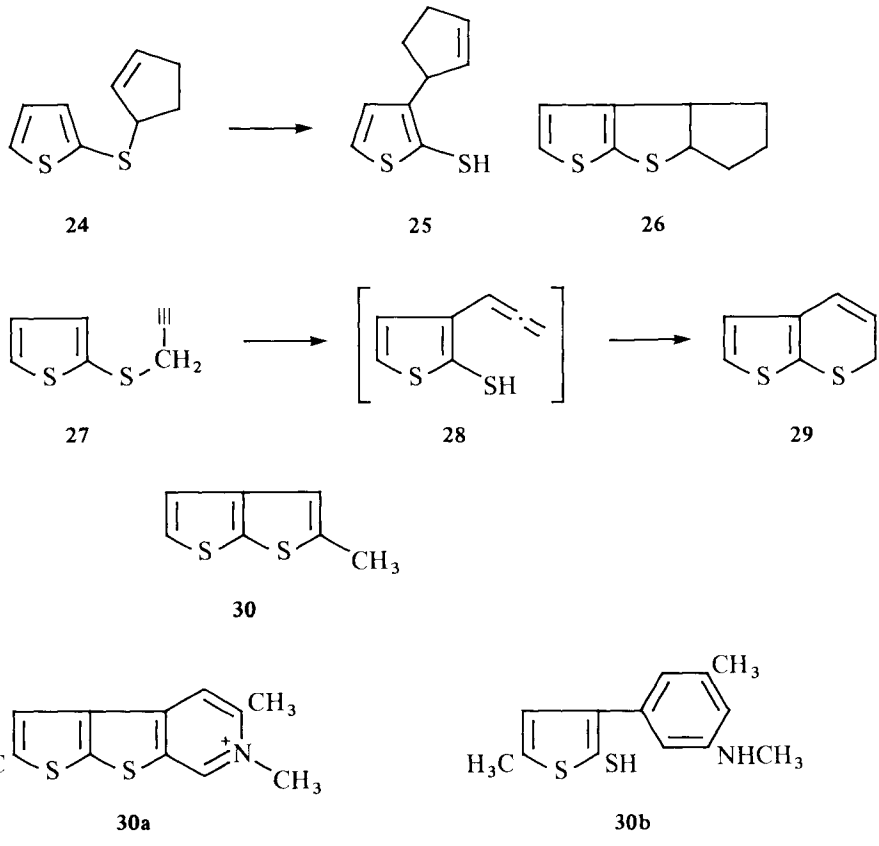


21 22 23 23a 23b 23c

Scheme 6

of the allyl group through a six-membered transition state (**22**) to give **23**[33] (Scheme 6).

The thio-Claisen rearrangement of (−)-*s-trans*-(3-penten-2-yl)-2-thienyl sulfide occurs with conservation of optical activity to give **23a**.[460] The thio-Claisen rearrangement has also recently been used to prepare **23c** from **23b**.[461] Kinetic investigations have shown that the thio-Claisen rearrangement is a noncatalytic first-order reaction with activation energies between 13.4 and 24.7 kcal/mol. The reactivities for **19** were found to decrease in the order **19d** > **19e** > **19f** > **19c** >



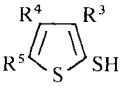
Scheme 7

19a > **19g**,[37] and **19b** reacted much faster than **19a**.[38] The rate of the thio-Claisen rearrangement is faster in acetone and acetonitrile than in isooctane, indicating some charge separation in the cyclic transition state.[33]

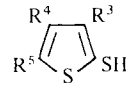
From the preparative point of view, there are some complications due to subsequent cyclization to cyclic thioethers.[39] Thus in addition to **25**,[40] **26** was obtained from **24** (Scheme 7). However, this ring closure of 3-allylthiophenethiols can intentionally be made the main reaction path in the presence of bases.[41] In the rearrangement of **27**, in HMPTA at 170 to 180°C, the possible intermediate allenic thiol (**28**) could not be detected, and **29** was obtained in 92% yield.[16]

In the presence of catalytic amounts of secondary and tertiary amines, the reaction was even more complicated and yielded **30**, as well as allenyl thienylsulfides and propynyl thienylsulfides.[16,29,42] A review of the thio-Claisen rearrangement has been published.[43] A very special method for the synthesis of a 2-thiophenethiol consists in the treatment of **30a** with base, which yields **30b**[464] (Scheme 7). Known 2-thiophenethiols, reference to their method of preparation, and physical properties are collected in Table 1.

TABLE 1. 2-THIOPHENETHIOLS

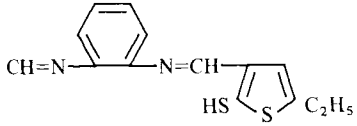
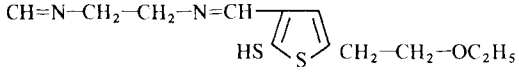
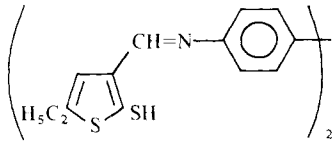


C_n	R^3	R^4
4	H	Br
	Br	H
	H	H
	H	H
	H	H
	H	H
	SH	H
5	CH=NH	H
	H	H
	CH_3	H
	H	H
	H	CH_3
	H	H
6	CH=NH	CH=NH
	Br	H
	CH=NH	H
	H	H
	SH	H
	SC_2H_5	H
7	CO_2CH_3	NH_2
	CO_2H	H
	$CH_2CH=CH_2$	H
	$CONH_2$	H
	CH=NH	H
	$CH=N(CH_3)_2$	H
	H	H
	CH_2NH_2HCl	H
8	$CONH_2$	H
	CH=NOH	H
	CO_2CH_3	H
	$CH_2-CH=CHCH_3$	H
	CH_3 | $CH-CH=CH_2$	H
	CH_3 | $CH_2-C=CH_2$	H
	H	H
	H	H
	H	H
	CH_3	H
	$CH_2CH_2NH_2 \cdot HCl$	H
9	$COCH_3$	CH_3
	3-Cyclopentyl	H
	$CH=NCH_2COO^-Na^+$	H



R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H	74–75/0.4		51	9
H	82–85/0.1		59	9
Cl	54/2		59	18
OH	67–69/0.3			14
H	50–51/4		51	8
SH	85/5		85	11
H	75–80/4		73.5	11
H		>360	83	25
OCH_3	102/16		57	81
H	85–86/30		52	9
CH_3	64/10		65	2
H	76–78/14		50	9
SCH_3	81–84/0.4		64	9
SH			88	28
C_2H_5	112–115/4		54	10
CH_3		155–156.5 (decomp.)	89	27
C_2H_5	84/13		82	19
C_2H_5	105–107/5		70	11
H	89–91/3		70	11
$CONH_2$		174–176	56	3
C_2H_5		119–121	90	27
H	68–71/3		20–91	41
C_2H_5				72
C_2H_5				68
H		160–161 (decomp.)		69
C_3H_7			71	8
C_2H_5				68
$CO_2C_2H_5$		217–218 (decomp.)	93	93
$CO_2C_2H_5$		108–109	79	93
C_2H_5	116–118/3		61	23
H	69–71/3			41
H	97–98/3			41
H	98–100/3			41
$CH_2CH_2-OC_2H_5$	112/5		74	22
$O-C(CH_3)_3$	59–61/0.1		73	14
$S-C(CH_3)_3$	105/1		54	15
$CH(CH_3)_2$	52–78/0.2–0.5		40	86
C_2H_5		227–229	18	21
$COCH_3$		101–104	45	4
H	110–111/2			40
C_2H_5		207–209	78.7	27

TABLE 1. *(Continued)*

C_n	R^3	R^4
	$CO_2C_2H_5$	H
	$CH{=}N(CH_3)_2$	H
	H	H
10	$COCH_3$	CH_3
	$NHCOCH_3$	CH_3
	H	H
11	$CH{=}N{-}CH(COO^-Na^+)CH_2COO^-Na^+$	H
	$CH_2CH{=}CH_2$	H
	$CH{=}N(C_2H_5)_2$	H
	CH=N-cyclohexyl	H
	CH=N-2-pyridyl	H
12	H	H
13	$CH{=}N{-}C_6H_5$	H
	CH=N-cyclohexyl	H
	$CH_2NH{-}C_6H_{11}HCl$	H
14	$CH{=}NC_4H_9$	$CH{=}NC_4H_9$
15	CH=N-β-naphthyl	H
	CH=N-cyclohexyl	H
	$CH(C_4H_9)$-NH-cyclohexyl	H
17	CH=N-β-naphthyl	H
18	$CH{=}N{-}C_6H_5$	$CH{=}N{-}C_6H_5$
	$CH{=}N{-}CH_2COO^-Na^+$	H
	CH=N-cyclohexyl	CH=N-cyclohexyl
	CH=N-β-naphthyl	H
20		H
		H
26		

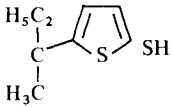
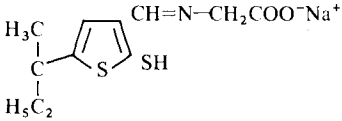
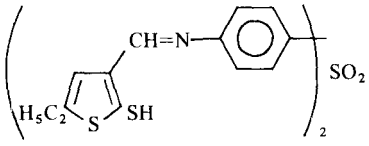
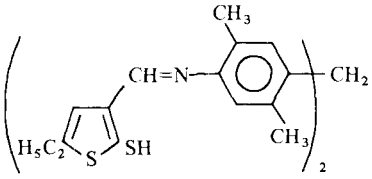
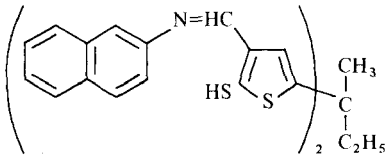
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
C_2H_5	136–140/4			23
C_2H_5	139.5–140.5		84	69
$SCH_2CH_2CH(CH_3)_2$	135–137/2.5		41.5	15
$CO_2C_2H_5$		61–62	47	93
$CO_2C_2H_5$		127–128	77	93
$S(CH_2)_5CH_3$	147–149/2		41.5	15
C_2H_5		280 (decomp.)		27
$C(CH_3)_3$				70
C_2H_5		69–70.5	60.5	69
H		103.5–105	87	25
CH_3				30
	160–162/0.05		80	26
C_2H_5				62
C_2H_5		98–99	67.6	24
C_2H_5				68
SH		165–166.5	55	28
H		169.5–170.5		25
$CH_2CH_2OC_2H_5$				22
H		160–162	54	25
C_2H_5		141.5–142.5	92.5	24
SH		200–202	52	28
			75	27
SH		208–211	54	28
$CH_2CH_2OC_2H_5$		119–120	40	22
C_2H_5		131	68	27
$CH_2CH_2OC_2H_5$		165–167	46	22
		250–252 (decomp.)	97.5	24

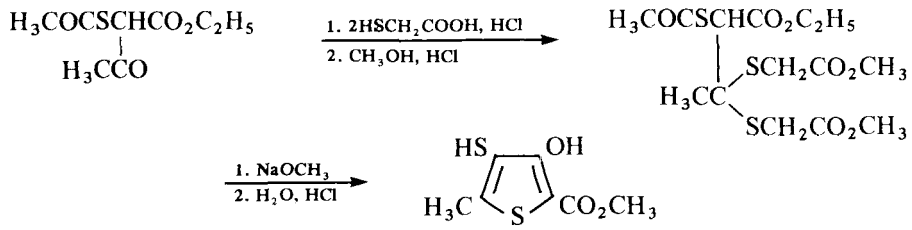
TABLE 1. (*Continued*)

C_n	R^3	R^4
		
31		
34		

3. Syntheses of 3-Thiophenethiols

The parent 3-thiophenethiol was obtained by pyrolysis of the "thiophene tars" from the commercial thiophene synthesis from butane and sulfur.[36] Another by-product from "thiophene tar," which was claimed to be 3,4-thiolanedithione (a tautomer of 3,4-thiophenedithiol),[36] was shown to be 5-methyl-1,2-dithiol-3-thione.[44] Substituted 3-thiophenethiols have also been obtained by ring-closure reactions. Through the Fiesselmann reaction (see Chapter I) the highly functionalized 3-thiophenethiol (**31**) was prepared in 50% yield (Scheme 8).[45]

Another route to 3-thiophenethiols starts from the easily available 3-oxotetrahydrothiophenes (**32**), which upon reaction with hydrogen sulfide give **33**. In the

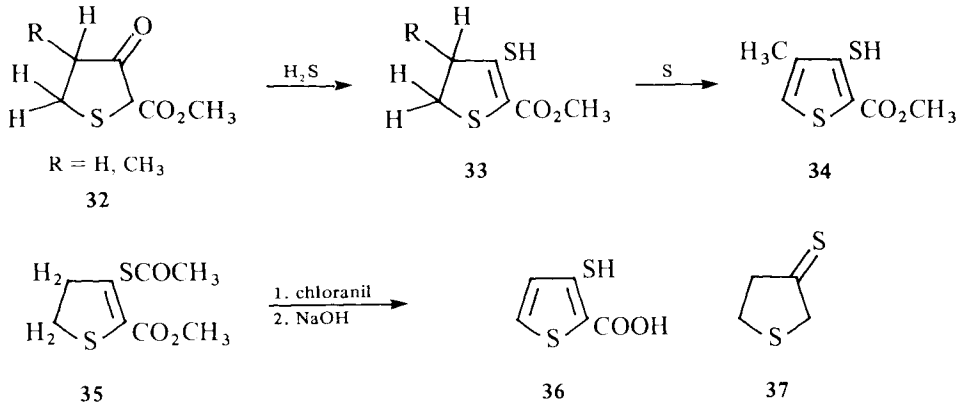


31

Scheme 8

R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
		239–241 (decomp.)	68.7	24
		248–250 (decomp.)	96.2	24
		226–228	92.5	26

case R = Me, **33** was aromatized with sulfur[46] to **34**. Compound **32** (R = H) was first acetylated to **35** and then aromatized with chloroanil and hydrolyzed with sodium hydroxide to yield **36**. Treatment of **33** (R = H) with 2*N* sulfuric acid gave **37**, which after acylation, aromatization with chloranil, and alkaline hydrolysis gave the parent 3-thiophenethiol[45] (Scheme 9). 2,4-Diphenyl-3-thiophenethiol, isolated as the disulfide, was formed in the thermal decomposition of 2,5-diaryl-1,4-dithiin.[87] The reaction of 3-thiethanone with methanolic sodium hydrogen sulfide gave 2,4-dimethyl-3-thiophenethiol and its disulfide.[88]



Scheme 9

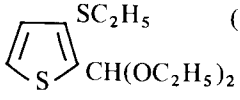
The reduction of sulfonyl derivatives is not of great importance for the preparation of 3-thiophenethiols since electrophilic sulfonation predominantly occurs in the α-positions. Only if the α-positions are blocked, as in 2,5-dimethylthiophene, has this route been used.[47,48] The use of 3-thiophenemagnesium bromide for the preparation of 3-thiophenethiols is also limited, as such reagents can only be obtained by the entrainment method. 3-Thiophenethiol was obtained in low yield from 3-thiophenemagnesium iodide.[36] The most-used method, first described in Reference 49, is the reaction of 3-thienyllithium derivatives obtained from 3-bromo- or 3-iodothiophenes with sulfur at −70°C.[9,39,49–52] The reaction had to be carried out rapidly at low temperatures to avoid alkylation of the 3-thiophenethiolate by the alkyl halide formed in the halogen–metal exchange.[49] On acidification of the product from the reaction of 2-*t*-butoxy-4-thienyllithium with sulfur, dealkylation occurred and gave the 2-hydroxy-4-thiophenethiol system, which was claimed to exist as 4-mercapto-3-thiolen-2-one.[53] Reaction of 4-bromo-3-thiophenethiol with two equivalents of butyllithium and sulfur was used for the synthesis of 3,4-thiophenedithiol.[44] It can also be prepared in a one-pot procedure from 3,4-dibromothiophene[54] and has become of increasing interest as a starting material for organic "metals."

Nucleophilic substitution of ethyl 4-chloro-5-formyl-2-methyl 3-thiophenecarboxylate with anhydrous sodium hydrogen sulfide in dry acetone gave an 82% yield of ethyl 5-formyl-4-mercapto-2-methyl 3-thiophenecarboxylate.[93]

Diazotization of methyl 3-amino-2-thiophenecarboxylate and methyl 3-amino-4-thiophenecarboxylate followed by reaction with potassium xantogenate and alkaline hydrolysis was used for the preparation of 3-mercapto-2- and 3-mercapto-4-thiophenecarboxylic acid.[482]

Furthermore, 3-alkylthiothiophenes can be dealkylated by sodium in liquid ammonia, and from 2,3-diethylthiothiophene and four equivalents of sodium in liquid ammonia 2,3-thiophenedithiol was obtained, which was characterized as the dibenzoyl derivative.[11] The main product of the reactions of the acetals **38** and **39** with two equivalents of sodium in liquid ammonia was **40** and **41**, respectively, which were characterized as benzoylated acetals and aldehydes or as thioethers through the reaction with 2,4-dinitrochlorobenzene[55] (Scheme 10). The tautomeric system (**42**) was obtained upon treatment of **38** with aqueous ammonia. On reduction with $LiAlH_4$, **43** was obtained. Reaction of **39** with primary amines leads to **44**.[55,56]

Thio-Claisen rearrangement of allyl thienyl sulfide in quinoline gave only a low yield of **45**, since further ring closure to **46** and **47** occurred. If the 2-position was blocked, as in **48**, **49** together with ring-closed products were obtained.[39] Heating of **50** in HMPT gave **52**, probably by way of the nonisolable **51**.[16,29] In the presence of catalytic amounts of secondary and tertiary amines, 2-methylthieno[3,2-b]thiophene could be obtained as the main product.[29] Using a method for phenol to thiophenol conversion, 3-hydroxy-2-carbomethoxythiophene has been converted to 3-mercapto-2-thiophenecarboxylic acid.[462] Known 3-thiophenethiols and their physical properties are given in Table 2.



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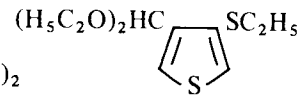

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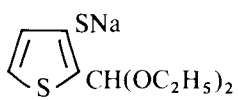

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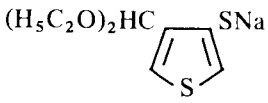

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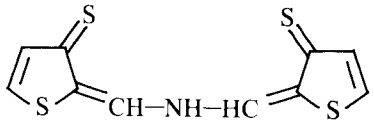

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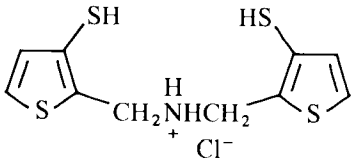

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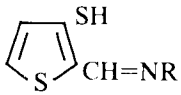
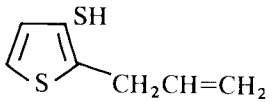


$R = C_6H_{11}, CH_2C_6H_5, \beta$-naphthyl

44



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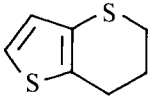

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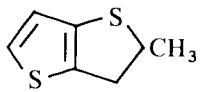

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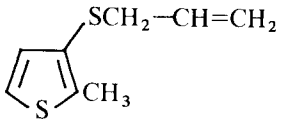

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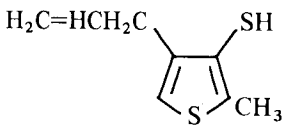
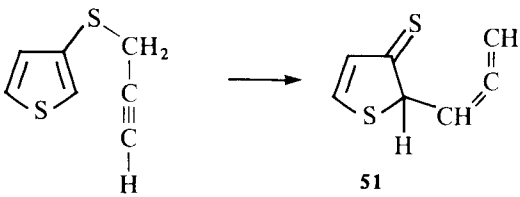


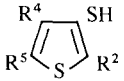
49

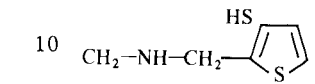


50 51 52

Scheme 10

TABLE 2. 3-THIOPHENETHIOLS



C_n	R^2	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
4	H	Br	H	91–93/1.5		67	9
	H	H	OH	118–121/1	53–54.5		53
	H	H	H	62–64/14		63	49
	H	SH	H	88–93/1.5		49	44
5	CO_2H	H	H		234	68	45
	CH_3	H	H	71–74/11		67	9
	H	CH_3	H				52
	H	H	CH_3	82–85/22		44	52
	H	SCH_3	H	90–91/0.3		50	9
	H	H	SCH_3	93–96/0.7		55	9
	SCH_3	H	H	71–72/0.4		43	9
6	CH_3	CH_3	H	75/12			88
	CH_3	H	CH_3	95–96/20		50	47
7	CO_2CH_3	CH_3	H			46	46
	$CH_2CH{=}CH_2$	H	H	72–74/3			41
	H	H	CH_2CSCH_3		52		145
8	CH_3	$CH_2CH{=}CH_2$	H				39
10	 HCl	H	H		129–131	43.5	56
11	CH=N-cyclohexyl	H	H		114–115	70	56
12	H	H	$CH_2CS{-}C_6H_5$		86		146
	$CH{=}N{-}CH_2{-}C_6H_5$	H	H		107–108	85	56
	CH=N-β-naphthyl				144–145		56

4. Physical Properties of Thiophenethiols

This section discusses physical properties connected with the thiol group. The electronic absorption spectra of some thiophenethiols have been measured, and their ionization constants have been determined by measuring the pH dependence of the optical densities of their aqueous alcohol solutions.[57] The data are collected in Table 3.

The dipole moments of 2- and 3-thiophenethiol and 2,5-dimethyl 3-thiophenethiol in benzene solution were found to be 1.50 D, 1.07 D, and 1.44 D, respectively.[58,59]

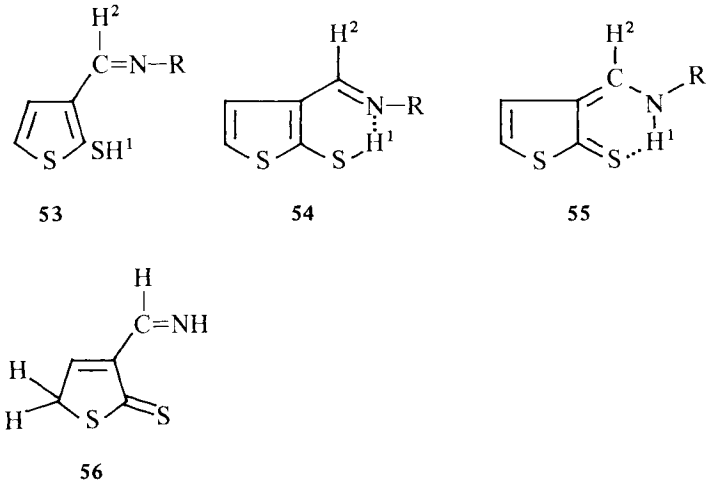
Simple thiophenethiols were shown by NMR and IR spectroscopy (SH stretching bands at 3.94–3.99 μ) to exist in the thiol form.[9,60,254] They show characteristic long-range couplings of the SH-hydrogen to the ring-hydrogens. Thus, in 2-thiophenethiols, J(SH-3) was found to be 1.40 to 1.60 Hz and J(SH-5) was 0.90 to 1.0 Hz. In 3-thiophenethiols J(SH-2) was 0.65 to 1.05 Hz and J(SH-5) was smaller than 0.3 Hz. Couplings between hydrogens of different side-chains have also been observed in 3- and 5-methyl-2-thiophenethiols and in 2-methyl-3-thiophenethiol, but not in 3-methyl-4-thiophenethiol.[61] The signs of these side-chain spin couplings were determined by selective double irradiation.[13,52]

In orthomercaptoaldimines the question of tautomerism is more complex, and four tautomeric forms (**53** to **56**) are possible, two of which contain intramolecular hydrogen bonds. It was shown by ^{1}H NMR and IR spectroscopy that in the solid state, in solution, and in the melt these compounds exist mainly as **55** (Scheme 11). With an increase in temperature a transition to **53** or **54** was observed. The chemical shift of the hydrogen taking part in the formation of the intramolecular hydrogen bond depends largely on the nature of the substituent at the nitrogen. The highest values, and therefore the strongest hydrogen bonds, were obtained with substituents having aromatic character. At the same time, the chemical shift for this hydrogen

TABLE 3. pK_a VALUES AT 20°C, WAVELENGTHS AND EXTINCTIONS[a] AT THE MAXIMA IN THE ABSORPTION SPECTRA OF HETEROAROMATIC THIOLS

Compound	λ (nm)	pK_a	λ(ε)
Thiophene-2-thiol	290	6.76 ± 0.05	219(3310), 255(7500), 295(5160), 305(4200), 317(3590)
Thiophene-3-thiol	280	6.80 ± 0.05	218(5220), 256(11600), 296(6000), 305(5450), 317(5780)
3-Allylthiophene-2-thiol	290	6.92 ± 0.05	
2-Allylthiophene-3-thiol	280	6.88 ± 0.07	
5-*tert*-Butyl-3-allylthiophene-2-thiol	290	7.04 ± 0.05	
5-Chlorothiophene-2-thiol	310	5.73 ± 0.05	206(4090), 258(6380), 310(4740)

[a]Liters per mole per centimeter.



Scheme 11

in the region $\delta = 12$ to 14 ppm is only slightly dependent on the concentration and on the nature of the solvent. A J(1, 2) coupling of 13 to 15 Hz was also observed.[24,28,62]

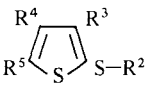
5. Reactions of Thiophenethiols

A. Introduction

In their chemical behavior thiophenethiols are quite similar to thiophenol, but in some cases their thermal stability is much less than that of the corresponding benzene derivative. Thus compounds like 5-bromo- or 3-bromo-2-thiophenethiol or 4-bromo-3-thiophenethiol decompose violently at room temperature within 30 minutes after their isolation by vacuum distillation, with the evolution of hydrogen bromide and hydrogen sulfide, leaving a brittle black tar.[9] 5-Chloro-2-thiophenethiol was somewhat more stable.[254] Thiophenethiols are often very sensitive toward oxidation, and the corresponding disulfides are unintentionally obtained as by-products in the preparation of thiols.[23,55] Thiophenedithiols are particularly air sensitive.[11] Salts of thiophenethiols are, of course, good nucleophiles.

B. Alkylation and Acylation of Thiophenethiols

Both 2- and 3-thiophenethiols have been reacted with α-haloacids or α-haloesters,[27,47,51,64,69,76,78,80] with ω-haloesters,[48] with alkyl halides,[5,24,56,69,74–75,77] with allyl halides,[16,37,38,40–42] with propargyl halides,[275,276] and with ω-*N*,*N*-dialkylaminoalkyl halides[7,70] in alkaline alcoholic or aqueous solution to give alkylthio

TABLE 4. ESTER DERIVATIVES AND RELATED COMPOUNDS OF 2-THIOPHENETHIOL 

C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	COCl	H	H	H	80/4.5		42	139
	$CONH_2$	H	H	H		118.5	30	139
6	COCl	H	H	SCF_3	50/0.05		14	139
	$COCH_3$	H	H	H	74–80/1.3		89	463
7	$COCH_3$	NHCHO	H	H		70–72	45	134
8	$COCH_3$	$NHCOCH_3$	H	H		102–103	80	134
11	$CON\left(CH\begin{matrix}CH_3\\CH_3\end{matrix}\right)_2$	H	H	H		119–121	96	250
12	COC_6H_5	H	H	SCN		79–80	63	165
13	$-\overset{S=O}{\overset{\|}{C}}-C_6H_2-2,4,6-CH_3$	H	H	H		Z 124–125 E 27–28.5	37	430
18	COC_6H_5	H	H	$SCOC_6H_5$		83.5–85	55	11

derivatives. From 1,2-dichloro- and 1,2-dibromoethane the mono-(2-thienyl)thiolated compound has been prepared.[70] 1,2-Di-(3-thienylthio)ethane has been obtained from 3-thiophenethiol and 1,2-dichloroethane.[64] Both 2- and 3-thiophenethiols have been reacted with ethylene chlorohydrin.[64,70] 2-Thiophenethiol has also been reacted with epichlorohydrin, glycerol dichlorohydrin, tetrachloropentane, and ethylenimine,[79] and with ethylene oxide.[246]

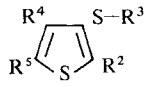
Under strongly acidic conditions (75% sulfuric acid), 2-thiophenethiol was reacted with isobutylene to give *tert*-butyl-2-thienylsulfide.[15,71,79] Other Lewis acid catalysts and olefins have also been used.[71] This approach was also used for the preparation of the unstable 4-*tert*-butylmercapto-3-thiolen-2-one from 4-mercapto-3-thiolen-2-one (the stable tautomeric form of 4-mercapto-2-hydroxythiophene).[53]

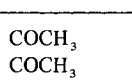
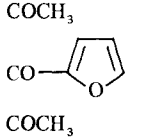
The thiophenethiolates can take part in nucleophilic aromatic substitution, which has sometimes been used for the characterization of more or less stable thiophenethiols. Usually, 2,4-dinitrochlorobenzene has been used as substrate.[10,19,20,24,26,55,254]

Copper-promoted reactions have been used when 2- and 3-thiophenethiolates are reacted with nonactivated aromatics such as halothiophenes[12] or orthoiodobenzoic acid.[63] Heating 3-bromo-4-thiophenethiol with potassium hydroxide and cupric oxide in DMF gave dithieno[3,4-*b*,3′,4′-e]-[1,4]dithiin.[50]

The Michael addition of thiophenethiolates to α,β-unsaturated compounds such as 3-nitrobenzal acetophenone,[10,22,81] acrylonitrile,[24,26,79] methyl methacrylate,[64,79]

TABLE 5. ESTER DERIVATIVES AND RELATED COMPOUNDS OF 3-THIOPHENETHIOL



C_n	R^2	R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Reference
6	NO_2	$COCH_3$	H	H	65–66	45	158
	H	$COCH_3$	H	H	41.5–43	76	64
7	NHCHO	$COCH_3$	H	H	117–119	55	158
8	$NHCOCH_3$	$COCH_3$	H	H	194–195	50	158
9	H		H	H	51–52	81	64
	CH_3	$COCH_3$	OH	CO_2CH_3	47	50	45
10	H	CO-3-pyridyl-2-Cl	H	H	74–75	11	229
	H		H	H	122.5	69	345
	$N(COCH_3)_2$	$COCH_3$	H	H	100–102	90	158
	H	COC_6H_5	H	H	69–70		64

maleic anhydride,[64] and ethyl maleate[79] has been used for the alkylation of thiophenethiols. Thiophenethiols have also been characterized as acyl derivatives through reaction with benzoyl chloride,[11,39,55,56,64] *p*-nitrobenzoyl chloride,[20,23,55] acetyl chloride,[64] and 2-furoyl chloride.[64] 3-Thiophenethiol has been used as the mercaptan component in the formation of thioacetals from butyraldehyde, acetone, 2-acetothienone, benzophenone,[64] and D-glucose.[81] A number of ester derivatives of thiophenethiols is given in Tables 4 and 5.

C. Various Reactions of Thiophenethiols

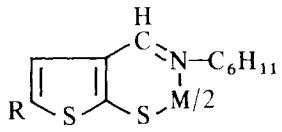
The reaction of thiophenethiols with secondary amines in toluene has no analogy in thiophenol chemistry and yields dialkylaminothiophenes in 40 to 80% yield. The best results were obtained with morpholine and pyrrolidine.[65] The reaction of sodium 3-thiophenethiolate with cyanogen bromide gave 3-thiocyanothiophene in low yield.[49] The reaction of lithium 2-thiophenethiolate with diazotized *p*-anisidine gave 2-thienyl-(*p*-methoxyphenyl) sulfide in 48% yield.[83] The reaction of 3-acetyl-5-carbethoxy-4-methyl 2-thiophenethiol with aqueous chloramine at 0°C gave the corresponding sulfenamide, which cyclized spontaneously to the corresponding thienoisothiazole.[93] Reaction of the aforementioned thiol with cyanogen bromide gave the disulfide.[93]

Upon reaction of thiophenethiols with iodine, the corresponding disulfides were obtained.[10,20,56] Oxidation of 5-chloro-2-thiophenethiol with H_2O_2 followed by phosphorus pentachloride was used for the preparation of 5-chloro-2-thiophenesulfonyl chloride.[245] Ferric chloride has also been used for the oxidation.[27] The reaction of 5-ethyl-2-mercapto-3-thiophene aldimine with hydroxylamine led also to oxidation of the thiol grouping to disulfide,[24] in addition to oxime formation.

The copyrolysis of 2-thiophenethiol with tetrafluoroethylene at 620–640°C gave 10 to 28% of 4,4,5,5,6,6-hexafluorocyclopenta[b]thiophene and 2 to 4% of 4,4,5,5,6,6,7,7-octafluorocyclohexa[b]thiophene. A radical mechanism by way of the 2-thienyldifluoromethyl radical has been suggested.[66]

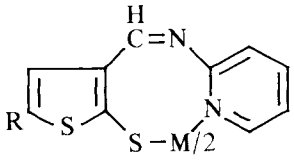
Goldfarb and co-workers have devoted considerable interest to the chemistry of orthomercaptoaldimines. Stable metal complexes such as **57**,[22,27,31,32] **58**,[30,67] and **59**[56] were obtained through reaction with the appropriate metal acetate in ethanol. The complexes of **57** ($R = (CH_2)_2CO_2C_2H_5$) show especially good solubility in organic solvents and have well-defined rather low melting points. These compounds have a slight inhibitory effect on the liquid phase oxidation of hydrocarbons.[22] The magnetic susceptibility and UV spectra of **58** ($R = C_2H_5$) have been measured and indicate a tetrahedral configuration.[30] Other types of chelates, such as **60**,[25] **61**,[22,27] and **62**,[23] have also been prepared (Scheme 12).

The reaction of bromine with **63** gave **64**, probably by way of the isomeric sulfenyl bromide. With **63**, (**R'** = H), **65** could be obtained.[68] Instead of **63**, zinc or nickel chelate (**57**) can be used in the reaction with bromine or NBS, which also gives **64**. From **59**, the [2,3-*d*]-isomer (**66**) was obtained as zinc bromide complex.[25,31] Acylation of **57** (M = Zn) gave **67**, whereas reaction with butyllithium gave **60**[25] (Scheme 13).



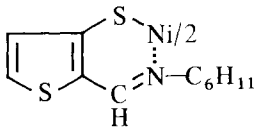
R = MeO, C_2H_5, $(CH_2)_2CO_2C_2H_5$
M = Zn, Ni, Co, Cu

57

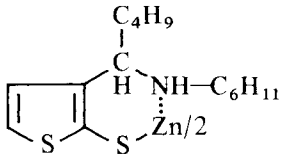


M = Ni, Co

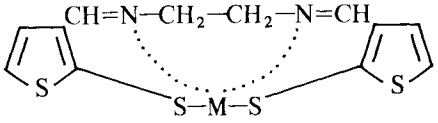
58



59

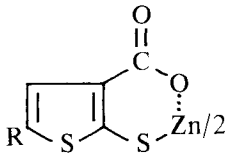


60



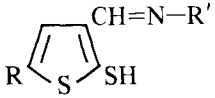
M = Cu, Co, Ni

61



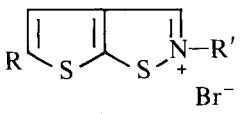
62

Scheme 12

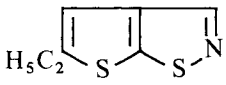


R = C_2H_5
R′ = H, C–C_6H_{11}

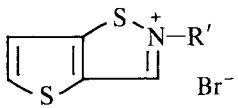
63



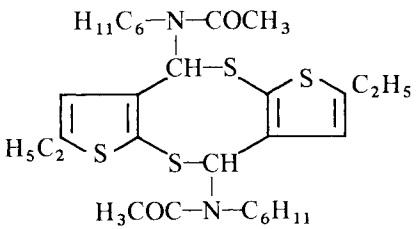
64



65

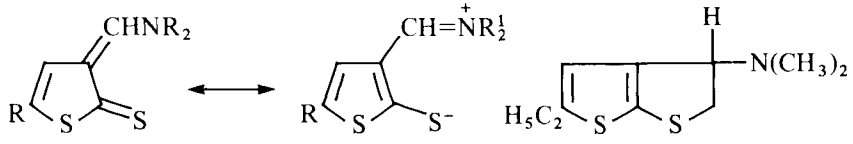


66



67

Scheme 13

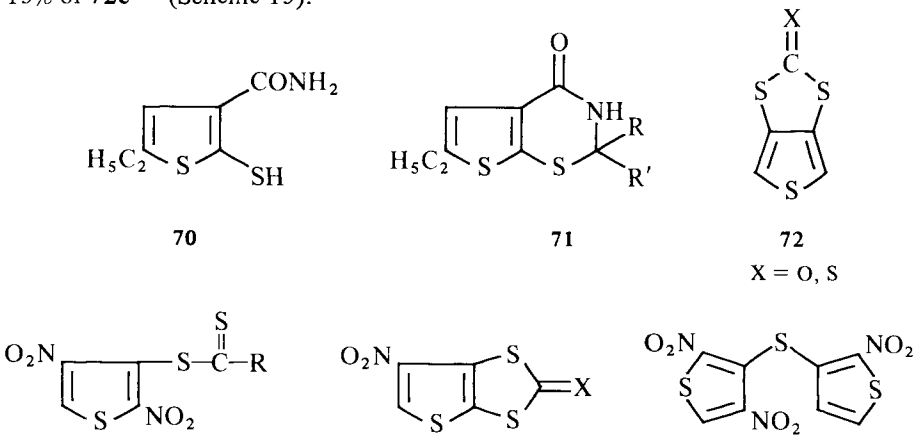


68 69

Scheme 14

The reaction of **63** (R = H or C_2H_5) with secondary amines, such as diethyl and dimethyl amine, gives the nontautomeric **68**. Its IR spectrum gives further evidence for the importance of the tautomeric structure **55**. At room temperature two methyl resonances are observed in the NMR spectrum of the dimethyl derivative indicating hindered rotation about the C–N bond due to a contribution from the zwitterionic resonance form. Reaction of **68** with chloroacetic acid, α-bromoacetone, and other α-halocarbonyl derivatives gave the corresponding thieno[2,3-b]-thiophene derivative through alkylation followed by ring closure.[69] The reaction of **68**, R = Et; R′ = Me with dimethylsulfonium methylide led to **69**[69] (Scheme 14).

Reaction of **70** with various ketones in ethanolic hydrogen chloride gave **71** in 70–100% yield.[72] The thiophenedithiols undergo some special reactions. Thus 3,4-thiophenedithiol reacts with carbon disulfide in sodium hydroxide to give **72** (X = S)[44,54] and with phosgene **72** (X = O) was obtained, which upon reaction with nitric acid in acetic anhydride gave the 2-nitro derivative[271] (Scheme 15). The compounds **72a** prepared by reaction of 2,4-dinitro-3-bromothiophene with sodium dimethyl dithiocarbamate and sodium *t*-butyl trithiocarbonate, respectively, were heated in glacial acetic acid. From **72a** (R = $N(CH_3)_2$) a 6% yield of **72b** (X = O) was obtained, whereas **72a** (X = $SC(CH_3)_3$) gave 16% of **72b** (X = S) and 15% of **72c**[271] (Scheme 15).



70 71 72

X = O, S

72a

R = $N(CH_3)_2$, $SC(CH_3)_3$

72b

X = O, S

72c

Scheme 15

III. ALKYL- AND ARYLTHIENYL SULFIDES

1. Introduction

Alkylthio- and arylthiothiophenes have been prepared by the following methods: (1) ring closure of aliphatic compounds; (2) alkylation or arylation of thiophenethiols; (3) from halothiophenes and alkyl- or arylthiolates by way of nucleophilic aromatic substitution; and (4) introduction of the thiophene–sulfur bond in appropriate thiophene derivatives, mainly through organometallic derivatives.

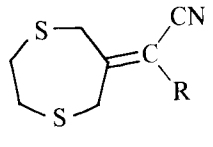
2. Syntheses of 2-Alkylthiothiophenes

Many of the general ring-closure reactions discussed in Part 1, Chapter I can be used for the synthesis of highly substituted 2-alkylthiothiophenes containing various other functional groups. Thus the Gewald reaction between **73**, sulfur, and diethylamine gave **74** in good yields.[89] Similarly, **75** has been obtained[90] (Scheme 16).

The most useful ring-closure reaction for the preparation of 2-alkylthiothiophenes is of the $C_3S + C$ type, such as the Gompper reaction (see Part 1, Chapter I). Condensation of active methylene derivatives (**76**) with carbon disulfide under basic conditions gives enethiolates (**77**), which upon alkylation with α-haloesters to **78** and ring closure give 3-amino-5-alkylthiothiophenes (**79**).[91,92]

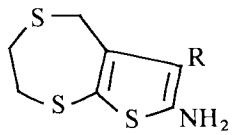
Other active methylene derivatives can be used, and with aroylacetonitriles, compounds such as **80** to **82**[92,96,115] have been prepared. From pentane-2,4-dione and carbon disulfide in the presence of aqueous potassium hydroxide, followed by successive treatment with ethyl bromoacetate, iodomethane, and alkali, **83** was prepared in 52% overall yield[93] (Scheme 17). Other active methylene derivatives that have been used are 1-cyanomethylpyridinium chloride[5,94] and benzylidene aminoacetonitrile,[95] which give compounds such as **84** and **85**. Biheterocyclic systems have also been prepared in this way. Starting from **85a**, **85c** was obtained by way of **85b**[465] (Scheme 18).

Alkylation of the enethiolate with α-bromoketones was used for the synthesis

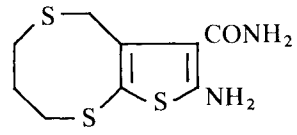


R = CN, $CONH_2$

73

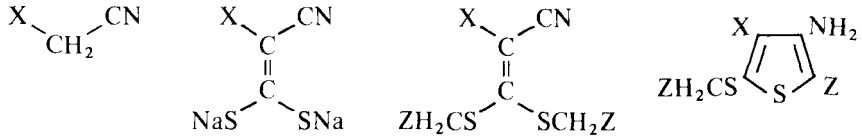


74



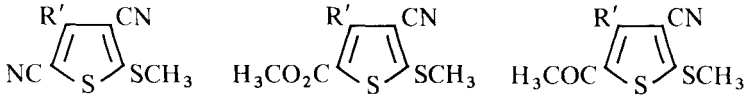
75

Scheme 16



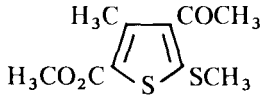
X = CN, CO_2R, $CONH_2$, C_6H_5
Z = CN, CO_2R, $CONH_2$

76 **77** **78** **79**



R′ = various aryl groups

80 **81** **82**



83

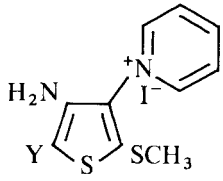
Scheme 17

of **86** from malonitrile,[92] and **87** was obtained by stepwise alkylation of the enethiolate with chloroacetamides and methyl iodide[97] (Scheme 18).

A recent use of the Gompper reaction for the synthesis of a 2-alkylthiothiophene derivative is the stepwise alkylation of an enethiolate of type **77** with methyl iodide and 4-bromoacetoacetate, which gave **88** upon ring closure under alkaline conditions.[98]

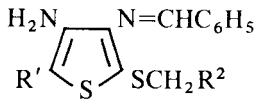
Another use of enethiolates for the synthesis of alkylthiothiophenes is the reaction of those derived from nitromethane **89**, which upon alkylation with an α-halocarbonyl compound to give **90**, ring close according to the $C_2S + C_2$ principle by electrophilic attack of the carbonyl atom on the nitro-bearing carbon of **90** to give **91**. The latter compound was alkylated to the *S*-methyl derivative, which is also obtained by ring closure of **92** in 25% sulfuric acid.[99] In other cases, intermediates of type **91** were oxidized to the corresponding disulfides[100] (Scheme 19).

An interesting approach to 2-dialkylsulfonium salts is the condensation of malonic acid derivatives with esters of thio or dithio acids in the presence of potassium alkoxides to give **93**, which was alkylated with chloromethyl methyl sulfide and converted to **94** by reaction with trimethyloxonium fluoborate. Upon cyclization of **94** with sodium cyanide, **95** was obtained[101] (Scheme 20).



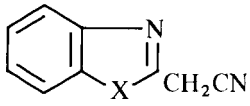
Y = CN, $CONH_2$, $CO_2C_2H_5$, COPh

84

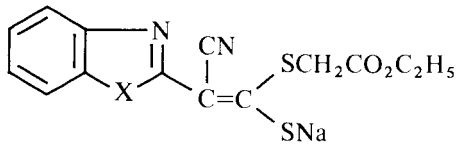


$R' = H, C_6H_5, COC_6H_5, COCH_3$
$R^2 = H, C_6H_5$

85

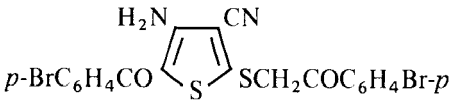


85a



85b

X = N—R, O, S



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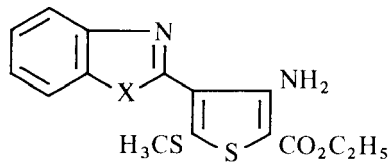

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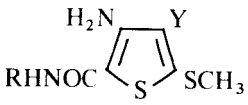
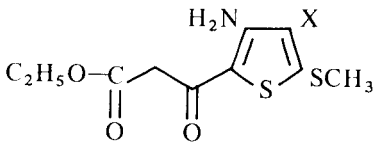


R = H, CH_3
Y = $CO_2C_2H_5$, CN, $CONHCH_3$, $CONH_2$

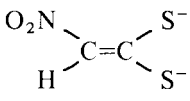
87



X = $CO_2C_2H_5$, CN

88

Scheme 18



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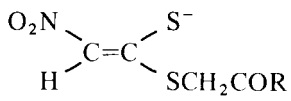

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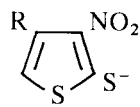

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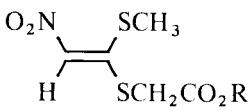

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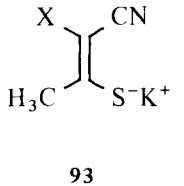
Scheme 19



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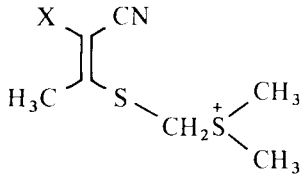
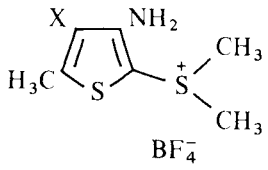


X = CN, $CO_2C_2H_5$

94



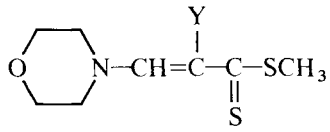
95

Scheme 20

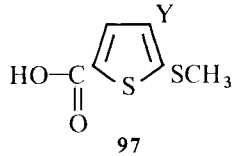
Another $C_3S + C$ approach to 2-alkylthiothiophenes was found by Smutny, who discovered that 3-amino-dithioacrylate esters such as **96** (Scheme 21; for more details see Part 1, Chapter I) react with α-halocarbonyl compounds, ethyl α-bromoacetate, for example, in the presence of triethylamine to give **97**.[102] Condensation of benzylidene aminoacetonitrile with carbon disulfide followed by alkylation and ring closure gave **97b**.[263]

A $C_3 + CS$ approach to 3-substituted 2-methylthiothiophenes consists of the treatment of 2-alkyne and allene derivatives with butyllithium and potassium *t*-butoxide in THF followed by carbon disulfide, *t*-butyl alcohol, HMPTA, and methyl iodide (Part 1, Chapter I). The only exception was *t*-butylallene, which for steric reasons gave 2-*t*-butyl-5-methylthiothiophene.[103]

Ring closure of C_4S-type compounds has been used for the preparation of 2-alkylthiothiophenes. Thus cyclization of allenyldithio esters such as **98**, prepared by metalation of dithio esters followed by alkylation with propargyl halides,[104] gave 2-alkylthiothiophenes (**99**) on treatment with sodium ethoxide in liquid ammonia.[105] Lithiated bissulfides (**100**) ring close to 2-methylthiothiophene in THF solution in the presence of HMPTA by way of nucleophilic attack on sulfur[106] (Scheme 22).



96 Y = H, CN



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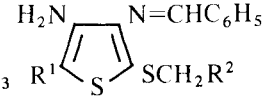
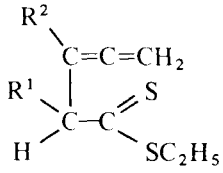


97b

Scheme 21



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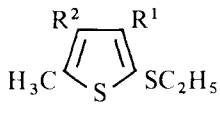

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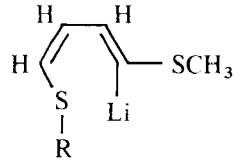
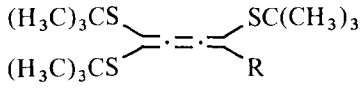


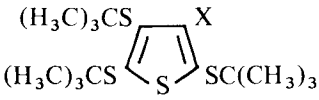
100

Scheme 22



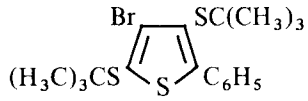
a. R = $SC(CH_3)_3$
b. R = C_6H_5

101

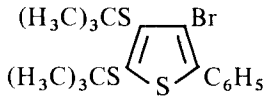


X = I, Br, H

102



103



104

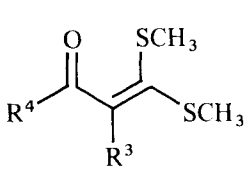
Scheme 23

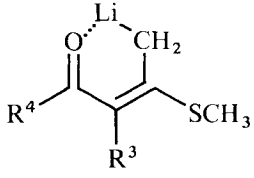
The reaction of alkylthio-substituted butatrienes (**101**) with iodine or bromine in carbon tetrachloride can be used for the synthesis of alkylthiothiophenes. From **101a** and iodine **102** (X = I) was obtained in 63% yield, whereas the reaction with bromine gave a mixture of **102** (X = Br) and **102** (X = H). Reaction of **101b** with bromine leads to a compound which is either **103** or **104**[107] (Scheme 23).

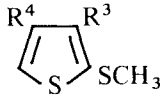
Some cases using the C_3SC-ring-closure principle for the preparation of alkylthiothiophenes are also known. Thus the regioselective deprotonation of **105** with LDA at −78°C in HMPA proceeds by way of **106** to give **107**[108,109] (Scheme 24).

Applying the C_2SC_2 principle, **108**, prepared through the reaction of dimethyl acetylenedicarboxylate with disulfur dichloride, reacted with sodium phenolate to give **109**, which upon heating for 5 minutes at 130 to 135°C gave **110**[110] (Scheme 25).

2-Alkylthiothiophenes have also been prepared from other ring systems. Thus the reaction of isothiazolium salts **111** with sodium benzoyl acetate gave **112** by



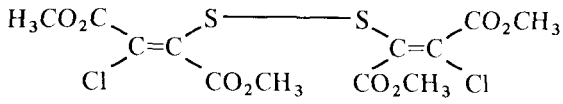




a. $R^3 = C_2H_5$, $R^4 = C_6H_5$
b. $R^3 = H$, $R^4 = C_6H_5$
c. $R^3 = H$, $R^4 = C_6H_4OCH_3$
d. $R^3 = OCH_3$, $R^4 = C_6H_5$
e. $R^3 = C_6H_5$, $R^4 = H$
f. $R^3 = C_6H_5$, $R^4 = OC_2H_5$

105 **106** **107**

Scheme 24



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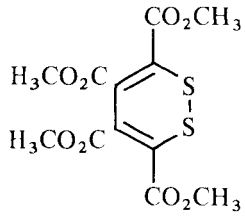

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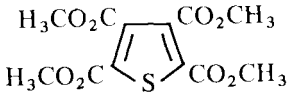
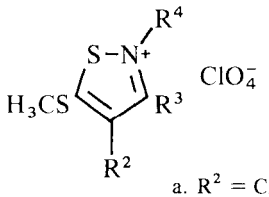


110

Scheme 25

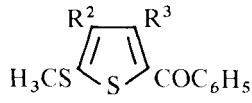
nucleophilic attack of a phenacyl ion on the ring-sulfur, followed by attack of the activated methylene group on the imine function to give recyclization to thiophenes.[111] The reaction of the anhydro-4-hydroxythiazolium hydroxide system **113** with acetylenic dipolarophiles such as dimethyl acetylenedicarboxylate yields 2-alkylthiothiophenes **115** by way of the cycloaddition product **114**[112] (Scheme 26).

Many 2-alkylthiothiophenes are prepared by alkylation of the corresponding alkali salts of 2-thiophenethiols, or by Michael addition. Recent examples are given



a. $R^2 = C_6H_5$, $R^3 = H$, $R^4 = C_6H_5$
b. $R^2 = H$, $R^3 = C_6H_5$, $R^4 = CH_3$

111



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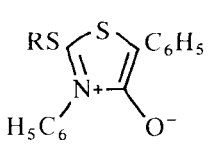

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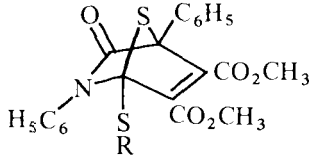
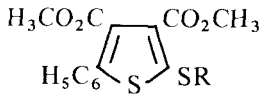


R = CH_3, C_2H_5, n-CH_3

114



115

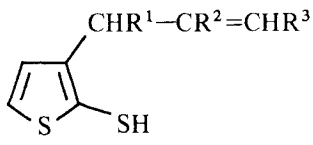
Scheme 26

in Reference 463. For details and references see Section II.5.B. and Table 5. The complex of *N,N*-dimethyl formamide with dimethyl sulfate has also been used for the methylation of thiophenethiolate.[114] Cyclization of 3-allyl-2-thiophenethiols formed in the thio-Claisen rearrangement constitute a route to cyclic sulfides. Thus heating of **116** usually leads to mixtures of **117** and **118**.[34,39,41] However, **119** gave only **120**[40] (Scheme 27).

In many cases the necessary thiols are not isolated, and the 2-alkylthiothiophenes are obtained in a one-pot procedure by reacting with Grignard reagent from a 2-bromo- or 2-iodothiophene with sulfur, followed by an alkylating agent.[115–117] A detailed description of the synthesis of 2-methylthiothiophene has appeared in *Organic Syntheses*.[118] A more convenient method, which eliminates the preparation of 2-halothiophenes, is the metalation of thiophenes with butyllithium followed by the reaction with sulfur and alkylating agent.[11,25,39,115,119–131] A prerequisite in the case of 3-substituted thiophenes is, of course, that metalation occurs regiospecifically. This is the case with 3-ethylthiothiophene and 3-thiophenealdehyde diethyl acetal, which allowed the preparation of 2,3-bis(ethylthio)-thiophene[11] and 2-ethylthio-3-thiophenealdehyde diethyl acetal.[25]

Another way of using 2-thienyllithium derivatives for the synthesis of 2-alkylthiothiophenes is their reaction with alkyl disulfides.[125,129,132,163] Metalation of 3-methylthiophene with butyllithium followed by reaction with dimethyl disulfide gave a mixture of 3-methyl-2-methylthio- and 3-methyl-5-methylthiothiophene, which upon renewed metalation and reaction with dimethyl disulfide gave 3-methyl-2,5-bis(methylthio)thiophene.[125] Instead of metalation of thiophenes, halogen–metal exchange has sometimes been used to advantage. Thus from 2,4- and 2,3-dibromothiophene, 4-bromo- and 3-bromo-2-ethylthiothiophene were prepared.[129,133]

2-Alkylthiothiophenes have also been obtained from 2-thiocyanothiophenes through hydrolysis with aqueous sodium sulfide to the thiolate, followed by



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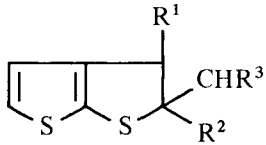

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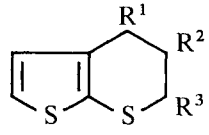

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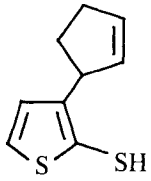

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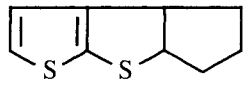


120

Scheme 27

alkylation.[134,135] The thiocyano derivatives are obtained by electrophilic thiocyanation with thiocyanogen. From 3,4-diaminothiophene, 3,4-diamino-2,5-bis(methylthio)thiophene was obtained by this route.[135]

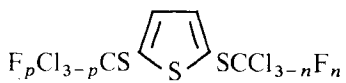
The reaction of aliphatic cuprous mercaptide with 2-bromothiophene was used for the preparation of 2-*n*-butylthio- and 2-ethylthiothiophene in 92 and 56% yield, respectively.[136] Activated bromothiophenes such as 2,5-dibromo-3,4-dinitrothiophene react with benzylthiolate to give 2,5-bis(benzylthio)-3,4-dinitrothiophene. In the case of 3,4-dibromo-2,5-dinitrothiophene, α-substitution also occurs with benzyl thiolate, yielding 2-benzylthio-3,4-dibromo-5-nitrothiophene. Further substitution occurs at the 4-position to give 2,4-bis(benzylthio)-3-bromo-5-nitrothiophene.[137] From 5-bromo-2-thiophenecarboxaldehyde and ethane thiolate, 5-ethylthio-2-thiophenecarboxaldehyde was obtained.[138;cf. Ref. 162] Other leaving groups than halogens, such as alkyl- or arylsulfonyl, can also be used in the preparation of alkylthiothiophenes by this approach.[243]

Another type of electrophilic substitution creating a thiophene–sulfur bond is the tin tetrachloride-catalyzed reaction of thiophene and 2-bromothiophene with perhalomethanesulfenyl chlorides ($Cl_{3-n}F_nSCl$, $n = 2$, 3) or chloroformylsulfenyl chloride (ClCOSCl), to give compounds of type **121**. The deactivating effect of the perhalomethanesulfenyl groups prevents further substitution. However, by reacting the Grignard reagent of **121** (X = Br) with perhalomethanesulfenyl chloride **122** could be synthesized[139] (Scheme 28). In connection with work on antiinflammatory agents, 2,3-bis-(4-fluorophenyl)thiophene was reacted with trifluoromethyl sulfenyl chloride and trifluoroacetic acid to give 5-trifluoromethylthio derivative.[256]

Radical reactions can also be used for the synthesis of 2-alkylthiothiophenes since α-selectivity is observed. Thus the reaction of 2-methylthiophene with 2-propanethiol, 30% hydrogen peroxide, and ferrous sulfate (Fenton's reagent) gave a 42% yield of 2-isopropyl-5-methylthiophene. Similarly, 2-ethyl- and 2-benzyl-5-methylthiophene were obtained in 55 and 70% yield, respectively. With primary thiols thiophene gave 2,5-bis(alkylthio)thiophenes.[138,140,141] Diazotization of **123** followed by reaction with potassium ethylxanthogenate led to **124**, which upon treatment with chloroacetate in the presence of sodium methoxide gave **126** by way of **125**[142] (Scheme 29). A recent reason for the synthesis of 2-thienylthioacetic acid derivatives is interest in their pharmacological properties.[257,258,261] Other alkylthio derivatives also show interesting pharmacological effects[259,260] (see Table 6).

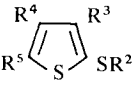
X = H, Br

121

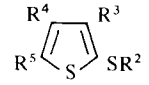


122

Scheme 28

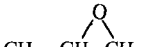
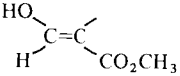
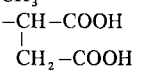
TABLE 6. 2-ALKYLTHIOTHIOPHENES 

C_n	R^2	R^3	R^4
5	$CClF_2$	H	H
	CF_3	H	H
	$CClF_2$	H	H
	CCl_2F	H	H
	CCl_3	H	H
	CF_3	H	H
	CH_3	H	NO_2
	CH_3	Br	H
	CH_3	Br	H
	CH_3	H	Br
	CH_3	H	H
	CH_3	H	H
	CH_3	D	H
	CH_3	H	D
	CH_3	H	H
	CH_3	H	F
	CH_3	H	H
	CH_3	NO_2	H
	CH_3	H	NO_2
	CH_3	H	H
	CH_3	H	H
	CH_3	H	H
6	CF_3	Br	Br
	CF_3	Br	H
	CCl_3	H	H
	CF_3	H	H
	$CClF_2$	H	H
	CF_3	H	H
	CF_3	H	H
	CF_3	H	H
	CH_3	Br	Br
	CH_2CO_2H	H	H
	CH_2CH_2Br	H	H
	C_2H_5	H	H
	CH_3	Br	H
	CH_2CH_2Cl	H	H
	CH_2CONH_2	H	H
	CH_3	NHCHO	H
	CH_2CO_2H	NH_2	H
	CH_3	NH_2	NH_2
	CH_2CH_2OH	H	H
	CH_2OCH_3	H	H
	CH_3	H	H
	CH_3	H	H
	CH_3	H	H
	C_2H_5	H	H
	CH_3	H	H



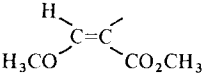
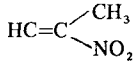
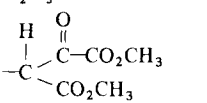
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
Br	71/2.5		81	139
Br	54/6		59	139
H	72/20		40	139
H	76/3.5		41	139
H	66/0.02	31	63	139
H	48/30		60	139
Br		35–36	97	219
Br	120–125/5		77	219
H	112–114/15		73	133
H	118–120/15		63	133
Br	113–116/8		82	133
Cl	80–82/10		51	124
H	75–76/20		70	133
H	58–60/9		46	133
D	67–68/15		63	133
H	60–61/10		79	163
F	76/32		78	163
H		81–82		219
H		21–22		219
NO_2		81–82	40	213
OH	70–72/0.1		63	14
H	80–82/22		60	117
SCF_3		36	98	139
SCF_3	53/1.2		77	139
CCl_3		69	90	139
$SCCl_2F$	57/0.2		14	139
$SCClF_2$	75/1.1		37	249
$SCCl_3$	73/0.06		75	139
$SCClF_2$	59/2.5		75	139
SCF_3	80/3.4		82	139
SCH_3		67.5		119
H		47–48	80	126
H	95–97/2		65	70
Br				138
CH_3	86–87/18		66	225
H	78–79/0.9		62	70
H		95–96	83	473
H		54	75	134
H		116–118	45	134
CN				474
H	94–95/1.2		84	70
H	55–56/0.45		88	463
OCH_3	107.5–108/14		79.5	81
$SeCH_3$	137–138/13		72	438
CH_3	76–77/10		75	132
H	69/7		72	115
SCH_3	126–127/10		27	115

TABLE 6. *(Continued)*

C_n	R^2	R^3	R^4
	$CH_2CH_2NH_2$	H	H
	CH_3	NH_2	NH_2
7	CH_3	H	H
	$CH_2C{\equiv}CH$	H	H
	CH_2CO_2H	H	H
	CH_2CH_2CN	H	H
		H	H
	CH_2CO_2H	H	H
	$CH_2CO_2CH_3$	H	H
	$CH_2CH{=}CH_2$	H	H
	$CH_2CHOHCH_2Cl$	H	H
	CH_3	$NHCOCH_3$	H
	C_2H_5	H	H
	$CH(CH_3)_2$	H	H
	CH_3	H	H
	$CH_2CH_2CH_3$	H	H
	CH_3	CH_3	H
	C_2H_5	H	H
	C_2H_5	H	H
	CH_3	SCH_3	H
	CH_3	CN	OH
8	CH_2COCH_3	H	H
	$CH{=}CHCO_2CH_3$	H	H
		H	H
	CH_3	$NHCOCH_3$	CH_3
	CH_3	$H_3C{-}C{=}N{-}OH$	CH_3
		H	H
	C_2H_5	H	H
	CH_2COOH	$NHCOCH_3$	H
	C_2H_5	Br	Br
	CH_3	CH_2Cl	CH_2Cl
	$CH_2CH_2OCH{=}CH_2$	H	H
	$CH_2CO_2CH_3$	H	H
	$(CH_2)_2CO_2CH_3$	H	H
	$CH_2CO_2CH_3$	H	H
	$CH_2CO_2C_2H_5$	H	H
	$(CH_2)_2CO_2CH_3$	H	H
	$CH_2CH{=}CHCH_3$	H	H
	C_2H_5	H	H
	C_2H_5	Br	H
	C_2H_5	H	Br
	C_2H_5	H	H
	C_4H_9	H	H
	CH_3	H	H
	C_2H_5	H	H

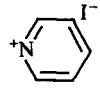
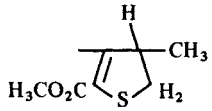
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H	103–104/0.8		78	
SCH_3		48	68	135
COCN		68–69	55	224
H	110–113/10		88–94	16
NO_2	120/0.01		29	8
H	111–112/0.7		60	79
H	83–84/0.55		65	79
CH_3		28–29		123
H	84–85/0.4		70	79
H	78–79/0.9		62	39
H	116–117/0.6		68	79
H		68–69	80	134
CH_2OH	142–146/16			74
H	45–46/3.0		67	75
C_2H_5	109–110/14		50.5	115
H	68–70/3.5		69	75
CH_3	98/14		78	193
CH_3	97/15		65	138
SCH_3	130–132/8		60	129
CH_3	94–96/1		38	225
H	109–111/3		56.7	122
H	150/0.01		70	8
CO_2CH_3		164–166	30	92
H	105/0.5	125	42	8
H		99–100	83	93
H		68–69	91	93
H		135–138	92	463
$-CH=CHNO_2$		62.5–64.5	55.5	21
H		148	60	134
SC_2H_5		150–151	85	119
SCH_3		78–78.5	79	119
H	80–81/0.6		74	463
CH_3	96–99/0.5			130
H	74/0.01		71.5	8
H	124–126/6		65.5	8
H	117–118/1.6		76	70
H	100/760		65	39
SC_2H_5	108–110/1.6		44.5	140
C_2H_5	110–112/2		36	10
C_2H_5	105/2		84	115
$(CH_2)_2Br$	111–114/1		30	21
Cl	117–124/8		54	138
$(CH_2)_2OCH_3$	116/8		40	22
$(CH_2)_2OH$	149–151/7		79	21

TABLE 6. (*Continued*)

C_n	R^2	R^3	R^4
	$CH_2CH_2CH_3$	H	H
	$CH_2CH(OCH_3)_2$	H	H
	CH_3	CH_2OH	CH_2OH
	$C(CH_3)_3$	H	H
	CH_3	CH_3	CH_3
	C_2H_5	H	H
	$CH(CH_3)_2$	H	H
	$(CH_2)_3CH_3$	H	H
	$CH_2CH(CH_3)_2$	H	H
	$CHCH_3C_2H_5$	H	H
	C_3H_7	H	H
	CH_3	H	H
	CH_3	CH_3	CH_3
	C_2H_5	H	H
	C_2H_5	H	SC_2H_5
	C_2H_5	SC_2H_5	H
	C_2H_5	H	H
9	$CH_2COOCH_2C{\equiv}CH$	H	H
	$CH_2COOCH_2CH{=}CH_2$	H	H
		H	H
	3-Cyclopentenyl	H	H
	$(CH_2)_4CCl_3$	H	H
	CH_3	H	
	CH_2COCH_3	H	H
	$CH_2CHCH_3CO_2CH_3$	H	H
	$CH_2CO_2CH_3$	H	H
	$(CH_2)_2CO_2CH_3$	H	H
	Cyclopentyl	H	H
	C_2H_5	CH_2Cl	H
	$(CH_2)_3CH_3$	H	H
	$CH_2CH(CH_3)_2$	H	H
	C_2H_5	CH_2OH	H
	$CH_2CH(CH_3)_2$	H	H
	$C(CH_3)_3$	H	H
	$(CH_2)_3CH_3$	H	H
	$(CH_2)_2CH(CH_3)_2$	H	H
	$(CH_2)_4CH_3$	H	H
	$CH(CH_3)_2$	H	H
	CH_3	SC_2H_5	H
10	C_2H_5	–CO–O–CO–	
		H	H
	$(CH_2)_2S$–2-thienyl	H	H
	2-Cyclohexenon	H	H

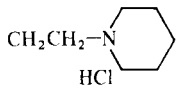
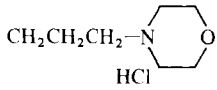
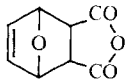
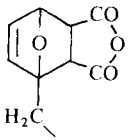
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
CH_2OH	148–155/16			74
H	120–124/1			76
SCH_3		73	81	212
H	74–75.5/4			71
CH_3	124–126/8			77
C_2H_5	102–103/10			120
CH_3	102–107/17		42	138
H	93–94/5.0		75	75
H	84–85/5.0		75	75
H	64–65/1		76	75
$SeCH_3$	131–132/4		76.8	438
SeC_3H_7	130/3		81	438
SCH_3				125
SC_2H_5	114/1.5		71	119
H	144–145/11		75	129
H	110–111/3		62.4	11
$(CH_2)_2NH_2$	127–130/3		43.1	21
H	148–149/1.2		70	463
H	124–125/0.5		76	463
H		65	70	8
H	114–116/6			40
H	134–135/0.8		87	79
OCH_3		49–50	68.5	81
C_2H_5	106–108/2		62.2	122
H	109–110/0.95		65	8
C_2H_5	117–118/2.5	72–73	71	121
CH_3	105/0.1		82	8
H	122–124/3		69	75
C_2H_5	120–122.5/3		69.3	220
CH_2OH	179–184/16			74
CH_2OH	119–120/0.5			74
C_2H_5	134/4		73.5	220
CH_3				206
CH_3	108–109/15		80	15
CH_3	125–130/16		43	140
H	80–82/0.6			73
H	122–123/9.0		81	75
C_2H_5				207
SC_2H_5	125–129/1.5		35	129
C_2H_5		79–80		161
H	124–125/0.5		44	8
H	159–160/0.56	20–21	58	127
H		60		152

TABLE 6. (*Continued*)

C_n	R^2	R^3	R^4
	$-CH(CO_2CH_3)CH_2CO_2CH_3$	H	H
	$CH_2CH=CH_2$	$CH_2CH=CH_2$	H
	$C(CH_3)_2CO_2C_2H_5$	H	H
	C_2H_5	$CH=CHNO_2$	H
	$CH_2CO_2C_2H_5$	$NHCOCH_3$	H
	C_2H_5	CH_2CN	H
	$(CH_2)_2CO_2CH_3$	H	H
	$C(CH_3)_2CO_2C_2H_5$	H	H
	$CH_2CO_2C_2H_5$	H	H
	$C(CH_3)_2CO_2C_2H_5$	H	H
	C_2H_5	H	H
	$(CH_2)_4CH_3$	H	H
	$(CH_2)_2CH(CH_3)_2$	H	H
	C_2H_5	CH_2OH	CH_2OH
	$(CH_2)_5CH_3$	H	H
	C_2H_5	H	H
	$CH(CH_3)-C_2H_5$	H	H
	$C(CH_3)_3$	H	H
	$(CH_2)_3CH_3$	H	H
	$CH_2CH(CH_3)_2$	H	H
	C_2H_5	C_2H_5	H
	C_2H_5	SC_2H_5	H
	C_2H_5	SC_2H_5	SC_2H_5
	C_2H_5	$(CH_2)_2NH_2$	H
11	$CH_2-C_6H_5$	Br	Br
	CH_3		NH
	$CH(CH_3)_2$	H	H
	$-CH_2C(OH)H-CH_2-S-2$-thineyl	H	H
		H	H
	C_2H_5	CH_2OCOCH_3	H
	$(CH_2)_2CO_2CH_3$	H	H
	$CH_2-CH=CH_2$	H	H
	C_2H_5	$CH_2OC_2H_5$	H
	$(CH_2)_5CH_3$	H	H
	$(CH_2)_4CH_3$	H	H
	$(CH_2)_2CH(CH_3)_2$	H	H

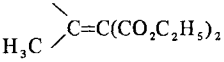
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H	145–146/0.8		95	79
H	88–89/4			34
Cl	99.0–99.5/0.8		53	80
C_2H_5		45–47	47	21
H		44	60	134
C_2H_5	130–131/4			220
C_2H_5	87/0.05		86	8
H	97–100/0.8		90	80
C_2H_5	128–132/2		53.3	121
H	97–100/0.8		90	80
$(CH_2)_2OC_2H_5$	138/8		73.2	22
CH_2OH	180–185/18			74
CH_2OH	182–184/18			74
SC_2H_5		56.5–57	90.5	212
H	122–123/6		78	75
$C(CH_3)_3$	80–81/1.4			140
C_2H_5				207
C_2H_5				207
C_2H_5				207
C_2H_5				207
C_2H_5	123–123.5/10		53	193
C_2H_5	142–144/4		80	11
H	147–150/0.3		60	129
C_2H_5	118–122/2		62	21
NO_2		140		137
CN		257	86	5
$CH=C(CN)_2$		154–156	63	277
H	194–195/0.6		74	247
H	120/0.01		88	8
C_2H_5	135–136/4		79	220
C_3H_7	114/0.05		67	8
$C(CH_3)_3$	104–106/3			70
C_2H_5	115–116/5		93	220
CH_2OH	198–202/18			74
C_2H_5				207
C_2H_5				207

TABLE 6. (*Continued*)

C_n	R^2	R^3	R^4
		H	H
		H	H
	$(CH_2)_6CH_3$	H	H
	$CH_2CHCH_2N(C_2H_5)_2$ (OH)	H	H
12		H	H
	$C_6H_3-2,4-NO_2$	SC_2H_5	H
	$CH_2CH=NN(H)-C_6H_3-2,4-NO_2$	H	H
	$CH_2CO-C_6H_5$	H	H
	$CH_2-C_6H_4-2-CO_2H$	H	H
	$CH_2-C_6H_5$	H	H
	$-CH(CH_2COOCH=CH_2)_2$	H	H
	C_2H_5	CH_2Cl	CH_2Cl
	$-CH(CO_2C_2H_5)CH_2CO_2C_2H_5$	H	H
	CH_3	CH_2OCOCH_3	CH_2OCOCH_3
	Cyclohexyl	H	H
	$(CH_2)_6CH_3$	H	H
	CH_3	$CH_2OC_2H_5$	$CH_2OC_2H_5$
	$CH_2CH(OCH_3)_2$	H	H
	$(CH_2)_7CH_3$	H	H
	$(CH_2)_5CH_3$	H	H
	$CH_2CH(C_2H_5)_2$	H	H
	C_4H_9	H	H
	$C(CH_3)_3$	H	H
	C_2H_5	SC_2H_5	SC_2H_5
13		H	H
	$H_2C-C_6H_4-2-CO_2H$	H	H
	$H_2CCO-C_6H_4-4-OCH_3$	H	H
	$H_2C-C_6H_4-2-CONH_2$	H	H

R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H		145–145.5	83	7
H		141.5–142	92	7
H	122–123/6.0		78	75
H	135–136/1		77	70
H		103–104	57	475
H		90–91		11
H		115		152
H		61	85	8
H		113–117	71	8
CH_3	114–116/ 0.5–0.7			140
H	132–133/0.9		51	463
C_2H_5	157–169/1		69	119
H	144–145/0.55		92	79
SCH_3		85.5–86.5	91	212
C_2H_5				207
CH_2OH	148–150/0.4			74
SCH_3	166/3		63.4	119
$CH_2CH(OCH_3)_2$				476
H	116–117/1.5		66	75
C_2H_5				207
C_2H_5				207
SC_4H_9	127.5–128.5/ 0.5		39	138
$SC(CH_3)_3$		66–68	85	15
SC_2H_5	175–177/1.7		45	129
H		66–67	82	475
CH_3		110		128
H		46	83.4	8
CH_3		81	128	128

TABLE 6. (*Continued*)

C_n	R^2	R^3	R^4
	C_2H_5	H	H
	$H_2C-C_6H_5$	H	H
	C_6H_{11}	H	H
	C_2H_5	H	H
		H	H
	CH_3	H	H
	C_2H_5	H	H
	C_2H_5	$H_2C-N(CH_2CH_2Cl)_2 \cdot HCl$	H
	$(CH_2)_8CH_3$	H	H
	$(CH_2)_6CH_3$	H	H
14	$(CH_2)_3CH(CH_3)_2$	H	H
	$-CH(CH_2COOCH_2C\equiv CH)-COOCH_2C\equiv CH$	H	H
	$H_2CCO-C_6H_5$	H	H
	$CH_2-C_6H_5$	CH_2Cl	H
	$-CH(CH_2-COOCH_2CH=CH_2)-COOCH_2CH=CH_2$	H	H
	C_2H_5	H	H
	$CH_2CO_2CH_3$	CN	C_6H_5
	CH_3	H	H
	C_2H_5	CH_2OCOCH_3	CH_2OCOCH_3
	$(CH_2)_7CH_3$	H	H
	$(CH_2)_9CH_3$	H	H
	$(CH_2)_5CH_3$	H	H
15	CH_3	$NHCOCH_2CO-C_6H_5$	NH_2
	C_2H_5	H	H

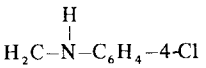
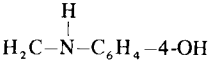
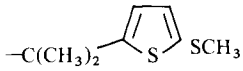
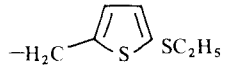
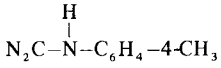
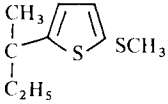
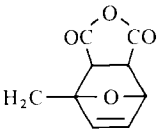
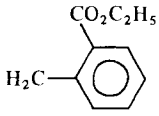
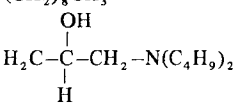
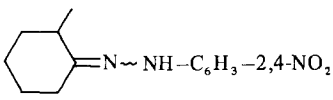
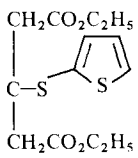
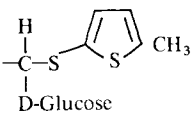
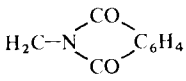
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
		15–16	81	214
C_2H_5	144.5–145/3		88	24
$CH{=}C(CN)_2$		162–163	61	277
		89–90	91	214
H	142–145/0.05		87	8
	169–169.5/0.2		68	26
	158–159/0.1		59	26
C_2H_5		92.5–94	47	220
H	144–145/12.0		82	75
C_2H_5				207
$SC(CH_3)_3$	123–125/0.01		70	15
H	174–175/0.9		64	463
C_2H_5		131	84	8
C_2H_5	182–184/3		55	220
H	162–163/0.55		77	463
	177–179/0.3	28–29	80	214
$OCOCH_3$		100.5–101.5	14	96
	165–166.5/0.1		72	26
SC_2H_5	190–198/3	37.5–38.5	69.5	212
C_2H_5				207
H	171–173/6		67	75
$SC(CH_3)_3$	131.5–135/ 0.01–0.02		34	15
CN		168	67	474
		75.5–76.5	87	475

TABLE 6. *(Continued)*

C_n	R^2	R^3	R^4
	C_2H_5	H	H
	$CH_2CO-C_6H_5$	H	H
		H	H
	C_2H_5	H	H
	$(CH_2)_{10}CH_3$	H	H
	$(CH_2)_8CH_3$	H	H
		H	H
16		H	H
		H	H
		H	H
	C_2H_5	H	H
	$(CH_2)_9CH_3$	H	H
	$(CH_2)_{11}CH_3$	H	H
17	C_2H_5		H

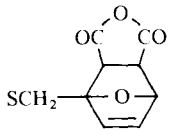
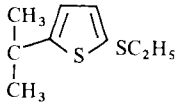
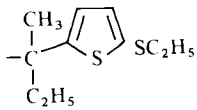
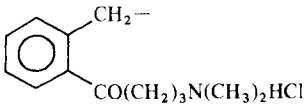
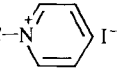
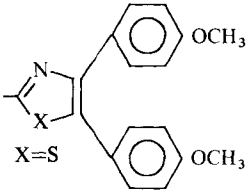
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
		67–68	83	475
C_3H_7	153–155/0.01		84	8
CH_3	103/0.8			128
	176–178/0.3		86.7	26
H	141–143/1.5		79	75
C_2H_5				207
H	155–156/0.6		73	70
H		183–184		152
H		137	32	8
CH_3		130–131	47.4	82
	180–182/0.1		83.2	26
C_2H_5				207
H	184–186/3.0		67	75
C_2H_5		63–64.5	68.5	220

TABLE 6. (*Continued*)

C_n	R^2	R^3	R^4
	C_2H_5	H	H
		H	H
	C_2H_5	H	H
	$(CH_2)_{12}CH_3$	H	H
18	$H_2C-C_6H_5$	Br	$SCH_2-C_6H_5$
	$H_2C-C_6H_5$	NO_2	NO_2
	$CO-C_6H_5$ $-CH-C_6H_5$	H	H
	$CO-C_6H_5$	$CO-C_6H_5$	H
	CH_3		
19	$CH-CH_2CO-C_6H_5$ $C_6H_4-3-NO_2$	H	H
	C_2H_5	$CH_2OC_2H_5$	H
20	$CH_2CO-C_6H_4-4-Br$	CN	NH_2
	$CH_2CH=NNH-C_6H_3-2,4-NO_2$	H	H
	$CH-CH_2CO-C_6H_5$ $C_6H_4-3-NO_2$	H	H
	$CH_2-C_6H_5$	$\overset{+}{N}(C_2H_5)_3Cl^-$	H
21		H	H
	X=O	H	H
	X=NH	H	H
	$CHCH_2CO-C_6H_5$ $C_6H_4-3-NO_2$	Br	H
	$CHCH_2CO-C_6H_5$ $C_6H_4-3-NO_2$	H	H

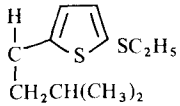
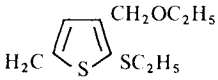
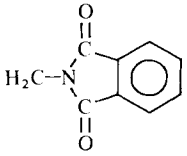
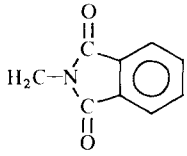
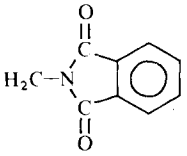
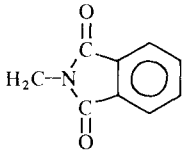
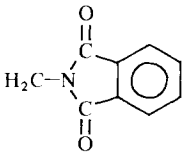
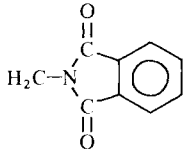
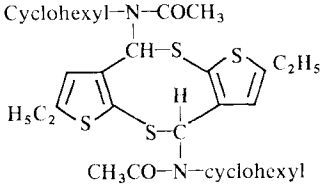
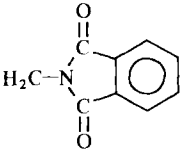
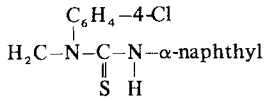
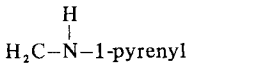
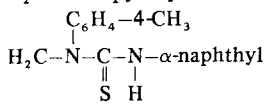
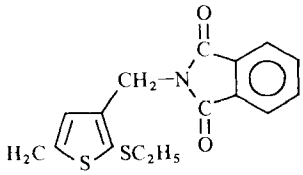
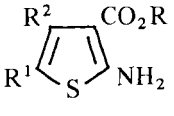
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
$H_2C-\underset{\displaystyle H}{\underset{\vert}{N}}-\beta$-naphthyl		29–30	89	214
H		136–137	19	268
	210–212/2		60.7	26
H	178–180/2		40	75
NO_2		115		137
$H_2C-C_6H_5$		214		137
H		97	84	8
C_2H_5		110 (decomp.)	55	11
SCH_3		193.5–194.5	100	119
H		117–118	85	10
	190/0.1			220
$CO-C_6H_4-4$-Br		201–202	75	92
$SCHCH=N-\underset{\displaystyle H}{\underset{\vert}{N}}-C_6H_3-2,4-NO_2$		196–197		476
OCH_3		82.5–83.5	87	10
C_2H_5		159.5–161	98	220
H		66	33	299
H		75	36	299
H		156	77	299
C_2H_5		84	98.5	10
C_2H_5		72.5–73.5	80.8	10

TABLE 6. (*Continued*)

C_n	R^2	R^3	R^4
22	$(CH_2)_{17}CH_3$	H	H
23	$CHCH_2CO-C_6H_5$ $C_6H_4-3\text{-}NO_2$	H	H
24	CH_3		
	C_2H_5	H	H
	$CH_2CH_2CH_3$	H	H
25	C_2H_5	H	H
26	C_2H_5		
	C_2H_5		
30			
31	C_2H_5		H

R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H		20–22		74
$(CH_2)_2OC_2H_5$		69–71		10
SCH_3		239	75	119
		139–143		214
		66–67		74
		139–140		214
C_2H_5		198.5		220
SC_2H_5		182.5	64.2	119
		193–195		25
		152–153		220



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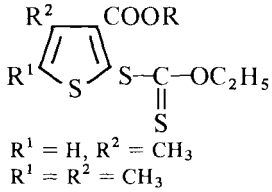

$R^1 = H, R^2 = CH_3$
$R^1 = R^2 = CH_3$

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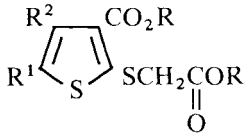
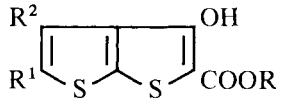


125

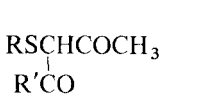


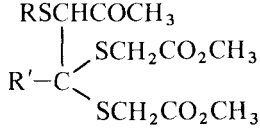
126

Scheme 29

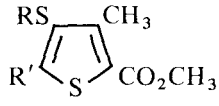
3. Syntheses of 3-Alkylthiothiophenes

Direct ring closure to 3-alkylthiothiophenes is often useful if highly substituted derivatives are desired. Especially useful in this connection is ring closure of the C_3 + CS type as in the Fiesselmann reaction (see Part 1, Chapter I). Thus reaction of **127** with two equivalents of thioglycolic acid in the presence of hydrogen chloride, followed by esterification, gave **128**, which upon ring closure with sodium methylate solution gave **129**[45] (Scheme 30). Similar reactions of **130** with thioglycolic acid followed by ring closure gave **131**.[45]

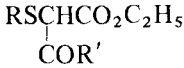


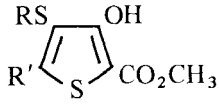


$R = C_2H_5, C_4H_9$
$R' = CH_3, C_6H_5$



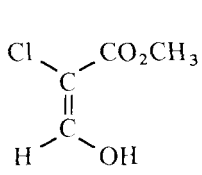
127 128 129





130 $R = C_2H_5, C_4H_9$ $R' = C_6H_5, CH_3$ 131

Scheme 30



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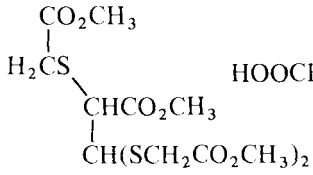

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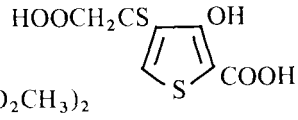


134

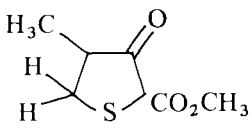
Scheme 31

Reaction of **132** with thioglycolic acid and esterification led to **133**, which upon treatment with potassium hydroxide in methanol ring closed to **134** in 35% yield[45] (Scheme 31).

Another useful route also worked out by Fiesselmann and co-workers starts from 3-oxotetrahydrothiophene (**135**), which upon reaction with hydrogen sulfide gives **136**. Reaction of **136** with α-halocarbonyl compounds, such as methyl chloroacetate, chloroacetone or phenacyl chloride, followed by base-catalyzed ring closure, gives **137**.[46] In the reaction with α,α-dichloroacetone, **138** was obtained[46] (Scheme 32).

Methylation of **136** followed by aromatization with chloroanil was used for the synthesis of methyl 3-methylthio-4-methyl-2-thiophenecarboxylate.[45] Alternatively, **135** can be reacted with methyl thioglycolate to yield **139**, which is then ring closed to **140**[142] (Scheme 33). Compound **139** can also be aromatized to **141** with bromine.[142]

The reaction of **142** with methyl thioglycolate gave **143** by way of a complex reaction path (see Part 1, Chapter I).[142] Reaction of **135** with benzyl chloride followed by aromatization with chloroanil was used for the synthesis of **144**.[143]



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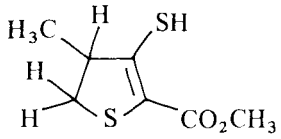
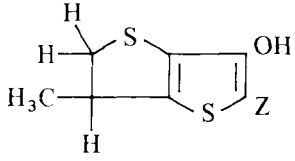
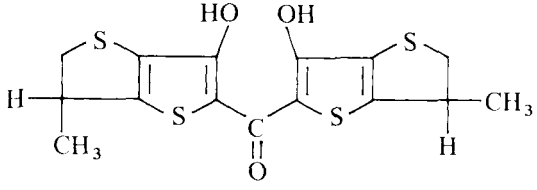


136



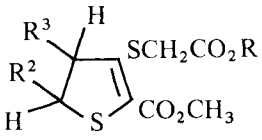
137

Z = CO_2CH_3, $COCH_3$, COC_6H_5, $COC(CH_3)_3$, $CONH_2$

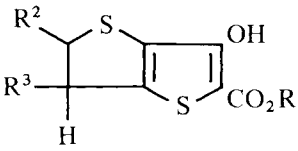


138

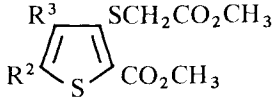
Scheme 32



139



140



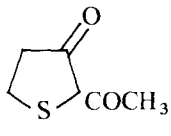
141

$R^2 = R^3 = H$
$R^2 = CH_3$, $R^3 = H$
$R^2 = H$, $R^3 = CH_3$

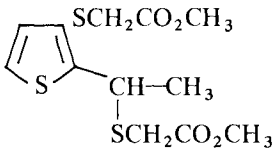
Scheme 33

These compounds are described in Ph.D. theses from Erlangen-Nürnberg; physical data are given in Table 6.

Recently the $C_3S + C$ ring closure was used for the synthesis of 3-alkylthio derivatives by the reaction of **143a** with bromonitromethane to give **143b**[466] (Scheme 34).



142



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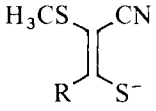
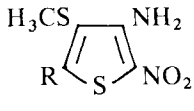
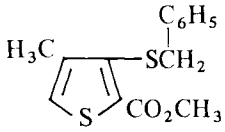


143a

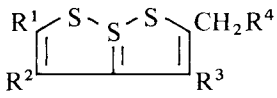


143b

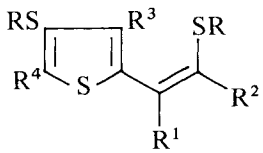
R = CN, $CONH_2$, $CO_2C_2H_5$



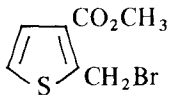
144



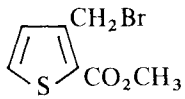
145



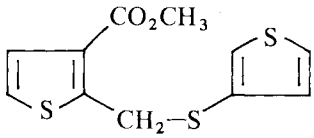
146



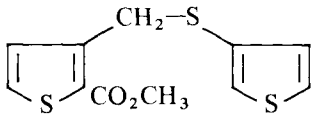
146a



146b



146c



146d

Scheme 34

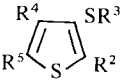
Reaction of 3-nitro-2,5-diphenyl-1,4-dithiin with methyl iodide-$AgBF_4$ led to 3-dimethylsulfonio-2,4-diphenyl-5-nitrothiophene tetrafluoroborate in low yield, which was demethylated by triethylamine to give 2,5-diphenyl-3-(methylthio)-5-nitrothiophene.[144] The reaction of **145** with alcoholic potassium hydroxide or sodium hydride followed by an alkylating agent such as dimethylsulfate or benzyl chloride gave **146**[145–147] (Scheme 34).

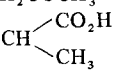
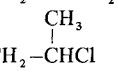
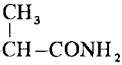
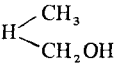
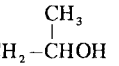
As in the case of 2-alkylthiothiophenes, the 3-alkylthiothiophenes have been prepared by alkylation of preformed 3-thiophenethiols or through Michael addition of 3-thiophenethiolates to α,β-unsaturated carbonyl derivatives (cf. Section II.5.B). The synthesis of ω-(*N,N*-dialkylamino)alkyl 3-thienylsulfides;[148–149] and of 1-carbethoxyalkyl 3-thienylsulfide[150] from 3-thiophenethiol may be mentioned as additional examples. Another recent example of this approach in connection with the synthesis of tricyclic systems of psychopharmacological interest is the preparation of **146c** and **146d** through the reaction between 3-thiophenethiolate and **146a** and **146b**, respectively, which then by $SnCl_4$-catalyzed intramolecular ring closure were converted to the desired tricyclic compound. 2-Thiophenethiolate was also reacted with **146a** and **146b** giving the analogous compounds.[270]

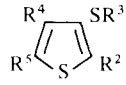
In connection with the synthesis of thienothiophenes, 3-thienylthioacetic acid[151] and 3-thienylthioacetaldehyde diethyl acetal[152] were prepared by the alkylation of 3-thiophenethiol with chloroacetic acid and bromoacetaldehyde diethyl acetal. For similar purposes, alkylation with 2-bromocyclohexanone was also carried out.[152] The reaction of sodium 3-thiophenethiolate with phthalide was used for the preparation of 2-(3-thienylthiomethyl)benzoic acid in 71% yield.[153] For more details concerning the alkylation of 3-thiophenethiols and references to 3-alkylthiothiophenes, see Section II. 5. B and Table 7.

Cyclization of 2-allyl-3-thiophenethiols formed in the thio-Claisen rearrangement of 3-allylthiothiophenes has been used for the synthesis of cyclic sulfides. Cyclization of **147** (R = H) gives predominantly **149**, depending on the solvent. In xylene of HMPA, the ratio of **149** to **148** was 9:1, whereas in *N,N*-dimethylacetamide the ratio was 7:3. With **147** ($R = CH_3$) only **149** ($R = CH_3$), was obtained.[39,41] If the 2-position is blocked by a methyl group, thio-Claisen rearrangement occurs to the 4-position, and a mixture of **150** and **151** is obtained[39] (Scheme 35).

3-Thienyllithium derivatives prepared at $-70°C$ through halogen–metal exchange of 3-halothiophenes with butyllithium has proven useful for the synthesis of alkylthiothiophenes. However, the reaction of the 3-thienyllithia with sulfur and an alkyl halide is complicated by the fact that the alkyl halide formed in the halogen–metal exchange can compete in the alkylation, causing a decrease in yield and separation difficulties.[154] However, if very reactive alkylating agents such as methyl chloro acetate or bromo acetone are employed, this approach can still be used.[155–159] In most cases it is nonetheless better to use the reaction of the 3-thienyllithium reagents with dialkyl disulfides for this purpose.[55,132,133,163,251] Metalation with butyllithium followed by reaction with sulfur and alkyl halides can be used with certain 2,5-disubstituted thiophenes. Thus from **152**, **153** was prepared by this method[161] (Scheme 36).

TABLE 7. 3-ALKYLTHIOTHIOPHENES 

C_n	R^2	R^3	R^4
5	H	CH_3	Br
	Br	CH_3	H
	D	CH_3	H
	H	CH_3	H
	H	CH_3	D
	H	CH_3	D
	H	CH_3	H
	H	CH_3	H
	Br	CH_3	H
6			H
	NO_2	CH_2CO_2H	H
	CN	CH_3	NH_2
	H	CH_2CO_2H	H
	H	CH_2CH_2Cl	H
	H	CH_2CONH_2	H
	H	CH_2CH_2OH	H
	H	CH_2CH_3	H
7	H	CH_2CO_2H	OH
	H	$CH_2C{\equiv}CH$	H
	CH_3	CF_2Cl	H
	H	$CH_2CO_2CH_3$	Cl
	CH_3	$CFCl_2$	H
	CH_3	CCl_3	H
	H	$CH_2CO_2CH_3$	H
	CH_3	CF_3	H
	H	CH_2COCH_3	H
	H		H
	CO_2CH_3	CH_3	H
	H	$CH_2CO_2CH_3$	H
	H	$CH_2CH{=}CH_2$	H
	H		H
	H		H
	$NHCOCH_3$	CH_3	H
	H		H
	H		H
	CH_3	C_2H_5	H
	H	$CH(CH_3)_2$	H
	H	CH_2CH_3	H
8	CH_3	CF_2Cl	SCF_3



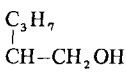
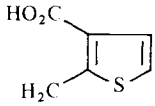
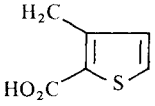
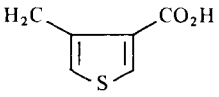
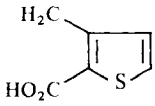
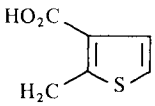
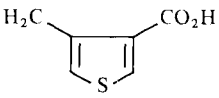
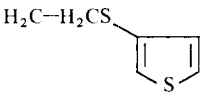
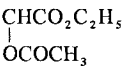
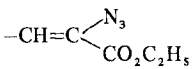
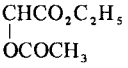
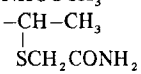
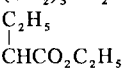
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H	116–118/10		76	133
H	67–71/0.1		87	478
H	75–76/2		70	133
Br	68–70/0.5		33	478
H	70–72/11		55	133
H				210
F	84–86/25		68	163
H	93–94/30		85	154
Br	115–120/0.5		53	478
H		170–172	50	158
H		194–196	65	158
NO_2			55	466
H		51.5–52.5	61	64
H	123/8		72	148
H		115.5–116		324
H	125/1		72	64
H	80–85/13		82	55
CO_2H		127	35	45
H	102–104/10		88–94	276
CH_3	53/0.9		66	139
H	122–127/1.0		73	157
CH_3	54/0.09		28	139
CH_3	84/0.1		56	139
F	94–101/1.2		78	157
CH_3	45/3		86	139
H	94–98/2		40	159
H		77.5–78.5	90	151
H		143	63	45
H	110–111/2		63.5	159
H	50–54/0.5		86	64
H	92–94/1		37	150
H		126–127		151
H		60–61	84	93
H	111/4		97	148
H	116–117/5		85	150
H	93–94/15			138
H	65–66/3			64
CH_3	109–110/17		82	55
CH_3	45/0.1		41	139

TABLE 7. (*Continued*)

C_n	R^2	R^3	R^4
	CH_3	CF_2Cl	SCF_2Cl
	CH_3	$CFCl_2$	SCF_3
	CH_3	CCl_3	$SCCl_3$
	CH_3	CF_3	SCF_3
	$-N(COCH_3)-CH_2-$		H
	H	$-C(H)(COOH)-CH_2COOH$	H
	$CH{=}CHNO_2$	C_2H_5	H
	$NHCOCH_3$	CH_2CO_2H	H
	NO_2	$CH_2CO_2C_2H_5$	H
	H	$CH_2-C(CH_3){=}CH_2$	H
	CH_3	$CH_2-CH{=}CH_2$	H
	H	$CH_2CO_2C_2H_5$	H
	CH_3	CH_2CO_2H	H
	H	$CH_2CO_2CH_3$	H
	H	$CH(C_2H_5)(COOH)$	H
	H	$CH_2CO_2C_2H_5$	H
	H	$CH_2CO_2CH_3$	H
	H	C_2H_5	H
	Br	$C(CH_3)_3$	H
	H	$(CH_2)_4Cl$	H
	H	$(CH_2)_4OH$	H
	H	$C(CH_3)_3$	H
	H	$CH_2CH(C_2H_5)OH$	H
	H	$CHCH_2OH(C_2H_5)$	H
	H	C_2H_5	H
	CH_2CH_2OH	C_2H_5	H
	CH_3	C_2H_5	CH_3
	H	$C(CH_3)_3$	H
	CH_3	CH_3	CH_3
	CH_3	C_2H_5	H
	H	C_2H_5	SC_2H_5
	$CH_2CH_2NH_2$	C_2H_5	H
9	CO_2CH_3	$CH_2CO_2CH_3$	H
	H	$CH_2CO_2CH_3$	CO_2CH_3
	H	$CH(CH_3)CO_2C_2H_5$	H
	H	$CH_2CO_2CH_3$	H
	CH_3	C_2H_5	OH
	CH_3	C_2H_5	OCH_3
	H	$CH_2-CH(C_3H_7)-OH$	H

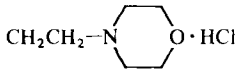
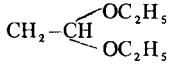
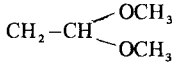
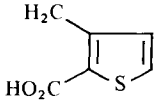
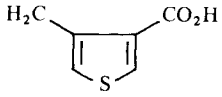
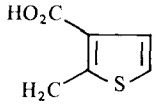
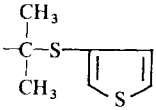
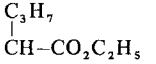
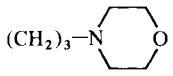
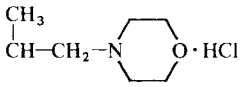
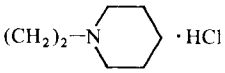
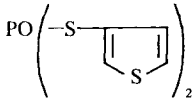
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
CH_3	62.5/0.01		50	139
CH_3	80/0.6		32	139
CH_3		127	83	139
CH_3	59/1.5		80	139
H		68–70	95	158
H		130–131	96	64
H		63–64	52.3	21
H		128	90	158
H		88–89	80	158
H	61–62/2		54	41
H	93–95/12		67	39
H	120–130/2		60	158
CH_3	173–180/1		83	47
CH_3	90–98/0.1			130
H	148–150/0.2			151
H	140–142/9			324
CH_3	118–126/1.5		53	157
CH_2CH_2Br	108–110/1		17.3	21
H	58–59/0.02		57	215
H	135/1.5		29	148
H	134–135/5		85	148
OH		53–54	65	53
H	115–118/0.5		53	150
H	122–124/0.5		84	150
CH_2CH_2OH	127–130/1–2		48	21
H	127–130/1–2		48	21
CO_2H		169	88	45
H	65–67/1			64
CH_3	120/18			77
CH_3	140–160/27			140
H	155–157/16		70	129
H	92–93.5/1		73.5	21
H		76		142
H		54–55		142
H	115–116/1		85	150
C_2H_5	127–130/2.5		61.5	26
CO_2CH_3	110/0.2		74	45
CO_2H		113	91	45
H	125–127/0.5		71	150

TABLE 7. (*Continued*)

C_n	R^2	R^3	R^4
	H		H
10	Cl		H
	Cl		H
	Cl		H
	H		H
	H		H
	H		H
	H		H
	NO_2		H
		CH_3	H
	H	2-Cyclohexanone	H
	CO_2CH_3	$CH_2CO_2CH_3$	CH_3
	H		H
	$NHCOCH_3$	$CH_2CO_2C_2H_5$	H
		CH_2CONH_2	H
	CH_3	C_2H_5	CH_3
	CH_3	$(CH_2)_3CO_2H$	H
	H		H

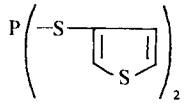
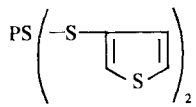
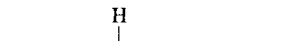
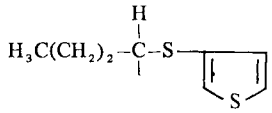
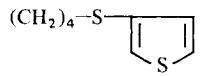
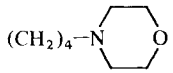
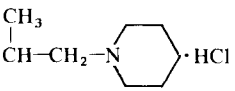
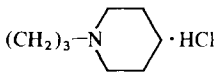
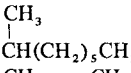
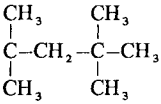
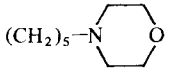
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H	133–135/0.5		82	150
H		91	42	472
H		125	72	472
H		127	65	472
H		155	80	472
H		109	53	472
H		156	48	472
H		54–55	97	64
H		106	40	158
H		61–64		272
H				152
H		58		142
H	144–146/1		65	158
H		42	65	158
H		137–138		142
CO_2CH_3	61/0.1		65	45
CH_3	211.5–212/18			48
H	116–118/0.5		83	150

TABLE 7. (*Continued*)

C_n	R^2	R^3	R^4
	CH_3	C_2H_5	OCH_3
	H		H
	H		H
	CH_3		H
11	CH_3		H
	CH_3		H
	CH_3		H
	H	$CH_2-C_6H_5$	H
	H		H
	H		H
	CH_3	C_4H_9	CH_3
	CH_3	C_4H_9	OCH_3
	CH_3	C_4H_9	OH
	H		H
	H		H
	H		H
12	Br	$CH_2-C_6H_5-2-CO_2H$	H
	H		H

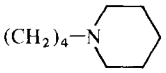
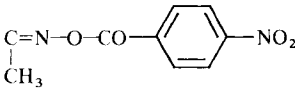
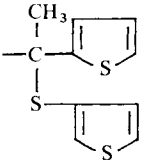
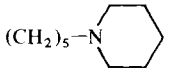
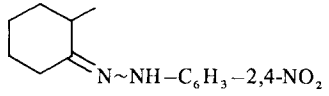
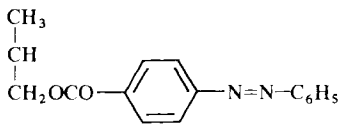
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
CO_2CH_3		Oil	92	45
H		109–110.5	77.5	148
H	115–120/1			152
CH_3	158–160/13			47
H		118	78	472
H		114	64	472
H		80	67	472
H		37–38	81	64
H	148–153/1		84	64
H	120–122/0.5		66	150
CO_2H		171	75	45
CO_2H		119	66	45
CO_2CH_3	123/0.2		81	45
H		157–158.5	85	148
H		95–96	77	148
H		145.5–150.5	83	148
H		129–132	92	153
H			51	64

TABLE 7. (*Continued*)

C_n	R^2	R^3	R^4
	H		H
	H		H
	H		H
	H	$CH_2CH{=}NN{-}C_6H_3{-}2,4\text{-}NO_2$	H
	H	$CH_2{-}C_6H_4{-}2\text{-}CO_2H$	H
	H	$CH_2CONH{-}C_6H_5$	H
	H	$CH_2{-}C_6H_4{-}2\text{-}CONH_2$	H
	H	$(CH_2)_2{-}C_6H_5$	H
	H		H
	H		H
	CH_3	C_4H_9	CH_3
	CH_3	$(CH_2)_3CO_2C_2H_5$	H
	CH_3	C_4H_9	OCH_3
	H		H
	H		H
	H		H
	H		H
	H		H
13	H		H

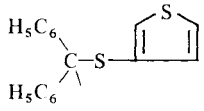
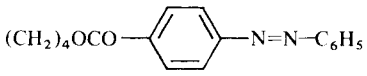
R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H		71.5–73	51	64
H		71.5–78	61	64
H		113		152
H	196/0.75	107		128
H		118–118.5		473
H		123		128
H	120–122/0.5		67	64
H	173–176/2		58	64
H		62–63	87	64
CO_2CH_3	125/0.2		73	45
CH_3	184/18			48
CO_2CH_3		Oil	95	45
H		148–150	92	148
H		172–173.5	83	148
H		120–121	81	148
H	108–111/1			64
H	102–113/1		76	64
H		135–136.5	87.5	148

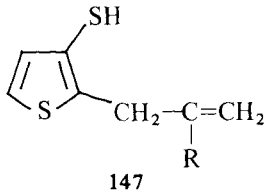
TABLE 7. (*Continued*)

C_n	R^2	R^3	R^4
	H		H
14		CH_3	H
	H		H
	CO_2CH_3	$CH_2-C_6H_5$	CH_3
	C_6H_5	C_2H_5	CH_3
	H	$H_2C-C_6H_4-2\text{-}CO_2C_2H_5$	H
	CH_3	$H_2C-C_6H_2-2\text{-}CO_2H$	H
	C_6H_5	C_2H_5	OCH_3
	C_6H_5	C_2H_5	OH
	H	CH_3	H
	H	$C_{10}H_{17}$	H
	H		H
15	C_6H_5	C_2H_5	CH_3
	C_6H_5	C_2H_5	OCH_3
16	H		H
	C_6H_5	C_4H_9	CH_3
	CH_3	$H_2C-C_6H_4-2\text{-}CO_2C_2H_5$	H
	C_6H_5	C_4H_9	OCH_3
	C_6H_5	C_4H_9	OH
	H	$C_{12}H_{25}$	H
17	C_6H_5	C_4H_9	CH_3
18	H	$C_{14}H_{29}$	H
19	H		H
20	H		H

R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H		131–133	89	148
H		160–162	87	93
H		85–86	79	64
H		45	75	143
CO_2H		121	61	45
H	186.5/3.8			128
CH_3	232/3	133		128
CO_2H		189	76	45
CO_2CH_3		87	54	45
$CH{=}C(SCH_3)(C_6H_5)$		163		146
H	118–122/1		55	64
H		89.5–91.5	93	148
CO_2CH_3	138/0.5		48	45
CO_2CH_3		47	90	45
H		147–148		152
CO_2H		124	73	45
CH_3	223/17			128
CO_2H		191	81	45
CO_2CH_3		94	47	45
H	174–176/8		60	64
CO_2CH_3	141/0.5		41	45
H		44–45	80	64
H		98–98.5		148
H		224–225		148

TABLE 7. *(Continued)*

C_n	R^2	R^3	R^4
21	H		H
	H		H
	H	$CH_2-C_6H_5$	H
23	CH_3	$CH_2-C_6H_5$	H
26	H	$CH_2-C_6H_5$	H



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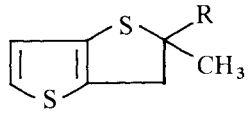

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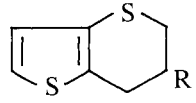

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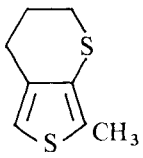

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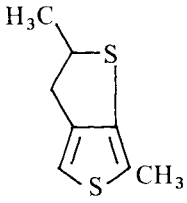

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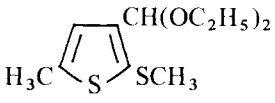
Scheme 35



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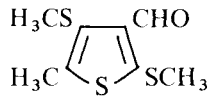


153

Scheme 36

R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
H		152	80	64
H		79–80		148
$CH{=}C(SCH_2{-}C_6H_5)(CH_3)$		76		145
$CH{=}C(SCH_2{-}C_6H_5)(C_2H_5)$		43		146
$HC{=}C(SCH_2{-}C_6H_5)(C_6H_5)$				146

Nucleophilic aromatic substitution of activated 3-bromothiophenes has also been used for the synthesis of 3-alkylthiothiophenes. Thus the reaction of 3-bromo-2-nitrothiothiophene with sodium disulfide or with thiocyanate in DMSO gave bis-(2-nitro-3-thienyl)disulfide and 2-nitro-3-thiocyanothiophenes, which upon reduction and alkylation, or hydrolysis and alkylation could be transformed to alkylthio derivatives.[158]

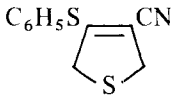
The tin tetrachloride-catalyzed reaction of 2,5-dimethylthiophene with perhalomethanesulfenyl chlorides yields 2,5-dimethyl-3-perhalomethylthiothiophenes.[139] The reaction of 2,5-dimethylthiophene with Fenton's reagent and ethyl mercaptan gave a low yield of 2,5-dimethyl-3-ethylthiothiophene.[140]

4. Syntheses of Arylthio-Substituted Thiophenes

Direct ring closure can also be used for the synthesis of arylthiothiophenes. Thus applying the Fiesselmann reaction to **127**, $R = C_6H_5$; $R^1 = CH_3$ and **127**, $R = R^1 = C_6H_5$ gave **129**, $R = C_6H_5$; $R^1 = CH_3$ and **129**, $R = R^1 = C_6H_5$, respectively. Similarly, from **130**, $R = R^1 = C_6H_5$, **131**, $R = R^1 = C_6H_5$ was obtained in 46% yield.[45] Reaction of **135** with thiophenolate followed by aromatization with chloroanil has been used for the preparation of methyl 4-methyl-3-phenylthio-2-thiophenecarboxylate.[143] Recently sulfuryl chloride was used as an efficient agent for the aromatization of dihydrothiophenes. From **154**, prepared from 4-cyano-3-oxotetrahydrothiophene, and from **155**, prepared from 2-carbomethoxy-3-oxotetrahydrothiophene, **156** and **157** were obtained in over 90% yield upon treatment with sulfuryl chloride.[164]

An often-used method for the synthesis of arylthiothiophenes is to react the appropriate thiophenethiol under basic conditions with an aromatic halide activated toward nucleophilic aromatic substitution. Most commonly used is 2,4-dinitrochloro- or bromobenzene.[10,19,20,24,26,55,134,165] Also, 2-chloro-3-nitrobenzene in dioxane or DMSO[166–168] and 4-trifluoromethyl-2-nitrochlorobenzene[169] have been used. In addition, activated halothiophenes can be used, as illustrated by the syntheses of **158** and **159** from 3-bromo-2-thiophenethiol and 3-thiophenethiol and methyl 2-bromo-3-nitro-2-thiophenecarboxylate.[167,170] From methyl 5-ethyl-2-bromo-3-thiophenecarboxylate and 2-thiophenethiol, **160** was obtained[171] (Scheme 37).

Lithium 2-thiophenethiolate gave 2-(*p*-methoxyphenyl)thienylsulfide in 46% yield upon reaction with *p*-methoxyphenyl diazonium chloride. In addition, minor amounts of 2-(*p*-methoxyphenylthio)-5-(*p*-methoxyphenyl)thiophene were also obtained.[83] Even more convenient in many cases is to interchange the nucleophilic and electrophilic components, since activated halothiophenes are more reactive in nucleophilic aromatic substitution than the analogous benzene derivatives. Thiophenols are often more stable than the analogous thiophenethiols. Thus, in connection with interest in pharmacological properties, especially antibacterial activity, aryl thienyl sulfides were prepared through the reaction of 2-iodo-5-nitrothiophene,[172–174] 2-bromo-3,5-dinitrothiophene,[175] 2,3-dichloro-5-nitrothiophene,[176] 3-bromo-2-nitrothiophene,[255] and 5-bromo-2-thiophenealdehyde[277] with various substituted thiophenols in the presence of base, mostly sodium ethylate or triethylamine. Especially interesting for preparative purposes are the reactions of **161**. With two equivalents of thiophenolate in ethanol with triethylamine as base,



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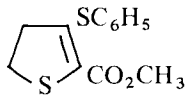

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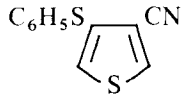

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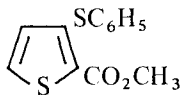

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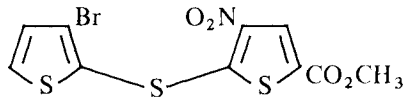

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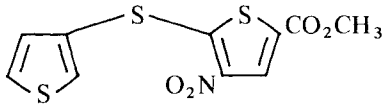

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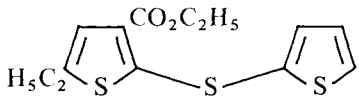

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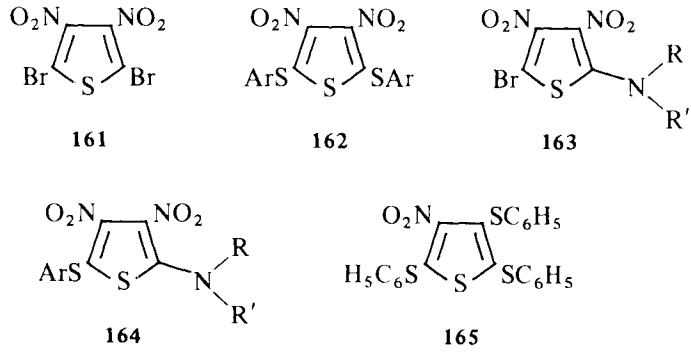
Scheme 37



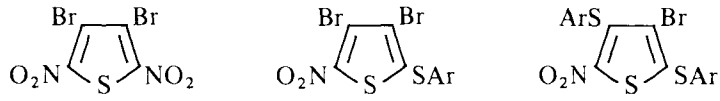
Scheme 38

162 was obtained.[137,175] It does not seem to be possible to achieve monosubstitution. However, if **161** is reacted with various primary or secondary amines, **163** can be obtained, which upon reaction with arylthiolates gives **164**. When **161** was reacted with three equivalents of sodium thiophenolate in dioxane, **165** was obtained[137] (Scheme 38).

The reaction of 2,4-dibromo-3,5-dinitrothiophene with thiophenols, such as thiophenol itself, *o*-, *m*-, and *p*-methylthiophenol, *p*-chlorothiophenol, and *p*-methoxythiophenol in dioxane in the presence of triethylamine was used for the preparation of 2-arylthio-4-bromo-3,5-dinitrothiophene or 2,4-diarylthio-3,5-dinitrothiophene by varying the reaction conditions.[274] The reaction of 2-bromo-3,4,5-trinitrothiophene with thiophenolates led to substitution of the 2-bromo and 4-nitro groups, which also gave 2,4-diarylthio-3,5-dinitrothiophene.[274]

The reaction of **166** is quite different from that of **161**. With one equivalent of thiophenolate, an α-nitro group is displaced to yield **167**, which upon further reaction leads to **168** through nucleophilic substitution of the bromine ortho to the nitro group[137] (Scheme 39).

In connection with studies on nucleophilic aromatic substitution, the kinetics of the reaction of 3-bromo-2-nitro-4-substituted thiophenes and of 3-bromo-4-nitro-2-substituted thiophenes with sodium thiophenolate in methanol was studied to obtain information about the transmission of substituent effects in systems with bonds of different order.[177] Recently the kinetics of the reaction of 3-alkyl-5-bromo-2-nitro-, 5-alkyl-3-bromo-2-nitro-, and 5-alkyl-3,4-dibromo-2-nitrothiophenes with sodium benzenethiolate in methanol at various temperatures have



Scheme 39

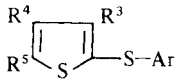
been studied. Independent of the position of the alkyl group (meta or para) with respect to the leaving bromine, an unexpected alkyl activation was observed.[178] Similar studies have been carried out with 2-bromo-3-nitro-, 2-bromo-5-nitrothiophene,[179] and 4-substituted 2,3-dihalogeno-5-nitrothiophenes.[267] The rates of nucleophilic substitution of 3-bromo-2-nitro- and 2-bromo-3-nitrothiophene with various *o*, *m*-, and *p*-substituted thiophene oxide ions have been measured in methanol at 20°C.[180] To study primary steric effects in nucleophilic substitution, some 5-nitrothiophenes and 3-alkyl-5-nitrothiophenes with different leaving groups in the 2-position were reacted with benzenethiolate. As leaving groups, Cl, Br, I, and $-SO_2Ph$ were used.[181,182] The arylthiothiophenes in the aforementioned reactions were characterized, and the compounds are given in Tables 7 and 8. For more details see the chapter on nucleophilic aromatic substitution.

Reaction of 3-bromo-2-nitrothiophene with potassium ethyl xanthogenate in ethanol offers a direct route to di-(2-nitro-3-thienyl)sulfide,[183] and from 5-nitro-2-iodothiophene and sodium disulfide bis-(5-nitro-2-thienyl)sulfide was obtained.[244] As mentioned before, other leaving groups, such as phenylsulfinyl, have also been used in addition to the halogens. Nitro groups are especially interesting. While 2,5-dinitrothiophene behaves normally, giving 2-arylthio-5-nitrothiophenes,[184,185] 3,4-dinitrothiophene yields 2-arylthio-4-nitrothiophenes.[184,186] A rather complex mechanism has been suggested for this cine substitution.[187]

With nonactivated halo compounds, the use of refluxing amide solvents such as DMF, *N,N*-dimethylacetamide, *N,N*-dimethylbutyramide, or *N*-methyl-2-pyrrolidone has been advocated. In this way 2,5-di(phenylthio)thiophene was obtained in 74% yield from 2,5-dibromothiophene and sodium thiophenolate.[188] 2-(*p*-Methylsulfonylphenylthio)thiophene was thus prepared by the reaction of 2-thiophenethiolate with 4-bromophenylmethylsulfone in DMF.[252] However, in most cases, copper-promoted reactions have been utilized. Thus all three isomeric dithienyl sulfides were prepared by condensation of the appropriate thiophenethiol with a bromothiophene in the presence of cuprous oxide in DMF,[12,189] and a detailed description of the preparation of 2,2′-dithienyl sulfide has appeared in *Organic Syntheses*.[190] Di(thienylthio)thiophenes have been prepared in a similar way through the reaction of 2- and 3-thiophenethiol with 2,5- or 3,4-dibromothiophene.[191] When the potassium salt of 3-bromo-4-thiophenethiol was heated with cuprous oxide in DMF, dithieno[3,4-b,3′,4′-c] [1,4] dithiin was obtained in 40% yield.[50]

Other example of the use of copper-promoted reactions are the preparation of 2-carboxyphenyl 2-thienylsulfide from thiosalicylic acid and 2-iodothiophene,[192] or from 2-thiophenethiol and *ortho*-iodobenzoic acid.[63] In connection with the synthesis or neuroleptica, 2-(2-thienyl)benzyl alcohol and 2-(5-chloro-2-thienyl)-benzyl alcohol were prepared in about 50% yield from 2-iodo- and 5-chloro-2-iodothiophene with 2-hydroxymethylthiophenol using anhydrous potassium carbonate and copper powder.[194] Other thiophenol derivatives have also been used.[253] Other examples in this connection are the preparation of [4-fluoro-2-(2-thienylthio)phenyl] acetic acid from 2-thiophenethiol and (4-fluoro-2-iodophenyl)acetic acid, or the corresponding bromo compound, and the preparation

TABLE 8. ARYL-2-THIENYLSULFIDES



C_n	R^3	R^4	R^5	Aryl	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
10	Br	Br	NO_2	C_6H_4-2-Cl		113		137
	Br	Br	NO_2	C_6H_4-4-Cl		134		137
	H	H	NO_2	C_6H_2-2,4,5-Cl		119–120	75	173
	Br	H	H	C_6H_3-2-NO_2-4-Cl		114–116	84	169
	NO_2	H	NO_2	C_6H_4-4-Br		133–134	88.8	175
	NO_2	H	NO_2	C_6H_4-2-Br		130–132	89	175
	Br	Br	NO_2	C_6H_5		110		137
	NO_2	H	NO_2	C_6H_4-4-Cl		132–134	91	175
	Cl	H	NO_2	C_6H_4-4-Cl		93–94	100	176
	Br	H	H	C_6H_4-2-NO_2		94–95	60	167
	Cl	H	NO_2	C_6H_5		96–97	65.6	176
	H	NO_2	H	C_6H_4-2-Cl		101		186
	H	H	NO_2	C_6H_4-4-Cl		42–42.5	50	173
	I	H	NO_2	C_6H_5		110		267
	H	H	H	C_6H_3-2,4-NO_2		119–120	89	204
	H	H	NO_2	C_6H_4-4-NO_2		130–133	71	172
	NO_2	H	NO_2	C_6H_5		155–156	85.1	175
	Br	H	H	C_6H_4-2-NH_2-4-Cl		52–55	75	169
	H	H	Cl	C_6H_5	128/2		44	197
	H	H	H	C_6H_4-4-NO_2		62		278
	H	NO_2	H	C_6H_5		56		186
	H	H	NO_2	C_6H_5		49		186
	NO_2	H	H	C_6H_5		102		179
	NO_2	H	NO_2	C_6H_4-2-NH_2		164	96.8	175
	Br	H	H	C_6H_4-2-NH_2	151–154/0.3		80	169
	Br	H	SO_2NH_2	C_6H_5		124–126	52	252
	H	H	SO_2NH_2	C_6H_4-4-Br		143–146	49	252

TABLE 8. (*Continued*)

C_n	R^3	R^4	R^5	Aryl	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	Cl	H	SO_2NH_2	C_6H_5		128–130	60	252
	H	Cl	SO_2NH_2	C_6H_5		95.5–97.5	46	252
	H	H	SO_2NH_2	C_6H_4-4-Cl		137–139	41	252
	H	H	SO_2NH_2	C_6H_4-3-Cl		107–108	77	252
	H	H	Cl	C_6H_4-2-CH_2Cl				194
	H	H	SO_2NH_2	C_6H_4-3-F		70–72	56	252
	H	H	SO_2NH_2	C_6H_4-4-F		106–107	59	252
	H	H	NO_2	C_6H_4-4-NH_2		98–100	91	172
	NH_2	H	H	C_6H_4-2-NH_2		81–83	80	134
	H	H	H	C_6H_4-4-OH		53.5–54.5	59	83
	H	H	H	C_6H_5	123/3		50.5	197
	H	H	H	C_6H_4-2-NH_2	105–115/0.4			168
	H	H	SO_2NH_2	C_6H_5		98–100	50.7	252
	H	H	SO_2NH_2	C_6H_4-4-OH		124–126	51	252
	H	H	SO_2NH_2	C_6H_4-4-NH_2		134–135	64	252
11	Br	H	H	C_6H_3-2-NO_2-4-CF_3		82–83	40	169
	H	H	Cl	C_6H_3-2-COOH-5-F		220–222	59	253
	Br	H	H	C_6H_3-2-NHCHO-4-Cl		105–106	83	169
	Br	H	H	C_6H_3-2-NH_2-4-CF_3		48–49	83	169
	Br	Br	NO_2	C_6H_4-3-CH_3		104		137
	Br	Br	NO_2	C_6H_4-4-CH_3		136		137
	H	H	H	C_6H_4-2-NCS	100–110/0.03			166
	H	H	H	C_6H_3-2-COOH-4-Cl		190–191		269
	H	H	Cl	C_6H_3-2-CH_2Cl-5-F		61–63	98	253
	Br	H	H	C_6H_4-2-NHCHO		108–109	86	169
	H	H	Cl	C_6H_3-2-CH_2OH-5-F		59–61	89	253
	Cl	CH_3	NO_2	C_6H_5		110		267
	Cl	H	NO_2	C_6H_4-4-CH_3		81–82	53	176
	H	H	SO_2NH_2	C_6H_4-3-CF_3		95–96	42	252

	I	CH_3	NO_2	C_6H_5	119		267
	NO_2	H	NO_2	C_6H_4-4-CH_3	128–130	64.2	175
	H	H	CH_3	C_6H_3-2,4-NO_2	105–106	85	204
	CH_3	H	H	C_6H_3-2,4-NO_2	120	63	204
	H	H	H	C_6H_4-2-CO_2H	195–196		192
	H	H	Cl	C_6H_4-2-CH_2OH	174–178/0.15	55	194
	H	H	Cl	C_6H_4-4-CH_3	143/3	38.1	197
	H	H	H	C_6H_4-2-NHCHO	110–112	50	168
	H	H	NO_2	C_6H_4-2-CH_3	57		137
	CH_3	H	NO_2	C_6H_5	65		181
	H	H	NO_2	C_6H_4-4-CH_3	39–40	41	185
	H	NO_2	H	C_6H_4-2-CH_3	78		186
	H	NO_2	H	C_6H_4-4-CH_3	58		186
	H	NO_2	H	C_6H_4-2-OCH_3	85		186
	H	H	H	C_6H_4-2-CH_2OH	37–38	75	194
	H	H	H	C_6H_4-4-OCH_3	144–146	48.8	83
	H	H	H	C_6H_4-4-CH_3	123/3	35	197
	H	H	SO_2NH_2	C_6H_4-2-CH_3	72–73	77	252
	H	H	SO_2NH_2	C_6H_4-4-CH_3	120.5–122.5	56	252
	H	H	SO_2NH_2	C_6H_4-4-SCH_3	99–100	46	252
	H	H	SO_2NH_2	C_6H_4-4-OCH_3	98–99	56	252
	H	H	SO_2NH_2	C_6H_4-4-SO_2CH_3	123–125		252
12	Br	H	H	C_6H_3-2-NHCHO-4-CF_3	82–84	93	169
	H	H	Cl	C_6H_3-2-CH_2CN-5-F	81–82	92	253
	H	H	Cl	C_6H_3-2-CH_2CO_2H-5-F	102–103	87	253
	H	H	Cl	C_6H_4-2-CH_2CN	155–160/0.01	70	194
	$NHCOCH_3$	H	H	C_6H_3-2-NO_2-4-Cl	178	80	134
	H	H	H	C_6H_3-2-$COCH_3$-4-Cl	74–76	41	269
	H	H	H	C_6H_3-2-CH_2CO_2H-4-Cl	134–138	34	269
	H	H	Cl	C_6H_4-2-CH_2CO_2H	110–111		194
	H	H	H	C_6H_3-2-CH_2CO_2H-5-F	129–131.5	62	171
	NO_2	H	NO_2	C_6H_4-2-$NHCOCH_3$	218–221	99.3	175
	$NHCOCH_3$	H	H	C_6H_4-2-NO_2	186	85	134
	H	H	NO_2	C_6H_4-4-$NHCOCH_3$	174–176	75	172

TABLE 8. (*Continued*)

C_n	R^3	R^4	R^5	Aryl	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	H	H	C_2H_5	C_6H_3-2,4-NO_2		128		19
	SC_2H_5	H	H	C_6H_3-2,4-NO_2	90–91			11
	Cl	H	SO_2NH_2	C_6H_4-4-$NHCOCH_3$		167–168	57	252
	H	Cl	SO_2NH_2	C_6H_4-4-$NHCOCH_3$		190–193	34	252
	H	H	H	C_6H_4-2-$NHCOCH_3$		93–94	94	168
	C_2H_5	H	NO_2	C_6H_5	Oil			182
	H	H	C_2H_5	C_6H_5	146/4		43	197
	H	H	SO_2NH_2	C_6H_4-4-$NHCOCH_3$		154–155	51	252
	H	H	CH_3	C_6H_4-4-OCH_3	158–160/0.5		32	83
	H	H	SO_2NH_2	C_6H_4-4-$SO_2N(CH_3)_2$		104–106	14	252
13	NO_2	H	NO_2	C_6H_4-2-$NHCOCH_2CH_2Cl$		144–145	92	175
	Br	H	H	C_6H_4-2-$NHCOCH_2CH_2Cl$		106–107	76	167
	NO_2	H	NO_2	C_6H_4-2-$NHCOC_2H_5$		177.5–178.5	96.3	175
	CH_2Cl	H	C_2H_5	C_6H_5	156/50 Pa		79	171
	CH_2CN	H	C_2H_5	C_6H_5	168/50 Pa		86	171
	H	NO_2	H	C_6H_2-2,4,6-CH_3		71		186
	$CH(CH_3)_2$	H	NO_2	C_6H_5	Oil			182
	$CH_2CH_2CH_3$	H	NO_2	C_6H_5	Oil			182
	CH_2OH	H	C_2H_5	C_6H_5	155–160/13 Pa		90	171
14	H	H	$CH{=}C(CN)_2$	C_6H_4-4-Cl		108–110	91	277
	H	H	$CH{=}C(CN)_2$	C_6H_5		65	92	277
	H	H	H	α-Naphthyl	180/3		42.5	197
	H	H	SO_2NH_2	β-Naphthyl		156	37	252
	NO_2	H	NO_2	C_6H_4-2-$NHCO(CH_2)_2CH_3$		165.5–166.5	98	175

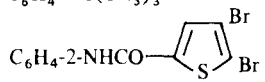
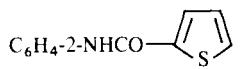
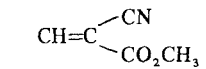
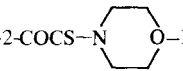
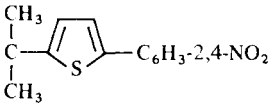
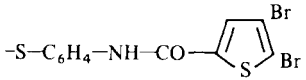
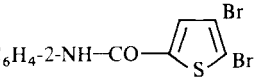
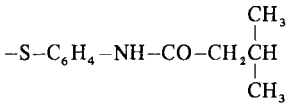
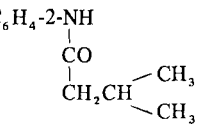
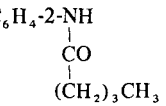
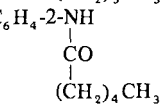
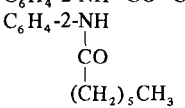
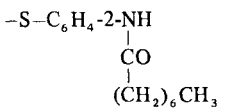
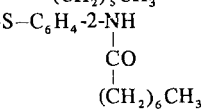
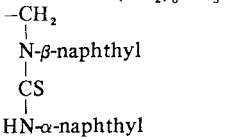
	H	H	$SC(CH_3)_3$	C_6H_3-2,4-NO_2	124–125		165
	CH_2CO_2H	H	C_2H_5	C_6H_5	73–75	86	171
	$C(CH_3)_3$	H	NO_2	C_6H_5	88		182
	H	H	SO_2NH_2	C_6H_4-4-$NHCOCH(CH_3)_2$	184–185	67	252
	H	H	SO_2NH_2	C_6H_4-4-$C(CH_3)_3$	73–74	56	252
15	NO_2	H	NO_2		220–221	70	175
	NO_2	H	NO_2		184.5–185.5	86.5	175
	H	H		C_6H_5	89–90	88	277
	NO_2	H	NO_2		176–177	97.1	175
	NO_2	H	NO_2	C_6H_4-2-$NHCO(CH_2)_3CH_3$	154–155	95	175
16	Br	S–C_6H_4-2-Cl	NO_2	C_6H_4-2-Cl	100		137
	Br	S–C_6H_4-4-Cl	NO_2	C_6H_4-4-Cl	155		137
	NO_2	NO_2	S–C_6H_4-2-Br	C_6H_4-2-Br	149–150	74.8	175
	NO_2	NO_2	S–C_6H_4-4-Br	C_6H_4-4-Br	246–247	94.8	175
	NO_2	S–C_6H_4-3-Cl	NO_2	C_6H_4-3-Cl	145		274
	NO_2	S–C_6H_4-4-Cl	NO_2	C_6H_4-4-Cl	184		274
	NO_2	NO_2	S–C_6H_4-2-Cl	C_6H_4-2-Cl	140		137
	NO_2	NO_2	S–C_6H_4-3-Cl	C_6H_4-3-Cl	144		137
	NO_2	NO_2	S–C_6H_4-4-Cl	C_6H_4-4-Cl	215–217	90.2	175
	S–C_6H_5	Br	NO_2	C_6H_5			137
	Br	S–C_6H_5	NO_2	C_6H_5	110		137
	NO_2	NO_2	S–C_6H_5	C_6H_5	172–173	94	175
	NO_2	S–C_6H_5	NO_2	C_6H_5	190		274
	NO_2	NO_2	SO_2–C_6H_5	C_6H_5	224–225		303
	H	S–C_6H_5	NO_2	C_6H_5	114		137
	NO_2	NO_2	S–C_6H_4-2-NH_2	C_6H_4-2-NH_2	163	83.3	175

TABLE 8. (*Continued*)

C_n	R^3	R^4	R^5	Aryl	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	H	H	$S-C_6H_5$	C_6H_5		48–49	32	188
	H	H	H	C_6H_3-2-COCS-  -HCl		120–123	42	269
	C_6H_{11}	H	NO_2	C_6H_5	Oil			182
	NO_2	H	NO_2	C_6H_4-2-$NHCO(CH_2)_4CH_3$		152–153	97	175
17	NO_2	H	NO_2	C_6H_4-2-$NHCO-C_6H_5$		213.5–214.5	99	175
	H	H	H	C_6H_4-4-$OCO-C_6H_5$		75–76	90	83
	H	H	H	C_6H_4-2-$NHCO-C_6H_5$		117–119	89	168
	NO_2	H	NO_2	C_6H_4-2-$NHCO(CH_2)_5CH_3$		142–143	94.4	175
18	Br	$-S-C_6H_4$-3-CH_3	NO_2	C_6H_4-3-CH_3		126		137
	Br	$-S-C_6H_4$-4-CH_3	NO_2	C_6H_4-4-CH_3		121		137
	NO_2	NO_2	$-S-C_6H_4$-2-CH_3	C_6H_4-2-CH_3		181		137
	NO_2	NO_2	$-S-C_6H_4$-3-CH_3	C_6H_4-3-CH_3		138		137
	NO_2	NO_2	$-S-C_6H_4$-4-CH_3	C_6H_4-4-CH_3		215–216	75.1	175
	NO_2	$-S-C_6H_4$-4-CH_3	NO_2	C_6H_4-4-CH_3		151		274
	NO_2	$-S-C_6H_4$-3-CH_3	NO_2	C_6H_4-3-CH_3		166		274
	NO_2	$-S-C_6H_4$-2-CH_3	NO_2	C_6H_4-2-CH_3		191		274
	H	H	$CH_2NH-C_6H_4$-4-Cl	C_6H_4-4-OCH_3		61–62	82	214
	H	H	C_6H_4-4-OCH_3	C_6H_4-4-OCH_3		120	4	82
	NO_2	$-S-C_6H_4$-4-OCH_3	NO_2	C_6H_4-4-OCH_3		168		274
	H	H	$-S-C_6H_4$-4-CH_3	C_6H_4-4-CH_3		59–60	76	189
	H	H	$CH_2NH-C_6H_4$-4-OH	C_6H_4-4-OCH_3		83–84	93.5	214
	NO_2	H	NO_2	C_6H_4-2-$NHCO(CH_2)_6CH_3$		136–137	91.3	175
19	H	H	$CH_2NH-C_6H_5$-4-CH_3	C_6H_4-4-OCH_3		53–54	91	214
20	NO_2	NO_2	$-S-C_6H_4$-2-$HNCOCH_3$	C_6H_4-2-$HNCOCH_3$		260.5–261	95.2	175
22	$-S-C_6H_5$	NO_2	$-S-C_6H_5$	C_6H_5		120		137
	NO_2	NO_2	$-S-C_6H_4$-2-$HNCO(CH_2)_2Cl$	C_6H_4-2-$HNCO(CH_2)_2Cl$		178–179	98	175
	H	H	CH_2NH-β-naphthyl	C_6H_4-4-OCH_3		85–86	79	214
	NO_2	NO_2	$-S-C_6H_4$-2-$HNCOC_2H_5$	C_6H_4-2-$HNCOC_2H_5$		202–203	71.1	175

24	H	H		C_6H_3-2,4-NO_2	100–104		26
	NO_2	NO_2	–S–C_6H_4-2-$HNCO(CH_2)_2CH_3$	C_6H_4-2-$HNCO(CH_2)_2CH_3$	198–199.5	91.7	175
26	NO_2	NO_2			248–249	73.2	175
	NO_2	NO_2	S–C_6H_4–NH–CO-2-thienyl	C_6H_4-2-NH–CO-2-thienyl	257.5–258.5	96.8	175
	NO_2	NO_2			206–207	92.8	175
	NO_2	NO_2	–S–C_6H_4–NH–CO–$(CH_2)_3CH_3$		178–179	93	175
28	NO_2	NO_2	–S–C_6H_4–NH–CO–$(CH_2)_4CH_3$		169–170	95.5	175
30	NO_2	NO_2	–S–C_6H_4–NH–CO–C_6H_5	C_6H_4-2-NH–CO–C_6H_5	240–241.5	90	175
	NO_2	NO_2	–S–C_6H_4–NH–CO–$(CH_2)_5CH_3$		167.5–168.5	91.4	175
32	NO_2	NO_2			164.5–165.5	97	175
33	H	H		C_6H_4-4-OCH_3	84–85		214

of ethyl 5-ethyl-2-(2-thienylthio)thiophene-2-carboxylate from ethyl 2-bromo-5-ethylthiophene-3-carboxylate and 2-thiophenethiol. 5-Chloro-2-(2-thienylthio)-acetophenone was prepared from 2-thiophenethiolate with 2,5-dichloroacetophenone in the presence of copper powder.[269] The phenyl analogue was obtained by using thiophenol instead of 2-thiophenethiol.[171] From 3-bromo-2,5-dimethylthiophene and *o*-aminothiophenol, 2-aminophenyl-3-(2,5-dimethylthienyl)sulfide has been obtained in low yield.[195].

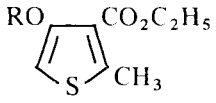
The reaction of di-(3-thienyl)iodonium chloride with sodium thiophenolate gave a 26% yield of phenyl 3-thienylsulfide.[196] The iodonium chloride was prepared through the reaction of 3-thienyllithium with *trans*-chlorovinyl iodoso dichloride. Heating 2-chlorothiophenes and thiophenols to 400 to 500°C leads to arylthiothiophenes in 40 to 50% yield.[197] In the reaction with hydrogen sulfide at 450 to 550°C with chlorothiophenes, di-(2-thienyl)sulfides are formed as by-products, in addition to 2-thiophenethiols.[18] Thienyllithium derivatives, prepared by metalation or halogen–metal exchange, can be used in several ways for the preparation of arylthiothiophenes. Thus the reaction of 2-thienyllithium with di-(2-thienyl)-disulfide has been used for the preparation of di-(2-thienyl)sulfide.[127] With 2-thienyllithium and di-(3-thienyl)sulfide or 3-thienyllithium and di-(2-thienyl)-sulfide, the unsymmetrical 2-thienyl-(3-thienyl)sulfide was obtained.[230]

The reaction of 5-fluoro-2-thienyllithium with the lithium salt of di-(*p*-hydroxyphenyl)disulfide gave (*p*-hydroxyphenyl)-(5-fluoro-2-thienyl)sulfide which, in connection with the preparation of compounds with antiinflammatory properties, was oxidized to the corresponding sulfone.[456]

The reaction of 2,5-dilithiothiophene obtained from 2,5-diidothiophene and phenyllithium with diphenyl disulfide gave 2,5-di(phenylthio)thiophene in low yield.[198] From 3-bromo-2-thienyllithium and di-(4-bromo-3-thienyl)disulfide, the unsymmetrical 3,4′-dibromo-2,3′-dithienyl sulfide was prepared.[199] A more convenient reagent for the conversion of thienyllithium derivatives to symmetrical di(thienyl)sulfides is their reaction with bis(phenylsulfonyl)sulfide. From various bromothienyllithium derivatives, di(bromothienyl)sulfides were obtained in 60 to 70% yields.[199,200] A third method for symmetrical sulfides, which has been applied to the preparation of di-(3-thienyl)sulfide, is the reaction of an aryllithium derivative with sulfur dichloride.[189]

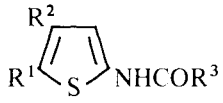
Finally, electrophilic aromatic substitution can also be used for the synthesis of arylthiothiophenes. Thus reactive thiophenes such as **169** and **170** react with sulfur chloride or sulfur dichloride in refluxing benzene without a catalyst to give **171** and **172**, respectively.[201] Similarly, **169** reacted with *o*-nitroarenesulfenyl chloride in dioxane without a catalyst to give **173**[202] (Scheme 40).

The reaction of thiophene itself with 2,4-dinitrobenzenesulfenyl chloride for the synthesis of 2-(2,4-dinitrophenylthio)thiophene, using $SnCl_4$ as catalyst, was described as early as 1950,[203] and was subsequently applied to 2-methyl- and 2,5-dimethylthiophene later.[204] Treatment of the 2,5-dinitrothienyl sulfides with potassium methoxide was used for preparation of the corresponding thiophenethiols.[204] Using iron as catalyst, arenesulfenyl chlorides without electron-withdrawing groups can also be used. With thiophene and benzenesulfenyl chloride,

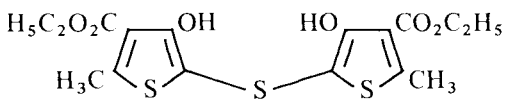


169

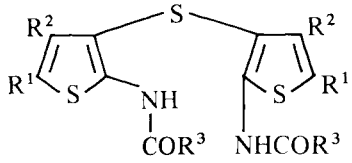
R = H, CH_3



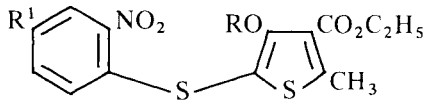
170



171



172



173

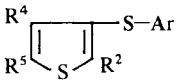
Scheme 40

phenyl 2-thienyl sulfide and 2,5-bis(phenylthio)thiophene were obtained in 33 and 40% yield, respectively.[205]

Reaction of ethyl 3-thienylglycolate with nitric acid in acetic anhydride gave ethyl α-acetoxy-(2-nitro-3-thienyl)thioglycolate[158] (Tables 8–12).

5. Physical Properties of Alkyl and Aryl Thienyl Sulfides

Gas-liquid chromatography (GLC) investigations of alkyl thienyl sulfides have been carried out, and the thermodynamics of dissolution of these compounds in the stationary phase (polyethylene glycol adipate and silicon rubber) was discussed.[206] Mass spectral fragmentation of 15 compounds of the 1-(5-ethyl-2-thienyl)-1-thiaalkane series has been studied because of their possible occurrence in petroleum fractions, coal, and other natural products.[207] The mass spectra of isomeric carbonyl-containing alkylthiothiophenes have been investigated.[265] IR and UV spectra of thienyl sulfides, especially of the isomeric di(thienyl)sulfides, have been discussed.[12,208] The UV absorption in the 260- to 275-mμ region is suggested to be due to the interaction of the 3pπ electrons of the sulfur with one of the thiophene rings.[12,208] Hydrogen bonds in thiophenes containing β-hydroxysulfide groupings have been studied by IR.[247] The photoelectron spectroscopy of bis-(2-thienyl)- and bis-(3-thienyl)sulfide and some bromo-substituted derivatives has been studied, and conclusions about the preferential conformation were drawn.[200] Radical cations have been obtained from 2,5-bis(alkylthio)thiophenes upon treatment with $AlCl_3$

TABLE 9. ARYL-3-THIENYL SULFIDES 

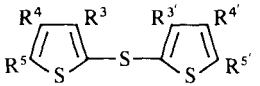
C_n	R^2	R^4	R^5	Aryl	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
10	H	Br	H	C_6H_3-2-NO_2-4-Cl		82–85	80	169
	NO_2	Br	H	C_6H_5		81		177
	NO_2	H	H	C_6H_4-3-Br		109		180
	H	Br	H	C_6H_4-2-NO_2		107–108	80	169
	NO_2	H	H	C_6H_4-4-Br		190		180
	NO_2	H	H	C_6H_4-3-Cl		112		180
	H	H	H	C_6H_3-2-NO_2-4-Cl		97–98	90	169
	NO_2	H	H	C_6H_4-4-Cl		179		180
	NO_2	H	H	C_6H_4-4-F		120		180
	H	H	H	C_6H_3-2,4-NO_2		132, 5–133		64
	NO_2	H	H	C_6H_4-3-NO_2		154		180
	NO_2	NO_2	H	C_6H_5		122		306
	NO_2	H	H	C_6H_5		174		180
	H	Br	H	C_6H_3-2-NH_2-4-Cl		56–58	85	169
	H	H	H	C_6H_4-2-NO_2		77–77.5	60	167
	NO_2	H	H	C_6H_5		92		177
	H	Br	H	C_6H_4-2-NH_2	178–179/0.9		89	169
	H	H	H	C_6H_3-2-NH_2-4-Cl	163–166/0.6		83	169
	NO_2	H	H	C_6H_4-4-NH_2		179		180
	H	H	H	C_6H_5	167–169/1		26	196
	H	H	H	C_6H_4-2-NH_2	156–160/1		80	167
11	H	Br	H	C_6H_3-2-NO_2-4-CF_3		79–81	88	169
	H	H	H	C_6H_3-2-NO_2-4-CF_3		72–72.5	84	169
	NO_2	CN	H	C_6H_5		125		177
	Br	H	H	C_6H_3-2-NHCHO-4-Cl		82–82.5	70	169
	H	Br	H	C_6H_3-2-HNCHO-4-Cl		101–102	84	169
	H	Br	H	C_6H_3-2-NH_2-4-CF_3	152–154/0.3		74	169

	H	Br	H	C_6H_4-2-HNCHO		96–97	72	169
	H	H	H	C_6H_4-2-HNCHO-4-Cl		76.5–77	90	169
	H	H	H	C_6H_4-2-NH_2-4-CF_3	116–128/0.3		74	169
	CH_3	H	H	C_6H_3-2,4-NO_2		133.5–136.5	90	55
	H	Br	H	C_6H_4-4-CH_3	165–168/1.5		84	189
	NO_2	H	H	C_6H_4-3-CH_3		101		180
	NO_2	CH_3	H	C_6H_5		53		478
	NO_2	H	H	C_6H_4-4-CH_3		68		180
	NH_2	H	H	C_6H_4-4-CO_2H				
	NO_2	H	H	C_6H_4-4-SCH_3		129		180
	NO_2	H	H	C_6H_4-4-OCH_3		135		180
	NO_2	H	H	C_6H_4-3-OCH_3		133		180
	NO_2	SO_2CH_3	H	C_6H_5		148		306
	SO_2CH_3	NO_2	H	C_6H_5		141		306
	H	H	H	C_6H_4-4-CH_3	113–114/0.4		50	189
12	Br	H	H	C_6H_3-2-HNCHO-4-CF_3		79–81	74	169
	H	Br	H	C_6H_3-2-HNCHO-4-CF_3		80–84	74	169
	H	H	H	C_6H_3-2-HNCHO-4-CF_3		86–88	71	169
	NO_2	H	H	C_6H_4-4-$COCH_3$		163		180
	H	H	H	C_6H_3-2-NO_2-4-$COCH_3$		108–108.5	80	170
	Br	H	H	C_6H_4-2-$HNCOCH_3$		69–70	96	169
	CH_3	H	CH_3	C_6H_3-2,4-NO_2		115	92	204
	CO_2H	CH_3	H	C_6H_5		108–115	80	143
	H	H	H	C_6H_3-2-NH_2-4-$COCH_3$		58–59	75	170
	H	H	H	C_6H_4-2-$HNCOCH_3$		62–63	96	169
	CH_3	H	CH_3	C_6H_4-2-N_3				195
	NO_2	H	H	C_6H_4-4-$N(CH_3)_2$		180		180
	CH_3	H	CH_3	C_6H_4-2-NH_2	114–120/0.3		16	195
13	Br	H	H	C_6H_4-2-$HNCO(CH_2)_2Cl$		69–70	81	167
	H	H	H	C_6H_4-2-$HNCO(CH_2)_2Cl$		59–60	70	167
	CO_2CH_3	CH_3	H	C_6H_5		102	61	143
	CH_3	CH_3	CO_2H	C_6H_5		178	70	45
	CO_2CH_3	CH_3	H	C_6H_5		102	61	143
	CH_3	OH	CO_2CH_3	C_6H_5		107	85	45

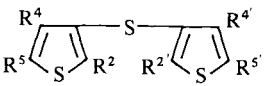
TABLE 9. (*Continued*)

C_n	R^2	R^4	R^5	Aryl	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	CH_3	OCH_3	CO_2H	C_6H_5		131	82	45
	NO_2	H	H	C_6H_2-2,4,6-CH_3		156		180
14	Br	H	H	C_6H_3-2-$HNCOCH_3$-4-$COCH_3$		143.5–144.5	60	170
	H	H	H	C_6H_3-2-$HNCOCH_3$-4-$COCH_3$		108.5–109.5	60	170
	CH_3	CH_3	CO_2CH_3	C_6H_5	74/0.2		49	45
	CH_3	OCH_3	CO_2CH_3	C_6H_5	Oil		96	45
15	Br	H	H	C_6H_4-2-$HNCO(CH_2)_2N(CH_3)_2$		94–95	71	167
16	$HNCOCH_3$	$-(CH_2)_4-$		C_6H_3-2-NO_2-4-Br		186–187	49.9	201
18	C_6H_5	CH_3	CO_2H	C_6H_5		142	78	45
	C_6H_5	OH	CO_2CH_3	C_6H_5		101	46	45
	C_6H_5	OCH_3	CO_2H	C_6H_5		198	69	45
19	$-HNCO-C_6H_5$	CH_3	CH_3	C_6H_3-2-NO_2-4-Br		218.5–219.5	50	201
	C_6H_5	CH_3	CO_2CH_3	C_6H_5		123	44	45
	C_6H_5	OCH_3	CO_2CH_3	C_6H_5		61	95	45
21	$-HNCO-C_6H_5$	$-(CH_2)_4-$		C_6H_3-2,4-NO_2		235–236	67	201
22	$-HNCO-C_6H_5$	$-(CH_2)_4-$		C_6H_4-4-CH_3		148–149	75	201

TABLE 10. 2,2′-DITHIENYL SULFIDES

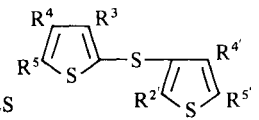


C_n	R^3	R^4	R^5	$R^{3'}$	$R^{4'}$	$R^{5'}$	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
8	NO_2	H	NO_2	NO_2	H	NO_2		196–198		172
	H	Br	H	H	Br	H			68	200
	Br	H	H	Br	H	H	170–173/0.08	54–55		199
	H	H	Cl	H	H	Cl			40	18
	H	H	NO_2	H	H	NO_2		104–105		244
	H	H	Br	H	H	H	140–142/1.3		54.5	127
	H	H	NO_2	H	H	H	154–158/0.08		53	127
	H	H	H	H	H	H	75–78/0.06		62	12
10	H	H	SCN	H	H	SCN		63.5–65	56	240
	H	H	CH_3	H	H	CH_3		19–20	31	127, 479
	H	H	SC_2H_5	H	H	H	160–162/0.7		63	127
11	CH_2Cl	H	C_2H_5	H	H	H			100	171
	CH_2OH	H	C_2H_5	H	H	H	166/0.3		80	171
12	H	H	S-2-Thienyl	H	H	H	214–220/10^{-4}		46	191
	CH_2CN	H	C_2H_5	H	H	H	170/0.8		72	171
	CH_2COOH	H	C_2H_5	H	H	H		77–78	89	171
	H	H	C_2H_5	H	H	C_2H_5			67	18
	H	H	$SCH_2CH(CH_3)_2$	H	H	H	148–152/0.01		84	127
	H	H	SC_2H_5	H	H	SC_2H_5	174–175/0.04		70	127
14	H	H	$SCH_2CH(CH_3)_2$	H	H	SC_2H_5	161.5–163.5/0.01		71	127
16	OH	$CO_2C_2H_5$	CH_3	OH	$CO_2C_2H_5$	CH_3		159–161.5	74.5	201

TABLE 11. 3,3′-DITHIENYL SULFIDES 

C_n	R^2	R^4	R^5	$R^{2'}$	$R^{4'}$	$R^{5'}$	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
8	H	Br	H	H	Br	H	164–165/0.06		83	199
	Br	H	H	Br	H	H		Oil	70	200
	I	H	H	I	H	H			72	200
	NO_2	H	H	NO_2	H	H		198–200		183
	H	H	NO_2	H	H	H		78.5–79.5	47	230
	H	H	H	H	H	H	115/0.4		48	199
26	NHCO–C_6H_5	CH_3	CH_3	NHCO–C_6H_5	CH_3	CH_3		251–252	94	201
30	NHCO–C_6H_5	$-(CH_2)_4-$		NHCO–C_6H_5	$-(CH_2)_4-$			234.5–236	96	201

TABLE 12. 2,3′-DITHIENYL SULFIDES



C_n	R^3	R^4	R^5	$R^{2'}$	$R^{4'}$	$R^{5'}$	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	References
8	Br	H	H	H	Br	H	168–172/0.15		94	199
	H	H	H	H	H	H	118/1.5		63	12
11	$NHCOCH{=}CH_2$	H	H	Br	H	H		103–104.5		167
12	H	H	S-3-Thienyl	H	H	H	$170–180/10^{-4}$		15	191
	H	H	H	H	S-2-Thienyl	H	$180–184/10^{-4}$		38.5	191
	$NHCOCH_3$	H	$COOCH_3$	H	H	H		102–102.5	52	170

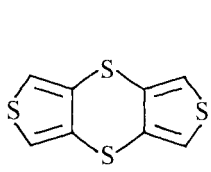
in nitromethane, and their ESR spectra interpreted in terms of unequally populated rotational isomers. Assignments of their structures was achieved by examining the effect of steric hindrance caused by bulky substituents on the ratio of conformers. Theoretical calculations (CNDO/2) have been carried out.[125] The polarographic behavior of dithienyl sulfides has been investigated.[209] Ring-deuteriated methylthiothiophenes were used in pioneering investigations of the ^1H NMR spectra of thiophenes.[210] The ^{19}F NMR spectra of fluoro-substituted methylthiothiophenes have been obtained.[163]

6. Reactions of Alkyl and Aryl Sulfides

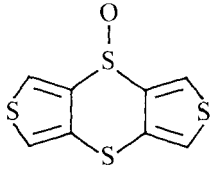
A. Reactions at the Sulfur Atom

As sulfides in general, alkyl and aryl thienyl sulfides are easily oxidized to sulfoxides and sulfones, with no complications from the thiophenic sulfur. Sulfoxides are obtained when the sulfides are treated with equivalent amounts of about 30% hydrogen peroxide in glacial acetic acid between 0°C and room temperature.[15,55,116,118,193,198,211,228,268] Reaction of **174** with one equivalent of hydrogen peroxide in methylene chloride–acetic acid at room temperature for six days gave **175**. With two equivalents under reflux, **176** was obtained[50] (Scheme 41).

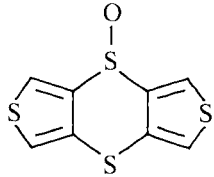
Upon oxidation of **177** with excess active manganese dioxide, not only the expected dialdehyde but also a sulfoxide with either structure **178** or **179** was obtained, which with silver oxide could be oxidized to the dicarboxylic acid with no interference from the sulfide and sulfoxide functionalities[212] (Scheme 42).



174

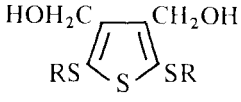


175



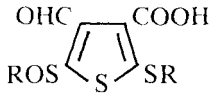
176

Scheme 41

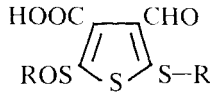


177

$R = CH_3, C_2H_5$



178

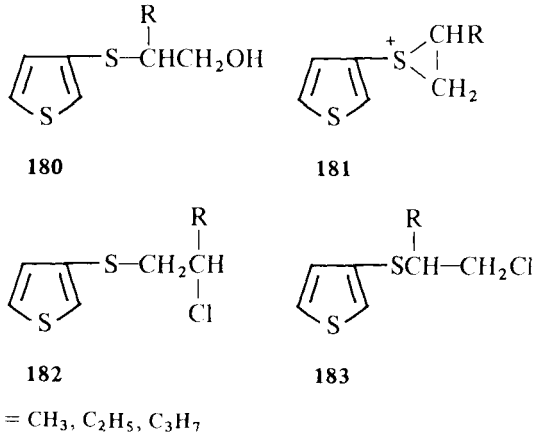


179

Scheme 42

Alkyl and aryl thienyl sulfides are easily oxidized with excess 30–40% hydrogen peroxide at about 100°C to the corresponding sulfones.[10–12,119,127,137–139,154,163,177,181,183,186,191–193,211,213,215,230,245,249,251,255,275] In a few cases, potassium permanganate in water or acetic acid has been used.[83,172,193,214] This method is useful if simultaneous oxidation of methyl or formyl groups is desired.[83,193] Chromic acid has also been used for the oxidation of 2,5-bis(phenylthio)thiophene to the bissulfone.[198] Sulfoxides and sulfones are further discussed and tabulated in Sections VII and VIII.

The reaction of 2-methylthio- and 3-methylthiothiophene with mercury iodide and methyl iodide in acetone leads to the dimethyl thienyl sulfonium triiodomercurates, which by anion exchange could be converted to the nitrates and perchlorates.[160,216] Reaction of **180** with thionyl chloride in pyridine leads to a mixture of **182** and **183** probably by way of the sulfonium intermediate **181**[150] (Scheme 43).



Scheme 43

B. Cleavage of the Carbon–Sulfur Bond in Alkyl Thienyl Sulfides

As discussed in Sections II.2 and II.3, alkylthiothiophenes are cleaved by sodium in liquid ammonia to give thiophenethiols.[10,11,19–21,23,24,26,27,32,55,56] In α,β-bis(alkylthio)thiophene the α-alkyl group is split off upon treatment with two equivalents of sodium in liquid ammonia.[399] However, 2-benzylthio-5-ethyl-3-thiophenecarboxaldehyde diethyl acetal is cleaved by sodium in liquid ammonia in the opposite way, giving 5-ethyl-3-thiophenealdehyde.[24] 2,4-Dinitrophenyl thienyl sulfides are cleaved by potassium hydroxide in methanol to give thiophenethiols and 2,4-dinitroanisole.[204] The thiophene–sulfur bonds are of course also cleaved upon Raney nickel desulfurization[115] (see also Part 1, Chapter VI).

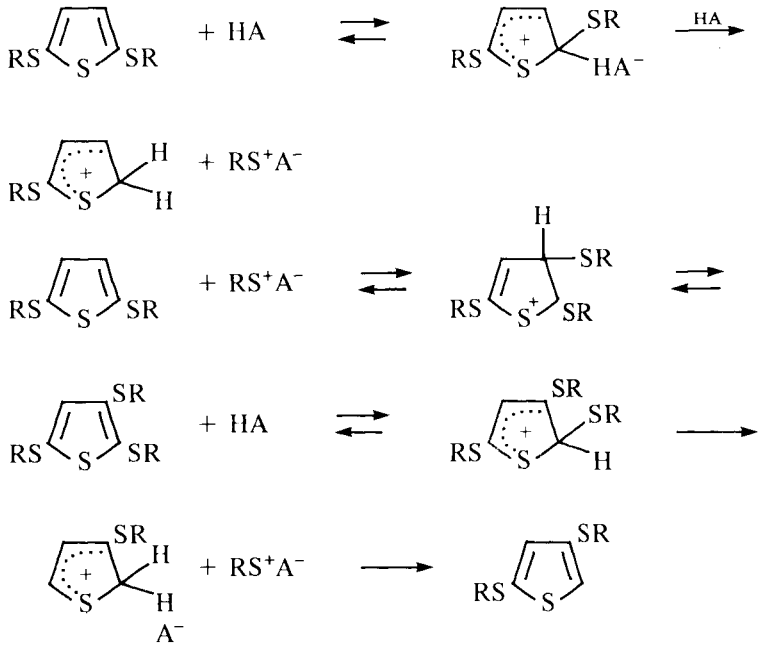
C. *Electrophilic Substitution of Alkyl and Aryl Thienyl Sulfides*

2-Alkythio groups direct predominantly to the 5-position in electrophilic aromatic substitution, as observed in Vilsmeyer formylation[21,217] and acetylation with acetyl chloride or acetic anhydride using tin tetrachloride and phosphoric acid.[115] Acetyl chloride, in the presence of excess $AlCl_3$ in methylene chloride at $-70°C$ gave 25% of the 5-isomer, 3% of the 3-isomer, and 15% of the 3,5-isomer.[218] To avoid decomposition, nitration must be carried out with fuming nitric acid in acetic anhydride at $-70°C$, which gives the 5- and 3-nitro derivatives in a 9 : 1 ratio.[219] Bromination of methyl 2-thienyl sulfide with a bromide–bromate mixture in concentrated hydrochloric acid gave the 5-bromo isomer. Bromine in chloroform was used for the preparation of the dibromo derivative.[219] If the 5-position is blocked by alkyl groups, electrophilic substitution of 2-alkylthiothiophenes, such as formylation,[24,26,193] acylation,[26,121,130,155] chloromethylation[220,221] and bromination,[193] occurs smoothly in the 3-position. However, 5-methoxy-2-methylthiothiophene is predominantly formylated in the 4-position owing to the well-known stronger *o-p* directing effect of the methoxy group.[81,251] 3-Alkylthiothiophenes undergo electrophilic substitutions such as bromination,[215] nitration,[216] formylation,[156,157] and acetylation,[155] in the 2-position. The kinetics of H–D exchange in 2- and 3-methylthiothiophene and 2,5-bis(methylthio)thiophene in solvents consisting of trifluoroacetic acid and acetic acid have been measured, and partial rate factors for the various thiophene ring positions were determined.[222,223] Formylation of 2,3′-dithienyl sulfide according to Vilsmeyer gives a complex mixture, whereas bis-(3-thienyl)sulfide is nitrated and formylated in the 2-position.[230]

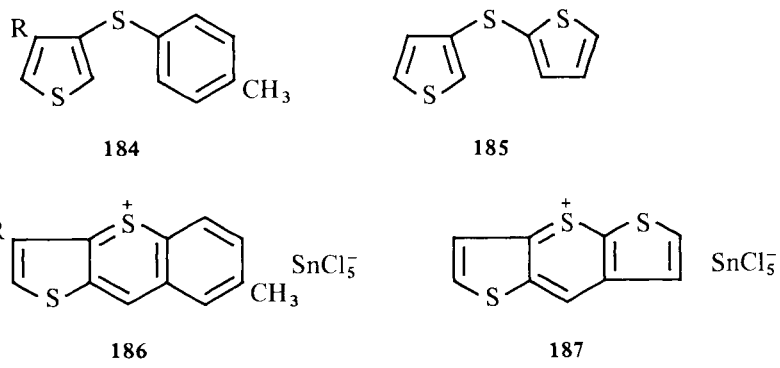
Treatment of 2,5-bis-(alkylthio)thiophenes with trifluoroacetic acid leads to the 2,4-isomer by way of an intermolecular disproportionation reaction initiated by C-protonation. Treatment of 2-methylthio-3,5-bis(ethylthio)thiophene and 2-methylthiothiophene with trifluoroacetic acid gave a mixture of 2,4-bis(ethylthio)-thiophene (~45%), 2,4-bis(methylthio)thiophene (~10%), and 2(4)-methylthio-4(2)-ethylthiothiophene (20%). The reaction path shown in Scheme 44 has been suggested.[129] This type of rearrangement is responsible for the fact that during formylation and acetylation of 2,5-bis(methylthio)thiophene, in addition to the 3-formyl- and 3-acetyl-substituted compounds, the isomeric 3,5-bis(methylthio)-2-acylthiophenes are also formed. The ratio of the 3- and 2-acyl-substituted compounds is about 1:4 during formylation and fluctuates between 100:1 and 5:4, depending on the conditions during acetylation.[227] Quantum mechanical calculations by the SCF MO LCAO method on the specificity of electrophilic attack and isomerization under C-protonation conditions of alkylthiothiophenes have been carried out.[248] The reaction of 2-(chlorodifluoromethylthio)thiophene with chlorodifluoromethane sulfenyl chloride in the presence of trifluoromethanesulfonic acid gave 2,5-bis(chlorodifluoromethylthio)thiophene in 37% yield.[249]

The reaction of dichloromethyl ether and $SnCl_4$ with aryl thienyl sulfides such as **184** and **185** gave the thiopyrylium salts **186** and **187**[189] (Scheme 45).

The reaction of 2-methylthiothiophene with tetracyanoethylene oxide gave 2-methylthio-5-thenoyl cyanide. It has been suggested that in the first step the sulfur

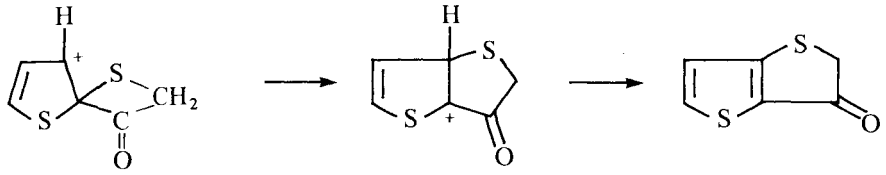


Scheme 44



Scheme 45

is involved, which gives a sulfonium dicyanomethylide and carbonyl cyanide. The latter then reacts with excess 2-methylthiothiophene.[224] α-(Thienylthio)-substituted acids, aldehydes, and ketones have been very useful for the synthesis of various thienothiophenes by intramolecular electrophilic substitution. This reaction proceeds smoothly with 3-substituted derivatives to the 2-position, giving thieno-[3,2-b]thiophene derivatives.[126,151,152,155,159] However, the corresponding 2-substituted derivatives either do not ring close[121] or do so in low yield,[152] mostly with ipso substitution followed by rearrangement, as indicated in Scheme 46, which

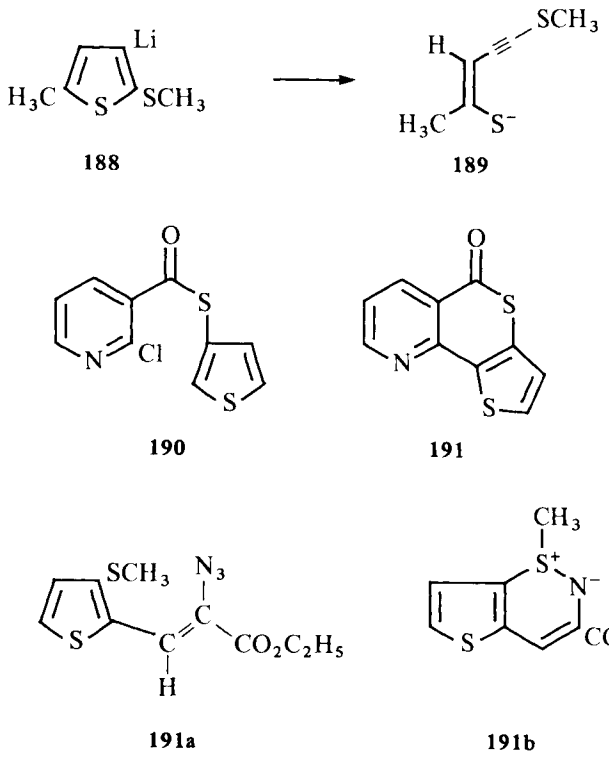


Scheme 46

again mainly yields thieno[3,2-b]thiophene derivatives.[122,126,159] The recent ring closure of methyl γ-(2-thienylthio)acetoacetates, achieved by alkylation of 2-thiophenethiolate with methyl γ-chloroacetoacetate in PPA apparently proceeded without rearrangement to the 3-thieno[2,3-b]thiophene acetates. Thieno[3,2-b]-thiophene derivatives were also prepared starting from (3-thienylthio)acetoacetates.[262]

D. Reactions of Alkylthiothiophenes with Organolithium Reagents

2-Alkylthiothiophenes with free 5-positions are conveniently metalated by butyllithium in the 5-position,[15,123,151] whereas in 3-substituted derivatives the alkylthio group selectively directs to the 2-position, as observed for 3-methylthio-,[154] 3-ethylthiothiophene,[123] and bis-(3-thienyl)sulfide.[230] However, a recent reinvestigation showed that the 2-lithio and 5-lithio derivatives are formed in the proportion of 3 to 1 upon metalation of 3-methylthiothiophene. Pure 3-methylthio-2-thienyllithium could be obtained by brominating 3-methylthiothiophene to 2-bromo-3-methylthiothiophene, which upon halogen–metal exchange at $-70°$ gave pure 3-methylthio-2-thienyllithium. Slow addition of 2-bromo-3-methylthiothiophene to an excess LDA at $-78°$ led exclusively to 5-bromo-3-methylthio-2-thienyllithium, which could be reacted with various electrophiles. With carbon dioxide 5-bromo-3-methylthio-2-thiophencarboxylic acid was obtained.[478] An exception is the bulky 3-*t*-butylthiothiophene, which upon reaction with butyllithium at 20°C gives a mixture of the 2-lithio and 5-lithio derivatives in a 3.3 : 1 ratio, determined as the carboxylic acids after reaction with carbon dioxide. In addition, 6.5% of the 2,5-dilithium derivative was obtained. At -25 to $-30°$C, greater selectivity was achieved, and the ratio of 2-lithio derivative to 5-lithio was 9 : 1.[215] If the 5-position in 2-alkylthiothiophenes is blocked by alkyl groups, the heteroatom-facilitated metalation occurs selectively in the 3-position.[123] However, the yields of 2-methylthio-5-methyl-3-thiophenecarboxylic acid and 2-methylthio-5-ethyl-3-thiophenecarboxylic acid obtained upon reaction of 5-methyl-2-methylthiothiophene and 5-ethyl-2-ethylthiothiophene with butyllithium followed by carbon dioxide were only 27 and 7%, respectively.[123] This indicates that ring opening of the 3-thienyllithium **188** derivative to **189** had occurred as demon-



Scheme 47

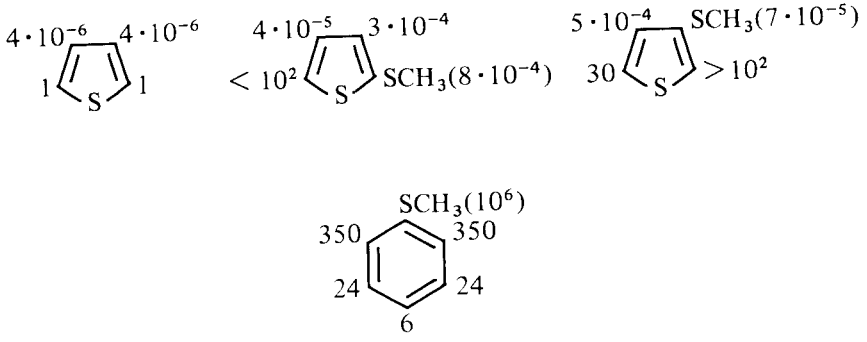
strated for **188** prepared by halogen–metal exchange from 3-bromo-5-methyl-2-methylthiothiophene[225] (Scheme 47).

Interestingly, 2,5-bis(methylthio)thiophene preferentially gives lithium–methylthio exchange with butyllithium leading to 5-methylthio-2-thienyllithium, which was trapped as the 5-methylthio-2-thiophenecarboxylic acid in 43% yield.[81] Metalation of 2-methoxy-5-methylthiothiophene with butyllithium followed by carbon dioxide and *N,N*-dimethylformamide gave only the 3-acid in 64% yield and the 3-aldehyde in 54% yield.[81] The absence of any product of metalation ortho to the methylthio group could be due to ring opening.

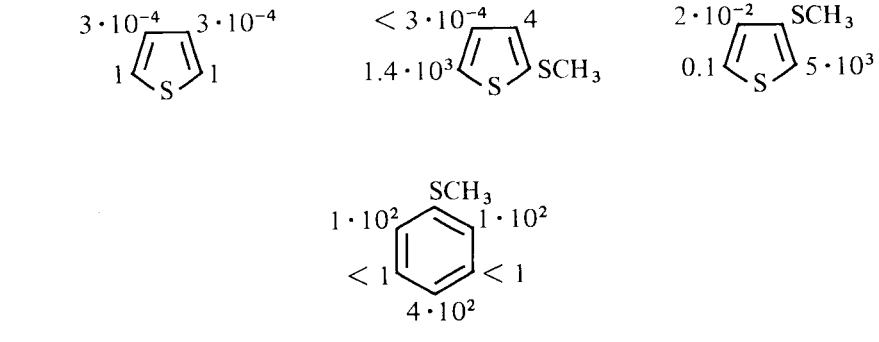
UV irradiation of **190** in benzene solution gave **191** as the main product.[229] Heating of **191a** led to the sulfimide **191b**.[272]

Kinetic data for base-catalyzed H–D exchange between isomeric methylthiothiophenes marked with deuterium in various positions have been measured in systems containing dimethyl sulfoxide and potassium or lithium *t*-butoxide.[223,226] The partial rate factors for both base- and acid-catalyzed exchange are given in Scheme 48.[223] The numbers beside the formulas for thioanisole are the partial rate factors for deuterium exchange in liquid ammonia, catalyzed by potassium amide, and, in acetic acid, catalyzed by sulfuric acid.

Exchange with base



Exchange with acid



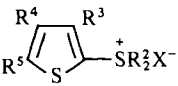
Scheme 48

IV. THIENYL SULFONIUM SALTS

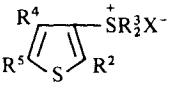
1. Preparation of Thienyl Sulfonium Salts

Only a few thienyl sulfonium salts have been prepared. Some of them have been obtained by direct ring closure of sulfonium salts, such as **94**, which upon treatment with sodium cyanide in methanol yields **95**[101] (Scheme 20).

The reaction of 3-nitro-2,5-diphenyl-1,4-dithiin with methyl iodide-$AgBF_4$ led to 3-dimethyl sulfonio-2,4-diphenyl-5-nitrothiophene in low yield.[144] The most convenient method is the alkylation of alkyl thienyl sulfides in the presence of mercuric iodide.[160,216] The initially formed rather unstable triiodomercurates were transformed to nitrates and perchlorates. A more convenient method is the direct reaction of thiophene or 2-methylthiophene with a mixture of dimethyl sulfoxide, phosphorus oxychloride, and perchloric acid, which gives dimethyl-(2-thienyl)sulfonium perchlorate and dimethyl-(5-methyl-2-thienyl)sulfonium perchlorate in 75 and 50% yield, respectively[160] (Tables 13 and 14).

TABLE 13. 2-THIENYL SULFONIUM SALTS 

C_n	R^2	R^3	R^4	R^5	X^θ	Melting Point (°C)	Yield (%)	Reference
6	CH_3	H	NO_2	Br	ClO_4	162–163	73	219
	CH_3	Br	H	Br	HgI_3	94–102	45	160
	CH_3	H	H	Br	HgI_3	128.5–129.5	69	160
	CH_3	H	H	Br	NO_3	143.5–144.5	96	160
	CH_3	H	H	H	ClO_4	135–138	76	160
	CH_3	H	H	H	HgI_3	89–91	80	160
	CH_3	H	H	H	NO_3	35–40	97	160
7	CH_3	H	H	CH_3	ClO_4	94–95	50	160

TABLE 14. 3-THIENYL SULFONIUM SALTS 

R^2	R^3	R^4	R^5	X^θ	Melting Point (°C)	Yield (%)	Reference
H	CH_3	H	H	ClO_4	141–142	86	216
H	CH_3	H	H	HgI_3	73–80	70	216
H	CH_3	H	H	NO_3	67–77	100	216

2. Reactions of Thienyl Sulfonium Salts

The dimethyl sulfonium salts are demethylated upon refluxing with saturated potassium chloride pyridine solution or pyridine. Best yields were obtained using an anion exchange resin in the acetate form.[160] Owing to the *meta*-directing effect of the dimethyl sulfonium group, bromination and nitration of dimethyl-(2-thienyl)-sulfonium perchlorate led to mixtures of the 4- and 5-substituted isomers. Compositions were determined after demethylation.[219] Nitration of dimethyl-(3-thienyl)sulfonium perchloride gave solely the 5-isomer, which was also demethylated to give methyl-(5-nitro-3-thienyl)sulfide.[216]

V. ARYL THIENYL DISULFIDES AND DI(THIENYL) DISULFIDES

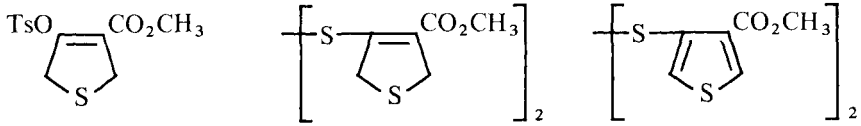
1. Preparation of Aryl Thienyl Disulfides and Di(thienyl) Disulfides

Ring closure of the products from enethiolates and α-halocarbonyl compounds according to the $C_2S + C_2$ principle, followed by iodine oxidation of the intermediate thiolate, has been used for the preparation of di-(2-thienyl) disulfides (see Scheme 19).[100] The reaction of 3-thietanone with methanolic sodium hydrogen sulfide gave, among other products, di-(2,4-dimethyl-3-thienyl) disulfide.[88] Bis-(2,4-diaryl-3-thienyl) disulfide was obtained from the thermal decomposition of 2,5-diaryl-1,4-dithiin.[187]

The reaction of **192** with sodium disulfide in acetone–methanol gave **193**, which was aromatized to **194** upon treatment with sulfuryl chloride[164] (Scheme 49). Compound **192** was obtained from 4-carbomethoxy-3-oxotetrahydrothiophene and tosyl chloride and *N*-methylmorpholine in methylene chloride. Reaction of 5-methyl-2(3H)-furanone with Lawesson's reagent gave di-(5-methyl-2-thienyl) disulfide in 32% yield.[479]

The most convenient method for the preparation of disulfides is, of course, the oxidation of the appropriate thiol. Air,[23,134] iodine,[10,20,55,56] potassium ferricyanide,[127] and ferric chloride[27] have been used as oxidizing agents.

Another convenient method for the synthesis of bis(thienyl) disulfides is the



192 **193** **194**

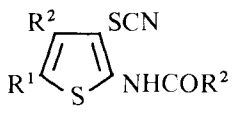
Scheme 49

reaction of activated halothiophenes, such as 2-chloro-3-nitro- or 3-bromo-2-nitrothiophene, with sodium disulfide (obtained by fusion of sodium sulfide and sulfur) in ethanol.[159,231,232] Alternatively, such activated halothiophenes are reacted with potassium hydrosulfide in methanol, followed by reaction with dimethyl sulfoxide or iodine.[183] The reaction of 5-bromo-2-nitrothiophene with potassium ethyl xanthogenate was used for the preparation of bis-(5-nitro-2-thienyl) disulfide.[183]

Some more special cases of disulfide preparation may also be mentioned. Thus reduction of thiophene sulfonyl chlorides with hydroiodic acid in acetic acid[117] or red phosphorus in the presence of iodine[233] has been used for the preparation of bis(thienyl) disulfides.

The reaction of 2-bromo-3-*t*-butylthiothiophene with thiocyanogen and anhydrous $AlCl_3$ gave bis-(2-bromo-3-thienyl) disulfide in low yield.[215] Disulfides **196** can also be prepared by heating 3-thiocyanothiophenes such as **195** in alcohol in the presence of piperidine[201] (Scheme 50).

The reaction of 2,5-dithiocyanothiophene with equimolar amounts of the dipotassium salt of cyclooctatetraene dianion in THF yields **197**, which upon treatment with aqueous acetic acid gave the interesting cyclic tetramer **198** in good yield. Its structure was proven by X-ray crystallography.[234] In the presence of 18-crown-6-ether the main product was linear poly-(2,5-thienylene) disulfide[234] (Scheme 50).



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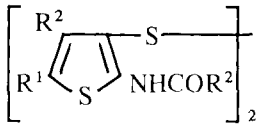

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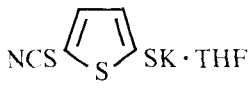

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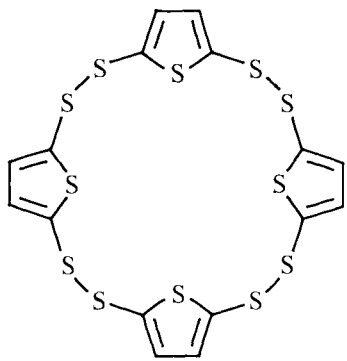


198

Scheme 50

Disulfides were also formed in the reaction of **169** with sulfur monochloride in benzene.[201] and as by-products in thio-Claisen rearrangements.[34,39]

Some unsymmetrical disulfides have been prepared through the reaction of 2-thiophenethiol with arylsulfenyl chlorides in carbon tetrachloride or by directly using the thiolate obtained from the reaction of the Grignard reagent from 2-iodothiophene with sulfur. The products could not be purified by distillation and were characterized by IR spectra and as dichloromercury derivatives.[235] Pyridyl 2-thienyl disulfide was obtained from 2-thiophenesulfenyl chloride and pyridine 2-thione.[235] The chloride had been prepared by the reaction of 2-thiophenethiol with chlorine in CCl_4 at $-15°C$. However, perhaps it should be pointed out that later work on the reaction of the potassium salt of 2-thiophenethiol with methyl benzenesulfenate gave a mixture of bis-(2-thienyl) disulfide and diphenyl disulfide.[236]

UV irradiation of *S*-(3′-thienyl)-2-chlorothionicotate gives bis-(3-thienyl) disulfide as a by-product.[229] Attempts to prepare the oxime from 5-ethyl-2-mercapto-2-thiophene aldehyde imine through reaction with hydroxylamine also led to the disulfide[24] (Tables 15 to 17).

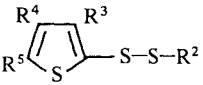
2. Reactions of Di(thienyl) Disulfides

The polarographic reduction of bis-(2-thienyl) and bis-(3-thienyl) disulfide has been studied.[237]

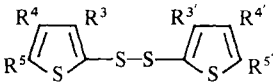
Oxidation of bis-(2-thienyl) disulfide with aluminium trichloride–methylene chloride gave the radical cation, which rearranged under the reaction conditions to the radical cation of dithieno[2,3-b,2′3′-e]-*p*-dithiin. The photoelectron and electron spin resonance spectroscopic assignments were supported by MNDO as well as parameterized HMO calculations.[264]

The reaction of organolithium compounds with disulfides leads to thioethers,[127] and the reaction of bis-(4-bromo-3-thienyl) disulfide with 3-bromo-2-thienyllithium was utilized for the synthesis of 3,4′-dibromo-2,3′-dithienyl sulfide.[199] In contrast to organolithium compounds, cyclooctatetraenyl dipotassium reacts with bis-(2-thienyl) disulfides only under electron transfer, yielding cyclooctatetraene and the potassium salt of thiophenethiolate.[165]

TABLE 15. UNSYMMETRICAL 2-THIENYL DISULFIDES



C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Yield (%)	Reference
8	3-Thienyl	H	H	H	123–125.5/1	79	230
9	2-Pyridyl	H	H	H	Oil	73	235
10	C_6H_4-4-Cl	H	H	H	Oil	100	235
	C_6H_5	H	H	H	Oil	100	235
11	C_6H_4-4-CH_3	H	H	H	Oil	100	235
	C_6H_4-2-CH_3	H	H	H	Oil	100	235

TABLE 16. 2,2′-DITHIENYL DISULFIDES 

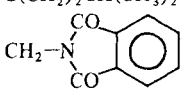
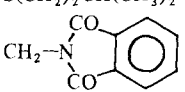
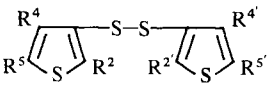
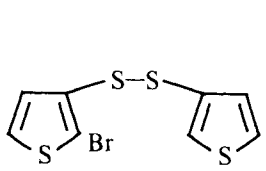
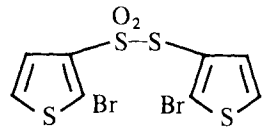
C_n	R^3	R^4	R^5	$R^{3'}$	$R^{4'}$	$R^{5'}$	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
8	NO_2	H	H	NO_2	H	H		180–181	79	183
	H	H	NO_2	H	H	NO_2		99.5–101.5	37	183
	SO_2NH_2	H	NO_2	SO_2NH_2	H	NO_2		216–217		183
	NO_2	H	SO_2NH_2	NO_2	H	SO_2NH_2		228–230		183
	H	H	H	H	H	H		56–57	67.5	127
10	H	H	CH_3	H	H	CH_3		38.5–39		20
12	$NHCOCH_3$	H	H	$NHCOCH_3$	H	H		163–165	40	134
	H	H	C_2H_5	H	H	C_2H_5			87.3	10
14	NO_2	CH_3	$COCH_3$	NO_2	CH_3	$COCH_3$		194–197	32	100
	NO_2	H	$CO_2C_2H_5$	NO_2	H	$CO_2C_2H_5$		189–191	39	100
	COOH	H	C_2H_5	COOH	H	C_2H_5		210–211	100	27
	H	H	$CH_2NHCOCH_3$	H	H	$CH_2NHCOCH_3$		157–157.5	55	117
	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3		89.5–90.5		77
	CN	H	$CO_2C_2H_5$	CN	H	$CO_2C_2H_5$		73–74	77	93
16	NO_2	CH_3	$CO_2C_2H_5$	NO_2	CH_3	$CO_2C_2H_5$		153–155	41	100
	OH	$CO_2C_2H_5$	CH_3	OH	$CO_2C_2H_5$	CH_3		117–118	63.6	201
	H	H	$SC(CH_3)_3$	H	H	$SC(CH_3)_3$		83–85	85	165
18	H	H	$S(CH_2)_2CH(CH_3)_2$	H	H	$S(CH_2)_2CH(CH_3)_2$	200–215/0.04			15
26	H	H		H	H			166–167	93	117
	NO_2	C_6H_5	$CO_2C_2H_5$	NO_2	C_6H_5	$CO_2C_2H_5$		140–143	34	100

TABLE 17. 3,3′-DITHIENYL DISULFIDES 

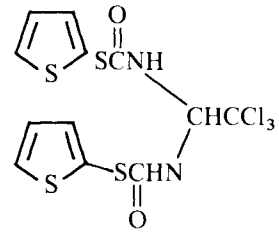
C_n	R^2	R^4	R^5	$R^{2'}$	$R^{4'}$	$R^{5'}$	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
8	Br	H	H	Br	H	H		60.5–62.5		215
	H	Br	H	H	Br	H		68–69	78	199
	NO_2	H	H	NO_2	H	H		205–208		183
	H	H	NO_2	H	H	NO_2		211–212	80	232
	H	H	H	H	H	H	130–131/0.2		63	49
10	CHO	H	H	CHO	H	H		137–138		56
	CH_3	H	H	CH_3	H	H		62.5–63	62.5	55
12	H	CO_2CH_3	H	H	CO_2CH_3	H		92–95	90	164
	CH_3	CH_3	H	CH_3	CH_3	H		53–54		88
20	$NHCOCH_3$	$-(CH_2)_4-$		$NHCOCH_3$	$-(CH_2)_4-$			200.5–201.5	85	201
26	$NHCOC_6H_5$	CH_3	CH_3	$NHCOC_6H_5$	CH_3	CH_3		207.5–208.5	68.5	201
30	$NHCOC_6H_5$	$-(CH_2)_4-$		$NHCOC_6H_5$	$-(CH_2)_4-$			187.5–188.5	75	201
32	C_6H_5	C_6H_5	H	C_6H_5	C_6H_5	H		128–129		87
36	C_6H_4-4-CH_3	C_6H_4-4-CH_3	H	C_6H_4-4-CH_3	C_6H_4-4-CH_3	H		183–185		87



199



200



201

Scheme 51

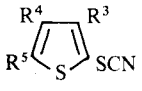
Oxidation of **199** with hydrogen peroxide in acetic acid gave **200**[215] (Scheme 51). Oxidation of bis-(5-nitro-2-thienyl) disulfide with nitric acid, followed by reaction with calcium carbonate gave the calcium salt of 5-nitro-2-thiophenesulfonic acid.[183] The oxidation of **193** with chlorine in methanol gave 4-carbomethoxy 3-thiophenesulfonyl chloride.[164]

VI. THIOCYANOTHIOPHENES

1. Preparation of Thiocyanothiophenes

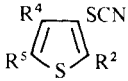
Although 2-thiocyanothiophene was first prepared through the reaction of thiocyanogen with thiophenemercury chloride or bis-(2-thienyl) mercury,[238] the best method for its preparation was developed a few years later by Söderbäck, that is in the reaction of thiophene with thiocyanogen, catalyzed by $AlCl_3$ or $Al(SCN)_3$.[239] With two equivalents of thiocyanogen, 2,5-di(thiocyano)thiophene was obtained. This procedure was later used by others for the thiocyanation of bromo- and alkylthiothiophenes.[240] Thiocyano derivatives of alkylthiothiophenes are claimed to be herbicides.[241] If the thiophene ring is activated toward electrophilic substitution, as in 2-acetamidothiophenes,[242] 3,4-diaminothiophenes,[135] acylated 3-aminothiophenes, or 3-methoxythiophene,[134] no catalyst is necessary in the reaction with thiocyanogen, which is formed during the reaction from bromine and ammonium thiocyanate.[134] The thiocyanogen solution can also be prepared in advance from bromine and lead thiocyanate.[239] 2-Acetamidothiophene has also been thiocyanated in the 5-position through the reaction with sodium thiocyanate in water in the presence of cupric sulfate.[273] 2-Thiocyanothiophene has also been obtained through the reaction of thiophene with *N*-chlorourea and potassium thiocyanate.[243]

Another method to prepare thiocyano-substituted thiophenes is the reaction of thiophenethiolates with cyanogen bromide, and in this way 3-thiocyanothiophene[49] and ethyl 4-formyl-5-thiocyano-2-thiophenecarboxylate[93] have been obtained. The reaction of di(thienyl) iodonium chlorides with sodium thiocyanate can also be used for the preparation of thiocyanothiophenes.[196] From activated halothiophenes such as 3-bromo-2-nitrothiophene, nucleophilic aromatic substitution with potassium thiocyanate in DMSO at 65°C gave an 85% yield of 2-nitro-3-thiocyanothiophene[158] (Tables 18 and 19).

TABLE 18. 2-THIOCYANOTHIOPHENES 

C_n	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	Br	Br	H	146–148/3	71–72.5	15	240
	Br	H	Br	135–137/3		56	240
	H	Br	Br	134–135/3		58	240
	Br	H	H	124–126/4	46–47	32	240
	H	H	Br	118–119/4		69	140
	H	H	H	108–110/12		98	139
	NH_2	H	H		46	45	134
6	H	H	SO_2CH_3		103–104	76	240
	H	H	SCN		87–88	53	239
	NH_2	NH_2	SCN		155	90	135
	NHCHO	H	H		126	65	134
	OCH_3	H	H		46	75	134
	H	H	SCH_3	138/1.8		58	240
7	H	SCN	$SOCH_3$		90–90.5	31	240
	H	SCN	SO_2CH_3		122–123	34	240
	Br	H	SC_2H_5	136–137/1.6		74	240
	H	H	$NHCOCH_3$		201–203 (decomp.)		273
	H	H	$SO_2C_2H_5$		68–69		240
	H	H	SC_2H_5	132–134/1.2		48	240
	$NHCOCH_3$	H	H		118	75	134
	H	SCN	$SO_2C_2H_5$		114.5–115	37	240
8	H	H	SC_3H_7	115–117/0.12		58	240
9	$NHCOCH_3$	$NHCOCH_3$	H		175–177	50	135
	H	H	$SO_2C(CH_3)_3$		114–115		240
	H	H	$SCH_2CH(CH_3)_2$	122–124/0.2		56	240
	H	H	$SC(CH_3)_3$	112–113/0.02		58	240
	H	H	SC_4H_9	127–131/0.2		55	240
10	$NHCOCH_3$	$NHCOCH_3$	SCN		220	65	135

TABLE 19. 3-THIOCYANOTHIOPHENES



C_n	R^2	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	Br	H	Br	133/1.5		6.5	240
	H	Br	H	150–153/12	54.6–56.0	37	196
	Cl	H	H	120–126/12		44	196
	H	H	Cl	121–124/11		17	196
	NO_2	H	H		87–88	80	158
	H	H	H	107–110/11		43	196
6	H	SCH_3	H		47.8–48.4	23	196
7	SCH_3	H	SCN		67.5–68	67	240
8	SC_2H_5	SCN	H	163/0.03	14–16	40	240
9	$NHCOCH_3$	CH_3	CH_3		181.5–182.5	81.3	242
11	$NHCOCH_3$	$-(CH_2)_4-$			163–163.5	85.5	242
14	$NHCOC_6H_5$	CH_3	CH_3		163.5–164.5	90	242
16	$NHCOC_6H_5$	$-(CH_2)_4-$			180.5–181.5	88.5	242

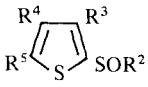
2. Reactions of Thiocyanothiophenes

Most of these reactions have been mentioned previously. Thiocyanothiophenes can be hydrolyzed with sodium sulfide in water to thiolates, which are oxidized to disulfides **201** or alkylated to give sulfides.[134, 135] The cleavage of thiocyanothiophenes by the dipotassium salt of the cyclooctatetraene anion to potassium thiophenethiolates has been mentioned previously.[165,234] The condensation of 2-thiocyanothiophene with chloral in the presence of concentrated sulfuric acid gave **201**[457] (Scheme 51), and not the compound claimed in Reference 238.

VII. THIOPHENE SULFOXIDES

1. Preparation of Thiophene Sulfoxides

As previously discussed (see Section II.6.A), sulfoxides are prepared by the oxidation of sulfides with equivalent amounts of about 30% hydrogen peroxide in glacial acetic acid between 0°C and room temperature.[15,55,116,158,193,198,211,212,228] Oxidation can be carried out in the presence of a thiocyano group,[240,268] whereas formyl groups must be protected as acetals before oxidation.[228] The compounds prepared are given in Tables 20 and 21.

TABLE 20. 2-THIOPHENE SULFOXIDES 

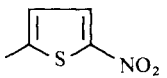
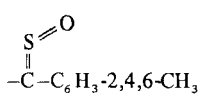
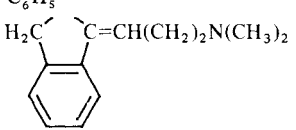
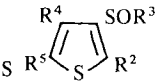
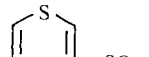
C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	CH_3	Br	H	Br		55–56	36	219
	CH_3	H	H	H	Oil		63	228
6	CH_3	H	H	CH_3	77–120/1		72	183
8	C_2H_5	H	H	C_2H_5	134–135/2		90	193
	$C(CH_3)_3$	H	H	H		48–49.5	93.5	15
		H	H	NO_2		135–136		244
10	C_6H_4-4-Br	H	H	SO_2NH_2		134–135	68	252
	C_6H_4-4-Cl	H	H	SO_2NH_2		140–141	62	252
	C_6H_4-3-Cl	H	H	SO_2NH_2		164–165	85	252
	C_6H_5	Cl	H	SO_2NH_2		117–119	66	252
	C_6H_4-3-F	H	H	SO_2NH_2		110–111	65	252
	C_6H_4-4-F	H	H	SO_2NH_2		123–124	79	252
	C_6H_5	H	H	SO_2NH_2		130–131	47	252
	C_2H_5	C_2H_5	H	C_2H_5	Oil			193
11	C_6H_4-4-CH_3	H	H	SO_2NH_2		118–120	63	252
	C_6H_4-4-SO_2CH_3	H	H	SO_2NH_2		153–156	48	252
	C_6H_4-4-OCH_3	H	H	SO_2NH_2		116–118	62	252
12	C_6H_4-NHCOCH$_3$	H	H	SO_2NH_2		195–197	38	252
14		H	H	H		155–156		431
16	C_6H_5	H	H	SOC_6H_5		124	35	198
17			H	H		Trans 234 (decomp.) Cis 139–141	98 89	116

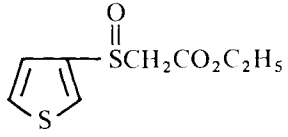
TABLE 21. 3-THIOPHENE SULFOXIDES 

C_n	R^2	R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Reference
8	H			H	145–146	40	50
	H	$CH_2CO_2C_2H_5$	H	H		50	158
10	H	C_6H_3-2,4-NO_2	H	H	161–163		55

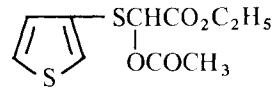
2. Reactions of Thiophene Sulfoxides

Upon further oxidation of sulfoxides, sulfones are obtained.[193] The reaction of alkyl 5-ethyl-2-thienyl sulfoxides with two equivalents of butyllithium at −70°C led to 5-ethyl-2-thienyllithium derivatives, which were trapped with carbon dioxide as carboxylic acids in 50% or lower yield.[193]

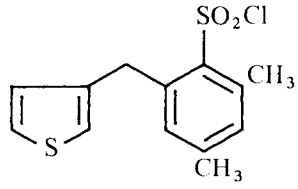
Treatment of **202** with acetic anhydride was used for the preparation of **203**[158] (Scheme 52). The acid dissociation constant for 2-methyl sulfinyl-3-thiophenecarboxylic acid has been determined.[211]



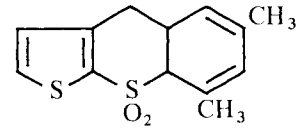
202



203



203a



203b

Scheme 52

VIII. ALKYL- AND ARYLSULFONYLTHIOPHENES

1. Preparation of Alkyl- and Arylsulfonylthiophenes

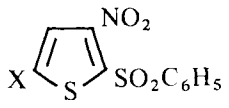
One of the best methods for the synthesis of alkyl- and arylsulfonylthiophenes is the oxidation of alkyl- and arylthienylsulfides with excess 30 to 40% hydrogen

peroxide at about 100°C. In a few cases potassium permanganate or chromic acid has also been used. (For references, see Section III.6.A.) The oxidative methods are especially important in the thiophene series since the Friedel-Crafts reaction between thiophenes and benzenesulfonyl chlorides usually leads to tar formation,[278] even when Friedel-Crafts catalysts weaker than $AlCl_3$ are used. An exception to this general observation is that when 2,5-dichlorothiophene was used with $AlCl_3$, a 25% yield of 2,5-dichloro-3-phenylsulfonylthiophene was obtained.[279] However, reversing the reactive compounds is more successful, and 2-phenylsulfonylthiophene,[278] 4-nitro-2-phenylsulfonylthiophene, and 5-methyl-2-phenylsulfonylthiophene[184,186] have been prepared by $AlCl_3$-catalyzed reactions of 2-thiophenesulfonyl chloride, 4-nitro-2-thiophenesulfonyl chloride, and 5-methyl-2-thiophenesulfonyl chloride with benzene.

A patent describes the preparation of 2-(*p*-methoxyphenyl)thiophene through the reaction of *p*-methoxybenzenesulfonyl chloride with thiophene in nitromethane in the presence of silver phosphate.[280] Bis-(2,5-dibromo-3-thienyl)sulfone was obtained as a by-product in the preparation of 2-bromo-2-thiophenesulfonyl chloride through the reaction of 2,5-dibromothiophene with chlorosulfonic acid.[281] Intramolecular cyclization of **203a** by treatment with $AlCl_3$ in methylene chloride gave **203b**[433] (Scheme 52).

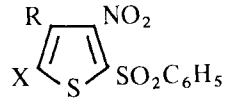
Alkylation of sodium 2-thiophenesulfinate, prepared through the reduction of 2-thiophenesulfonyl chloride with sodium sulfite heptahydrate in water, has been used for the synthesis of 2-alkylsulfonylthiophenes.[282–284] The same approach was used for the preparation of 2-alkylsulfonyl-5-phthalimidomethylthiophenes.[117] Another approach to the thiophenesulfinates is the reaction of thienyllithium derivatives with sulfur dioxide. Thus reaction of 3-thienyllithium with sulfur dioxide followed by sodium chloroacetate gave 3-thienylsulfonylacetic acid in 64% yield.[154] A very recent method of utilizing thienyllithium derivatives for sulfone synthesis consists of their reaction with trifluoromethanesulfonic anhydride at −70°C, which gives trifluoromethylsulfonylthiophenes in good yields.[285] The reaction of 5-substituted thiophenesulfinates with acrylonitrile was used for the preparation of 3-(2-thiophenesulfonyl)-2-halopropanenitriles.[286] Previously the reaction of 2-thiophenesulfinate with methyl vinyl sulfone has been used for the synthesis of 1-(2-thiophenesulfonyl)-2-methanesulfonyl ethane.[287] A very often used method for the preparation of alkyl- or arylsulfonylthiophenes is the reaction of activated halothiophenes with alkyl- or arylsulfinates. The compounds were mainly prepared in connection with extensive studies of the detailed mechanism of nucleophilic aromatic substitution in the thiophene series, where the alkyl- and arylsulfonyl groups constitute excellent leaving groups. Among the thiophenes that have been prepared by the reaction with benzenesulfinate or substituted benzenesulfinates are various 5-substituted 3-nitro-2-phenylsulfonylthiophenes **204**,[288] compounds of type **205**,[289] **206**,[182,290] and **207**[291] (Scheme 53).

The reactions are usually carried out by heating in ethanol or dioxane for a few hours. 2,5-Dibromo-3,4-dinitrothiophene was converted to the corresponding 2,5-diarylsulfonyl derivatives by reaction with two equivalents of phenylsulfinate or *p*-toluenesulfinate.[137] 2,5-Dibromo-3,4-dinitrothiophene could also first be



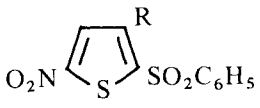
204

X = Br, $CONH_2$, CO_2CH_3, SO_2CH_3, $COCH_3$, CN, NO_2



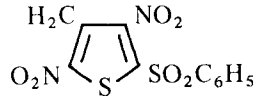
205

R = H, X = NO_2
R = CH_3, X = NO_2
R = CH_3, X = H



206

R = H, CH_3, C_2H_5, C_3H_7, *i*-C_3H_7, C_6H_{13}, *t*-C_4H_9, Br, $CONH_2$, CO_2CH_3, SO_2CH_3, CN, NO_2



207

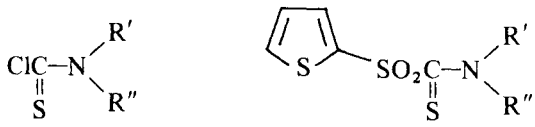
Scheme 53

transformed to 2-bromo-3,4-dinitro-5-amino derivatives through reaction with sec. amines such as morpholine, which then on reaction with arylsulfinates yielded 5-arylsulfonyl-3,4-dinitro-2-aminothiophenes.[137] The reaction of 2-chloro-3,5-dinitrothiophene with phenylsulfinate, *p*-toluenesulfinate, and *p*-nitrophenylsulfinate gave the corresponding 2-arylsulfonyl-3,5-dinitrothiophenes.[292] The reaction of 2,4-dibromo-3,5-dinitrothiophene with phenylsulfinic acid in ethanol in the presence of triethylamine somewhat unexpectedly leads to trisubstitution, giving 2,4,5-tris(phenylsulfonyl)-4-nitrothiophene.[274] From 2-bromo-3,4,5-trinitrothiophene and benzenesulfinate, 2,5-bis(phenylsulfonyl)-3,4-dinitrothiophene was prepared.[274] From 3,4-dibromo-2,5-dinitrothiophene and benzenesulfinate, 3,4-dibromo-2-nitro-5-phenylsulfonylthiophene was synthesized. Instead of phenylsulfinate, diphenylthiosulfone ($C_6H_5SSO_2C_6H_5$) can be used in the presence of sodium carbonate to achieve this reaction.[137]

The reaction of sodium benzenesulfinate with 5-bromo-2-thiophenealdehyde in *N,N*-dimethylformamide at 130 to 140°C gave a 75% yield of 5-phenylsulfonyl-2-thiophenealdehyde.[277] With very efficient leaving groups, such as in di-(3-thienyl)-iodonium chloride, reaction with sodium phenylsulfinate can be used for the preparation of phenylsulfonyl derivatives. This method was used for the preparation of 3-phenylsulfonylthiophene, 4-methyl-, and 4-methylthio-3-phenylsulfonylthiophene.[196] Heating of 2-chloromercurythiophene with cupric phenylsulfinate in acetonitrile gave a 24% yield of 2-phenylsulfonylthiophene.[293]

A special type of sulfones was obtained through the reaction of 2-thienylsulfinate with thiocarbamoyl chloride **208** yielding **209**[294] (Scheme 54).

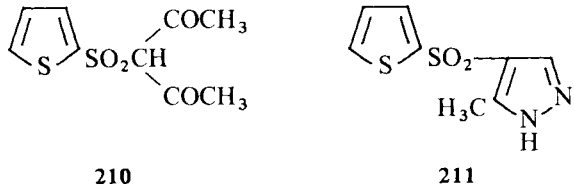
Another route to alkylsulfonylthiophenes is reaction of 2-thiophenesulfonyl



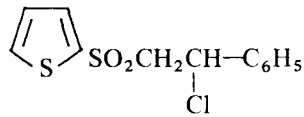
208 209

Scheme 54

chloride with carbanions. Thus the reaction with the sodium derivative of acetylacetone gave **210**, which upon reaction with hydrazine was ring closed to **211**[286] (Scheme 55).



210 211



212

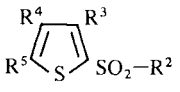
Scheme 55

The copper-catalyzed addition of 2-thiophenesulfonyl chloride to styrene gave **212** in almost quantitative yield, which upon treatment with triethylamine in benzene gave 2-(*trans*-β-styrylsulfonyl)thiophene.[295]

One of the reasons for the synthesis of alkyl- and arylsulfonylthiophenes is such potential pharmacological properties as their antibacterial effects,[172–174,252,296,297] and fungicidal,[298] diuretic, and anticonvulsant[252] effects.[469] They have also found use as nonsteroidal antiinflammatory agents,[256,456,467,468] such as 4,5-bis-(4-methoxyphenyl)-2-thienylsulfonylimidazoles, -oxazoles, and -thiazoles[299] (Tables 22 to 28).

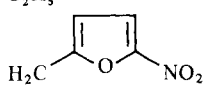
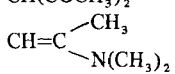
2. Physical Properties of Alkyl- and Arylsulfonylthiophenes

The UV spectra of various di(thienyl)sulfones[12] and di(thienylsulfonyl)thiophenes[191] have been measured and discussed. The interaction of the sulfonyl group with thiophene rings has been studied by IR spectroscopy.[300] The *cis* and *trans* isomers of 1-(*p*-chlorophenyl)-2-(2-thienylsulfonyl)ethene have been assigned by IR and ^{1}H NMR spectroscopy.[296] The mass spectral fragmentation of di(thienyl)-sulfones has been studied, and a 1,2-migration of a thienyl group from sulfur to oxygen observed.[301] In addition, the negative ion mass spectra of such compounds

TABLE 22. 2-ALKYLSULFONYLTHIOPHENES 

C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	CF_3	H	NO_2	Br		86	85	285
	CF_3	H	H	Br		Oil	72	285
	CF_3	H	NO_2	H		35	90	285
	CF_3	H	H	H		37.5	100	139
	CH_3	Br	NO_2	H		168–170		306
	CH_3	H	NO_2	Br		158	70	285
	CH_3	H	NO_2	Cl		150–152		398
	CH_3	H	NO_2	I		157	82	285
	CH_3	H	H	Br		70	62	285
	CH_3	H	H	Cl		72–75		398
	CH_3	H	F	H		81–82	82	163
	CH_3	H	H	F		54–55	68	163
	CH_3	H	H	I		85	68	285
	CH_3	H	H	NO_2		93–94	50	213
	CH_3	H	NO_2	H		172	100	285
	CH_3	H	NO_2	NH_2		187–189		398
	CH_3	H	H	H		46.5–47	36	282
6	$CClF_2$	H	H	$CClF_2$		96	56	249
	CF_3	H	H	CF_3		87.5	100	139
	CF_3	H	SO_2CF_3	H		109	65	285
	CH_3	H	H	CN		137–137.5		117
	CH_3	CH_3	NO_2	Br		174		283
	C_2H_5	H	Br	Br		81.5–82		307
	CH_2CH_2Br	H	H	H		83		287
	C_2H_5	H	Br	H		60.5–62		307
	C_2H_5	H	H	H	120/2.5		27	282
	CH_3	H	H	CH_3		40	63.5	193
	CH_3	CH_3	H	H		62		283

TABLE 22. (*Continued*)

C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
	CH_3	H	SO_2CH_3	H		164	48	285
	CH_3	H	H	CH_2NH_2		183–184	56	117
	CH_3	H	H	$CH_2NH_2 \cdot HCl$		213–214	85	117
7	$CH_2C{\equiv}CH$	H	H	H		56	94	275
	C_2H_5	H	Br	CH_3		73–74		307
	$CSN(CH_3)_2$	H	H	H		108–109	60	294
	$(CH_2)_2CH_3$	H	H	H	153–154/6.5		70	282
	C_2H_5	H	H	CH_3	125–127/0.4		50	307
	C_2H_5	SO_2CH_3	H	H		127–129		399
	CH_3	$SO_2C_2H_5$	H	H		113–114		399
	CH_3	H	H	$SO_2C_2H_5$		78–81	60	129
	$(CH_2)_2SO_2CH_3$	H	H	H		145–146		287
	C_2H_5	H	H	$CH_2NH_2 \cdot HCl$		196–197	84	117
8	CH_3	CH_2Cl	CH_2Cl	SO_2CH_3		214–215		119
	$C(CH_3)_3$	H	H	H		131–132	92	15
	$(CH_2)_3CH_3$	H	H	H	163–165/3		29	282
	C_2H_5	H	H	CH_2CH_3	145/4			193
	$CH_2CH(CH_3)_2$	H	H	H	150–152/2		47	15
	C_2H_5	$SO_2C_2H_5$	H	H		104.5–105.5	53.5	11
	C_2H_5	H	H	$SO_2C_2H_5$		105–105.5	93	119
9		H	H	H		172–174	65.7	284
	$CH(COCH_3)_2$	H	H	H			78	286
		H	H	H		110	99	275
	$(CH_2)_4CH_3$	H	H	H	162–163/2		33	282
	$C(CH_3)_3$	H	H	CH_3		56.5–58.5	71.5	15

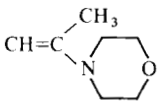
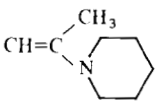
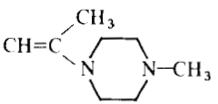
	C_2H_5	SO_2CH_3	H	C_2H_5		80–82		399
	CH_3	$SO_2C_2H_5$	H	$SO_2C_2H_5$		178–181	65	129
	CH_3	$SO_2C_2H_5$	H	C_2H_5		95–96		399
10	$(CH_2)_2SO_2$-2-thienyl	H	H	H		207–208		287
	C_2H_5	CH_2CN	H	C_2H_5		67.5–68	83	220
	C_2H_5	CH_2Cl	CH_2Cl	$SO_2C_2H_5$		114–115	80	119
	CH_3	H	NO_2			104		311
	$(CH_2)_5CH_3$	H	H	H	160/2		30	282
	$CH(CH_3)_2$	H	H	$SO_2CH(CH_3)_2$		94–97.4		138
	C_2H_5	$SO_2C_2H_5$	$SO_2C_2H_5$	H		201–203	80	129
	C_2H_5	$SO_2C_2H_5$	H	$SO_2C_2H_5$		189–191	90	129
	C_5H_{11}	H	H	$CH_2NH_2 \cdot HCl$		206–207	85	117
	$CH_2C_6H_4$-4-NO_2	H	H	H		177	9	282
11		H	H	H		127	86	275
12	$CH{=}CHC_6H_5$	H	H	H		97–99	81	295
	$CH_2CHClC_6H_5$	H	H	H		92–93	93	295
		H	H	H		70	86	275
		H	H	H		128	98	275
	$C(CH_3)_3$	H	H	$SO_2C(CH_3)_3$		221.5–223.5		15
	C_4H_9	H	H	$SO_2C_4H_9$		68.3–69.3		138

TABLE 22. *(Continued)*

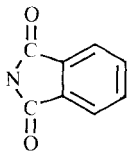
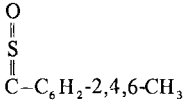
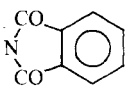
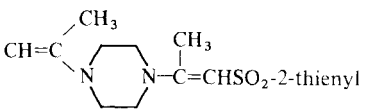
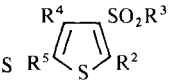
C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
13	CH_3	H	H			220	72	213
	CH_3 C_6H_5	H	H	$NHCO \cdot C_6H_4$-2-COOH		220		213
		H	H	H		116–118	84	295
	$CH_2C_6H_5$	H	H	C_2H_5		136–138		138
	$(CH_2)_2CH(CH_3)_2$	H	H	$C(CH_3)_2$		95.5–97.5	59	15
14		H	H	H		E 105–105.5 X 166–169	81 65	431
	$CH_2C_6H_5$	CH_2Cl	H	C_2H_5		54.5–55.5		220
	C_2H_5	CH_2OCOCH_3	CH_2OCOCH_3	$SO_2C_2H_5$		148.5	85	212
15	C_2H_5	$SO_2CH_2C_6H_5$	H	C_2H_5		104–105		399
17	$CH_2C_6H_5$	C_2H_5	H	C_2H_5		103–104		399
18	$CH_2C_6H_5$	H	H	$SO_2CH_2C_6H_5$		246–247		138
	Cyclo-Pentyl	H	H			101–101.5		117
		H	H	H		207–211	83	275

TABLE 23. 3-ALKYLSULFONYLTHIOPHENES



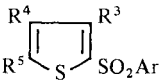
C_n	R^2	R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Reference
5	H	CF_3	H	NO_2	38	73	285
	H	CF_3	H	H	45	80	285
	H	CH_3	Br	NO_2	190		306
	H	CH_3	H	F	90–91	74	163
	H	CH_3	H	NO_2	155	66	285
	H	CH_3	H	H	76–77	84	154
6	H	CH_2CO_2H	H	H	117–118	64	154
8	Br	$C(CH_3)_3$	H	H	116–116.5	53	215
	CH_3	C_2H_5	H	CH_3	59–59.8		140
	H	$C(CH_3)_3$	H	H	165–166	79	245
	H	C_2H_5	$SO_2C_2H_5$	H	126–128	70	129
23	CH_3	$CH_2C_6H_5$	H	$CH{=}C(SO_2CH_2C_6H_5)(C_2H_5)$	165–166		146
26	H	$CH_2C_6H_5$	H	$CH{=}C(SO_2CH_2C_6H_5)(C_6H_5)$	146		146

have been studied. They show simple fragmentation patterns as the base peak is produced by cleavage α to sulfur.[302] The pK_a value for 2-methylsulfonyl-3-thiophenecarboxylic acid has been determined.[211]

3. Reactions of Alkyl- and Arylthienylsulfones

The alkyl- or arylsulfonyl groups are good leaving groups in nucleophilic aromatic substitution, and thiophenes with such groups have been extensively used in many kinetic investigations on various aspects of this substitution reaction. Thus leaving group effects in the piperidino substitution of **204** were elucidated,[288,290] as well as the influence of primary steric effects in compounds of type **205** and **206**[181,182,289] and secondary steric effects in **207**.[291] The $k_H/k_{i\text{-}Pr}$ ratios for the substitution of 2,4-dinitro-3-phenylsulfonylthiophene and **207** with aniline, piperidine, and *N*-methylaniline were found to be 60, 96, and 110, respectively, indicating the occurrence of a large kinetic secondary steric effect with the phenylsulfonyl leaving group.[291] Various linear free-energy correlations have been obtained. (For more details, see the chapter on nucleophilic aromatic substitution in thiophenes.)

The reaction is also of appreciable synthetic importance, as illustrated in the reaction of **213** with alkyl- or arylthiolates in ethanol with alkoxides to give **214** or **215**. The synthetic importance results from the fact that **213** is prepared by dimetalation of 2-*t*-butylsulfonylthiophene in the 3- and 5-position followed by reaction with *N,N*-dimethylformamide[245] (Scheme 56). This type of nucleophilic substitution cannot be carried out with 2-*t*-butylsulfonyl-3,5-thiophenedicarboxylic acid owing to the poorer electron-attracting ability of the carboxylate group.

TABLE 24. 2-ARYLSULFONYLTHIOPHENES 

C_n	R^3	R^4	R^5	Aryl	Melting Point (°C)	Yield (%)	Reference
10	Br	Br	NO_2	C_6H_5	189–190		137
	Br	H	NO_2	C_6H_5	155–156		290
	NO_2	H	Br	C_6H_5	180		288
	H	H	H	C_6H_3-2,4-NO_2	142–143		203
	H	H	NO_2	C_6H_4-4-NO_2	193–195		172
	NO_2	H	NO_2	C_6H_5	179		292
	H	NO_2	H	C_6H_5	117	100	186
	Br	H	SO_2NH_2	C_6H_5	186–188	81	252
	H	H	SO_2NH_2	C_6H_4-4-Br	179–180	93	252
	Cl	H	SO_2NH_2	C_6H_5	147–148	72	252
	H	Cl	SO_2NH_2	C_6H_5	151–152	72	252
	H	H	SO_2NH_2	C_6H_4-4-Cl	159–161	78	252
	H	H	SO_2NH_2	C_6H_4-4-F	153–154	79	252
	H	H	SO_2NH_2	C_6H_4-3-F	155–156	62	252
	H	H	NO_2	C_6H_4-4-NH_2	158–159	94	172
	H	H	H	C_6H_5	119–120	78.5	197
	H	H	H	C_6H_4-4-OH	181–182	55	83
	H	H	H	C_6H_3-2,5-OH	186		278
	H	H	H	C_6H_4-4-NH_2	134		278
	H	H	SO_2NH_2	C_6H_5	137.5–139	75	252
	H	H	SO_2NH_2	C_6H_4-4-OH	164–166	70	252
	H	H	SO_2NH_2	C_6H_4-4-NH_2	195–196	61	252
11	NO_2	H	CN	C_6H_5	183		288
	CN	H	NO_2	C_6H_5	175		290
	H	H	SO_2NH_2	C_6H_4-3-CF_3	148	86	252
	H	H	Cl	C_6H_4-4-CH_3	81–82	80.5	197
	CH_3	H	NO_2	C_6H_5	125		181

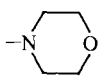
	NO_2	CH_3	H	C_6H_5	135–136		289
	NO_2	H	SO_2CH_3	C_6H_5	206		288
	SO_2CH_3	H	NO_2	C_6H_5	155–156		290
	NO_2	NO_2	$NHCH_3$	C_6H_5	205		137
	H	H	SO_2NH_2	C_6H_4-4-$CONH_2$	240–242	58	252
	H	H	CH_3	C_6H_5	91–92.5	95	305
	H	H	H	C_6H_4-4-CH_3	113–114	83.4	197
	H	H	H	C_6H_4-4-OCH_3	116–117	85	83
	H	H	SO_2NH_2	C_6H_4-2-CH_3	161–162	85	252
	H	H	SO_2NH_2	C_6H_4-4-CH_3	163.5–164.5	67	252
	CH_3	H	SO_2NH_2	C_6H_5	183–184	63	252
	H	H	SO_2NH_2	C_6H_4-4-OCH_3	126–127	63	252
	H	H	SO_2NH_2	C_6H_4-4-SO_2CH_3	238–240	72	252
12	H	H	NO_2	C_6H_4-4-$NHCOCH_3$	190–191.5	64	172
	H	H	C_2H_5	C_6H_3-2,4-NO_2	128		10
	Cl	H	SO_2NH_2	C_6H_4-4-$NHCOCH_3$	120–125	62	252
	H	Cl	SO_2NH_2	C_6H_4-4-$NHCOCH_3$	230–233	67	252
	H	H	H	C_6H_4-4-$NHCOCH_3$	106		278
	C_2H_5	H	NO_2	C_6H_5	135		182
	H	H	SO_2NH_2	C_6H_4-4-$COCH_3$	138.5–140.5	83	252
	H	H	SO_2NH_2	C_6H_4-4-$NHCOCH_3$	261–263	56	252
	H	H	CH_3	C_6H_4-4-OCH_3	73.5–74.5	66	83
	$NHCH_3$	NO_2	$NHCH_3$	C_6H_5	205		303
	H	H	SO_2NH_2	C_6H_4-4-$SO_2N(CH_3)_2$			
13	NO_2	$CH(CH_3)_2$	NO_2	C_6H_5	154		291
	$CH(CH_3)_2$	H	NO_2	C_6H_5	155		182
	$CH_2CH_2CH_3$	H	NO_2	C_6H_5	76		182
	H	H	H	C_6H_2-2,4,6-CH_3	114–115.5	50	433
14	H	H	$CH{=}C(CN)_2$	C_6H_5	165–167	86.5	277
	H	H	SO_2NH_2	β-Naphthyl	228–230	71	252
	H	H	H	α-Naphthyl	107–108	82	197
	NO_2	NO_2		C_6H_5	240		137

TABLE 24. (*Continued*)

C_n	R^3	R^4	R^5	Aryl	Melting Point (°C)	Yield (%)	Reference
	$C(CH_3)_3$	H	NO_2	C_6H_5	112		182
	H	H	SO_2NH_2	C_6H_4-4-$NHCOCH(CH_3)_2$	218–220	92	252
	NO_2	NO_2	$N(C_2H_5)_2$	C_6H_5	143		137
	H	H	CH_3	C_6H_2-2,4,6-CH_3	93–94.5	50	433
	H	H	SO_2NH_2	C_6H_4-4-$C(CH_3)_3$	161–162	73	252
15	NO_2	NO_2	NH-2-pyridyl	C_6H_5	250		303
	H	H	$CH{=}C(CN)(CO_2CH_3)$	C_6H_5	173–174	88	277
	NO_2	NO_2		C_6H_5	208		137
16	NO_2	NO_2	NH–C_6H_3-2,4-Cl	C_6H_5	217		303
	NO_2	NO_2	C_6H_4-4-Br	C_6H_5	220		303
	NO_2	NO_2	NHC_6H_4-2-Cl	C_6H_5	227		303
	NO_2	NO_2	NHC_6H_4-4-NO_2	C_6H_5	235		303
	NO_2	NO_2	NHC_6H_4-3-NO_2	C_6H_5	211		303
	NO_2	NO_2	$SO_2C_6H_5$	C_6H_5	263–264		274
	NO_2	NO_2	NHC_6H_5	C_6H_5	210		303
	NO_2	NO_2	$SO_2C_6H_5$	C_6H_5	263–264		137
	H	H	$SO_2C_6H_5$	C_6H_5	143–144		198
	C_6H_{11}	H	NO_2	C_6H_5	71		182
17	NO_2	NO_2	NHC_6H_4-2-CH_3	C_6H_5	196		137
	NO_2	NO_2	NHC_6H_4-2-OCH_3	C_6H_5	225		137
	NO_2	NO_2	NHC_6H_4-4-OCH_3	C_6H_5	198		137
18	$N(C_2H_5)_2$	NO_2	$N(C_2H_5)_2$	C_6H_5	136		303
	$NHCH_2CH(CH_3)_2$	NO_2	$NHCH_2CH(CH_3)_2$	C_6H_5	106		303
19	NO_2	NO_2	NHC_6H_2-2,4,6-CH_3	C_6H_5	237		137

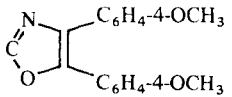
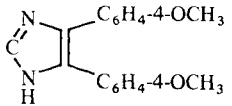
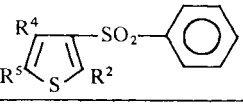
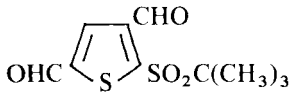
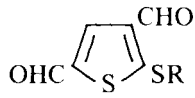
20		NO_2		C_6H_5	194		303
21	H	H	H		127	47	299
	H	H	H		179	75	299
22	NHC_6H_4-3-Br	NO_2	NHC_6H_4-3-Br	C_6H_5	177		303
	NHC_6H_4-4-Br	NO_2	NHC_6H_4-4-Br	C_6H_5	231		303
	NHC_6H_4-3-Cl	NO_2	NHC_6H_4-3-Cl	C_6H_5	178		303
	NHC_6H_4-4-Cl	NO_2	NHC_6H_4-4-Cl	C_6H_5	220		303
	NO_2	$SO_2C_6H_5$	$SO_2C_6H_5$	C_6H_5	216–217		274
	NO_2	NO_2	$NH-C_6H_4-C_6H_5$	C_6H_5	221		303
	NHC_6H_5	NO_2	NHC_6H_5	C_6H_5	186		303
	$NHcycloC_6H_{11}$	NO_2	$NHcycloC_6H_{11}$	C_6H_5	174		303
	NHC_6H_{13}	NO_2	NHC_6H_{13}	C_6H_5	104		303
23	NHC_6H_4-4-Br	NO_2	NHC_6H_4-2-CH_3	C_6H_5	172–173		303
24	$NHCH_2C_6H_5$	NO_2	$NHCH_2C_6H_5$	C_6H_5	136		303
	NHC_6H_4-3-CH_3	NO_2	NHC_6H_4-3-CH_3	C_6H_5	178		303
	NHC_6H_4-4-CH_3	NO_2	NHC_6H_4-4-CH_3	C_6H_5	190		303
	NHC_6H_4-2-OCH_3	NO_2	NHC_6H_4-2-OCH_3	C_6H_5	149		303
	NHC_6H_4-4-OCH_3	NO_2	NHC_6H_4-4-OCH_3	C_6H_5	192		303
	NHC_7H_{15}	NO_2	NHC_7H_{15}	C_6H_5	75		303
26	NHC_6H_4-4-$N(CH_3)_2$	NO_2	NHC_6H_4-4-$N(CH_3)_2$	C_6H_5	197		303
	NHC_8H_{17}	NO_2	NHC_8H_{17}	C_6H_5	58		303
34	NH-β-naphthyl	NO_2	NH-β-naphthyl	C_6H_5	219		303
	$NHC_6H_4C_6H_5$	NO_2	$NHC_6H_4C_6H_5$	C_6H_5	210		303

TABLE 25. 3-PHENYLSULFONYLTHIOPHENES 

C_n	R^2	R^4	R^5	Melting Point (°C)	Yield (%)	Reference
10	Cl	H	Cl	126.5–128	56	279
	NO_2	H	H	140–141		255
	H	H	H	119–120	28	196
11	H	CH_3	H	81–82	22	196
	H	SCH_3	H	170–171	46	196
15	NO_2	NO_2		174		274

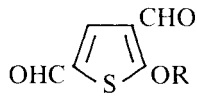


213



214

$R = C_2H_5, CH_2C_6H_5, C_4H_9, C_6H_5$



215

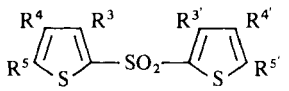
$R = CH_3, C_2H_5$

Scheme 56

However, on treatment of the acid with sodium in liquid ammonia, the *t*-butylsulfonyl group is eliminated and 2,4-thiophenedicarboxylic acid is obtained.[245] The reaction of 2-nitro-3-phenylsulfonylthiophene with azide ion has been used for the preparation of 3-azido-2-nitrothiophene.[255] The reaction of 3,4-dinitro-2,5-diphenylsulfonylthiophene with thiophenolate gives 2-phenylthio-, 2,5-diphenylthio-, and 2,3,5-triphenylthio derivatives, depending on the number of moles of thiophenolate employed. With one equivalent of amines, 2-amino-substituted 5-phenylsulfonyl-3,4-dinitrothiophene was obtained, while two moles gave a mixture of 2,4-diamino-substituted 5-phenylsulfonyl-3-nitrothiophenes and 2,3-diamino-5-phenylsulfonyl-3-nitrothiophene. With phenoxide only monosubstitution was obtained.[303]

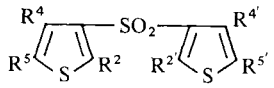
The claim that 3-*t*-butylsulfonylthiophene is dimetalated in the 2- and 5-position[245] was later shown to be erroneous.[53] A more careful investigation showed that the 2-lithium and 2,4-dilithium derivatives were produced upon treatment with butyllithium in ether-THF. After reaction with carbon dioxide and methylation, a 42% yield of dimethyl 3-*t*-butylsulfonyl-2,4-thiophenecarboxylate was obtained.[53] The structure was proven by Raney-nickel desulfurization. However, when the reaction is carried out in ether, small amounts of the 2,5-dicarboxylic acid are also formed. The behavior of 2- and 3-*t*-butylsulfonylthiophenes on treatment with butyllithium differs markedly from that of *t*-butylsulfonylbenzene,

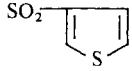
TABLE 26. 2′-THIENYL-2-SULFONYLTHIOPHENES



C_n	R^3	R^4	R^5	$R^{3'}$	$R^{4'}$	$R^{5'}$	Melting Point (°C)	Yield (%)	Reference
8	NO_2	H	H	NO_2	H	H	261–263		297
	H	H	NO_2	H	H	NO_2	160–163		297
	H	H	Br	H	H	H	121–123	79	127
	H	H	NO_2	H	H	H	85–86.5	95	127
	H	H	H	H	H	H	130.5–131.5		12
10	H	H	$SO_2C_2H_5$	H	H	H	97–97.5	65	127
12	H	H	SO_2-2-thienyl	H	H	H	167–168		191
	$NHCOCH_3$	H	H	$NHCOCH_3$	H	H	194–195		297
	H	H	$NHCOCH_3$	$NHCOCH_3$	H	H	124–126		297
	H	H	$NHCOCH_3$	H	H	$NHCOCH_3$	295–298		297
	H	H	$SO_2CH_2CH(CH_3)_2$	H	H	H	155–156	83.5	127
	H	H	$SO_2C_2H_5$	H	H	$SO_2C_2H_5$	187–187.2	89	127
	H	H	$SO_2CH_2CH(CH_3)_2$	H	H	$SO_2C_2H_5$	112–112.5	72	127

TABLE 27. 3'-THIENYL-3-SULFONYLTHIOPHENES



C_n	R^2	R^4	R^5	$R^{2'}$	$R^{4'}$	$R^{5'}$	Melting Point (°C)	Reference
8	Br	H	Br	Br	H	Br	177–178	281
	NO_2	H	H	NO_2	H	H	273	183
	H	H	H	H	H	H	165	12
	H		H	H	H	H	206	191
12	$NHCOCH_3$	H	H	$NHCOCH_3$	H	H	221–222	297

which on treatment with excess alkyllithium yields lithium *t*-butylsulfinate and 2,6-dilithium-1-alkylbenzenes.[304]

5-Methyl-2-*t*-butylsulfonylthiophene is of course only metalated in the 3-position, and from the lithium derivative the aldehyde was prepared.[15] 3-Methylsulfonylthiophene, despite the free α-position, is metalated in the methyl group, giving 3-thienylsulfonylacetic acid upon reaction with carbon dioxide.[154]

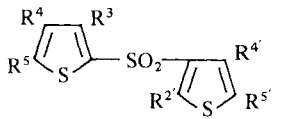
Metalation of **216** with butyllithium followed by *N,N*-dimethylformamide gave two isomeric aldehydes in the proportion 1 : 1.2. The minor component was shown to be **217**, whereas the structure of the major one was not determined[83] (Scheme 57).

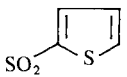
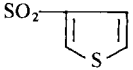
Metalation of 2-benzenesulfonylthiophene with butyllithium occurs in the 2-position, giving 2-benzenesulfonyl-5-thiophenecarboxylic acid in 60% yield after reaction with carbon dioxide.[305]

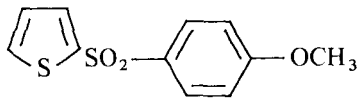
The Truce-Smiles rearrangement of **217a** has been investigated. On treatment of **217a** (R = H) with one equivalent of butyllithium in ether or potassium *t*-butoxide in DMSO, **217b** ($R = CH_3$) was obtained upon acidification. Owing to the acidity of the free α-position of **217a** (R = H), two equivalents of butyllithium are necessary to obtain **217b** (R = H). Treatment with one equivalent of butyllithium followed by CO_2 gave **217a** (R = COOH). The intermediate **217a** (R = Li) is not stable on standing at room temperature and gives sodium mesitylene sulfinate as the only isolable product. The mesitylsulfonyl-substituted thiophenes (**217a**) are the first example of a system that undergoes rearrangement in aprotic media with a change in aryl orientation. A suggested mechanism involves a β-elimination from the cyclic intermediate **217c**, leading to **217d**[433] (Scheme 57).

In electrophilic substitution the sulfonyl group is deactivating and *meta*-directing. Thus the nitration of 3-bromo-2-methylsulfonylthiophene gives 3-bromo-2-methylsulfonyl-5-nitro- and 3-bromo-2-methylsulfonyl-4-nitrothiophene in a 1:2 ratio. Some desulfonylation also occurs to give 3-bromo-2,4-dinitrothiophene.[177] Mixtures of 4- and 5-nitro isomers were also obtained in the nitration of 3-methyl-2-methylsulfonylthiophene. Mercuration and bromination of such a mixture was used for the preparation of 2-bromo-4-methyl-5-methylsulfonyl-3-nitrothiophene,

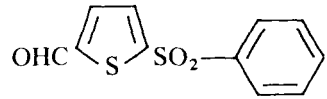
TABLE 28. 3′-THIENYL-2-SULFONYLTHIOPHENES



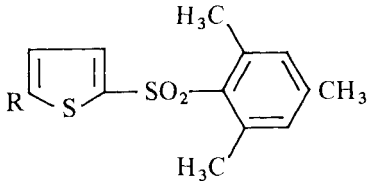
C_n	R^3	R^4	R^5	$R^{2'}$	$R^{4'}$	$R^{5'}$	Melting Point (°C)	Yield (%)	Reference
8	H	H	NO_2	NO_2	H	H	161–163		297
	NO_2	H	H	NO_2	H	H	263–265		297
	H	H	H	H	H	H	131–132	87	230
12	H	H	H	H		H	214–215		191
	H	H		H	H	H	164		191
	H	H	$NHCOCH_3$	$NHCOCH_3$	H	H	140–142		297
	$NHCOCH_3$	H	H	$NHCOCH_3$	H	H	184–187		297



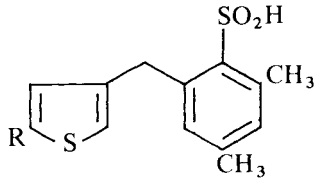
216



217

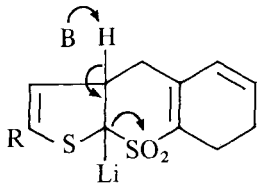


217a



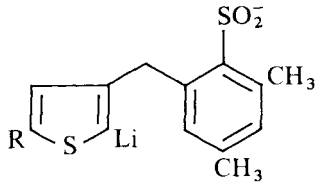
217b

R = H, CH_3, COOH, Li



217c

R = CH_3, Li

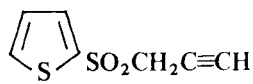


217d

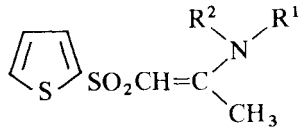
R = CH_3, Li

Scheme 57

as only the 4-nitro isomer with a free α-position undergoes mercuration.[283] Nitration of 2-iodo-5-methylsulfonylthiophene leads to 2-iodo-5-methylsulfonyl-3-nitrothiophene,[288] and 2-bromo-5-trifluoromethylsulfonylthiophene also gives only the 3-nitro isomer.[285] Bromination of 5-ethylsulfonylthiophene in the presence of excess anhydrous aluminium trichloride in chloroform gave the initial sulfone, the 5-bromo-, 4-bromo-, and 4,5-dibromo-2-ethylsulfonylthiophene in the proportions 0.9 : 0.4 : 1 : 0.8. If the 5-position is blocked, as in 5-ethylsulfonyl-2-methylthiophene, this type of bromination yields 68% of 3-bromo-5-ethylsulfonyl-2-methylthiophene.[307]



218



219

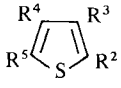
Scheme 58

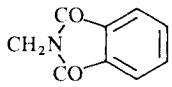
The reaction of **218** with various amines in ether at 0°C gave **219** in very high yields[275] (Scheme 58).

IX. THIOPHENESULFINIC ACID AND DERIVATIVES

1. Preparation of Thiophenesulfinic Acids

Two main methods have been used for the preparation of thiophenesulfinic acids. One consists of the reaction of 2-thienyllithium[287] or 3-thienyllithium derivatives[154] with sulfur dioxide. Grignard reagents have also been used.[308] The other is the reduction of thiophenesulfonyl chlorides with sodium sulfide solution[117,213,278,282,294,309-311] (Table 29).

TABLE 29. THIOPHENESULFINIC ACIDS 

C_n	R^2	R^3	R^4	R^5	Melting Point (°C)	Reference
4	SO_2H	H	H	H	65–67	287
	H	SO_2H	H	H	55–63	154
12	SO_2H	H	H	$NHCOC_6H_5$-2-CO_2H	138 ($0.5\,H_2O$)	213
17	SO_2H	H	H		117–118 (decomp.)	117

2. Reactions of Thiophenesulfinic Acids

The free sulfinic acids are quite unstable and decompose easily. They may be oxidized by air and disproportionate. Therefore the salts are often used directly for the preparation of sulfones, either by alkylation[117,154,282] or by Michael addition.[287,313] (See also Section VIII.1 for more details.)

2-Thienylsulfinic acid as well as other sulfinic acids can be used as analytical reagents for certain metal ions.[309]

The reaction of 2-thiophenesulfinate with trichloromethylsulfenyl chloride gives the trichloromethylthiosulfonate (2-$ThSO_2SCCl_3$), which was of interest in connection with investigation of fungicides.[310] The reaction of 2-thienylsulfinic acid with isocyanates in the presence of 1-methylimidazole as catalyst was used in connection with the preparation of 6-sulfamidopenicillanic and -cephalosporanic acids.[312]

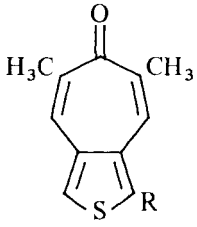
X. THIOPHENESULFONIC ACIDS AND DERIVATIVES

1. Preparation of Thiophenesulfonic Acids

2-Thiophenesulfonic acid is one of the longest-known thiophene derivatives. It was prepared as early as 1883 by treating coal tar benzene with 96% sulfuric acid.[306] A simple laboratory procedure that kept polymerization to a minimum was worked out by Steinkopf and Ohse[314] in the 1920s and consisted of the addition of thiophene to 95% sulfuric acid at 30 to 40°C. (For more details about this early work, see Hartough's monograph.) Alkylthiophenes with long alkyl groups have been sulfonated in connection with work on detergents.[315,316] Special interest has been devoted to the synthesis of sulfonic acids derived from 2-acetylaminothiophenes. Reaction of 2-acetylaminothiophene with 100% sulfuric acid at room temperature was used for the preparation of 2-acetylamino-5-thiophenesulfonic acid, isolated as the barium salt.[317] Heating of 2-acetylaminothiophene for a few minutes at 100°C with 100% sulfuric acid gave 2-acetylamino-3,5-thiophenedisulfonic acid.[318] Reaction with sulfuric acid has also been used for the synthesis of the more complex sulfonic acid **220b** from **220a**.[319] The preparation of the sodium salt **220c**, which shows diuretic activity,[454,455] has been described (Scheme 59).

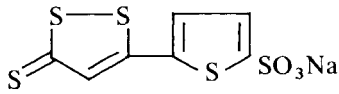
Treatment of 2-methylthiophene with concentration sulfuric acid led to a complex sulfonic acid due to trimerization of the methylthiophene under the acidic conditions.[320]

3-Thiophenesulfonic acid has been prepared according to Langer[321] by sulfonation of 2,5-dibromothiophene followed by debromination with 5% sodium amalgam in aqueous solution.[322,323] This sequence can be performed without isolation of the intermediate 2,5-dibromo-3-thiophenesulfonyl chloride.[324] Reaction of 2,5-dibromothiophene with excess fuming sulfuric acid has also been used for the preparation of the anhydride of 2,5-dibromo-3,4-thiophenedisulfonic acid, which was hydrolyzed with barium oxide or sodium hydroxide to the 2,5-dibromo-3,4-thiophenedisulfonic acid. By reduction with 5% sodium amalgam, the dibromo



220

a. R = H
b. R = SO_3H



220c

Scheme 59

compound gave 3,4-thiophenedisulfonic acid;[325,326] (see also Reference 327). Similarly 3,4-thiophenedisulfonic acid was also prepared from 2,5-dichloro-3,4-thiophenedisulfonic acid.[327]

A milder sulfonation method for acid-sensitive thiophenes has been developed by Terentyev and co-workers, who used a pyridine-SO_3 complex.[328–331] Reaction at room temperature with pyridine bissulfur trioxide led to the 2-monosulfonic acid (isolated as the barium salt) in 86% yield.[332] At higher temperatures, a mixture of 2,5- and 2,4-thiophenedisulfonic acids was obtained.[332] The reaction of 2-chloro-, 2-bromo-, and 2-iodothiophene with pyridine sulfur trioxide at about 100°C gave the corresponding 5-sulfonic acids in 95, 90, and 77% yield, respectively.[333] A comparison of the sulfonation of thiophene and of 2,5-dimethylthiophene with pyridine sulfur trioxide, pyridine bis(sulfur trioxide), and dioxane sulfur trioxide has been carried out. The two latter reagents are similar in acetone and give 2-thiophenesulfonic acid in 86 and 75% yield, respectively, and 2,5-dimethyl-3-thiophenesulfonic acid in 94 and 95% yield, respectively, at room temperature. Pyridine sulfur trioxide reacts slower, and temperatures of 130°C must be used with 2,5-dimethylthiophene.[334] The sulfonation of *t*-butyl-substituted thiophenes offers special problems owing to facile de-*t*-butylation in acidic media. However, when 2,5-di-*t*-butylthiophene and 2-*t*-butyl-5-methylthiophene were sulfonated with pyridine bis(sulfur trioxide) or with sulfur trioxide in dichloroethane using 1.3 to 1.4 molecular equivalents of sulfur trioxide, the β-substituted sulfonic acids were obtained. If 2,5-di-*t*-butylthiophene was sulfonated with five equivalents of sulfur trioxide, one of the *t*-butyl groups was eliminated, and a disulfonic acid was formed. In the sulfonation of 3,5-di-*t*-butyl-2-methylthiophene, one *t*-butyl group was eliminated, and a monosulfonic acid was obtained in low yield identical to the sulfonation product from 2-*t*-butyl-5-methylthiophene, which probably is 2-*t*-butyl-5-methyl-4-thiophenesulfonic acid.[335]

The most important way to introduce the sulfonic acid functionality is the reaction of thiophenes with chlorosulfonic acid, which leads directly to the sulfonyl chloride and is discussed in Section X.3.

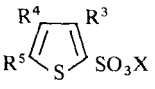
The sulfonyl chlorides can then be hydrolyzed to the sulfonic acid but more often are converted to esters, amides, hydrazides, and other derivatives, which are of greater interest (see Section X.3).

5-Chloro-2-thiophenesulfonic acid has been prepared by the oxidation of 5-chloro-2-thiophenethiol with 30% hydrogen peroxide in acetic acid.[254]

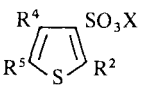
Some patents describe the use of thiophenesulfonic acids in nickel plating[336–339] (Tables 30 and 31).

2. Reactions of Thiophenesulfonic Acids

The only reaction of importance besides desulfonylation is the conversion of salts of thiophenesulfonic acids to the sulfonyl chlorides, which is usually achieved by treatment of the salts of sulfonic acids with PCl_5.[340–342] 2-Acetylamino-5-thiophenesulfonyl chloride was prepared through the reaction of 2-acetylamino-

TABLE 30. 2-THIOPHENESULFONIC ACIDS AND THEIR SALTS 

C_n	R^3	R^4	R^5	X	Melting Point (°C)	Yield (%)	Reference
4	H	H	Br	0.5 Ba		90	333
	H	H	Cl	0.5 Ba		94.8	333
	H	Cl	Cl	Na	360 (decomp.)		323
	H	H	I	0.5 Ba		77	333
	H	SO_3	H	Ba			318
	H	H	Br	*S*-[1]Naphthylmethylisothiuronium	142–143		333
	H	H	Cl	*S*-[1]Naphthylmethylisothiuronium	138–139		333
	H	H	I	*S*-[1]Naphthylmethylisothiuronium	151–152		333
	H	SO_3	NH_2	0.5 Ba			318
	H	H	H	*S*-[1]Naphthylmethylisothiuronium	174.5–175		333
	H	SO_3	H	H			343
	H	H	NH_2	H			343
	H	SO_3	NH_2	H			343
5	H	H	CH_3	H	119.5–121		305
6	H	SO_3	$NHCOCH_3$	Ba			317
	H	H	$NHCOCH_3$	0.5 Ba			317

TABLE 31. 3-THIOPHENESULFONIC ACIDS AND THEIR SALTS 

C_n	R^2	R^4	R^5	X	Melting Point (°C)	Reference
4	Br	H	Br	(IR)-Bornyl amine	266–267	324
	H	H	NO_2	H		244
6	CH_3	H	CH_3	*S*-[1]Naphthylmethylisothiuronium	195	334
9	CH_3	H	$C(CH_3)_3$	*p*-Toluidine	184.5–185.5	335
12	$C(CH_3)_3$	H	$C(CH_3)_3$	*p*-Toluidine	193–194	335

5-thiophenesulfonic acid with PCl_5 in acetyl chloride.[343] Treatment of dry sodium 3-thiophenesulfonate with $POCl_3$ gives the sulfonyl chloride.

3. Preparation of Thiophenesulfonyl Chlorides

The use of chlorosulfonic acid for the preparation of 2-thiophenesulfonyl chloride was first described by Steinkopf and Höpner.[340] However, under their conditions, appreciable hydrolysis of the sulfonyl chloride occurred, so treatment of the dry salt with PCl_5 was used to increase the yield. A 50% yield has been obtained by this approach.[278,359] In later modifications, in which chlorosulfonation was carried out at -15 to $-5°C$ and chloroform was added before work-up, a 72% yield of 2-thiophenesulfonyl chloride was reported (after vacuum distillation).[213] Other authors using quite similar conditions report only a 37% yield.[344] The most recent method, used by several groups, is the reaction of thiophene with excess chlorosulfonic acid and equivalent amounts of PCl_5 at 20°C, giving yields of about 70%.[345–347]

Reaction of thiophene with excess chlorosulfonic acid, first at $-10°C$ and then at 100°C, gave a 34% yield of 2,4-thiophenedisulfonyl chloride.[327] However, recent NMR analysis of the reaction product from 2-thiophenesulfonyl chloride with chlorosulfonic acid at 100°C showed that the 2,4- and 2,5-bissulfonyl chlorides were formed in a 2 : 1 ratio and in 70% total yield.[347] The reaction with chlorosulfonic acid has also been applied to many substituted thiophenes. 5-Methyl-2-thiophenesulfonyl chloride[348] was prepared from 2-methylthiophene, and 5-bromo-[349] and 5-chloro-2-thiophenesulfonyl chloride from 2-bromo- and 2-chlorothiophene.[327,350,351] Excess chlorosulfonic acid and heating at 100°C led to 2-chloro-3,5-thiophenedisulfonyl chloride in low yield.[327] From 2,3,4-trichlorothiophene, the 5-sulfonyl chloride has been prepared.[352,353] 5-Methyl- and 5-ethyl-2,4-thiophenesulfonyl chlorides have also been prepared by reaction with chlorosulfonic acid, first at $-10°C$ and then at 150°C. Two isomeric sulfonyl chlorides were obtained from 3-methylthiophene upon dichlorosulfonation and transformed to the amides. Without definite proof the amides were assigned as 3-methyl-2,4-thiophenesulfonylamide (m.p. 236 to 238°C) and 3-methyl-2,5-thiophenesulfonylamide (m.p. 168°C). The disulfonyl chloride derived from 2-ethyl-4-methylthiophene has also been obtained.[354]

The chlorosulfonation of 2-acetamidothiophene has been studied extensively in connection with work on compounds of pharmacological interest, and conditions for the preparation of 2-acetamido-5-thiophenesulfonyl chloride[355] and 2-acetamido-3,5-thiophenedisulfonyl chloride[244,273,327] have been investigated. 2-Acetamidomethyl- and 2-phthalimidomethylthiophene have also been chlorosulfonated[356] by this method.

2-Acetamido-5-chlorothiophene gave, most probably, 2-acetamido-5-chloro-3-thiophenesulfonyl chloride.[327]

Deactivated thiophenes, such as 2-thiophenecarboxylic acids,[357,358] 2-carbethoxythiophene,[359] 2-chloro-3-thiophenecarboxylic acid,[360] and 2,2′-dithienyl ketones,[327]

can also be smoothly chlorosulfonated. It was suggested that reaction occurred in the α-position.[327,360] However, it was recently shown that 2-thiophenecarboxylic acid gives the 2,4- and 2,5-sulfonyl chlorides in a 4 : 1 ratio.[347] With 2-thiophenecarboxamide this ratio was 9 : 1, and the 4-isomer was obtained pure by recrystallization.[347] 2-Bromo-5-nitro-3-thiophenesulfonyl chloride was prepared from 2-bromo-5-nitrothiophene[183] owing to the *meta*-directing effect of the nitro group. Similarly, 5-chloro-2-thiophenecarbox-*N*-methylamide gave the 3-sulfonyl chloride.[327]

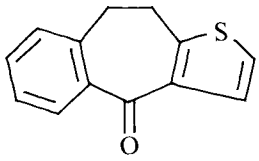
Also, more complex thiophene derivatives such as **221** have been monochlorosulfonated in the α-position of the thiophene ring and dichlorosulfonated to **222**[361] (Scheme 60).

An interesting halogen dance was observed upon reaction of 2,5-dibromothiophene with chlorosulfonic acid at 110°C, which led to 2,4-dibromo-3,5-thiophenedisulfonyl chloride.[327]

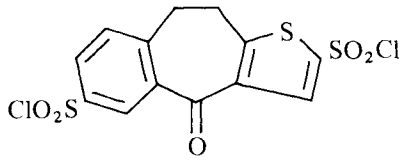
Some alternative methods for the chlorosulfonation of thiophene have been described. A French patent describes the preparation of 2,4-thiophenedisulfonyl chloride from sulfuryl chloride and thiophene.[362] The complex between pyrosulfuryl chloride and *N,N*-dimethylformamide has also been used for the smooth chlorosulfonation of thiophene.[363–365]

Thiophenesulfonyl chlorides have recently been prepared by reaction of thiophene derivatives with a 1 : 1 *N,N*-dimethylformamide–SO_2Cl_2 complex.[480] 2-Methoxythiophene, however, gave 5-methoxy-2-thiophene aldehyde.

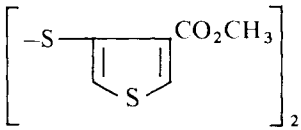
As mentioned in Section X.2, thiophenesulfonyl chlorides have been prepared by the reaction of salts of thiophenesulfonic acids with PCl_5 or $POCl_3$. Some confusion exists in the literature concerning some chlorinated thiophenesulfonyl chlorides. Profft and Kubat treated what they believed was 2,4-dichlorothiophene with oleum, followed by PCl_5 treatment of the sodium salt, and obtained a monosulfonyl chloride, m.p. 56°C, described as 2,4-dichloro-5-thiophenesulfonyl chloride, and a disulfonyl derivative, m.p. 90.5°C, believed to be 2,4-dichloro-3,5-



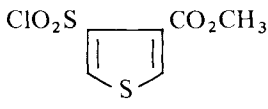
221



222



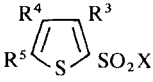
223



223a

Scheme 60

thiophenedisulfonyl chloride.[323,342] In a later paper, Profft and Sölf[366] stated that the starting material has been 2,3-dichlorothiophene and the sulfonyl chloride obtained was 2,3-dichloro-5-thiophenesulfonyl chloride, which previously had been shown to melt at 56°C.[350] However, this would indicate that the disulfonyl derivative melting at 90.5°C is 2,3-dichloro-4,5-thiophenedisulfonyl chloride, which seems highly unlikely since electrophilic substitution in the 4-position of a thiophene containing a strongly deactivating group in the 5-position is unknown.

TABLE 32. 2-THIOPHENESULFONYL HALIDES 

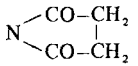
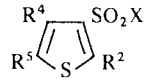
C_n	X	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
		H	H	H	88–93/2.5		79	481
4	Cl	Cl	Cl	Cl		55–56		350
	Cl	SO_2Cl	Cl	Cl		90.5		323
	Cl	Cl	SO_2Cl	Cl		90.5	70	342
	Cl	H	SO_2Cl	Br		98–101		341
	Cl	Br	Br	H		118		341
	Cl	H	SO_2Cl	I		87–88		341
	Cl	H	NO_2	Cl		50–51	78	371
	Cl	Cl	H	Cl		56	74.4	342
	Cl	H	Cl	Cl		55–56		350
	Cl	H	H	Br		45	88	8, 481
	F	H	H	Cl		111–113	50	367
	Cl	H	H	I		50–51	43	333, 481
	Cl	H	NO_2	H		48		278
	Cl	H	H	NO_2		45–47		340
	Cl	H	H	Cl		28	60	348, 481
	Cl	H	H	SO_2Cl		44–46		340
	Cl	H	SO_2Cl	H		80		341
	F	H	NO_2	H		58–60	52	367
	F	H	H	NO_2		35–37	52	367
	Br	H	H	H		48–49	60	346
	Cl	H	H	H		31.5–33		340
	F	H	H	H	75–76/1			340
5	Cl	H	NO_2	CH_3		75.5–76		348
	Cl	H	SO_2Cl	CH_3		96		426
	Cl	H	H	CH_3	96–98/3		56	348, 481
	Cl	CH_3	H	H	98–99/0.5			324, 481
	F	H	H	CH_3	44/0.1		60	367
6	Cl	H	SO_3Cl	$NHCOCH_3$		144–144.5		244
	Cl	H	H	$NHCOCH_3$		139–141	35.3	343
	Cl	H	SO_2Cl	C_2H_5		102–103		354
	Cl	H	H	C_2H_5	70–72/0.1		78	8
7	Cl	H	H	$CH_2NHCOCH_3$		88–89		356
	Cl	H	H	C_3H_7	118–121/0.6		77	8
	Cl	H	H			138–140	30	213

TABLE 33. 3-THIOPHENESULFONYL HALIDES



C_n	R^2	X	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Reference
4	Br	Cl	H	NO_2		66–67	183
	H	Cl	H	NO_2		45–47	244
	H	Cl	SO_2Cl	H		153–154	327
	H	Cl	H	H		47–48	341
5	CH_3	Cl	NO_2	Br		103–104	178
	CH_3	Cl	H	Br	105–107/0.2		178
6	CH_3	Cl	H	CH_3	115–130/2.5		47, 481
7	CH_3	Cl	CH_3	CH_3	154/15		77
12	$C(CH_3)_3$	Cl	H	$C(CH_3)_3$		91–92.5	335

Oxidation of the disulfide **223** with chloride in aqueous methanol gave **223a** in 90% yield[164] (Scheme 60).

Diazotization of methyl 3-amino-2-thiophenecarboxylate with sulfur dioxide in the presence of cupric chloride gave 2-carbomethoxy-3-thiophenesulfonyl chloride, which with zinc and acetic acid was reduced to di-(2-carbomethoxy-3-thienyl)disulfide.[482]

2-Thiophenesulfonyl fluoride and a number of substituted derivatives have been prepared by the reaction of 2-thiophenesulfonyl chlorides with aqueous ammonium fluoride.[322,340,367] 2-Thiophenesulfonyl bromides were prepared from 2-thiophenesulfonyl hydrazides, potassium bromide, and potassium bromate in 10% hydrochloric acid[346,368] (Tables 32 and 33).

4. Reactions of Thiophenesulfonyl Chlorides

A. Electrophilic Aromatic Substitution

Thiophenesulfonyl chlorides have been extensively used to direct substituents into certain positions utilizing the strong *meta*-directing power of the sulfonyl group, which can subsequently be removed by acid hydrolysis. Thus 3-nitrothiophene has been prepared by nitration of 2-thiophenesulfonyl chloride with fuming nitric acid to give 4-nitro-2- and 5-nitro-2-thiophenesulfonyl chloride in a 4:1 ratio.[213] After separation of the 4-nitro isomer, hydrolysis gave 3-nitrothiophene.[278,340,344,369] 5-Nitro-2-thiophenesulfonyl chloride has also been obtained in pure form.[213] Similar approaches have been used for the preparation of 2-methyl-3-nitrothiophene,[348] 2-chloro-3-nitrothiophene,[370,371] and 2-bromo-3-nitrothiophene[183] by way of 2-methyl-5-thiophenesulfonyl chloride, 2-chloro-, and 2-bromo-5-thiophenesulfonyl chloride, respectively. Some nitro dechlorosulfonation was observed in the nitration of 5-chloro-2-thiophenesulfonyl chloride.[371] Although

5-chloro-2-thiophenesulfonyl chloride could be chlorosulfonated[327] and nitrated,[351] attempts to chlorinate or brominate failed.[351]

B. Quantitative Studies on the Reactivity of Thiophenesulfonyl Halides

The reaction rate constants of 2-thiophenesulfonyl chloride[372] and 3-thiophenesulfonyl chloride[322] with some substituted anilines have been measured in methanol at different temperatures. The reactions are second order overall and *pseudo* first order with respect to each reactant. The rate constant values are greater with electron-donating substituents and lower with electron-withdrawing groups in the anilines. 3-Thiophenesulfonyl chloride was found to be more reactive than the 2-isomer, but less than benzenesulfonyl chloride. The slopes of Hammett and Brønsted plots for 2- and 3-thiophenesulfonyl chlorides were very similar ($\rho = -2.25$ for both isomers, $\beta = 0.53$ for the 2-isomer, and $\beta = 0.54$ for the 3-isomer) and also similar to those obtained for benzenesulfonyl chloride. These results indicate a similar addition-elimination mechanism, in which the rate-determining step is the nucleophilic attack of the aniline on the substrate. Studies of the leaving-group effect in the reaction of 2-thiophenesulfonyl fluoride, -chloride, and -bromide with anilines in methanol showed that the relative activation parameters fit well with a two-step addition-elimination mechanism in which the rate-determining step is the S-N bond formation for the chloride and bromide and S-F bond breaking for the fluoride.[346] The kinetics of the reaction of substituted thiophenesulfonyl chlorides and fluorides (5-OMe, 5-Me, H, 5-Cl, 4-NO_2, and 5-NO_2) with anionic and neutral nucleophiles were studied in various water-solvent mixtures and in water at 25°C.[367,373] For the reaction of chlorides with H_2O, AcO^-, and N_3^-, and for the hydrolysis of the fluorides, U-shaped Hammett plots were observed, whereas for the reaction of sulfonyl chlorides with aniline pyridine imidazole and OH^- an approximately linear Hammett correlation was found. A common chloride ion effect on the hydrolysis rate constants appears to be absent.[367]

The hydrolysis reactions of substituted 2-thiophenesulfonyl chlorides (5-methyl, H, 5-chloro, and 5-nitro) catalyzed by silver nitrate have been studied in water at 25°C. For this catalysis the *pseudo* first-order constants depend on the first power of silver ion concentration, whereas nitrate anion is not involved in the transition state. The corresponding curved Hammett plot suggested a transition state with a partially developed sulfonylium character. The catalytic effect of silver nitrite was also investigated.[374] A comparison with uncatalyzed hydrolysis reaction indicates that 2-thiophenesulfonyl chlorides are hydrolyzed by an S_N2-type mechanism, which can shift toward an S_N1 or S_AN process depending on the ring substituents. The kinetics of hydrolysis, methanolysis, and ethanolysis of 2- and 3-thiophenesulfonyl chlorides were compared with those of 2- and 3-furyl- and benzenesulfonyl chloride. Fair correlations with Taft's σ^* values for heterocycles were found, and even better correlations using two-parameter equations.[375] The

reaction of thiophenesulfonyl chlorides with various nucleophiles has, of course, also been used for the synthesis of esters, amides, azides, and hydrazides, which are treated in the appropriate sections.

5. Esters of Thiophenesulfonic Acids

Esters of thiophenesulfonic acids are prepared through the reaction of the sulfonyl chlorides with alcohols in dry pyridine or other pyridine bases or alkali.[358] In this way the esters of 2-thiophenesulfonic acid with butane-1,4-diols[376] and 2-nitro-2-methyl-1-propanol[377] have been prepared. The latter esters were investigated as alkylating agents. The ester between 2-thiophenesulfonic acid and butyne-1,4-diol was prepared in aqueous acetonitrile containing potassium hydroxide.[376] Esters of 3,4,5-trichloro-2-thiophenesulfonic acid with different phenols were prepared as potential insecticides[352] and the esters of 5-chloro-2-thiophenesulfonic acid with substituted 2,4-dinitrophenols as pesticides.[378] Cyanomethyl 2-thiophenesulfonate, which showed fungicidal properties, was prepared through the addition of aqueous sodium cyanide to 2-thiophenesulfonyl chloride and formaldehyde in toluene.[379] Insecticidal 2-thiophenesulfonyl phosphorodithioates were prepared through the reaction of 2-thiophenesulfonyl chloride with $(EtO)_2PS_2NH_4$ in acetone.[380] Esters of 2-thiophenesulfonic acid and *N*-alkylglycolamides have been prepared as herbicides.[381] 3-(2-Thienylsulfonyloxy)aniline, prepared from 2-thiophenesulfonyl chloride and *meta* aminophenol, has been diazotized and coupled to monoazo dyes to make polyester fibers.[382] Esters of thiophenesulfonic acids are collected in Table 34.

6. Amides of Thiophenesulfonic Acid

A. Preparation of Thiophenesulfonamides

Many thiophenesulfonamides have been prepared by the reaction of the sulfonyl chloride with aqueous or liquid ammonia for characterization purposes,[164,183,281,318,319,324,327,332,333,340–342,361,362,383–387,450] but also because of their potential biological activity.[213,244,354–356,388–390] They are given in Tables 35 and 36.

As mentioned previously, many anilides have been prepared in connection with kinetic investigations on the reaction between thiophenesulfonyl chlorides and various anilines[322,346,372] and for other reasons.[244,343] However, the main purpose of the preparation of various *N*-substituted amides derived from different thiophenesulfonic acids is their potential medicinal value. Different amides derived from primary alkylamides,[386] anilines[347,349,353] and secondary amines, such as dimethylamine, cyclohexylamine, *N*-methylaniline, and various others,[349,391] have been obtained. Compounds such as **223b** have been prepared as potential anticancer agents,[357] as diuretic **224**,[359,451] and as potential hypolipidemic agents

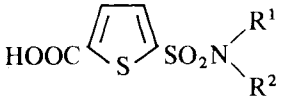
(225).[360] Compound **226** showed no activity as an insect chemosterilant[452] (Scheme 61). The thiophenesulfonamide grouping also occurs in synthetic *N*-substituted prostaglandincarboxamides,[392] penicillins,[393] and 2-aminooxazolo-[4,5-b] pyridines with various pharmacological activities.[394]

Long-chain *N,N*-dialkyl derivatives of 2-thiophenesulfonamide have been investigated as plasticizers and waxes.[395] The main technical application of thiophenesulfonamides, and especially of aminothiophenesulfonamides, is as components in the synthesis of azo dyes.[396–400] Anthraquinone disperse dyes containing the 2-thiophenesulfonamide grouping have also been prepared.[401–406]

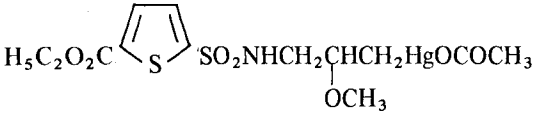
B Reactions of Thiophenesulfonamides

N-Chloro and *N*-bromo derivatives of 2- and 3-thiophenesulfonamides were obtained upon reaction with chlorine or bromine in alkaline medium.[407] However, with 2-thiophenesulfonamides temperatures below 30°C must be used, since otherwise halogen–sulfonamide exchange occurs, leading to 2-halothiophenes.[408] The stability of aqueous solutions of the sodium salts of *N*-chlorosulfonamides of thiophene and benzene have been compared.[409] *N*-Halo derivatives have also been obtained from 3,5-thiophenedisulfonamides.[387] The *N*-halo derivatives gave dibenzyl disulfilimines upon reaction with dibenzylsulfide.[387]

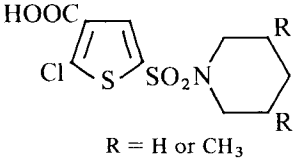
Condensation of 2-thiophenesulfonamide with carbon disulfide in the presence



223b

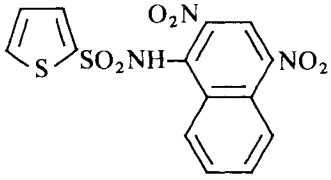


224



R = H or CH_3

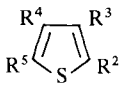
225



226

Scheme 61

TABLE 34. THIOPHENESULFONIC ACID ESTERS



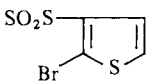
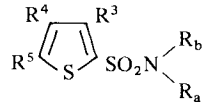
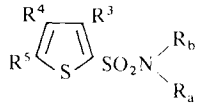
C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	SO_2SCCl_3	H	H	H	Oil			310
8	Br		H	H		112–113.5		215
	$SO_3C_2H_5$	H	H	$NHCOCH_3$		106–108		343
	$SO_3CH_2C(CH_3)_2NO_2$	H	H	H		85.7–86.7	75	377
10	$SO_3C_6H_5$	H	NO_2	Br		95		311
11	$SO_3C_6H_4$-3-OCH_3	H	H	H		51–53		278
12	$SO_3CH_2C{\equiv}CCH_2O_3S$-2-thienyl	H	H	H		96–97	66	376
15	$SO_3C_6H_5$	H	NO_2			116		311

TABLE 35. 2-THIOPHENESULFONIC ACID AMIDES

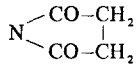
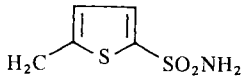


C_n	R^3	R^4	R^5
4	Cl	H	Cl
	H	Cl	Cl
	H	NO_2	Br
	H	Br	Br
	H	NO_2	Cl
	H	Cl	Cl
	H	H	Cl
	Cl	H	Cl
	H	H	Br
	H	H	Cl
	SO_2NH_2	Cl	Cl
	Cl	SO_2NH_2	Cl
	H	H	I
	H	NO_2	H
	H	H	NO_2
	H	SO_2NH_2	Br
	H	SO_2NH_2	Cl
	H	H	H
	H	NH_2	H
	H	H	NH_2
	H	SO_2NH_2	H
	H	H	H
5	H	H	Cl
	CH_3	H	H
	H	H	CH_3
	H	H	CH_2NH_2
	CH_3	H	SO_2NH_2
	H	SO_2NH_2	CH_3
	CH_3	SO_2NH_2	H
6	H	H	H
	H	H	Cl
	H	H	$NHCOCH_3$
	H	H	H
	H	SO_2NH_2	$NHCOCH_3$
	H	SO_2NH_2	C_2H_5
	H	SO_2NH_2	C_2H_5
7	H	H	Cl
	H	H	H
	H	H	H
	H	H	Cl
	H	H	Cl
	H	H	$CH_2NHCOCH_3$
	CH_3	SO_2NH_2	C_2H_5
	H	SO_2NH_2	$CH(CH_3)_2$



R_a	R_b	Melting Point (°C)	Yield (%)	Reference
Cl	Cl	76–78	85	342
H	Cl	187		323
H	H	151–154		183
H	H	181–184	62	252
H	H	155–157	75	351
H	H	157		323
H	Cl	124.5		386
H	H	157	70	342
H	H	144		341
H	H	114–116	62	351
H	H	312–315 (decomp.)		323
H	H	312–315 (decomp.)	68	342
H	H	163–164		333
H	H	165–166		389
H	H	135–136		389
H	H	222–223	32	
H	H	218–219	43	387
H	H	144.5–146		332
H	H	132–133		389
H	H	137–138		389
H	H	213–214	30	387
$=C(S^-K^+)_2$		202–204 (decomp.)	47	410
H	CH_3	44	33	386
H	H	146		324
H	H	119–119.5		348
H	H	96–97		356
H	H	168		354
H	H	202	48	388
H	H	236–238		354
H	$COCH_3$	98–100	60	286
H	C_2H_5	52	33	386
H	H	212–214		343
CH_3	CH_3	67–69	69	447
H	H	246–247 (decomp.)		244
H	H	205–206	45	354
H	H	205–206	45	354
		64–66	32	351
$SCCl_3$	$COCH_3$	95–96	50	286
H	$CH_2–CH=CH_2$	54–56		359
H	$CH_2CH_2CH_3$	14	9	386
H	$CH(CH_3)_2$	41	18	386
H	H	123–124		356
H	H	228–230		354
H	H	210–212		354

TABLE 35. (*Continued*)

C_n	R^3	R^4	R^5
	H	SO_2NH_2	$(CH_2)_2CH_3$
8	H	H	H
	H	H	
	H	H	$CO(CH_2)_2CO_2$
	H	H	NH_2
	H	Cl	Cl
	Cl	H	Cl
	H	H	H
	H	H	Cl
	H	H	H
	H	SO_2NH_2	$(CH_2)_3CH_3$
9	H	H	Cl
	H	H	Cl
	H	H	H
	H	H	NH_2
	H	H	H
	H	H	
	H	H	Cl
	H	H	$Si(CH_3)_3$
10	H	H	Cl
	H	H	Cl
	H	H	Cl
	H	H	H
	H	H	H
	H	H	Cl
	H	H	Br
	H	H	H

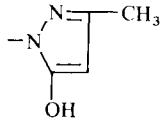
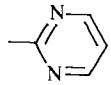
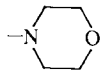
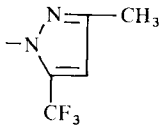
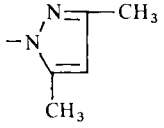
R_a	R_b	Melting Point (°C)	Yield (%)	Reference
H	H	160–162		354
		185–188	50	286
H	H	218	90	213
H	H	216–218 (decomp.)		213
H		204–205		389
C_2H_5	C_2H_5	91		323
C_2H_5	C_2H_5	91	70	342
		104–105	63	347
H	$(CH_2)_3CH_3$	19	22	386
H	$CH_2CH(OCH_3)CH_2Hg$			359
H	H	155–157	81	383
H	3-Pyridyl-2-Cl	175–177	72	351
H	2-Pyridyl	214–215	75	351
		199–210	50	286
H	2-Pyridyl	162		389
		65	70	286
H	H	202–204	15	388
H	$(CH_2)_4CH_3$	32	31	386
CH_3	CH_3	75–77	41	447
H	C_6H_4-4-Br	122–124	75	351
H	C_6H_4-4-NO_2	124–125	69	351
H	C_6H_4-3-NO_2	113–114	52	351
H	C_6H_3-2,4-Cl	115	65	347
H	C_6H_3-3,4-Cl	116–118	60	347
H	C_6H_4-4-Cl	111–113	71	351
H	C_6H_5	94–95		333
H	C_6H_4-4-Br	107–109	70	347

TABLE 35. *(Continued)*

C_n	R^3	R^4	R^5
	H	H	H
	H	H	H
	H	H	Cl
	H	H	Cl
	H	H	Cl
	H	H	I
	H	H	H
	H	H	H
	H	H	Cl
	H	H	H
	H	H	Cl
11	H	H	H
	H	H	Cl
	H	H	Cl
	H	H	Cl
	H	H	Cl
	H	H	Cl
	H	H	Cl
	H	NO_2	Cl
	H	H	H
	H	H	H
	H	H	H
	H	H	H
	H	H	H
	H	H	$NHCOCH_3$
	H	H	Cl
	H	H	H
	H	H	Cl
12	H	H	Cl
	H	NO_2	Cl
	H	H	Cl
	H	H	$NHCOC_6H_4$-2-CO_2H
	H	H	$NHCOCH_3$

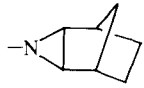
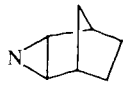
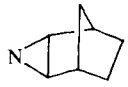
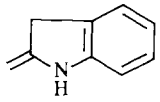
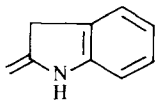
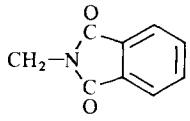
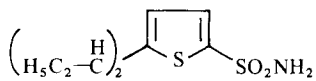
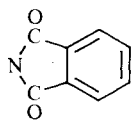
R_a	R_b	Melting Point (°C)	Yield (%)	Reference
H	C_6H_4-3-Cl	114		372
H	C_6H_4-4-Cl	115–116	63	347
H	C_6H_5	83–84	39	351
H	C_6H_4-2-OH	130–132	55	351
H	C_6H_4-4-OH	137–138	68	351
H	C_6H_5	124–125		333
H	C_6H_4-3-NO_2	163	40	347
H	C_6H_5	99.5–100		332
H	Cyclohexyl	74–76	59	351
H	Cyclohexyl	86–88	55	391
H	$(CH_2)_5CH_3$	47		386
H	COC_6H_5	108–110	56	286
CH_3	C_6H_5	77–79	69	351
H	C_6H_5-4-CH_3	102–104	60	351
H	C_6H_4-3-CH_3	72–73	65	351
H	C_6H_4-2-CH_3	80–82	62	351
H	C_6H_4-4-OCH_3	98–99	58	351
H	C_6H_4-2-OCH_3	61–62	69	351
		125–127	38	351
H	C_6H_4-4-CH_3	115	58	347
H	C_6H_4-3-CH_3	88–89		372
CH_3	C_6H_5	105–106	60	391
H	C_6H_4-4-OCH_3	104		372
H	C_6H_4-3-OCH_3	72–73		372
H	2-Pyridyl	243.5–245.5		343
		59–61	45	351
		69.5–70	39	347
H	$(CH_2)_6CH_3$	46	46	386
	–N-indolyl	58–59	45	351
		199 (decomp.)		351
		207–208	75	351
H	H	261		213
H	C_6H_5	218–220		343

TABLE 35. (*Continued*)

C_n	R^3	R^4	R^5
	H	H	Cl
	H	H	H
	H	H	H
13	H	H	
	H	H	CH_3
	H	H	Cl
14	H	H	H
	H	H	Cl
	H	H	H
	H	H	
	H	$SO_2NHCH_2CH(CH_3)_3$	C_2H_5
16	H	H	Cl
18	H	H	
	H	$SO_2NHC_6H_5$	$NHCOCH_3$
	H	SO_2NH-cyclohexyl	C_2H_5
19	H	H	H
20	H	H	H
22	H	$SO_2NHC_6H_4$-4-CH_3	$C(CH_3)_3$
32	H	$SO_2NS(CH_2C_6H_5)_2$	Br
	H	$SO_2NS(CH_2C_6H_5)_2$	Cl
	H	$SO_2NS(CH_2C_6H_5)_2$	H
44	H	H	H

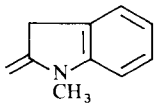
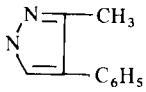
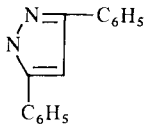
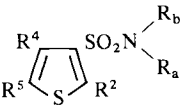
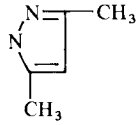
R_a	R_b	Melting Point (°C)	Yield (%)	Reference
H	C_6H_4-4-$N(CH_3)_2$	139–140	63	351
$(CH_2)_2OCOCH_3$	$(CH_2)_2OCOCH_3$	Oil		395
$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	b.p. 147/0.05	92	395
H	H	171–173	61	356
		197–199	76	351
H	4-Isoquinolyl	180–181	69	351
H	α-Naphthyl-2,4-NO_2	185–186		452
H	β-Naphthyl	106–107	72	351
		83–85	65	286
H	H	218–220	20	384
H	$CH_2CH(CH_3)_2$	121–122		354
H	2-Biphenyl	100–101	78	351
H	C_6H_5	226	62	213
H	C_6H_5	170–171		244
H	Cyclohexyl	118–120		354
		141–142	63	286
$(CH_2)_7CH_3$	$(CH_2)_7CH_3$	b.p. 200–205/75	71	395
H	C_6H_4-4-CH_3	222–225	47	335
$=S(CH_2C_6H_5)_2$		207–208		387
$=S(CH_2C_6H_5)_2$		212–213		387
$=S(CH_2C_6H_5)_2$		200–201		387
$(CH_2)_2OCO(CH_2)_{16}CH_3$	$(CH_2)_2OCO(CH_2)_{16}CH_3$	73.5–77		395

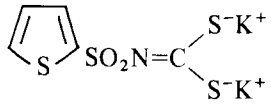
TABLE 36. 3-THIOPHENESULFONIC ACID AMIDES



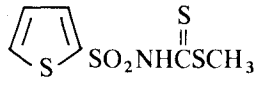
C_n	R^2	R^4	R^5	R_a	R_b	Melting Point (°C)	Yield (%)	Reference
4	Br	H	Cl	H	H	179–180	Low	387
	Cl	H	Br	H	H	159–160	55	387
	Br	H	Br	H	H	153–154	43	387
	Br	H	NO_2	H	H	199–200		183
	H	H	Br	H	H	152–153	40	387
	H	H	NO_2	H	H	171–173		244
	H	H	H	H	H	142		321
	H	H	NH_2	H	H	158 (decomp.)		244
	H	SO_2NH_2	H	H	H	308–310		327
6	CH_3	H	CH_3	H	H	141–142		334
10	H	H	H	H	C_6H_4-4-Cl	108		322
	H	H	H	H	C_6H_4-3-Cl	83		322
	H	H	H	H	C_6H_4-3-NO_2	166–167		322
	H	H	NO_2	H	C_6H_5	135–136		244
	H	H	H	H	C_6H_5	111–112		322
	H	H	CO_2H			154–156	50	286
11	H	H	H	H	C_6H_4-4-CH_3	114–115		322
	H	H	H	H	C_6H_4-3-CH_3	71		322
	H	H	H	H	C_6H_4-4-OCH_3	128		322

of potassium hydroxide gave the isolable dipotassium salt **227**, which, however, without isolation could be methylated with methyl iodide to give **228**[410] (Scheme 62).

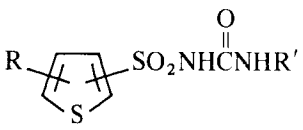
The *N*-substituted *N*-thiophenesulfonylureas (**229**) are of medicinal importance



227



228



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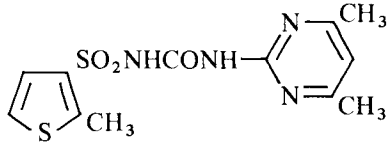


230

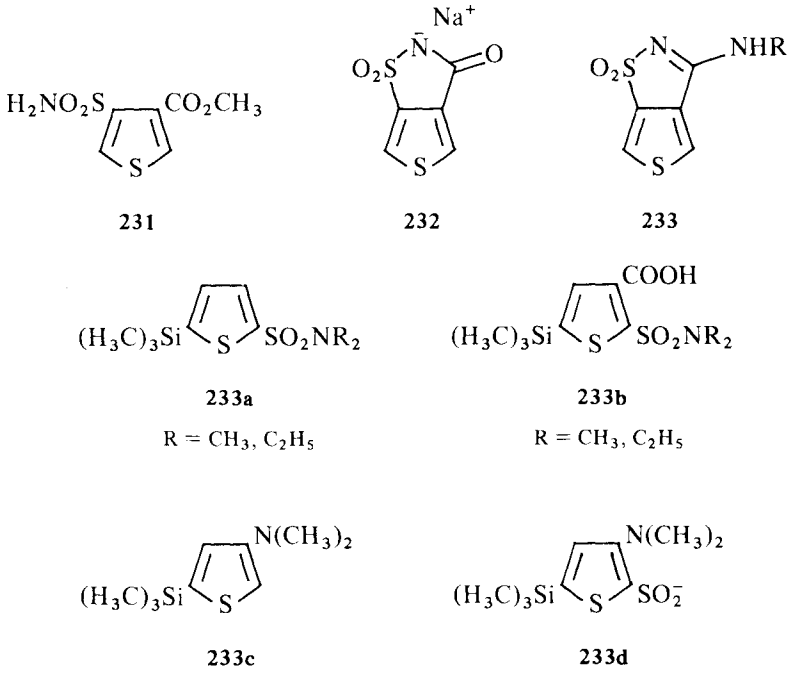
Scheme 62

and are most conveniently prepared by the reaction of sulfonamides with isocyanates in the presence of base.[411-413] Compounds **230** show herbicidal activity.[414] Such compounds can also be prepared by the reaction of sulfonylisocyanates with amines.[249] Upon reaction of 5-substituted 2-thiophenesulfonamides with phenylisothiocyanate in DMF containing sodium hydroxide, *N*-substituted thiophenesulfonylthioureas were obtained in 94 to 98% yield.[453]

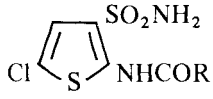
Intramolecular ring closure of the anion from **231** gave the new artificial sweetener **232**. The two other isomers have been analogously prepared.[164,415] Compound **232** gave **233** upon reaction with P_2O_5 and an amine chloride in the presence of a tertiary amine[416] (Scheme 63).

Metalation of **233a** ($R = CH_3$) with butyllithium in ether followed by CO_2 gave **233b** ($R = CH_3$) in low yield, and much starting material was recovered. A very interesting reaction occurred when **233a** ($R = CH_3$) was reacted with butyllithium-TMEDA, which gave **233c** in 39% yield. An intramolecular mechanism by way of a four-membered transition state, giving **233d** as an intermediate, has been suggested. Interestingly, **233a** ($R = C_2H_5$) gave only 3-lithiation, both with butyllithium and with butyllithium-TMEDA, and **233b** ($R = C_2H_5$) was obtained in much better yield than **233b** ($R = CH_3$).[447]

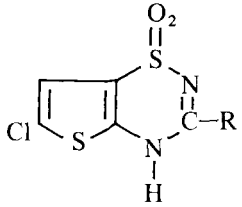
Heating of **234** led by intramolecular ring closure to **235** active against hypertension[417] (Scheme 64).



Scheme 63



234



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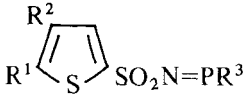
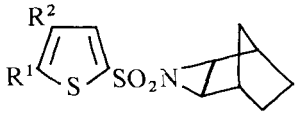


236



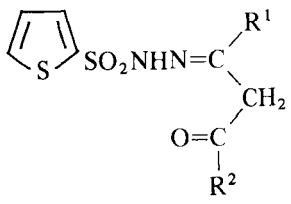
237

$R^1 = R^2 = H$
$R = Bu, Ph, \quad R^1 = Cl, \quad R^2 = H$
$R^1 = Cl, \quad R^2 = NO_2$

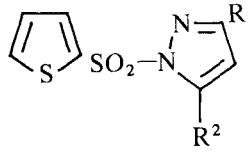
Scheme 64

7. Other Derivatives of Thiophenesulfonic Acids Containing a Sulfur–Nitrogen Bond

2-Thiophenesulfonyl azide has been prepared by the reaction of 2-thiophenesulfonyl chloride with sodium azide in aqueous acetone.[301,347] Similarly, 5-chloro-2-thiophenesulfonyl azide and 4-nitro-2-chlorosulfonyl azide and mixtures of 2,4- and 2,5-thiophenedisulfonyl azides were obtained.[347,351] These sulfonyl azides were reacted with triphenylphosphine, tri-*n*-butylphosphine, and norbornene to give **236** and **237**[347,351,391] (Scheme 65). The azides were further reacted with indole and 1-methylindole to give 2-sulfonyliminoindolines.[351]



238



239

$R^1 = CH_3, \quad R^2 = OC_2H_5$
$R^1 = CH_3, \quad R^2 = CF_3$
$R^1 = CH_3, \quad R^2 = C_6H_5$
$R^1 = R^2 = C_6H_5$

Scheme 65

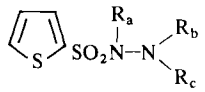
The reaction of thiophenesulfonyl chlorides with 85% hydrazine hydrate in ether or THF was used for the preparation of thiophenesulfonylhydrazine.[301,346,348,351,358,419]

The thiophenesulfonyl hydrazines have been reacted with various aldehydes to give hydrazones,[286,347,418,419] and isothiocyanates to give thiosemicarbazones.[418,419] The reaction of thiophenesulfonyl chlorides with substituted hydrazines was used for the synthesis of the 2-benzylhydrazide[420] and *N*-acetylhydrazide[286] of 2-thiophenesulfonic acid.

The reaction of 2-thiophenesulfonyl hydrazide with β-dicarbonyl derivatives gave **238**, which was converted to **239**.[286] The reaction of the salt **227**, suspended in inert solvents such as methylene chloride, benzene, or carbon tetrachloride, with phosgene gives 2-thienylsulfonylisothiocyanate in 63% yield.[421–423] Ethyl chloroformate or PCl_5 can be used instead of phosgene in this reaction[422] (Scheme 65; see Tables 37–43).

8. Physical Properties of Thiophenesulfonyl Derivatives

Electron diffraction data show that the molecular conformation of 2-thiophenesulfonyl chloride is characterized by the perpendicular arrangement of the plane of the five-membered ring and the CSCl plane. The sulfur bond configuration in the sulfonyl group is consistent with the structural variations observed in a series of sulfonyl chlorides. Bond lengths and bond angles are given in **240** and **241**. The values within parentheses are estimated total errors[424] (Scheme 66). The

TABLE 37. 2-THIOPHENESULFONYLHYDRAZIDES 

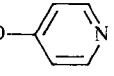
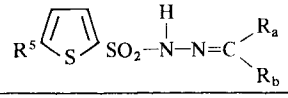
C_n	R^5	R_a	R_b	R_c	Melting Point (°C)	Yield (%)	Reference
4	Br	H	H	H, HCl	131	52	419
	Cl	H	H	H, HCl	133	51	419
	H	H	H	H	68–69	60	346
	H	H	H	H, HCl	128	55	418
6	H	$COCH_3$	H	H	152–156	42	286
	H	H	H	$COCH_3$	140–141	85	286
7	H	$SCCl_3$	H	$COCH_3$	191–192	56	286
8	H	H	H	SO_2-2-thienyl	232 (decomp.)	35	347
	H	H	$COCH_3$	$COCH_3$	143–144	70	286
9	H	$SCCl_3$	$COCH_3$	$COCH_3$	129	30	286
10	H	H	H		170–173	86	347
	H	$COCH_3$	$COCH_3$	$COCH_3$	112–113	92	286
11	H	H	H	COC_6H_5	233–234	60	286
18	H	COC_6H_5	H	COC_6H_5	171–173	55	286

TABLE 38. 2-THIOPHENESULFONYLHYDRAZONES



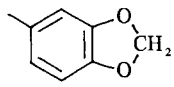
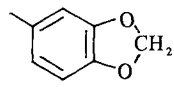
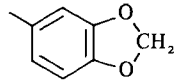
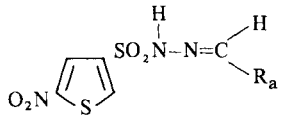
C_n	R^5	R_a	R_b	Melting Point (°C)	Yield (%)	Reference
7	H	CH_3	CH_3	120–122	80	347
9	H	CF_3	CH_2COCF_3	120	70	286
	H	H	2-Thienyl	106–107	77	347
	H	H	2-Furyl	106–108	90	347
	H	CH_3	CH_2COCF_3	104–107	63	286
10	H	Cyclohexanone		134–135	66	347
	H	CH_3	$CH_2CO_2C_2H_5$	117–118	86	286
	H	H	$(CHOH)_4CH_2OH$	137–138	50	347
11	Br	H	C_6H_3-2,4-Cl	208–210		419
	Cl	H	C_6H_3-2,4-Cl	211–212		419
	H	H	C_6H_3-2,4-Cl	91		418
	H	H	C_6H_3-2,6-Cl	165–166	60	347
	H	H	C_6H_3-3,4-Cl	177–179	67	347
	Br	H	C_6H_4-4-OH	88		419
	Br	H	C_6H_5	89		419
	H	H	C_6H_4-4-Br	148–150	75	347
	Br	H	C_6H_4-2-OH	215–216		419
	Cl	H	C_6H_5	84		419
	Cl	H	C_6H_4-4-OH	88		419
	Cl	H	C_6H_4-2-OH	211–212		419
	H	H	C_6H_4-4-Cl	142–143	92	347
	H	H	C_6H_4-3-F	147–149	82	347
	H	H	C_6H_4-4-F	136–138	72	347
	H	H	C_6H_4-2-OH	204	60	418
	H	H	C_6H_4-4-NO_2	170–173	68	347
	H	H	C_6H_4-3-NO_2	196–198	45	347
	H	H	C_6H_5	143–144	70	347
	H	H	C_6H_4-2-OH	204		418
	H	H	C_6H_4-3-OH	93–95	70	347
	H	H	C_6H_4-4-OH	163–164	68	347
	H	H	C_6H_3 2,4-OH	155–156	60	347
12	Br	H		204–205		419
	Cl	H		198–199		419
	H	H		196–197		418
	Br	H	C_6H_4-2-CH_3	86–87		419
	Br	H	C_6H_4-4-CH_3	80–81		419

TABLE 38. (*Continued*)

C_n	R^5	R_a	R_b	Melting Point (°C)	Yield (%)	Reference
	Br	H	C_6H_4-4-OCH_3	169–170		419
	Br	H	C_6H_3-4-OH-3-OCH_3	169–171		419
	Cl	H	C_6H_4-4-CH_3	90–91		419
	Cl	H	C_6H_4-2-CH_3	81–83		419
	Cl	H	C_6H_4-4-OCH_3	156		419
	Cl	H	C_6H_3-4-OH-3-OCH_3	154		419
	H	H	C_6H_4-2-CH_3	87–88		418
	H	H	C_6H_4-4-CH_3	148–149	80	347
	H	H	C_6H_4-4-OCH_3	171–173	78	347
	H	H	C_6H_3-4-OH-3-OCH_3	160–161		418
13	Br	H	CH=CH–C_6H_5	164–167		419
	Cl	H	CH=CH–C_6H_5	189–191		419
	H	H	CH=CH–C_6H_5	157–158		418
	Br	H	C_6H_4-4-$N(CH_3)_2$	93		419
	Cl	H	C_6H_4-4-$N(CH_3)_2$	79–80		419
	H	H	C_6H_3-3,4-OCH_3	143–144	60	347
	H	H	C_6H_4-4-$N(CH_3)_2$	167–170	57	347
14	H	CH_3	$CH_2COC_6H_5$	126–128	78	286
15	Br	H	α-Naphthyl	156–157		419
	Cl	H	α-Naphthyl	147		419
	H	H	α-Naphthyl	143		418
19	H	C_6H_5	$CH_2COC_6H_5$	107–110	82	286

TABLE 39. 5-NITRO-3-THIOPHENESULFONYLHYDRAZONES



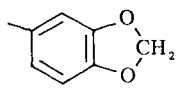
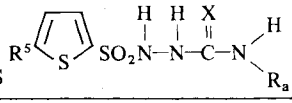
C_n	R_a	Melting Point (°C)	Reference
11	C_6H_3-2,4-Cl	213–214	428
	C_6H_5	83	418
	C_6H_4-4-OH	87	418
	C_6H_4-2-OH	220–221	418
12		204	418
	C_6H_4-4-CH_3	91	418
	C_6H_4-4-OCH_3	170–172	418
	C_6H_3-3-OCH_3-4-OH	189–191	418
13	CH=CH–C_6H_5	167	418
	C_6H_4-4-$N(CH_3)_2$	272–274	418
15	α-Naphthyl	154	418

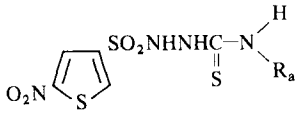
TABLE 40. 2-THIOPHENESULFONYLSEMICARBAZONES



C_n	R^5	X	R_a	Melting Point (°C)	Yield (%)	Reference
5	H	O	H	214–217	64	347
6	H	O	H[a]	235–236	63	347
9	Br	S	C_4H_9	115–116		419
	Cl	S	C_4H_9	87–89		419
	H	S	C_4H_9	117		418
11	Br	S	C_6H_4-4-Cl	215		419
	Cl	S	C_6H_4-4-Br	224–225		419
	Br	S	C_6H_4-4-Br	218–219		419
	Cl	S	C_4H_4-4-Cl	220–222		419
	Br	S	C_6H_5	189		419
	H	S	C_6H_4-4-Br	229–230		418
	H	S	C_6H_4-4-Cl	205–206		418
	Cl	S	C_6H_5	201		419
	H	S	C_6H_5	198–199		418
12	Br	S	$CH_2C_6H_5$	148–149		419
	Br	S	C_6H_4-2-CH_3	176–177		419
	Br	S	C_6H_4-4-CH_3	214		419
	Br	S	C_6H_4-4-OCH_3	224		419
	Cl	S	C_6H_4-2-CH_3	168		419
	Cl	S	C_6H_4-4-CH_3	213–214		419
	Cl	S	$CH_2C_6H_5$	203–204		419
	Cl	S	C_6H_4-4-OCH_3	216–217		419
	H	S	C_6H_4-2-CH_3	197–199		418
	H	S	C_6H_4-4-CH_3	201–203		418
	H	S	C_6H_5	157		418
	H	S	C_6H_4-4-OCH_3	210–212		418

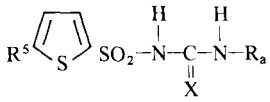
[a] $R^4 = SO_2NHNHCONH_2$

TABLE 41. 5-NITRO-3-THIOPHENESULFONYLTHIOSEMICARBAZONES

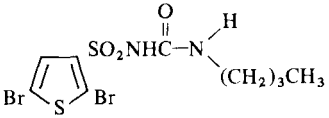


C_n	R_a	Melting Point (°C)	Yield (%)	Reference
9	C_4H_9	86		418
11	C_6H_4-4-Br	222		418
	C_6H_4-4-Cl	214		418
	C_6H_5	195		418
12	C_6H_4-4-CH_3	207	62	418
	C_6H_4-2-CH_3	174–175		418
	$CH_2C_6H_5$	196–197		418
	C_6H_4-4-OCH_3	229–230		418

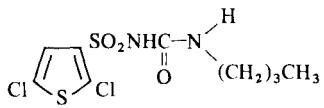
TABLE 42. UREA DERIVATIVES OF 2-THIOPHENESULFONIC ACID



C_n	R^5	R_a	X	Melting Point (°C)	Yield (%)	Reference
8	Cl	$CH_2-CH=CH_2$	O	131.5–132.0		411
	Br	$CH(CH_3)_2$	O	165.5–167.5		411
	Br	$(CH_2)_2CH_3$	O	165–166.5		411
	Cl	$CH(CH_3)_2$	O	155–156.5		411
	Cl	$(CH_2)_2CH_3$	O	170.5–172.5	76	411
	H	$(CH_2)_2CH_3$	O	140–140.5	80–90	411
	H	$CH(CH_3)_2$	O	147–148.5	80–90	411
9	Br	$CH(CH_3)C_2H_5$	O	135–136		411
	Br	$CH_2CH(CH_3)_2$	O	166–167.5		411
	Br	$(CH_2)_3CH_3$	O	125–127	85	411
	Cl	$CH(CH_3)C_2H_5$	O	127.5–129		411
	Cl	$CH_2CH(CH_3)_2$	O	163–164		411
	Cl	$(CH_2)_3CH_3$	O	132.5–133.5		411
	H	$(CH_2)_3CH_3$	O	152–154.5	80	411
	H	$CH_2CH(CH_3)_2$	O	179–182.5	80–90	411
	H	$CH(CH_3)C_2H_5$	O	162.5–163.5	80–90	411
10	Br	$(CH_2)_2CH(CH_3)_2$	O	131.5–133.0		411
	Cl	$(CH_2)_2CH(CH_3)_2$	O	132–133		411
	H	$(CH_2)_2CH(CH_3)_2$	O	133.5–135.5	80–90	411
11	Br	C_6H_5	S		95	453
	Cl	C_6H_5	S		95	453
	I	C_6H_5	S		95	453
	H	C_6H_5	S		95	453
	Br	Cyclohexyl	O	176.5–177.0		411
	H	Cyclohexyl	O	191–192	80–90	411
12	CH_3	C_6H_5	S		95	453



m.p. 185–186°C
Ref. 411

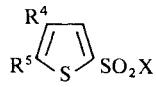


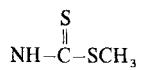
m.p. 159–161°C
Ref. 411

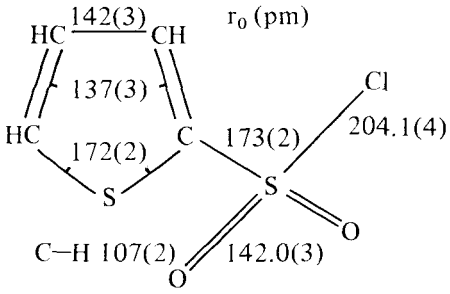
quadrupole resonances of chlorine have been determined for a number of sulfonyl chlorides including 2-thiophenesulfonyl chloride.[425] ^1H NMR data for some thiophenesulfonyl chlorides have been obtained.[426]

The IR spectra of various thiophenesulfonamides have been discussed, and the asymmetrical and symmetrical SO_2-stretching frequencies, as well as the NH- and S-N-stretching frequencies, for a large number of compounds have been tabulated.[351,427,428] In KBr disks only one NH-stretching absorption band due to associated sulfonamide was observed, whereas in CCl_4 solution two bands due to free

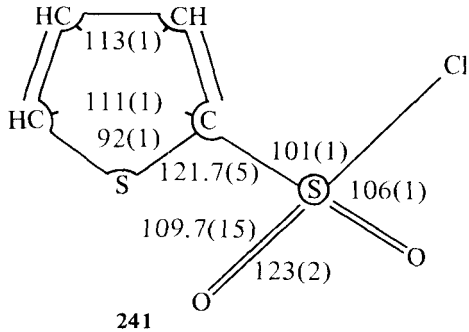
TABLE 43. MISCELLANEOUS NITROGEN DERIVATIVES OF 2-THIOPHENESULFONIC ACID



C_n	R^4	R^5	X	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
4	H	Cl	N_3		34–36	75	351
	H	H	N_3		31–33	35	347
5	H	H	N=C=S	93/0.02		63	422
6	H	H			104–105	24	410
10	NO_2	Cl	$N=P(OC_2H_5)_3$		Oil		351
16	H	H	$N=P(C_4H_9)_3$				391
22	H	Cl	$N=P(C_6H_5)_2$		145–146	65	351
	H	H	$N=P(C_6H_5)_3$		160–162	55	347



240



241

Scheme 66

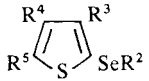
and associated NH groups are present. A good correlation was found between the Hammett substitution constants and the NH frequencies.[428]

The mass spectral fragmentation patterns for various thiophenesulfonamides have been discussed.[351,429] The UV spectra of 31 2-thiophenesulfonamides were discussed in relation to the absorption of some parent compounds, and the spectral changes were correlated with substituent effects.[428]

XI. VARIOUS COMPOUNDS CONTAINING THIOPHENE–SULFUR BONDS

Stepwise oxidation of the dithiocarboxylate **242** with peracids leads first to the *cis-trans* isomeric aryl arylthiosulfines **243** and **244**, which were separated. Further oxidation gave the aryl arylsulfinylsulfines **245** and **246** and the aryl arylsulfonyl-

TABLE 44. 2-THIOPHENESELENO DERIVATIVES



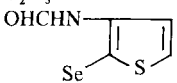
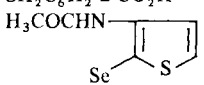
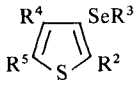
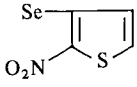
C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	CN	NH_2	H	H		53	20	134
	CH_3	H	H	Br	95/5		53	475
	$(Br)_2CH_3$	H	H	H		64–65	97	475
	CH_3	H	H	H	80–82/15		73.2	440
6	CN	NHCHO	H	H		129	60	134
	CN	OCH_3	H	H		68	60	134
	CH_3	H	Br	CH_3	90–92/1	55	70.9	440
	CH_3	NHCHO	H	H		58–60	70	134
	$(Br)_2CH_3$	H	H	CH_3		55–56	87	475
	C_2H_5	H	H	H	79–82/7		73.3	437
	CH_3	H	H	CH_3	94–95/14		70	440
7	CN	$NHCOCH_3$	H	H		123	65	134
	$COCH_3$	NHCHO	H	H		71–72	45	134
	CH_3	$NHCOCH_3$	H	H		67	75	134
8	$COCH_3$	$NHCOCH_3$	H	H		94–95	50	134
	CH_2CO_2H	$NHCOCH_3$	H	H		112–114	35	134
	$(CH_2)_3CH_3$	H	H	H	120–121/13		75.3	475
	C_2H_5	H	H	C_2H_5	106–109/8		64.6	437
10		NHCHO	H	H		171–172	60	134
	$CH_2CO_2C_2H_5$	NHCHO	H	H		48	45	134
12	C_6H_4-2-NO_2	$NHCOCH_3$	H	H		192–194	60	134
	$CH_2C_6H_2$-2-CO_2H	H	H	H		127–128	55	476
		H	H	H		183	75	134

TABLE 45. 3-THIOPHENESELENO DERIVATIVES 

C_n	R^2	R^3	R^4	R^5	Boiling Point (°C/mm Hg)	Melting Point (°C)	Yield (%)	Reference
5	NO_2	CN	H	H		90–92	85	158
	H	CH_3	Br	H	106–108/3		78.9	439
	H	CH_3	H	H	95–96/18		81	439
6	H	$COCH_3$	H	H		86	45	158
7	H	$CH_2CO_2CH_3$	H	H	126–132/2		50	477
8	NO_2		H	H		198–200	50	158
	$NHCOCH_3$	$COCH_3$	H	H		155–156	50	158
	NO_2	$CH_2CO_2C_2H_5$	H	H		57–58	65	158
	H	$CH_2CO_2C_2H_5$	H	H	103–105/1		40	158
	H	$(CH_2)_3CH_3$	Br	H	127–129/4		37	439
	H	$(CH_2)_3CH_3$	H	H	90–95/2		66	477
10	$NHCOCH_3$	$CH_2CO_2C_2H_5$	H	H		79	50	158

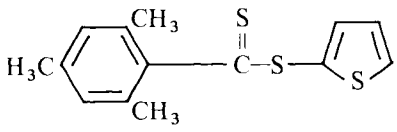
sulfines **247** and **248**.[431] The oxidation of **242** can also be carried out with ozone, which yields a 45 : 55 mixture of **244** and **243**.[430] The assignments of the E- and Z-isomers (**243**) and (**244**) are based on $Eu(DPM)_3$-induced chemical shifts of the *ortho* methyl groups.[432] Restricted rotation around the mesityl–carbon bond in **245** and **246** was studied by dynamic NMR, and $\Delta G^{\ddagger}$ values of 23.7 kcal/mole (K) and 19.1 kcal/mole (K) were observed for **245** and **246**, respectively.[434] Oxidation of **249** with peracid gave only **250**[431] (Scheme 67).

Mass spectral studies of **243** and **244** show an oxygen migration of the CSO function to the adjacent sulfur atom. The α-thioxosulfoxide thus formed underwent a 1,2-aryl shift from sulfur to oxygen. The compounds **245** and **246** show a migration of the mesityl-C=S=O group to the adjacent sulfoxide oxygen atom. Finally, **247** and **248** show almost no loss of the aryl sulfonyl group, but migration of the mesityl-C=S=O group to the sulfonyl oxygen was an important fragmentation route.[431]

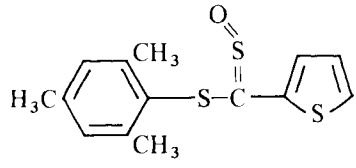
Oxidation of the disulfide **251** with hydrogen peroxide in acetic acid gave **252**.

Reaction of 3-thiophenethiol with dicyanogen in butylamine gave **253**.[435] Heating 3-thiophenethiol with PCl_3 in pyridine and toluene, and with thiophosphoryl chloride in the same solvent system, gave **254** and its PS derivative, respectively.[436] Thermal decomposition of dinitrothienyl-dithiocarbamates **255a** and *tert*-butyltrithiocarbonates (**255b**) leads to **256a1** and **256a2**, respectively[271] (Scheme 68).

The recent interest in heterofulvalenes, which are π-donors in charge-transfer complexes displaying metallic conductivity, has led to the synthesis of the condensed system **256a**, and isomeric systems. Thus the successive treatment of 3-bromothiophene with butyllithium, sulfur, or selenium followed by butyllithium, sulfur or selenium and thiophosgene gave **256b** in 30 to 45% yield. To obtain



242



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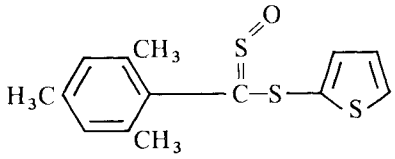

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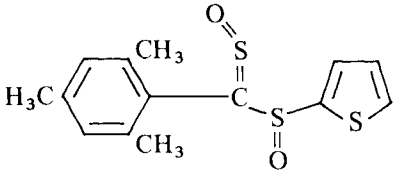

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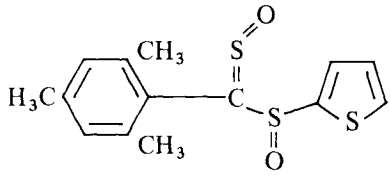
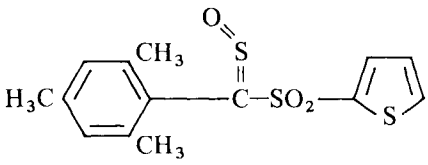
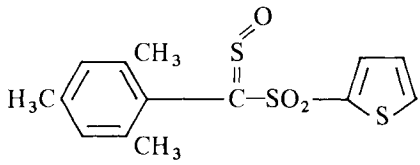


246



247



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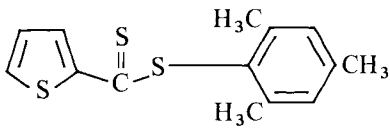

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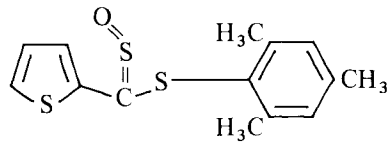

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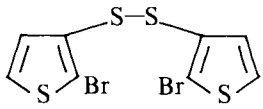

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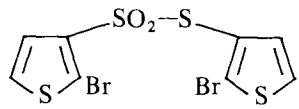
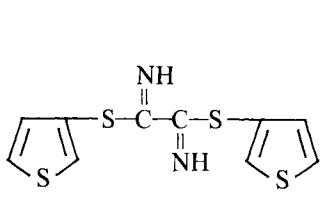


252

Scheme 67



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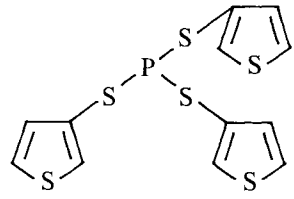
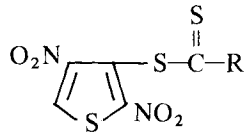
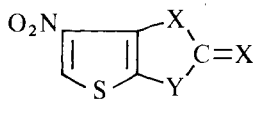


254



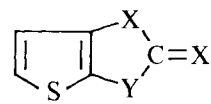
255

a. R = $N(CH_3)_2$
b. R = $SC(CH_3)_3$



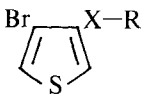
256a

1. X = O
2. X = S



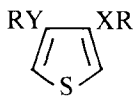
256b

1. X = Y = Se
2. X = S, Y = Se
3. X = Y = S

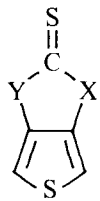


256c

X = S or Se

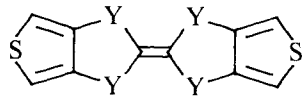


256d



256e

1. X = Y = Se
2. X = S, Y = Se
3. X = Y = S
4. X = Y = Te



256f

Scheme 68

256e a multistep route had to be employed. Reacting 3,4-dibromothiophene with butyllithium at −70°C followed by dimethyl disulfide or dimethyldiselenide gave **256c**, which upon renewed reaction with BuLi, dimethyl disulfide or diselenide gave **256d**. Compound **256d** was dealkylated with sodium amide in liquid ammonia at −70°C and then reacted with thiophosgene to give the desired **256e**,[458] (cf. also Reference 470) (Scheme 68). A somewhat modified route to **256e3** has also been described.[459] Compound **256e** (X = Y = Te) has also recently been prepared.[470] By *S*-methylation or by treatment with trimethylphosphite **256e** was converted to the desired **256f**.

XII. COMPOUNDS CONTAINING THIOPHENE–SELENIUM AND THIOPHENE–TELLURIUM BONDS

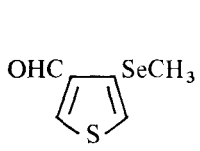
1. Compounds with Thiophene–Selenium Bonds

Compounds containing thiophene–selenium bonds are in general prepared in analogy with the corresponding sulfur compounds. Thus 2-alkylselenothiophenes were obtained by metalation of thiophene with butyllithium, followed by reaction with selenium and an alkylating agent. In this way 2-methylselenothiophene,[124] 5-methyl-2-methylselenothiophene,[124] 2-ethylselenothiophene,[437] 5-ethyl-2-ethylselenothiophene,[437] 2-methylthio-5-methylseleno-, 2-methylthio-5-propylseleno-, and 2-propylthio-5-methylselenothiophene[438] were obtained. The use of methyl chloroacetate as the alkylating agent gave methyl 5-ethyl-2-thiopheneselenoacetate.[437] 3-Alkylselenothiophenes were obtained from 3-halothiophenes by halogen–metal exchange followed by reaction with selenium and an alkylating agent. As in the corresponding sulfide synthesis, alkylation by the alkyl halide formed during the halogen–metal exchange (mostly butyl bromide) competes. On reaction with methyl iodide, a mixture of 3-methylseleno- and 3-butylselenothiophene in a 3 : 1 ratio was obtained.[439] The method is thus useful only for the preparation of butylseleno derivatives. However, reaction of 3-thienyllithium with dimethyl diselenide gave 3-methylselenothiophene in 81% yield.[439] Using this reaction, 4-bromo-3-methylselenothiophene and 4-bromo-2-methylseleno-5-methylthiophene were also prepared. Both 2- and 3-alkylselenothiophene undergo electrophilic substitution reactions such as bromination,[124] formylation, and acylation predominantly in the 5- and 2-position, respectively.[439] In the acetylation of 2-methylselenothiophene, 15% of the 3-isomer was obtained as a by-product.[440] When the 5-position is blocked, as in 5-methyl-2-methylselenothiophene, $SnCl_4$-catalyzed acylation occurs in the 3-position.[440] Competitive experiments indicate that 2-methylthiothiophene is somewhat more reactive than 2-methylselenothiophene in electrophilic substitution.[440] There is a marked difference between the reaction of 2-methylthiothiophene and 2-methylselenothiophene toward butyllithium. Whereas the former is metalated in the 5-position, the latter gives lithium–methylseleno exchange leading to 2-thienyllithium and butyl methyl selenide.[440,441] If 2-bromo-5-methylselenothiophene is reacted with butyllithium, halogen–metal exchange is faster, and 5-methylseleno-2-thienyllithium is obtained. If the bromine is β-positioned, as in 4-bromo-2-methylseleno-5-methylthiophene, methylseleno–lithium exchange is faster, giving 4-bromo-5-methyl-2-thienyllithium.[440] 3-Alkylselenothiophenes, in contrast to the 2-isomers, are metalated by butyllithium in the α-positions and do not give alkylseleno–lithium exchange. However, the lithiation is not regioselective, and after reaction with carbon dioxide and esterification a mixture of 56% ethyl 3-methylseleno-2-thiophenecarboxylate and 44% ethyl 4-methylseleno-2-thiophenecarboxylate was obtained. The mixture of 3-butylseleno-2-thienyllithium and 4-butylseleno-2-thienyllithium, obtained upon metalation with butyllithium, was reacted with selenium and methyl iodide to give a

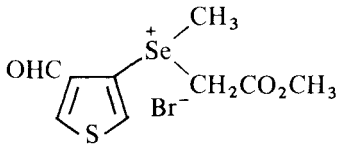
mixture of 2-methylseleno-3-butylselenothiophene and 2-methylseleno-4-butylselenothiophene.[439]

The UV spectra of alkylselenothiophenes have been compared with those of the corresponding alkoxy- and alkylthiothiophenes. An increase in the bathochromic shift was observed in the series OR < SR < SeR. The intensity of the long-wave band of the Se derivatives was lower than those of the corresponding S derivatives.[442]

A detailed investigation of the mass spectral fragmentation of the selenides, sulfides, and ethers of furan, thiophene, and selenophene has been carried out. A fragmentation reaction consisting of splitting off alkyl, insertion of a heteroatom in the cycle, and loss of one of the heteroatoms as C=X has been discussed in detail.[438] Reaction of **257** with methyl bromo acetate followed by treatment with acetic anhydride and pyridine and hydrolysis gave the seleno[2,3-c]thiophene-



257



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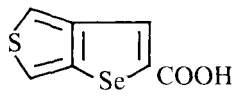
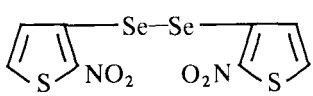
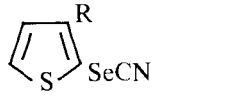


259

Scheme 69

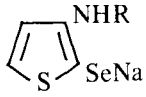


260

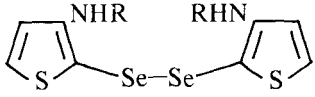


R = $NHCOCH_3$, NHCHO, OCH_3

261

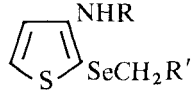


262



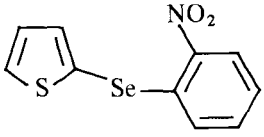
263

R = $COCH_3$, CHO

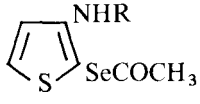


264

R = $COCH_3$, R′ = H
R = $COCH_3$, R′ = $CO_2C_2H_5$
R = CHO, R′ = H

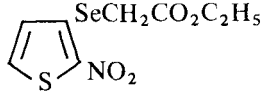


265



266

R = CHO, $COCH_3$



267

Scheme 70

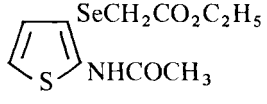
carboxylic acid **259** by way of the nonisolated selenonium salt **258**[443] **(Scheme 69)**.

The diselenide **260** was obtained by nucleophilic aromatic substitution between 3-bromo-2-nitrothiophene and sodium diselenide in ethylene glycol at 50°C.

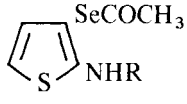
With potassium selenocyanate, 2-nitro-3-selenocyanothiophene was obtained.[158] Selenocyanates (**261**) are also obtained when thiophenes with electron-donating substituents in the 3-position are reacted with potassium selenocyanate and bromine in methanol at 0°C.[134,444] These selenocyanates are excellent starting materials for the preparation of various compounds containing thiophene–selenium bonds. Treatment with sodium sulfide in water gives a solution of the selenolate **262**, which upon acidification with acetic acid in the presence of air gives the diselenides. Alkylation of **262** gives the alkylseleno derivatives **264**, and by arylation with *ortho* nitrochlorobenzene **265** was obtained. Acetylation of **262** with acetic anhydride gave **266**.[134]

Reaction of 2-nitro-3-selenocyanothiophene with sodium borohydride followed by ethyl bromoacetate was used for the preparation of **267**, which could be transformed to compounds **268** by reductive processes (Scheme 70). Compounds **269** were also prepared from 2-nitro-3-selenocyanothiophene.[158]

Compounds containing thiophene–selenium bonds are also formed upon treatment of the thienoisoselenazole **270** with methyllithium. Thus **271** and **272** were found by combined GLC mass spectrometry. Analogous products were obtained from **273**[445] (Scheme 71).

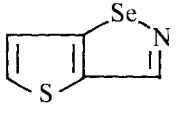


268

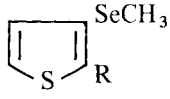


269

R = CHO, $COCH_3$

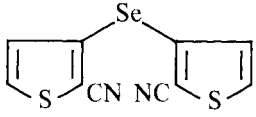


270

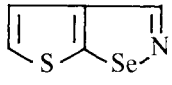


271

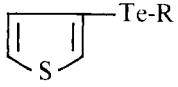
R = CHO, CN



272



273



274

R = C_4H_9, $CH_2CH_2CO_2H$

Scheme 71

2. Compounds with Thiophene–Tellurium Bonds

Reaction of 2-thienyllithium with elemental tellurium in THF followed by addition of dichloromethane and air oxidation gave di-(2-thienyl)ditelluride in 74% yield.[446] The intermediate lithium 2-thiophenetellurolate was also transformed to alkyl tellurides and telluroacetals.[447] Different 3-alkyltellurothiophenes **274**, as well as di-(3-thienyl)ditelluride, have recently been obtained.[471]

Reduction of the ditelluride with sodium borohydride gives sodium 2-thiophenetellurolate, which is an excellent reagent for the reductive dehalogenation of a variety of α-haloketones and acids. The reduction can in many cases be carried out by using sodium borohydride and catalytic amounts of the sodium or lithium 2-thiophenetellurolate. Phenylthio, acyloxy, and mesyloxy groups are also removed from the α-position of acetophenone. The reaction most probably proceeds by way of the α-(2-thienyl)tellurocarbonyl derivative, followed by enolate anion and ditelluride formation.[448] Vicinal dibromides were also debrominated to the olefins by sodium borohydride and catalytic amounts of bis-(2-thienyl)telluride.[449] Recently 2-thienyl-tellurol generated *in situ* has been found to act as selective reductants of representative organic substrates such as azo and nitro derivatives, imines and aromatic aldehydes.[481]

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CHAPTER III

Formyl and Acyl Derivatives of Thiophenes and Their Reactions

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I. INTRODUCTION

An earnest but naive author had every intention of updating the chapter on aldehydes and ketones in Hartough's monograph[1] (55 pages, 130 references) by giving full coverage to all relevant publications that appeared during the period 1949 to 1981 (through *Chemical Abstracts*, Vols. 43 to 94 inclusive). However, such was the vast output of research during this period that to have fulfilled this aim would have required a complete book. Hence a somewhat wiser author now offers his apologies to workers whose publications have been overlooked or given scant coverage.

This chapter covers derivatives in which the formyl or acyl group is directly attached to the thiophene nucleus; those containing the following ring substituents are excluded since they are covered elsewhere: $-CO_2H$, $-CN$, and related compounds, $-Ar$ (aryl or hetero aryl), and $-CH{=}CHR$ and $-C{\equiv}CR$.

Work on aldehydes and ketones during this period can be divided into distinct phases. Earlier workers described the routine preparation of new compounds with the aid of all formylating and acylating agents then available, and showed that in the main they had properties typical of aromatic aldehydes and ketones. When the

value of Raney nickel hydrodesulfurization was appreciated, ketones were prepared in abundance as precursors to long-chain aliphatic molecules. The preparation of macrocyclic compounds containing the thiophene ring then provided a stimulating challenge which was elegantly met, particularly by Russian workers. Next, the development of sophisticated spectroscopic and chromatographic techniques meant that substitution reactions could be investigated more fully and that by-products could be readily identified. Conformational studies of thiophene aldehydes and ketones then attracted unusual and prolonged interest and were supported by molecular orbital calculations of increasing complexity. Attention now seems to be centered around the synthetic challenge of preparing derivatives with less usual substituents, so orientated that they may be used for building up polycyclic systems. Certainly this branch of thiophene chemistry has acquired an aura of sophistication similar to that which now pervades the rest of organic chemistry.

During the last 30 years this area has been dominated by a constant flow of research contributions from two research groups in particular: those of Professors Gol'dfarb (Moscow) and Gronowitz (Lund). It is hoped that this chapter adequately reflects their outstanding contributions to thiophene chemistry.

II. ALDEHYDES

Throughout this chapter, the abbreviations 2-Th and 3-Th are used to denote the 2- and 3-thienyl radicals respectively.

1. Preparation of Thiophene and Alkylthiophene 2- and 3-Carboxaldehydes

A. By the Vilsmeier-Haack Reaction

Because thiophene is highly activated toward electrophilic substitution in the 2-position, Vilsmeier-Haack formylation with phosphoryl chloride and either dimethylformamide (DMF)[2] or *N*-methylformanilide (NMFA)[3] provides easy access to the 2-carboxaldehyde. No 3-isomer has been detected in this reaction.[4] Competitive experiments have shown that selenophene is more readily formylated than thiophene.[5] Formylation of thiophene and some of its alkyl derivatives with $POCl_3$-DMF[6,7] or with the related system, $COCl_2$-DMF,[8,9] has been studied kinetically. The former reaction follows third-order kinetics overall and is first order in each reagent.[6,7]

Thiophenes containing the following substituents invariably undergo formylation in the 5-position: 2-alkyl,[10–23] 2-$(CH_2)_nCO_2R$ ($n = 3$–6),[24–27] 2,3-dialkyl,[28–30] 3,4-dialkyl,[31] and 2,3,4-trialkyl.[31] 2,5-Dialkyl derivatives are formylated in the 3-position.[14,18–20] 3-Alkylthiophenes are generally formylated in the 2-position,[13,17,18,28,30] but some 5-formyl contaminant has been observed for 3-methylthiophene.[32,33] Interestingly, the presence of the large 3-*t*-butyl group gives rise to 5-substitution only.[20]

Of mainly academic interest are the preparations of thiophene-2-carboxaldehyde by the formylation of thiophene with DMF-triphenylphosphine dibromide (45% yield),[34] DMF-cyanuric chloride (5%),[35] $POCl_3$-1,4-diformylpiperazine (77%), or $POCl_3$-1-formylpiperazine (55%).[36]

B. By Reactions Involving Organometallic Intermediates

Reaction of a thienyllithium derivative or a thienylmagnesium halide with a formylating agent provides a versatile route to thiophene derivatives. Thiophene and its alkyl derivatives are metalated in the α-position by *n*-butyllithium,[28,32,37] but this route generally offers no advantages over the Vilsmeier-Haack method just described. 3-Methylthiophene gives mainly the 5-carboxaldehyde by this route,[28,37] but the product is contaminated with the 2-isomer[32] (that is, the reverse of the situation observed for Vilsmeier-Haack formylation[32,33]).

Of far more practical use is the observation that bromothiophenes undergo halogen–metal exchange when treated with an alkyllithium at a low temperature. The resulting thienyllithium can then be treated with dimethylformamide. Thiophene-3-carboxaldehyde[38] and a number of its alkyl derivatives are thus easily accessible.[32,39–42] In a variant of this method, the organolithium derivative from 4- or 5-bromothiophene-2-carboxaldehyde (protected as the acetal) reacts with cyclohexanone, then the product is hydrolyzed and dehydrated, to give 4- or 5-(cyclohexen-1-yl)thiophene-2-carboxaldehyde in good overall yield.[43]

A few alkylthiophene carboxaldehydes have been prepared by reaction of the appropriate thienylmagnesium halide with DMF[32] or triethyl orthoformate.[44–46]

2-Bromothiophene is converted directly into the 2-carboxaldehyde (76%) by carbonylation with a mixture of CO–H_2–$(PPh_3)_2PdBr_2$–Bu_3N at 130°C under pressure.[47]

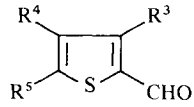
C. By Rieche Formylation

Formylation of thiophene with $MeOCHCl_2$,[48] $BuOCHCl_2$, or $MeSCHCl_2$[49] (all in the presence of $SnCl_4$) gives the 2-aldehyde in high yield (90, 86, and 72% respectively). 3-Methylthiophene is formylated by $MeOCHCl_2$-$SnCl_4$ in the 2-position (46%).[50]

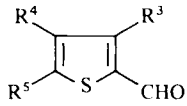
D. From Compounds Containing a $-CH_2X$ Side-Chain (X = Halogen, OH, or NH_2)

Such compounds are readily converted into the corresponding aldehydes. Preparations of thiophene-2-[51] and 3-carboxaldehyde[52] from a halomethyl derivative by the Sommelet method are described in *Organic Syntheses*. Other applications of this method have been given.[45,53–55] 3-Bromomethylthiophene is smoothly oxidized

TABLE 1. THIOPHENE 2-CARBOXALDEHYDE AND ITS ALKYL DERIVATIVES

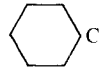
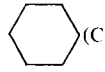
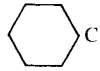
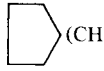


Substituents			Melting Point	Boiling Point
R^3	R^4	R^5	(°C)	(°C/mm Hg)
H	H	H		63–66/6
				89–91/21
				97–100/27
				71–72/10
Me	H	H		100–101/15
				84–85/3.5
H	Me	H		84–86/8
H	H	Me		82–83/7
				113–114/25
Me	Me	H	69–70	
Me	H	Me		101–102/8
H	Me	Me		114–116/15
Me	Me	Me	46–47	116–117/5
H	H	Cyclopropyl		135/18
				120/8
Cyclopropyl	H	H		132/10
H	Me	Et		126–127/14
H	H	Et		117–119/18
H	H	Pr		129/15
H	H	Pr^i		239/760
H	H	Bu		145/18
				143–146/22
H	H	Bu^t		246/760
				107–108/3.6
				135–136/25
H	Bu^t	H		249–250/760
H	H	Me_2CHCH_2–		133/20
H	—(CH_2)$_4$—			145–147/13



Yield (%)	Method[a]	Reference	Melting Point of Derivatives (°C)[b] (Ref.)[c]	Boiling Point of Acetals (°C/mm Hg) (Ref.)[cd]
74	Sommelet	55	Thio. 185–186(105); Semi. 213(61)	DiEt 96–98/14(107)
48–53	Sommelet	51		DiMe 73/10(111)
71–74	VH(NMFA)	3		Cyclic 110–115/15(87)
76–78	VH(DMF)	2		
69	Grignard	32	Thio. 185–187(104); Semi. 194.5–195(32);	
80	VH(DMF)	17	PH 148–149(18)	
61	Li(DMF)	37	2,4-DNP 235–236(103); NPH 179–181	Cyclic 121–122/12
75	VH(DMF)	2	Thio. 160–161(104); PH 125–126(18)	
81	VH(NMFA)	18		
83	VH(NMFA)	31	Semi. 238–240(108)	
69	Li(DMF)	37	NPH 221–223; 2,4-DNP 253–254(103)	
	VH(NMFA)	28	Semi. 223	
79	VH(NMFA)	31		
56	VH(DMF)	13		
87	VH(DMF)	23		
75	VH(DMF)	13		
59	VH(DMF)	30	Thio. 203	
58	Grignard	44	2,4-DNP 220; Semi. 194	DiEt 116/10(106)
79	VH(NMFA)	10	Thio. 119; 2,4-DNP 202	
78	VH(NMFA)	20	Thio. 203; Semi. 219	
	VH[e]	11	Thio. 105	
80	VH(NMFA)	19	Ox. 61–62	
80	VH(NMFA)	16	Thio. 197(16), 182–183(104);	DiEt 109–110/5(107)
76	VH(DMF)	17	Semi. 249(16), 215–216(19, 54); Ox. 86(16)	
91	VH(NMFA)	19		
86	VH(NMFA)	20	Thio. 186; Semi. 221; 2,4-DNP 221; Ox. 79	
77	VH(NMFA)	15	Thio. 152	
83	VH(NMFA)	29	2,4-DNP 261(74); Ox. 170(74)	

TABLE 1. *(Continued)*

Substituents			Melting Point (°C)	Boiling Point (°C/mm Hg)
R^3	R^4	R^5		
H	H	$Me(CH_2)_4$—		150/14
H	H	$Me_2CH(CH_2)_2$—		152–154/18
H	H	$Me(CH_2)_5$—		160/13
H	H	$EtCMe_2CH_2$—		148–150/13
H	H	Et_2CHCH_2—		165–167/22
H	H	Cyclohexen-1-yl	57–59	
H	Cyclohexen-1-yl	H	38–39	
H	H	$Me(CH_2)_6$—		173/13
H	H	$Me(CH_2)_2CMe_2CH_2$—		160–161/15
H	H			180/13
H	H	$Me(CH_2)_7$—		190/14
H	H			215/18
H	H	$Me(CH_2)_9$—		210–212/14
H	H	5-Adamantyl	129–130	
H	H	$Me(CH_2)_{10}$—		225–226/18
H	H	$Me(CH_2)_{11}$—	34	224–228/15
H	H			236/17
H	H	$Me(CH_2)_{13}$—	43	250–252/20
H	H			270–275/15
H	H	$MeO_2C(CH_2)_3$—		172–175/6.5
H	H	$EtO_2C(CH_2)_3$—		187/13
H	H	$MeO_2C(CH_2)_4$—	63–64	182–186/6
			66–67	163–165/1.5
H	H	$MeO_2C(CH_2)_5$—	36–37	195–197/13
H	H	$MeO_2CCH_2CHMe(CH_2)_2$—		160/2
H	H	$EtO_2C(CH_2)_6$—	28.5–29.5	190/2

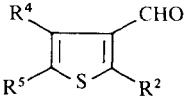
[a] VH(NMFA) and VH(DMF) = Vilsmeier-Haack using *N*-methylformanilide and dimethylformamide respectively; Li(DMF) = organolithium compound and dimethylformamide; Grignard = by way of Grignard Reagent.

[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone: Semi. = semicarbazone; Ox. = oxime (often a mixture of isomers); PH = phenylhydrazone; NPH = *p*-nitrophenylhydrazone.

Yield (%)	Method[a]	Reference	Melting Point of Derivatives (°C)[b] (Ref.)[c]	Boiling Point of Acetals (°C/mm Hg) (Ref.)[cd]
	VH[e]	11	Thio. 106	
	VH[e]	11	Thio. 121	
	VH[e]	11	Thio. 99	
46	VH(DMF)	12	Thio. 149	
68	VH(DMF)	12	Thio. 117	
33–45	See text	43		
34	See text	43		
	VH[e]	11	Thio. 102	
48	VH(DMF)	12		
	VH[e]	11	Thio. 147	
	VH[e]	11	Thio. 94	
	VH[e]	11	Thio. 150	
	VH[e]	11	Thio. 92	
80	VH(DMF)	22	2,4-DNP 283–284; Ox. 207–208	
57	VH(NMFA)	10	Thio. 97; 2,4-DNP 167	
36	VH(NMFA)	10	Thio 95; 2,4-DNP 162	
	VH[e]	11	Thio. 91	
71	VH(NMFA)	10	Thio. 97; 2,4-DNP 158	
	VH[e]	11	Thio. 82; 2,4-DNP 155	
68	VH(DMF)	27		
83	VH(NMFA)	26	Semi. 163.5–165	
79	VH(DMF)	24		
94	VH(NMFA)	26	Semi. 165; Ox. 54–55	
77	VH(NMFA)	26	Semi. 159–160; Ox. 62–63	
84	VH(NMFA)	26	Semi. 167–168	
84	VH(NMFA)	25	Ox. 42–52; Ox. of acid 136–137.5	

[c] Reference to derivative is given in parentheses unless its melting point or boiling point is quoted in the reference to the preparation.
[d] DiEt = diethyl acetal: DiMe = dimethyl acetal; Cyclic = 1,3-dioxolane.
[e] DMF and NMFA were both used.

TABLE 2. THIOPHENE 3-CARBOXALDEHYDE AND ITS ALKYL DERIVATIVES[a]



Substituents			Boiling Point				Melting Point of Derivatives (°C)	Boiling Point of Acetals (°C/mm)
R^3	R^4	R^5	(°C/mm)	Yield (%)	Method	Reference	(Ref.)	(Ref.)
H	H	H	86–87/20	70	Li(DMF)	38	2,4-DNP 235–237(38), 236–237(67); PH 137–138(38); Thio. 151–152(104);	DiEt 96/13(110) Cyclic 103–104/10(109)
			72–78/12	54–71	Sommelet	52	Ox. 113–114(309)	
H	Me	H	82–84/13	57	Li(DMF)	32	Semi. 194–195	
Me	H	H	80.5–82/10	44	Li(DMF)	32	Semi. 190–191	
H	H	Me	80–87/10	59	Li(DMF)	41	Semi. 206–207.5(42)	DiEt 105–108/10(41)
Me	H	Me	102/14	90	Sommelet	53	2,4-DNP 260(53),	
			115/13		VH(NMFA)	14	248–249(103); Semi.	
			97–99/11	85	Li(DMF)	112	270(53), 234–236(66); Ox. 109(53); PH 95–96(18)	
H	Me	Me	103–106/12	80	Li(DMF)	112	2,4-DNP 274–275	
H	H	Et	218–220/760	13	Grignard	46	2,4-DNP 200–200.5(39)	
			80–100/2	66	Li(DMF)	39	Semi. 209–211(39)	
Et	H	Et	114.5–115/8.5	51,48	Grignard, Sommelet	45	2,4-DNP 188; Semi. 178	
Me(or Pr^n)[b]	H	Pr^n(or Me)	130–132/15	17	VH(NMFA)	10	2,4-DNP 182, Semi. 228	
Me	H	Bu^t	96–97/4		VH(NMFA)	19	Semi. 215.5–217	
Bu^t	H	Bu^t	148–150/13	75	Li(DMF)	40	2,4-DNP 219(20);	
			144–145.5/10	36	VH(NMFA)	19	Semi. 231(20); Ox. 106(20), 131–132(19)	
Bu^t	Me	Bu^t	155/13	77	VH(NMFA)	20	2,4-DNP 221; Semi. 225; Ox. 95	

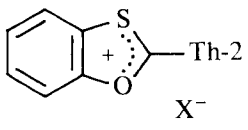
[a]The abbreviations and conventions used are those listed in the footnotes to Table 1.
[b]Structure uncertain.

to the 3-aldehyde (56%) by 2-nitropropane in ethanolic NaOEt;[56] 2-chloromethylthiophene gives the 2-aldehyde (62%) in a one-pot reaction which involves successive hydrolysis to the alcohol and oxidation with dichromate.[57] Thiophene-2-carboxaldehyde has been obtained by oxidation of the corresponding hydroxymethyl compound with silver carbonate-celite (94%),[58] acidified dichromate (65%),[57] dimethyl sulfoxide activated by oxalyl chloride (92%),[59] activated manganese dioxide (70%),[60] or potassium persulfate (43%).[61] Oxidation of 2-methylthiophene by O_2-$Co(OAc)_2$ in the presence of 9,10-dibromoanthracene gives the 2-carboxaldehyde as an isolable intermediate.[62] Warming 2-thenylammonium bromide (2-$ThCH_2\overset{+}{N}H_3Br^-$) with dimethyl sulfoxide gives 2-ThCHO (72%).[63] 3-Methylthiophene is easily converted into the 3-(dibromomethyl) compound, which gives the 3-carboxaldehyde (30% overall) with aqueous sodium carbonate and pyridine.[64]

Aldehydes prepared by the above general routes are listed in Tables 1 and 2. The less common procedures which follow are generally excluded from the tables unless they are of particular value for a given compound.

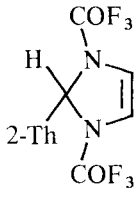
E. From Carboxylic Acid Derivatives

Acid chlorides have been reduced to the corresponding aldehyde with sodium aluminum tri-*t*-butoxide (63%)[65] or catalytically (Rosenmund method) (55 to 65%).[66] Tin(II) chloride reduction of the iminochloride from thiophene-3-carboxanilide (Sonn-Müller method) gives the 3-carboxaldehyde (80%).[67] Thiophene-3-carbonitrile is reduced to the aldehyde with tin(II) chloride-HCl (Stephen's method) (71%)[68] or with sodium bis(2-methoxyethoxy)aluminum hydride (yields are solvent variable).[69]



(X = ClO or BF_4)

1



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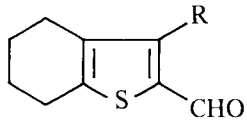

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F. From Other Heterocycles

2-Mercaptophenol reacts with thiophene-2-carboxylic acid in the presence of $HClO_4$-$POCl_3$[70] or with the 2-carbonitrile in the presence of HBF_4[71] to give the 1,3-benzoxathiolium salt (**1**). The product of the reduction of salt (1) with $LiAlH_4$ or $NaBH_4$ is a mixed acetal, hydrolysis of which gives the 2-carboxaldehyde (68 and 77% overall, respectively), in an experimentally straightforward procedure.

The imidazoline (2), formed by treatment of thiophene with imidazole and trifluoroacetic anhydride, undergoes alkaline hydrolysis to give 2-ThCHO (79%).[72]

Oxidation of either 2-methoxy-2*H*-thiopyran or thiopyrylium iodide with manganese dioxide in chloroform gives thiophene-2-carboxaldehyde (27 and 71% respectively).[73]

G. *Miscellaneous Methods*

The chloro substituent in 2-chlorocyclohex-1-ene-1-carboxaldehyde (obtained from cyclohexanone by Vilsmeier-Haack formylation) is readily replaced by $-SCH_2CHO$ (presumably as the acetal). The resulting dialdehyde cyclizes spontaneously in the alkaline medium, to give the aldehyde (3; R = H).[74]

Thiophene is dicyanovinylated by treatment with $ClCH{=}C(CN)_2 - AlCl_3$. Alkaline hydrolysis of the resulting 2-ThCH=$C(CN)_2$ gives 2-ThCHO (30% overall).[75] The secondary alcohol obtained by reaction of 2-thienylmagnesium bromide with *p*-dimethylaminobenzaldehyde is cleaved by diazotized sulfanilic acid to give thiophene-2-carboxaldehyde (50 to 75%) and *p*-$HO_3SC_6H_4N{=}NC_6H_4NMe_2$-*p*.[76] Of academic interest is the preparation of thiophene-2- and 3-carboxaldehydes by UV irradiation of the *S*-aryl esters of substituted thiophene-2- or 3-carbothioic acids (ThCOSAr).[77]

H. *Isotopically Labeled Aldehydes*

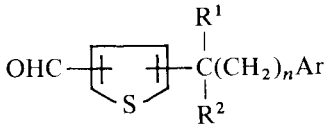
The acetal of a bromothiophene carboxaldehyde undergoes halogen–metal exchange with butyllithium at a low temperature; addition of deuterium oxide or MeOD followed by mineral acid gives the appropriate ring-deuterated aldehyde.[78,79] Alternatively, the thienyllithium derivative can be formed from a deuterated halogenothiophene; treatment with dimethylformamide then gives the deuteroaldehyde.[80,81] The latter method is of particular value for polydeuterated aldehydes. By using the forementioned methods, the bromine atoms in 2,4-dibromothiophene may be replaced successively in a single synthetic step by CHO and D, to give 4-deuterothiophene-2-carboxaldehyde (41%).[80]

Formylation of thiophene with phosphoryl chloride and perdeuterodimethylformamide gives the 2-CDO derivative.[33] This has also been obtained by oxidation of 2-$ThCD_2OH$ with silver carbonate on celite[82] or pyridinium chlorochromate,[83] and by decarboxylation of 2-$ThCOCO_2D$.[84] Sonn-Müller reduction of 2-ThCCl(=NPh) with $SnCl_2$-TCl affords the tritiated aldehyde, 2-ThCTO.[85]

The oxygen-labeled aldehyde, 2-$ThCH^{18}O$ is conveniently obtained by treating the unlabeled 2-carboxaldehyde with $H_2{}^{18}O$ in the presence of perchloric acid.[84] ^{35}S-Thiophene-2-carboxaldehyde has been prepared by treatment of 3-chlorocyclopentane-1,2-dione with hydrogen ^{35}S-sulfide.[86]

2. Preparation of Thiophene-2- or 3-Carboxaldehydes Containing an (Aryl-substituted)Alkyl Side-Chain

This section is concerned with aldehydes of structure **4**. Most interest has been centered around the bis-(2-thienyl)methanes (**5**). Compounds **5**; $R^3 = R^4 = H$ readily undergo Vilsmeier-Haack formylation to give the 5-carboxaldehyde **5**; $R^3 = H$, $R^4 = CHO$;[87-91] often the 5,5′-dialdehyde (**5**; $R^3 = R^4 = CHO$) is also formed.[88,89,92] Similar results are obtained by successive treatment of the parent compound (**5**; $R^3 = R^4 = H$) with butyllithium and dimethylformamide.[93,94] A 5-alkylated bis-(2-thienyl)methane (**5**; R^3 = alkyl, $R^4 = H$) readily gives the 5′-carboxaldehyde (**5**; R^3 = alkyl, $R^4 = CHO$).[19,89,90,95]



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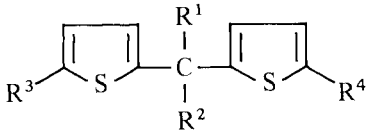

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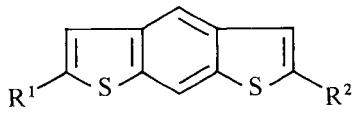

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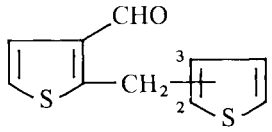

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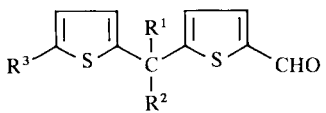
Attempted formylation of the 5,5′-disubstituted compound (**5**; $R^3 = R^4 = Cl$, $R^1 = R^2 = H$) by the Rieche method ($SnCl_4$ –$MeOCHCl_2$) gave *inter alia* a low yield of the tricyclic compound (**6**; $R^1 = R^2 = Cl$), formed by intramolecular cyclization of the initially formed 3-carboxaldehyde (direct Bradsher reaction).[96] Aldehyde (**7**; 2-isomer) (obtained from the corresponding bromo compound by metal–halogen exchange/formylation) is cyclized by HBr to **6**; $R^1 = R^2 = H$;[97] aldehyde (**7**; 3-isomer) undergoes an analogous cyclization into the 2-position with polyphosphoric acid.[98] Bis-(3-thienyl)methane, as might be expected, undergoes the direct Bradsher reaction more readily than does its 2-isomer (**5**; $R^1 = R^2 = R^3 = R^4 = H$) and gives the cyclized product **6**; $R^1 = R^2 = H$ (33%) with either $POCl_3$–DMF or $SnCl_4$–$MeOCHCl_2$.[96]

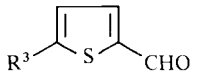
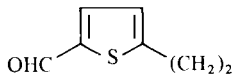
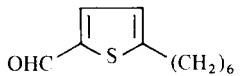
Vilsmeier-Haack formylation of the unsymmetrical diarylmethane, 2-$ThCH_2Ar$, takes place entirely in the thiophene ring when Ar = phenyl,[15] but predominantly (80%) in the selenophene ring when Ar = selenophene-2-yl.[5]

Formylation of 2-$Th(CH_2)_6$Th-2 readily gives the expected 5,5′-dialdehyde;[99,100] 2-$Th(CH_2)_3Ph$ is formylated in the 5-position of the thiophene ring.[101] Unexpect-

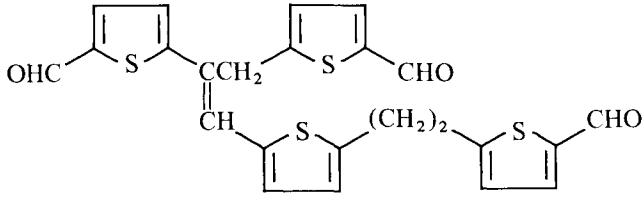
TABLE 3. THIOPHENE CARBOXALDEHYDES CONTAINING AN (ARYL SUBSTITUTED) ALKYL SIDE-CHAIN[a]



Substituents			Melting Point	Boiling Point				Melting Point of Derivatives (°C)
R^1	R^2	R^3	(°C)	(°C/mm)	Yield (%)	Method	Reference	(Ref.)
H	H	H	33–34	153–155/3	91, 63	VH(NMFA)	90, 91	Ox. 93.5–95; Semi. 207–209; Cyclic Acetal b.p. 179–180/5(87)
H	H	Me		156–158/3	44	VH(NMFA)	19	Ox. 119–120 and 99–99.5(90)
				152–156/3	37	Li(DMF)	90	(two isomers)
H	H	CHO	95		75	Li(DMF)	93	
Me	Me	H		202–205/15	40	VH(DMF)	88	Semi. 238
Me	Me	Me		225/28	67	VH(DMF)	89	Semi. 240
Me	Me	CHO	79	257–259/15	25	VH(DMF)	88	Disemi. 320–322
			87.5–88		83	VH(DMF)	92	
			72		82	Li(DMF)	93	
Me	Et	H		160–162/3	64	VH(DMF)	87	Ox. 103–104; Semi. 173(89)
Me	Et	Me		210–215/15	66	VH(DMF)	89	Semi. 174
Me	Et	CHO		260–265/15	10	VH(DMF)	89	Disemi. 289
Et	Pr^n	Et		164–170/0.2	82	VH(NMFA)	95	2,4-DNP 153–154

R^3						
$PhCH_2$		195/13	43	VH(NMFA)	15	Thio. 175
$Ph(CH_2)_2$		208/14		VH(NMFA)	11	Thio. 141
$Ph(CH_2)_3$		222–225/19	69	VH(DMF)	101	
p-Bu^t-$C_6H_4CH_2$		218–220/13		VH(NMFA)	11	Thio. 170
	136.5–138		17	VH(DMF)	102	Di-2,4-DNP 296–298
	86–87		70	VH(DMF)	99	
	86.5–87.5		85	VH(NMFA)	100	Di-p-nitrophenylhydrazone 176–177
			Others			
2-(2-Thenyl),3-CHO		124–130/0.5–0.7	40	Li(DMF)	97	2,4-DNP 156.5–158
2-(3-Thenyl),3-CHO		90–110/0.02	79	Li(DMF)	98	

[a]The abbreviations and conventions used are those listed in the footnotes to Table 1.



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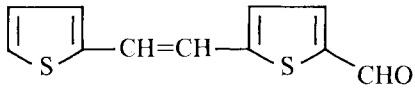

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edly, formylation ($POCl_3$—DMF) of 2-Th$(CH_2)_2$Th-2 gives only 5 and 17% respectively, of the 5-aldehyde and 5,5′-dialdehyde. Aldehydes **8** (9%) and **9** (0.5%) have also been isolated from this reaction.[102] (See Table 3.)

3. Reactions of Thiophene and Alkylthiophene 2- and 3-Carboxaldehydes

A. General

Because thiophene-2-carboxaldehyde is so readily available, it is used routinely when a new reaction of aromatic aldehydes is being investigated in general. In consequence, its reported reactions are so numerous that some of the more trivial ones deliberately have been excluded. For the most common reactions, only a representative sample of references is included. When a common reaction is clearly applicable also to aldehydes with ring substituents other than alkyl (e.g., halogens, nitro), it is mentioned in this section and not repeated later.

Physical and chemical properties of thiophene aldehydes have been reviewed, with particular emphasis on substituent effects.[113] A comprehensive review of the syntheses of thiophene derivatives of pharmaceutical importance includes many reactions of aldehydes and ketones, drawn mainly from the patent literature.[114]

B. Oxidation

For preparative purposes, aldehydes are usually oxidized to carboxylic acids by means of silver oxide. Typical procedures are given in References 37, 92, and 115. The formylation product[19] of 5-*t*-butyl-2-methylthiophene has been oxidized to the 3-carboxylic acid by silver oxide to establish its structure.[116] Aldehydes containing a sensitive group in the ring have been oxidized by HgI_2-KI.[117] Acidified dichromate will oxidize aldehydes without affecting an alkyl side chain.[24,27]

Thiophene-2-carboxaldehyde undergoes oxidation to the carboxylic acid with molecular oxygen in alkaline HMPA solution,[118] or with nickel peroxide in aqueous alkaline solution.[119]

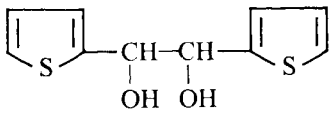
C. *Reduction*

Thiophene aldehydes are reduced conventionally to the primary alcohol by use of sodium borohydride or lithium aluminum hydride. The following reagents have also been used for the same purpose: iron and acetic acid,[57] formamidinesulfinic acid,[120] synthesis gas (H_2—CO) in the presence of cobalt(II) acetate,[121] and dibutylin hydride.[122] Thiophene-2-carboxaldehyde undergoes asymmetric reduction with $LiAlD_4$ in (−)-quinine to give (+)-2-ThCHD(OH) (32% optical purity).[123] Hydrogenation of 2-ThCHO in methanol in the presence of Re_2S_7 gives a mixture of 2-$ThCH_2OMe$ (48%) and 2-ThMe (16%).[124]

The kinetics of the Cannizzaro reduction-oxidation reaction have been studied with the aid of the tritium-labeled 2-carboxaldehyde.[85]

Conventional Huang-Minlon reduction has been applied widely for the preparation of methylthiophenes (see, for example, Reference 125). Semicarbazones have been reduced successfully by the Wolff-Kishner procedure.[28,108]

The electrochemical reduction of thiophene-2-carboxaldehyde has been studied extensively by Russian workers.[126–128] By this means, the dimeric reduction product **10** has been prepared in up to 80% yield.[126] The same product (**10**) is obtained (10%), along with 2-ThCH(OH)CH(OH)CH=CH_2 (50%), when a mixture of 2-ThCHO and acraldehyde is reduced with Zn—AcOH.[129] Treatment of thiophene-2-carboxaldehyde with triethylsilane-trifluoroacetic acid gives the saturated ether **11** (65%).[130]



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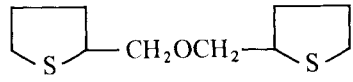


11

The polarographic reduction of thiophene aldehydes has been studied in detail.[131–137] Under these conditions the aldehydes behave similarly to the benzene analogues,[132] but 2-carboxaldehydes are reduced more readily than their 3-isomers.[133] Thiophene-2-carboxaldehyde is reduced polarographically to a dimer in acidic media and to the corresponding saturated dimer in neutral or basic media.[134]

When thiophene carboxaldehydes are treated with Raney nickel, they undergo both hydrodesulfurization and reduction of the formyl group to give an aliphatic primary alcohol.[19,91]

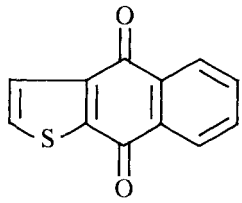
D. Carbon Nucleophiles: Addition

a. HYDROGEN CYANIDE

Thiophene 2-carboxaldehyde undergoes enzyme-catalyzed addition of HCN, to give the D-cyanohydrin in a state of high optical purity.[138] Thiophene-3-carboxaldehyde forms a cyanohydrin which is hydrolyzed by hydrochloric acid to 3-ThCH(OH)CO_2H.[139]

b. GRIGNARD AND RELATED ORGANOMETALLIC REAGENTS

1,2-Addition of Grignard reagents takes place, as expected, to give the appropriate secondary alcohol,[14,140–146] which may be oxidized to the corresponding ketone[143] or dehydrated to the alkene.[14,140] Dialkyl cadmiums (+ 2$MgBr_2$)[144] and lithium alkyls[147] react similarly. In a synthetically useful reaction, 3-ThCHO reacts with ortho lithiated *NN*-diethylbenzamide: spontaneous cyclization followed by aerial oxidation affords a one-pot route to the quinone **12**.[148] Related quinones are obtained similarly. When treated with the dianion of methyl acetoacetate, thiophene-2-carboxaldehyde gives 2-ThCH(OH)$CH_2COCH_2CO_2$Me in 93% yield.[149] With trimethylallyltin ($Me_3SnCH_2CH{=}CH_2$) in the presence of $BF_3 \cdot Et_2O$, thiophene-2-carboxaldehyde gives the homoallylic alcohol, 2-ThCH(OH)$CH_2CH{=}CH_2$ (90%).[150]



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c. ACETYLIDES

With HC≡CNa,[151] RC≡CMgBr,[152] ArC≡CMgI,[153] and $Et_3SiC{\equiv}CMgBr$,[154] addition takes place normally to give the secondary alcohol, which may be oxidized to the acetylenic ketone. In an interesting homologation reaction, 2-ThCHO reacts with *trans*-MeOCH=CHC≡CMgBr. The resulting alcohol is hydrogenated to 2-ThCH(OH)-$(CH{=}CH)_2$OMe, which gives 2-Th$(CH{=}CH)_2$CHO by acidic hydrolysis of the vinyl ether group.[155]

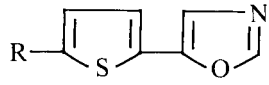
d. REFORMATSKI REACTION

Thiophene aldehydes give the expected β-hydroxy ester in the Reformatski reaction with α-bromoesters,[156–159] allyl bromide,[160] or α-bromoalkynes.[160,161] With ethyl γ-bromocrotonate[160,162] the rearrangement product, ThCH(OH)CH$(CH{=}CH_2)$-CO_2Et, may also be formed.[160]

e. OTHER ADDITIONS

Thiophene-2-carboxaldehyde reacts with (diazomethyl)diphenylphosphine oxide [N_2=CHP(O)Ph_2] to give the aldol like addition product, 2-ThCH(OH)(N_2=)-CP(O)Ph_2.[163]

In the presence of methanolic potassium carbonate, thiophene-2-carboxaldehydes undergo addition to tosylmethylisocyanide ($TosCH_2NC$) to give high yields of the oxazoles (**13**).[164]



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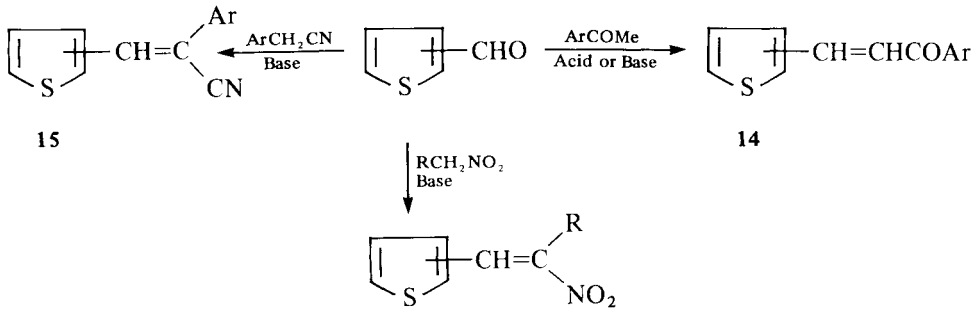
E. Carbon Nucleophiles: Addition-Elimination

a. ALDOL CONDENSATION AND RELATED REACTIONS

This is one of the most widely studied areas of thiopene chemistry, and it is impossible to attempt to give it exhaustive coverage.

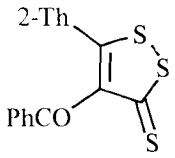
Thiophene aldehydes condense readily with aromatic methyl ketones (Claisen-Schmidt reaction) to give the chalcone analogues **14** (Scheme 1). Generally, this reaction is carried out in aqueous alcoholic alkali.[57,162,165–178] However, aqueous sodium carbonate or ethanolic sodium ethoxide have also been used.[179] In some cases the intermediate β-hydroxy ketone has been isolated.[177] Heterocyclic methyl ketones (Scheme 1; Ar = heteroaryl) readily participate in this reaction.[162,176,179–185] In this case, although alkaline catalysts are usually preferred,



15 **14** **16**

Scheme 1

acidic catalysts have been used successfully.[181] Thiophene-2-carboxaldehyde undergoes the normal Claisen-Schmidt reaction with acetylferrocene.[186,187] With aromatic ketones of the type $ArCOCH_2Me$ (HCl gas catalyst)[188] or $PhCH_2COR$,[189] condensation with 2-ThCHO takes place on the methylene group as expected. When heated with sulfur in a high-boiling solvent, the product from the former reaction (2-ThCH=CMeCOPh) gives the heterocycle **17**.[188] Indene condenses with 2-ThCHO at the benzylic methylene group.[190]



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With aliphatic ketones, condensation takes place normally at the methyl group of acetone,[162,191] sodium pyruvate,[162] acetylenic methyl ketones ($MeCOC{\equiv}CR$),[192] and the α-hydroxy ketones $[R^1R^2C(OH)COMe]$.[193] Alicyclic ketones undergo condensation at an α-methylene group[166,179,194–196] The direction of the condensation reaction with unsymmetrical aliphatic ketones depends mainly on the nature of the catalyst used. With EtCOMe[197] and other ketones of the type RCH_2COMe,[198] the base-catalyzed reaction takes place at the methyl group, whereas the acid- (gaseous HCl)[199] or metal ion- (Cu^{2+}—Zn^{2+})[200] catalyzed condensation takes place at a methylene group. With $Me_2CHCOMe$ in the presence of gaseous HCl, the major product is $2\text{-ThCH(Cl)C(COMe)Me}_2$, resulting from reaction at the α-CH group; reaction at the $\alpha\text{-CH}_3$ group is a less significant process.[201]

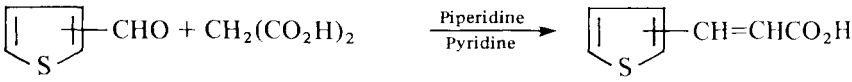
Ethanal,[162,202] propanal,[203] heptanal,[20] 2-chloroethanal,[162] and (2-ferrocenyl) ethanal[204] undergo the base-catalyzed condensation with thiophene carboxaldehydes in the expected manner. With 2,5-dimethoxytetrahydrofuran (which acts as a source of succindialdehyde), thiophene-2-carboxaldehyde gives the biscondensation product, 2-ThCH=C(CHO)C(CHO)=CHTh-2, in the presence of KOAc—AcOH.[205]

b. CONDENSATION WITH NITRILES AND NITRO COMPOUNDS

The nitriles $ArCH_2CN$ react with thiophene carboxaldehydes to give the condensation products **15** (Scheme **1**).[14–16,20,101,170,206–210] The product from the condensation of 2-ThCHO and 2-ThCH_2CN has the trans configuration; it is converted into the cis isomer by sunlight.[208] The condensation with nitro compounds, RCH_2NO_2 (Scheme **1**), is catalyzed by sodium hydroxide,[211–213] or butylamine.[214,215] High yields of the products **16** are obtained if the condensation is carried out on a Schiff's base preformed from the aldehyde and an aliphatic primary amine.[46,216]

c. KNOEVENAGEL AND RELATED REACTIONS

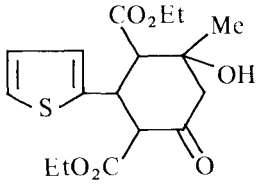
The Doebner reaction (Scheme 2) has been widely used for preparing β-thienylacrylic acids.[13,170,211,217] By an appropriate modification of the reaction conditions



18

Scheme 2

(AcOH-piperidine,[218] Et_3N–AcOH,[219] or NH_3–EtOH,[170,220]), the intermediate dicarboxylic acid ThCH=$C(CO_2H)_2$ can be isolated. This can be decarboxylated in hot acetic anhydride to give a mixture of the cis and trans acrylic acids **18**.[219] If the reaction with malonic acid is carried out in the presence of ammonium acetate, the β-amino acid ThCH(NH_2)CH_2CO_2H is obtained preferentially, together with the acrylic acid (**18**).[21,221] The ammonium salt ThCH=$C(CO_2H)CO_2NH_4$ can be isolated as an intermediate under controlled conditions.[21] 3-(2-Thienyl)acrylic acid has been prepared by the condensation of thiophene-2-carboxaldehyde with (tetraacetoxy)silane in the presence of potassium carbonate.[222] With thiophene carboxaldehydes, the carboxylic acids, $CH_2(CN)CO_2H$,[223] $CH_2(CONHPh)CO_2H$,[218] $CH_2(SO_2NHPh)CO_2H$,[224] and $CH_2(SO_2Ar)CO_2H$,[225] all undergo a Doebner-type reaction with loss of the carboxyl group. The numerous other reactions of thiophene carboxaldehydes with "active methylene" compounds are summarized in Table 4 (**19**–**22**).



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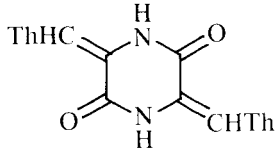

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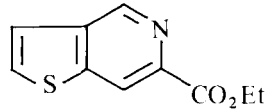
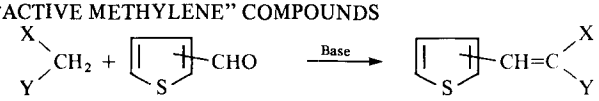


22

The condensation products (**19**) are often of synthetic importance. The rhodanine derivatives can be hydrolyzed by alkali to give the α-mercaptoacrylic acids, ThCH=C(SH)CO_2H, from which α-amino acids are readily prepared.[238] Likewise, saturation of the double bonds in product **21**, followed by hydrolysis, gives β-thenylalanine.[244] Thermolysis of the *t*-butyl ester 2-ThCH=C(COMe)CO_2Bu^t in the presence of toluene-*p*-sulfonic acid gives the αβ-unsaturated ketone, 2-ThCH=CHCOMe.[232] Flash pyrolysis of the condensation products with 3-methyl-5(4*H*)-isoxazolone provides a convenient route to 2- or 3-ThC≡CH.[243] Treatment of 2-ThCH=C(SMe)SOMe with ethanolic hydrogen chloride gives the homologous ester 2-$ThCH_2CO_2Et$ (80%).[236] Thermolysis of the condensation products of 2- or 3-ThCHO with ethyl azidoacetate gives the two isomeric thienopyrroles.[235] Thermolysis of the analogous product from 3-methylthiophene-2-carboxaldehyde gives the thienopyridine **22**.[246]

TABLE 4. CONDENSATION OF THIOPHENE-2- or 3-CARBOXALDEHYDES WITH "ACTIVE METHYLENE" COMPOUNDS



19

X	Y	Base	Reference
MeO	CO_2Et	NaOEt or NaH	226
EtS	CO_2Et	NaOEt or NaH	226
Me_2N	CO_2Et	NaOEt or NaH	226
CN	CO_2Bu^t	Piperidine	227
CN	CO_2Et	Piperidine	228
CN	$CSNH_2$	Et_3N	229
CN	NO_2	None	230
CN	CN	Piperidine	57
NO_2	CO_2Et	$TiCl_4$-pyridine	231
MeCO	CO_2Bu^t	Piperidine	232
MeCO	CO_2Et	$TiCl_4$-pyridine	231
		Piperidine	14, 15, 162[a]
MeCO	COMe	$TiCl_4$-pyridine	233
$(EtO)_2PO$	CO_2Et	$TiCl_4$-pyridine	234
$(RO)_2PO$	$PO(OR)_2$	$TiCl_4$-pyridine	234
N_3	CO_2Et	NaOEt	235
MeSO	SMe	Triton B	236, 237[b]
—SCSNHCO— (Rhodanine)		NaOAc-AcOH	57, 238, 239
—CONHCONHCO— (Barbituric Acid)		None	213, 220
—$COOCMe_2OCO$— (Meldrum's acid)		Piperidine	240
—CONHNPhCO—		Pyridine	241
—COON=CPh— [3-Phenyl-5(4*H*)-isoxazolone]		None	242
—COON=CMe— [3-Methyl-5(4*H*)-isoxazolone]		None	243
—$NHCOCH_2NHCO$— (Dioxopiperazine)		NaOAc-AcOH	244[c]
—$NAcC_6H_4$-*o*-CO— (1-Acetylindoxyl)		Piperidine	245

[a] 3-Carboxaldehydes appear to behave normally. 2-Carboxaldehydes give the cyclized product **20.**

[b] Product is the cis isomer.

[c] Gives the bis condensation product **21.**

Thiophene-2-carboxaldehyde condenses with the malondialdehyde derivative $[Me_2NCH{=}CHCH{=}NMe_2]^+ ClO_4^-$ to give an intermediate, which, on hydrolysis, affords 2-ThCH=C$(CHO)_2$ (61%).[247] An alkyl isocyanoacetate (RO_2CCH_2NC) condenses with thiophene-2-carboxaldehyde in two ways: in the presence of pyrrolidine the base reacts with the NC-function to give 2-ThCH=C(CO_2R)-

$N{=}CHN(CH_2)_4$ (*E*-isomer); in the presence of sodium hydride a single stereoisomer of the *N*-formyl derivative, 2-ThCH=C(CO_2R)NHCHO, is obtained.[248,249] In a Knoevenagel-like reaction, diethyl fluorooxaloacetate ($EtO_2CCOCHFCO_2Et$) reacts with thiophene-2-carboxaldehyde to give the α-fluoroacrylic ester, 2-ThCH=$CFCO_2Et$.[250] Thiophene carboxaldehydes react with ethyl acetate-NaOEt to give the acrylic esters $ThCH{=}CHCO_2Et$ (50 to 60%).[211]

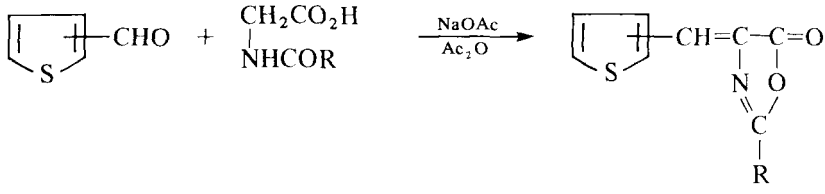
Compounds (ArMe) containing a reactive methyl group condense with thiophene carboxaldehydes to give the stilbene analogoues ArCH=CHTh. Examples of ArMe (with condensing agent in parentheses) include: 2,4,6-trinitrotoluene (piperidine);[14,57] 4-methylpyridazine (NaOH–DMSO);[251] 4-methylcinnoline ($ZnCl_2$);[252] 2-methylquinoline-4-carboxylic acid (Ac_2O);[253] methyl 5-methyl-4-nitrothiophene-2-carboxylate (piperidine);[254] a condensed 2-methylpyrimidine derivative;[255] and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (by using a metal fluoride as catalyst, the intermediate alcohol can be isolated).[256]

d. PERKIN, STOBBE, AND DARZENS REACTIONS

Thiophene carboxaldehydes readily undergo a modified Perkin reaction with an arylacetic acid ($ArCH_2CO_2H$) in the presence of NEt_3–Ac_2O,[56,208,257–259] K_2CO_3–Ac_2O[81] or NEt_3–AcOH[260] to give the αβ-unsaturated carboxylic acid ThCH=C-$ArCO_2H$. A mixture of stereoisomers is formed in which the cis isomer predominates (contrast the preferred formation of the trans product in the analogous condensation with $ArCH_2CN$).[208]

The use of α-acylamido acids in the Perkin reaction leads to the formation of arylidene derivatives of oxazolone (azlactones) (Scheme 3),[2,31,239,261–264] from which α-amino[2,262,263] and α-keto acids,[261] can be prepared by standard procedures. Use of 3-benzoylpropionic acid under similar conditions gives a butenolide derivative (**23**; R=Ph, CH replaces N).[265]

Stobbe condensation of thiophene-2-carboxaldehyde with dimethyl succinate in the presence of potassium *t*-butoxide gives the half-ester, 2-ThCH=C(CO_2Me)-CH_2CO_2H (predominantly trans), together with some αβ-dithenylidenesuccinic acid, 2-ThCH=C(CO_2H)C(CO_2H)=CHTh-2.[266] Use of dimethyl phenylsuccinate in this reaction gives a stereoisomeric mixture of the corresponding half-esters.[267] In an analogous reaction, thiophene-2-carboxaldehyde and its alkyl derivatives condense with dimethyl glutarate in the presence of sodium hydride to give the half-ester 2-ThCH=C(CO_2Me)$CH_2CH_2CO_2H$, and, in some cases, the by-product, αα′-di-2-thenylideneglutaric acid.[268]



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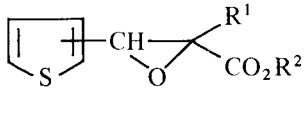
Scheme 3



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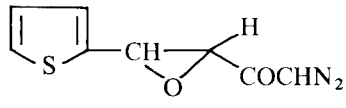

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Thiophene carboxaldehydes undergo the Darzens reaction with α-haloesters ($R^1CHXCO_2R^2$) to give the glycidic esters **24**,[269–272] which on saponification and decarboxylation yield the homologous ketone $ThCH_2COR^1$.[271,272]

The base-catalyzed reaction of 2-ThCHO with methanolic bromoform, to give α-methoxy-2-thienylacetic acid (20%), probably proceeds by way of the Darzens-related intermediate, 2-ThCH(O)CBr$_2$.[273] With 3-chloro-1-diazopropanone ($ClCH_2COCHN_2$), thiophene-2-carboxaldehyde yields the Darzens-type product **25**.[274]

It is convenient to mention here the reactions of thiophene carboxaldehydes with other diazoalkanes. Prolonged treatment of 2- or 3-ThCHO with diazomethane gives the appropriate methyl ketone in high yield.[275] With the ω-diazo esters, $RCHN_2$, 2-ThCHO yields the ketones 2-$ThCOCH_2R$ [$R = (CH_2)_nCO_2Me$].[276]

e. BENZOIN CONDENSATION

In the presence of sodium cyanide, thiophene-3-carboxaldehyde gives the benzoin analogue 3-ThCH(OH)COTh-3.[40] Thiophene aldehydes also react readily with benzaldehyde to give the mixed condensation product ThCOCH(OH)Ph.[139,277]

f. WITTIG AND RELATED REACTIONS

There are numerous examples of the preparation of alkenes (mainly stilbene analogues) from thiophene carboxaldehydes, either by the conventional Wittig reaction[278–287] or by the Horner-Emmons modification[80,288–293] thereof. The former method usually gives a mixture of stereoisomers;[279–281,285,287] the latter gives largely the trans isomer.[289,293]

The use of stabilized phosphoranes or, more recently, of phosphonate carbanions gives ready access to a wide range of thiophenes containing an unsaturated side chain, Th—X, where X = $CH{=}CHCO_2Et$,[294,295] CH=CHCHO,[296] $CH{=}CBrCO_2Et$,[297] $CH{=}CClCO_2H$,[298] $(CH{=}CH)_2Ph$,[299] $CH{=}CHSO_2Me$,[300] $CH{=}CCOOCH_2CH_2$,[301] or CH=CHOMe.[302] The last compound can be usefully converted into the homologous aldehyde, 2-$ThCH_2CHO$, by treating it with HCl—MeOH, to give the acetal, 2-$ThCH_2CH(OMe)_2$, which will then undergo ready acidic hydrolysis.[302] In a useful one-flask synthesis of an unsymmetrical benzoin, 5-methylthiophene-2-carboxaldehyde reacts with $(EtO)_2POCHPhOSiMe_3$, and the product undergoes successive rearrangement, fragmentation, and hydrolysis to give ArCH(OH)COPh (Ar=5-methyl-2-thienyl) in 92% overall yield.[303]

The rate constant for the reaction of 2-ThCHO with benzoylmethylene triphenylphosphorane ($PhCOCH{=}PPh_3$) in methanolic solution has been determined.[304]

The dibromoalkene, 2-$ThCH{=}CBr_2$, is obtained by treatment of thiophene-2-

carboxaldehyde with triphenylphosphine and tetrabromomethane.[305] In an unusual alkene synthesis, which may proceed by way of a carbene mechanism, acetylbromoberyllium (AcBeBr) reacts with 2-ThCHO to give 2-ThCH=CHTh-2 (trans) (26%).[306]

Treatment of thiophene-2-carboxaldehyde with either sulfur[307] or selenium ylides[308] gives the appropriate oxirane.

F. Reactions with Nitrogen Nucleophiles

a. OXIMES

Heating thiophene aldoximes with acetic anhydride,[309,310] or heating their toluene-*p*-sulfonic acid salt[311] alone, gives the corresponding nitrile in high yield. Thiophene-2-carboxaldehyde is converted into the nitrile in a one-flask reaction, by way of the oxime, by treating it with pyridine hydrochloride and nitroethane (88% yield),[312] or with hydroxylamine hydrochloride and pyridine in boiling toluene (78%),[313] or by treating the oxime *in situ* with a carbodi imide in the presence of Cu^{2+}–Et_3N (93%).[314]

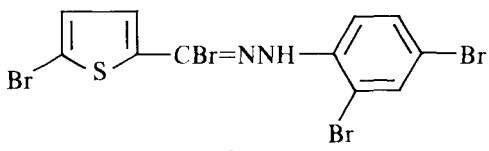
Thiophene-2-carboxaldoxime is reduced to 2-ThCH_2NH_2 (62%) by Al–Hg in methanol.[315] Reduction with Raney nickel or Raney cobalt additionally removes the sulfur atom and provides a primary aliphatic amine.[315] When 2-ThCH=NOH is treated with chlorine, substitution takes place at the 5-position in the ring rather than in the side-chain; however, with ethereal nitrosyl chloride, 2-ThCCl=NOH is formed. This reacts as the nitrile oxide in the presence of NEt_3 and can undergo 1,3-dipolar cycloaddition reactions.[316]

The IR spectra of some thiophene aldoximes have been recorded.[317] The higher melting thiophene-2-carboxaldoxime appears to be the *anti*-isomer because it shows a single absorption band at 4868 cm^{-1} in the near IR; *syn*-oximes show two bands in this region.[318] The composition of a mixture of *syn* and *anti* 2-ThCH=NOH can be determined polarographically.[319,320] The ^1H NMR spectra of some thiophene aldoximes have been determined;[321,322] long-range coupling between the side-chain proton and the ring protons has been observed.[322] That 2-ThCH=NOH exists predominantly in the *anti* form has been shown unambiguously by measuring the large germinal ^{15}N–H coupling in the NMR spectrum of the ^{15}N-enriched molecule.[323]

Anti-thiophene-2-carboxaldoxime forms complexes with many metal ions[324] and has been used for the determination of palladium(II),[325,326] rhodium(III),[327] and ruthenium(III).[328]

b. SUBSTITUTED HYDRAZONES AND RELATED DERIVATIVES

The mechanism for the formation of the phenylhydrazone of 2-ThCHO has been studied in detail.[329,330] Bromination of 2-ThCHO phenylhydrazone in acetic acid gives the tetrabromo compound (**26**) (65%),[331] nitration with an alkyl nitrate in liquid ammonia in the presence of potassamide gives 2-Th$C(NO_2)$=NNHPh



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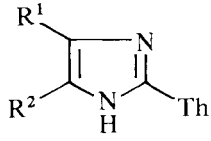

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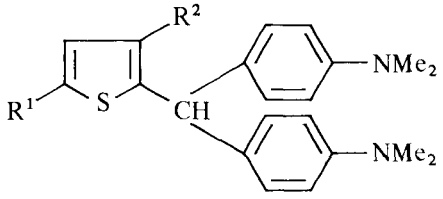

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(83%);[332] treatment with tetracyanoethene in DMF causes substitution in the benzenoid ring to give the tricyanovinyl product 2-ThCH=NNHC$_6$H$_4$[C(CN)=C(CN)$_2$]-*p*;[333] oxidation with peroxyphthalic acid gives the azoxy compound 2-ThCH$_2$NO=NPh.[334] Treatment of the arylhydrazone 2-ThCH=NNHAr with sodamide in refluxing xylene gives the amidine 2-ThC(NH$_2$)=NAr.[335,336]

Numerous thiosemicarbazones have been prepared in connection with the study of tuberculostatic compounds (see References 10, 11, 16, 104). The structure of 2-ThCHO thiosemicarbazone has been determined by X-ray crystallography.[337] Thiophene-2-carboxaldehyde forms substituted hydrazones with dimethylhydrazine,[338,339] (2-benzothiazolyl)hydrazine (the two geometrical isomers may be separated,[340] triaminoguanidine nitrate,[341] ArCONHNH$_2$,[342] RNHCSNHNH$_2$,[342,343] *o*-ClC$_6$H$_4$NHCOCH$_2$CONHNH$_2$,[344] *p*-EtOC$_6$H$_4$NHCOCONHNH$_2$,[345] and 4-amino-1,2,4-triazole.[346] Thermolysis of the last compound gives 1,2,4-triazole and thiophene-2-carbonitrile (70%).[346]

Heating the sodium salt of a thiophene aldehyde tosylhydrazone gives the diazo compound ThCHN$_2$, which, in the presence of an adjacent styryl group, will cyclize with retention of nitrogen.[278] Otherwise it loses nitrogen, and the resulting carbene dimerizes to give the cis and trans isomers of ThCH=CHTh as the major products; some ring-opened product is also formed.[347] 2-Thienyldiazomethane has also been formed by MnO_2 oxidation of the 2-carboxaldehyde hydrazone.[348]

Certain 2,4-dinitrophenylhydrazones may be prepared by means of an interesting substitution reaction in which a polymethylthiophene couples with the 2,4-dinitrobenzenediazonium ion at one of the *methyl groups*.[103]

Unsymmetrical azines, ThCH=NN=CHAr, may be obtained by reaction of a thiophene carboxaldehyde with the phosphazine Ph$_3$P=NN=CHAr.[349] Thermolysis of the symmetrical azines, ThCH=NN=CHTh, gives various products (depending on the conditions) including ThCH=CHTh,[350–352] ThCN,[350] and the imidazole **27**; R^1=R^2=Th.[352] Oxidation of a symmetrical azine with peroxyacetic acid (1 mole) gives the mono-*N*-oxide.[353]

c. REACTIONS WITH AMINES

Thiophene carboxaldehydes react readily with a wide range of primary aromatic and aliphatic amines to give the expected anil.[46,57,162,186,213,216,354-357] The rate constant for the reaction of 2-ThCHO with aniline in acetonitrile has been determined.[304] The anils from 2- or 3-ThCHO and a 2,2-dialkoxyethylamine [$H_2NCH_2CH(OR)_2$] can be cyclized in a Pomeranz-Fritsch reaction to the appropriate thienopyridine.[212,358] The anil from 2-aminobenzenethiol and 2-ThCHO has been used as a specific test reagent for zinc ions.[359] The ^{13}C NMR spectrum of the anil from 2-ThCHO and *n*-butylamine has been discussed.[360]

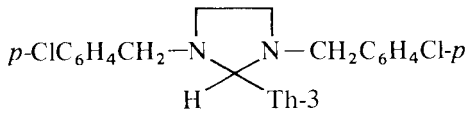
In the presence of $ZnCl_2$, *N,N*-dimethylaniline reacts with thiophene-2-carboxaldehydes (2 mole equivalent), to give the leuco base (**28**) corresponding to a thiophene analogue of malachite green.[361]

d. MISCELLANEOUS REACTIONS

In the presence of formic acid, thiophene-2-carboxaldehydes undergo the Leuckart reaction with DMF,[362] formamide,[315] or a secondary aliphatic amine (R_2NH),[363,364] to give 2-$ThCH_2NMe_2$, 2-$ThCH_2NH_2$, or 2-$ThCH_2NR_2$, respectively.

With ammonium chloride and potassium cyanide, thiophene aldehydes give the α-aminonitrile, which can be hydrolyzed *in situ* to the α-amino acid $ThCH(NH_2)$-CO_2H (Strecker synthesis).[67,141,365-368] Thiophene-2-carboxaldehyde is converted into the carboxamide 2-$ThCONH_2$, either by the Willgerodt reaction (70%)[141] or by liquid-phase ammoxidation in the presence of nickel peroxide (87%);[369] it is converted into the 2-carbonitrile (2-ThCN) by vapor-phase ammoxidation over a Mo—Bi—Sb catalyst.[370] The bis amide 3-$ThCH(NHCOR)_2$ is formed by treatment of 3-ThCHO with $RCONH_2$—Ac_2O.[170]

Thiophene carboxaldehydes provide a source of heterocyclic compounds containing the >N—CTh—N< unit. Treatment of 2-ThCHO with a diketone, ArCOCOAr,



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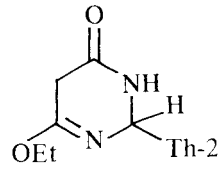

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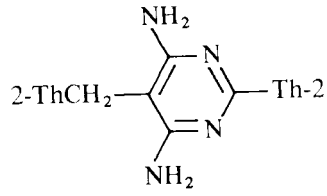

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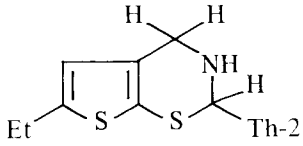

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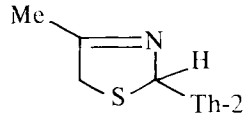

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in the presence of $AcONH_4$–$AcOH$[371] or with cyanogen–HCl[372] gives the imidazoles **27**; $R^1=R^2=Ar$ or $R^1=R^2=Cl$, respectively. 1,2-Bis-(*p*-chlorobenzylamino)ethane is a specific reagent for aldehydes; with 3-ThCHO it gives the imidazoline **29**.[373] Thiophene-2-carboxaldehyde reacts with the malondiimidate $[CH_2(EtOC{=}NH)_2]$[374] or the malondiamidine $[CH_2(H_2NC{=}NH)_2]$[375] to give the pyrimidine derivatives (**30**) or (**31**), respectively. The mechanism of the latter reaction is complex, but probably involves the initial formation of an aminal.

Thiophene-2-carboxaldehyde reacts with the hydrochloride salt of 3-(aminomethyl)-5-ethylthiophene-2-thiol to give the thienothiazine derivative (**32**),[376] or with a mixture of ammonia and an α-mercaptoketone to give a Δ^3-thiazoline [e.g., **33** (from mercaptoacetone)].[377]

G. Reactions with Oxygen or Sulfur Nucleophiles

a. ACETALS: PREPARATION

Dimethyl and diethyl acetals are most commonly obtained by treatment of the aldehyde with the appropriate trialkyl orthoformate in the corresponding alcohol in the presence of a trace of hydrochloric acid.[106,107,378,379] Ammonium nitrate[380] or one of the lanthanoid chlorides[381] is also an effective catalyst for this reaction. Acetals have also been obtained by use of the system $Si(OR)_4$–ROH–H_3PO_4.[111,382] The anodic oxidation of 2-thienylmethanol in methanolic sulfuric acid gives 2-$ThCH(OMe)_2$ as the main product.[383]

Cyclic acetals (1,3-dioxolanes) are invariably formed from the aldehyde and ethane-1,2-diol in the presence of toluene-*p*-sulfonic acid.[87,109]

The boiling points of the known acetals of thiophene and alkylthiophene carboxaldehydes are given in Tables 1 and 2.

b. ACETALS: REACTIONS

The use of acetals as blocking groups to enable other substituents to be introduced at various points in the thiophene ring has been reviewed.[384] The acetals of thiophene-2- and 3-carboxaldehydes are lithiated by butyllithium in the 5- and 2-positions respectively. Reaction with an appropriate reagent (in brackets) and subsequent hydrolysis gives the following substituted aldehydes: 2-CHO,5-I (I_2[385] or $MeC{\equiv}CI$[111]); 2-CHO, 5-Br ($MeC{\equiv}CBr$[111]); 2,5-diCHO (DMF[386]); 2-CHO, 5-CO_2H (CO_2[387]); 2-CHO, 5-$SiMe_3$ (Me_3SiCl[380]); 2-CHO,5-COEt ($(EtCO)_2O$[379]); 2-CHO,5-CH_2OMe ($MeOCH_2Cl$[388]); 3-CHO,2-I (I_2[385,389,390]); 3-CHO,2-Br (Br_2[391]); 2,3-diCHO (DMF,[110,392]); 3-CHO,2-CO_2H (CO_2[109]); 3-CHO,2-COPh (PhCN[393]);

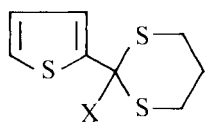
3-CHO,2-SEt (Et_2S_2[394]); 3-CHO,2-SCH_2CO_2Me [(a) S, (b) $ClCH_2CO_2Me$[378]]; 3-CHO,2-SeMe,5-Me [(a) Se, (b) MeI,[41]]; 3-CHO,2-$SeCH_2CO_2Et$ [(a) Se, (b) $BrCH_2CO_2Et$[395]]; 3-CHO,2-$B(OH)_2$[butyl borate[396]]; 3-CHO,2-TeR [(a) Te, (b) RX[397]]; 3-CHO,2-$CMe(OH)CH(OMe)_2$ (methylglyoxal dimethyl acetal[398]). The last compound has been converted by means of a four-stage synthesis into 7-methylthieno[3,2-*c*]pyridine.[398]

The diethyl acetal of 2-ThCHO reacts with ethyl vinyl ether in the presence of $ZnCl_2$, to give 2-$ThCH(OEt)CH_2CH(OEt)_2$ (which on hydrolysis gives 2-ThCH=CHCHO),[111] and with PhC≡CH–$ZnCl_2$–DMF, to give 2-$ThCH(OEt)C{\equiv}CPh$.[382] The acetal 2-$ThCH(OR)_2$ condenses with acetophenone or with a substituted benzyl methyl ketone in the presence of triphenylmethyl perchlorate to give a pyrylium[399] or a 2-benzopyrylium salt[400] respectively.

When a thiophene aldehyde acetal undergoes hydrodesulfurization with Raney nickel, the acetal function is retained,[87,107] thus enabling long-chain aliphatic aldehydes to be obtained from suitably substituted thiophene precursors.[87]

c. THIOACETALS

2-(2-Thienyl)-1,3-dithiane (**34**; X = H) is formed by reaction of 2-ThCHO with propane-1,3-dithiol-HCl.[401] Surprisingly, only two reactions have been noted in which this derivative is used as a means of reversing the polarity of the aldehydic carbon atom. Its lithio derivative (**34**; X = Li) undergoes regiospecific 1,4-addition to various $\alpha\beta$-unsaturated ketones[401] and reacts with nitrile oxides (ArCN→O) to give the oximes (**35**).[402] The last are hydrolyzed to the diketones, 2-ThCOCOAr, by CF_3CO_2H-aq. HCHO.



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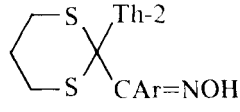

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d. OTHER REACTIONS WITH OXYGEN NUCLEOPHILES

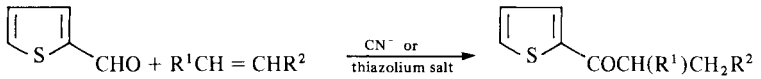
Thiophene 2-carboxaldehyde and some ring-substituted derivatives react in the same way as benzaldehyde toward hydroxide ion. The equilibrium constant has been measured spectrophotometrically.[403]

Thiophene carboxaldehydes form the thenylidene diacetates [$ThCH(OAc)_2$] by reaction with acetic anhydride in the presence of tin(II) chloride,[404,405] zinc chloride,[406] phosphoric acid, or methanesulfonic acid.[407] Nitration of the diacetates is considered in the section on substitution reactions.

H. Miscellaneous Addition Reactions

In the presence of cyanide ion (or a thiazolium salt) thiophene-2-carboxaldehydes behave as in the benzoin condensation by generating a nucleophilic species [e.g.,

TABLE 5. ADDITION REACTIONS OF THIOPHENE CARBOXALDEHYDES TO ACTIVATED DOUBLE BONDS



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Scheme 4

Starting Material (36)	Product (37)	Reference
αβ-Unsaturated ester	γ-Keto ester ($R^2 = CO_2Et$)	408
αβ-Unsaturated ketone	1,4-Diketone (R^2 = COR or COAr)	409
Substituted acrylonitrile	γ-Keto nitrile (R^2 = CN)	409, 410
Divinyl ketone [$(CH_2{=}CH)_2CO$]	1,4,7-Triketone (R^1 = H, $R^2 = COCH_2CH_2COTh\text{-}2$) (addn. of two mol. of 2-ThCHO)	411
A vinyldiketone ($MeCOCH_2CH_2COCH{=}CH_2$)	1,4,7-Triketone (R^1 = H, $R^2 = COCH_2CH_2COMe$)	412
Mannich base ($ArCOCH_2CH_2NMe_2$)	1,4-Diketone (R^1 = H, R^2 = COAr)	413
Mannich base ($Me_2C{=}CHCOCH_2CH_2\overset{+}{N}Me_3I^-$)	Unsaturated 1,4-diketone (R^1 = H, $R^2 = COCH{=}CMe_2$)	414
Benzylidene acetylacetone [$PhCH{=}C(COMe)_2$]	Triketone [2-ThCOCHPhCH$(COMe)_2$]	415
Arylidene alkyl acetoacetate [$ArCH{=}C(COMe)CO_2R$]	Diketone ester [2-ThCOCH(Ar)–CH(CO_2R)(COMe)]	415
Ethyl (3-benzoyl)acrylate ($PhCOCH{=}CHCO_2Et$)	Diketone ester ($R^1 = COPh$, $R^2 = CO_2Et$)	415
(3-Aroyl)acrylic acid (Na salt) ($ArCOCH{=}CHCO_2^-$)	1,4-Diketone (R^1 = H, R^2 = COAr)[a]	415
Divinyl sulfone [$(CH_2{=}CH)_2SO_2$]	1,4-Diketone (R^1 = H, $R^2 = COTh\text{-}2$)[b] and 1,4-disulfone [$(CH_2{=}CHSO_2CH_2)_2$]	416

[a] Formed by decarboxylation of the intermediate β-keto acid.

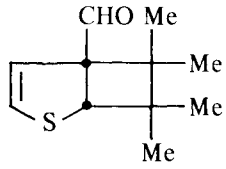
[b] Formed by base (B)-catalyzed fragmentation of intermediate sulfone ($2\text{-}ThCOCH_2SO_2CH{=}CH_2$), and subsequent reaction of the products $2\text{-}ThCOCH{=}CH_2$ and $CH_2{=}CHSO_2^-\overset{+}{B}H$ with 2-ThCHO and $(CH_2{=}CH)_2SO_2$, respectively.

2-ThC̄(OH)CN], which will then undergo Michael addition to activated double bonds, with the subsequent loss of CN^-, to give 1,4-diketones or related compounds (Scheme 4; Table 5).

The base-catalyzed condensation of thiophene-2-carboxaldehyde with dimethylphosphorus acid leads to the α-(2-thienyl)phosphinic acid [2-ThCH(OH)PO(OMe)$_2$].[417]

Thiophene-2-carboxaldehyde undergoes addition of ethoxyethyne (EtOC≡CH) in the presence of BF_3—Et_2O, then the product undergoes rearrangement and hydrolysis to give the αβ-unsaturated ester 2-ThCH=$CHCO_2Et$ (53%).[418]

In the photochemical reaction of thiophene-3-carboxaldehyde with 2,3-dimethylbut-2-ene, the initially formed oxetane undergoes [2 + 2] cycloreversion in the reverse sense to that by which it was formed, to give the alkene 3-ThCH=CMe_2 (46%). The [2 + 2] ring adduct **38** is also formed (9%) in this reaction.[419]



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I. Substitution Reactions of Thiophene and Alkylthiophene 2- and 3-Carboxaldehydes

a. NITRATION

The nitration of 2-thenylidene diacetate (or of thiophene-2-carboxaldehyde in acetic anhydride) with nitric acid has been extensively reported.[404,420–427] Earlier workers[422,426] isolated eutectic mixtures of the 4- and 5-nitro isomers from the reaction. It is now established that the 5-isomer predominates (>90%).[423,424,426] The same isomer is obtained from the nitration of thiophene-2-carboxaldehyde with copper(II) nitrate in acetic anhydride.[177] Nitration of thiophene-2-carboxaldehyde with nitric acid in sulfuric acid gives mainly the 4-nitro compound (ca. 70%),[421,428,429] together with some 5-nitro isomer and a mixture of the nitrodeformylation products 2,4- and 2,5-dinitrothiophene.[428,429] Nitration with KNO_3—H_2SO_4 or with nitronium tetrafluoroborate—H_2SO_4 again gives a mixture of the 4- and 5-nitro isomers, in which the proportion of the former increases as the concentration of the sulfuric acid is increased, owing to the participation of the protonated carbonyl group.[428,430] Nitration of the unprotonated aldehyde with *N*-nitropicolinium tetrafluoroborate in acetonitrile gives approximately equal amounts of the 4- and 5-nitro products.[428,430] In contrast, when the complex of 2-ThCHO with $HSbCl_6$ is nitrated with nitronium tetrafluoroborate, the 4-nitro compound is formed (94%) with the almost total exclusion of the 5-isomer.[431] Nitration of 2-ThCHO with fuming nitric acid in trifluoroacetic acid gives a mixture of the

3-, 4-, and 5-nitro isomers (ca. 1.5, 55, and 45%, respectively) and small amounts of 2-nitrothiophene, formed by means of the nitrodecarbonylation reaction.[432]

The nitration of thiophene-3-carboxaldehyde has been less extensively studied. With nitric acid–sulfuric acid, the 5-nitro isomer is the only product isolated;[32,433] with acetyl nitrate or copper(II) nitrate on the diacetate, a mixture of the 2- and 5-nitro compounds (3 : 2.3 respectively) is formed;[405] with nitric acid–trifluoracetic acid, all three nitroaldehydes are formed [5- (ca. 80%), 4- (ca. 8%), 2- (ca. 10%)].[432] SCF MO LCAO calculations by the CNDO/2 method confirm that electrophilic attack in 3-ThCHO is favored at the 5-position in both the free and complexed form. They also confirm the experimental observation that the 3-carboxaldehyde undergoes *ipso*-substitution much less readily than the 2-isomer.[434] Calculations of the localization energies for electrophilic attack in 2-ThCHO and 3-ThCHO by the ω-technique gives results that are not in good agreement with experimental observations, irrespective of which model (p or d) for thiophene is used.[435]

Polarography is often a useful method for the analysis of mixtures of isomers formed during the nitration of a thiophene carboxaldehyde,[421] but the method is not reliable when the *ipso*-substitution products, 2,4- and 2,5-dinitrothiophene, are present or when the analysis is carried out in alkaline solution.[428]

The nitration of a few alkylthiophene-2-carboxaldehydes has been reported. 5-Methylthiophene-2-carboxaldehyde substitutes entirely in the 4-position, whereas the analogous 5-cyclopropyl compound also gives some nitrodecarbonylated product (ca. 6%).[23] 2-Carboxaldehydes containing a 5-$(CH_2)_nCO_2Me$ side-chain ($n = 3$ or 4) are nitrated in the 4-position,[24,27]

b. HALOGENATION

The bromination of thiophene-2-carboxaldehyde[33,424,436] or its 4-methyl derivative[437] in chloroform solution gives the 5-bromo-2-carboxaldehyde, together with a small amount of the corresponding 2-carboxylic acid.[436] If, however, the bromination is carried out in the presence of an excess of aluminum chloride ("swamping effect"), either in the absence of a solvent or in chloroform, substitution is essentially confined to the 4-position;[42,438–440] any dibromination occurs in the 4,5-positions.[42,440] This is because the aldehydic carbonyl group is made even more electron attracting by complexation with $AlCl_3$. The electron density decreases more in the 5-position than in the 4-position, analogous to the p- and m-positions in benzene, leaving the latter the more prone to substitution. This reaction provides a most useful means for altering the orientation of substitution in thiophene derivatives.[384] Similar results are obtained with the $HSbCl_6$ complex.[438] In contrast to the bromination of furan-2-carboxaldehyde, no ring *chlorination* is observed when the thiophene analogue is treated with Br_2–$AlCl_3$.[441] Bromination of thiophene-2-carboxaldehyde in sulfuric acid in the presence of silver sulfate gives a mixture of the 4- and 5-bromo isomers and the 4,5-dibromo compound.[442] Bromination of 3-methylthiophene-2-carboxaldehyde in the presence of an excess of $AlCl_3$ gives a mixture of the 4-bromo (18%) and 4,5-dibromo compounds (59%).[112]

The bromination of thiophene-3-carboxaldehyde in chloroform solution unex-

pectedly yields the 2,5-dibromo compound;[391,443] in the presence of an excess of $AlCl_3$ it yields first the 5-bromo,[391] then the 4,5-dibromo compound.[444] With bromine (3 moles) in the presence of $AlCl_3$, the 2,4,5-tribromo compound (70%) is obtained.[444]

The chlorination of thiophene carboxaldehydes has been less thoroughly investigated than bromination. However, the substitution pattern seems to be similar in most cases: 2-ThCHO gives the 4-chloro compound in the presence of excess of $AlCl_3$;[445] dichlorination of 3-ThCHO under similar conditions gives mainly the 4,5-dichloro product.[444]

Thiophene-3-carboxaldehyde has been iodinated in the presence of iodic acid, to give the 5-iodo compound;[390] similar treatment of the 2,5-dimethyl-3-carboxaldehyde gives the 4-iodo compound.[112]

c. CHLOROMETHYLATION

The products from the chloromethylation of thiophene-2-carboxaldehyde depend markedly on the reagents and conditions employed. It seems well established that the use of chloromethyl methyl ether and aluminum chloride (2.2 moles) gives wholly the 4-chloromethyl compound;[446,447] reducing the amount of $AlCl_3$ to 0.9 mole gives mainly the 5-chloromethyl compound.[446] Use of bis(chloromethyl) ether with $AlCl_3$ (1.8 mole) in chloroform gives the 4-chloromethyl compound (63%).[448] A detailed study of the reaction has shown that the 4-, 5-, and 4,5-di-(chloromethyl) compounds can be formed in this reaction; which one predominates depends on the solvent used and on the ratio and order of mixing of the reactants.[42,446] The differences in behavior observed with chloromethyl methyl ether and bis(chloromethyl) ether have been assigned to the differing basicities of the two reagents.[446] A study of the chloromethylation of thiophene-2-carboxaldehyde with $(ClCH_2)_2O$ in 60–100% sulfuric acid has shown that, in keeping with the principles already discussed, increasing the acidity increases the electron-withdrawing capability of the carbonyl group and promotes the formation of the 4-CH_2Cl product.[449]

Chloromethylation of 2-ThCHO with trioxane–$ZnCl_2$–HCl gives mainly the 5-chloromethyl compound, together with smaller amounts of the 4-isomer and of the 4,5-bis(chloromethyl) compound;[450] under similar conditions, chloromethylation of 5-methylthiophene-2-carboxaldehyde takes place in the 4-position (79%).[451] With paraformaldehyde and hydrogen chloride in chloroform, thiophene-2-carboxaldehyde yields a mixture (1 : 1) of the 4- and 5-chloromethyl isomers.[447]

d. MEERWEIN ARYLATION

Thiophene-2-carboxaldehyde gives the 5-aryl derivative (<50%) by treatment with a diazonium salt in acetone in the presence of copper(II) chloride.[452]

4. Physical Properties of Thiophene-2- and 3-Carboxaldehydes

A. Conformational Studies

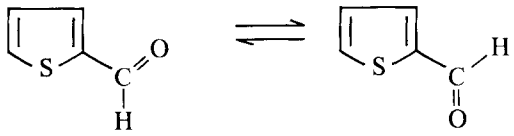
a. THIOPHENE-2-CARBOXALDEHYDE

The study of a possible equilibrium between the two rotational isomers O,S-*cis* and O,S-*trans* (Scheme 5) has attracted a seemingly disproportionate amount of attention. Ironically, much of this work was prompted by the appearance of multiple absorptions in the carbonyl region of the IR spectra of 2-ThCHO in solution. These are now known to be due to Fermi resonance (see the following section, "IR spectroscopy"), and not to the existence of a conformational equilibrium, as was originally thought.

Initially, the microwave spectrum of 2-ThCHO was interpreted as favoring the O,S-*trans* isomer in the gas phase,[453] but a subsequent reassignment of the spectrum indicated the predominance of the O,S-*cis* form.[454] All evidence now points to the existence of 2-ThCHO entirely in the O,S-*cis* form both in the gas phase and in solution. The conformation of 2-ThCHO has been studied by comparing experimental and calculated dipole moments[455–459] and by measurement of Kerr constants.[456,458] Ultrasonic relaxation in liquid 2-ThCHO was attributed to the perturbation of the equilibrium between the rotational isomers.[460] In an extension of this method, the kinetics of the isomerization, O,S-*trans*⇌O,S-*cis*, were later studied by the ultrasonic pulse technique, and the potential energy barrier was estimated as about 42 kJ/mole.[461]

However, the most reliable investigations of the conformational equilibrium are those involving NMR spectra. Useful information has been obtained from the ^{1}H NMR spectrum by examination of chemical shifts,[462] solvent effects,[462–464] stereospecific long-range coupling,[462,465,466] lanthanide shifts,[463] (including computer-simulated shifts[467]), nuclear Overhauser effect,[463–465] and variable temperature effects.[464] The ^{1}H NMR spectrum of 2-ThCHO in the nematic phase of a liquid crystalline solvent has shown that the molecule exists in an exclusively O,S-*cis* conformation which is planar, or nearly so.[468] ^{1}H NMR Spectra of the molecule partially orientated in anisotropic soap solutions have been compared with those obtained in liquid crystalline media.[469]

^{13}C NMR Spectra have been used less widely for studying conformational



O, S-*trans* O, S-*cis*

Scheme 5

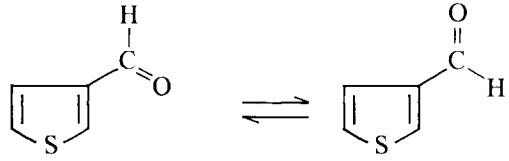
equilibrium. However, variable temperature studies have demonstrated the occurrence of rotational isomerism for 2-ThCHO, even though the O,S-*cis* form is the preferred conformer over a wide temperature range.[470] Long-range couplings in the proton-coupled ^{13}C NMR spectrum are not as useful for conformational assignments as the analogous ^{1}H NMR couplings.[471] For 2-carboxaldehydes, the barrier to internal rotation of the CHO group is related to the ^{13}C—H coupling constant of the carbon atom in the aldehyde group; this parameter gives a quantitative measure of conjugation along the C—CHO bond.[472]

The equilibrium (Scheme 5) has also been studied by ESR spectroscopy:[473,474] the radical ion seems to contain both conformers.[474]

Molecular orbital calculations of varying degrees of complexity confirm the greater stability of the O,S-*cis* conformer: CNDO/2 (with or without the sulfur 3d orbitals);[463] Pariser-Pople-Parr,[475,476] extended Hückel;[477,478] Dewar $\sigma\pi$,[478] and *ab initio*.[479] It is widely accepted that the greater stability of the O,S-*cis* conformer is due mainly to electrostatic interaction between the sulfur and oxygen atoms.[455,463,467,475,479] Moreover, the O,S-*trans* conformer will be destabilized by orbital interactions.[466,479] An electron-withdrawing group in the 5-position lowers the energy barrier between the two conformers of 2-ThCHO (e.g., 5-nitrothiophene-2-carboxaldehyde contains 40% of the O,S-*trans* conformer).[457,465] For the 2-carboxaldehyde, the stability of the O-*cis* conformation increases progressively in passing from furan to thiophene to selenophene.[465]

b. THIOPHENE-3-CARBOXALDEHYDE

The conformational preference of the 3-aldehyde is not so well defined as that of its 2-isomer: electrostatic interactions favor the O,S-*cis* form **39** (by 2 kJ/mole), whereas orbital interactions favor the O,S-*trans* form **40**.[479] CNDO/2 MO Calculations show that the trans conformer **40**,[434] or a nonplanar form of it,[480] should be



39 **40**

the more stable. Experimental results are generally in agreement with this prediction. Examination of stereospecific long-range ^{1}H NMR coupling constants,[481,482] and other NMR data[480] shows that, in solution at room temperature, 3-ThCHO contains a mixture of the two conformers **39** and **40** in which the latter predominates (80%). Simulated lanthanide shifts likewise indicate a preference for the O,S-*trans* form.[483] The equilibrium has also been studied by means of dipole moments[456,459] and the Kerr effect,[456] but the results are generally less satisfactory than those obtained from NMR data.

B. Spectroscopy

a. ULTRAVIOLET

There have been no systematic studies of the UV spectra of thiophene carboxaldehydes: the few spectra that have been recorded have been compared with those of thiophenes containing a range of other ring substituents. The smaller bathochromic shift of the thiophene chromophore in the 3-carboxaldehyde compared with that of the 2-isomer provides evidence that the 2-position in thiophene affords more effective conjugation than the 3-position.[484-486]

b. INFRARED

The IR spectrum of thiophene-2-carboxaldehyde has been examined in detail.[317, 487,488] The C=O absorption band for 2-ThCHO occurs at a lower frequency than that of the 3-isomer because of the greater single bond character of the C=O bond in the former case.[489] This follows from the increased conjugation of the substituent in the 2-position over that in the 3-position, as is evident from the classical resonance structures that can be drawn for the two aldehydes (cf. the UV spectra just mentioned).

Much of the interest in the IR spectra of thiophene aldehydes centers around the interpretation of the multiple absorptions shown by the 2-carboxaldehyde in the carbonyl region of the solution spectrum. The twin carbonyl bands shown in the Raman spectrum of 2-ThCHO were thought originally to be due to intermolecular association.[490] Later, the doublet in the IR spectrum was discussed in terms of the existence of two conformers (Section II.4.A under "Conformational Studies") (cf. Reference 491). Around the same time it was suggested that it may be due to the operation of Fermi resonance.[492] Subsequent studies on the spectra of 2-ThCHO and its deuterated, ring brominated, and ^{18}O derivatives at various temperatures and in several solvents have confirmed this belief.[84,493-495] It is suggested that the temperature sensitivity of the separation of the lines in the doublet can be used as a criterion to differentiate between Fermi resonance and rotational isomerism.[495]

The observed splitting of the carbonyl band in the spectrum of 3-ThCHO in $C_2H_2Cl_4$ solution is likewise assigned to the operation of Fermi resonance, rather than to the presence of rotational isomers.[496]

c. NUCLEAR MAGNETIC RESONANCE

The ^1H NMR spectra of 2-ThCHO[322,497-500] and 3-ThCHO[322,498] have been discussed in terms of simple resonance theory[498,501] and analyzed in more detail.[499,500] Long-range coupling is observed between H-5 and —CHO in 2- and 3-carboxaldehydes ($J = 1.05-1.40$ and $<0.4-0.8$ Hz, respectively).[322,497,502,503] Proton-proton coupling constants for 2-ThCHO and 3-ThCHO have been calculated with some degree of success by the perturbed SCF INDO method.[504]

Details of the ^{13}C NMR spectra of the 2-[499,505-507] and 3-carboxaldehydes[505] have been published. The ^{13}C NMR shifts of monosubstituted thiophenes (including 2- and 3-CHO) have been correlated with reactivity parameters.[508] The ^{13}C NMR

spectrum of the 2-carboxaldehyde has been compared with the spectra of its furan, selenophene, and tellurophene analogues.[499] A rigorous theoretical treatment of lanthanide-induced ^{1}H and ^{13}C shifts in the spectra of 2-ThCHO has shown that they are primarily diamagnetic (complexation) shifts and not contact shifts, as had been assumed previously.[509]

The protonation of thiophene-2-carboxaldehyde has been studied by ^{1}H NMR spectroscopy;[431,510] in SO_2—SbF_5—HSO_3F at $-80°C$ the aldehyde is protonated on its oxygen atom to give the O,S-*cis* conformer.[510] Complex formation between $AlCl_3$ or $AlBr_3$ and 2-ThCHO has been examined by ^{1}H[431] and ^{13}C NMR spectroscopy.[78,511] Complexation of a carbonyl substituent with $AlBr_3$ or $HSbCl_6$ does not alter its normal order of electron-withdrawing ability (i.e., CHO > COMe > CO_2Me).[431]

The role of NMR spectroscopy in investigating the conformation of thiophene aldehydes has already been discussed (Section II.4.A under "Conformational Studies").

d. OTHER SPECTRA

The mass spectrum of thiophene-2-carboxaldehyde has been obtained.[512]

The ESR spectra of 2-ThCHO[473,474] and 3-ThCHO[474] have been determined; the latter is poorly resolved, probably because increased localization of the unpaired electron on the substituent leads to lower stability of the radical. Hyperfine splitting constants, calculated by the INDO SCF-MO method, are not in good agreement with those obtained experimentally.[513]

The vertical ionization energies of the two highest MOs of the 2-carboxaldehyde have been obtained from its photoelectron spectrum.[514]

C. Miscellaneous Physical Properties

Various physical parameters for thiophene-2-carboxaldehyde and its *O*-protonated form have been calculated by the CNDO/2 method.[515]

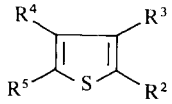
Molecular ionization potentials (by electron impact),[516] gas-liquid chromatography data,[517] densities, refractive indices, and surface tensions[518] have been tabulated for a range of thiophene aldehydes (and ketones).

5. Thiophene Di-, Tri-, and Tetra-Carboxaldehydes

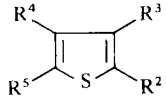
A. Preparation

A monocarboxaldehyde may be protected as an acetal, which can then be treated successively with butyllithium and DMF, to give an aldehydoacetal, hydrolysis of which yields the dialdehyde. By this means 2-ThCHO has been converted into thiophene-2,5-dicarboxaldehyde[111,386] and 3-ThCHO into the 2,3-dicarboxal-

TABLE 6. THIOPHENE DI-, TRI-, AND TETRA-CARBOXALDEHYDES



R^2	R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Method[a]
CHO	H	H	CHO	116–118	36	A
				114–115	90	B
				117, 118–119	0.8, 8.5	E
				115–116	83	F
CHO	CHO	H	H	78, 78.9	85, 88	B
				78	20	D
H	CHO	CHO	H	81	59	D
				78–80	23	G
CHO	H	CHO	H	81	20	D
				80–81	85	G
				78.8–79.5	92	C
				80–81	51	E
Me	CHO	CHO	Me	92–93	81	H
				95–96	32	D
				95.5–96.5	57	I
CHO	H	CHO	Me	106–107	57	E
CHO	Me	Me	CHO	179–181	54	A
CHO	Br	H	CHO	118, 116	35, 18	D
CHO	CHO	Br	H	112	68	C
				117	20	D
CHO	CHO	H	Br	83	–	C
Br	CHO	CHO	Br	149–150	63	D
CHO	H	CHO	Cl	110–111	86	B
Cl	CHO	CHO	Cl	89–90	25, 92	D, I
CHO	CHO	Cl	Cl	96	18	I
CHO	I	H	CHO	168	11	D
CHO	OBu^t	H	CHO	75	60	L
CHO	CHO	OBu^t	H	b.p. 125/1 mm	60	D
CHO	OMe	OMe	CHO	122	87, 43	D, G
CHO	OBu^t	OBu^t	CHO	109	30	L
CHO	OH	OH	CHO	150	40	J
CHO	OH	H	CHO	119	50	J
SMe	CHO	CHO	SMe	134–135	60	A
				135.5–136.5	low	I
SEt	CHO	CHO	SEt	73.5–74	60	I
SO_2Bu^t	CHO	H	CHO	151–152	59	K
CHO	SO_2Bu^t	H	CHO	148.5–149	36	K



References	Melting Point of Derivatives (°C)[b] (Ref.)[c]	Boiling Point of Acetals (°C/mm) (Ref.)[cd]
539	mono Ox. 184–185 (187); Ox. 201 (387), 209, 240 (534); mono-2,4-DNP 277 (534);	mono-DiEt 152–154/11 (Ox. m.p. 95–96) (386); DiEt 115–116/2 (111);
111, 386	2,4-DNP 295 (534); Semi. 270 (534), 285 (539); PH 231 (534)	mono-DiMe 143–148/11 (111); mono-Cyclic 134–138/2 (524)
531, 532		
450		
110, 392	3-mono Ox. 117 (544); Ox 216 (514); 2,4-DNP 312 (110)	3-mono-Cyclic 120–121/0.1 (392); 2-mono-DiEt 95/0.2 (526);
529	Semi. 290 (529)	3-mono-DiEt 123/4 (2,4-DNP m.p. 179) (110)
529	mono-2,4-DNP 310	
541		
529		
110	Ox. 222; 2,4-DNP 290	
42		
533		
540	2,4-DNP 285	
528		
536		
450		
537		
529, 519		DiEt 142/05 (519)
521		2-mono-DiEt 130/0.5 (2,4-DNP m.p. 151); DiEt 102/1 (521)
529		
521		3-mono-DiEt 120–122/1; DiEt 133–135/1
530		
543		
530	Ox. 175–176, 2,4-DNP 299	
583	Ox. 204	
390		
522		
522		
527	2,4-DNP 260	
522		
522		
522		
538		
535		
538		
523		
523		

TABLE 6. *(Continued)*

R^2	R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Method[a]
CHO	CHO	CHO	H	119	50	C
CHO	CHO	H	CHO	82	–	C
CHO	CHO	CHO	CHO	92	–	B

[a] A = oxidation of di-CH_2OH. B = BuLi/DMF on acetal. C = BuLi/DMF on bromoacetal. D = BuLi/DMF on a mono- or dibromo or diiodo compound. E = Sommelet reaction. F = Kröhnke reaction. G = reduction of dinitrile. H = oxidation of di-CH_2OEt. I = oxidation of di-CH_2Cl or di-CH_2Br. J = dealkylation of *t*-butyl ether. K = BuLi/DMF on $-SO_2Bu^t$. L = BuLi/DMF on the appropriate *t*-butoxythiophene.

[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi = semicarbazone;

dehyde.[110,392] Thiophene-2,3,4-tri- and 2,3,4,5-tetra-carboxaldehydes have been obtained likewise from the 3,4-di- and 2,3,4-tri-acetals respectively.[519,521]

Two formyl groups may be introduced successively in a one-flask procedure by reaction of a suitable thiophene derivative with BuLi-DMF.[522,523] There is no need specifically to protect the first formyl group since the reaction intermediate itself, namely, $ThCH(OLi)NMe_2$, serves this purpose.

Low temperature halogen–metal exchange with butyllithium followed by treatment of the resulting thienyllithium derivative with DMF affords a very versatile route to di- and tri-aldehydes. In its simplest form, the halogen atom of a halothiophene-2- or 3-carboxaldehyde acetal may be replaced by a formyl group,[519,521,524–526] or a dihalogeno compound may be converted directly into the corresponding diformyl compound.[527–529]

Alternatively, by appropriate regulation of reaction conditions (particularly temperature), a mono- or di-halogenothiophene may be converted into a range of dialdehydes by selective halogen–metal exchange or metalation in an unsubstituted position, followed in each case by formylation. The following guidelines generally apply: (1) a 2-halo substituent is replaced more readily than a 3-substituent of the same type;[519,521,529] (2) a 2-unsubstituted 3-bromothiophene gives the 2,3-dialdehyde by a combination of halogen–metal exchange and metalation;[522,529] (3) an iodo substituent is replaced more readily than a bromo or chloro substituent.[530]

The Sommelet reaction on a bis(chloromethyl)thiophene gives only a low yield of dialdehyde (<10%);[450,531,532] the reaction is more successful when applied to a mono(chloromethyl)thiophene carboxaldehyde.[533] The conversion of a bis(chloromethyl)thiophene into the dialdehyde is more readily achieved by the Kröhnke procedure (*p*-nitroso-*N*,*N*-dimethylaniline on the bis(pyridinium) salt, followed by acidic hydrolysis of the resulting nitrone.[450,534] Alternatively, the bis(chloromethyl) compound may be oxidized directly to the dicarboxaldehyde by using DMSO–

References	Melting Point of Derivatives (°C)[b] (Ref.)[c]	Boiling Point of Acetals (°C/mm) (Ref.)[cd]
519		2,3-bis-DiEt 141–143/1.5 (521); 3,4-bis-DiEt 125/0.5 (519); 2,3,4-tris-DiEt 158/0.5 (521)
519		2,3-bis-DiEt 149–151/1.5 (521)
521	Tetra ox. 250 (520)	3,4,5-tris-DiEt 168–170/0.5 (m.p. 32)

Ox = oxine (often a mixture of isomers); PH = phenylhydrazone; NPH = *p*-nitrophenylhydrazone. Melting points refer to the bis derivative unless the prefix "mono" is shown.

[c] If a reference is not given, the melting point or boiling point of the derivative is quoted in the reference to the preparation.

[d] DiEt = diethyl acetal; DiMe = dimethyl acetal; cyclic = dioxolane. Boiling points refer to the bis derivative unless the prefix "mono" is shown.

$NaHCO_3$[535] or 2-nitropropane—KI—NaOEt.[536] 3,4-Bis(bromomethyl)-2,5-dichlorothiophene is converted into the corresponding 3,4-dicarboxaldehyde (92%) by treatment with silver trifluoroacetate in acetonitrile.[530] Bis(hydroxymethyl)thiophenes are oxidized by manganese dioxide[537–539] or chromic acid[539] to the dialdehydes; their bis(ethyl ethers) are similarly oxidized in high yield by N_2O_4 in chloroform at −30°C.[540]

Several dinitriles have been reduced successfully to the dialdehyde by use of diisobutylaluminum hydride.[110,385,527,541,542] (See Table 6.)

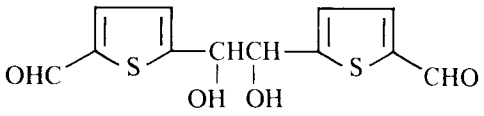
B. Reactions

a. GENERAL

Dialdehydes are oxidized (silver oxide)[386,450] and reduced ($LiAlH_4$)[392,530] normally. Reduction of thiophene-2,5-dicarboxaldehyde with zinc and acetic acid gives the meso form of the 1,2-diol (**41**); electrochemical reduction at a mercury electrode at pH 1 to 3 gives a mixture of the meso and (±) isomers of **41** (7:3).[545]

Dialdehydes give the bis(secondary alcohol) with an acetylenic Grignard reagent (2 moles).[546]

Dialdehydes undergo aldol and Knoevenagel-type reactions with a variety of ketones[547,548] and "active methylene" compounds respectively.[450,531,548] When the

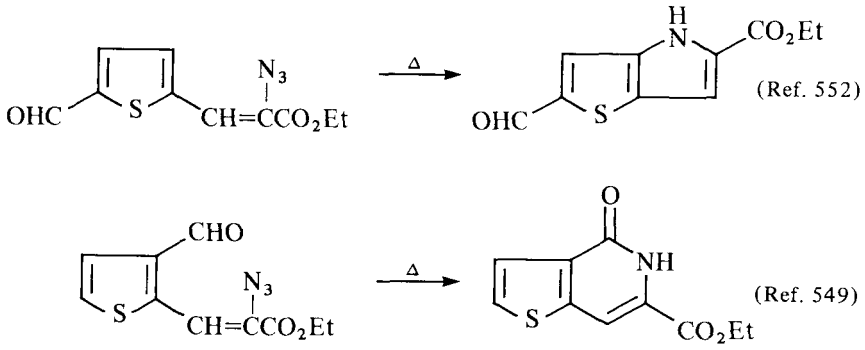


41

two formyl groups are adjacent, cyclization reactions may take place (see section b). Dialdehydes condense with ethyl azidoacetate (1 or 2 moles) in the presence of base; the monocondensation product is best obtained from the monoacetal.[549–552] The products undergo thermolytic cyclization; typical examples are shown in Scheme 6.

Dialdehydes undergo the conventional Wittig reaction at either one or both of the formyl groups.[524,553] They form anils with amines[450,534,554] and undergo the Leuckart reaction with formic acid and a secondary aliphatic amine.[555] The 3-(monoxime) of thiophene-2,3-dicarboxaldehyde rearranges to 2-formylthiophene-3-carboxamide in the presence of sodium carbonate;[544] monoximes in which the free CHO group is protected as an acetal give the carbonitrile when treated with PCl_5.[385,556]

In an interesting homolytic substitution reaction, thiophene-2,5-dicarboxaldehyde reacts with the 1-adamantyl radical to give three products: the 3-(1-adamantyl)-2,5-dicarboxaldehyde (10%), formed by normal ring substitution; 5-(1-adamantyl)thiophene-2-carboxaldehyde (19%), formed by adamantyl-deformylation; and 5-(1-adamantyl)thiophene-2,4-dicarboxaldehyde (56%) formed

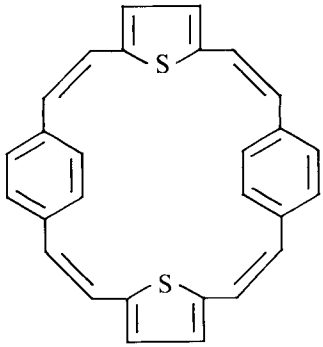


Scheme 6

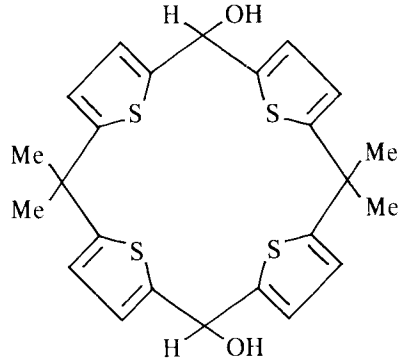
by *ipso* attack in the 5-position, followed by rearrangement (rather than displacement) of the formyl group.[557] The last product is also obtained by homolytic substitution of thiophene-2,4-dicarboxaldehyde with the 1-adamantyl radical.

b. CYCLIZATION REACTIONS

By condensing thiophene-2,5-dicarboxaldehyde with α,ω-bifunctional compounds, $X(-\overset{|}{C}-)_nX$, macrocyclic rings have been formed in low yield. For example, macrocyclic Schiff's bases ($X = NH_2$),[558] a 21-thiaporphin (X = a 2-carboxypyrrole),[559] and annulene analogues (e.g., **42**) ($X = CH_2\overset{+}{P}Ph_3B\bar{r}$) have been obtained.[560,561] In an alternative approach to macrocyclic compounds, the dialdehyde **5**; $R^1 = R^2 = Me$; $R^3 = R^4 = CHO$ has been condensed with the dilithio derivative **5**; $R^1 = R^2 = Me$;



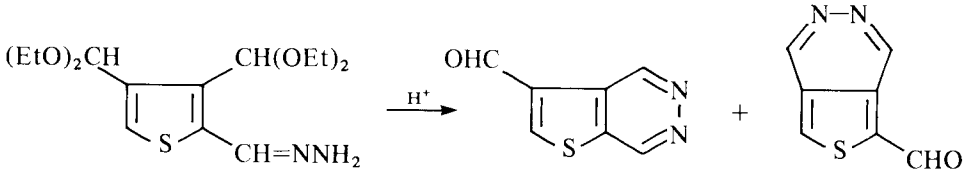
42



43

$R^1 = R^4$ = Li under conditions of high dilution, to give the dihydroxytetramethylthiaporphyrinogen **43** (4%).[93,94]

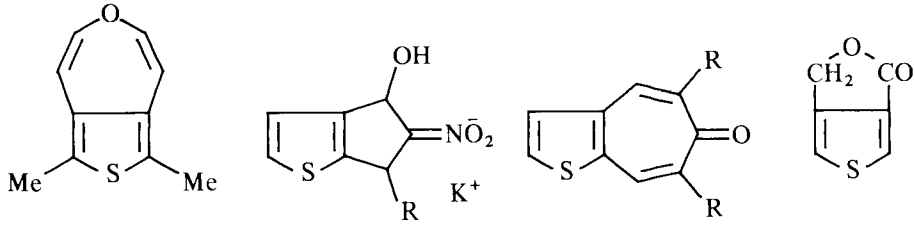
Thiophenes containing adjacent formyl groups undergo a range of cyclization reactions. With hydrazine, a thienopyridazine is readily obtained.[536,562] Interestingly, when the hydrazone **44** is cyclized by acidic hydrolysis of the acetal functions, a



44 45 46

mixture of the expected thieno[2,3-*d*]pyridazine (**45**) and the rearranged product (**46**) is obtained. Attempts to prepare the cyclized product **46** from the appropriate isomer of hydrazone (**44**) gave the same mixture of products.[562]

Several bi- and polycyclic systems[540,563–565] have been made in low yield by condensation of a 2,3- (or 3,4-) dicarboxaldehyde in a Wittig reaction with an α,ω-bis-ylide (e.g., **47** from 2,5-dimethylthiophene-3,4-dicarboxaldehyde and $Ph_3P{=}CHOCH{=}PPh_3$).[540]



47 48 49 50

TABLE 7. HALOTHIOPHENE CARBOXALDEHYDES

Substituents on Thiophene Ring			Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)
R^3	R^4	R^5			
Chlorothiophene-2-carboxaldehydes					
Cl	H	H	100–101/14		36
H	Cl	H	45–47/0.025		74
H	H	Cl	100–105/18		45
			91–92/13		59
			52–53/0.5		43
			85–88/5–6		33
Cl	Cl	H		61–62	56
H	Cl	Cl		56	80
Cl	H	Cl		35–36	83
				58	50
Cl	Cl	Cl		83	70
Chlorothiophene-3-carboxaldehydes					
R^2	R^4	R^5			
Cl	H	H	95–97/1	25	71
			60–62/0.1		92
			88–90/10		33
H	Cl	H	115–117/15		73
H	H	Cl	100–102/16		70
Cl	H	Cl	105–106/15	24–24.5	35
H	Cl	Cl		59–60	44
Cl	Cl	Cl		58	9
Bromothiophene-2-carboxaldehydes					
R^3	R^4	R^5			
Br	H	H	122–123/18	24–25	86, 70
			91–92/3		69, 85
H	Br	H	114–115/11	44–45, 46.5–47	55, 75
			125–132/20	46.5–47, 43–44.5	91, 68
H	H	Br	148–150/40		66, 57
			81–84/4		32
			114–115/14		70
			112–113/13		
			121.5–122.5/19		79
H	Br	Br		82–82.5	1.4
Br	Br	H		98	57
Br	H	Br		48	
Br	H	Me		30–32	65
Me	Br	H		73.5–74.5	18
Me	H	Br	114–116/4		
Me	Br	Br		124–125	59

Chlorothiophene-2-carboxaldehydes		
Method[a]	Reference	Melting Point of Derivatives (°C)[b] (Ref.)[c]
A	577	Semi. 214–216, Thio. 213–214
E	445	
A	578	Ox. 140
B	18	PH 109–110
A	17	
C	104	Thio. 164–165
D	577	Ox. 151–153; Semi. 257–258; Thio. 226–228
D	577	
D	577	Ox. 144–146; Semi. 244–246; Thio. 238–240; NPH 264–266
F	579	Ox. 153; Semi. 227; Thio. 198; PH 140; 2,4-DNP 272
F	580	Ox. 175–176; 2,4-DNP 208–210; DiMe 41–42; DiEt b.p. 124–126/2–3 mm; Cyclic b.p. 146/2–3 mm
Chlorothiophene-3-carboxaldehydes		
G	543	DiMe b.p. 50–52/0.1 mm
H	40	Thio. 196–198 (104)
I	581	
H	582	Cyclic b.p. 142–143/15 mm
H	582	Cyclic b.p. 137–140/16 mm
D	577	Ox. 129–131; Semi. 257–258; Thio. 232–233 (104)
E	444	Ox. 146.5–147.5
F	583	Semi. 237
Bromothiophene-2-carboxaldehydes		
H	584, 42, 32	Semi. 195–196 (32), 208.5–209.5 (42); Ox. 145–146 (42),
A	67, 593	159 (391); Thio. 246 (391); DiEt b.p. 115–117/5 mm (585); Cyclic b.p. 152–155/10 mm (586)
H	32, 42	Semi. 206–207 (32), 232–232.5 (42); Ox. 156.5–157.5 (42), 174 (391); Thio. 216 (391); DiEt b.p. 111–113/5 mm (585); Cyclic b.p. 144–146/10 mm (586)
E	42, 439	
E	424, 436	Semi. 217–218 (436); 200–201 (111), 202.5–203.5 (42);
C	104	Ox. 138–139 (42), 149 (587), 152–154 (391); Thio.
B	18	182–184 (104); PH 112–113 (18); DiEt b.p. 124–128/9 (111), 102–104/11 mm (79); Cyclic b.p. 138–139/10 mm (586)
J	111	
H	42	
E	42	Ox. 164–165
H	521	2,4-DNP 242; DiEt b.p. 135/1 mm
H	519	
H	582	Cyclic b.p. 162–164/10 mm
E	112	Semi. 246.5–247.5
E	437	Ox. 139
E	112	Semi. 289–290

TABLE 7. *(Continued)*

Substituents on Thiophene Ring					
R^2	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)
Bromothiothiophene-3-carboxaldehydes					
Br	H	H	108–110/15	34	23
			98–102/11		60
				34–35	25
H	Br	H	118–120/13		47, 35
H	H	Br	114–116/17–18		59
H	Br	Br		89.5–90.5	43
Br	H	Br		47–49	62
				45–46	28
Br	Br	Br		100–102	70
Iodothiophene-2-carboxaldehydes					
R^3	R^4	R^5			
I	H	H		81–82	55, 60
				79–80	25
				79–80	67
H	I	H	140–144/14	76	36
H	H	I		49	34
				51–52	37
				54	
				55.5–56	18
I	H	I		104	27
I	Me	Me		107.5–109	89
Iodothiophene-3-carboxaldehydes					
R^2	R^4	R^5			
I	H	H		69–70	14, 68
				68–70	29
H	I	H		73	22
				71.5–72.5	30
				71.5–72.5	71
H	H	I		74	26
Me	I	Me		59–60	83
Fluorothiophene-2-carboxaldehydes					
R^3	R^4	R^5			
F	H	H	73–75/12		69
H	F	H		36–37	59
H	H	F	60–61/13		63
			66–67/15		69
			66–67/15		56

Bromothiophene-3-carboxaldehydes		
Method[a]	Reference	Melting Point of Derivatives (°C)[b] (Ref.)[c]
K	391	Ox. 86
I	581	Thio. 192–194 (104), 235 (391)
C	32	
H	32, 391	Semi. 184–185; Thio. 221; Ox. 104 Cyclic b.p. 147–149/10 mm (586); DiEt b.p. 119–120/8 mm (588)
E	391	Ox. 91; Thio. 180
E	444	Cyclic b.p. 179–182/13 mm
C	269	2,4-DNP 244–246; DiEt b.p. 108/0.9 mm (521)
E	391	Thio. 266; Ox. 136; Cyclic 30–31 (443)
E	444	
Iodothiophene-2-carboxaldehydes		
H	390, 529	Ox. 149; Thio. 256
H and L	389	DiEt b.p. 100/0.1 (526)
L	389	
H	390	Ox. 186; Thio. 238
H	390	Thio. 238; Ox. 162
M	590	
I	589	2,4-DNP 277; DiEt b.p. 118/1 mm
N	33	
H	390	
H	112	Semi. 268
Iodothiophene-3-carboxaldehydes		
K	390, 389	Ox. 115; Thio. 234; DiEt b.p. 122/4 mm
H and K	389	
H	390	Ox. 163; Thio. 233
H and L	389	
L	389	
E	390	Ox. 125; Thio. 188
E	112	2,4-DNP 255.5–256.5
Fluorothiophene-2-carboxaldehydes		
A	591	
H	591	Ox. 121–122
O	592	2,4-DNP 257–258
A	591	Ox. 125
H	591	

TABLE 7. (*Continued*)

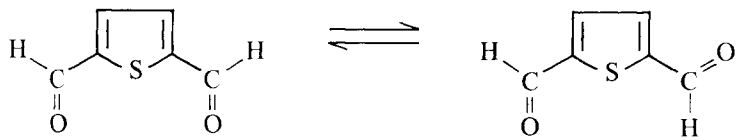
Fluorothiophene-3-carboxaldehydes					
Substituents on Thiophene Ring					
R^2	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)
H	H	F	65–67/13		59

[a] A = Vilsmeier-Haack formylation (DMF); B = Vilsmeier-Haack formylation (NMFA); C = Sommelet reaction; D = Rieche formylation; E = halogenation; F = oxidation of $-CH_2Cl$; G = hydrolysis of $-CHBr_2$; H = metal–halogen exchange/DMF; I = Grignard reagent/DMF or triethyl orthoformate; J = metalation/BrC≡CMe; K = metalation/halogen; L = metal–halogen exchange/halogen; M = oxidation of $-CH_2OH$; N = (a) thallium(III) trifluoroacetate, (b) KI; O = metalation/DMF.

Thiophene-2,3-dicarboxaldehyde undergoes base-catalyzed condensation with nitromethane under carefully controlled conditions, to give the dihydroxynitronate **48**; R = OH (100%).[566] In a related reaction, the same dialdehyde is converted into the 3-acetal, then the free 2-CHO group reacts with nitromethane, to give the $2\text{-}CH{=}CHNO_2$ compound. This is hydrogenated, and the acetal is hydrolyzed to give 2-(β-nitroethyl)thiophene-3-carboxaldehyde, which cyclizes with methanolic KOH to the hydroxynitronate **48**; R = H.[567] This readily loses water, to give the thiophene isostere of 2-nitroindene. The procedure may be repeated on the 2-acetal of thiophene-2,3-dicarboxaldehyde. There are many examples of tropone analogues (e.g., **49**), obtained by means of a bisaldol condensation of a ketone, RCH_2COCH_2R, with thiophene-2,3- (or 3,4-)dicarboxaldehyde.[526,528,536,568–570] Thiophene-3,4-dicarboxaldehyde undergoes photocyclization in CCl_4 solution to the lactone (**50**); with the 2,3-dicarboxaldehyde, a mixture of the two possible analogous lactones is obtained.[571]

C. *Conformational Studies*

Studies of IR,[572] ESR,[537] and ^1H NMR (in anisotropic[469] or liquid crystalline media[573,574]) spectra and of dipole moments[455,459] have shown that thiophene-2,5-dicarboxaldehyde exists in solution as an equilibrium mixture of the O,S,O-*cis*, *cis* (**51**) (major contributor) and O,S,O-*cis*,*trans* conformers (**52**). The conformations



51 **52**

Fluorothiophene-3-carboxaldehydes

Method[a]	Reference	Melting Point of Derivatives (°C)[b] (Ref.)[c]
H	591	Ox (*anti*) 102–103

[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi. = semicarbazone; Ox. = oxime (often a mixture of isomers); PH = phenylhydrazone; NPH = *p*-nitrophenylhydrazone; DiEt = diethyl acetal; DiMe = dimethyl acetal; Cyclic = 1,3-dioxolane.
[c] If a reference is not given, the melting point (or boiling point) of the derivative is quoted in the reference to the preparation.

of the other isomeric thiophene dicarboxaldehydes have been studied by dipole moments[459] and ^{1}H NMR spectroscopy (long-range coupling).[575]

The ESR spectrum of the radical anion of thiophene-2,5-dicarboxaldehyde, produced by metal reduction in an ethereal solvent, shows a marked linewidth alternation owing to the oscillation of the countercation between two equivalent carbonyl groups.[576]

6. Halothiophene Carboxaldehydes

A. Preparation

Haloaldehydes and their derivatives, prepared in the main by methods already described in Section II.1.A are listed in Table 7. The table also includes halo derivatives prepared by halogenation of thiophene carboxaldehydes.

The methods used to prepare alkylthiophene carboxaldehydes are generally applicable without modification to the preparation of their halo counterparts. Phosphoryl bromide must be used for the Vilsmeier-Haack formylation of bromothiophenes since phosphoryl chloride promotes a halogen interchange reaction.[18] Halogen–metal interchange reactions have been used widely for the preparation of halothiophene carboxaldehydes and are particularly useful for the preparation of the otherwise rather inaccessible iodothiophene carboxaldehydes from dibromothiophenes. The first bromine atom is replaced by a formyl group (BuLi-DMF); this remains protected as its lithium complex [ThCH(OLi)NMe_2], while the second bromo substituent is replaced by iodo on successive treatment with BuLi and iodine.[389]

The dimethyl acetal of 2-chlorothiophene-3-carboxaldehyde has been obtained by treatment of 2-chloro-3-(dibromomethyl)thiophene with methanolic potassium carbonate in the presence of 1,4-diazabicyclo[2.2.2.]octane.[543] Generally, acetals and other derivatives listed in Table 7 are prepared by the usual methods.

B. *Chemical Reactions*

a. GENERAL

Reactions are generally similar to those already discussed (Section II.3) for alkylthiophene carboxaldehydes. The haloaldehydes are oxidized to the carboxylic acid by silver oxide[42,593] or by alkaline hydrogen peroxide,[577] and are reduced to the alcohol by sodium borohydride[389] or iron and acetic acid.[579] Aldehydes containing a β-bromo substituent in the thiophene ring undergo normal Huang-Minlon reduction,[42] but those with an α-bromo substituent undergo simultaneous hydrodebromination.[112,594] Bromo- and iodo-thiophene carboxaldehydes undergo dehalogenation prior to polarographic reduction of the carbonyl group.[595,596] The oxime of 4-bromothiophene-2-carboxaldehyde is reduced by $LiAlH_4$ to the corresponding 2-aminomethyl compound, which is isolated as the acetamido derivative.[597] There are examples of the following reactions: formation of alcohols by reaction with organolithium compounds,[598,599] Wittig reaction,[389,589,600] cyanohydrin formation,[583] Cannizzaro reaction,[579,601] Claisen-Schmidt reaction,[391,583,602] Knoevenagel and related reactions,[199,269,424,579,603] Perkin and related reactions[583,604] Schiff's base formation,[579,604] aminal formation with morpholine,[64] and conversion of oximes into nitriles with acetic anhydride.[390,391,578,587,591,605] When 2,5-dichlorothiophene-3,4-dicarboxaldehyde reacts with PBr_5, the two aldehyde functions are converted successively, as expected, into $-CHBr_2$ groups; one of the chloro substituents may also be replaced by bromine.[530]

b. ELECTROPHILIC SUBSTITUTION

The nitration of 3-bromothiophene-2-carboxaldehyde was shown to give the 4-nitro derivative (35 to 43%).[67,593] A subsequent study has shown that the 5-nitro isomer is also formed (13 to 14%), together with the nitrodecarbonylated products, 2,4- and 2,5-dinitro-3-bromothiophene (17 to 18 and 3% respectively).[584] 5-Chlorothiophene-2-carboxaldehyde is nitrated normally in the 4-position, but further nitration of the product gives mainly the nitrodecarbonylated product, 2-chloro-3,5-dinitrothiophene.[606] Seemingly, the nitrodecarbonylation reaction is favored by an electron-withdrawing group in a β-position in the ring.

Bromination of 3-bromothiophene-2-[^{2}H]carboxaldehyde in chloroform gives the 3,5-dibromo compound, together with the bromodecarbonylated product, tetrabromothiophene.[33]

c. NUCLEOPHILIC SUBSTITUTION

The synthetic importance of the halothiophene carboxaldehydes lies in their ability to undergo nucleophilic replacement of the halogen substituent. This may be done

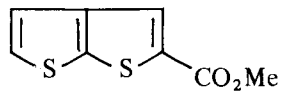


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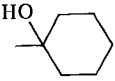
TABLE 8. NUCLEOPHILIC REPLACEMENT REACTIONS OF HALOTHIOPHENE CARBOXALDEHYDES (OR THEIR ACETALS)

By Direct Replacement

Starting Material (Substituents)	Reagent	Substituent Introduced	References
5-Br, 2-CHO	Et_2NH	5-NEt_2	607
	PhSNa-acetone	5-SPh	608
	$PhSO_2Na$-DMF	5-SO_2Ph	608
	EtSH–KOH–EtOH	5-SEt	609
	CuCN–DMF	5-CN	610
3-Me, 5-Br, 2-CHO	CuCN–DMF	5-CN	610
4-Me, 5-Br, 2-CHO	CuCN–DMF	5-CN	610
5-I, 2-CHO	2-ThC≡$\bar{C}C\dot{u}$-pyridine	5-C≡C–Th-2	611
	MeC≡$\bar{C}C\dot{u}$-pyridine	5-C≡CMe (junipal)[a]	590
5-I, 2-$CH(OEt)_2$	(a) MeC≡$\bar{C}C\dot{u}$-pyridine (b) H^+	5-C≡CMe, 2-CHO (junipal)	589
Iodoaldehyde acetals (various)	(a) CuCN-pyridine or quinoline (b) H^+	Cyanocarboxaldehydes	385
2-Cl, 3-CHO	$HSCH_2CO_2Me$-base	2-SCH_2CO_2Me[b]	64
3-Br, 2-CHO	NaN_3–DMSO	3-N_3	612
2-Cl, 3,5-diCHO	NaN_3-EtOH	2-N_3	543
2-Cl, 3,5-diCHO	Piperidine	2-Piperidino	64
2-Cl, 3,5-diCHO	$PhCH_2SH$	2-SCH_2Ph	64

By Way of a Thienyllithium Intermediate

Reagent[c]	Substituent Introduced[d]	References
DMF	Various dicarboxaldehydes[e]	42, 521, 524, 526
$DCON(CD_3)_3$	–CDO	521, 525
$MeCONMe_2$	–COMe	521, 529
EtCN	–COEt	529
$EtO_2CCONEt_2$	–$COCONEt_2$	529
CO_2	–CO_2H	586
(a) (b) Ac_2O	–CH_2CH_2OAc	613
Cyclohexanone		43
$MeOCH_2Cl$	–CH_2OMe	388
I_2	–I	389
$B(OBu)_3$	–$B(OH)_2$	443, 582, 614
Toluene-*p*-sulfonyl azide	–N_3[f]	615
Bu_2Se_2	–SeBu	585
(a) S (b) $ClCH_2CO_2Me$	–SCH_2CO_2Me[g]	588
(a) ClCH=$CHCl_2$-*trans* (b) $NaNO_2$	–NO_2	616

[a] Hydrodehalogenation also takes place.

[b] Cyclizes to **53.**

[c] The thienyllithium derivative is first formed by treating a halothiophene carboxaldehyde acetal with an alkyllithium at a low temperature.

[d] After acidic hydrolysis.

[e] See Table 6.

[f] After fragmentation of the resulting triazene lithium salt.

[g] Cyclizes with NaOEt in the presence of an adjacent CHO group to a thienothiophene, (cf. **53**).

either directly or by allowing an acetal to undergo halogen–metal exchange, then treating the resulting thienyllithium with an appropriate reagent. The scope of these reactions is illustrated in Table 8.

C. *Physical Properties*

a. CONFORMATIONAL STUDIES

Halothiophene-2-carboxaldehydes invariably exist in the O,S-*cis* conformation (cf. Scheme 5). This conclusion follows from studies of dipole moments,[456,617] Kerr effect,[456] ^{1}H NMR coupling constants,[592,618] X-ray crystallography,[618] variable temperature ^{1}H NMR spectroscopy,[618] and nuclear Overhauser effect.[619]

The conformations of some iodothiophene-3-carboxaldehydes, as studied by ^{1}H NMR spectroscopy[620] and dipole moments,[617] depend on the position of the iodine atom. Generally they are O,S-*trans* (cf. **40**).

b. NMR SPECTRA

The ^{1}H and ^{19}F NMR spectra of a series of fluorothiophene carboxaldehydes and their oximes have been examined.[621] Long-range coupling between the aldehydic proton and 4-H in 3-bromothiophene-2-carboxaldehyde ($J = 0.05$ Hz) has been studied at considerable length.[622–627] Long-range coupling has also been observed in 2-bromothiophene-3-carboxaldehyde[628] and in the cyclic acetals of various bromothiophene-2- and 3-carboxaldehydes.[586]

7. Nitrothiophene Carboxaldehydes

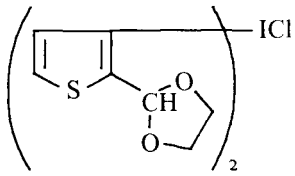
A. *Preparation*

The majority of nitro aldehydes have been prepared by means of a nitration reaction (Section II.3.I, "Substitution Reactions"). Otherwise, they are most commonly obtained by oxidation of the corresponding hydroxymethyl compound with *N*-bromosuccinimide-$CaCO_3$[605,629,630] or concentrated nitric acid.[631] Halomethyl compounds are oxidized to the carboxaldehyde by selenium dioxide[433,632] or copper(II) nitrate,[433] but the yields may be low. In an unusual reaction, 2-bromomethyl-3-nitrothiophene reacts with copper(II) nitrate to give a mixture of 5-bromo-3-nitrothiophene-2-carboxaldehyde and the corresponding alcohol.[633] It is believed that the reaction proceeds by means of copper(II) bromide, which can then behave as a brominating agent. 3-Bromomethyl-2-nitrothiophene is conveniently converted into the 3-carboxaldehyde by the Kröhnke reaction.[634] The readily available 2-methyl-3-nitrothiophene has been converted into the 2-carboxaldehyde by the following routes: (1) successive conversion into 2-$CHBr_2$ (*N*-bromosuccinimide) and 2-$CH(OAc)_2$ (NaOAc) and acidic hydrolysis of the latter;[629] (2) direct conversion into 2-$CH(OAc)_2$ (very low yield) by oxidation with CrO_3–H_2SO_4–AcOH–Ac_2O;

[433,633] and (3) treatment with *p*-nitroso-*N*,*N*-dimethylaniline, followed by acidic hydrolysis of the resulting mixture of anil and nitrone.[634]

In a novel synthesis of nitro aldehydes, a bromothiophene carboxaldehyde (as the acetal) undergoes halogen–metal exchange, and the resulting thienyllithium compound is treated with *trans*-1-chlorovinyl-2-iodosodichloride ($ClCH{=}CHICl_2$). The resulting bis(thienyl)iodonium salt (e.g., **54**) then reacts with sodium nitrite in DMF to give a mixture of the nitroaldehyde acetal and the iodoaldehyde acetal.[616,635]

Nitrothiophene aldehydes prepared by the foregoing routes are listed in Table 9.



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B. Reactions

a. GENERAL

Nitrothiophene carboxaldehydes are usually oxidized to the corresponding carboxylic acid by use of chromic acid.[24,426,427] Oxidation of 3,5-dinitrothiophene-2-carboxaldehyde with tetrabutylammonium permanganate in pyridine proceeds with decarboxylation to give 2,4-dinitrothiophene.[429] The polarographic reduction of 5-nitrothiophene-2-carboxaldehyde in aqueous solution or in ethanol may proceed by means of the hydrate[637] or hemiacetal respectively.[638]

Nitroaldehydes undergo the aldol reaction with appropriate aldehydes and ketones,[177,578,639–641] and there are many examples of Knoevenagel-type reactions with "active methylene" compounds.[404,423,578,631,642,643] Yields in the latter reactions are often lower than usual; 5-nitrothiophene-2-carboxaldehyde, for example, fails to condense under the normal conditions with arylacetonitriles, diethyl malonate, or 2,4,6-trinitrotoluene.[424] This aldehyde undergoes an unusual self-condensation reaction in the presence of pyridine–Ac_2O, to give a low yield of the diacetoxy compound **55**.[644] There are examples of the Perkin reaction (low yields),[645,646] of oxazolone formation with α-acylamido acids,[578,629,647] and the Wittig reaction.[640,648,649]

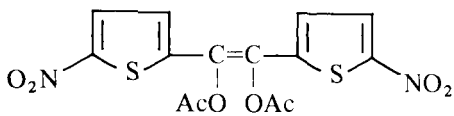

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TABLE 9. NITROTHIOPHENE CARBOXALDEHYDES

Nitrothiophene-2-carboxaldehydes							
Substituents on Thiophene Ring							
R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (Ref.)[c]
NO_2	H	H	52–53	3	A	433	2,4-DNP 246–247
			52–53	31	B	616	Cyclic 65.5–67
			54–55 (b.p. 113–127/2–3 mm)	Low, 35	A	634, 629	Semi. 247–248 (629)
H	NO_2	H	61, 56, 55–56	–, –, 12	C	578, 432, 420	Ox. 172; PH 200; Semi. 270, Thio. 283; *OO*-diacetate 78 (578) 2,4-DNP 290–294 (422)
H	H	NO_2	74.5–75	50, 45	D	632, 433	Semi. 223 (632), 235–236 (433)
			74	40	E	605	252–255 (104), 269 (424),
			77, 74, 74	80, –, –	C	424, 578, 423	233–235 (425), 242–243 (404);
			72–73, 75–76	–, 76	C	425, 404	Ox. 160–163 (578), 164 (423);
			77–77.5	33	C	427	Thio. 185 (424), 288–290 (578), 255–258 (425); 2,4-DNP 325 (427); PH 178 (578, 423); NPH 254–255 (427); *OO*-diacetate 73 (578); DiMe b.p. 153–155/5 mm; DiEt b.p. 157–158/5 mm (636)
H	NO_2	Me	91–93	38	C	23	
H	NO_2	Cyclopropyl	82–83	71	C	23	
NO_2	H	Br	78.5–79.5	26	D	633	Semi. 269; 2,4-DNP 252–253
Br	NO_2	H	108–109	65, 43, 35	C	584, 67, 593	
Br	H	NO_2	87–88	13	C	584	
H	NO_2	Cl	101–102	73	C	606	
H	NO_2	$(CH_2)_3CO_2Me$	70.5–72.5	82	C	27, 24	2,4-DNP 202–203.5 (24)
H	NO_2	$(CH_2)_4CO_2Me$	Oil	92	C	27, 24	

Nitrothiophene-3-carboxaldehydes							
R^2	R^4	R^5					
NO_2	H	H	55.5–56.5	–, 37	E	629, 631	Ox 150 (544); PH 213–215;
			55–56	97	F	634	Thio. 243–244 (631); Semi. 265–266 (629)
H	NO_2	H	71–71.5	50 (as acetal)	B	635	Cyclic 67.5–68
H	H	NO_2	82–83	69, 65	C	433, 32	NPH 223–224; Semi. 215–216

[a] A = From 2-methyl-3-nitrothiophene; B = $NaNO_2$ on dithienyliodonium salt; C = nitration of the appropriate aldehyde; D = oxidation of $-CH_2X$ (X = halo); E = oxidation of $-CH_2OH$; F = Kröhnke reaction.

[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi. = semicarbazone; Ox. = oxime (often a mixture of isomers); PH = phenylhydrazone; NPH = *p*-nitrophenylhydrazone; DiEt = diethyl acetal; DiMe = dimethyl acetal; Cyclic = 1,3-dioxolane.

[c] If a reference is not given, the melting point (or boiling point) of the derivative is quoted in the reference to the preparation.

The nitroaldehydes form Schiff's bases normally;[605,634] their oximes are dehydrated to nitriles with acetic anhydride.[423,650]

Dialkyl acetals of 5-nitrothiophene-2-carboxaldehyde are conveniently prepared by treating the aldehyde *O,O*-diacetate with the appropriate alcohol in the presence of a trace of concentrated sulfuric acid, then removing water azeotropically.[636]

b. SUBSTITUTION REACTIONS

Nitration of 4-nitrothiophene-2-carboxaldehyde proceeds mainly with deformylation to give 2,4-dinitrothiophene, together with a small amount of the 4,5-dinitro-2-carboxaldehyde; with 5-nitrothiophene-2-carboxaldehyde, nitrodeformylation is a minor reaction, and the major product is the 3,5-dinitro-2-carboxaldehyde.[429] Reaction of 5-nitrothiophene-2-carboxaldoxime with N_2O_4 in acetonitrile gives 2,4-dinitro-5-(trinitromethyl)thiophene (50%).[651]

5-Nitrothiophene-2-carboxaldehyde undergoes *ipso* attack by the nucleophilic 1-adamantyl radical, to give 5-(1-adamantyl)thiophene-2-carboxaldehyde (46%).[652]

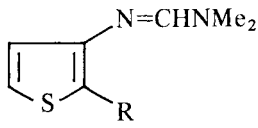
C. Conformational Studies

On the basis of the Kerr effect[456] and dipole moment data,[456,457] it has been shown that 5-nitrothiophene-2-carboxaldehyde exists in carbon tetrachloride solution as a mixture of two conformers (see Scheme 5). However, the ESR spectrum of the electrochemically generated anion radical from 5-nitrothiophene-2-carboxaldehyde indicates the existence of only one conformer.[653]

8. Aminothiophene Carboxaldehydes

A. Preparation

Since the free amines are rather unstable, aminothiophene carboxaldehydes are usually obtained as their acylamino derivatives. They are usually prepared by Vilsmeier-Haack formylation of a 2-[17,406,578,654–657] or 3-acylamidothiophene.[656,658–660] The same reaction proceeds satisfactorily on a 2- or 3-(*t*-amino)thiophene.[661] Recent work has shown that the conditions must be carefully controlled during the formylation of an acetamidothiophene.[656,657] For example, treatment of 3-acetamidothiophene with a Vilsmeier reagent ($POCl_3$-DMF) gives the 2-formyl derivative, the formamidines (**56**; R = H or CHO) and the thienopyridines (**57**; R = H or CHO);[658–660] which product predominates depends critically on the reaction



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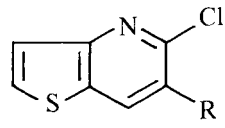

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conditions. In other cases diformylation has been observed.[656] Sometimes (e.g., with 3-acetamido-2,5-dichlorothiophene) only the unformylated formamidine derivative (**56**; R = Cl and Cl in 5-position) is obtained.[658]

More recently, the reduction of an azidothiophene carboxaldehyde with hydrogen sulfide has provided a convenient source of the corresponding amino aldehyde.[543,612]

5-Acetamidothiophene-2-carboxaldehyde has been made by the reductive acetylation (Fe—AcOH—Ac_2O) of 5-nitrothiophene-2-carboxaldehyde diacetate.[406] The nitro group in 5-nitrothiophene-2-carboxaldehyde semicarbazone has been reduced catalytically to amino.[662]

Bromothiophene carboxaldehydes undergo nucleophilic displacement of halogen by a secondary amine.[607] When 5-bromothiophene-3-carboxaldehyde diethyl acetal is treated with potassium in liquid ammonia, the product is the acetal of 4-aminothiophene-3-carboxaldehyde.[658]

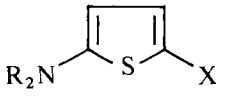
Aminothiophene-2- and 3-carboxaldehydes are listed in Table 10.

B. Reactions

Surprisingly few reactions of aminothiophene carboxaldehydes have been reported. *N*-Acetyl derivatives are hydrolyzed with sulfuric acid to the free amino aldehydes; the latter can be converted into the *N*-formyl derivative by treatment with formic acetic anhydride.[658]

Acylamidoaldehydes undergo the Doebner, Knoevenagel,[654] and Wittig reactions[663] and form oxazolones with α-acylamido acids.[654] Their oximes are converted into nitriles by acetic anhydride.[578]

5-(*N*,*N*-Dialkyl)aminothiophene-2-carboxaldehydes (**58**; X = CHO) react in acetic acid solution with a *p*-nitrobenzenediazonium salt to give an azo dye (**58**; X = N=$NC_6H_4NO_2$-*p*), with the elimination of the formyl group as formic acid.[607] In the belief that 5-(dimethylamino)thiophene-2-carboxaldehyde (**58**; R = Me,



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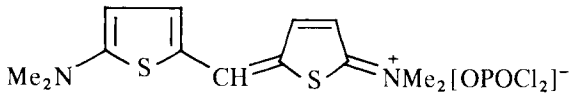

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X = CHO) might behave in the Vilsmeier-Haack reaction as a second-order vinylogue of DMF, it was treated with phosphoryl chloride. The product failed to react as a formylating agent, and has been shown to be an analogue (**59**) of Michler's Hydrol Blue.[664,665]

When treated with base, 2-aminothiophene-3,5-dicarboxaldehyde undergoes a facile ring-opening-recyclization reaction, to give 4-cyanothiophene-2-carboxaldehyde.[543]

The amino group in 3-aminothiophene-2-carboxaldehyde may be replaced by the

TABLE 10. AMINO- AND ACYLAMINO-THIOPHENE CARBOXALDEHYDES

2-Carboxaldehydes							
Substituents on Thiophene Ring							
R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (Ref).
NH_2	H	H	67	100	A	658	*N*-formyl 97 (658)
			68–70	85	B	612	
NHAc	H	H	72	88, 50	C, C	656, 658	
$N(CH_2)_4$	H	H	103–104	25	C	661	
$N(CH_2)_4O$	H	H	63–64	55	C	661	
H	H	NHAc	183.5–184	33–89	C, D	17, 406, 578, 654, 656	2,4-DNP 307–308 (406); Semi. 260.5–261, (406); PH 255–256 (654); Ox. 216, 270, 198–202 (406, 578, 17); Thio. 237 (406); Semi. of 5-NH_2 176–177 (662)
H	H	NMe_2	88–90	60	C	661	
H	H	NEt_2	24 (b.p. 122/0.1)	69	E	607	
H	H	$N(CH_2)_4$	102–106	45	C	661	
H	H	$N(CH_2)_5$	93–95	60	C	661	
H	H	$N(CH_2)_4O$	125–127	80	C	661	
H	H	$N(CH_2)_4N$	164–166	50	C	661	
H	CHO	NHAc	>250	89	C	656	
H	CHO	NH_2	>150	49	B	543	
NHCOPh	NHCOPh	H	179–181	80	F	663	

			3-Carboxaldehydes			
R^2	R^4	R^5				
NHAc	H	Me	85–86	62	C	657
NHAc	Me	Me	136	72, 73	C, C	657, 655
NHAc	——$(CH_2)_4$——		124	79, 78	C, C	657, 655
NHCOPh	Me	Me	156–157	80	C	655
NHCOPh	——$(CH_2)_4$——		134–135	80	C	655
$NHCOCH_2Ph$	——$(CH_2)_4$——		105.5–106.5	84	C	655
H	NHAc	H	147	20	G	658

[a] A = Hydrolysis of an acylamino derivative; B = reduction of an azido compound; C = Vilsmeier-Haack formylation ($POCl_3$-DMF); D = Vilsmeier-Haack formylation ($POCl_3$-NMFA); E = nucleophilic displacement from a haloaldehyde; F = oxidation of $-CH_2OH$; G = K—NH_3 on bromoacetal, then hydrolysis.

[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi. = semicarbazone; Ox. = oxime (may be a mixture of isomers); PH = phenylhydrazone.

following substituents by means of the diazonium salt: —SCN, —SeCN,[666] —$NHNH_2$ (with spontaneous cyclization),[667] and —N_3.[668,669] The products are readily cyclized to give a range of bicyclic systems. Thienopyrimidines,[655,658] thienopyridines,[655,670,671] and thienopyrroles[672] are obtained directly from the parent 2-CHO, 3-NH_2 or 2-NH_2, 3-CHO compounds (or their acylamino derivatives) by conventional procedures.

C. Spectroscopy

The effect of amino and formyl substituents on the π electron structure of thiophene has been examined by ^1H and ^{13}C NMR and by UV spectroscopy. Experimental values have been compared with those obtained by SCF MO calculations.[673]

9. Hydroxy-, Alkoxy-, and Aryloxy-thiophene Carboxaldehydes

A. Preparation

Vilsmeier-Haack formylation of either a hydroxy or alkyloxy compound (generally the latter) proceeds well under mild conditions and is the most widely used preparative method. By using $POCl_3$–*N*-methylformanilide and raising the temperature to 50–60°C, products of the type **60** have been formed (> 50%) from 5-(R-substituted)-2-methoxythiophenes.[674,675] The formylation of 2-methoxythiophene with $POCl_3$-DMF follows second-order kinetics (cf. third order for thiophene and methylthiophenes), in which the rate-determining step is the formation of the adduct between the two reagents.

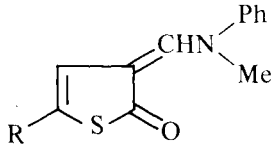
Hydroxythiophene carboxaldehydes are conveniently obtained either by dealkylation of an appropriate ether[522,676,677,687] or by oxidation of a formylboronic acid with ethereal hydrogen peroxide.[678]

Aldehydes prepared by these and other methods are listed in Table 11.

B. Reactions

Few reactions of hydroxythiophene carboxaldehydes have been reported, but their alkoxy derivatives have been studied more extensively and appear to behave normally. Thus they are reduced to the alcohol,[683] undergo the mixed benzoin condensation,[683] form chalcone analogues with aromatic methyl ketones,[676] form Schiff's bases,[680] and condense with rhodanine.[679] 2-Hydroxy-5-methylthiophene-3-carboxaldehyde is said to form a Schiff's base, but not a semicarbazone or thiosemicarbazone.[685]

3-*t*-Butoxythiophene-2-carboxaldehyde is a useful starting material for preparing bicyclic systems. It undergoes the aldol condensation normally with an aromatic



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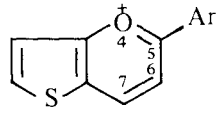

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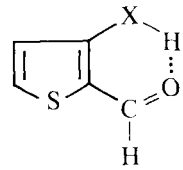

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methyl ketone (ArCOMe); then the product is cyclized by $HClO_4$—HCl to give the 5-aryl thieno[3,2-*b*]pyrylium salt **61**.[676] Alternatively, it will undergo the Knoevenagel condensation with ethyl cyanoacetate or related compounds, then the product can be cyclized and hydrolyzed to give a 5-oxothieno[3,2-*b*]pyran derivative.[522,677,687] With ethyl bromoacetate, 3-hydroxythiophene-2-carboxaldehyde forms the 3-OCH_2CO_2Et derivative, which undergoes base-catalyzed cyclization with the 2-CHO group to give a thieno[3,2-*b*]furan.[522]

C. Spectroscopic and Conformational Studies

IR and NMR Studies have shown that 3-hydroxythiophene-2-carboxaldehydes exist in solution entirely as the enol form.[522,678] In solution in carbon tetrachloride, 3-hydroxythiophene-2-carboxaldehyde exists in the O,S-*trans* form (**62**; X = O), owing to intramolecular hydrogen bonding, and therefore shows a long-range coupling of C*H*O to 4-H. However, in solvents such as acetone the hydrogen bonding is intermolecular, and the molecule exists in the normal O,S-*cis* conformation (cf. Scheme 5), with long-range coupling to 5-H.[618]

D. Other Physical Properties

The acidic dissociation constants of 2-formyl-, 2-acetyl-, and 2-cyano-3-hydroxythiophene have been determined in aqueous DMSO. These compounds are more acidic than their phenolic analogues.[688]

10. Thiophene Carboxaldehydes Containing a Substituent in Which a Sulfur (or Selenium or Tellurium) Atom is Attached Directly to the Ring

A. Preparation

Most of the preparative methods are similar to those described earlier for other substituted aldehydes. The Vilsmeier-Haack reaction is used most commonly: a 2-(alkylthio)thiophene is thus formylated in the 5-position;[689–694] if this is already occupied, the formyl group enters the 3-position.[39,535,692,695–698] A 3-

TABLE 11. HYDROXY- AND ALKOXYTHIOPHENE CARBOXALDEHYDES

2-Carboxaldehydes								
Substituents on Thiophene Ring			Boiling Point	Melting Point				Melting Point of Derivatives
R^3	R^4	R^5	(°C/mm)	(°C)	Yield (%)	Method[a]	References	(°C)[b]
OMe	H	H		82–84	51, 83	A, A,	679, 687	
OH	H	H		88–89.5	54	B	678[c]	Thio. 226–228 (676)
				90	56, 80	C	676, 687	
H	H	OMe	130–135/16		58	D	680	Thio. 170–171
			79–81/0.9	24–26	67, 84	A, A	683, 679	NPH 171–172 (683)
H	H	OEt	136–139/15		55	D	680	NPH 163.5–164; Thio. 155–156
H	H	OPr	147–149/14		59	D	680	NPH 128; Thio. 147–148
H	H	OBu^n	148–156/20		40	D	680	Thio. 160–161.5
H	H	OC_5H_{11}	175–178/15		63	D	680	Thio. 98–99.5
OBu^t	H	H	80/0.1		62	A	676	
OBu^t	OBu^t	H	115/1		50	A	522	
OMe	OMe	H		69–69.5	69	E	33	
H	Br	OMe		113–114	68	E	681	
SMe	H	OMe		77.5–78.5	77	A	682	

R^2	R^4	R^5	3-Carboxaldehydes					
OMe	H	H		58–59	92	A	684	DiMe b.p. 90–98/0.5 mm; Ox. 148 (544)
OBu^t	H	H	90/0.1		37	A	676	
H	OBu^t	H	84/0.05		71	A	676	
H	H	OMe	115–118/13		62	A	682	2,4-DNP 229–231; DiEt b.p. 138/13 mm
OMe	H	Me	98–100/3		50	E	674	2,4-DNP 201–202
OH	H	Me		112	47	E	685	
OMe	H	Et	110–115/3		47, 63	D, E	674	DiEt b.p. 126–127/6 mm; Semi. 198–200
OMe	H	OMe		41–43	39	E	686	
OMe	H	SMe		48–49	54	A	675	2,4-DNP 213–215
SMe	H	OMe	132–138/4		57	F	682	2,4-DNP 181–182

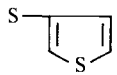
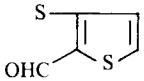
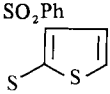
[a] A = Metalation (or metal–halogen exchange)/DMF; B = H_2O_2 on 3-$B(OH)_2$; C = dealkylation of an ether; D = Vilsmeier-Haack formylation ($POCl_3$-NMFA); E = Vilsmeier-Haack formylation ($POCl_3$-DMF); F = Me_2S_2 on metalated acetal.

[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi. = semicarbazone; NPH = *p*-nitrophenylhydrazone; Ox; = oxime; DiMe = dimethyl acetal; DiEt = diethyl acetal.

[c] The unstable 4-OH, 3-CHO is formed similarly.

TABLE 12. (ALKYLTHIO)- AND (ARYLTHIO)THIOPHENE CARBOXALDEHYDES AND

(Alkylthio)- and (Arylthio)thiophene-2-carboxaldehydes

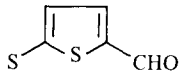
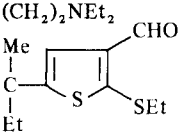
Substituents on Thiophene Ring			Boiling Point	Melting Point
R^3	R^4	R^5	(°C/mm)	(°C)
SH	H	H		Unstable
H	H	SH		Unstable
SMe	H	H	115–120/1.5	
SEt	H	H	106–109/2	
SMe	H	SMe		87–88
SEt	H	Me		28–29.5
SCH_2CO_2Me	H	H	166–168/2.5	
SCH_2CO_2Me	H	Et	160–163/1.5	
	H	H	160–180/2.5	
	H	H		158–159
SCN	H	H		113
H	H	SMe	–, 78/0.35	26, –
H	H	SOMe		67–68
H	H	SO_2Me		>100
H	H	SEt	114.5–116/1 142–165/15	
H	H	SPr	96–97/0.35	
H	H	SBu^t	125–127/3	
H	H	SPr^i	114/2.5	
H	H	SBu^n	109–110/0.4	
H	H	SBu^i	96–98/0.4	
H	H	$S(CH_2)_4Me$	126–128/0.7	
H	H	$S(CH_2)_2CHMe_2$	103.5/0.15	
H	H	$S(CH_2)_5Me$	113.5/0.2	
H	H	$S(CH_2)_6Me$	157.5–157.9/1.7	
H	H	$S(CH_2)_{11}Me$		33.5–34.5
H	H	$S(CH_2)_{17}Me$		58.5–60
H	H	SPh		86–88
H	H	SO_2Ph		72–73
H	H			30–31

(Alkylthio)- and (Arylthio)thiophene-2-carboxaldehydes

Yield (%)	Method[b]	References	Melting Point of Derivatives (°C)[c] (Ref.)[d]
	A	705	Disulfide 137–138
	A	106	Mercury salt 166
59	B	706	
82	D	700, 701	2,4-DNP 206–207; Semi. 178–179.5; DiEt b.p. 107–108/2 mm
79	E	697	
78	D	700	2,4-DNP 185.5–186.5; DiEt b.p. 119–121/2 mm
44	D	699	Semi. 158–159
79	D	707	
22	E	702	PH 156–158
63	E	702	PH (bis) 193–195
30	F	666	
58, 57	C, D	689, 694	Ox. 80.5; 2,4-DNP 215–216; Semi. 186; Thio. 144–145; (689) NPH 173–173.5 (694); Cyclic b.p. 108–109/0.025 (708)
57	G	708	
15, 30	H, G	689	2,4-DNP 276–277
74, 82	C, D	693, 694	Thio. 163–164; NPH 164–165; (694)
45	I	609	Semi. 179–180 (693), DiEt b.p. 105–106/2 mm (106)
94	D	694	NPH 131.5–132.5; Thio. 130.5–132
74	C	692	Semi. 199–200
65	D	694	NPH 157–158; Thio. 149–150
75	D	694	NPH 109–110; Thio. 122–123
80	D	694	NPH 150–151; Thio. 139–140
95	D	694	NPH 126–127; Thio. 106.5–107.5
85	D	694	NPH 117–118; Thio. 124.5–126
89	D	694	NPH 120–121; Thio. 103.4–104.5
89	D	694	NPH 100–101; Thio. 89–90
73	D	694	NPH 80–81.5; Thio. 106–107
84	D	694	NPH 88–90; Thio. 110.5–111.5
65	I	608	
75	I	608	
69, 49	C, E	690	Semi. 229–231, PH 121–123

TABLE 12. *(Continued)*

(Alkylthio)- and (Arylthio)thiophene-2-carboxaldehydes

Substituents on Thiophene Ring			Boiling Point	Melting Point
R^3	R^4	R^5	(°C/mm)	(°C)
H	H			70.5–71.5
H	H	$SC_6H_4 \cdot OMe$-*p*		64–65
H	H	$SO_2C_6H_4 \cdot OMe$-*p*		148–149
H	H	$SC_6H_4 \cdot OCOPh$-*p*		84–85
H	H	$SC_6H_4 \cdot OH$-*p*		153–154
		(Alkylthio)- and (Arylthio)thiophene-3-carboxaldehydes		
R^2	R^4	R^5		
SMe	H	H	119–121/1	
			108–110/1	
SMe	H	I		111–113
SMe	H	Me	120–122/2	ca. 20
SMe	H	SMe		36.5–37.5
SMe	SMe	Me		
SMe	Br	SMe		101.5
SMe	CH_2OH	SMe		81–82
SEt	H	H		
SEt	H	Et	118–119/2	
			132–134/4	
			127–128/4	
SEt	H	CHO		103–105
SEt	CH_2OH	SEt		64.5
SEt	H	$(CH_2)_2OAc$	146–147/0.1	
SEt	H	$(CH_2)_2OEt$	179–180/6	
SEt	H	$(CH_2)_2NEt_2$	158–160/1.1	
SEt	H		Oil	
SBu^t	H	Me	123–125/2	
SO_2Bu^t	H	Me		93–94.5
SPh	H	CHO		110–112
SCH_2Ph	H	Et	180–187/1	
SCH_2Ph	H	CHO		125.5–126.5
STh-3	H	CHO		121–123
SCH_2CO_2Me	H	H	156–161/4	53–55
SCH_2CO_2Et	H	Et	165–173/2	
H	H	SMe	83–85/0.1	
H	SMe	H	109–110/0.1	
			98–105/0.3	53–55

(Alkylthio)- and (Arylthio)thiophene-2-carboxaldehydes

Yield (%)	Method[b]	References	Melting Point of Derivatives (°C)[c] (Ref.)[d]
11, 63	C, E	690	PH (bis) 190–193
54	C	691	Semi. 198.5–199.5
	E	691	
13	C	691	Semi. 208–209
56	J	691	Semi. 211–212

(Alkylthio)- and (Arylthio)thiophene-2-carboxaldehydes

68	E	32	Semi. 180–182
44	B	706	
80	K	682	
71	D	709	PH 69–70.5 (709); DiEt b.p. 112/1.5 mm (710)
54	D	535	Semi. 190–191; DiEt b.p. 162–163/4 mm
27	B	711	$NaHSO_3$ adduct 106–107
79	L	535	Cyclic 29.5–30
90	M	538	Ox. 120–122
74 (as acetal)	B	394	2,4-DNP 167–168; Semi. 194–195; DiEt b.p. 113–114/3 mm
86	D	39	2,4-DNP 150–150.5; DiEt b.p. 137–138/1 mm; Cyclic
81, 78	D, C	695	b.p. 146–146.5/2 mm (106)
64	N	712	
90	O	523	
98	M	538	
72	D	698	
84	D	696	2,4-DNP 140.5–141.5; DiEt b.p. 184/6 mm
50	B (modified)	714	DiEt b.p. 147–177/2.5 mm
60	D	715	Semi. (bis) 222–223.5; DiEt (bis) b.p. 200/0.06 mm
10	C	692	Semi. 273
41	E	692	
51	O	523	
80	D	39	2,4-DNP 163; DiEt b.p. 188–189/1 mm
84	O	523	
70	O	523	
80	B	378	
55	D	713a	Semi. 171.5–172.5
58	E	32	Semi. 173–174
57	E	700	DiEt b.p. 125/2.5 mm
46	E	32	Semi. 191–192

TABLE 12. (*Continued*)

(Alkylseleno)- and (Alkyltelluro)thiophene-2-carboxaldehydes				
Substituents on Thiophene Ring			Boiling Point	Melting Point
R^3	R^4	R^5	(°C/mm)	(°C)
SeMe	H	H	150–155/2.5	
$SeBu^n$	H	H	139–140/2	
SeCN	H	H		111
$SeCH_2CO_2Me$	H	H	150–152/0.5	
H	H	SeMe	125–126/3	18
H	$SeBu^n$	H	125–130/1	
TeMe	H	H	125/1.5	88
$TeBu^n$	H	H	160/1	
(Alkylseleno)- and (Alkyltelluro)thiophene-3-carboxaldehydes				
R^2	R^4	R^5		
SeMe	H	H	135–140/2.5	
SeMe	H	Me		34–35
H	SeMe	H	121–124/2	
			125/2	
TeMe	H	H	135/2	45
H	TeMe	H	120/0.8	55
$TeBu^n$	H	H	160/1	

[a] Including SCN and SeCN compounds, sulfones, and sulfoxides.

[b] A = Reduction of an acetal of the corresponding alkylthiothiophene-2-carboxaldehyde; B = metalation (or metal–halogen exchange) of a protected aldehyde (or a bromo derivative), followed by treatment with an S (or Se or Te) compound; C = Vilsmeier-Haack formylation ($POCl_3$-DMF); D = Vilsmeier-Haack formylation ($POCl_3$-NMFA); E = metalation (or metal–halogen exchange) of an (alkylthio)thiophene (or a bromo derivative), followed by treatment with DMF; F = from corresponding amino compound by way of diazonium salt; G = Oxidation of SMe compound; H = Sommelet reaction; I = nucleophilic displacement from a bromo

(alkylthio)- or 3-(alkylseleno-) thiophene is formylated in the 2-position.[395,699–702] 5-(Methylthio)thiophene-2-carboxaldehyde, a by-product from the Vilsmeier-Haack formylation of 2,5-bis(methylthio)thiophene, is formed, not by direct replacement of a methylthio substituent, but by successive protonation, loss of the SMe group, and formylation of the vacant 2-position.[535,697,703] 2,5-Bis(*t*-butylthio)thiophene is not formylated by DMF–$POCl_3$.[692] Vilsmeier-Haack formylation of 3-(3-thienylthio)-thiophene gives, in addition to small amounts of the expected mono- and di-aldehydes, a mixture of the cyclized products (**63**; X = O or H_2).[702] Attempted Rieche formylation of aryloxy- or arylthiothiophenes with dichloromethyl methyl ether–$SnCl_4$ gives the corresponding pyrylium or thiopyrylium salts [e.g. **64** from 3-(thienylthio)thiophene].[704]

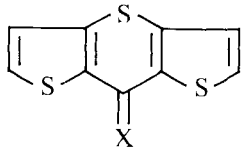
(Alkylseleno)- and (Alkyltelluro)thiophene-2-carboxaldehydes			
Yield (%)	Method[b]	References	Melting Point of Derivatives (°C)[c] (Ref.)[d]
55	B	706	
83	C	585	Semi. 168.5–169; DiEt b.p. 142–143/2 mm
45	F	666	
70	D	395	
85	C	41	Semi. 177.5–178.5
74	B	585	DiEt b.p. 131–133/1 mm
10	B	397	
34	B	397	
(Alkylseleno)- and (Alkyltelluro)thiophene-3-carboxaldehydes			
61	B	706	
26	B	41	Semi. 196.5–197; DiEt b.p. 117–120/2 mm
69	E	585	
75	B	706	
55	B	397	
50	B	397	
34	B	397	

aldehyde; J = hydrolysis of corresponding benzoyloxy compound; K = iodine on lithio derivative; L = by electrophilic substitution; M = oxidation of $-CH_2OH$; N = from the chloromethyl compound; O = RS^- on 2-SO_2Bu^t.

[c] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi. = semicarbazone; Ox. = oxime; PH = phenylhydrazone; NPH = *p*-nitrophenylhydrazone; DiEt = diethyl acetal; DiMe = dimethyl acetal; Cyclic = 1,3-dioxolane.

[d] If a reference is not given, the melting point (or boiling point) of a derivative is quoted in the reference to the preparation.

Other preparative procedures are summarized in the footnotes to Table 12. For convenience, this table also includes the few thiocyanato- and selenocyanothiophene carboxaldehydes that have been obtained by diazotization of the appropriate aminoaldehyde.[666]



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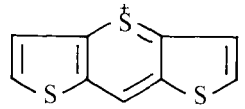


$[SnCl_5]^-$

64

B. Reactions

a. OXIDATION

Oxidation to the carboxylic acid with silver oxide proceeds normally;[41,682,705,713a,715] with permanganate, the sulfur atom in the side-chain is also oxidized (to the sulfone).[691,709] Peroxyacetic acid oxidizes the alkylthio side-chain in a thiophene aldehyde (in which the CHO group is usually protected) to either the sulfoxide[708] or the sulfone.[689,692]

b. REDUCTION

(Alkylthio)thiophene carboxaldehydes undergo normal Huang-Minlon reduction.[609,692,709] Reduction of (alkylthio)thiophene carboxaldehyde acetals with sodium in liquid ammonia is summarized in Scheme 7. The precise products depend on the number of g atoms of sodium used in the reduction and on the work-up procedure. The iminomethyl thiols (**65**; X = NH) are obtained only when the two functional groups in the starting material are adjacent.[106] The free mercaptoaldehydes obtained by hydrolysis of the mercaptoacetal [or by reduction of a thiocyanato compound with sodium sulfide[666]] are unstable and readily give polymers or the disulfide.[106,666,700]

c. GENERAL REACTIONS

(Alkylthio)thiophene carboxaldehydes undergo reactions expected of aldehydes: Schiff's base formation,[694] Cannizzaro reaction,[694] Knoevenagel reaction,[608,701] and hydrogensulfite addition.[711]

d. SUBSTITUTION REACTIONS

2,5-Bis(methylthio)thiophene-3-carboxaldehyde is readily brominated in the 4-position;[535] 2-(methylthio)thiophene-3-carboxaldehyde is iodinated (I_2-HgO) in the 5-position.[682] In the presence of two formyl groups, a *t*-butylsulfonyl substituent is replaced by a sulfur or oxygen nucleophile.[523]

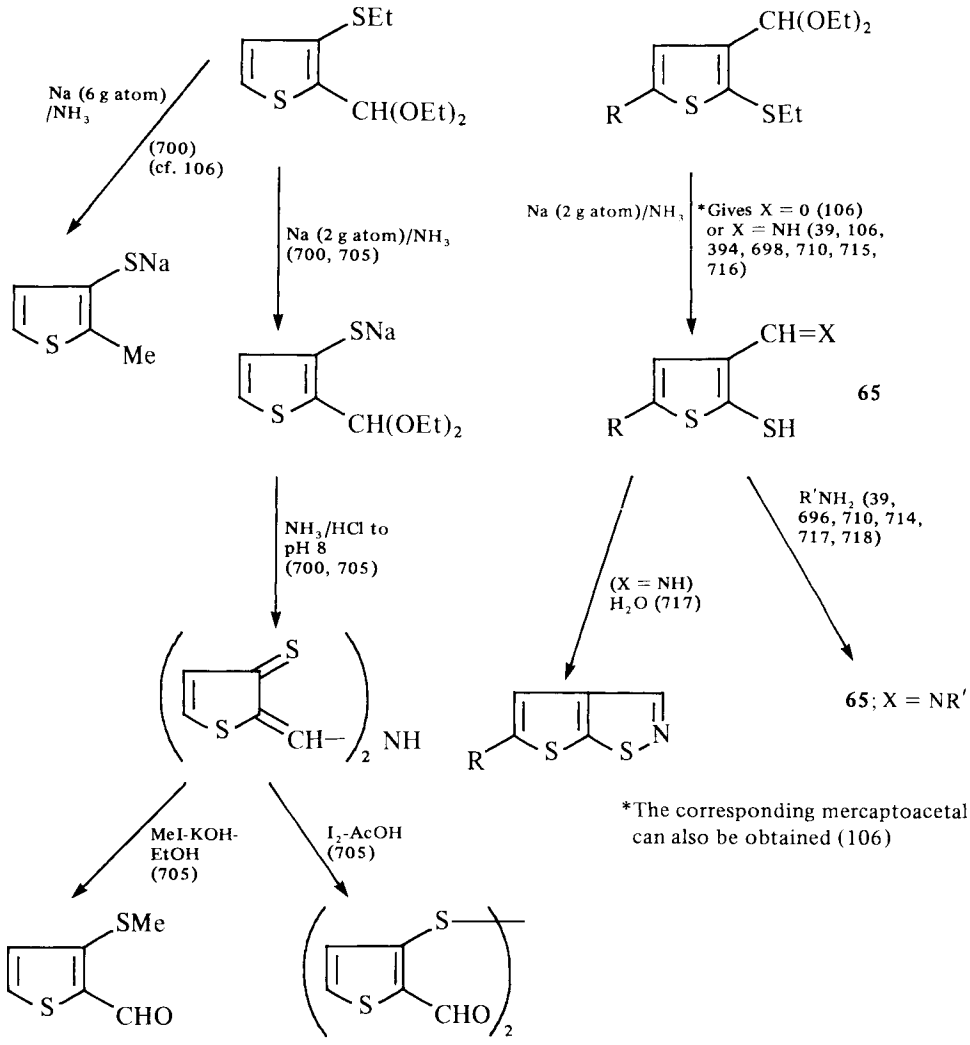
e. CYCLIZATION REACTIONS

The conversion of 2-(methylthio)thiophene-3-carboxaldehyde into a thienoisothiazole[717] by means of the acetal is shown in Scheme 7. The same result may be achieved by treatment of the aldoxime with PPA; the analogous (methylseleno) compounds are cyclized to the thienoisoselenazole by treatment of the aldehyde with bromine and ammonia.[706]

Thiophenes containing an SCH_2CO_2R or $SeCH_2CO_2R$ group adjacent to the formyl substituent undergo base-catalyzed cyclization to the thieno- or selenothiophene respectively.[378,395,588,699,707,713a]

C. Spectroscopic and Related Studies

IR and ^1H NMR investigations show that, because of chelation, 3-mercaptothiophene-2-carboxaldehyde exists in the normally unfavored O,S-*trans* confor-



Scheme 7

mation (**62**; X = O).[666] The ^{1}H NMR spectra of (methylseleno)thiophene carboxaldehydes are similar to those of their (methylthio) analogues, except that coupling is also observed between the selenium atom and the protons of the methyl group.[719]

The conformation of 2-(methyltelluro)thiophene-3-carboxaldehyde and related compounds has been investigated by means of dipole moments.[720]

TABLE 13. MISCELLANEOUS THIOPHENE CARBOXALDEHYDES

Substituents on Thiophene Ring			Melting Point				
R^3	R^4	R^5	(°C)	Yield (%)	Method[a]	References	Derivatives
Azidothiophene-2-carboxaldehydes							
N_3	H	H	55	'excellent'	A	669	[b]
			56.5–57	48	B	612	
			57–58	88	C	615	
Azidothiophene-3-carboxaldehydes							
R^2	R^4	R^5					
N_3	H	CHO	decomp.	61	B	543	
H	N_3	H	50–52	85	C	615	[c]
2-Formylthiophene Boronic Acids							
R^3	R^4	R^5					
$B(OH)_2$	H	H	[d]	57, 66	E, D	727, 614	
$B(OH)_2$	H	Me	[d]	25, 28	D, E	582	
$B(OH)_2$	H	Br	117–125	70	F	443	
$B(OH)_2$	H	NO_2	125–130	22	F	728	
$B(OH)_2$	Br	H	126–128	65	E	443	
H	H	$B(OH)_2$	[d]	57	D	614	[e]
3-Formylthiophene Boronic Acids							
R^2	R^4	R^5					
$B(OH)_2$	H	H	[d]	50	D	396	
$B(OH)_2$	H	Me	126–136	18	E	582	
$B(OH)_2$	H	Et	116–118	26	E	582	
$B(OH)_2$	H	Pr	120–123	32	E	582	
$B(OH)_2$	H	Cl	[d]	39	D	582	
$B(OH)_2$	H	Br	92–93	95	F	443	
$B(OH)_2$	H	NO_2	150–155	70	F	728	
$B(OH)_2$	Cl	H	[d]	50	D	582	
$B(OH)_2$	Br	H	112–120	75, 65	E, D	443	
H	$B(OH)_2$	H	135–180	49	D	614	[f]

[a] A = From an amino compound by means of diazotization; B = sodium azide on a haloaldehyde; C = toluene-*p*-sulfonyl azide on a protected bromoaldehyde; D = trialkyl borate on a lithio derivative (CHO protected as acetal); E = trialkyl borate on a lithio derivative (CHO protected as its complex with DMF); F = by eletrophilic substitution.

[b] Dimethyl acetal, melting point 25° (721); 1,3-dioxolane, m.p. 36–37° (615); oxime, m.p. 110° (612).

[c] 1,3-Dioxolane, boiling point 100–102°/15 mm (615).

[d] Melts with decomposition over a wide range.

[e] Phenylhydrazone, melting point 130–140° (decomp.) (614)

[f] Oxime decomposes at approximately 180° (614).

11. Miscellaneous Thiophene Carboxaldehydes

A. Azido Derivatives

a. PREPARATION

Azidothiophene carboxaldehydes have been prepared (Table 13) by three general methods: (1) nucleophilic replacement of the halogen atom in a haloaldehyde by use of sodium azide;[543,612] (2) by treatment of the diazonium salt from an amino-carboxaldehyde with sodium azide;[668,669] (3) by reaction of the lithio derivative of a protected aldehyde with toluene-*p*-sulfonyl azide and fragmentation of the resulting triazene lithium salt with aqueous tetrasodium pyrophosphate deca-hydrate.[615]

b. GENERAL REACTIONS

Azidoaldehydes are reduced to the aminoaldehydes by hydrogen sulfide in basic solution.[543,612,670]

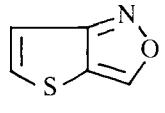
Azidothiophene carboxaldoximes are converted into the corresponding nitriles by use of 2,4,6-trichloro-*s*-triazine[612] or hydroxylamine-*O*-sulfonic acid.[721]

Acetal formation with methanolic trimethyl orthoformate proceeds quantitatively in the presence of praseodymium chloride.[721]

c. CYCLIZATION REACTIONS

The readily available 3-azidothiophene-2-carboxaldehyde provides a versatile starting material for preparing a range of condensed thienoheterocycles. Heating it gives the formally orthoquinonoid thienoisoxazole **66**.[669,722] Treating it with hydrazine replaces the azido group by $-NHNH_2$, with subsequent cyclization to thieno[3,2-*c*]pyrazole.[667] The formyl group readily undergoes the Knoevenagel condensation, and the products are cyclized thermally (Scheme 8).

The azido group in 3-azidothiophene-2-carboxaldehyde reacts conventionally with isoprene or an "active methylene" compound, XCH_2CN, to give a triazoline or triazole respectively. The former is cyclized (hν, then heat) to the thienoazepine derivative **67**;[726] the acetal of the latter **68** cyclizes to the triazolothienopyrimidine when the protecting group is removed.[721]



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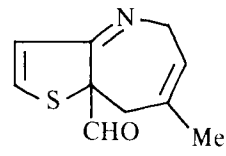

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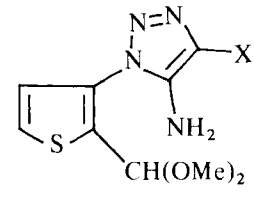

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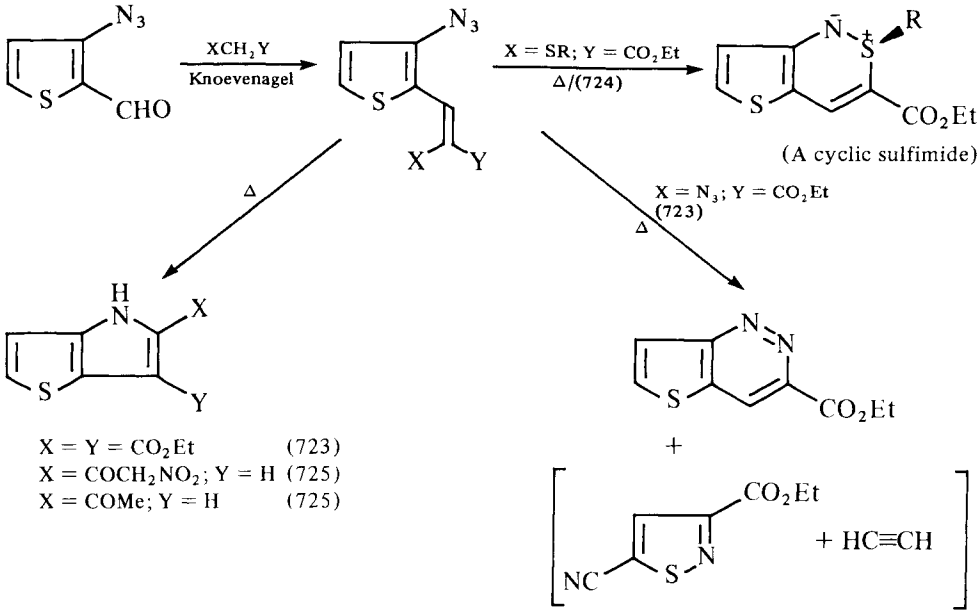


Scheme 8

B. Formylthiophene Boronic Acids

a. PREPARATION

These are invariably prepared by treatment of a thienyllithium with a trialkyl (usually tri-*n*-butyl) borate. The lithio precursor may be obtained from the acetal of a thiophene carboxaldehyde by metalation, or from its bromo derivative by metal–halogen exchange.[443,582,614] Alternatively, in a "one-flask" reaction, the formyl group may first be introduced by reaction of a lithio derivative with DMF. It remains protected as the ThCH(OLi)NMe_2 complex while the borono group is introduced as just described.[443,582,727]

b. GENERAL REACTIONS

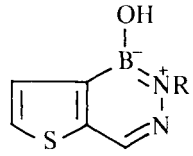
The formylboronic acids are oxidized normally to the carboxylic acid by silver oxide.[678] Treatment with hydrogen peroxide replaces the borono group by —OH, thus affording a facile route to hydroxythiophenes.[678]

c. SUBSTITUTION REACTIONS

2-Formylthiophene-3-boronic acid and 3-formylthiophene-2-boronic acid are brominated[443] and nitrated[728] in the 5-position. In the nitration of the 2-aldehyde, 4-nitrothiophene-2-carboxaldehyde is also formed (57%) as a result of a proto-deboronation reaction.[728] Protodeboronation is a facile process, especially in the presence of hydrochloric acid.[396]

d. CYCLIZATION REACTIONS

Thiophenes containing adjacent formyl and borono substituents are cyclized by hydrazine derivatives, $RNHNH_2$, to thienodiazaborines (e.g., **69**; R = H, Ph, Me, or $PhSO_2$).[396,443,582,614] Use of hydroxylamine gives an analogous thienooxazaborine (**69**; NR replaced by O).[614]



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III. KETONES

1. Preparation of Thienyl or Alkylthienyl Ketones

A. Friedel-Crafts Acylation and Related Reactions

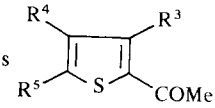
a. GENERAL

This is undoubtedly the most widely used route to acyl- and aroylthiophenes; ketones thus prepared are listed in Tables 14 to 16. When thiophene itself undergoes acylation with a range of acylating agents in the presence of various catalysts, the 2-isomer is formed almost entirely (>99%); the ratio of 2- to 3-substituted product varies from 140 to >1000, depending on the selectivity of the electrophile.[4] A 2-substituted thiophene is acylated predominantly in the 5-position; for 2-ethylthiophene, a small amount of 3-acyl product has also been detected.[884] 3-Alkylthiophenes generally give a mixture of 2- and 5-acyl derivatives (cf. References 745 and 881). Although tin(IV) chloride and aluminum chloride remain the most widely used catalysts for acylation with an acid chloride or anhydride, boron trifluoride (e.g., Reference 740), iodine (e.g., References 774 and 805), perchloric acid (e.g., References 730, 731, 760, and 885), magnesium perchlorate,[732,733,886] and heteropolyacids (particularly $H_4SiMo_{12}O_{40}$)[887] have also been employed. Boron trifluoride-Et_2O, $SnCl_4$, and $FeCl_3$ have been found to be the most efficient catalysts for the acetylation of thiophene with acetic anhydride.[888]

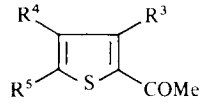
b. WITH ALUMINUM CHLORIDE

Thiophene and its alkyl derivatives are more readily acetylated (MeCOCl) than they are chloroacetylated ($ClCH_2COCl$) in the presence of $AlCl_3$.[798] The competitive

TABLE 14. ACYLTHIOPHENES (INCLUDING THOSE WITH AN ALKYL OR ARALKYL RELATED REACTIONS

2-Acetylthiophenes 

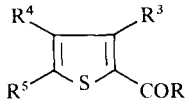
R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)
H	H	H	88–89/10	
			214/760	
Me	H	H	74–74.5/4	
H	Me	H	85–85.5/4	
H	H	Me	79–83/0.5	
			98–100/8	
Me	Me	H	61.5/0.15	
Me	H	Me	61/0.15	
H	Me	Me	76/0.2	
Me	Me	Me	76/0.15	
Me	H	$(CH_2)_{15}Me$	187/0.025	
H	H	Et	67/0.2	
H	H	$(CH_2)_2OAc$	142–145/1	
H	H	CH_2SO_2Et		111–112
Pr^i	H	H	58/0.6	
H	Pr^i	H	73/0.5	
$(CH_2)_2CO_2H$	H	H		114–116
H	Bu^t	H	259/760	
H	H	CH_2CHMe_2	130–132/10	
H	H	Bu^t	146/13	
H	H	$(CH_2)_3CO_2Me$		42–43
H	H	$(CH_2)_3CO_2Et$	209–211/16	
H	H	$(CH_2)_3CO_2Pr^i$	185–188/3.5	15–16.5
H	H	$(CH_2)_4Me$	155/10	
——$(CH_2)_4$——		Me	175–176/18	57
H	——$(CH_2)_4$——		171/15	

2-Acetylthiophenes 

Yield	Method[a]	Refer ences	Melting Point of Derivatives (°C)[a] (Ref.)[a]
95,95,85	F,J,J	729,730, 731	Semi. 189–190 (732); Thio. 147–148 (104); Ox.
92–95,77	K,L	733,734	112–113 (108); 2,4-DNP 254 (738); NPH 182.5–183.5
63,70,94	B,D,E	735,736, 737	(108); Cyclic 33–34 (739)
71,ca. 90	M,G	740,108	Semi. 206–207 (740); Ox. 84.5–86 (108)
12,ca. 90	M,G	740,108	Semi. 219–220 (740); Ox. 132.5–134 (108)
78	B	741	Ox. 124 (738); Thio. 161–163 (104); Semi.
81	M	740	223–224 (740), 215–217 (108)
ca. 90	G	108	Ox. 122–123 Semi. 234–235
ca. 90	G	108	Ox. 63.5–64.5; Semi. 217–219.5
ca. 90	G	108	Ox. 143–144.5; Semi. 238–240
ca. 90	G	108	Ox. 126.5–127.5; Semi. 239.5–241.5
80	I	742	
ca. 90	G	108	Ox. 108.5–110; Semi. 210–211.5
60	G	743	
53	B	744	Ox. 161.5–162.5
31	A	745	Semi. 183–185.5
48	A	745	Semi. 210.5–211.5
67	D	746	
82	B	20	Semi. 249; Thio. 192; Ox. 113; 2,4-DNP 226
–,70 to 75	B,G	747,748	Semi. 204–205 (747)
88	B	16	Semi. 219 (749), 252 (16), 2,4-DNP 221 (749) Thio. 194; Ox. 118
90	D	750	2,4-DNP 173–174; Acid 56–57.5
	B	751	Ox. 57–59 (830)
86	G	24	
70–85,92	G,A	748,752	Semi. 212; 2,4-DNP 127.5 (752)
70	A	829	2,4-DNP 155; Ox 111
90	A	792	Semi. 264; Ox. 152; 2,4-DNP 265

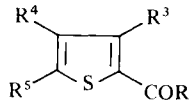
TABLE 14. *(Continued)*

R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)
H	H	$CH_2CH_2CHMe_2$	89–92/0.2	
H	H	$(CH_2)_4CO_2Me$	201/10	53–55
H	H	$(CH_2)_5CO_2Me$	212/10	41–42
H	H	$(CH_2)_6CO_2Et$	192/2	
H	H	$(CH_2)_6Me$	179.5/11.5	
H	H	$(CH_2)_7Me$	190/12	15
H	H	$(CH_2)_8Me$	213–214/18	32–32.5
H	H	$(CH_2)_9Me$	181/3	
H	H	$(CH_2)_{10}Me$	224/12	44.5–45
H	H	$(CH_2)_{10}CO_2Me$		47.5–49.5
H	H	$(CH_2)_{11}Me$	234–235/14	36.5
H	H	$(CH_2)_{15}Me$	226–228/3	53.5
H	H	$(CH_2)_{17}Me$		62
H	H	1-Adamantyl		119–120

Other 2-Acylthiophenes  (Arranged in Order of Increasing Complexity of R)

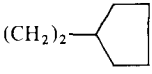
R	R^3	R^4	R^5
CF_3	H	H	Me
CF_3	H	H	Et
CF_3	H	H	Bu^t
Et	H	H	H
Et	Me	H	H
Et	H	Me	H
Et	H	H	Me
Et	H	H	CH_2CO_2Et
Et	H	H	$(CH_2)_3CO_2Et$
Et	H	H	Bu^t
Et	H	H	$(CH_2)_5CO_2Me$
Pr	H	H	H

Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
83	D	753	Semi. 215–216; 2,4-DNP 170–171
71	B	754	Ox. 114–115; Acid 83–84
87	B	754	Ox. 96–97; Acid 101.5–102
82	B	25	Ox. 80–82; Acid 80–81
90	A	752	Semi. 211.5; 2,4-DNP 127.5–128
77	A	752	Semi. 209; 2,4-DNP 125
78	A	755	Semi. 204; 2,4-DNP 120
63	D	756	
93	A	752	Semi. 203; 2,4-DNP 123
92	B	757	Acid 79–81
82	A	752	Semi. 200; 2,4-DNP 113.5–114
85	A	752	Semi. 193; 2,4-DNP 118; Ox. 82–83
62	D	756	
70	J	22	Ox. 213.5–214.5

Other 2-Acylthiophenes  (Arranged in Order of Increasing Complexity of R)

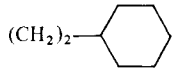
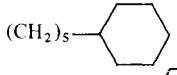
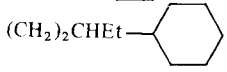
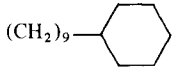
Boiling Point (°C/mm)	Melting Point (°C)	Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
80/20			H	758	
85/20			H	759	
110/20			H	759	
82–83/5		92,69	F,J	729,760	Semi. 166–167 (732);
227/760		70,89	B,E	735,737	Thio. 127–128 (105) DiEt b.p. 102–104/13 mm (379)
85–86/4		80	M	740	Semi. 189–190
98–99/5		11	M	740	Semi. 204–205
93–94/4.5	31	82,87	M,A	740,761	Semi. 203–204 (740); 2,4-DNP 220 (738)
177/11		71	B	762	Acid 83–84.5
197–198/10		75	B	754	Semi. 112–113; Acid 71–72
152/13		82	B	16	Semi. 235; Thio. 187; Ox 116
172–173/1.6		60	B	754	Acid 61–62
96–97/5		96,78,94	F,B,E	729,763, 737	Semi. 174–175 (732); Thio. 170–171 (105); 2,4-DNP 167 (738)

TABLE 14. (*Continued*)

R	R^3	R^4	R^5
Pr	Me	H	H
Pr	H	Me	H
Pr	H	H	Me
Pr	H	H	Et
Pr	H	H	CH_2CO_2Et
Pr	H	H	Bu^t
Pr	H	H	$(CH_2)_4Me$
Pr^i	H	H	H
Pr^i	H	H	Et
Bu^n	H	H	H
Bu^n	H	H	Et
Bu^i	H	H	H
CHMeEt	H	H	H
Bu^t	H	H	H
Bu^t	H	H	Bu^t
$(CH_2)_4Me$	H	H	H
$(CH_2)_4Me$	H	H	Pr
$(CH_2)_4Me$	H	Me	$(CH_2)_{12}Me$
$(CH_2)_3CHMe_2$	H	H	H
CMe_2Et	H	H	H
$(CH_2)_2CHMeCH_2OAc$	H	H	H
Cyclopentyl	H	H	H
$(CH_2)_5Me$	H	H	H
$(CH_2)_5Me$	H	H	Et
$CMe_2(CH_2)_2Me$	H	H	H
Cyclohexyl	H	H	H
$(CH_2)_6Me$	H	H	H
$(CH_2)_6Me$	H	H	Et
$(CH_2)_6Me$	H	H	$(CH_2)_7Me$
$(CH_2)_6Me$	H	Me	$(CH_2)_{12}Me$
	H	H	H

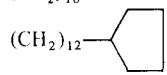
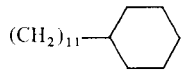
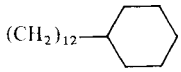
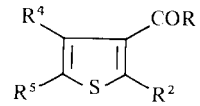
Boiling Point (°C/mm)	Melting Point (°C)	Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
98–99/5		59	M	740	Semi. 147–148
108.5–109/5		38	M	740	Semi. 192–193
105–106/4.5		97	M	740	Semi. 199–200
137/14		70	A	44	Semi. 197; 2,4-DNP 172
189–190/11		84	B	762	Acid 78–79
159/13		76	B	16	Semi. 205
100/0.005			D	764	
108/15		90,80,70	B,F,E	747,729, 765	Semi. 150; Ox. 99–100 (766);
		74	D	767	2,4-DNP 156–157 (767)
146–148/20			A	768	
106–107/6		95,76	F,B	729,735	Semi. 168 (763)
153/17		75	A	44	Semi. 173; 2,4-DNP 167.5
92–93/5		90,73	F,B	729,735	2,4-DNP 159–160 (769)
116/12		84,73	E,D	770,767	2,4-DNP 127–127.5 (770)
113–114/14		57,75,62	E,E,B	770,729, 766	Semi. 132–133 (766); 2,4-DNP 169 (770); Ox. 143 (766)
		94	B	771	
119–120/6		95,80,65	F,B,E	729,735, 737	Semi. 117 (11); 2,4-DNP 156 (738)
100–110/0.005		45	D	764	2,4-DNP 98
Oil			B	772	
267/760		83	B	735	2,4-DNP 171–172 (769)
134–135/11		26	B	12	
126–136/0.1		70	B	773	2,4-DNP 175–176
128–129/7		80	E	770	2,4-DNP 157
170–171/22		84	B	774	
180/13		77,90	A,B	752,774	Semi. 155; 2,4-DNP 129 (752); Ox. 39 (774)
132/11		70	B	12	
	43–44	82,88	E,B	770,735	Semi. 152 (770)
152–153/8		70,86,67	E,F,D	770,729, 756	2,4-DNP 118.5 (764)
191/12.5		71	A	752	Semi. 139; 2,4-DNP 124
	32	58	D	756	
	31.5–32		B	772	
191–192/16			B	775	Semi. 148

TABLE 14. (*Continued*)

R	R^3	R^4	R^5
$(CH_2)_7Me$	H	H	H
$(CH_2)_7Me$	H	H	$(CH_2)_8CO_2Et$
	H	H	H
$(CH_2)_8Me$	H	H	H
$(CH_2)_8Me$	H	H	$(CH_2)_7CO_2Et$
$(CH_2)_8Me$	H	Me	$(CH_2)_{12}Me$
$(CH_2)_3CHEt(CH_2)_2Me$	H	H	H
$(CH_2)_9Me$	H	H	H
$(CH_2)_9Me$	H	H	Et
$CHMe(CH_2)_7Me$	H	H	H
$(CH_2)_{10}Me$	H	H	H
$(CH_2)_{10}Me$	H	H	Me
$(CH_2)_{10}Me$	H	H	Et
$(CH_2)_{10}Me$	H	Me	$(CH_2)_{12}Me$
	H	H	H
	H	H	H
$(CH_2)_{11}Me$	H	H	H
$(CH_2)_3CHMe(CH_2)_3CHMeCH_2Me$	H	H	$(CH_2)_{15}Me$
$(CH_2)_{12}Me$	H	H	H
$(CH_2)_{12}Me$	H	H	$(CH_2)_3CHMeCH_2CHMeCO_2Me$
$(CH_2)_{12}Me$	H	Me	$(CH_2)_{12}Me$
$(CH_2)_{12}Me$	H	Me	$(CH_2)_{18}Me$
$(CH_2)_{13}Me$	H	H	H
$(CH_2)_{14}Me$	H	H	H
$(CH_2)_{14}Me$	H	H	Et
$(CH_2)_{14}Me$	H	H	$(CH_2)_{15}Me$
$(CH_2)_{14}Me$	H	Me	$(CH_2)_{12}Me$
$(CH_2)_{14}Me$	H	Me	$(CH_2)_{14}Me$
$(CH_2)_{14}Me$	H	Me	$(CH_2)_{16}Me$
	H	H	H
$(CH_2)_{15}Me$	H	H	H

Boiling Point (°C/mm)	Melting Point (°C)	Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
130/0.5			D	776	2,4-DNP 106–106.5 (755)
202–206/0.5		48	B	763	Acid 67–68
146–148/3		60	B	777	
184/9		63,68,93	E,D,B	770,756, 778	2,4-DNP 118.5–119 (779), Semi. 114 (11)
220/0.3		85	B	763	Acid 67–68
	33.5–35		B	772	
105/0.04		87	B	774	Semi. 143; 2,4-DNP 96
136–137/0.05		80,29	B,A	774,10	Semi. 95–96 (10)
223/13		77	A	752	Semi. 145–146; 2,4-DNP 103
197–199/18			B	780	Semi. 130
158–160/0.8	22	82,–	L,A	734,752	2,4-DNP 95 (752)
	37–39	81	L	734	
226–227/15	31	71	A	752	Semi 125–126, 2,4-DNP 96
	44.5		B	772	
168–170/2		83	B	781	
217/14			B	11	Semi. 149
130–135/0.04		90	B	772	
200/0.01	33.5	60	B	782	
	33.5–34.5	68	B	778	Semi. 108 (10)
265–270/0.1		86	B	773	
	42–43		B	772	
	49–50		B	772	
	31–33		B	772	
214–215/2.5	42.5	65,63, 86,60,	A,D, B,E,	752,756, 783,770	Semi. 100.5–101 2,4-DNP 93–94 (752)
235/3	46.5–47.5	77	A	752	Semi. 123–124; 2,4-DNP 87
	71	42	D	756	
	40–40.5		B	772	
	45		B	772	
	44–49.5		B	772	
203.5–204.5/2		46	B	781	
170–178/0.025	44–45		B	772	

TABLE 14. *(Continued)*

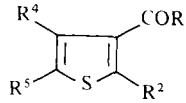
R	R^3	R^4	R^5
$(CH_2)_{16}Me$	H	H	H
$(CH_2)_{16}Me$	H	Me	$(CH_2)_{12}Me$
$(CH_2)_{16}Me$	H	Me	$(CH_2)_{14}Me$
	H	H	H
$(CH_2)_{17}Me$	H	H	H
	H	H	H
$(CH_2)_{17}Me$	H	Me	$(CH_2)_{12}Me$
	H	H	H
$(CH_2)_{18}Me$	H	H	H
$(CH_2)_{20}Me$	H	H	H
2-Acylthiophenes in Which the Acyl Group Contains an Aromatic or Heteroaromatic Ring			
CH_2Ph	H	H	H
CH_2Ph	H	H	Et
$(CH_2)_2Ph$	H	H	H
$(CH_2)_3Ph$	H	H	H
$CHPh_2$	H	H	H
$CH_2C_6H_4OMe$-*p*	H	H	H
$CH_2C_6H_4Br$-*o*	H	H	H
CH_2(1-Naphthyl)	H	H	H
CH_2SPh	H	H	H
$(CH_2)_2C_6H_4Me$-*p*	H	H	H
$(CH_2)_2C_6H_4Cl$-*p*	H	H	H
3-Acylthiophenes 			
R	R^2	R^4	R^5
Me	Me	H	Me

Boiling Point (°C/mm)	Melting Point (°C)	Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
	51	83,88,68	D,B,E	756,783, 737	
	39–40	77	B	772	
	47.5–48		B	772	
260–263/ 13			B	11	
195–200/ 0.025			B	772	
229–231.5/2	44	68	B	781	
	39.5–40		B	772	
247–250/ 1.0	37		B	784	
	58–58.5		B	772	
	67	24	B	899	

2-Acylthiophenes in Which the Acyl Group Contains an Aromatic or Heteroaromatic Ring

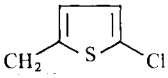
165/5	51	82,86,72	B,B,D	785,735, 746	2,4-DNP 182.5–184 (746)
205–206/ 13	63	91	A	44	Semi. 192; 2,4-DNP 175.5
203–205/ 15	33,45–45.5	80,88	A,B	786,735	
212/20		76,60	B,A	787,786	Semi. 149 (787)
	134.5–136	55	B	735	
165/2		47	C	785	
155–168/ 0.01	61.5–62	69	B	788	
262/18	85	74,70,60	B,C,A	785,785, 786	
174/1.0	54–56	66	B	789	Semi. 117–118
225–226/ 17		90	A	786	
232–235/ 16	54	90	A	786	

3-Acylthiophenes



Boiling Point (°C/mm)	Melting Point (°C)	Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
96–105/8		91	B	790	Semi. 215; Ox. 83; PH 70 (766)
114–115/ 15		70,75	B,A	766,774	Thio. 157 (105)

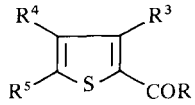
TABLE 14. (*Continued*)

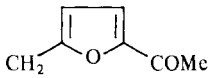
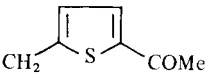
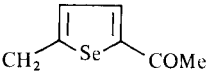
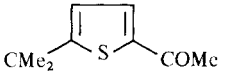
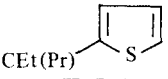
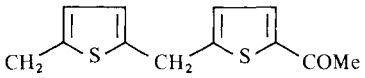
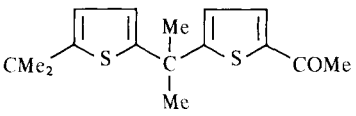
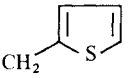
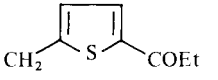
R	R^2	R^4	R^5
Me	Me	Me	Me
Me	Me	—$(CH_2)_4$—	
Me	Et	H	Et
Me	Et	Et	Et
Me	Et	Pr	Et
Me	Et	Bu^n	Et
Me	Et	$(CH_2)_4$ Me	Et
Me	Me(or Bu^t)[b]	H	Bu^t(or Me)[b]
Me	Et(or Bu^t)[b]	H	Bu^t(or Et)[b]
Me	Bu^t	H	Bu^t
Et	Et	H	Et
Pr	Et	H	Et
Pr^i	Me	H	Me
Bu^n	Et	H	Et
Bu^t	Me	H	Me
$(CH_2)_4$Me	Et	H	Et
$(CH_2)_5$Me	Et	H	Et
$(CH_2)_6$Me	Et	H	Et
$(CH_2)_8$Me	Et	H	Et
$(CH_2)_{14}$Me	Et	H	Et
(R=Aralkyl)			
CH_2Ph	Et	H	Et
$(CH_2)_2$Ph	Me	H	Me
$(CH_2)_3$Ph	Me	H	Me
$(CH_2)_2C_6H_4$Me-*p*	Me	H	Me
$(CH_2)_2C_6H_4$Cl-*p*	Me	H	Me
CH_2(1-Naphthyl)	Me	H	Me
	Me	H	Me

Boiling Point (°C/mm)	Melting Point (°C)	Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
74–75/ 0.5		56	J	791	Ox. 111.5–112.5; Semi. 159–160 (108)
155–157/ 12		80–85	B	29	
135/14.5		88,76	A,B	792,793	Semi. 170; 2,4-DNP 153 (792)
154/18.5		48	A	792	2 4-DNP 140
141/9.5		40–45	A	45	2,4-DNP 109
150–151/ 8.5		40–45	A	45	2 4-DNP 90–91
160/9		40–45	A	45	2,4-DNP 105
122– 123.5/10		86	B	793	Semi. 219–220; 2,4-DNP 158.5–159.5
127– 128/9		86	B	793	Semi. 175, 2,4-DNP 152–153
162/13	78	83	B	16	
133.5/11		86	A	45	Semi. 142; 2,4-DNP 146
147.5/12		92	A	45	Semi 142; 2,4-DNP 109
126–127/ 15		88	B	766	Semi. 109; Ox. 97
154/11		90	A	45	Semi. 113; 2,4-DNP 112
97–99/5		39,56	B,B	794,766	Semi. 177–178; Ox. 146 (766)
162.5/9.5		82	A	45	Semi. 92; 2,4-DNP 97.5
174/9		79	A	45	
184– 184.5/8.5		84	A	45	2,4-DNP 58
209.5/10.5		78	A	45	2,4-DNP 61
214/3	34	80	A	45	2,4-DNP 71.5–72
(R=Aralkyl)					
205.5– 207/11		79	A	45	
209–210/ 15		40	A	786	
216–218/ 14		30	A	786	
217–219/ 14		40	A	786	
		60	A	786	
		50	A	786	
160–162/0.2		73	B	795	2,4-DNP 152–153

TABLE 14. (*Continued*)

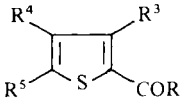
2-Acylthiophenes in Which the Thiophene Ring Contains an Aralkyl Group



R	R^3	R^4	R^5
Me	H	H	$(CH_2)_2Ph$
Me	H	H	$(CH_2)_3Ph$
Me	H	H	$(CH_2)_4Ph$
Me	H	H	$CH_2C_6H_4COMe$-*p*
Me	H	H	$(CH_2)_2C_6H_4COMe$-*p*
Me	H	H	$(CH_2)_3C_6H_4COMe$-*p*
Me	H	H	$(CH_2)_4C_6H_4COMe$ *p*
Me	H	H	
Me	H	H	
Me	H	H	
Me	H	H	
Me	H	H	
Me	H	H	
Me	H	H	
Et	H	H	
Et	H	H	
$(CH_2)_4Me$	H	H	$CH_2C_6H_3(OMe)_2$-3,5

[a] See the corresponding footnotes to Table III.15.
[b] Structure uncertain.

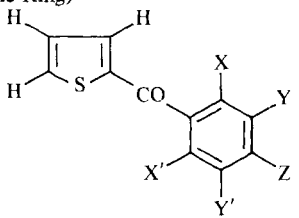
2-Acylthiophenes in Which the Thiophene Ring Contains an Aralkyl Group



Boiling Point (°C/mm)	Melting Point (°C)	Yield	Method[a]	References	Melting Point of Derivatives (°C)[a] (Ref.)[a]
215–216/14		78	B	787	Semi. 220–221
226–228/16		54	A	787	Semi. 191
240–241/22		60	A	787	Semi. 200–201
275–280/19	80		A	751	Semi. (bis) 299–300
	106		A	751	Semi (bis) 315
292/20		26	A	787	Semi. (bis) 266–268
	77	26	A	787	Semi. (bis) 229–230
192–205/2–3	95.5–96.5	46	G	796	
	124–125	46	N	797	
232–233/0.2		5	D	5	
	75–75.5	60	N	774	
	62	64	G	93	
170–178/1.5		31	J	95	
	115.5–116.5	78	B	798	
272–278/0.8		61	A	799	Semi. (bis) 228
			G	99	2,4-DNP 154–155; Ox 98.5–99 5
	100.5–101.5	57	G	99	
	53–54	42	B	800	

TABLE 15. AROYL AND HETEROAROYL THIOPHENES (INCLUDING THOSE WITH AN ALKYL SUBSTITUENT IN THE THIOPHENE RING) PREPARED BY FRIEDEL-CRAFTS AND RELATED REACTIONS

2-Benzoylthiophenes (No Other Substituents in the Thiophene Ring)



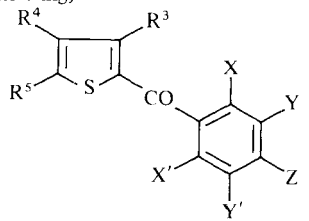
(X, X′, Y, Y′, Z = H, Unless Stated Otherwise)

X	Y	Z	X′ or Y′	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	Reference	Melting Point of Derivatives (°C)[b] (References)[c]
H	H	H	H		56–57	51, 73, 86	J, E, B	760, 737, 735	Ox. 113–114 (*E*), 114 (*Z*) (802)
						80, 70	F, F	729, 801	
		F		142–145/4	99	79, 45	A, B	803, 735	
		Cl		208–210/16	99.5	36, 50	A, C	804, 805	Ox. 139–140 (806)
		Br		218–220/20	103	26, 80	A, A	804, 807	
		Me			75–76	93	B	735	Ox. 123.5–124 (806)
		Et		200–205/12		75	B	803	
		CH_2Br			85.5	59	B	803	
		CN			149	11	A	808	
		NO_2			175	63	B	809	
		OMe		230–235/18	76	76, 83, 60–80	C, A, B	805, 804, 810	Phenol 116 (804); Ox. 112 (806)
		SMe		245–248/18	64	65	P	804	
		SEt		245–250/18		62	P	804	
		OAc		236–238/16	88.5	11–42	B	811	Phenol 109.5
F				180/5		82	B	812	
Cl				139/0.5	42	77	B	812	
Br				174/5	62	79	B	812	
NO_2				175/0.5	90, 102	30, 31, 50	B, B, B	812, 809, 813	

Me				124/0.15		58	A	814	
OMe				208/18		39	A	815	Phenol b.p. 137/1 mm (812)
NHTs					124.5–125.5	83	B	816	
CO_2H					147–148	32, 70	O, O	804, 817	
	OAc			236–240/16	68	11–15	B	811	Phenol 131.5
	OMe			210–212/24		65	A	818	
	Br				64.5–65.5	56, 80	B, A	819, 807	
	NO_2				125	28	B	809	
Cl		F		129–130/0.5		83	B	803	
Me		F		105–106/0.2		32	A	803	
Cl		Cl		209/17	74	40	B	812	
OH		OPr			57–58	52	A	820	
OH		OC_8H_{17}			33–34	60	A	820	
	Br	OMe			127		A	821	Phenol 183
	Cl	OMe		240/13	124		A	821	Phenol 180
	NO_2	Cl			80	47	A	822	
	NO_2	OMe			128	92	A	822	
Cl	Cl	OCH_2CO_2H			157		P	823	
Me		Me	X′ = Me		66–68	60–80	B	810	
Me		Me	X′ = Bu^t		98–100	60–80	B	810	
Me		Bu^t	X′ = Me		112–113	60–80	B	810	
Cl			X′ = Cl	187/5	101	20	B	812	
CO_2Et			X′ = NO_2		114–115	51	B	849	Acid 217
	OMe		Y′ = OMe	250/4.5	46.5–47	75	B	800	

TABLE 15. *(Continued)*

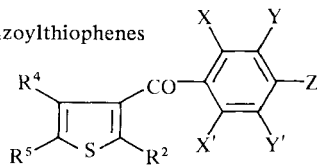
2-Benzoylthiophenes (With Other Substituents in the Thiophene Ring)



R^3	R^4	R^5	X	Y	Z	X′ or Y′	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	Reference	Melting Point Derivative (°C)
H	H	Me					142–144/2.5		54, 81	B, A	735, 814	
H	H	Me			Cl		235–240/25	90	35	A	804	
H	H	Me			Br		236–240/17	84	58	A	804	
H	H	Me			F			68	55	A	803	
H	H	Me			OMe		235–238/17	75	69	A	804	Phenol 136
H	H	Me	CO_2H					136	34, 86	O, O	804, 824	
H	H	Me	NO_2					105–107		B	813	
H	H	Me		Cl	OMe		250/13	143		A	821	Phenol 183
H	H	Me		Br	OMe			142		A	821	Phenol 188
H	H	Me		NO_2	OMe			160	27	A	822	
H	H	Me	Cl	Cl	OCH_2CO_2H			176		P	823	
H	H	Me	CO_2H	Cl		X′ = Cl		160–161	57	O	825	Me ester 97–98
H	Me	H						91–92	81	B	735, 814	
H	Me	H	CO_2H					135	78	O	824	
Me	H	H	NO_2					100	55	A	826	
Me	H	H	CO_2H	Cl		X′ = Cl		164–165	65	O	825	Me ester 107–108

Me	Me							62–63		A	827	
H	H	Et	OMe				165/3	41	35	B	812	
H	H	Et	F				171/5		69	B	812	
H	H	Et	Cl				192/5		66	B	812	
H	H	Et	Br				163/2		75	B	812	
H	H	Et	Me				179/5		72	B	812	
H	H	Et	CO_2H					103	19	O	768	
H	H	Et			F		180/5	38.5	40	B	812	
H	H	Et			Cl			90	54	B	828	
H	H	Et			Br			102	90	B	828	
H	H	Et			OMe		241–243/21	48		A	768	Phenol 126
H	H	Et			Me			69		A	768	
H	H	Et			Et			56		A	768	
H	H	$(CH_2)_3Me$		OMe		Y′ = OMe	190–210/0.02		53	B	800	
H	H	$(CH_2)_3CO_2Me$		OMe		Y′ = OMe	220/0.01	42–43	78	B	800	

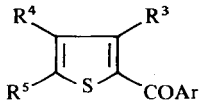
3-Benzoylthiophenes

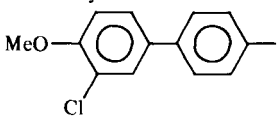


R^2	R^4	R^5	X	Y	Z	X′ or Y′						
Me	H	Me	H	H	H	H		44.5–45	72	A	831	
Me	H	Me			Cl		213–215/17		44	A	804	
Me	H	Me			Br		220–222/17		30	A	804	
Me	H	Me	NO_2					89–90		B	813	
Me	H	Me	CO_2H	Cl		X′ = Cl		172–173	44	O	825	Me ester b.p. 180–181/ 0.4 mm
H	H	H			OMe			67–67.5	72	P	808	

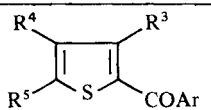
TABLE 15. (*Continued*)

Miscellaneous 2-Aroylthiophenes



R^3	R^4	R^5	Ar	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives
H	H	H	1-Naphthyl		69–70	53, 69	E, F	770, 729	
H	H	H	2-CO_2H-1-Naphthyl		220–222	27	A	832	
H	H	H	2-Naphthyl		89	75	B	833	
H	H	H	1-Br-2-Naphthyl		95–96	83	B	832	Ox. 191–192
H	H	H	Ferrocenyl		124–126	63	P	834	Ox. 138 (835)
H	H	H			145	65	P	836	

2-Heteroaroylthiophenes



R^3	R^4	R^5	Ar	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives
H	H	H	2-Furyl	140–141/5	25.5	28	F	729	Ox. 86–87 (837)
H	H	H	2-Thienyl	159–160/1	89.5–90	60, 66 26, 77	F, D D, B	729, 838, 812, 839	Ox. 132–133 (837)
H	H	H	5-Cl-2-Thienyl		72	95	P	804	Ox. 109–111 (837)
H	H	H	5-Me-2-Thienyl	185–186/6	48.5–50	82	B	19	Ox. 98–99

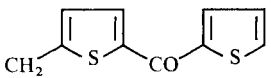
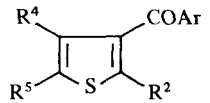
H	H	H	3-Me-2-Furyl	126–127/0.9		80	B	840	
H	H	H	5-CO_2Me-2-Furyl		113–114	19	P	841	
H	H	H	3-Furyl		46	28	B	842	
H	H	H	Selenophene-2-yl		99–100	86	B	843	
H	H	H	2-Me-Selenophene-5-yl		55–56	88	B	5	
H	H	H	2-Et-Selenophene-5-yl		36–37	89	B	5	
H	H	H	2-Dibenzofuryl	280/13	120	33	P	844	
H	H	H	2-Et-3-Benzofuryl	224–226/14		66	P	845	
H	H	H	5-NO_2-2-Thiazolyl		162–165	51	B[d]	846	
H	H	H	2-Thieno[3,2-*b*]thienyl		113–114	78	D	847	
H	H	H	2-Thieno[2,3-*b*]thienyl		101–102		D	847	
H	H	H	1-Et-2-Imidazolyl		52	16	P	848	
H	H	Me	5-Me-2-Thienyl	212–214/13	48–49	88	B	91	
H	H	Me	5-Cl-2-Thienyl	220–222/15	83	52	A	804	
H	H	Me	Selenophene-2-yl	192–193/1		89	B	5	2,4-DNP 168–169
H	H	Me	5-NO_2-2-Thiazolyl		154–156	79	B[d]	846	
Me	H	H	5-NO_2-2-Thiazolyl		189–190	25	A	846	
H	H	Et	2-Thienyl		41		A	768	
H	H	Et	5-Cl-2-Thienyl	228–230/23			A	768	
H	H	Et	5-Br-2-Thienyl		44		A	768	
H	H	Et	5-Et-2-Thienyl		81		A	768	
H	H	Et	2-Furyl	195–197/20			A	768	
H	H	Et	Selenophene-2-yl		36–37	89	B	5	
H	H		2-Thienyl		123	98	D	93	
H	H	2-Thenyl	2-Thienyl		104	77,12	B, B	93, 91	

TABLE 15. *(Continued)*

3-Heteroaroylthiophenes



R^2	R^4	R^5	Ar	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives
H	H	H	2-Thienyl	133–136/2	63	63	P	309	2,4-DNP 221–222
Me	H	Me	5-Cl-2-Thienyl	209–211/15	70	78	A	804	
Me	H	Me	2,5-Me_2-3-Thienyl		63–64	91	B	87	
Bu^t	H	Bu^t	2,5-diBu^t-3-thienyl		221–222	80	B	87	

[a] A = Acid chloride-$AlCl_3$; B = acid chloride-$SnCl_4$; C = acid chloride-I_2; D = acid-P_2O_5 or PPA or H_3PO_4; E = $Si(OCOR)_4$-$SnCl_4$; F = $SiCl_3(OCOR)$-$SnCl_4$; G = acid anhydride-H_3PO_4; H = $(CF_3CO)_2O$ in 1,2-dichloroethane; I = acid anhydride-$ZnCl_2$; J = acid anhydride-$HClO_4$; K = acid anhydride or acid chloride-$Mg(ClO_4)_2$; L = RCO_2H–$(CF_3CO)_2O$–H_3PO_4; M = acid anhydride-BF_3; N = acid anhydride-I_2; O = dicarboxylic acid anhydride-$AlCl_3$; P = thiophene acid chloride with aromatic or heteroaromatic compound and a Lewis acid catalyst.

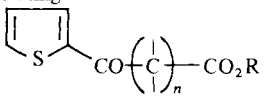
[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi. = semicarbazone; Ox. = oxime (may be a mixture of isomers); PH = phenylhydrazone; NPH = *p*-nitrophenylhydrazone; DiEt = diethyl acetal; Cyclic = ethylene acetal (1,3-dioxolane).

[c] If a reference is not given, the melting point of the derivative is quoted in the reference to the preparation.

[d] With $TiCl_4$ catalyst.

TABLE 16. ACYL THIOPHENES, PREPARED BY FRIEDEL-CRAFTS ACYLATION, IN WHICH THE ACYL GROUP CONTAINS A TERMINAL ESTER OR CARBOXYL GROUP

2-Acylthiophenes (with No Other Substituents in the Thiophene Ring



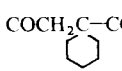
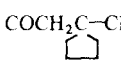
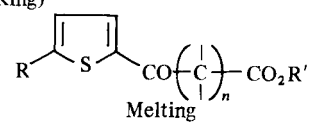
Acyl Group	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
$n = 2$						
$CO(CH_2)_2CO_2H$		115–116	70	C	850	Ox. 135 (851)
$CO(CH_2)_2CO_2Me$	174/16		80, 65	B, A	26, 792	Semi. 142; 2,4-DNP 172; Acid 120 (792); Ox. 76–77 (25)
		168–169	12, 40	B, D	852	
		137–138	61, 33	B, D	852	
$n = 3$						
$CO(CH_2)_3CO_2H$		93–94	45	C	850	Ox. 123–124 (851)
$CO(CH_2)_3CO_2Me$	173/11		74	B	26	
$CO(CH_2)_3CO_2Et$			75	A	853	2,4-DNP 119.5–120.5
$COCH_2CHMeCH_2CO_2Me$	173–174/13		86	B	26, 854, 855	
$COCH_2CMe_2CH_2CO_2H$	210–215/25	78	27	D	856	
$COCH_2CHEtCH_2CO_2Me$	153/2		84	B	857	
$COCH_2CEt_2CH_2CO_2H$	190–191/1.5		67	D	858	
$COCH_2CMe(Pr)CH_2CO_2H$	198–199/2.5	107		D	859	
$COCH_2CMe(Bu^i)CH_2CO_2H$	118/8		70	D	860	
		82	72	D	861	

TABLE 16. *(Continued)*

Acyl Group	R	Boiling Point (°C/mm)	Melting Yield (°C)		(%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
$COCH_2CMe(C_5H_{11})CH_2CO_2H$		187/9	60	D	862			
$COCH_2CHPhCH_2CO_2Me$		82–84	84	B	863			
$n = 4$								
$CO(CH_2)_4CO_2H$		78–79	33, 66	C, C	850, 864		Ox. 116.5–118 (851)	
$CO(CH_2)_4CO_2Me$		185–186/12	83	B	26			
$CO(CH_2)_4CO_2Et$		163–166/2	67	B	865			
$n \geqslant 5$								
$CO(CH_2)_5CO_2Et$		203.5–205/9.5	78	A	755		2,4-DNP 125; Acid 64	
$CO(CH_2)_6CO_2Et$		145–150/0.1	54	B	763		2,4-DNP 92	
$CO(CH_2)_7CO_2Et$		224.5–226/10	70, 60	A, B	755, 763		2,4-DNP 105.5; Acid 59–60 (755), 86–87 (866)	
$CO(CH_2)_8CO_2H$		54–55	77	C	850		Ox. 106–106.5 (851)	
$CO(CH_2)_8CO_2Et$		184–185/1	63	B	865			

2-Acylthiophenes (with a 5-Substituent in the Thiophene Ring)



Acyl Group	R	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
$n = 2$							
$CO(CH_2)_2CO_2H$	Me		112	76	D	767	
$CO(CH_2)_2CO_2Me$	Me	184/15	46.5	91, 84	A, B	867, 868	2,4-DNP 165; Acid 109 (867)
$CO(CH_2)_2CO_2H$	Et		94–95	82	D	767	

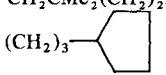
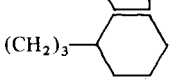
$CO(CH_2)_2CO_2Me$	Et		32	69	A	792	2,4-DNP 152.5; Acid 94
$CO(CH_2)_2CO_2H$	Pr		95–96	71	D	767	2,4-DNP 193–194
$CO(CH_2)_2CO_2Me$	Pr^i			90	B	869	Acid 105–106
$CO(CH_2)_2CO_2Me$	$(CH_2)_2CO_2Me$		42–43	80	B	870	
$CO(CH_2)_2CO_2H$	Bu^n		94–95	79	D	767	2,4-DNP 158–159 (767); Ox. 108–109 (830)
$CO(CH_2)_2CO_2H$	Bu^i		102, 104–105	63, 84	D, D	12, 767	Ox. 127–128 (830); 2,4-DNP 189–190 (767)
$CO(CH_2)_2CO_2H$	Bu^t		114	59	D	20	
$CO(CH_2)_2CO_2Me$	$(CH_3)_2CO_2Me$		37–39	85	B	870	
$CO(CH_2)_2CO_2H$	$(CH_2)_3CO_2Et$			80	D	871	Di-acid 138–138.5
$CO(CH_2)_2CO_2H$	$CH_2CH(Me)Et$		92–94	74	D	767	Ox, 103–104 (830)
$CO(CH_2)_2CO_2H$	$(CH_2)_2CHMe_2$		111	76	D	12, 780	
$CO(CH_2)_2CO_2H$	CH_2CMe_3		126	100	D	12	
$CO(CH_2)_2CO_2Me$	2-Thenyl	219–220/4	34	72	B	872	Acid 125.5–126.5
$CO(CH_2)_2CO_2H$	$(CH_2)_6Me$		102	ca. 60	D	774	
$CO(CH_2)_2CO_2H$	$CH_2CMe_2(CH_2)_2Me$		75	62	D	12	
$CO(CH_2)_2CO_2H$			105		D	775	
$CO(CH_2)_2CO_2H$			99		D	775	
$CO(CH_2)_2CO_2H$	$(CH_2)_4CHEt(CH_2)_2Me$		70	ca. 60	D	774	
$CO(CH_2)_2CO_2H$	1-Adamantyl		183–185	94	D	22	Me ester 93.5–94
$CO(CH_2)_2CO_2H$	$(CH_2)_{10}Me$		108–109	ca. 60	D	774	
$CO(CH_2)_2CO_2H$	$CH_2CHMe(CH_2)_7Me$		110		D	780	
$CO(CH_2)_2CO_2H$	$(CH_2)_{11}Me$		107		D	780	
$CO(CH_2)_2CO_2Me$	$(CH_2)_{15}Me$		30	80	B	783	
$n = 3$							
$CO(CH_2)_3CO_2H$	Me		118–120	72	D	767	2,4-DNP 231–232
$CO(CH_2)_3CO_2Me$	Me	186–187/10	41–42.5	87	B	873	
$CO(CH_2)_3CO_2Et$	Me	205/14		80	A	779	Acid 116.5–117
$CO(CO_2)_3CO_2H$	Et		90–92	71	D	767	2,4-DNP 230–231
$CO(CH_2)_3CO_2Me$	Et	165–167/2	18.5	70	B	874	

TABLE 16. *(Continued)*

Acyl Group	R	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
$CO(CH_2)_3CO_2Et$	Et	206.5/13	42–42.5	88	A	853	2,4-DNP 109–110; Acid 88.5–89
$CO(CH_2)_3CO_2H$	Pr		87–88	67	D	767	2,4-DNP 209–210
$CO(CH_2)_3CO_2Et$	Pr	217/16		78	A	779	2,4-DNP 106; Acid 85
$CO(CH_2)_3CO_2H$	Bu^n		90	81	D	767	2,4-DNP 192–193; Ox. 106–108 (830)
$CO(CH_2)_3CO_2Me$	Bu^n	215–216/10		86	B	874	
$CO(CH_2)_3CO_2H$	Bu^i		113–114	79	D	767	2,4-DNP 190–191; Ox. 83–85 (830)
$CO(CH_2)_3CO_2Me$	Bu^i	177/3		90	B	25	
$CO(CH_2)_3CO_2Et$	Bu^t	227–228/15		77	A	779	2,4-DNP 173; Acid 77
$CO(CH_2)_3CO_2Me$	$(CH_2)_3CO_2Et$		45–47	80	B	870	
$CO(CH_2)_3CO_2Me$	$(CH_2)_4OCOMe$		42–44	95	B	875	
$CO(CH_2)_3CO_2H$	$CH_2CH(Me)Et$		107–109	62	D	767	
$CO(CH_2)_3CO_2Me$	$(CH_2)_4CO_2Me$		67.5–69	74	B	100, 876	
$CO(CH_2)_3CO_2Me$	2-Thenyl	220–223/4	50–50.5	64	B	872	
$CO(CH_2)_3CO_2Me$	$(CH_2)_5Me$	188–189/2		86	B	874	
$CO(CH_2)_3CO_2Et$	$(CH_2)_6Me$	251/18	102.5	78	A	779	2,4-DNP 96.5; Acid 102
$CO(CH_2)_3CO_2Et$	$(CH_2)_9Me$	231–232/4	24–25	72	A	779	2,4-DNP 82–83; Acid 104.5
$CO(CH_2)_3CO_2Et$	$(CH_2)_{10}Me$		59	70	A	779	2,4-DNP 79: Acid 106
$COCH_2CHMeCH_2CO_2H$	Me		79–80	70	D	877	
$COCH_2CHMeCH_2CO_2Et$	$(CH_2)_8Me$	200/0.1		12	B	776	
$COCH_2CMe_2CH_2CO_2H$	Me	215–220/15		46	D	856	Semi. 297
$COCH_2CMe_2CH_2CO_2H$	Et	220–225/13	56	44	D	856	Semi. 195
$COCH_2CMe_2CH_2CO_2H$	$(CH_2)_2CHMe_2$	230–232/19		67	D	856	Semi. 197
$COCH_2CMe_2CH_2CO_2H$	$(CH_2)_6Me$	245–250/12	36	62	D	856	
$COCH_2C(CH_2)CH_2CO_2H$	Me		78	63	D	861	

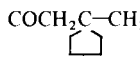
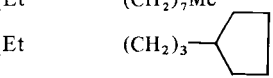
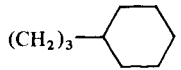
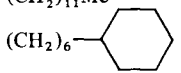
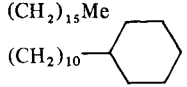
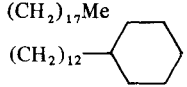
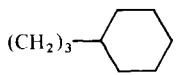
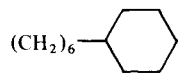
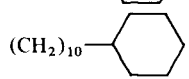
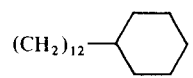
	Et		90	74	D	861	
$n = 4$							
$CO(CH_2)_4CO_2Et$	Et	217–218/13		70, 81	A, B	779, 878	Acid 92.5–93.5 (779)
$CO(CH_2)_4CO_2Me$	Bu^n			66	B	767	Acid 66–68
$CO(CH_2)_4CO_2Me$	Bu^i			63	B	767	Acid 62–63
$CO(CH_2)_4CO_2Et$	$(CH_2)_3CO_2Et$		50–52	82	B	870	
$CO(CH_2)_4CO_2Me$	$(CH_2)_2CHMe_2$	170–175/0.5	36–37	80	B	769	2,4-DNP 103–105; Acid 60–61
$CO(CH_2)_4CO_2Me$	$CH_2CH(Me)Et$			51	B	767	Acid 59–60
$CO(CH_2)_4CO_2Et$	$(CH_2)_4CO_2Me$	224–225/0.5		72	B	100, 876	
$CO(CH_2)_4CO_2Et$	2-Thenyl			60–70	B	866	Acid 128–129
$CO(CH_2)_4CO_2Me$	$(CH_2)_3CHMe_2$	135–140/1	33	78	B	769	2,4-DNP 90; Acid 61–61.5
$CO(CH_2)_4CO_2Et$	$(CH_2)_5CO_2Me$	233–237/1	33–34.5	78	B	100, 876	
$CO(CH_2)_4CO_2Et$	$(CH_2)_7Me$	211–212/0.4		76	B	763	Acid 64–65
$CO(CH_2)_4CO_2Et$					B	775	Acid 65
$CO(CH_2)_4CO_2Et$	$(CH_2)_8CO_2Et$			71	B	866	Di-acid 103
$CO(CH_2)_4CO_2Et$	$(CH_2)_{15}Me$		39–40	66	B	783	
$n = 6$							
$CO(CH_2)_6CO_2Et$	$(CH_2)_3CO_2Me$			79	B	879	Di-acid 101.5–102
$CO(CH_2)_6CO_2Et$	$(CH_2)_2CHMe_2$	200–210/1.5		84	B	769	2,4-DNP 98–99; Acid 50–50.5
$n = 7$							
$CO(CH_2)_7CO_2Et$	$(CH_2)_4Me$			68	B	763	Acid 67–68
$CO(CH_2)_7CO_2Et$	$(CH_2)_3CO_2Et$				B	866	Di-acid 61–62
$CO(CH_2)_7CO_2Et$	$(CH_2)_8CO_2Et$			75	B	866	Di-acid 93
$n = 8$							
$CO(CH_2)_8CO_2Me$	Me		40.5–41.5	84	B	880	
$CO(CH_2)_8CO_2Et$	Bu^n	194/0.3		54	B	763	Acid 63–64
$CO(CH_2)_8CO_2Et$	Bu^i			80	B	767	Acid 56–58
$CO(CH_2)_8CO_2Et$	$(CH_2)_3CO_2Et$			47	B	879	Di-acid 99
$CO(CH_2)_8CO_2Et$	$CH_2CH(Me)Et$			80	B	767	Acid 51–53
$CO(CH_2)_8CO_2Et$	$(CH_2)_7Me$		32.5–33.5	78	B	778	

TABLE 16. (*Continued*)

Acyl Group	R	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
$CO(CH_2)_8CO_2Et$				63	B	777	Acid 66–66.5
$CO(CH_2)_8CO_2Et$	$(CH_2)_9Me$		48–49	66	B	778	
$CO(CH_2)_8CO_2Et$	$(CH_2)_{11}Me$		44–45	74	B	783	
$CO(CH_2)_8CO_2Et$				66	B	781	Acid 71.5–72
$CO(CH_2)_8CO_2Et$	$(CH_2)_{13}Me$		61–62	62	B	778	
$CO(CH_2)_8CO_2Et$	$(CH_2)_{15}Me$		58.5–59.5	37	B	778	
$CO(CH_2)_8CO_2Et$				82	B	781	Acid 78.5–79
$CO(CH_2)_8CO_2Et$	$(CH_2)_{17}Me$		58–59	80	B	783	
$CO(CH_2)_8CO_2Et$				75	B	781	Acid 82–82.5
$n = 10$							
$CO(CH_2)_{10}CO_2Me$				70	B	777	Acid 75–75.5
$CO(CH_2)_{10}CO_2Et$				46, 72	B, B	781, 784	Acid 76.5–77 (781); 91.5–92 (784)
$CO(CH_2)_{10}CO_2Me$				64	B	784	Acid 93.5
$CO(CH_2)_{10}CO_2Me$				72	B	784	Acid 92

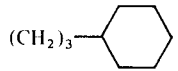
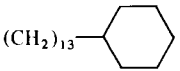
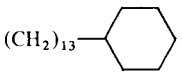
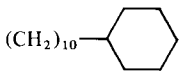
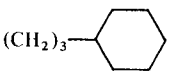
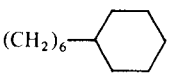
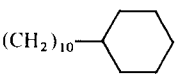
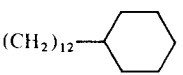
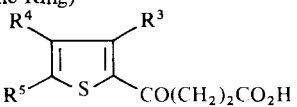
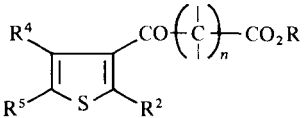
$n = 11$					
$CO(CH_2)_{11}CO_2Me$		52	B	784	Acid 74.5–75
$CO(CH_2)_{11}CO_2Me$		30	B	784	Acid 84–84.5
$n = 13$					
$CO(CH_2)_{13}CO_2Me$		47	B	784	Acid 86.5–87
$n = 14$					
$CO(CH_2)_{14}CO_2Et$		53	B	781	Acid 90.5
$n = 15$					
$CO(CH_2)_{15}CO_2Me$		52	B	784	Acid 86–87
$n = 16$					
$CO(CH_2)_{16}CO_2Et$		90	B	781	Acid 91–91.5
$CO(CH_2)_{16}CO_2Et$		48	B	781	Acid 92.5–93.5
$CO(CH_2)_{16}CO_2Et$		50	B	781	Acid 94.5–95

TABLE 16. (*Continued*)

Acyl Group	R^2	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
2-Acylthiophenes (with a 3- or 4-Substituent in the Thiophene Ring)									
									
Acyl Group	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
	Me	H	H		109–111	32	D	881	
	H	Me	H		115–117	64	D	881	
	H	Bu^t	H		119	60	D	20	
	H	Me	Me		161	76	D	30	
	H	Me	Et		128	56	D	30	
3-Acylthiophenes									
									
	R^2	R^4	R^5						
$n = 2$									
$CO(CH_2)_2CO_2H$	Me	H	Me		111	ca. 60	D	774	
$CO(CH_2)_2CO_2Me$	Me	H	Me	184/18		73	A	882	2,4-DNP 202; Acid 114
$CO(CH_2)_2CO_2H$	Me	Et	Me		92	ca. 60	D	774	
$CO(CH_2)_2CO_2H$	Et	H	Et		80	71	D	45	Semi. 155
$CO(CH_2)_2CO_2Me$	Et	H	Et	189–190/11		64, 81	A, B	45, 883	Semi. 96.5; 2,4-DNP 117.5 (45)
$CO(CH_2)_2CO_2H$	Pr	H	Pr		71–72		D	780	

$CO(CH_2)_2CO_2Me$	Me	H	Bu^t	192–194/17		72	A	829	Acid 108
$CO(CH_2)_2CO_2Me$	Bu^t	H	Bu^t	160/2	74–76	78	B	883	
$n = 3$									
$CO(CH_2)_3CO_2Et$	Me	H	Me	199–200/16		70	A	882	2,4-DNP 113; Acid 85
$CO(CH_2)_3CO_2H$	Et	H	Et		58	75	D	45	Semi. 161
$CO(CH_2)_3CO_2Et$	Et	H	Et	200.5–201/10		67	A	45	2,4-DNP 114
$CO(CH_2)_3CO_2Me$	Bu^t	H	Bu^t		53–55	75	B	883	
$COCH_2CMe_2CH_2CO_2H$	Me	H	Me	215–220/20		68	D	856	
$n = 4$									
$CO(CH_2)_4CO_2Et$	Me	H	Me	155.5–156.5/0.5		83, 62	B, A	100, 882	2,4-DNP 103; Acid 98 (882)
$CO(CH_2)_4CO_2Et$	Me	$(CH_2)_5CO_2Me$	Me	209–214/1		82	B	100	
$n = 5$									
$CO(CH_2)_5CO_2Et$	Me	H	Me		37.5	58	A	882	2,4-DNP 100; Acid 58.5

[a] A = Keto-acid chloride-$AlCl_3$; B = keto-acid chloride-$SnCl_4$; C = $Si(OCOR)_4$–$SnCl_4$; D = dicarboxylic acid anhydride-$AlCl_3$.

[b] Semi. = semicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Ox. = oxime.

[c] If a reference is not given, the melting point of the derivative is quoted in the reference to the preparation.

acetylation (MeCOCl-$AlCl_3$) of thiophene, its alkyl derivatives, and mesitylene, gives results that vary with the order of mixing of the reactants, the amount of catalyst used, and the time and temperature of the reaction. In some cases the acetylation of the normally less reactive aromatic compound is observed.[889] When 2-acetylthiophene is treated with benzene—$AlCl_3$ at 110°C, acetophenone (18%) is formed by transacylation.[890] Heating 2-acetyl- or 2-benzoylthiophene with PhCOCl and MeCOCl, respectively, in the presence of an excess of $AlCl_3$ gives the same mixture of products (2-acetyl- and 2-benzoylthiophene; 2,4- and 2,5-diacetyl-, and 2,4- and 2,5-dibenzoylthiophenes) in each case, probably as a result of simultaneous acylation, deacylation, and transacylation reactions.[891] Under the rather drastic conditions employed, there also exists the possibility that 2-acetylthiophene might isomerize to the 3-isomer. 3-Acetylthiophenes behave normally under these conditions. A 2-*t*-butyl group[829] or a 2-$SiMe_3$ group[892] may be replaced by an acyl group during acylation with an acid chloride–$AlCl_3$. Amines of the type 2-$ThCH_2NR_2$ (R = H or Me) undergo ring acylation in the presence of an excess of $AlCl_3$ because the formation of a complex effectively prevents *N*-acylation or cleavage reactions.[893]

c. WITH TIN(IV) CHLORIDE

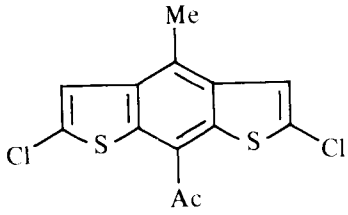
Thiophene is readily acylated in the presence of $SnCl_4$, whereas benzene is not. Hence benzene is the preferred solvent for this reaction. Thiophene and benzene may be separated by treating a mixture of the two with Ac_2O—$SnCl_4$, then distilling off the residual benzene.[894] Furan is more reactive than thiophene towards acetylation with acetic anhydride by a factor of 9.3 to 12, depending on the catalyst used ($SnCl_4$ or I_2).[895] In consequence, in a mixture of furan and thiophene, the former is acetylated (AcCl—$SnCl_4$) preferentially (90%) and 2-thenylfuran is acetylated (Ac_2O—H_3PO_4) on the furan ring.[841] Selenophene exhibits a reactivity intermediate between that of furan and thiophene toward acetylation with Ac_2O—$SnCl_4$.[896] The following order of reactivity of $SnCl_4$-catalyzed acetylations of substituted thiophenes has been established from competitive experiments: 2,5-Me_2 > 2-Me > 2,5-Et_2 > thiophene.[897] Primary steric effects are less important in the acetylation ($SnCl_4$—Ac_2O) of alkylthiophenes than in the acetylation of alkylbenzenes.[898]

Tin(IV) chloride is especially suitable as a catalyst for acylation with unsaturated acid chlorides since, in contrast to $AlCl_3$, it does not catalyze the addition of thiophene to the double bond.[899] When thiophene is acylated ($SnCl_4$) with the mixed anhydride, $AcOCOCH_2R$, the product is mainly 2-$ThCOCH_2R$; with $AcOCOCHR_2$, it is mainly 2-acetylthiophene.[900] The acid chlorides of 2-(ethoxycarbonyl)-3-nitrobenzoic acid and of 6-(ethyoxycarbonyl)-2-nitrobenzoic acid both give ethyl 3-nitro-2-(2-thenoyl)benzoate when treated with thiophene—$SnCl_4$.[849] Rearrangements of ketones of this type are discussed more fully in Section 3.G (under "Miscellaneous Reactions").

A 3-*t*-butyl[793] or a 2-(ethylthio) group[709] is replaced by an acetyl group during the acetylation of an alkylthiophene with AcCl—$SnCl_4$; a 2-*t*-butyl group is not similarly replaced.[793] When thiophene is treated with *p*-acetoxybenzoyl chloride—$SnCl_4$, the expected product is admixed with 2-acetylthiophene, resulting from intermolecular transfer of an acetyl group.[811]

d. WITH FREE CARBOXYLIC ACIDS

Ketones are conveniently obtained by acylation of thiophene derivatives with a carboxylic acid in the presence of phosphorus pentoxide, phosphoric acid, or polyphosphoric acid (Tables 14 and 15). Similar reagents also catalyze acylation with acid anhydrides, and this is perhaps the most convenient method for preparing 2-acetylthiophene.[1] However, the higher acid anhydrides are not readily available. With H_3PO_4—AcOH, 2-(selenophene-2-ylmethyl)thiophene is acetylated mainly (75%) in the selenophene ring.[5] (Arylmethyl)thiophenes ($ArCH_2Th$), in which Ar contains a thiophene ring or an activated benzene ring, undergo the direct Bradsher reaction when treated with AcOH—PPA[93,901] or RCOCl—$SnCl_4$.[800] For example, 2-chloro-5-(5-chlorothenyl)thiophene yields the tricyclic compound **70** by use of the former method.[901]



70

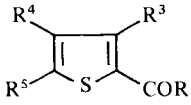
A very convenient method for the acylation of thiophenes with a free carboxylic acid involves refluxing the acid with $SiCl_4$ in benzene, then treating the resulting tetraacyloxysilane, $Si(OCOR)_4$, *in situ* with thiophene and $SnCl_4$.[737,770] $ZnCl_2$, $BeCl_2$, BF_3, and $TiCl_4$ have replaced $SnCl_4$ as the catalyst, but yields are low, except with $TiCl_4$.[902] Triacyloxyboranes (from RCO_2H—BBr_3) also acylate thiophene, but tetraacyloxygermanes (from RCO_2H—$GeCl_4$) are unreactive.[903] (Monoacyloxy)trichlorosilanes (from RCO_2H and excess of $SiCl_4$) are more reactive acylating agents than the tetraacyloxy compounds just described.[729,801]

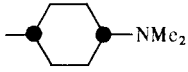
e. WITH TRIFLUOROACETIC ANHYDRIDE

Trifluoroacetic anhydride in 1,2-dichloroethane will trifluoroacetylate thiophene and alkylthiophenes without the use of a Lewis acid catalyst.[758,904] In an extensive quantitative study of this reaction, Marino and his colleages have determined the relative reactivities of thiophene and other 5-membered heterocycles and of thiophene and several of its 2-substituted derivatives.[759,896,905,906] A mixture of trifluoroacetic anhydride and a carboxylic acid behaves as the mixed anhydride, $CF_3COOCOR$, which gives the acyl (rather than the trifluoroacetyl) derivative by reaction with a thiophene in the absence of a catalyst.[758,907] In the case of a long-chain acid, the reaction is accelerated by the addition of phosphoric acid.[734] In related reactions, mixtures of 2-benzoyloxypyridine and trifluoroacetic acid,[908] *N*-benzoylimidazole and trifluoroacetic acid, or *N*-trifluoroacetylimidazole and benzoic acid[909] all behave as $PhCOOCOCF_3$, and benzoylate thiophene in very high yield (up to 100%).

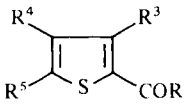
TABLE 17. ACYL, AROYL, AND HETEROAROYL THIOPHENES (INCLUDING THOSE THAN FRIEDEL-CRAFTS ACYLATION

2-Acylthiophenes



R	R^3	R^4	R^5	Boiling Point (°C/mm)
Me[d]	Me	H	H	98–99/14
Me[d]	H	Me	H	75–77/1.5
Me[d]	H	Me	Me	98–100/2.5
Me[d]	H	—$(CH_2)_4$—		
Me	H	H	2-Furylmethyl	135–138/3
Et	H	H	Et	131/14
$(CH_2)_3OH$	H	H	H	128–135/0.2
Pr^{i}[d]	H	H	H	56–58/0.2
Bu^{n}[d]	H	H	H	129–132/15
$(CH_2)_3CO_2Me$[e]	H	H	H	120–121/0.5
$(CH_2)_4CO_2Me$[e]	H	H	H	131–132/0.6
$(CH_2)_5CO_2Me$	H	H	H	139.5/0.6
$(CH_2)_6CO_2Me$	H	H	H	154/0.3
CH_2CHPh_2	H	H	H	
$CH_2CH(2\text{-Th})_2$	H	H	H	
$CH_2CHPh(2\text{-Th})$	H	H	H	
$CH_2CHMe(2\text{-Th})$	H	H	H	140–142/0.15
$CH_2CHPh(1\text{-naphthyl})$	H	H	H	
$CH_2CH(2\text{-Th})1\text{-naphthyl}$	H	H	H	
$COCMe_2Ph$	H	H	H	135/2
$COCEt_2Ph$	H	H	H	
$COCMe_2(2\text{-thienyl})$	H	H	H	134/1.5
	H	H	H	164–167/2
1-Methyl-2-piperidyl	H	H	H	123–127/3
1-Methyl-3-piperidyl	H	H	H	147–149/4
1-Methyl-4-piperidyl	H	H	H	145–147/3
(1-Methyl-2-piperidyl)methyl	H	H	H	145–150/3
2-Pyridylmethyl	H	H	H	167–172/1
3-Pyridylmethyl	H	H	H	176–180/4
(6-Methyl-2-pyridyl)methyl	H	H	H	156–157/1.5
$(CH_2)_3$-2-pyridyl	H	H	H	183–184/2
(2-Pyridyl-1-oxide)methyl	H	H	H	
(6-Methyl-2-pyridyl-1-oxide)methyl	H	H	H	
2-Quinolylmethyl	H	H	H	220–223/2
4-Quinolylmethyl	H	H	H	
9-Acridinylmethyl	H	H	H	

WITH AN ALKYL GROUP IN THE THIOPHENE RING), PREPARED BY METHODS OTHER

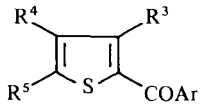


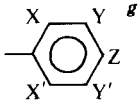
Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
	86	E	141	
	62, 66	N, R	533, 1248	2,4-DNP 259–260 (1248)
	55	N	914	
35	52	L	74	Ox. 156; 2,4-DNP 260
	16	E	796	Semi. 196–197
	75	E	44	Semi. 213; 2,4-DNP 192.5
	76	B	915	2,4-DNP 160.5–162
	91	B	143	
	58	D(Li)	147	Semi. 165–167
	57	M	276	Acid 77–78
	54	M	276	Acid 79
	53	M	276	Acid 66
	31	M	276	Acid 59
176–177	59	Q	916	Semi. 236–237
95–96	63	Q	916	Semi. 225–226
179–181	53	Q	916	Semi. 238–239
41–43		Q	917	2,4-DNP 176–178
152–153	74	Q	918	Semi. 242–243
108–108.5	55	Q	918	Semi. 236–237
87.5	44, 70	D(Li), D(Mg)	785	
86	23, 31	D(Li), D(Mg)	785	
	Low	D(Li), D(Mg)	785	
	73	E	919	HCl salt 174–176
	25	E	920	Picrate 197–198
	6	E	920	HCl salt 182–183
52	22	E	920	HCl salt 198–200
	26	E	920	
28.5–29.5	43, 74	G, G	921, 922	2,4-DNP 194.5–195.5 (921); PH 105–106; Picrate 154–155 (922)
	22	G	923	Picrate 150–150.5
40–41	83, –	G, G	924, 925	
	20	H	926	Semi. 167–168
153–154	83	G	927	
117–118	73	G	927	
125.5–126.5	76	G	924	
84–84.5	69	G	928	
216–217	69–87	G	929	

TABLE 17. (*Continued*)

R	R^3	R^4	R^5	Boiling Point (°C/mm)
CF_3	H	H	H	54–57/1
CHF_2	H	H	H	77–80/11
CF_2CF_3	H	H	H	66.5–67.5/21
$(CF_2)_2CF_3$	H	H	H	91.5–92/32
$(CF_2)_6CF_3$	H	H	H	64.5–66/0.3

2-Aroyl- and 2-Heteroaroylthiophenes



Ar	R^3	R^4	R^5	
Ph[f]	H	H	Me	
Ph	H	H	Et	199–200/13
Ph	H	H	Bu^t	171.5/1.5
Ph	Me	H	H	104–108/0.05
Ph	H	$-(CH_2)_4-$		
 [g]				
X=Me	H	H	H	
X=CO_2H[f]	H	H	H	
X=CO_2H	Me	H	H	
X=CO_2H	Et	H	H	
X=OH	H	H	H	140–145/3
Z=OH	H	H	H	
Z=C_6H_4OH-*p*	H	H	H	
X=NH_2, Y′=Cl	H	H	H	
X=CO_2H, Y=NO_2	H	H	H	
X=CO_2H, Z=NO_2	H	H	H	
X=CO_2H, X′=NO_2	H	H	H	
X=CO_2H, Y′=NO_2	H	H	H	
X=CO_2H, X′=Cl	H	H	H	
X=CO_2H, Y=Cl	H	H	H	
X=CO_2H, Y′=Cl	H	H	H	
X=CO_2H, Z=Cl	H	H	H	
X=CO_2H, X′=Y=Cl	H	H	H	
X=CO_2H, X′=Y=Y′=Z=Cl	H	H	H	
2-Thienyl	H	H	H	
3-Me-2-thienyl	Me	H	H	125–126/0.4
5-Me-2-thienyl	H	H	Me	125–126/0.01
2-Pyrrolyl	H	H	H	136–138/0.1

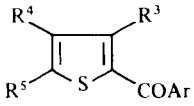
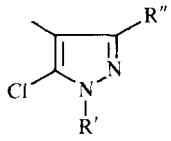
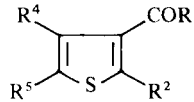
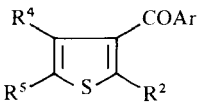
Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
	82, 39, 55	C	930, 931, 932	Ox. 113–120 (932)
	75	C	931	
	17	E	933	2,4-DNP 107–108
	32	E	934	2,4-DNP 90–91
	19	E	933	2,4-DNP 92–93.5
	2-Aroyl- and 2-Heteroaroylthiophenes			
24	54, 32	I, B	539	
	70	E	44	2,4-DNP 125
63	65	L	74	
	38, 71	B, D(Mg)	814	
71	91	L	74	
	61 (As imine)	D(Mg)	935	2,4-DNP 177–178
145	60, 91	A, A	824, 936	
137	60	A	936	
105	87	A	936	
	33	O	937	Ox. 128–129
103.5–104.5	22	O	937	
185		O	938	Me ether 177
97–98		F	939	Ox. 140–141
217	31	A	824, 940	
192.5–193.5	22, 26 (Crude)	A	824 940	
191–192	20	A	824, 940	
147, 179–180	33, 52 (Crude)	A	824, 940	Y′=NH_2 218–219
239	30	A	824	
129	35	A	824	
226	47	A	824	
155	14	A	824	
146	75, 82	A, A	824, 825	Me ester 63–64 (825)
207	86	A	824	
90–90.5	67, 92	J, P	941, 942	
	75	P	942	
50–51	60	P	942	
78	59, 31	E, E	943, 944	

TABLE 17. (*Continued*)

Ar	R^3	R^4	R^5	Boiling Point (°C/mm)
2-Pyridyl	H	H	H	138–140/0.6
4-Me-2-pyridyl	H	H	H	
3,4-diMe-2-pyridyl	H	H	H	125–140/0.8
4,5-diMe-2-pyridyl	H	H	H	
3-Pyridyl	H	H	H	
4-Pyridyl	H	H	H	
				
R′=R″=Me	H	H	H	
R′=Ph, R″=Me	H	H	H	148–150/0.15
R′=Me, R″=Pr	H	H	H	108–110/0.15
R′=Me, R″=Pr^i	H	H	H	128–130/0.4
R′=Me, R″=Bu^n	H	H	H	128–130/0.15
R′=Ph, R″=Me	H	H	H	
R′=Me, R″=Ph	H	H	H	

3-Acylthiophenes 

R	R^2	R^4	R^5	
Me	H	H	H	
Me	Me	H	H	64–67/2
Me[d]	Me	H	Me	95–105/15
Me	Et	H	Me	60–65/0.6
Me[d]	Bu^t	H	Bu^t	141–144/12
Et	H	H	H	103–116/10
Et	H	H	Me	114–116/12
Et	H	H	Bu^t	91–93/0.7
Pr	H	H	H	80–83/4
Bu^n	H	H	H	80–81/2
Bu^t	H	H	H	118–119/23
$(CH_2)_4Me$	H	H	H	150–163/10
CH_2(3-Thienyl)	H	H	H	
CF_3	H	H	H	164–165/760

3-Aroyl- and 3-Heteroaroylthiophenes 

Ar	R^2	R^4	R^5	
Ph	H	H	H	125–127/1

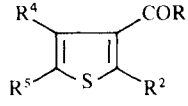
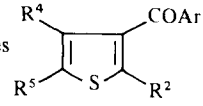
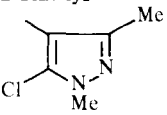
Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
	67, –	D(Mg), B	945, 946	Ox. 170–180 (947)
61–61.5	70	D(Li)	948	
	73	D(Li)	948	HCl salt 162–164
101–103	90	D(Li)	948	
94–97	91, –	D(Mg), B	947, 946	Ox. 162–167 (947)
94–97	83, –	D(Mg), B	947, 946	Ox. 149–150 (947)
97–99	71, 85	E, B	949	
	70	B	949	
	74	B	949	
	79	B	949	
	80	B	949	
84–86	88	B	949	
181–183	80	B	949	
		3-Acylthiophenes 		
57–58	57,	D(Mg),	950,	2,4-DNP 268 (950);
	68, 71	E, B	951, 951	Semi. 173–174 (141);
	95, 100	B, M	83, 275	PH 114 (953); Cyclic acetal 34–35 (952)
	49	E	954	Ox. 68.5–69.5
	17, 54	I, S	955, 794	Semi. 211–212 (794)
	42	C	956	
76–77		E	116	
	66, 61,	E, C	309, 957,	Semi. 186–188 (951), 195–196
	67, 22	B, E	951, 960	(766); Thio. 154–154.5; 2,4-DNP 214–215 (309); Ox. 67–68 (766)
	64	C	958	
	67	C	958	
	62	E	309	Semi. 170–171; 2,4-DNP 166–166.5
	56	E	309	Semi. 133–133.5; 2,4-DNP 164–165
		D(Mg)	766	Semi. 139–140; Ox. 143
25–26	71	C	957	
75	85	K	40	
	50	C	932	Ox. 97–98
		3-Aroyl- and 3-Heteroaroylthiophenes 		
63–64	75,	D(Li),	951	2,4-DNP (951); Cyclic acetal
	75, 56	B, D(Mg)	951, 309	76 (393)
	67, 78	E, S	309, 1036	

TABLE 17. *(Continued)*

Ar	R^2	R^4	R^5	Boiling Point (° C)
Ph	Me	H	H	150/0.3
Ph	H	Me	H	170/0.05
Ph	Me	H	Me	117–118/0.5
C_6H_4Me-*o*	H	H	H	114/0.03
$C_6H_4CO_2H$-*o*	Me	H	Me	
C_6H_4OMe-*p*	H	H	H	
C_6H_4CN-*p*	H	H	H	
3-Thienyl	H	H	H	
3-(4,5-diMe-3-thienyl)	H	Me	Me	
2-Thienyl	H	H	H	
	H	H	H	
2-Pyridyl	H	H	H	170–180/1
3-Pyridyl	H	H	H	
4-Pyridyl	H	H	H	
4-Me-2-pyridyl	H	H	H	
3,4-diMe-2-pyridyl	H	H	H	
4,5-diMe-2-pyridyl	H	H	H	

[a] A = Substituted phthalic anhydride + Grignard; B = oxidation of —CH(OH)—; C = thienyllithium + $RCONMe_2$ or $RCONEt_2$; D(Li) = nitrile + organolithium derivative; D(Mg) = nitrile + Grignard; E = organometallic derivative + acid chloride or acid anhydride or ester; F = thienylmagnesium halide + substituted 2-methyl-4*H*-3,1-benzoxazin-4-one and hydrolysis of the resulting NHAc compound; G = "active methyl" compound + $ThCO_2R$; H = Michael addition of 2-ThCOMe to 2-vinylpyridine; I = from an acetylenic precursor; J = 2-thienyllithium + CO_2; K = reduction of a benzoin ($SnCl_2$-HCl-EtOH); L = $R^5C(Cl)=CR^4(CHO)$ + (a) Na_2S—DMF, (b) $RCOCH_2Cl$; M = aldehyde + diazo compound; N = reduction (Zn-dioxane-H_2O) of $—CH_2Cl$; O = Fries rearrangement; P = thienyllithium + Me_2NCOX (X = OEt or OPh or Cl); Q = addition of Grignard reagent to $\alpha\beta$-unsaturated C=O compound; R = hydrodehalogenation of a halothiophene; S = decarboxylation of a thiophene carboxylic acid.

f. MISCELLANEOUS ACYLATING AGENTS

With thiophene, the benzoic acid dihalophosphoric anhydride [$PhCO_2P(O)X_2$; X = Cl or F] gives 2-benzoylthiophene (84 to 92%) without the need for a catalyst.[910] 2-Acetylthiophene is obtained similarly from acetic anhydride and $Cl_2P(O)OP(O)Cl_2$ [i.e., $MeCO_2P(O)Cl_2$ is formed *in situ*]. 2-Benzoylthiophene is obtained (60%) by treatment of thiophene with tribenzoyl phosphate (from PhCOCl and Ag_3PO_4).[911] Thiophene is acetylated by the mixed sulfonic–carboxylic acid anhydride, $MeCOOSO_2Me$,[912] and by acetyl toluene-*p*-sulfonate.[913]

B. Methods Not Involving Friedel-Crafts Acylation

Ketones that have been prepared by the following methods are listed in Table 17.

Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
	58	R	831	
	62	D(Li)	831	
	6.5	I	955	
	46	D(Li)	831	
127	62	A	936	
64	50	B	828	
118–118.5	11	B	808	
78–80	45–89, 94	P, B	942, 147	
75–76	90	B	112	
62–63	72	B	951	
86–88	84	B	949	
		B	946	
73–76		B	946	
98–101		B	946	
94–95	52	D(Li)	959	
	53	D(Li)	959	HCl salt 198–200
69–70	63	D(Li)	959	

[b] Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Semi. = semicarbazone; Ox. = oxime (may be a mixture of isomers); PH = phenylhydrazone; Cyclic acetal = 1,3-dioxolane.

[c] If a reference is not given, the melting point of the derivative is quoted in the reference to the preparation.

[d] This compound is also listed in Table 14.

[e] This compound is also listed in Table 16.

[f] This compound is also listed in Table 15.

[g] Substituents = H, unless stated otherwise.

a. FROM ORGANOMETALLIC DERIVATIVES OF THIOPHENE

Thienyllithium derivatives[147,393,785,831,948,959] or thienylmagnesium halides[766,935,945,947,961] react smoothly with nitriles, particularly if the nitrile does not possess an α-hydrogen atom,[951] and the resulting imines are readily hydrolyzed to the ketone. Several ketones have also been obtained by treatment of a lithiothiophene derivative[796] or a thiophene Grignard reagent[116,951] with a carboxylic anhydride.

Because of the instability of 3-thienyllithium, these methods are not always satisfactory for 3-acyl derivatives. However, if 3-thienyllithium is first converted into the Grignard reagent with $MgBr_2$, and this is treated with acetic anhydride at −70°C, 3-acetylthiophene is obtained in 68% yield.[951] If the lithio derivative is treated successively with cadmium chloride (or zinc chloride) and acetic anhydride, a mixture of 2- and 3-acetyl derivatives ensues.[951] When 2-thenylmagnesium chloride reacts with acetic anhydride or acetyl chloride, rearrangement takes place

to give 3-acetyl-2-methylthiophene (25 to 35%).[954] Analogously, 3-thenylmagnesium bromide gives 2-acetyl-3-methylthiophene (55%) with acetyl chloride.[962] A substituted phthalic anhydride undergoes opening of the anhydride ring when treated with a 2-thienylmagnesium halide to give a 2-thenoylbenzoic acid (or a mixture of two isomers if the original anhydride was not substituted symmetrically.[809,824,825,936,940]

The reaction of a thienyllithium derivative (ThLi) with an *N,N*-dimethylcarboxamide ($RCONMe_2$) has been used widely for the preparation of the acyl derivatives, ThCOR.[956-958] If the amide is replaced by an *N,N*-disubstituted carbamate derivative (Me_2NCO_2R or Me_2NCOCl), the symmetrical ketone, ThCOTh, is obtained in high yield.[942] The same ketone is also obtained by treating ThLi with carbon dioxide.[941] Treatment of a 2-thienyllithium with lithium benzoate affords 2-benzoylthiophene in 63% yield.[963] Ketones containing an amino function have been obtained by treating 2-thienylmagnesium bromide with an aminocarboxylic ester.[919,920]

A few ketones have been made by 1,4-addition of 2-thienylmagnesium bromide to an $\alpha\beta$-unsaturated carbonyl compound.[916,917]

Bis-(2-thienyl) ketone may be obtained by carbonylation of 2-chloromecurithiophene with carbon monoxide in the presence of Li_2PdCl_4[965] or LiCl-$[Rh(CO)_2Cl]_2$.[966]

b. FROM THIOPHENES THAT ALREADY CONTAIN A CARBONYL GROUP

A thiophene carbonyl chloride reacts with a dialkylcadmium[44,141,309,960] or with ZnPhBr[44] to give the alkyl or phenyl ketone, respectively. Ketones (ThCOR) are obtained from ThCN and RMgBr.[808,950] Thiophene-2-carbonyl chloride reacts with a pyrrolyl (or indolyl) magnesium bromide to give the appropriate pyrrolyl (or indolyl) thienyl ketone (Oddo reaction).[943,944,964] Thiophene carboxylic esters ($ThCO_2R$) undergo base-catalyzed condensation with nitrogen heterocycles containing an "active" methyl group (Het-Me) to give the ketones, Het-CH_2COTh.[921-925,927-929] Thiophene-2-carboxylic acid is converted into bis-(2-thienyl) ketone (71%) by treatment of the thioate, 2-ThCOS-(2-pyridyl), with bis-(1,5-cyclooctadiene)nickel.[967]

The unsaturated ketones, 2-ThCOCH=CHAr, react with arylmagnesium halides (Ar'MgBr) by 1,4-addition to give the saturated ketones, 2-$ThCOCH_2CH(Ar)Ar'$.[916,918] 2-Acetylthiophene undergoes Michael addition to 2-vinylpyridine to give (2-pyridyl)$(CH_2)_3$COTh-2 (20%).[926] It also undergoes acid-catalyzed addition to the Schiff's bases, $ArN{=}CHC_6H_4F$-*p*, to give 2-$ThCOCH_2CH(NHAr)C_6H_4F$-*p*.[968]

A few (hydroxyaroyl)thiophenes have been obtained by Fries rearrangement of the appropriate phenolic ester (ArOCOTh), either photolytically[937] or with aluminum chloride.[938]

Thiophene carboxaldehydes are converted into the ketones, $ThCOCH_2R$, by treatment with diazoalkanes, $RCH{=}N_2$.[275,276] The benzoin analogue, 3-ThCH(OH)-COTh-3, is reduced by tin(II) chloride in ethanolic HCl to 3-$ThCH_2$COTh-3.[40]

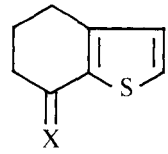
Some ketones with substituents in normally inaccessible positions have been obtained by decarboxylation of acylthiophene carboxylic acids,[794] dehalogenation

($Cu—EtCO_2H$) of chlorothiophenes containing an aroyl substituent,[831] and reduction (Zn—aqueous dioxane) of chloromethyl compounds ($—CH_2Cl \rightarrow —Me$).[533,914]

c. OXIDATIVE METHODS

Secondary alcohols, normally obtained from the appropriate aldehyde by means of a Grignard reaction, have been oxidized to the corresponding ketone by use of $CrO_3—H_2SO_4$,[539,808] Jones reagent,[949] $CrO_3—AcOH$,[147,946,951] CrO_3—pyridine,[112,814] pyridinium chlorochromate,[143] $CuSO_4$—pyridine,[828] $Pb(OAc)_4$—pyridine,[83] and manganese dioxide.[915]

2-Ethyl- and 2-benzylthiophene are oxidized in the liquid phase to 2-acetyl- and 2-benzoylthiophene respectively by use of oxygen in the presence of cobalt(II) acetate as catalyst and sodium bromide or 9,10-dibromoanthracene as a promoter.[969-971] Other products (notably the secondary alcohol or its acetate ester) are also formed, so this method is yet of little preparative importance. 4,5,6,7-Tetrahydrobenzo[*b*]thiophene (**71**; $X = H_2$) is oxidized by Ce^{4+} in aqueous acetic acid to the ketone **71**; X = O.[972]



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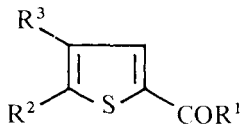
d. FROM OPEN-CHAIN PRECURSORS

The acetylenes, $MeCOCH(COR)CH_2C{\equiv}CH$ (R = Me or Ph), are cyclized in low yield by H_2S—HCl to 3-acetyl- or 3-benzoyl-2,5-dimethylthiophene, respectively.[955] The diacetylene, $PhCOC{\equiv}C—C{\equiv}CMe$, gives 2-benzoyl-5-methylthiophene (54%) when treated with H_2S in alkaline solution.[539] The acetylenic aldehyde, $R^2C{\equiv}CCHO$, undergoes Michael addition of $R^1COCH_2S^-$; spontaneous cyclization of the product yields ketone (**72**; $R^3 = H$).[973] Vilsmeier-Haack formylation of the ketone, $R^2COCH_2R^3$, gives the (chlorovinyl)aldehyde, $R^2C(Cl)=C(CHO)R^3$. On successive treatment with Na_2S—DMF and $ClCH_2COR^1$, this gives the ketone (**72**) in good yield.[74]



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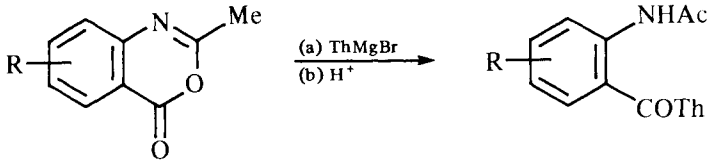
e. FROM OTHER HETEROCYCLES

A thienylmagnesium halide reacts with a 2-methyl-4*H*-3,1-benzoxazin-4-one, to give an (*o*-acetamidobenzoyl)thiophene (Scheme 9).[939,974] This is a useful procedure, since the starting material is readily available.



Scheme 9

2-Benzoylthiophene has been obtained (71%) by treatment of *N*-methylisothiazolium perchlorate with sodium benzoylacetate.[975]

f. MISCELLANEOUS METHODS

2-Acetylthiophene has been prepared in 48% yield by treatment of 2-iodothiophene with a mixture of CO, $SnMe_4$, and $Ni(CO)_2(PPh_3)_2$ in HMPA.[976] It may also be obtained (76%) by treating the di-(2-thienyl) iodonium salt $[(2\text{-Th})_2I^+Br^-]$ with the organoiron complex, $Li[MeCOFe(CO)_4]$.[977]

g. PERFLUOROACYL THIOPHENES AND RELATED COMPOUNDS

Standard Friedel-Crafts acylation procedures do not generally succeed with fluorinated acids, acid chlorides, or anhydrides. However, perfluoroacyl compounds have been prepared from 2-thienylmagnesium bromide and the appropriate acid chloride using the reverse addition technique.[933,934] The most satisfactory procedure seems to be the acylation of a thienyllithium derivative with a fluorocarboxylic acid[930] or its *N*,*N*-dimethyl or *N*,*N*-diethyl amide.[930–932]

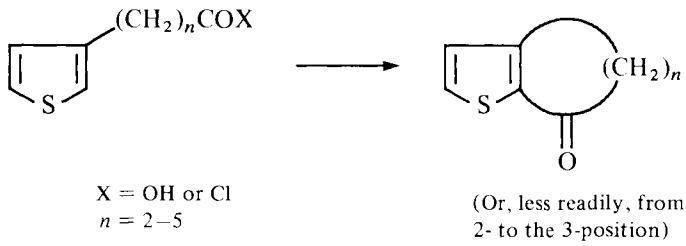
Treatment of thiophene with the Vilsmeier-like fluorinated immonium salt, $ClCH(F)CF{=}N^+Et_2BF_4^-$, affords 2-ThCOCHCl(F) (52%).[978]

2. Preparation of Cyclic Ketones

A. Rings Containing Five to Eight Atoms

Such ketones are most readily obtained by intramolecular Friedel-Crafts cyclizations of ω-thienylalkanoic acids or their acid chlorides (e.g., Scheme 10), using the methods listed in Table 18.

Six-membered rings are formed the most readily. For example, if a thiophene derivative contains two $-(CH_2)_nCO_2H$ side-chains, that in which $n = 3$ cyclizes



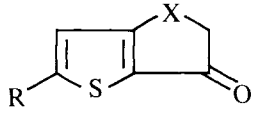
X = OH or Cl
n = 2–5

(Or, less readily, from the 2- to the 3-position)

Scheme 10

preferentially.[870] If the cyclization (Scheme 10; $n = 3$) is carried out with PPA in the presence of an aliphatic acid anhydride (normally Ac_2O), by-products may be formed in which an acyl group has been introduced into the 2-position of the cyclized product.[881,915,993,997] Cyclizations into the 2-position are preferred (Scheme 10); if attempts are made to force cyclization into the 4-position by introducing a *t*-butyl group or a halogen atom into the 2-position, the blocking group may be lost during cyclization with aluminum chloride[829,989] or PPA.[746,986]

For the preparation of five-membered ring ketones, PPA (on the carboxylic acid) is the reagent of choice; for six- and seven-membered rings, $SnCl_4$ (on the acid chloride) is preferred.[865,983] The dilution principle is employed when seven-membered rings are prepared.[853] Eight-membered rings are formed with considerable difficulty unless the cyclization is from the 3- into the 4-position (with positions 2- and 5- blocked); in this case PPA gives a yield of about 60%, whereas $SnCl_4$ gives no cyclized product.[983] Cyclization reactions may proceed with rearrangement, due to an initial *ipso* attack of the electrophile in the more reactive 2-position.[1005,1012] For example, treating (2-thienylthio)acetic acid with concentrated sulfuric acid gives the same ketone (**73**; R = H, X = S) as that obtained from the corresponding 3-thienyl isomer.[1005] A claim[1016] that β-(5-methyl-2-thienyl)propoionic acid cyclizes with rearrangement to (**73**; X = CH_2, R = Me) has been refuted.[958]



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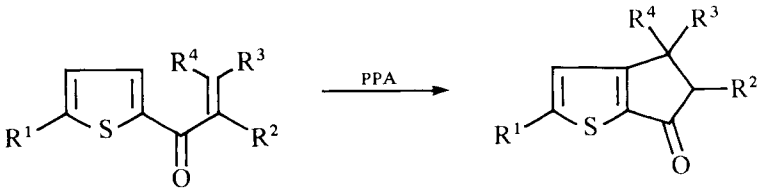
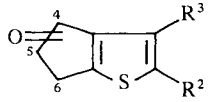
Five-membered ring ketones are conveniently obtained by cyclization of αβ-unsaturated ketones with PPA (Scheme 11).[746,958,979,984,985] Treating a thiophene

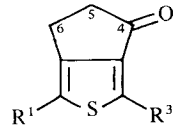


Scheme 11

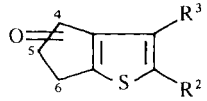
TABLE 18. CYCLIC (EXCLUDING MACROCYCLIC) KETONES PREPARED BY ELEC-



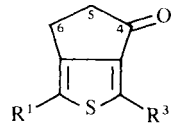
Position of C=O Group	R^2	R^3	Other Substituents	Boiling Point (° C)	Melting Point (° C)
4-C=O	H	H		110/0.2	115–117
4-C=O	H	H	5-Me	115–119/9	39–40
4-C=O	H	H	5-[-$(CH_2)_5$-][d]		95–96
4-C=O	H	H	6-[-$(CH_2)_5$-][d]		102–103
4-C=O	H	H	6-Bu^t	Oil	
4-C=O	H	H	5-Ph	185/2	103–104
4-C=O	H	H	6-Ph	130–135/0.1	93–94
4-C=O	H	Me			76
4-C=O	Me	Me			
4-C=O	Bu^t	H	5-Me	95–96/0.3	
4-C=O	Me	H			65–66
4-C=O	Me	H	5-Me	81–83/0.1	
4-C=O	Cl	H	6-[-$(CH_2)_5$-][d]		100–101
6-C=O	H	H		110/7	92–93
6-C=O	H	H	4-Me	130–132/12	
6-C=O	H	H	5-Me	106/2	
6-C=O	H	H	4,4-DiMe	120–123/11	
6-C=O	H	H	4-Ph		84.5–85
6-C=O	H	H	5-Ph	180/1	96–97
6-C=O	H	H	4-[-$(CH_2)_5$-][d]		38–39
6-C=O	Me	H			53–54
6-C=O	Me	H	5-Me	81–82/0.15	
6-C=O	Bu^t	H	5-Me	124–126/1	
6-C=O	Br	H			116
6-C=O	Cl	H	5-Me	91/0.8	
6-C=O	SMe	H	5-Me	127–130/0.8	
6-C=O	H	H	4-S (replacing 4-CH_2)		96.5–97.5



	R^1	R^3			
4-C=O	H	Bu^t	5-Me	125/3	
4-C=O	Me	Me		110–114/0.2	31
4-C=O	Me	Me	5-Me	143/16	
4-C=O	Cl	Cl			65–66
4-C=O	Cl	Cl	5-[-$(CH_2)_5$-][d]		78–79



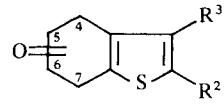
Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
36	E	979	
54, 77	E, G	979, 746	Semi. 190–192; 2,4-DNP 243–245; Ox. 121–122 (979)
81	E	980	
43	E	980	
92	E	981	2,4-DNP 187–190
16	E	979	
35	D	838	2,4-DNP 250; Ox. 214
3	E	28	
30	E	28	Ox. 158
50	G	958	
30	G	958	
61	G	958	
88	E	980	
44, 60, 28	F, F, A	979, 982	2,4-DNP 255–255.5 (982)
68	G	746	2,4-DNP 197–202
60, 58	E, A	979, 983	Semi. 183–185 (979); 2,4-DNP 257 (983);
84, 78	G, G	746, 984	Ox. 121–123 (979); 127.5 (983)
69	G	746	
75, 27	G, G	746, 985	2,4-DNP 175–178 (746); *E*-Ox. 166; *Z*-Ox 200 (985)
22, 72, 3	E, F, G	979, 746	
71	E	980	
24	G	958	
82	G	958	
54	G	958	
38	E	746	2,4-DNP 263
50, 68	G, G	979, 958	2,4-DNP 218–219 (979)
20	G	958	
90	I	1005	



50–60	E	986	2,4-DNP 242
80–90	E	983, 987	2,4-DNP 299; Ox. 205 (983)
70	E	983	2,4-DNP 224; Ox. 170
50–60, 81	B, B	988, 982	Ox. 228; $R^1 = R^3 = H$ (by reduction) 81–82 (982)
49	E	980	

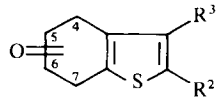
TABLE 18. *(Continued)*

Position of C=O Group	R^1	R^3	Other Substituents	Boiling Point (°C/mm)	Melting Point (°C)
4-C=O	Cl	Cl	5-Me	145/2	37
4-C=O	Cl	Cl	6-Me		45–46
4-C=O	Cl	Cl	6-[-$(CH_2)_5$-][d]		139–140



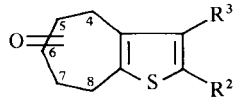
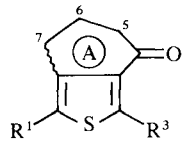
	R^2	R^3			
4-C=O	H	H		125–130/7	35–36.5
4-C=O	H	H	5-Me	158/20	
4-C=O	H	H	6-Me	141–141.5/11	69
4-C=O	H	H	7-Me	90/0.5	
4-C=O	H	H	5-[-$(CH_2)_5$-][d]		44–45
4-C=O	H	H	6-[-$(CH_2)_5$-][d]		66–68
4-C=O	H	H	7-[-$(CH_2)_5$-][d]		42–44
4-C=O	Me	H		148/12	29–30
4-C=O	H	Me		88/0.2	
4-C=O	Et	H		165/14	
4-C=O	Pr^i	H		88–89/0.05	
4-C=O	Bu^t	H		170–171/13	
4-C=O	H	Bu^t		179/13	
4-C=O	Me	Me		97/0.6	48–49
4-C=O	Et	Me		164–165/16	
4-C=O	——$(CH_2)_5$——			157–159/2	55–56
4-C=O	COMe	H			87–88
4-C=O	COMe	H	7-[-$(CH_2)_5$-][d]		125–126
4-C=O	COEt	H		186/1	77–78
4-C=O	$CO(CH_2)_4Me$	H		190/1	41–42
4-C=O	COMe	Me			127.5–129
4-C=O	$(CH_2)_2CO_2H$				115
4-C=O	$(CH_2)_3CO_2H$	H			114–115
4-C=O	$(CH_2)_4CO_2H$	H			78–80
4-C=O	$(CH_2)_5CO_2H$	H			92–93
4-C=O	Cl	H		150–152/10	39–40
4-C=O	Br	H			80–81.5
7-C=O	H	H		153/18	34.5
7-C=O	H	H	6-Me	160/17	69.5
7-C=O	H	H	5-Me	148/12	48
7-C=O	Bu^t	H		140/1.5	
7-C=O	Cl	H		155–156/10	34.5–35.5

Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
50–60	B	988	2,4-DNP 245; R^1 = Cl, R^3 = H (by reduction) 52
66	B	989	
86	E	980	



Excellent, 90	A, D	792, 990	Semi. 235; 2,4-DNP 258 (792) Ox. 130–131 (990)
78	A	983	2,4-DNP 235; Ox. 103
–, 36	A, H	991, 992	Semi. 188–189; 2,4-DNP 259.5; Ox. 149–149.5 (991)
50	H	992	
82	E	852	
72	E	852	
92	E or D	993	
–, 99, 85	A, A, D	867, 994 995	Semi. 254; 2,4-DNP 284 (867); Ox. 108 (868)
55	H	992	
91	A	792	Semi. 233; 2,4-DNP 249.5; Ox. 91–92
85	A	869	
42	A	20	Semi. 249
	A	20	Semi. 238
26, 10	A, H	30, 992	Semi. 199 (30)
79	A	30	
74	A	996	Ox. 91
Low, 12	D, D	915, 997	2,4-DNP 227–240 (915)
9	D	993	
26	D[e]	997	
34	D[e]	997	
85	D	881	DiOx. 175–177
70	D	870	Ox. 194–195
74	E	871	Ox. 148–149 (870)
70	D	870	Ox. 167–168
75	D	870	Ox. 114–115.5
70	A	998	Semi. 219 (804); Ox. 107–108.5
55	D	990	Ox. 114.5–115.5
81, 78	A[f]	983, 999	2,4-DNP 265; Ox. 166.5 (983)
81	A	983	2,4-DNP 204
77	A	983	2,4-DNP 268.5; Ox. 139
50–60	E	986	2,4-DNP 260
80	A	1000	Ox. 177–178

TABLE 18. *(Continued)*

Position of C=O Group	R^2	R^3	Other Substituents	Boiling Point (°C/mm)	Melting Point (° C)
					
4-C=O	H	H		156/13	
4-C=O	H	H	5-Me	157.5/18	
4-C=O	H	H	6-Me	112–113/1	
4-C=O	H	H	7-Me	90–94/0.5	
4-C=O	H	H	6-Et	125–126/2	
4-C=O	H	H	6-Me,6-Pr	151–153/4	
4-C=O	H	H	6,6-DiEt	146–148/3	
4-C=O	H	H	6-Me,6-Bu^i	185/7	
4-C=O	H	H	6-[-$(CH_2)_4$-][g]		50
4-C=O	H	H	6-Me,6-pentyl	142/6	
4-C=O	H	H	6-Ph	180–183/2	
4-C=O	Me	H		108/1.5	
4-C=O	Me	H	6-Me	121–124/1.5	
4-C=O	Me	H	6-[-$(CH_2)_4$-][g]		52
4-C=O	Et	H		170/13	
4-C=O	Et	H	6-[-$(CH_2)_4$-][g]	165/1	
4-C=O	Pr	H		175/13.5	
4-C=O	Bu^n	H		187–188/10	
4-C=O	Bu^i	H		168–170/8	
4-C=O	Bu^t	H			60.5
4-C=O	$(CH_2)_5Me$	H		162–164/2	
4-C=O	$-(CH_2)_5-$				85–86
4-C=O	$(CH_2)_6Me$	H		217–218/14.5	
4-C=O	$(CH_2)_9Me$	H		198/5	
4-C=O	$(CH_2)_{10}Me$	H		223–225/5	
4-C=O	Cl	H		157/6	
8-C=O	H	H		160/17	
8-C=O	H	H	7-Me	161/17	
8-C=O	Bu^t	H		140/1	
8-C=O	Cl	H		168/10	43–44
					
Size of Ring A	R^1	R^3			
6	Me	Bu^t		175/16	52
6	Me	H		157–158/17	49–50

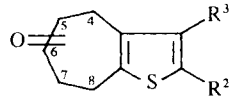
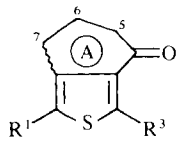
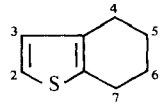
Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
			
53	A	853	Semi. 187; 2,4-DNP 233; Ox. 100–101
70	A	983	2,4-DNP 193
85	A	873	Semi. 166–167; Ox. 69–71
66	A	203	
92	A	857	
	B	859	2,4-DNP 126
64	B	858	
ca. 70	E	860	2,4-DNP 112
55	A	861	2,4-DNP 162
65	E	862	2,4-DNP 148
57	A	863	Ox. 161–162
90	A	877, 779	Semi. 198; 2,4-DNP 245 (779); Ox. 123–124 (873) and 76–78 (1001)
63	A	877	
80	A	861	2,4-DNP 210
90	A	853	Semi. 191; 2,4-DNP 184; Ox. 43–45 (874)
84	A	861	
88	A	779	Semi. 167–168; 2,4-DNP 173; Ox. 72–73 (874)
91	C	874	Ox. 36–37.5
86	C	874	Ox. 63.5–64.5
68	A	779	Semi. 170–171; 2,4-DNP 187; Ox. 110–112 (874)
91	A	874	Ox. 48–49
73	A	996	Ox. 92
80	A	779	Semi. 118–118.5; 2,4-DNP 107
70	A	779	Semi. 114; 2,4-DNP 107
68	A	779	Semi. 118; 2,4-DNP 102
59	C	874	Ox. 88–90
68	A	983	2,4-DNP 227; Ox. 113.5
71	A	983	2,4-DNP 188.5
50–60	E	986	2,4-DNP 196
90	A	1000	Semi. 199–201; Ox. 96–97
			
	A	829	
	A	829	2,4-DNP 275; Ox. 113

TABLE 18. *(Continued)*

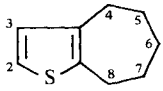
Size of Ring A	R^1	R^3	Other Substituents	Boiling Point (°C/mm)	Melting Point (° C)
6	Me	Me		152–153/13	46
6	Me	Me	6-Me		57.5
6	Me	Me	5-Me	158–158.5/17	
6	Et	Et		140/3.5	
6	Cl	Cl		127–129/2	42–43
7	Me	Me		170/17	
7	Me	Me	5-Me	180/17	
7	Et	Et		176–177/11.5	
7	Cl	Cl		133–134/2	
				175/2	46
7	Cl	Cl	5-Me	155/2	45
8	Me	Me		173–174/15	41
8	Me	Me	5-Me		

6-Ring Ketones with a Heteroatom in the Carbonyl-Containing Ring



Position of C=O	Heteroatom and Position	Other Substituents	Boiling Point (°C/mm)	Melting Point (°C)
4-C=O	6-*N*-Tosyl			170/171
4-C=O	6-S		170/15	42
4-C=O	6-S	5-Me	166/14	
4-C=O	7-S		170/15.5	61
7-C=O	5-N-Tosyl			181–183
7-C=O	5-N-Methanesulfonyl			123–123.5
7-C=O	5-N-Benzyl			
7-C=O	5-N–$CH_2C_6H_4Cl$-*o*			
7-C=O	4-S		177/15	71
7-C=O	5-S		180–180.5/18	67
7-C=O	5-S	6-Me	177/14	44
7-C=O	5-S	6-CO_2Me		165–168

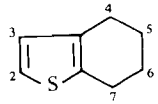
7-Ring Ketones with a Heteroatom in the Carbonyl-Containing Ring



4-C=O	6-S		195/15	78
4-C=O	6-S	5-Me	200/15	95.5
8-C=O	4-S		181/12	55
8-C=O	5-S		175–185/13	
8-C=O	6-S		203/17	89
8-C=O	6-S	7-Me	205/15	127

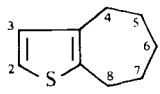
Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
100, 80	A, A	994, 983	2,4-DNP 280 (983)
70	A	983	2,4-DNP 278; Ox. 153
82	A	983	2,4-DNP 252; Ox. 135
91	A	45	2,4-DNP 217; Ox. 122
71	B	1002	2,4-DNP 317; Ox. 177 (988); R^1 = Cl, R^3 = H (by reduction) 82–83.5 (1002)
78	A	1003	Semi. 138 (1003); 2,4-DNP 222.5; Ox. 130 (983)
30	A	983	
	A	45	2,4-DNP 150
65	B	1002	R^1 = Cl, R^3 = H (by reduction) 50–52;
50–60	B	988	2,4-DNP 215; Ox. 158
50–60	B	988	R^1 = Cl, R^3 = H (by reduction) 35
60	E	1003, 983	2,4-DNP 149.5; Ox. 122 (983)
2	E	983	(Not characterized)

6-Ring Ketones with a Heteroatom in the Carbonyl-Containing Ring



Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (Ref.)[c]
23	A	1004	
65, 40	A, J	1006, 1007	2,4-DNP 226 (1006)
70	A	1006	2,4-DNP 224.5
89	A	1008	Semi. 249.5; 2,4-DNP 260; Ox. 128
64	A	1004	
72	A	1004	
60	I	1004	HCl salt 134–135
58	I	1004	HCl salt 129–130
90	A	1008	Ox. 178; Semi. 272; 2,4-DNP 245
48, ca. 60	J, A	1007, 1009	2,4-DNP 244 (1009)
60	A	1009	2,4-DNP 196.5; Ox. 153
20	K	1010	

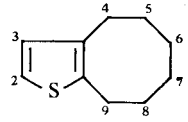
7-Ring Ketones with a Heteroatom in the Carbonyl-Containing Ring



60	A	1011	2,4-DNP 246; Ox. 132
75	A	1011	2.4-DNP 188
60	A	1008	Semi. 238; 2,4-DNP 200; Ox. 123
10	A	1009	2,4-DNP 200
60	A	1011	2,4-DNP 238; Ox. 165
75	A	1011	2,4-DNP 110; Ox. 131

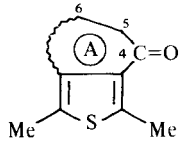
TABLE 18. (*Continued*)

8-Ring Ketones with or without a Heteroatom in the Carbonyl-Containing Ring



Position of C=O	Heteroatom and Position	Other Substituents	Boiling Point (°C/mm)	Melting Point (°C)
4-C=O	None			45.5–47.5
4-C=O	None	2-Et	190/17	
9-C=O	6-S		182/18	109.5
9-C=O	6-S	7-Me	185/15	133

Miscellaneous Ketones with a Heteroatom in the Carbonyl-Containing Ring



(Atoms in ring A numbered consecutively from 4 C=O)

Size of Ring A				
5	6-S			115–118
6	6-S			68
6	6-S		190/18	86
6	6-S	5-Me	189/15	94
6	7-S			51
7	6-S		203/19	77
7	6-S	5-Me	200/16	104.5
7	8-S		181/16	34
8	7-S		178–180/2	96
8	7-S	6-Me	187/2	124

[a] A = acid chloride—$SnCl_4$; B = acid chloride—$AlCl_3$; C = acid chloride—$TiCl_4$; D = acid-PPA/Ac_2O; E = acid-PPA; F = acid-HF; G = $\alpha\beta$-unsaturated ketone-PPA; H = from 3-mercaptocyclohexanone (see text); I = acid-H_2SO_4; J = acid-P_2O_5; K = Dieckmann cyclization of diester (see text).

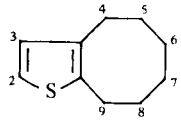
[b] Semi. = semicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Ox. = oxime.

directly with an $\alpha\beta$-unsaturated acid, $R^3R^4C{=}CR^2CO_2H$, in the presence of PPA gives the same ketone; however, the yield is low, presumably because of polymerization of the unsaturated acid under these conditions.[958]

A few ketones have been prepared in low yield by the thionation reaction shown in Scheme 12.[28,1017]

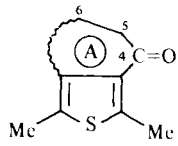
6,7-Dihydrobenzo[*b*]thiophen-4(5*H*)-ones (**74**) have been obtained by treatment of a 3-mercaptocyclohexanone with glyoxal or a 1,2-diketone (Scheme **13**).[992] The parent compound (**74**; $R^1 = R^2 = R^3 = H$) has been made by Michael addition

8-Ring Ketones with or without a Heteroatom in the Carbonyl-Containing Ring



Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (Ref.)[c]
9	B	878	Semi. 213–215
8, 48	A, B	779, 878	2,4-DNP 209.5 (878)
60	A	1012	2,4-DNP 238; Ox. 167
60	A	1012	2,4-DNP 195; Ox. 182

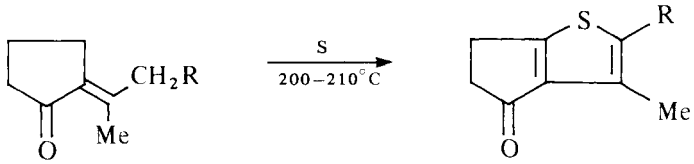
Miscellaneous Ketones with a Heteroatom in the Carbonyl-Containing Ring



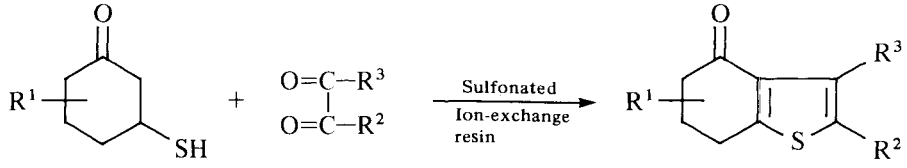
(Atoms in ring A numbered consecutively from 4 C=O)

	F	1331	
40	J	1007	
	A	1013	2,4-DNP 273; Ox. 200
	A	1013	2,4-DNP 223; Ox. 108
61	E	1014	
81	A	1015	2,4-DNP 261; Ox. 170
93	A	1015	
67	A	1015	2,4-DNP 203; Ox. 114
6	A	1012	2,4-DNP 160
6	A	1012	

[c] If a reference is not given, the melting point of the derivative is quoted in the reference to the preparation.
[d] Spirocyclohexane.
[e] $(RCO)_2O$ replaces Ac_2O.
[f] $SOCl_2$ (no catalyst) on acid.
[g] Spirocyclopentane.



Scheme 12

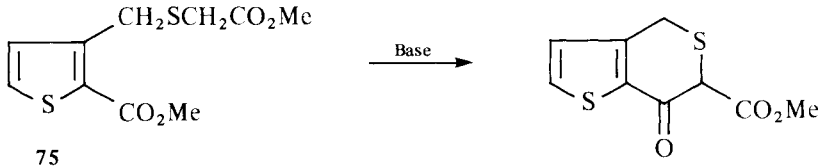


74

Scheme 13

of mercaptoacetaldehyde diethylacetal to cyclohex-2-enone and cyclization of the product.[1018]

The di-ester (**75**) undergoes Dieckmann cyclization to the β-keto ester (**76**).[1010]



75 76

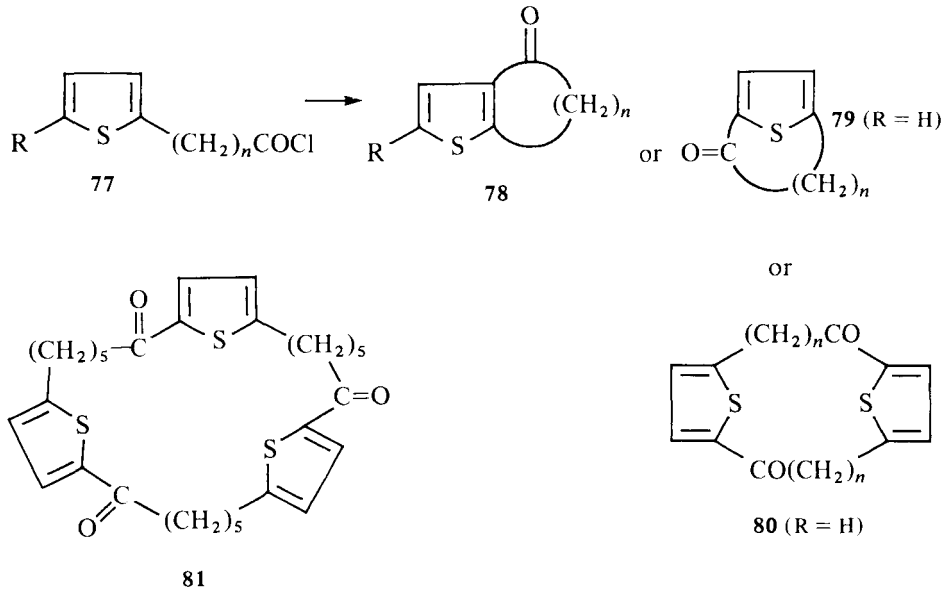
B. Macrocyclic Ketones

There have been two excellent reviews of macrocycles containing the thiophene ring.[1019,1020]

Gol'dfarb's school has thoroughly investigated the preparation of thiophene ketones as precursors to biologically important, sulfur-free (i.e., after treatment with Raney nickel) macrocycles (e.g., exaltone, macrolide antibiotics).[876] Two general approaches have been used.

a. FRIEDEL-CRAFTS ACYLATION

The aim is to effect intramolecular cyclization of ω-(2-thienyl)alkanoyl chlorides (**77**) (Scheme 14). The cyclization of **77** (R = H, $n = 3$ or 4) to the six- and seven-membered ring ketones (**78**; R = H, $n = 3$ or 4) respectively in the presence of $SnCl_4$[865] has also been discussed in the previous section. For the higher ring ketones, the careful control of cyclization conditions is essential to achieve the optimum yield of product. Gol'dfarb has found that, as well as employing the usual high dilution conditions, the presence of an active heterogeneous surface is also desirable. Good yields are obtained by using partially hydrolyzed aluminum chloride etherate as the catalyst or by conducting the reaction in the presence of silica or alumina gel of coarse pore size.[865,878] For **77** (R = H, $n = 5$) the eight-ring

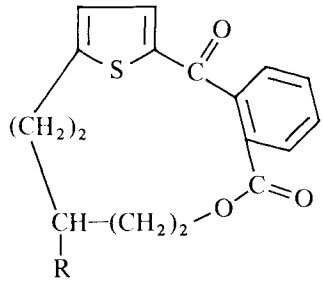


Scheme 14

cyclic ketone **78** was formed in 9% yield in the presence of $AlCl_3 \cdot Et_2O—H_2O$. In addition, the intermolecular dimer **80** ($n = 5$) and trimer **81** were obtained in low yield.[878] With the intermediate chain length, $n = 5$ to 9, an increasing amount of the dimer **80** was observed.[878,1021] Cyclization into the second α-position was first noted at $n = 8$ (8%), and good yields (50 to 64%) of the ketone **79** were obtained for $n = 9$ to 12.[878] The yield of **79** ($n = 9$) increased to 75% when silica gel was added to the $AlCl_3 \cdot Et_2O—H_2O$ catalyst.[1022] Cyclization of **77** (R = H) to (**79**) may conveniently be carried out with $(CF_3CO)_2O—H_3PO_4$ in acetonitrile; yields are somewhat lower than before, but by use of this reagent the scope of the reaction has been extended to include the preparation of ketones (**79**), for which $n = 13$ and 17.[1023] Reliable rate data for cyclization under these conditions have recently been determined.[1024]

The cyclization of the 5-methyl derivatives (**77**; R = Me, $n = 9—11$) has been studied.[880,1025,1026] For $n = 9$, cyclization takes place entirely into the 4-position (i.e., the larger of the two possible rings is formed);[880] for $n = 10$ or 11, cyclization occurs into both the 3- and 4-positions (with the latter predominating).[880,1025] ω-(3- or 4-Methyl-2-thienyl)alkanoyl chlorides ($n = 9$ or 10) cyclize into the 5-position in very good yield ($AlCl_3 \cdot Et_2O—SiO_2—CHCl_3$), to give the products analogous to **79**, $n = 9$ or 10.[1026,1027]

In a search for a convenient source of macrocyclic keto lactones, the Russian school have prepared a series of macrocycles typified by **82**, R = H or Me by intramolecular cyclization of the acid chloride of the appropriate acid ester.[854,875,1028]



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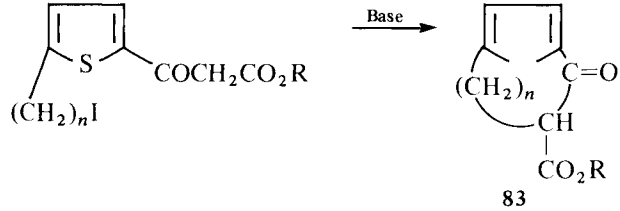
b. INTRAMOLECULAR CYCLIZATION OF AN ACTIVATED METHYLENE GROUP WITH AN ω-IODOMETHYLENE GROUP

In this method (Scheme 15), a β-keto ester group in the 2-position undergoes intramolecular alkylation by the 5-(ω-iodoalkyl) side-chain by use of high dilution conditions in the presence of finely powdered potassium carbonate in butanone,[757, 876, 1029–1031] or potassium *t*-butoxide,[1032] or other alkali metal carbonates.[1033] High yields of cyclic β-keto ester (**83**) are obtained when $n = 9$ or 11.[757, 876, 1029–1032] Hydrolysis of **83** then gives the cyclic ketone. When $n = 7$, only a dimeric bis-(β-keto ester) (cf. **80**) is obtained (ca. 50%).[757, 876, 1029] The roles of the base and solvent in this reaction have been studied.[1034] It has been found that the rate of the intramolecular cyclization ($n = 9$) increases with the radius of the alkali metal cation and the surface area of the carbonate.[1033]



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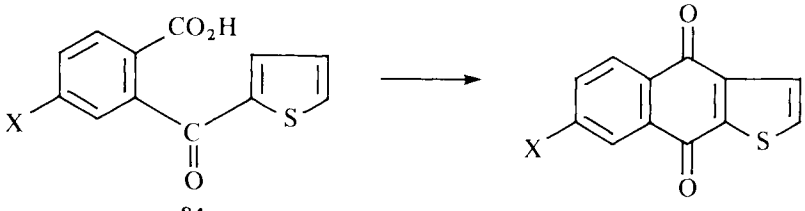
Scheme 15

Note: Macrocyclic α-ketols have been prepared by way of the acyloin condensation on an appropriate thiophene-2,5-diester.[100, 876, 1021] However, since their keto group is not attached directly to the thiophene nucleus, they are outside the scope of this chapter.

C. Thiophene Analogues of Anthraquinone

These are obtained by conventional Friedel-Crafts cyclization of substituted *o*-(2-thenoyl)benzoic acids (Scheme 16).[825, 936, 940, 1035] The cyclization proceeds



84 85

Scheme 16

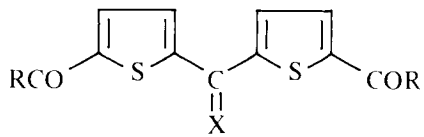
either with or without rearrangement: rearrangement is a function of the substituent(s) on the benzene ring and not of the cyclizing agent.[940,1035] If the group $X = NO_2$ or Cl and is situated meta to the thenoyl group, (i.e., as in **84**), then normal cyclization to the quinone **85** occurs. If, however, it is in the corresponding ortho or para position, rearrangement takes place to give the same quinone (**85**). With the NH_2 group, the converse situation applies.[1035]

3. Reactions of Thienyl Ketones (Exlcuding Those Involving α-Hydrogen Atoms)

A. Oxidation

Methyl ketones are oxidized routinely to the carboxylic acid by hypohalite (e.g., References 141, 954, and 1037) or by successive treatment with iodine, pyridine, and sodium hydroxide (e.g., References 116, 713, and 750). In the presence of high concentrations of hypohalite, the oxidation of 2-acetyl-5-ethylthiophene gives some 4-chloro- (or 4-bromo-)5-ethylthiophene-2-carboxylic acid, in addition to the expected product. This anomalous reaction is apparently favored by the presence of an ethyl group α to the sulfur atom.[1037] 2-Acetylthiophene has been oxidized to the carboxylic acid (57%) by molecular oxygen in HMPA.[118]

An acylthiophene containing another carbon side-chain in the ring may be oxidized to the thiophene dicarboxylic acid with $KMnO_4$[744,954] or $K_3Fe(CN)_6$.[796] Alternatively, it may be selectively oxidized to the diketone by use of $KMnO_4$—$Mg(NO_3)_2$ in neutral solution (e.g., 2-acetyl-5-ethylthiophene gives 2,5-diacetylthiophene).[1038] The (thenyl)substituted diketone (**86**; X = H_2 R = Me or 2-thienyl) is oxidized to the triketone (**86**; X = O, R = Me or 2-thienyl) by oxygen in ethanolic KOH[93,797] or by manganese dioxide.[93] A methyl group in the 3- or 5-position of the thiophene ring is oxidized to the carboxylic acid by oxygen in the presence of $Co(OAc)_2\frac{1}{N}NaBr$ without affecting a 2-acetyl group also present in the molecule.[1039]



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Anodic oxidation of 2-acetylthiophene in the presence of MeOH–NH_4Br gives the 5-bromo compound (12%).[1040] Oxidation of 2-acetyl-5-nitrothiophene with nitric acid gives (5-nitro-2-thienyl)glyoxylic acid (30%) and 5-nitrothiophene-2-carboxylic acid (23%).[425]

The gas-phase oxidative ammonolysis of 2-acetylthiophene over titanium vanadate at 370°C gives thiophene-2-carbonitrile.[1041]

B. Reduction

The kinetics of the reduction of some acyl-[1042] and aroylthiophenes[807] to the corresponding alcohols by sodium borohydride in propan-2-ol have been measured.

The Huang-Minlon modification of the Wolff-Kishner reaction has been used innumerable times for the reduction of ketones to the corresponding alkyl- (or benzyl-) thiophenes. The kinetics of the Wolff-Kishner reduction of diaryl ketone hydrazones have been investigated.[1043] Sterically hindered ketones that do not form hydrazones are not reduced by the Huang-Minlon procedure.[1044] A halothienyl ketone undergoes normal Huang-Minlon or Clemmensen reduction if the halo substituent occupies a β-position in the ring (e.g. Reference 713); a corresponding α-substituent is replaced by hydrogen under similar conditions (e.g. References 577, 742, and 1044). Thioketals are hydrodesulfurized under Wolff-Kishner conditions.[742] In carrying out Huang-Minlon reduction of a ketone, the formation of ketazines is minimized by the use of 60 to 65% (rather than 100%) hydrazine hydrate.[779]

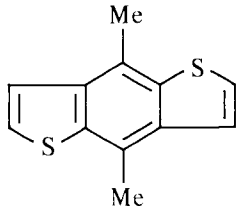
The Clemmensen procedure provides a widely used alternative method for reduction of the keto group and proceeds satisfactorily even when readily reducible halogen atoms are present.[876] Several modifications of the conventional procedure have been used: zinc and methanolic sulfuric acid reduces some 2-acylthiophenes[764] and 2-(*o*-carboxybenzoyl)thiophene is reduced by zinc in aqueous ammonia,[1045] preferably with the addition of copper(II) sulfate.[97] A mixture of $LiAlH_4$–$AlCl_3$ effectively reduces $>C=O$ to $>CH_2$ especially in the case of aroylthiophenes.[40,93,800] 2-Acetylthiophene is reduced to a mixture of 2-ethylthiophene (52%) and its tetrahydro derivative (26%) by water gas ($H_2 + CO$) in the presence of a $Co_2(CO)_8$ catalyst.[1046]

Hydrogenation of thienyl ketones under pressure in the presence of a metal sulfide catalyst yields a variety of products: with cobalt polysulfide the $>C=O$ is reduced to $>CH_2$, any bromo substituent is removed, and the thiophene ring may or may not be saturated;[738] with Re_2S_7 in dioxane and ethanol, 2-acetylthiophene gives 2-ethylthiophene;[124] with tungsten and nickel sulfide, a saturated hydrocarbon is obtained as a result of hydrosulfurization.[1047] 2-Acetyl- and 2-benzoylthiophene undergo ionic hydrogenation (to 2-ethyl- and 2-benzyltetrahydrothiophene respectively) with Et_3SiH–CF_3CO_3H;[130,1048] the reaction is accelerated by the addition of $BF_3 \cdot Et_2O$,[1049,1050] a large excess of CF_3CO_2H, toluene-*p*-sulfonic acid and its lithium salt, or lithium perchlorate.[1051]

Hydrodesulfurization of acylthiophenes with Raney nickel is a much-used syn-

thetic and degradative procedure (e.g., Reference 876) and is discussed fully in Part 1 Chapter VI. It is sufficient here to note that by varying the reaction conditions the keto group may be either preserved or reduced to the alcohol.[87,763,879] In some cases hydrodesulfurization produces small amounts of dimeric products, in addition to the expected monomers.[1052] Raney cobalt is less reactive than Raney nickel for desulfurizing acylthiophenes.[1053]

The electrolytic reduction of 2-acetylthiophene has been extensively studied. The dimeric reduction product, 2-ThCMe(OH)CMe(OH)Th-2, is usually formed,[1054–1056] but it may be accompanied by the product of the pinacolone rearrangement [$(2\text{-Th})_2$CMe(COMe)],[1057,1058] the dehydration product [CH_2=C(2-Th)C(2-Th)=CH_2],[1057] or the tricyclic product **87**.[1055,1059]



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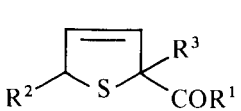
Electrolytic reduction of 2-benzoylthiophene gives predominantly the corresponding alcohol or the pinacol analogue, depending on the conditions used; the latter may undergo the pinacolone rearrangement.[1060] Cathodic reduction of 2-benzoylthiophene in the presence of vinyl acetate gives the crossed hydrocoupled product, 2-ThCPh(OH)CH(OAc)Me (48%).[1061]

2-Acetylthiophene and its oxime show similar characteristics on polarographic reduction to those of the benzene analogues;[132] they are more easily reduced than the corresponding 3-isomers.[133] 2-Acetylthiophene and its ring-substituted derivatives are reduced polarographically either to the alcohol or to the pinacol analogue;[134,1062] the presence of a bromine atom facilitates the reduction of the carbonyl group.[1062] The polarography of 2-benzoylthiophenes and of di(2-thienyl) ketone has been studied.[1063] The composition of a mixture of isomeric nitrothienyl[1064] or bromothienyl ketones[1062] may be established by polarography.

Birch reduction of a 5-alkyl-2-acylthiophene with Na–NH_3–EtOH, followed by the addition of an alkyl halide (R^3X) gives the 2,5-dihydrothiophene (**88**).[1065]

C. Reactions with Carbon Nucleophiles

Thienyl ketones undergo the Reformatski reaction with α-bromoesters,[158,159,838,1066–1068] ethyl γ-bromocrotonate (which also gives a small amount of rearranged product), and allyl bromide.[160] With propargyl bromide, the expected hydroxyalkyne may[1069] or may not[160] be formed. 2-Thienyl ketones (2-ThCOR) give the



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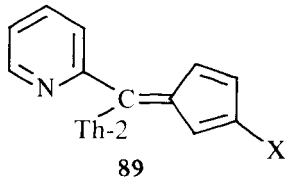

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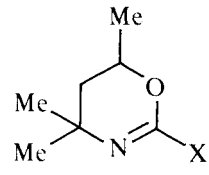


90

expected β-hydroxy compound, 2-ThCR(OH)CH_2SOMe (as a mixture of diastereoisomers), when treated with dimethyl sulfoxide in the presence of a strong base.[1070]

2-Pyridyl 2-thienyl ketone reacts with cyclopentadiene in a Knoevenagel reaction to give a mixture of the fulvene **89** (X = H) and the 2-fulvenylmethanol **89** [X = 2-ThC(OH)(2-pyridyl)].[945] In the presence of butyllithium, 2-acetylthiophene condenses with the active methyl group in the dihydrooxazine **90** (X = Me) to give the expected intermediate **90** [X = CH_2CMe(2-Th)OLi]. Reduction ($NaBH_4$) of the double bond in the latter compound and subsequent hydrolysis affords the αβ-unsaturated aldehyde, 2-ThC(Me)=CHCHO in a one-flask reaction.[1071]

Acyl and aroylthiophenes undergo the Stobbe reaction as expected with dimethyl succinate,[1072–1075] dimethyl methylsuccinate.[1076] dimethyl phenylsuccinate,[267] and dimethyl homophthalate.[1077] Hippuric acid condenses with 2-acetylthiophene in tetrahydrofuran in the presence of Ac_2O–$Pb(OAc)_4$ to give the expected oxazolone derivative (cf. Scheme 3).[1078]

Thienyl ketones (2-ThCOR) may be converted into the αβ-unsaturated esters, 2-ThCR(=$CHCO_2$Et) by means of the Horner-Emmons modification of the Wittig reaction.[742,1079] 2-Acetylthiophene reacts with tributyl phosphine and sodium chlorodifluoroacetate in *N*-methylpyrrolidine to give the alkene, 2-ThCMe(=CF_2).[1080] It seems that difluorocarbene may be generated *in situ*; this is then trapped by the tributyl phosphine to give an ylide, which undergoes the Wittig reaction in the normal way.

D. Reactions with Nitrogen Nucleophiles

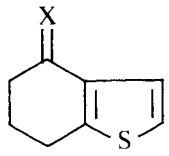
a. OXIMES

The Beckmann rearrangement of oximes has been investigated extensively, mainly by Russian workers, who have subjected the resulting amides to reductive hydrodesulfurization and thus developed a versatile route to aliphatic amino compounds.[1081] The rearrangement often produces a mixture of isomeric amides, namely, the *N*-acylthienylamine or the thiophene *N*-alkylcarboxamide; this is the main factor limiting its synthetic usefulness. In some cases starting with a configurationally pure oxime leads to a pure amide (e.g., References 802, 1082); in other cases it does not (e.g., Reference 985). Control of temperature is important. The rearrangement of (*E*)-2-acetylthiophene oxime, for example, is kinetically controlled at low temperatures; elevation of temperature, however, causes (*E*) → (*Z*) isomer-

ization, favored by S . . . H—O hydrogen bonding in the (*Z*)-oxime.[656] Thus Meth-Cohn and his coworkers have found that the oximes of acetylthiophenes rearrange to the acetamidothiophenes in excellent yield with ethereal PCl_5, provided that the temperature of the reaction is kept low and that the product is isolated rapidly under neutral conditions.[656] Use of PCl_5-ether had previously given poor yields of acetamidothiophenes.[406,658] However, with aroylthiophene oximes, this reagent has given good yields of the thiophene *N*-arylcarboxamide.[802,806,837] Benzene- (or *p*-toluene-)sulfonate esters of oximes are rearranged conveniently by dissolving them in benzene and passing the resulting solution through an acid- or alkaline-washed column of alumina.[1082] The oxime of 3-acetyl-2,5-dimethylthiophene underwent rearrangement to the 3-acetamido compound (90%) with Ac_2O—HCl, whereas the more usual reagents gave unsatisfactory results.[1083] Some rearrangements of thiophene open-chain ketoximes have been carried out with PPA,[806,837] but this reagent offers no advantages over those already mentioned.[1084] The Schmidt reaction of acetylthiophenes with chloroformic hydrazoic acid provides an alternative route to acetamidothiophenes;[658,1085] in the sole example of the use of this reagent with aroylthiophenes, the direction of the migration depends markedly on the environment of the aroyl group.[1086]

With cyclic ketoximes, the rearrangement product depends on the reagent used. For six- and seven-membered rings, with the carbonyl group attached to the 3-position of the thiophene ring, rearrangement of the *O*-benzenesulfonate ester (usually by treating it with ethanolic sodium acetate) generally gives the lactam in which the nitrogen atom is adjacent to the thiophene ring;[857,863,870,873,1001] for a carbonyl group in the corresponding 2-position of a six-membered ring,[1000] or for a carbonyl group in a five-membered ring, rearrangement generally gives the isomeric lactam with the carbonyl group attached to the thiophene ring.[985,1084] Rearrangement with PPA gives similar results, but there is a greater tendency to form mixtures of isomeric lactams.[874,985,995,1000,1001,1084,1087] The Schmidt reaction on a cyclic ketone usually gives mainly the lactam in which the C=O group is attached to the thiophene ring.[990,995,998,1000]

The oxime (**91**; X = NOH) is conveniently converted into 4-acetamidobenzo-[*b*]thiophene by treatment with dry HCl in AcOH—Ac_2O.[868,1088]



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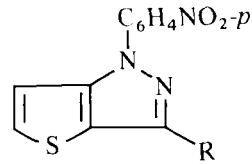

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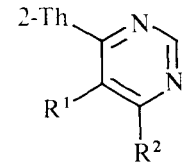

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2-Acetylthiophene oxime reacts with acetylene in alkaline solution to give 2-(2-pyrrolyl)thiophene (60%) or its *N*-vinyl derivative.[1089] The same oxime reacts

with dichloromethane in aqueous sodium hydroxide in the presence of a phase transfer catalyst to give the methylene dioxime, $[2\text{-ThCMe(=NO)}]_2CH_2$ (89%).[1090] Demethylation of 2-(*o*-methoxybenzoyl)thiophene oxime with pyridine hydrochloride gives 2-(2-thienyl)benzoxazole (54%).[1091]

b. HYDRAZONES AND SUBSTITUTED HYDRAZONES

The hydrazone of a 2-aroylthiophene is oxidized by manganese dioxide or Ag_2O–$MgSO_4$, to the diaryldiazomethane, $2\text{-ThCAr}(N_2)$.[1092] This diazo compound reacts with dichlorocarbene to give $2\text{-ThCAr}(=CCl_2)$.[1092–1094] The phenylhydrazones of some thienyl ketones give indoles in the Fischer reaction.[768,1095] The *p*-nitrophenylhydrazones of 2-thienyl ketones (2-ThCOR) are cyclized to the thieno[3,2-*c*]-pyrazoles (**92**) by PPA.[1096]

c. REACTIONS WITH AMINES

2-Thienyl ketones undergo the Pomeranz-Fritsch cyclization to a thienopyridine derivative when treated successively with 2,2-diethoxyethylamine and PPA.[212,1097] 2- or 3-Acetylthiophene condenses with 3-aminopyridine-4-carboxaldehyde, to give a 1,7-naphthyridine derivative.[1098] Thienyl ketones undergo the Pfitzinger reaction with alkaline isatin (which reacts as $o\text{-}H_2NC_6H_4COCO_2Na$), to give quinoline analogues (e.g., References 16, 44, 768, 867); however, 2-acetyl-3,5-dinitrothiophene does not undergo this reaction.[1099]

2-Acetyl- and 2-propionylthiophene form enamines with secondary aliphatic amines (R_2NH) in the presence of $TiCl_4$.[1100,1101] 2-Cyclopropyl thienyl ketone does not form an enamine under these conditions; instead it gives the homoallylic rearrangement product $2\text{-ThCNR}_2(=CHCH_2CH_2NR_2)$.[1102]

d. MISCELLANEOUS REACTIONS

Ketones, ThCOR, are converted into the amines, $ThCH(NH_2)R$, by treatment with ammonium formate[785] or formamide,[1103,1104] and into the corresponding *N*-methyl amine by use of *N*-methylformamide (Leuckart reaction).[785] With formamide, 2-propionylthiophene gives the expected amine,[1104] together with a by-product **93** (R^1 = Me, R^2 = H).[1105] 2-(*o*-Nitrobenzoyl)thiophene undergoes reductive cyclization under Leuckart conditions to give **93** (R^1R^2 = fused benzenoid ring).[826]

By careful control of reaction conditions, it has been possible to convert acetylthiophenes into thienylacetic acids (by the amides), using the Willgerodt reaction.[54,66,141,790,954,1106] Propionyl- and *n*-butyrylthiophenes give analogous products.[44,1107] The conversion of an acetylthiophene into the corresponding thienylacetic ester is also accomplished by use of the acid-catalyzed reaction with methanolic thallium(III) nitrate.[791]

Thienyl ketones form hydantoins by treating them with ammonium carbonate and KCN.[309,735,1108,1109] 2-Acetylthiophene reacts with aniline and cyanide ion to give the α-aminonitrile 2-ThCMe(CN)NHPh, which loses HCN in the presence of methanolic KOH, giving the ketimine 2-ThCMe(=NPh).[1110]

E. Reactions with Oxygen Nucleophiles

a. ACETALS: PREPARATION

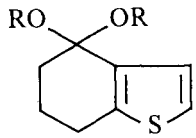
Acetals (and thioacetals) are made by conventional routes. Cyclic acetals containing a bromomethyl group in the 4-position of a 1,3-dioxolane ring are conveniently obtained by treating the ketone with epibromohydrin in the presence of tin(IV) chloride;[839,1111] 5-(bromomethyl)-5-methyl-1,3-dioxanes are prepared by acetalization of a ketone with $HOCH_2CMe(CH_2Br)CH_2OH$ in the presence of toluene-*p*-sulfonic acid.[1112]

Unusually, treatment of 2-acetylthiophene with triethyl orthoformate under conditions which normally would give the acetal, leads to 1,3,5-tri(2-thienyl) benzene.[1113]

b. ACETALS: REACTIONS

Acetals are used widely to protect the keto group during the introduction of a second functional group into the molecule by the metalation (e.g., References 739, 1114) or metal–halogen exchange reactions (e.g., Reference 1115; see also Section III. 1.*B*).

The dialkyl acetals (**94**; R = Me or Et) are unstable and readily lose an alcohol (1 mole) to give a 4-alkoxy-6,7-dihydrobenzo[*b*]thiophene.[1116]



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F. Substitution Reactions

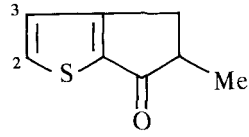
Note: Many of the general comments made with reference to aldehydes (Section II.3.I under "Substitution Reactions") apply also to ketones and are not repeated here.

a. NITRATION

Nitration of 2-acetyl-,[423,428,431,1117,1118] 2-propionyl-,[1104] or 2-benzoylthiophene[1119] takes place in the 4- and 5-positions; when a 5-alkyl group is present, nitration is confined to the 4-position.[16,738] The amount of 4-nitro isomer increases as the degree of protonation of the 2-COR group increases;[428,431,1119] for example, with HNO_3–Ac_2O, 2-ThCOMe gives 50% of the 4-isomer,[428] but the percentage is

increased to 89% by nitration with NO_2BF_4 in the presence of $SbCl_5$—HCl.[431] Nitration of the ketoxime gives the 5-nitro isomer in increased yield; hydrolysis of this provides a practicable source of a 5-nitro-2-acylthiophene.[1118] The composition of mixtures of 4- and 5-nitro-2-acylthiophenes may be estimated by polarography.[421]

The cyclic ketone **91** (X = O) is nitrated in the 2-position.[997] The five-membered cyclic ketone **95** is nitrated in the 2- (55%) and 3-positions (45%), contrary to a previous report that only the 2-nitro isomer is formed;[1120] some ring-opened product (12%) is also isolated.[1121]



95

b. HALOGENATION

Most of the studies to date have concerned bromination. Clearly, an enolizable ketone may be substituted either in the ring or in an α-position. However, by varying the reaction conditions, the direction of substitution can usually be controlled. For example, ketone (**91**; X = O) is brominated in the α-position in ether, but in the 2-position of the thiophene ring in acetic acid.[1122] Usually, bromination is carried out in the presence of an excess of $AlCl_3$ ("swamping effect"), in which case acyl[438,439,713,1123-1125] and aroyl thiophenes[819] are substituted mainly in the 4-position; in addition, small amounts of 5-bromo and 4,5-dibromo compounds are usually formed. The complexes (1 : 1 and 1 : 2) formed between 2-ThCOMe and $AlCl_3$ or $AlBr_3$ have been investigated by physical methods.[78,511,1126] Bromination of 2-acetylthiophene in sulfuric acid in the presence of silver sulfate also gives a mixture of 4- and 5-bromo and 4,5-dibromo compounds.[442]

Predominantly 5-substitution of a 2-acylthiophene may be achieved by use of bromine-aqueous sodium acetate,[1127] *N*-bromosuccinimide in Ac_2O–AcOH,[1128] or hypobromous acid in AcOH–$HClO_4$.[1129] Alternatively, an acetal may be brominated in chloroform-pyridine.[111]

3-Acetylthiophene is brominated in the 5-position by Br_2—$AlCl_3$[1130] or Br_2—NaOAc(aq).[1127]

A few ketones have been iodinated by use of I_2—HgO,[972] I_2—HIO_3,[112] or ICl—$CHCl_3$.[439]

c. CHLOROMETHYLATION

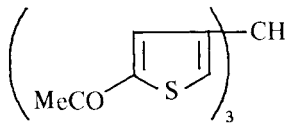
Chloromethylation of 2-acylthiophenes with HCl—HCHO—$ZnCl_2$ generally gives a mixture of the 4- and 5-chloromethyl compounds, from which the latter can often be isolated on a preparative scale;[447,451,1131,1132] under these conditions, 5-alkyl-2-

acylthiophenes give the 4-CH_2Cl compound only.[450,1133] With bis(chloromethyl) ether in 60 to 100% sulfuric acid, 2-acetylthiophene gives a similar mixture of isomers; increasing the acidity favors the formation of the 4-CH_2Cl compound.[449] Chloromethylation of 2-acylthiophenes with $ClCH_2OMe$,[446,447] $(ClCH_2)_2O$,[446,1136,1137] or HCHO[1134,1135] in the presence of aluminum chloride usually gives a mixture of 4- and 5-chloromethyl isomers and some 4,5-bis(chloromethyl) compound. With $AlCl_3$ (1 mole), the 5-CH_2Cl isomer predominates, but with $AlCl_3$ (2 moles), the 4-CH_2Cl compound can be formed almost exclusively.

d. FRIEDEL-CRAFTS ALKYLATION

2-Acylthiophenes undergo isopropylation with Me_2CHCl–$AlCl_3$, mainly in the 4-position.[745,1138]

Under appropriate conditions di(thienyl)methane derivatives can be isolated from chloromethylation reactions involving $AlCl_3$, since the chloromethyl compound, as it is formed, can alkylate a second molecule of acylthiophene (mainly in the 4-position).[1133,1136] Substituted di- and tri(thienyl)methanes and dithienyl ketones can be formed directly by treating 2-acetylthiophene with aluminum chloride and CH_2Cl_2, $CHCl_3$, or CCl_4, respectively.[1139,1140] In this reaction, for which careful control of conditions is essential, alkylation takes place mainly in the 4-position. The triarylmethane (**96**) from the reaction with $AlCl_3$–$CHCl_3$ gives 2 : 1 clathrates with a wide range of organic compounds.[1140]



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Some 2,5-di-*t*-butyl-3-acylthiophenes undergo protodeacylation with concomitant migration of a *t*-butyl group when treated with HCl–HCO_2H; the corresponding 2,5-diethyl compounds are stable under these conditions.[883]

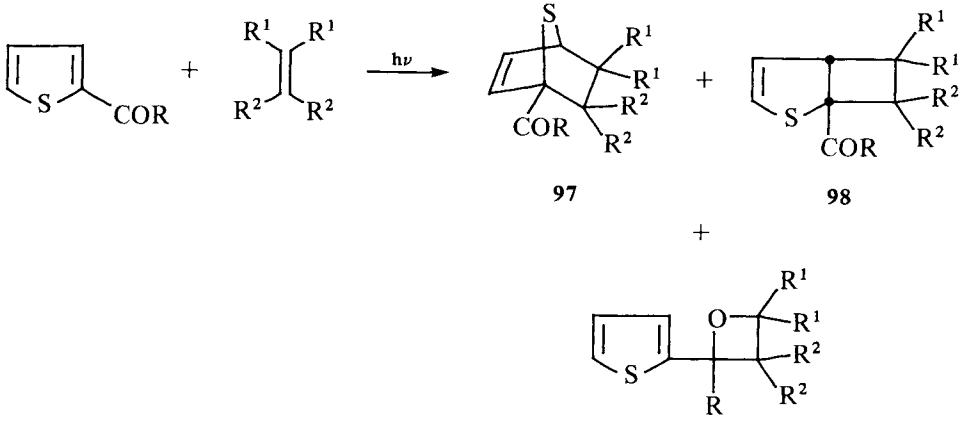
e. ACYLATION

As expected in the light of previous discussion, Friedel-Crafts acylation of 2-acetylthiophene and its 5-alkyl derivatives in the presence of $AlCl_3$ takes place mainly in the 4-position.[794,1114] Acylation of 3-acetylthiophene and its 2,5-dialkyl derivatives occurs in the 5- and 4-positions, respectively.[794,1114]

G. Miscellaneous Reactions

a. PHOTOCHEMICAL REACTIONS

Photoaddition of an alkene to a thienyl ketone can generally take place in three possible ways (Scheme 17): [4 + 2] addition to the thiophene ring, to give adduct

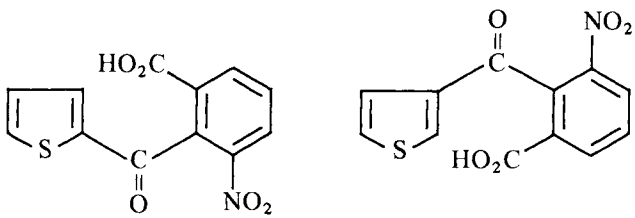


Scheme 17

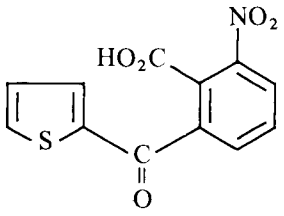
97; [2 + 2] ring addition to give a cyclobutane derivative **98**; addition to the carbonyl group to give an oxetane **99**. With 2-acetylthiophene, all three products may be obtained, but **97** predominates.[1141] Addition of an unsymmetrical alkene gives two isomeric forms of **97**. With a 2-aroylthiophene (2-ThCOAr), the oxetane is formed in high yield;[814,1141-1143] an oxetane of type **99** ($R^1 = H$) may lose formaldehyde to yield an alkene, 2-ThCAr(=CR^2R^2).[1143] Irradiation of bis-(2-thienyl) ketone with 2,3-dimethylbut-2-ene gives the pinacol, $(2\text{-Th})_2C(OH)$-$C(OH)(Th\text{-}2)_2$ (24%) and tar.[1141] 3-Acetylthiophene does not undergo any addition reactions with alkenes;[419] 3-aroylthiophenes give the oxetane or the alkene derived therefrom by loss of formaldehyde.[419,831,1143] With dimethyl acetylenedicarboxylate, 3-aroylthiophenes give unsaturated adducts analogous to **98**.[831]

b. REARRANGEMENT REACTIONS

Complex rearrangements occur when substituted *o*-(2-thenoyl)benzoic acids are treated with concentrated sulfuric acid (Hayashi rearrangement). Careful investigations by Newman and Ihrman[940] have shown that an earlier claim[1035] that 3-nitro-2-(2-thenoyl)benzoic acid (**100**) is rearranged to 3-nitro-2-(3-thenoyl)benzoic acid (**101**) before ring closure to a quinone is in error. They have also demonstrated that ketone (**100**) is rearranged to 6-nitro-2-(2-thenoyl)benzoic acid (**102**), contrary to a report[809] that **102** is rearranged to **100**. The reaction proceeds by the ipso intermediate **103**, the formation of which reflects again the high reactivity of an α-position relative to a β-position.[940]



100 **101**



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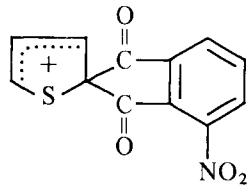

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c. CLEAVAGE REACTIONS

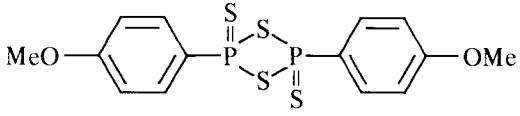
Aryl thienyl ketones (ThCOAr) are cleaved by potassium *t*-butoxide in ether–water solution to, *inter alia*, the carboxylic acids, $ThCO_2H$ and/or $ArCO_2H$.[963,1144,1145] With 2- or 3-benzoylthiophene the acidic product is essentially benzoic acid;[963,1144] introduction of two ortho chlorine atoms into the phenyl substituent increases the amount of thiophene carboxylic acid to 72%.[1145]

d. CONVERSION OF KETONES INTO ALKYNES

Treating an acetylthiophene with phosphorus pentachloride in benzene yields a mixture of $ThCCl_2(Me)$ and $ThCCl(=CH_2)$ that, when subjected to dehydrohalogenation with sodamide in liquid ammonia, gives the alkyne, ThC≡CH.[741,1146,1147] Alternatively, the acetylthiophene may be allowed to react with $POCl_3$-DMF to give the β-chloroaldehyde, 2-ThCCl(=CHCHO); this fragments in alkaline dioxane to give 2-ThC≡CH (87%).[1148] The base-induced reaction of the dialkyl diazomethylphosphonate, $(RO)_2P(O)CHN_2$, with 2-ThCOPh gives the alkyne, 2-ThC≡CPh (44%).[1149] Methylation (Me_2SO_4) of the thioacetal, $2\text{-ThC(SMe)}_2CH_2CO_2Et$, followed by elimination of the resulting sulfonium group (as Me_2S) with alkali gives the alkynic ester, $2\text{-ThC}{\equiv}CCO_2Et$.[1150]

e. THIONATION OF KETONES

The usual reagent for this transformation is phosphorus pentasulfide (e.g., References 28, 812, 828). Thioketones are also obtained by treating an aroylthiophene with the thionophosphine sulfide dimer (**104**)[1151] or by treating the corresponding ketoxime with a thiocarboxylic acid.[1152]



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f. OTHER REACTIONS

In the presence of base, a dialkyl phosphite [e.g., $(EtO)_2PH(=O)$] will undergo addition to a thienyl ketone to give the α-hydroxyphosphonate, 2-ThCR(OH)[PO-$(OEt)_2$]; this is readily rearranged by base to the phosphate, 2-ThCHR[$OPO(OEt)_2$]. The latter is stable if R = Ph,[1153] but when R = Me, diethyl phosphate is readily lost, to give 2-ThCH=CH_2.[1154]

In the presence of sulfuric acid, methyl 2-thienyl ketone reacts with thiophene to give 1,1,1-tri-(2-thienyl)ethane [$(2\text{-Th})_3CMe$] (54%).[1155] 2-Acetylthiophene may be distinguished from its 3-isomer by means of a colour test: with boiling acetic acid containing a few drops of concentrated sulfuric acid, the former gives a yellowish-brown color, whereas the latter gives a light green color.[1156]

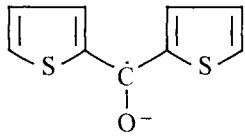
4. Physical Properties of Thienyl Ketones

A. Conformational Studies

As with thiophene-2-carboxaldehydes, 2-thienyl ketones exist essentially in the O,S-*cis* conformation (cf. Scheme 5). This conclusion follows an extensive investigation of a wide range of alkyl and aryl thiophenes by ^1H NMR spectroscopy (chemical shifts,[1157–1162] solvent shifts,[463,464] coupling constants,[592,1157] nuclear Overhauser effect,[463,464,619] lanthanide-induced shifts,[463] and computer simulation of lanthanide-induced shifts,[467,1163]), ^{13}C NMR spectroscopy,[471] IR spectroscopy,[464.487] ESR spectroscopy,[473,474] dipole moments,[455,458,492,1164–1170] Kerr constants,[1164,1169,1170] and X-ray crystallography.[1171]

In contrast to the 2-carboxaldehydes, the substituent 2-COR group in a 2-thienyl ketone may not be coplanar with the ring, especially in the presence of an adjacent *t*-butyl group.[464] In some methyl ketones the acetyl group is believed to be twisted out of the plane of the ring by 30°, even when there is no bulky adjacent substituent.[1170] However, the effect is most marked for the aryl ketones, 2-ThCOAr. Here the thienyl group conjugates more effectively than a substituted phenyl substituent and is thus coplanar with the C—CO—C plane. For steric reasons, however, the aryl group may be twisted considerably out of coplanarity with the rest of the molecule. The extent of twisting has been investigated by ^1H NMR spectroscopy,[1157,1159–1162] UV absorption spectroscopy,[810,1161,1172] IR spectroscopy,[1165,1172] ESR spectroscopy,[1173] dipole moments,[458.1164,1166,1168,1169] and Kerr contants.[458,1164,1169]

For heteroaryl 2-thienyl ketones, the conformation of the heteroaryl group has been considered. For example, with (2- or 3-furyl) 2-thienyl ketone, the thienyl substituent has the usual preferred O,S-*cis* conformation, but the furyl group shows no preferred conformation.[1158,1167] The conformational isomers of the ketyl radical (**105**), generated from bis-(2-thienyl) ketone, have been examined by ESR spectroscopy.[1174] The S,O,S-*cis*,*cis* conformer (**105**) is destabilized by 3-H, 3′-H interactions, so the S,O,S-*trans*,*trans* and S,O,S-*trans*,*cis* conformers are preferred.



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3-Thienyl ketones have been less widely studied. An examination of simulated lanthanide-induced shifts shows that 3-acetylthiophene exists as an equilibrium mixture of the O,S-*cis* and O,S-*trans* conformers (cf. **39** and **40**).[483] The conformation of 3-benzoylthiophene has been studied by dipole moments [492,1166] the planes of the two rings are mutually perpendicular.[1166] The crystal structure of 2-pyrrolyl 3-thienyl ketone shows that the molecule exists in a twisted conformation.[1175]

The conformations of some thioketones have also been studied,[1157,1160–1162, 1165,1168,1176] with aryl 2-thienyl thioketones, steric effects are more prominent than with the oxygen analogues,[1161] and there is a greater degree of twisting of the aryl substituent.[1162]

B. Spectroscopy

Note: Those spectroscopic studies referred to in the previous section are not considered again here.

a. ULTRAVIOLET

There have been several compilations of UV spectra (e.g. References 484, 486, 738, 772, 1177), including those of some cyclic ketones.[1178] A few systematically compare the effects of acyl (or aroyl) substituents in the 2- and 3-positions.[485,1179] The spectra show clearly that a carbonyl group conjugates more strongly in the 2-position than in the 3-position.[484,485] For aryl 2-thienyl ketones there is a linear relationship between the absorption maxima of the two bands and the σ^* value of the aryl substituent.[1180] The effect of ortho substituents on the spectra of 2-benzoyl- and 2,5-dibenzoylthiophenes is ascribed to steric hindrance of the interaction between the phenyl and carbonyl groups.[827] In connection with studies of photochemical reactivity, the UV absorption and phosphorescence emission spectra of some substituted benzoylthiophenes were analyzed, and partial energy diagrams were constructed.[808,814,831] A molecular orbital treatment of the UV spectrum of 2-benzoylthiophene has been published.[1181]

The UV and IR spectra of the adduct between 2-acetylthiophene and $AlCl_3$ confirm the formation of a stable complex with a weakened carbonyl bond.[1182]

b. INFRARED

IR data have been published for several methyl thienyl ketones[317,490,1183,1184] and for other acylthiophenes.[772] The frequency of the carbonyl absorption for 3-thienyl

ketones is greater than that for the corresponding 2-isomers, showing that conjugation is more effective in the 2-position.[1183,1184] Owing to steric inhibition of resonance, the C=O absorption in 3-acetyl-2,5-di-*t*-butylthiophene is at a higher frequency than that in the corresponding 2,5-dimethyl compound.[1183] The magnitude of the inductive and mesomeric effects in 2- and 3-acylthiophenes has been discussed on the basis of a comparison of the frequency and intensity of the $\nu_{C=O}$ and $\nu_{C=C}$ bands.[1185] Comparison of the IR spectra of methyl phenyl ketones and methyl 2-thienyl ketones shows that the thiophene nucleus is a better transmitter of substituent conjugation effects than the benzene nucleus.[1186] The absorption shifts in 5-substituted 2-acetylthiophenes are related linearly to Hammett's σ-value for the 5-substituent.[1184] For 2-aroylthiophenes (2-ThCOAr), the C=O stretching frequencies have been correlated with the sum of the Hammett σ constants of both substituents.[1180]

The IR spectra of some thienyl ketones and their thioketone analogues have been compared.[828]

c. NUCLEAR MAGNETIC RESONANCE

The ^{1}H NMR spectra of various acetylthiophenes,[498,499,1187] other acylthiophenes,[772] and several cyclic ketones have been recorded and analyzed.[1178] The ^{13}C NMR spectrum of 2-acetylthiophene[506,507] has been compared with that of the 3-acetyl isomer[508] and with the ^{13}C spectra of the 2-acetyl-furan, -selenophene, and -tellurophene analogues.[499] The protonation of some substituted acetyl-[1188-1190] and benzoylthiophenes[1191] in aqueous sulfuric acid has been studied by ^{1}H NMR spectroscopy. For the protonation of 2-aroylthiophenes in SO_2—SbF_5—FSO_3H at $-80°C$, the nature of the substituents in the thiophene ring and the configuration of the molecule are the key factors in determining whether a proton is accepted by the C=O group, alone, or by the thiophene ring as well.[510] Mesityl 2-thienyl ketone is also protonated in the benzene ring.

d. MASS SPECTRA

Spectra of 2-benzoylthiophene[512,1192,1193] and of a range of acylthiophenes[512,1192, 1194,1195] have been recorded. Rearrangement ions have been identified;[1194,1195] in particular, 2-benzoylthiophene (and to a lesser extent 2-acetylthiophene) gives a rearranged M—CO ion.[512,1192] A comparative electron-impact study of 2-(2-nitrobenzoyl)thiophene, 2-(2-nitrobenzoyl)-3-methylthiophene, and some related benzenoid derivatives has been carried out.[1196]

The molecular ionization potentials of some thienyl ketones have been determined by an electron-impact method and the values compared with those for the corresponding oxygen, selenium, and nitrogen heterocyclic ketones.[516]

e. ESR SPECTRA

Free radicals of the isomeric dithienyl and phenyl thienyl ketones have been produced by electrolysis and their ESR spectra determined. The efficiency in delocalization of the unpaired electron follows the order 2-thienyl > phenyl > 3-thienyl.[1197]

5. Reactions of Ketones Involving α-Hydrogen Atoms

A. Bromination

Methyl ketones are normally converted into the bromoacetyl derivative by use of bromine in chloroform[768,1198,1199] or carbon tetrachloride;[713,1200] when there is a nitro group in the thiophene ring, the solvent is usually acetic acid.[1104,1198] The results of a study of the α-bromination of a series of 5-substituted 2-acetylthiophenes in the presence of an acidic catalyst are in accord with Hammett's rule, assuming that the 2- and 5-positions in thiophene correspond to the para position in a benzenoid compound.[1201] Methyl ketones have also been brominated with pyridinium bromide perbromide.[1202]

Other acylthiophenes have undergone α-bromination with bromine in ether (with or without an $AlCl_3$ catalyst)[761,1125] or in dichloromethane.[1203]

The six-membered cyclic ketone (**91**; X = O) undergoes side-chain bromination with bromine in ether;[1122,1204] in acetic acid, the thiophene ring is brominated.[1122] The corresponding seven-membered ring ketone (**78**; R = H or Me, $n = 4$) gives the αα-dibromo compound with phenyltrimethylammonium tribromide;[203,877] the reagent is more selective than Br_2—CCl_4.[877]

B. Aldol-Type Reactions

There are numerous references to the base-catalyzed condensation of methyl thienyl ketones with aldehydes to give αβ-unsaturated carbonyl compounds (Claisen-Schmidt reaction) (cf. Scheme 1). We give only a representative selection of aldehydes used: substituted benzaldehydes,[172,175,177,1205] heterocyclic aldehydes.[182,1206,1207] aromatic dialdehydes,[1208,1209] and acetylenic aldehydes.[192]

The products from the condensation of substituted 2-acetylthiophenes with salicylaldehyde derivatives undergo acid-catalyzed cyclization to 2-(2-thienyl)-benzopyrylium salts.[1210,1211] 2-Acetylthiophene condenses with the chloroacraldehydes, CCl_2=CXCHO (X = H or Cl), under acidic conditions to give the expected products;[1212,1213] the former is readily cyclized by acid to 6-(2-thienyl)-2-pyrone.[1212]

2-Acetylthiophene undergoes self-condensation in the presence of $HClO_4$—Ac_2O to give 2-ThCOCH=C(Me)Th-2.[1214]

C. Mannich Reactions

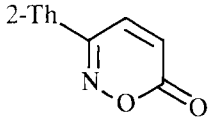
Mannich bases have been formed by reaction of thiophene ketones with formaldehyde and a series of secondary amines covering an almost unimaginable range of structural types. We cite representative references for 2-acetylthiophenes,[1215–1221] 2-propionylthiophenes,[979,1215,1222,1223] 3-acetylthiophene,[1224] 3-propionylthiophene,[1225] and five-,[1204] six-,[1226,1227] and seven-membered cyclic ketones.[1226]

2-Acetylthiophene undergoes aminomethylation with ammonium chloride and formaldehyde to give the tertiary amine, $(2\text{-ThCOCH}_2\text{CH}_2)_3\text{N}\cdot\text{HCl}$.[1228]

Further examples of the formation of Mannich bases are given in Section III.13, in which their conversion into $\alpha\beta$-unsaturated ketones is discussed.

D. Other Reactions

Isopropyl 2-thienyl ketone is cyanoethylated by acrylonitrile in the presence of sodium ethoxide.[765] 2-Acetylthiophene undergoes Michael addition to 1-nitro-2-(dimethylamino)ethene ($\text{Me}_2\text{NCH=CHNO}_2$); loss of dimethylamine from the adduct gives the nitro ketone, $2\text{-ThCOCH=CHCH}_2\text{NO}_2$, which can be cyclized by HCl to the 1,2-oxazine derivative **106**.[1229] Michael addition of 2-acetylthiophene to the substituted acrylonitrile, $(\text{MeS})_2\text{C=C(CN)CO}_2\text{Me}$, followed by loss of methanethiol and cyclization, gives the 2-pyrone **107** (88%).[1230] 2-Acetylthiophene undergoes acid-catalyzed addition to the Schiff's base, $\text{ArCH=NAr}'$, to give the β-arylaminoketone, $2\text{-ThCOCH}_2\text{CHAr(NHAr}')$.[1231]



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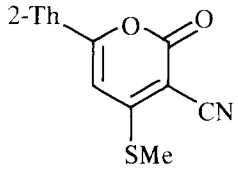

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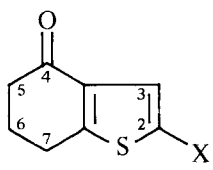
Treatment of the cyclic ketone **108** (X = H) with the Vilsmeier reagent from *N*-methylformanilide and phosphoryl chloride gives a mixture of the aldehydes **108** (X = CHO) and **109** (Y = H) and the hydroxymethylene derivatives **110** (X = O) and **110** ($X = \overset{+}{\text{N}}\text{PhMe}$).[1122] The related ketone **108** (X = H, 7-CH_2 replaced by S) behaves normally with DMF—POCl_3, giving the chloroaldehyde **109** (Y = S).[1232] When treated with the adduct of cyanuric chloride and DMF, 2-acetylthiophene gives the chloroaldehyde, 2-ThCCl=CHCHO, which condenses with a second molecule of starting ketone to give the unsaturated compound, 2-ThCOCH=CHCH=CCl(Th-2).[1233]



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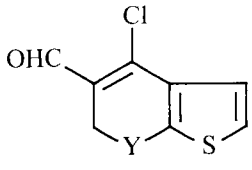

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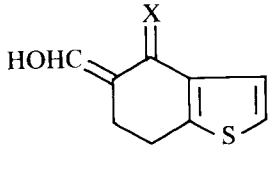

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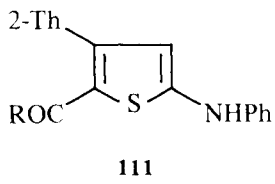

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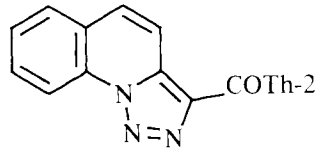


112

2-Acetylthiophene reacts with phenyl isothiocyanate in the presence of sodium hydride; the product, 2-ThCOCH=C(NHPh)SNa, cyclizes when treated with an α-haloketone, $RCOCH_2X$, to give the aminoketone **111**.[1234]

2-Acetylthiophene gives the α-oximinoketone, 2-ThCOCH=NOH, when treated with nitrous acid.[1200] When (2-quinolyl)methyl 2-thienyl ketone is treated with toluene *p*-sulfonylazide, the *v*-triazolo derivative (**112**) is obtained (85%).[1235] Conventional oxidation of methyl thienyl ketones with selenium dioxide gives the appropriate α-ketoaldehyde.[577,589,1236] An α-hydrogen atom is replaced by $-SO_3H$ or −SePh when a thienyl ketone is treated with dioxane sulfotrioxide[1237] or benzene selenyl chloride respectively.[958]

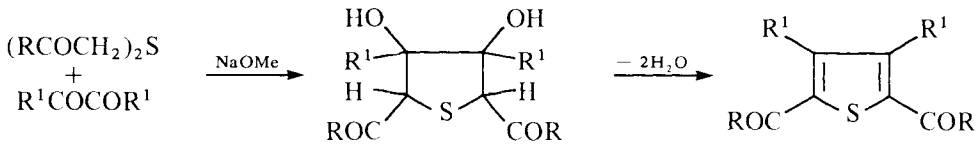
Reactions leading to a dicarbonyl side-chain are discussed in Section III.13.

6. Diacylthiophenes and Acylthiophene Carboxaldehydes

A. Preparation

Most of the general preparative procedures (which are listed in the footnotes to Table 19) have been described in Sections II.5 and III.1 and need not be discussed further.

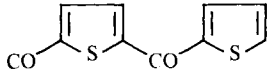
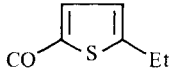
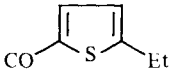
However, some new methods, based mainly on open-chain starting materials, have been announced. The sulfide, $RCOCH_2SCH_2COR$ (R = alkyl or aryl), reacts readily with glyoxal[1240] or a 1,2-diketone[1244] in the presence of base to give the bis-aldol product **113**. With glyoxal (R^1 = H), this undergoes spontaneous loss of water to give the symmetrical diketone **114** (R^1 = H);[1240] otherwise the diol can be isolated and converted smoothly into the diketone by treating it with $SOCl_2$-pyridine[1244] (Scheme 18).



113 114

Scheme 18

TABLE 19. DIACYL AND DIAROYL THIOPHENES AND ACYLTHIOPHENE CARBOX-

Substituents on Thiophene Ring				Boiling Point (°C/mm)
R^2	R^3	R^4	R^5	
Diacylthiophenes				
H	COMe	COMe	H	
H	$COBu^t$	$COBu^t$	H	
Me	COMe	COMe	Me	195–196/13
Me	COMe	$COBu^t$	Me	
COMe	H	H	COMe	
$COBu^t$	H	H	$COBu^t$	
$COBu^n$	H	H	$COBu^n$	
$CO(CH_2)_8Me$	H	H	$CO(CH_2)_8Me$	
$COCF_3$	H	H	$COCF_3$	
COMe	H	H	$COCH_2CHMe_2$	
COMe	Me	Me	COMe	
COMe	H	COMe	H	180–185/26
Me	COMe	H	COMe	
Et	COMe	H	COMe	140–143.5/4
Me	—$CO(CH_2)_2CO$—		Me	
Acylaroylthiophenes				
Me	COMe	COPh	Me	
COMe	H	H	COPh	
COPh	COMe	H	H	
Diaroylthiophenes				
H	COPh	COPh	H	
H	COTh-2	COTh-2	H	
COPh	COPh	H	H	
COPh	H	H	COPh	
COC_6H_4Me-*p*	H	H	COC_6H_4Me-*p*	
COC_6H_4Cl-*p*	H	H	COC_6H_4Cl-*p*	
COC_6H_4Br-*p*	H	H	COC_6H_4Br-*p*	
$COC_6H_4NO_2$-*p*	H	H	$COC_6H_4NO_2$-*p*	
COC_6H_4OMe-*p*	H	H	COC_6H_4OMe-*p*	
$COC_6H_3(OMe)_2$-3,5	H	H	$COC_6H_3(OMe)_2$-3,5	
COTh-2	H	H	COTh-2	
COTh-2	H	H		
	H	H		
CO(Mesityl)	H	H	CO(Mesityl)	
COPh	Me	Me	COPh	
COC_6H_4Me-*p*	Me	Me	COC_6H_4Me-*p*	
Acylthiophene Carboxaldehydes				
COMe	H	CHO	H	
COMe	H	CHO	Me	

Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point (°C) or Boiling Point (°C/mm) of Derivatives[b] (Ref.)[c]
Diacylthiophenes				
83	29	F	1238	
88–89	53	E	1239	
88–89	87, 48	I, F	794, 1238	
66–67	Low	I	794	
171.5–172	4, 50	A, E	1114, 1240	
105.5–106	75, 86	D, E	537, 1240	
112–113	62	E	1240	
113–113.5	85	E	1240	
46–48	36	D	537	
108–109	18	I	1192	
65–66	80–90	L	827	
76.5–78	85, 78, 12	H, I, F	1114, 1114, 1238	
94–95	57	I	794	
47–48	60	I	794	
122	50–60	H	1247	
Acylaroylthiophenes				
90–91	Low	I	794	
123	66	C	739	2,4-DNP (mono) 214–216
82	27	C	393	
Diaroylthiophenes				
115–115.5	34	E	1241	
143–144	By-product	O	1242	
80–81	47	C	1243	
115	45, 95	G, E	539, 1240	
143.5–144	96	E	1240	
244–245	91	E	1240	
254–255	95	E	1240	
192–194	74	E	1240	
192.5–193	92	E	1240	
96–96.5	95	E	1240	
182.5–183	80	E	1240	
258–260	70–96	K	93	
114–114.5	86	E	1240	
146–147		M	827	
101.5–102.5	85	E	1244	
71.5–72.5	95	E	1244	
Acylthiophene Carboxaldehydes				
86–87	66, 40	B, J	1115, 533	2-DiEt 128–134/5 (1115)
110–111	18	J	450	

TABLE 19. *(Continued)*

Substituents on Thiophene Ring				Boiling Point
R^2	R^3	R^4	R^5	(°C/mm)
CHO	H	COMe		
CHO	H	—4-CO(CH$_2$)$_3$—		
COMe	H	H	CHO	
COEt	H	H	CHO	140/2
CHO	Br	H	COMe	
CHO	COMe	H	CHO	
COMe	CHO	H	CHO	
CHO	CHO	H	COMe	
COMe	CHO	H	H	
CHO	COMe	H	H	
CHO	COEt	H	H	
COPh	CHO	H	H	165–185/5
H	CHO	COMe	H	

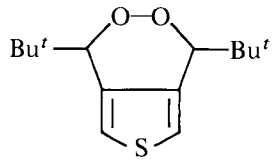
[a] A = (RCO)$_2$O on lithio derivative of acetal; B = DMF on lithio derivative of acetal; C = nitrile on lithio derivative of acetal; D = RCONMe$_2$ or RCONEt$_2$ on a lithio derivative; E = from an open-chain compound (see text); F = photolysis of a 1,2,3-thiadiazole; G = oxidation of an alcohol; H = reduction of —COCH$_2$X (X = Cl or Br); I = Friedel-Crafts acylation of an acylthiophene or a thiophene carboxaldehyde; J = Sommelet reaction; K = oxidation of ThCH$_2$ to ThCO; L = diethyl ethoxymagnesiomalonate on acid chloride; M = acid chloride on a bis-

Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point (°C) or Boiling Point (°C/mm) of Derivatives[b] (Ref.)[c]
100	48	D	521	2-DiEt 108–110/0.5; 2,4-Bis(cyclic) 135–142/05
63–64	76	B	1122	
104–105	48, 30, Very low	B, J, A	1115, 893 379	2-DiEt 129–137/5 (1115)
101–101.5	37, 40, 18, 66	J, N, A, B	1132, 1132 379, 379	2,4-DNP 199–201 (1132); 2-DiEt 150–155/13 (379)
91	63	D	521	2-DiEt 134–135/0.8; 2,5-Bis(cyclic) 69
80	35, 54	D, B	521	2,5-Bis(cyclic) 158–160/2; 3,5-Bis(cyclic) 58
89		D	521	3,5-Bis(DiEt) 144–148/0.9
	78	B	521	2,5-Bis(cyclic) 48
49–49.5	72, 40, 33	B, D, B	526, 529, 1245	2-Cyclic 45 (526) 3-Cyclic 60 (529)
61	70	B	529	3-Cyclic 40
92	40	C	529	
	16	C	393	
	85	B	1246	4-Cyclic 112–115/0.1

(chloromercuri) compound; N = oxidation of $-CH_2Cl$; O = thiophene-3,4-bis(carbonyl chloride) + thiophene/$AlCl_3$.

[b] 2,4-DNP = 2,4-Dinitrophenylhydrazone; DiEt = diethyl acetal; cyclic = cyclic acetal (1,3-dioxolane).

[c] If a reference is not given, the melting point (or boiling point) of the derivative is quoted in the reference to the preparation.



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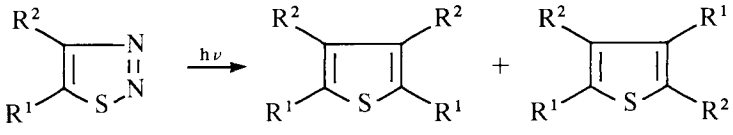
Propiophenone (PhCOEt) reacts with thionyl chloride in pyridine to give 3,4-dibenzoylthiophene (34%); PhCOPr gives the corresponding 2,5-dimethyl compound, but the yield is unacceptably low (7%).[1241] 3,4-Dipivaloylthiophene has been obtained in 53% yield by treating the acetylenic sulfide, $(Bu^tC{\equiv}CCH_2)_2S$ with triplet oxygen in the presence of potassium *t*-butoxide; by similar treatment of the intermediate cyclic peroxide **115** the yield is increased to 98%.[1239]

Photolysis of the 1,2,3-thiadiazoles (**116**; R^1 or R^2 = acyl or aroyl) gives, *inter alia*, a mixture of two symmetrical diketones (Scheme 19); these two isomers are not photochemically interconvertible.[1238]



116

Scheme 19

B. Reactions

General reactions and conformational preferences[455,537] are similar to those of the thiophene dialdehydes (Section II.5).

Treatment of 2,5-diacetylthiophene with 1-adamantyl radicals gives the 4-substituted diacetyl compound and the adamantyl–deacetylation product, 5-(1-adamantyl)-2-acetylthiophene; in contrast to the 2,5-dicarboxaldehyde, no rearrangement product is obtained.[557]

The reductions of 2-acetylthiophene-3- and 5-carboxaldehyde have been studied by polarography.[1245]

7. Halothienyl Ketones

A. Preparation

Ketones containing a halo atom in the thiophene ring are listed in Table 20. Methods used to prepare them are listed in the footnotes to the table; most have been fully described in earlier sections.

The action of acetyl chloride on a thienylcopper derivative provides a useful route to di- and tri-chlorothienyl ketones.[1250,1253] In the Friedel-Crafts acylation of a bromothiophene, it should be noted that a 2-bromo substituent may be replaced by the incoming acyl group.[1256,1259,1260] The bromine cation thus generated can attack a vacant position in the thiophene ring, or replace a 2-acyl substituent, thus giving rise to a range of brominated byproducts.[1256,1259]

B. Reactions

a. REDUCTION

Halothienyl ketones are reduced normally to the alcohol by use of sodium borohydride (e.g. Reference 589) or aluminum isopropoxide.[577]

Wolff-Kishner reduction proceeds normally for a 3-bromothienyl ketone;[598,713,1124] Clemmensen or Wolff-Kishner reduction of a 2-halothienyl ketone may also bring about hydrodehalogenation.[577,742,1044] The sterically hindered bis-(4-bromo-3-thienyl) ketone does not easily undergo Wolff-Kishner reduction; Clemmensen reduction in dioxane provides a convenient alternative procedure.[598]

The selective reductive removal of a halo substituent from an α-position has been put to good use for the preparation of halo- or alkylthienyl ketones that are otherwise inaccessible. The following reagents are commonly used: Raney nickel in the presence of methanolic triethylamine,[1255] copper and quinoline,[67,439,593] copper and propionic (or formic) acid,[1000,1002] copper and benzoic acid,[1248] zinc and acetic acid,[982,988] and sodium borohydride and palladized charcoal.[988] Attempts to prepare thiophene analogues of fluorenone by the Ullmann cyclization (Cu-DMF) of bisaryl ketones containing a bromo substituent in each ring have been only partially successful;[599,1144,1261] often both bromine atoms are removed, but no cyclized product is obtained,[599,1261] Chlorothienyl ketones have been hydrodechlorinated electrolytically.[988]

When halothienyl methyl ketones are reduced polarographically, dehalogenation precedes reduction of the carbonyl group.[595,596] The composition of a mixture of 2-acetyl-4- and 5-bromothiophenes may be estimated by polarography.[1123]

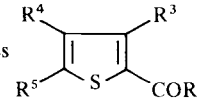
b. ELECTROPHILIC SUBSTITUTION

5-Chloro-[1262,1263] and 5-iodo-2-acetylthiophene[1264] are nitrated in the 4-position. 2-[1265] and 3-Acetyl-4-bromothiophene[1266] are both nitrated in the 5-position. When 2-acetyl-3-bromothiophene is nitrated, the 4-nitro compound (46%) is obtained, together with the nitro–deacetylation products, 3-bromo-2,4- and 2,5-dinitrothiophene.[1266] 2-Acyl-5-bromothiophenes are also prone to nitrodeacylation reactions;[750,1267,1268] a 4-nitro group[606] or a 3-acetamido group[24] aids the 2-(nitrodeacylation) process, whereas a 4-acetamido group prevents nitration or nitrodeacylation.[606]

Bis-(4,5-dimethyl-3-thienyl) ketone is iodinated in the two vacant 2-positions by iodine–iodic acid.[112]

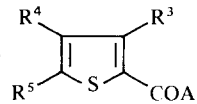
TABLE 20. HALOTHIENYL KETONES

2-Acylchlorothiophenes

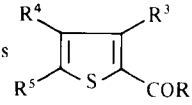


R	R^3	R^4	R^5	Boiling Point (°C/mm)
Me	Cl	H	H	117–118/15
Me	H	H	Cl	
Et	H	H	Cl	132–133/15
Pr	H	H	Cl	137–138/14
CH_2Ph	H	H	Cl	210–211/12
$(CH_2)_2CO_2H$	H	H	Cl	
CF_3	H	H	Cl	75/20
Me	Cl	Cl	H	
Et	Cl	Cl	H	
Pr	Cl	Cl	H	
CH_2Ph	Cl	Cl	H	
Me	H	Cl	Cl	
Et	H	Cl	Cl	
Pr	H	Cl	Cl	
CH_2Ph	H	Cl	Cl	
$(CH_2)_2CO_2Me$	H	Cl	Cl	
$(CH_2)_3CO_2Me$	H	Cl	Cl	
$(CH_2)_4CO_2Me$	H	Cl	Cl	
Me	Cl	H	Cl	
Et	Cl	H	Cl	
CH_2Ph	Cl	H	Cl	
Me	Cl	Cl	Cl	
Et	Cl	Cl	Cl	
Pr	Cl	Cl	Cl	
Bu^n	Cl	Cl	Cl	
$(CH_2)_4Me$	Cl	Cl	Cl	
$(CH_2)_6Me$	Cl	Cl	Cl	
$(CH_2)_7Me$	Cl	Cl	Cl	
$(CH_2)_8Me$	Cl	Cl	Cl	

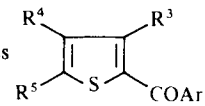
2-Aroyl- or 2-Heteroaroylchlorothiophenes



Ar				
Ph	H	H	Cl	193–195/16
C_6H_4Cl-*o*	H	H	Cl	210–212/16
$C_6H_4CO_2H$-*o*	H	H	Cl	
C_6H_4Cl-*p*	H	H	Cl	220/16
C_6H_4Br-*p*	H	H	Cl	232/16
C_6H_4Me-*p*	H	H	Cl	210/16
C_6H_4Et-*p*	H	H	Cl	216–218/16
C_6H_4Ph-*p*	H	H	Cl	280–285/20
C_6H_4OMe-*p*	H	H	Cl	235/15

2-Acylchlorothiophenes 

Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
	75	F	577	
45–47	85, 70	F	795, 740	Ox. 140 and 184 (1249); Semi 233–234 (740)
47	78, 82	F	740, 761	Semi. 217–218 (740)
38–39	83, 78	F	740, 761	Semi. 210.5–211.5 (740)
87	40	F	761	
122	73	F	804	
		F	759	
54	87, 74	F, B	577, 1250	Thio. 171–172 (577)
68	71	F	577	Thio. 156–157
43	69	F	577	Thio. 114–115
77–78	68	F	577	2,4-DNP 181–183
66–67	56, 96	J, F	1251, 577	Thio. 217–218; Semi. 264–266 (577)
56–57	86	F	577	Thio. 184–186
32–33	78	F	577	Thio. 161
93	93	F	577	NPH 235–237
65–66	44	F	577	Acid 120–121
67–68	62	F	577	Acid 113–115
63–64	47	F	577	Acid 93–94
35	78	F	577	Thio. 215–216
53	87	F	577	Thio. 169–170
29–30	56	F	577	2,4-DNP 185–187
79–80	90, 76	F, B	1252, 1253	2,4-DNP 235; Ox. 130 (1254)
53–54	78	F	1254	2,4-DNP 215
33–34	74	F	1254	
43–45	71	F	1254	
45–47	84	F	1254	
34–36	88	F	1254	
38–39	88	F	1254	
34–35	89	F	1254	

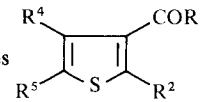
2-Aroyl- or 2-Heteroaroylchlorothiophenes 

64	54, 34, 76	F	804, 805, 735	Ox. 82 (806)
	93	F	804	
129–130, 101	70, 41	E, E	936, 804	
105	78, 58	F, F	804, 805	
116	66	F	804	
87	100	F	804	
55–56	99, 74	F, F	804, 803	
143	86	G	804	
86	99	F	804	Phenol 138

TABLE 20. (*Continued*)

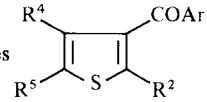
Ar	R^3	R^4	R^5	Boiling Point (°C/mm)
C_6H_4SMe-*p*	H	H	Cl	260/18
$C_6H_3NO_2(OMe)$-3,4	H	H	Cl	
2-Fluorenyl	H	H	Cl	310/18
3-Indolyl	H	H	Cl	
2-Me-3-Indolyl	H	H	Cl	
5-Cl-2-Thienyl	H	H	Cl	229–231/20
5-Br-2-Thienyl	H	H	Cl	235–237/15
2-Furyl	H	H	Cl	183/15
Ph	Cl	Cl	H	
Ph	H	Cl	Cl	
Ph	Cl	H	Cl	
Ph	Cl	Cl	Cl	

3-Acylchlorothiophenes



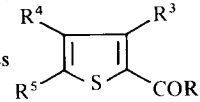
R	R^2	R^4	R^5	
Me	H	H	Cl	
$(CH_2)_2CO_2H$	H	H	Cl	
$(CH_2)_3CO_2H$	H	H	Cl	
Et	Cl	H	Cl	
Pr	Cl	H	Cl	143–144/17
CH_2Ph	Cl	H	Cl	
$(CH_2)_2CO_2Me$	Cl	H	Cl	165–167/4
$(CH_2)_3CO_2Me$	Cl	H	Cl	156–157/2
Me	Cl	Cl	Cl	
Et	Cl	Cl	Cl	
Pr	Cl	Cl	Cl	
CH_2Ph	Cl	Cl	Cl	
Me	Me	H	Cl	

3-Aroyl- or 3-Heteroaroylchlorothiophenes



Ph	H	H	Cl	
Ph	Cl	H	Cl	192–194/17
2-Thienyl	Cl	H	Cl	210–212/20

2-Acylbromothiophenes



R	R^3	R^4	R^5	
Me	Br	H	H	102–105/4
Me	Br	H	Et	122–125/3

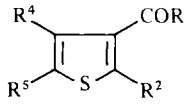
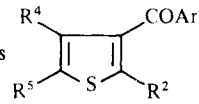
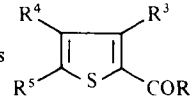
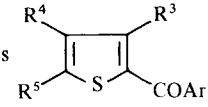
Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
99	74	F	804	
160	48	F	822	
139	58	G	804	
218	80	L	804	
173	60	L	804	
127	69	F	804	
124	72	F	804	
54	62	F	804	
97–97.5	67	F	577	2,4-DNP 202–204
62–63	68	F	577	NPH 201–203
32.5–33	73	F	577	2,4-DNP 225–227
65–67	90	F	1254	2,4-DNP 210; Ox. 125
	3-Acylchlorothiophenes 			
57–58.5	56	H	1255	
142–143	79	H	1000	
93–94	85	H	1000	
63–64.5	–, 63	F	1256, 424	2,4-DNP 206–207 (1256)
		F	424	
67		F	424	
65–66.5	84	F	1000	Acid 116–117
	61	F	1000	Acid 92–93
79	18	F	577	Thio. 230–233
55–56	47	F	577	Thio. 215–216
34	6	F	577	Thio. 178–179
119	11	F	577	
40.5–41	55	F	897	
	3-Aroyl- or 3-Heteroaroylchlorothiophenes 			
67–69		G	1257b	
	14	F	424	
		F	424	
	2-Acylbromothiophenes 			
	52	F	1124	Semi. 196.5–198 (1124); Cyclic acetal 34–36 (582)
	61	F	1124	Semi. 188–191

TABLE 20. *(Continued)*

R	R^3	R^4	R^5	Boiling Point (°C/mm)
Me	H	Br	H	105–107/4
Et	H	Br	H	130–132/9
Pr	H	Br	H	144–144.5/11
Pr^i	H	Br	H	127–129/8
Bu^i	H	Br	H	114–114.5/4
Bu^t	H	Br	H	
Me	H	Br	Me	93–97/0.8
Me	H	Br	Et	124–126/4
Me	H	H	Br	105/0.5
Et	H	H	Br	112–113/5
Pr	H	H	Br	124–125/5
Pr^i	H	H	Br	128.5–129.5/8
Bu^i	H	H	Br	149–150/13
Bu^t	H	H	Br	
CF_3	H	H	Br	84/20
CH_2Ph	H	H	Br	222/14
$(CH_2)_2CO_2H$	H	H	Br	
$(CH_2)_3CO_2H$	H	H	Br	
$(CH_2)_4CO_2Me$	H	H	Br	
1-Me-4-Piperidyl	H	H	Br	158–162/1
CH_2-(1-Me-2-Piperidyl)	H	H	Br	152–153/3
Me	H	Me	Br	116–168/3
Me	Br	H	Br	
Me	Br	Br	H	
Me	H	Br	Br	
Me	Br	Br	Br	

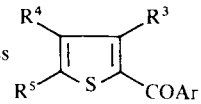
2-Aroyl- or 2-Heteroaroylbromothiophenes



Ar				
Ph	H	H	Br	
C_6H_4Cl-*o*	H	H	Br	224/17
$C_6H_4CO_2H$-*o*	H	H	Br	
C_6H_4Cl-*p*	H	H	Br	228–230/16
C_6H_4Br-*p*	H	H	Br	244/16
C_6H_4SMe-*p*	H	H	Br	265–268/18
C_6H_4SEt-*p*	H	H	Br	265–268/18
C_6H_4OMe-*p*	H	H	Br	245–248/17
$C_6H_3NO_2(Cl)$-3,4	H	H	Br	

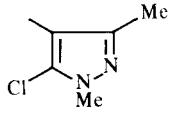
Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
	65, 67, 45	D, D, H	439, 713b, 593	Semi. 214–215 (439); DiEt 118–125/8 (1115)
41–41.5	61, 46	D	582, 1125	Semi. 188.5–189.5; 2,4-DNP 222–223 (1125)
	47	D	1125	2,4-DNP 201–201.5
	61	D	1125	2,4-DNP 202.5–203
	43	D	1125	2,4-DNP 217–218
33–35	62	H	439	2,4-DNP 145–146
	75	D	1127	
	56	F	1124	Semi. 235–236
95–96	68, 80, 66	F	1258, 1259, 740	2,4-DNP 268 (1258); Semi. 234–235 (740); Thio. 200–201 (104); Cyclic acetal 66–67 (111)
53–55	22, 71	F	1256, 740	2,4-DNP 241–242 (1256); Semi. 215–216 (740)
36–37	83, 63	F	740, 1125	2,4-DNP 185.5–186.5 (1125); Semi. 208–209 (740)
	65	F	1125	2,4-DNP 165–168
		F	1125	2,4-DNP 176–177
59–59.5	61	D or F	439	
		F	759	
		F	761	
142	41	F	804	
137–139	25	F	750	2,4-DNP 212–214
		F	750	Acid 116–118
73–74	17	K	920	
	20	K	920	
68		F	1248	
44–45, 87–88	90, –	F	1259, 1104	
82–82.5	1	F	897	
85–86	90	F	1259	
131–132	78	F	1259	

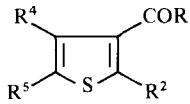
2-Aroyl- or 2-Heteroaroylbromothiophenes

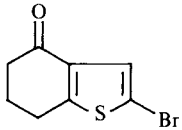


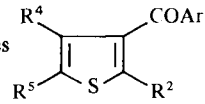
75.5–76	–, 76	F	819, 735	
	99	F	804	
175, 156	65, 56	E	936, 804	
105	74	F	804	
116	100	F	804	
106	71	G	804	
95	57	G	804	
103	66	F	804	Phenol 133
95	16	F	822	

TABLE 20. (*Continued*)

Ar	R^3	R^4	R^5	Boiling Point (°C/mm)
Ph	H	Br	H	
C_6H_4OMe-*p*	H	Br	H	
$C_6H_3NO_2(OMe)$-3,4	H	Br	H	
Ph	Br	H	H	174–175/1.5
C_6H_4Br-*o*	Br	H	H	
Ph	H	Br	Br	
C_6H_4OMe-*p*	H	Br	Br	
$C_6H_3NO_2(OMe)$-3,4	H	Br	Br	
2-Me-3-Indolyl	H	H	Br	
5-NO_2-2-Thiazolyl	H	H	Br	
	H	H	Br	
3-Thienyl	Br	H	H	150/0.1
3-Br-2-Thienyl	Br	H	H	170–180/3
4-Br-3-Thienyl	Br	H	H	
2-Br-3-Thienyl	Br	H	H	185–187/0.5
2-Br-Selenophene-3-yl	Br	H	H	
4-Br-Selenophene-3-yl	Br	H	H	

3-Acylbromothiophenes 

R				
Me	H	H	Br	
Me	H	Br	H	137/12
Me	Br	H	Br	
Et	Br	H	Br	
Me	Br	Br	Br	
				

3-Heteroaroylbromothiophenes 

Ar				
4-Br-3-Thienyl	Br	H	H	180–184/0.5
4-Br-3-Thienyl	H	Br	H	
2-Br-Selenophene-3-yl	H	Br	H	
4-Br-Selenophene-3-yl	H	Br	H	

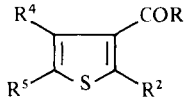
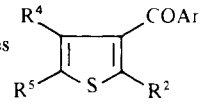
Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
83–84	82	G	819	
88	77	F	822	
135	74	F	822	
	71	F	393	Cyclic acetal 74
92.5–93	46	F	1144	
76.5–77.5	93	G	819	
133	25	F	822	
164	74	F	822	
174		L	804	
167–169	15	F	846	
103–105	71	I	949	
	54	I	598	2,4-DNP 243–244
99–101	24	G	1275	
63–64	70	I	1275	
	50	I	1275	
	72	I	1261	
86	61	I	1261	
3-Acylbromothiophenes 				
63–64	80	D	1130	
	40, 61	A, I	1246, 1266	Cyclic acetal b.p. 103/0.01 (1246)
55–56	35	F	1259	
108–110	25	F	1256	2,4-DNP 195–196
130–131	50	F	1259	
78–79	98	D	1122	Cyclic acetal 42–44
3-Heteroaroylbromothiophenes 				
		I	1275	
85.5–86	65, 80	I	598	2,4-DNP 248–248.5
	38	I	1261	
72	57	I	1261	

TABLE 20. (*Continued*)

Fluoro- and Iodothienyl Ketones

Substituents on Thiophene Ring				Boiling Point
R^2	R^3	R^4	R^5	(°C/mm)
COMe	H	H	F	100–102/35
COMe	H	F	H	
COMe	F	H	H	85–86/13
H	COMe	H	F	
COMe	H	H	I	
COEt	H	H	I	
COC_6H_4Me-*p*	H	H	I	
COMe	I	H	H	
CO(3I-2-Thienyl)	I	H	H	
CO(3I-4,5-DiMe-2-Thienyl)	I	Me	Me	
CO(4I-2,5-DiMe-3-Thienyl)	I	Me	Me	
$CO(5\text{-}NO_2\text{-}2\text{-Thiazolyl})$	H	H	I	
I	CO(2I-3-Thienyl)	H	H	
I	CO(2I-4,5-DiMe-3-Thienyl)	Me	Me	
I	H	—4-$CO(CH_2)_3$—		

[a] A = $RCONMe_2$ on lithio derivative; B = RCOCl on thienylcopper derivative; C = halogen and lithio derivative of acetal; D = halogenation of a thiophene derivative; E = halothienylmagnesium halide or halothiophene-$AlCl_3$ with phthalic anhydride; F = Friedel-Crafts acylation of a halothiophene; G = Friedel-Crafts reaction with a halothiophene carbonyl chloride; H = hydrodehalogenation of a dihalothiophene; I = oxidation of a secondary alcohol; J = methyllithium on a carboxylic acid; K = halothienylmagnesium halide with ester; L = indolylmagnesium bromide with a halothiophene carbonyl chloride.

Fluoro- and Iodothienyl Ketones

Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b] (References)[c]
16–17	–, 52, 72	F	810, 591, 592	2,4-DNP 246–248 (592)
23–24	66	A	591	
	60	F	591	
40–41	62	A	591	
129	40	F	611	
57	66	F	589	
83–84		F	1276	2,4-DNP 195–197
64–66	83[d]	F	1277	Cyclic acetal 70 (526)
115–115.5	89	I	1275	
198–199.5	92	I	112	2,4-DNP 252–253
188.5–190	90	I	112	
209–210	12	F	846	
		C	1275	Cyclic acetal 123–124
170	91	D	112	
98	84	D	972	

[b] Semi. = semicarbazone; Thio. = thiosemicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; NPH = *p*-nitrophenylhydrazone; Ox. = oxime; Cyclic acetal = 1,3-dioxolane; DiEt = diethyl acetal.

[c] If a reference is not given, the melting point of the derivative is quoted in the reference to the preparation.

[d] By NMR analysis of isomer mixture.

c. NUCLEOPHILIC SUBSTITUTION

The halo substituent in a 2-acyl-5-halothiophene is replaced by treatment with a copper(I) acetylide,[589,611] copper(I) cyanide in pyridine or quinoline,[1269] or triphenylphosphine.[1270] As expected, the introduction of a nitro group into the thiophene ring increases the reactivity of the halogen atom toward displacement by nitrogen,[587,1262,1264,1268,1271] oxygen,[1262,1272] or sulfur nucleophiles.[1265,1266] However, when 5-bromo-4-nitro-2-thienyl methyl ketone is treated with copper(I) cyanide, the bromo substituent is replaced by hydrogen.[1269]

Replacement reactions involving the treatment of an acetal of the haloketone with butyllithium, then with another reagent, are similar to those discussed for the halothiophene carboxaldehydes (Section II.6).

d. MISCELLANEOUS REACTIONS

The configurations of the two stereoisomeric oximes of 2-acetyl-5-chlorothiophene have been investigated by Beckmann rearrangement with ethereal phosphorus pentachloride.[1249] Schmidt reaction of 3-acetyl-5-chlorothiophene with hydrazoic acid gives the 3-acetamido compound (42%).[1255]

2-Acetyl-5-bromothiophene undergoes palladium(II)-catalyzed reaction with the allylic alcohol, CH_2=CHCHMe(OH), thereby replacing the bromo substituent by $-CH_2CH_2COMe$ (86%).[1273]

C. NMR Spectroscopy

The ^1H and ^{19}F spectra of 2-acetyl-4- or 5-fluorothiophene, 3-acetyl-5-fluorothiophene, and their oximes have been examined.[621] The O,S-*cis* conformation of 2-acetyl-4,5-dibromothiophene has been established by application of the nuclear Overhauser effect.[619]

The ^{79}Br NQR frequencies of some bromo-2-thienyl ketones have been measured.[1274]

8. Nitrothienyl Ketones

A. Preparation

Most are obtained by nitration of a thienyl ketone (Section III.3, "Substitution Reactions"). Other methods are indicated in the footnotes to Table 21.

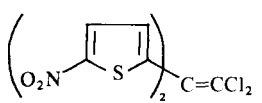
B. Reactions and Spectroscopy

Reactions are similar to those described in Section III.3 for thienyl ketones generally, and need not be discussed further.

TABLE 21. NITROTHIENYL KETONES

Substituents on Thiophene Ring				Melting Point	Yield			Melting Point of Derivatives
R^2	R^3	R^4	R^5	(°C)	(%)	Method[a]	References	(°C)[b] (References)
COMe	H	H	NO_2	107–108	83	D	1118	Ox. 188–189 (1118) and 218 (423); BPH 222 (423)
COEt	H	H	NO_2	89–89.5	–, 91	A, D	1104, 1118	Thio. 238 (1104); Ox. 178–179 (1118)
COPh	H	H	NO_2	110	70	C	807	
CO(5-NO_2-2-Thienyl)	H	H	NO_2	152–154	42	F	1279	
COMe	H	Br	NO_2	91–92		A	1265	
COMe	H	NO_2	H	126–128	85	A	1118	BPH 198 (423)
COEt	H	NO_2	H	140–141	–, 90	A	1104, 1118	
COPh	H	NO_2	H	121.5–123	60, 7	E, C	1278c	
COMe	H	NO_2	Cl	85–87	89, 78	A	1262, 1263	
COMe	H	NO_2	I	127		A	1264	
COMe	H	NO_2	Bu^t	80		A	16	
COMe	Br	NO_2	H	108–109	46	A	1266	
COMe	NO_2	H	NO_2	78	78	B	1104	
COMe	H	NO_2	NO_2	123	62	A	738	Thio. 232–235 (104)
——2-$COCHMeCH_2$——		H	NO_2	99–101	21, 55	A	1120, 1121	
——2-$COCHMeCH_2$——		NO_2	H	94–96	45	A	1121	
H	COMe	Br	NO_2	127–128		A	1266	
——$(CH_2)_3CO$-3——		H	NO_2	114–115	82	A	997	
——$(CH_2)_3CO$-3——		NO_2	Me	108–110	48	A	997	

[a] A = Nitration of the appropriate thienyl ketone; B = diethyl ethoxymagnesiomalonate on 3,5-dinitrothiophene-2-carbonyl chloride; C = Friedel-Crafts aroylation; D = nitration of a thienyl ketoxime, followed by hydrolysis; E = deamination of 3-amino-4-nitro-2-thienyl phenyl ketone; F = oxidation (CrO_3-AcOH) of



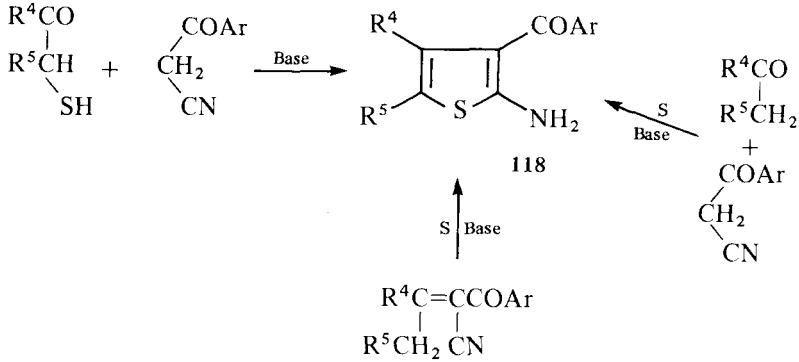
[b] Thio. = thiosemicarbazone; Ox. = oxime; BPH = *p*-bromophenylhydrazone.

The conformation of 2-acetyl-5-nitrothiophene has been investigated by ESR spectroscopy.[653]

9. Aminothienyl Ketones

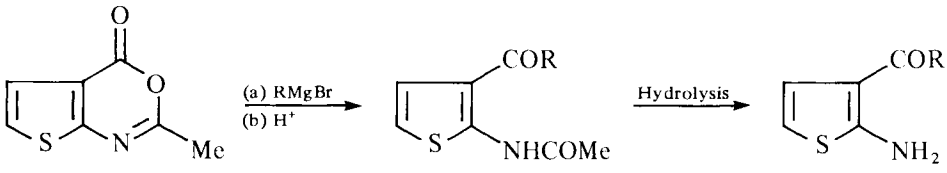
A. Preparation

The preparation of 2-amino-3-aroylthiophenes has been revolutionized by the introduction of the Gewald procedure, in which either an α-mercaptocarbonyl compound reacts with an aroylacetonitrile or a carbonyl compound reacts with the aroylacetonitrile in the presence of sulfur in a suitable solvent (Scheme 20).[543,1280-1293] Yields are sometimes improved if the Knoevenagel condensation product (**117**) is isolated prior to the heating with sulfur. The relative inaccessibility and high reactivity of acylacetonitriles means that the Gewald procedure is carried out almost exclusively with aromatic ketonitriles. In an extension of the Gewald method, an αβ-unsaturated aldehyde, Ar′CH=CHCHO, reacts with an aroylacetonitrile and sulfur to give the aminoketone (**118**; $R^4 = H$, $R^5 = CSAr'$) in low yield.[1294] The thioketone group (CSAr′) in the last compound is readily transferred into the aroyl group (COAr′) by successive treatment with thionyl chloride and water, thus affording 2-amino-3,5-diaroylthiophenes.[1295]



Scheme 20

Another method which has had limited use for preparing 2-amino-3-thienyl ketones involves the reaction of a Grignard reagent with a readily obtainable 2-methyl-4*H*-thieno[2,3-*d*][1,3]oxazin-4-one (Scheme 21).[1282] The method has the advantage that it can be used for preparing 3-acyl-, as well as 3-aroylketones, but suffers from the disadvantage that alcoholic by-products are formed, resulting from the action of the Grignard reagent on the required ketone. However, it also

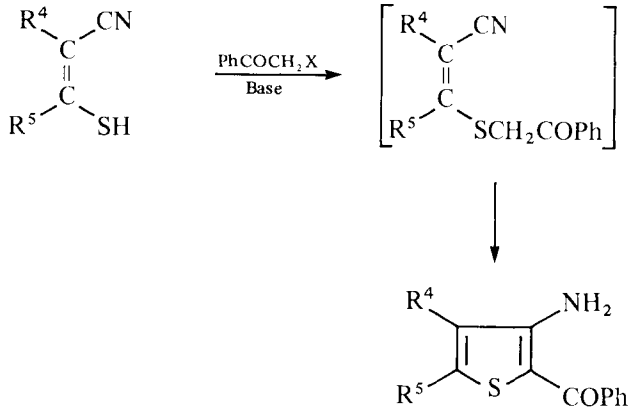


Scheme 21

has the advantage that it can be adapted to give isomeric aminoketones, provided that the amino and acyl groups occupy adjacent positions in the ring.[1257,1296,1297]

In the most general approach to 3-amino-2-thienyl ketones, a 3-mercaptoacrylonitrile derivative reacts with phenacyl chloride under basic conditions; the intermediate sulfide normally cyclizes spontaneously (Scheme 22),[1298–1300] thus giving access to a range of multifunctional aminothienyl ketones. In a related reaction, mercaptoacetone undergoes Michael addition to 2-chloroacrylonitrile; subsequent cyclization and dehydrohalogenation gives 2-acetyl-3-aminothiophene (64%).[1301]

2,5-Bis(benzoyl)-3-*N*,*N*-dimethylaminothiophene is obtained by heating the unsaturated amine, $PhCOCH{=}CHNMe_2$, with S_2Cl_2.[1302]



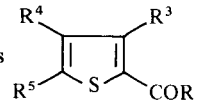
Scheme 22

3-(*t*-Amino)thiophenes have enaminelike character and react with acid chlorides or disubstituted ketenes to give the appropriate 2-acyl compound.[1303,1304] Similarly, 3-pyrrolidinothiophene undergoes a facile cycloaddition reaction with 2,4,6-trimethylbenzonitrile oxide to give the ketoxime **119**.[1305]

5-(Secondary-amino)-2-thienyl ketones have been obtained by the route shown in Scheme 23 (see References 1306–1308; cf. also Reference 1234). The starting materials (**120**) are adducts of isothiocyanates (RNCS) with enamines or nitroketene aminals. The 5-(*t*-amino)2-thienyl ketones (**122**) may be obtained by treatment of the 5-phenyl-*N*-(1,3-oxathiol-2-ylidene)tertiary iminium hydrogen sulfates (**121**) with an "active methylene" compound in basic solution (Scheme 24).[1309]

TABLE 22. AMINOTHIENYL KETONES

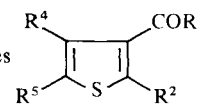
2-Acyl- or 2-Aroylaminothiophenes



R	R^3	R^4	R^5	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivative (°C)[b]
Me	NH_2	H	H	82–83	64	I	1301	
Me	NHAc	H	H	95	60	D	658	3-NH_2 81
Me	NMe_2	NO_2	NHAllyl	95–97	20	N	1306	
Me	NHMe	NO_2	NHPh	145–147	26	N	1306	
Me	NPh(Pr^i)	H	NPh(Pr^i)	148–150	23	M	1303	
$CHCl_2$		H	Me	83–84	30	M	1304	
$CHPh_2$		H	Me	111–111.5	17	M	1304	
Ph	NHAc	H	H	96–97		H	1297a	3-NH_2 103
Ph	NHAc	H	Cl	81–82	72	D	1255	3-NH_2 151.5–152
Ph	NPh(Pr^i)	H	NPh(Pr^i)	98–100	69	M	1303	
$C_6H_4NO_2$-*p*	NPh(Pr^i)	H	NPh(Pr^i)	147–149	70	M	1303	
Ph	NMe_2	H	COPh	184–185	17	I	1302	
C_6H_4Cl-*o*	NHAc	H	Cl	124–127		D	1255	3-NH_2 137–140
C_6H_4Cl-*o*	NHAc	H	CF_3	110	57	H	1296c	3-NH_2 109–110
Ph	NH_2	NO_2	H	176–177	84	G	1278c	
Ph	NHAc	Cl	H	183–185	57	L	1297b	3-NH_2 123–124
Ph	NHAc	Cl	Cl	132–136	79	K	1297b	3-NH_2 111–112
Ph	NH_2	CN	OH	270	64	I	1300	3-NHAc 190–192
Ph	NH_2	CN	Me	153	70	I	1298	
Ph	NH_2	NH_2	SMe	143	88	I	1299	
Ph	NHMe	NO_2	NHPh	150–151	47	N	1306	

Ph	NMe_2	NO_2	NHMe	159–161	49	N	1306	
Ph	NMe_2	NO_2	NHPh	140–142	48	N	1306	
Me	H	NHAc	Me	167	65	F	738	
Me	H	NHC_6H_4SH-*o*	NO_2	165–167	95	E	1271	
Me	H	NHAc	NHAc	255–257	34	F	1313	
Me	H	H	NHAc	271	93	D	1312	
Me	H	NO_2	NH_2	225–227	88	E	1262	5-NHAc 201 (1313)
Me	H	NO_2	$NHBu^n$	96.5–97.5		E	1262	
Me	H	NO_2	Piperidino	96		E	587	
Me	H	NO_2	NHPh	138.5–139.5	79	E	1262	
Me	H	NO_2	$NHC_6H_4CO_2H$-*o*	>260	98	E	1268	
Me	H	NO_2	$NHC_6H_3CO_2H$(Me)-2,4	>260	95	E	1268	
Me	H	NO_2	$NHC_6H_3CO_2H$(Cl)-2,4	>260	96	E	1268	
Me	H	NO_2	$NHC_6H_3CO_2H$(Cl)-2,5	>260	96	E	1268	
Ph	H	H	NH_2	160	64	J	1294, 1295	5-NHAc 221
Ph	Me	H	NH_2	163–165	24	J	1310	
C_6H_4Me-*p*	H	H	NH_2	176	49	J	1295	

3-Acyl or 3-Aroylaminothiophenes



R	R^2	R^4	R^5					
Me	NH_2	$-(CH_2)_4-$		196	24	A	543	
Me	NHMe	Me	COPh	151–153	36	N	1307	
Me	NMe_2	Me	COPh	134–136	74	P	1309	
Me	Piperidino	Me	COPh	121–123	73	P	1309	
Et	NHAc	H	H	73.5–74	19	H	1282	2-NH_2 140–142
Et	NHAc	H	Cl	156.5–157.5	17	K	1282	
Ph	NH_2	H	H	153–154	30, 75, 70	A/B, B	1289, 1288	2-NHAc 117–118 (1288)
						B	1285	2-NHCHO 152 (1285)
Ph	NH_2	Me	H	150–151	35, 40	A/B, B	1289, 1281	
Ph	NH_2	H	Me	123–126	72	A	1290	

TABLE 22. (*Continued*)

R	R^2	R^4	R^5	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivative (°C)[b]
Ph	NH_2	H	Et	87–88	70	A	1284	
Ph	NH_2	H	Cl	155	79	K	1288	
Ph	NHAc	H	Cl	102.5–103.5	67	K	1282	
Ph	NHAc	H	COPh	182	85	O	1295	2-NH_2 207
Ph	NHAc	H	COC_6H_4OMe-*p*	183	70	O	1295	2-NH_2 186
Ph	NHAc	H	COC_6H_4Me-*p*	168	91	O	1295	2-NH_2 194
Ph	NH_2	H	CSPh	185	23	C	1294	
Ph	NH_2	H	CSC_6H_4OMe-*p*	205	18	C	1294	
Ph	NH_2	H	CSC_6H_4Me-*p*	168	19	C	1294	
Ph	NH_2	Me	Me	140–141	53, 72	A	543, 1284	
Ph	NH_2	Et	Me	127.5–129	65	A	1283	
Ph	NH_2	Pr	Et	133–134.5	79	A	1283	
Ph	NH_2	$-(CH_2)_4-$		155	93, 40, 80	A, A, C	543, 1280	
Ph	NHAc	Cl	Cl	160–161	88	D	1278b	2-NH_2 165–167
Ph	NMe_2	Me	COPh	146–147	45	P	1309	
Ph	Piperidino	Me	COPh	132–133	82	P	1309	
Ph	Morpholino	Me	COPh	160–162	85	P	1309	
C_6H_4Me-*o*	NH_2	H	H	158	74, 60	B	1287, 1285	2-NHAc 90–91.5 (1282)
C_6H_4Me-*o*	NH_2	H	Et	110–112	58	A	1284	
C_6H_4Cl-*o*	NH_2	H	H	137–139	47	B	1282	2-NHAc 132–132.5
C_6H_4Cl-*o*	NH_2	H	Me	160–162	75	A	1284	
C_6H_4Cl-*o*	NH_2	H	Et	132–133	61	A	1284	
C_6H_4Cl-*o*	NHAc	H	Cl	180–181	77	K	1282	
C_6H_4Cl-*o*	NH_2	Me	Me	151–152	59	A	1284	
C_6H_4Br-*o*	NH_2	H	H	152–152.5	34	B	1282	2-NHAc 122.5–123.5
C_6H_4Br-*o*	NH_2	H	Et	123–125	60	A	1284	
C_6H_4Br-*o*	NHAc	H	Cl	162–163	76	K	1282	
C_6H_4I-*o*	NH_2	H	H	162–165	28	B	1282	2-NHAc 125.5–127
C_6H_4I-*o*	NHAc	H	Cl	124–126	49	K	1282	
C_6H_4F-*o*	NH_2	H	H	144–146	58, 60	B	1287, 1282	2-NHAc 143.5–144.5

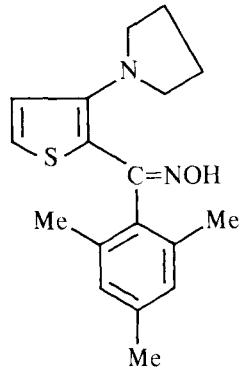
C_6H_4F-*o*	NH_2	Me	H	163–164	36	B	1293	2-NHAc 96–96.5
C_6H_4F-*o*	NH_2	H	Et	114–116	68	A	1284	
C_6H_4F-*o*	NHAc	H	Cl	159–160.5	62	K	1282	
C_6H_4F-*o*	NHAc	Me	Cl	140–140.5	82	K	1293	
C_6H_4OMe-*o*	NH_2	H	H	164.5–165	42	B	1287	
C_6H_4OMe-*o*	NH_2	H	Et	145–147	73	A	1284	
$C_6H_4NO_2$-*o*	NH_2	H	H	114–116	48	A	1286	
$C_6H_4NO_2$-*o*	NH_2	H	Me	131.5–133	51	A	1286	
$C_6H_4NO_2$-*o*	NHAc	H	COMe	209–211	47	D	1286	2-NH_2 181–183
$C_6H_4NO_2$-*o*	NH_2	H	Et	99–101	73	A	1286	
$C_6H_4NO_2$-*o*	NH_2	Me	H	161–163	45, 46	A/B, A	1289, 1286	
$C_6H_4NO_2$-*o*	NH_2	Et	H	185–186	28	A	1286	
$C_6H_4NO_2$-*o*	NH_2	Me	Me	179–181	18	A	1286	
$C_6H_4CF_3$-*o*	NH_2	H	H	129–131	78	B	1287	
$C_6H_4SO_2Me$-*o*	NH_2	H	H	217–218	79	B	1287	
C_6H_4Cl-*m*	NH_2	Me	H	182–183	45	A/B	1289	
C_6H_4Me-*p*	NHAc	H	COPh	157	83	O	1295	2-NH_2 222
C_6H_4Me-*p*	NH_2	H	CSPh	202	21	C	1294	
C_6H_4Cl-*p*	NH_2	H	H	180–181.5	28	B	1282	2-NHAc 107–108.5
C_6H_4Cl-*p*	NHAc	H	Cl	119–121	41	K	1282	
C_6H_4Cl-*p*	NH_2	Me	H	154–155	50	A/B	1289	
C_6H_4Cl-*p*	NH_2	Me	Me	127–129	52	A	1284	
C_6H_4OMe-*p*	NHAc	H	COPh	169	85	O	1295	2-NH_2 182
C_6H_4OMe-*p*	NH_2	H	CSPh	170	24	C	1294	
$C_6H_3(Cl)_2$-2,3	NH_2	H	H	168–169	74	B	1287	
$C_6H_3Me(NO_2)$-2,3	NH_2	H	H	117–120	78	B	1287	
$C_6H_3(Cl)_2$-2,6	NH_2	H	H	207–208	86	B	1292	
$C_6H_3(F)_2$-2,6	NH_2	H	H	130–132	56	B	1287	
2-Thienyl	NH_2	H	H	121	70	B	1285	2-NHCHO 124
2-Thienyl	NH_2	Me	H	121–123	48	B	1283	
2-Furyl	NH_2	H	H	118	60	B	1285	2-NHCHO 143
2-Pyridyl	NH_2	H	H	122–124	50	B	1291	
Me	Me	NHAc	Me	137–138	86	D	1083	4-NH_2 89–90

TABLE 22. (*Continued*)

R	R^2	R^4	R^5	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivative (°C)[b]
Ph	H	NHAc	H			H	1257a	4-NH_2 110 (25% overall)
Ph	H	NHCHO	Cl	b.p. 170/ 0.001 mm	48	K	1257b	
Ph	Me	NHAc	Me	140–141	79	D	1083	4-NH_2 175–177
C_6H_4Cl-*o*	CF_3	NHAc	H			H	1296b	4-NH_2 Oil
$C_6H_4CF_3$-*o*	H	NHCOPh	H	160–161	64	H	1296a	4-NH_2 Oil
C_6H_4Cl-*m*	Me	NHAc	Me	141–142	76	D	1083	4-NH_2 235–237
C_6H_4Me-*m*	Me	NHAc	Me	136–137	75	D	1083	4-NH_2 226–228
C_6H_4Cl-*p*	Me	NHAc	Me	150–152	88	D	1083	4-NH_2 230–232

[a] A = Gewald method (ketone + aroylacetonitrile + sulfur); B = Gewald method (α-mercapto carbonyl compound + aroylacetonitrile); C = modified Gewald procedure (see text); D = Friedel-Crafts acylation of an acylaminothiophene; E = nucleophilic displacement of a halogen atom from a halonitrothiophene; F = reductive acetylation of a nitro compound; G = nitration of a protected aminothienyl ketone, followed by hydrolysis; H = Grignard reagent on a 4*H*-thieno[1,3]oxazin-4-one (see text); I = from an open-chain precursor (see text); J = decarboxylation of an amino carboxylic acid; K = halogenation reaction; L = selective dehalogenation of a dihalo compound; M = substituted ketene or acid chloride on a 3-*t*-amino thiophene; N = isothiocyanate adduct + α-haloketone (see text); O = from a thioketone; P = from an *N*-(1,3-oxathiol-2-ylidene)tertiary iminium salt + 1,3-diketone (see text).

[b] The entries in the earlier columns relate to the product obtained from the particular reaction used: if it is an amine, the derivative quoted is an acylamino compound; if it is an acetamidothiophene, the derivative is the free amine (obtained by hydrolysis).



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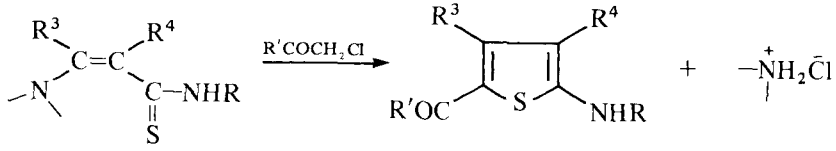
The amines (**122**) lose the 2-benzoyl group when treated with potassium *t*-butoxide in aqueous DMSO.[1309]

Some 5-amino-2-aroylthiophenes have been obtained by the facile decarboxylation of the corresponding 4-carboxylic acid.[1294,1295,1310]

Other amines (or their acylamino derivatives) have been prepared by conventional Friedel-Crafts acylation reactions,[658,1083,1255,1278,1311,1312] reductive acetylation of a nitro group[738,1313] or nucleophilic displacement of the halogen atom from a halonitro compound by an amine.[587,1262,1264,1268,1271]



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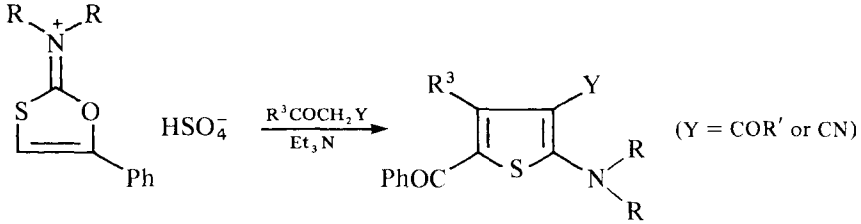
Scheme 23



121 122

Scheme 24

3-Amino- (and 3-acetamido-)2-benzoyl-4,5-dihydrothiophene are aromatized in high yield by treating them with sulfuryl chloride.[1314]

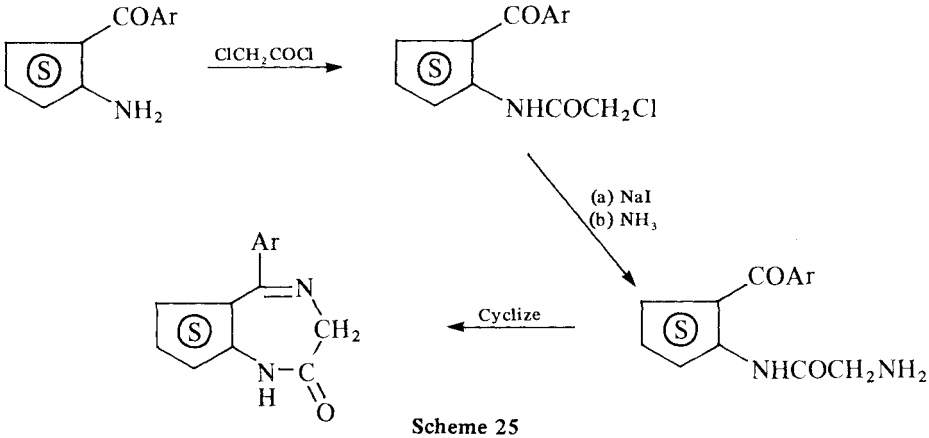
Aminothienyl ketones are listed in Table 22.

B. Reactions

a. CYCLIZATION

Thiophenes containing adjacent amino and aroyl groups have been used extensively for the preparation of thieno analogues of the 1,4-benzodiazepine tranquilizers. The most commonly used route is outlined in Scheme 25.[658,1083,1255,1278,1282–1284,1286,1287,1290,1291,1296,1297,1315]

They have also been cyclized by standard routes to thienopyridines[1083,1289] and thienopyrimidines.[1282,1289,1293,1316,1317] Thieno[1,4]oxazepine derivatives have been made by a modification of Scheme 25.



Scheme 25

b. SUBSTITUTION

2-Amino- and 2-acetamido-3-aroylthiophenes are chlorinated in the 5-position by *N*-chlorosuccinimide[1288] and sulfuryl chloride respectively.[1282] The latter reagent has also been used to chlorinate other acylaminothienyl ketones.[1257b]

c. DIAZOTIZATION

3-Amino-2-acyl- (or 2-aroyl-)thiophenes have been diazotized, thus allowing the amino group to be replaced by $-N_3$,[669] $-SCN$ or $-SeCN$,[666] or $-H$.[1278c]

10. Hydroxy-, Alkoxy-, and Aryloxythienyl Ketones

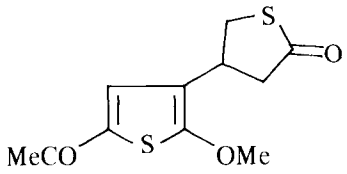
A. Preparation

Many alkoxythienyl ketones have been made by conventional methods (Table 23). However, problems arise because of the high reactivity of alkoxythiophenes toward electrophiles and because of the ease of ether cleavage.

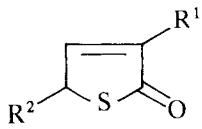
2-Methoxythiophene is acetylated under Vilsmeier-Haack conditions ($AcNMe_2$-$COCl_2$) considerably faster (by a factor of 5×10^3) than it is formylated under similar conditions (DMF—$COCl_2$).[8] This method appears not to have been used preparatively. However, as an alternative, methoxythienyllithium derivatives may be treated with $AcNMe_2$.[527,687]

t-Butoxythienyl methyl ketones have been prepared by the action of acetic anhydride on a Grignard reagent (from ThLi and $MgBr_2$).[1319,1320]

Anomolous results are observed when 2-methoxythiophene is subjected to Friedel-Crafts acetylation; even at 0° C, as a consequence of ether cleavage, the by-product **123** is obtained.[1251] The 3,5-diacetyl compound is also obtained (20%) in addition to the expected 5-acetyl derivative.[1311] Acetylation ($AcCl—SnCl_4$) of



123



124

2-acetoxy-3-bromothiophene gives the 5-acetyl derivative (60%), together with the lactone **124** ($R^1 = Br$, $R^2 = H$); the latter is the only product from attempted acetylation of 3-bromo-2-*t*-butoxythiophene.[1251]

3,4-Dimethoxythiophene is conveniently bisaroylated by treatment of the bis-acetoxymercuri derivative with an aroyl chloride in the absence of a catalyst; unusually, with benzoyl chloride the reaction is accompanied by demethylation of the ether group.[1321]

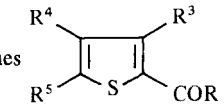
2-Acetoxythiophene undergoes a transacylation reaction when treated with $BF_3 \cdot Et_2O$ to give its 5-acetyl derivative and the lactone **124** ($R^1 = R^2 = H$). When the 5-position is occupied by a methyl group, a Fries-like reaction occurs to give 3-acetyl-2-hydroxy-5-methylthiophene (40%) and the lactone **124** ($R^1 = H$, $R^2 = Me$).[1322]

2-Acyl (or aroyl)-3-hydroxythiophenes are readily accessible from the base-catalyzed intramolecular cyclization of the keto esters, $MeO_2CCH{=}CR^1(SCH_2COR^2)$;[1323-1325] if $R^1 = H$, the starting material is easily obtained by Michael addition of a mercaptoketone to methyl acetylenecarboxylate.[1324, 1325] 2,5-Diacyl-3,4-dihydroxythiophenes are obtained (20 to 40%) by treatment of the tetraketone, $R^1COCH_2COCOCH_2COR^2$, with sulfur dichloride.[1326]

Alkoxynitrothienyl ketones are conveniently prepared by treatment of the corresponding halonitro compound with the appropriate alkoxide ion.[1262,1272]

TABLE 23. ALKOXY- AND HYDROXYTHIENYL KETONES

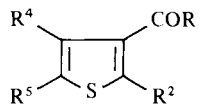
2-Thienyl Ketones



R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivative (°C)[b] (Reference)[c]
Me	OH	H	H	47–49/0.2	51.5–52.5	92, 30, 12	E, B, B	1319, 1325 1324	Ox. 55 (687)
Me	OMe	H	H		65	32	H	687	Ox. 133
Me	OBu^t	H	H	94–96/0.1		75	D	1319	Ox. 126 (687)
Me	OMe	OMe	H	102/0.5		94	A	1251	
Me	OH	OH	COMe		175–177	26	B	1326	
Me	OMe	OMe	COMe		182	35	H	527	
Me	OH	OH	COPh		112	33	B	1326	
Me	H	H	OMe		34–35	15, 57, 24	A	683, 1251 1311	NPH 198–199 (683)
Me	H	H	OAc		103–105	45	F	1322	
Me	H	NO_2	OH		65		G	1262	
Me	H	NO_2	OMe		158–159	80	G	1262	
Me	H	NO_2	OEt		125–126	50	G	1262	
Me	H	NO_2	OAllyl		89–91	46	G	1272	
Me	H	NO_2	OPh		122–123	70	G	1262	
Me	H	COMe	OMe		123–127	20[d]	A	1311	
Me	H	Br	OAc		66	60	A	1251	5-OMe 111–112
CF_3	H	H	OMe	110–112/17	54–54.5		A	905	
Bu^i	OH	OH	$COBu^i$		40–45	20	B	1326	
Bu^t	OH	OH	$COBu^t$		128–129	40	B	1326	
Ph	OH	OH	COPh		184–185	33	B	1326	
					120	20	C	1321	

Ph	H	H	OMe	45–46.5	60–80	A	810
				57	50	A	807
Ph	OH	H	OMe	58–60	81	B	1323
C_6H_4OMe-*o*	OMe	H	H	94	65	A	1321
C_6H_4OMe-*o*	OMe	OMe	H	Oil	80	A	1321
C_6H_4OMe-*o*	OMe	OMe	COC_6H_4OMe-*o*	114	15	C	1321
Mesityl	H	H	OMe	81–82	60–80	A	810
3-OMe-2-Thienyl	OMe	H	H	141	70	A	1321
3-OMe-2-Thienyl	OMe	OMe	H	70	95	A	1321

3-Thienyl Ketones



R	R^2	R^4	R^5					
Me	OH	H	H	46–48/0.2		71	E	1320
Me	OMe	H	H		127–128	1	A	683
Me	OBu^t	H	H	75–77/0.05		74	D	1320
Me	OH	H	Me		Oil	40	F	1322
Me	H	OH	H	63–65/0.2	51–53	91	E	1319
Me	H	OBu^t	H	78–80/0.2		70	D	1319

[a] A = Friedel-Crafts acylation; B = from an open-chain compound (see text); C = acid chloride on acetoxymercuri compound; D = acetic anhydride on Grignard reagent (from the thienyllithium and $MgBr_2$); E = dealkylation of an ether; F = 2-Acetoxythiophene derivative and $BF_3 \cdot Et_2O$; G = nucleophilic displacement of halogen from a halonitrothiophene; H = $MeCONMe_2$ on the thienyllithium.

[b] Ox. = oxime; NPH = *p*-nitrophenylhydrazone.

[c] If a reference is not given, the melting point of the derivative is quoted in the reference to the preparation.

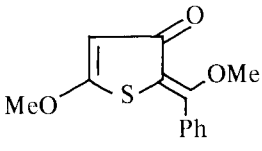
[d] By analysis of the total reaction product.

B. Reactions

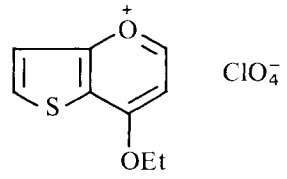
a. GENERAL

Alkoxythienyl ketones are usually dealkylated by treatment with pyridine hydrochloride;[677,687] for *t*-butoxy compounds, however, it is sufficient to pyrolyze the ether in the presence of toluene-*p*-sulfonic acid.[1319,1320]

2-Benzoyl-3-hydroxy-5-methoxythiophene is methylated by diazomethane on the oxygen atom of the aroyl group to the give the unsaturated ether **125** (62%) (in addition to the expected 3,5-dimethoxy compound).[1323]



125



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b. SUBSTITUTION REACTIONS

Attempts to brominate methoxythienyl methyl ketones in the acetyl group often lead additionally to substitution in the ring; ring bromination is minimized by using copper(II) bromide.[1251] When treated wih pyridinium bromide perbromide, 2-acetyl-5-methoxythiophene undergoes an unusual replacement of the methoxy group by bromine.[1251] The methoxy group in 2-acetyl-5-methoxy-4-nitrothiophene is readily replaced by pipderidine in methanolic solution.[1327]

c. CYCLIZATION REACTIONS

Aroylthiophenes in which both rings contain a methoxy function adjacent to the carbonyl group are readily dimethylated and cyclized to xanthone analogues.[1321] Treatment of 2-acetyl-3-hydroxythiophene with triethyl orthoformate in the presence of perchloric acid gives the thienopyrylium salt **126**.[677]

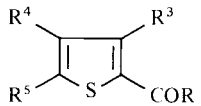
C. Physical Properties

Thiophenes containing adjacent hydroxy and acetyl groups exist entirely as the enol tautomer in solution (^{1}H NMR spectroscopy);[1319,1320] their acidities have been investigated.[688,1328]

The crystal structure of 2-acetyl-3-hydroxythiophene has been determined.[1329] The mass spectrum of 3-acetyl-4-hydroxythiophene has been discussed.[1330]

TABLE 24. THIENYL KETONES CONTAINING A SUBSTITUENT IN WHICH A SULFUR (OR SELENIUM OR TELLURIUM) ATOM IS ATTACHED DIRECTLY TO THE RING

(Alkylthio)-2-acylthiophenes and Related Sulfur Compounds

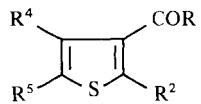


R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivative (°C)[b]
Me	SH	H	H		32		E	666	Disulfide 182–183
Me	SMe	H	H		66–67	78	A	1335	Ox. 96–97
Me	SCN	H	H		78	45	D	666	
Me	SMe	H	SMe		58–59	10	A	697	
Me	SCH_2CO_2Et	H	Et	171–173/2	51.5–52.5		A	748	
Me	SPh	NO_2	H		94		H	1266	
Me	H	SEt	Me				A	609	Semi. 202.5–204
Me	H	SPh	NO_2		143		H	1265	
Me	H	H	SH	Oil		21	G	1332	SAr 136–137
Me	H	H	SMe		53	40, 25	A	1260, 1311	Ox. 97 (1260)
Me	H	H	SEt	122–122.5/1		37	A	1332	2,4-DNP 156–156.5
Me	H	H	SPr	150–156/2.5		36	A	748	
Me	H	H	SPr^i	160–164/10		49	A	748	
Me	H	H	SBu^n	137–140/0.6		60	A	748	
Me	H	H	SBu^i	131–133/0.5		57	A	748	
Me	H	H	$S(CH_2)_4Me$	180–184/4.5		45	A	748	
Me	H	H	$SCH_2CH_2CHMe_2$	182–186/14		54	A	748	
Me	H	H	$S(CH_2)_5Me$	166–168/0.8		57	A	748	
Me	H	H	$S(CH_2)_6Me$	170–174/0.5		59	A	748	
Me	H	H	$S(CH_2)_7Me$	170–175/0.3		58	A	748	
Me	H	H	$S(CH_2)_8Me$	173–180/0.4		55	A	748	
Me	H	H	SCH_2CO_2Me	166–170/2	43.5–44	78	A	1336	

TABLE 24. (*Continued*)

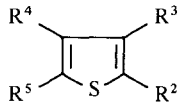
R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivative (°C)[b]
Me	H	COMe	SMe		119.5–120.5	15	A	1311	
Me	H	COMe	SCH_2CO_2Me		136–137	35	A	1336	
Me	Me	COMe	SH		101–104	45	C	1333	
CF_3	H	H	SMe	148/20			A	905	
Et	H	H	SMe	94–103/0.4		30	A	958	

(Alkylthio)-3-acylthiophenes



R	R^2	R^4	R^5						
Me	SMe	H	H		32–34	3	A	1311	
Me	SCH_2CO_2Me	H	H		81–82	34	A	952	
Me	SMe	H	Me		97	90	A	1260	
Me	SMe	H	Et		48–49	80	A	713a	Semi. 199–200
Me	SEt	H	Me			97	A	609	Semi. 181–182
Me	SEt	H	Et		47.5–48	87	A	1260	Semi. 165–166
Me	SMe	H	SMe		745–75	29–46, 35	A	1260, 697	
Me	SCH_2CO_2Me	H	Me		68–70.5	77	A	952	
Me	SCH_2CO_2Et	H	Et		45–45.5	87	A	713b	
Me	SMe	H	CMe(Et)Ar[c]		119.5–120	43	A	715	
Me	SEt	H	CH_2Ar[d]		126–127		A	715	
Me	SEt	H	CMe(Et)Ar[d]		101–102	66	A	715	
Me	SEt	H	$CHBu^iAr$[d]		89.5–90.5	22	A	715	
Me	H	SPh	NO_2		127		H	1266	
Me	SMe	Me	H		51–52	91	F	1335	Ox. 68–69
Et	Et	Et	SEt	124.5/2			A	709	2,4-DNP 89–90

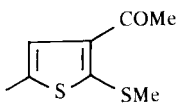
Selenium and Tellurium Derivatives

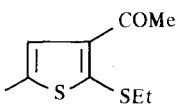


R^2	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivative (°C)[b]
COMe	SeH	H	H				E	666	Diselenide 190–192
COMe	SeCN	H	H		103	50	D	666	
COMe	H	H	SeMe		35.5	75	A	41	Semi. 200–201.5
SeMe	COMe	H	Me		91.5–92.5	25	A	41	
COMe	TeMe	H	H		104	20	B	397	
COMe	$TeBu^n$	H	H	161/1		56	B	397	
COMe	H	$TeBu^n$	H	165/1		35	B	397	
TeMe	COMe	H	H	140/0.8	79	42	B	397	
H	COMe	$TeBu^n$	H	170/1.5		45	B	397	

[a] A = Friedel-Crafts acylation; B = lithio derivative of acetal + (a) Te, (b) RX; C = from an open-chain compound (see text); D = via the diazonium salt of corresponding amine; E = reduction of a thiocyanate or selenocyanate; F = decarboxylation of a carboxylic acid; G = cleavage of a sulfide; H = nucleophilic displacement of bromide from a bromonitro compound.

[b] Semi. = semicarbazone; 2,4-DNP = 2,4-dinitrophenylhydrazone; Ox. = oxime; SAr = 2,4-dinotrophenyl sulfide.

[c] Ar = 

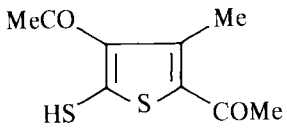
[d] Ar = 

11. Thienyl Ketones Containing a Substituent in Which a Sulfur (or Selenium or Tellurium) Atom is Directly Attached to the Ring

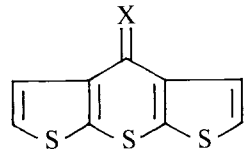
A. Preparation

These ketones, mostly prepared by standard methods, are contained in Table 24.

Although the alkylthio compounds are quite stable, the corresponding thiols are generally unstable and readily give the disulfide. Free acetylthiophenethiols (or selenols) have been prepared by reduction of the corresponding –SCN (or –SeCN) compound,[666] or by cleavage of the sulfide, $-SCH(C_6H_4NO_2\text{-}m)$-$CH_2COPh$, with lead(II) acetate in dioxane.[1332] 3,5-Diacetyl-4-methylthiophene-2-thiol (**127**) is conveniently prepared (45%) by treatment of $Ac_2CHCS(\bar{S})$ (from acetylacetone and CS_2) with chloroacetone.[1333] An attempt to prepare the 2,2′-dithiol of bis-(3-thienyl) ketone by treatment of the acetal with butyllithium and sulfur gave the cyclized products **128** (X = S or O) and the acetal of the latter.[1334]



127



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B. Reactions

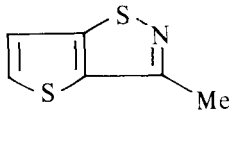
a. GENERAL

(Alkylthio)thienyl methyl ketones are best oxidized to the corresponding carboxylic acid by treating them with iodine and pyridine, followed by alkaline hydrolysis of the resulting pyridinium salt.[713a,715,1260] Their oximes undergo the Beckmann rearrangement to the corresponding acetamido compound.[1335]

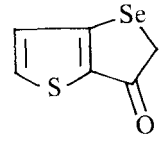
b. CYCLIZATION REACTIONS

3-Acetylthiophenes containing a $2\text{-}SCH_2CO_2Me$ substituent undergo base-catalyzed cyclizations to thieno[2,3-*b*]thiophenes;[952,1336] the [3,2-*b*]-isomers are formed analogously.[713b]

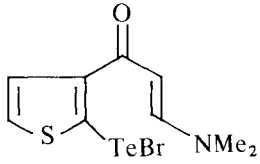
The *O*-*p*-nitrobenzoyl derivative of the oxime of 2-acetyl-3-(methylthio)-thiophene is cyclized in boiling acetic acid to the thienoisothiazole **129** (67%).[1335] The ketone **130** is formed in high yield by treatment of 2-acetyl-3-selenocyanato-thiophene with methanolic ammonia.[666] Enamines of the type **131**, obtained by reaction of the corresponding methyl ketone with the dimethyl acetal of DMF, give the telluropyrone **132** (or related structures) when treated with hypophosphorous acid.[1337]



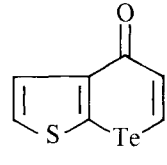
129



130



131



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12. Miscellaneous Thienyl Ketones

A. Azidothienyl Ketones

Only 2-acetyl-3-azidothiophene appears to have been reported (Table 25). Heating converts it into a substituted thieno[3,2-*c*]isoxazole (cf. **66**).[669]

B. Acetylthiophene Boronic Acids

These are obtained (Table 25) by a method similar to that used for the corresponding carboxaldehydes (Section II.11).[582]

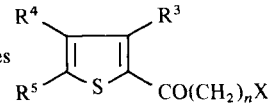
TABLE 25. MISCELLANEOUS THIENYL KETONES

Substituents on Thiophene Ring				Melting Point			
R^2	R^3	R^4	R^5	(°C)	Yield (%)	Method[a]	Reference
Acetylthienylboronic Acids							
COMe	$B(OH)_2$	H	H	110–125	32, 35	A, B	582
COMe	$B(OH)_2$	H	NO_2	134–139	28	C	1338
COMe	$B(OH)_2$	NO_2	H	119–124	19	C	1338
$B(OH)_2$	COMe	H	H	120–140	20, 13	A, B	582
$B(OH)_2$	COMe	H	NO_2	149–154	74	C	1338
3-Azido-2-thienyl Methyl Ketone							
COMe	N_3	H	H	58	Excellent	D	669

[a] A = Tributyl borate on a lithio derivative (COMe protected as acetal); B = tributyl borate on a lithio derivative (COMe protected as complex with *NN*-dimethylacetamide); C = by nitration reaction; D = sodium azide on a diazonium salt.

TABLE 26. ω-HALOALKYL THIENYL KETONES[a]

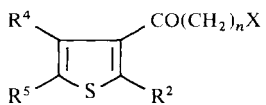
2-Thienyl Ketones



$(CH_2)_nX$	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[b]	References	Melting Point of Derivative (°C)[c]
$n = 1$									
CH_2Cl	H	H	H	140–146/20	47–48	21	C	743	
CH_2Cl	H	H	Br	108–109/0.6	96–97	78	B	1339	
CH_2Cl	H	H	Me	138–140/10	50–51.5		B	798	
CH_2Cl	H	H	$COCH_2Cl$		161	5	E	1363	
CH_2Cl	H	Cl	H		98–99	37	B	1339	
CH_2Cl	H	Br	H		57–58	37	B	1339	
CH_2Cl	H	Cl	Cl		61–62	84	B	577	
CH_2Cl	H	Br	Br	128–129/0.8	90–91	91	B	1339	
CH_2Cl	Cl	H	H		77–78	56	B	1339	
CH_2Cl	Br	H	H		79–80	56	B	1339	
CH_2Cl	Cl	H	Cl	125–128/2.5	76–77	53, 82	B	577, 1339	
CH_2Cl	Br	H	Br	130–131/0.6	92–93	89	B	1339	
CH_2Cl	Cl	Cl	H		70–71	93	B	577	
CH_2Cl	Br	Br	H	151–152/0.8	98–99	95	B	1339	
CH_2Cl	Cl	Cl	Cl	120–121/1.2	75–76	91	B	1339	
CH_2Cl	Br	Br	Br	159–160/1	114–115	65	B	1339	
CH_2Br	H	H	OMe	Oil		15	D	1251	
$n = 2$									
$(CH_2)_2Cl$	H	H	Br		58–59	76	B	1259	
$(CH_2)_2Cl$	H	Cl	Cl		67–68	95	B	577	
$(CH_2)_2Cl$	H	Br	Br		102–103	83	B	1259	
$(CH_2)_2Cl$	Cl	H	Cl		40.5–41.5	88	B	577	

$(CH_2)_2Cl$	Br	H	Br	157–159/0.6		90	B	1259	
$(CH_2)_2Cl$	Cl	Cl	H		61–62	88	B	577	
$(CH_2)_2Cl$	Br	Br	Br		117–118	84	B	1259	
$n = 3$									
$(CH_2)_3Cl$	H	H	Br		44–45	72	B	1259	
$(CH_2)_3Cl$	H	Br	Br		45–46	80	B	1259	
$(CH_2)_3Cl$	Br	H	Br	170–173/0.6		91	B	1259	
$(CH_2)_3Cl$	Br	Br	Br		90–91	85	B	1259	
$n = 4$									
$(CH_2)_4Cl$	H	H	H	110–116/0.1	38–39	93	A	876, 1346	Semi. 148–149
$n = 6$									
$(CH_2)_6Cl$	H	H	H	132–134/0.3	28–30	89	A	876, 1346	Semi. 123–124
$n = 8$									
$(CH_2)_8Cl$	H	H	H	167–169/1.5	23–25	78	A	876, 1031	Semi. 101.5–102.5
$n = 10$									
$(CH_2)_{10}Cl$	H	H	H	193–197/1.0	39–40	79	A	876, 1346	Semi. 108.5–109.5
$(CH_2)_{10}Br$	H	H	H		42–43	82	A	878	
$(CH_2)_{10}Br$	H	H	Me		60–61	86	A	1025	

3-Thienyl Ketones



$(CH_2)_nX$	R^2	R^4	R^5						
$n = 1$									
CH_2Cl	H	H	COMe	165–170/1.5	94.5–95	56	B	1114	
CH_2Cl	Cl	H	Cl	111–113/0.08	42.5–43.5	95	B	795	
CH_2Cl	Br	H	Br		87–88	38	B	1259	

TABLE 26. *(Continued)*

$(CH_2)_nX$	R^2	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[b]	References	Melting Point of Derivative (°C)[c]
CH_2Cl	Me	H	Me	137–140/9	54.5–55		B	798	
CH_2Cl	Br	Br	Br		108–109	45	B	1259	
$n = 2$									
$(CH_2)_2Cl$	Cl	H	Cl		33–34	64	B	577	
$(CH_2)_2Cl$	Br	H	Br		56–57	38	B	1259	
$(CH_2)_2Cl$	Br	Br	Br		72–73	50	B	1259	
$n = 3$									
$(CH_2)_3Cl$	Br	H	Br	161–165/0.6		38	B	1259	
$(CH_2)_3Cl$	Br	Br	Br		105–106	48	B	1259	

[a] α-Haloketones prepared by direct halogenation of an alkyl ketone are excluded.
[b] A = Friedel-Crafts acylation (acid chloride-$SnCl_4$); B = Friedel-Crafts acylation (acid chloride-$AlCl_3$); C = chloroacetic anhydride-H_3PO_4; D = $BrCH_2COBr$ on Grignard reagent (from a thienyllithium + $MgBr_2$); E = $ZnCl_2$ on a bisdiazoketone.
[c] Semi. = semicarbazone.

2-Acetylthiophene-3-boronic acid is cyclized by hydrazine or substituted hydrazines to thienodiazaborine derivatives (cf. **69**).[1338] On nitration, it gives the 4- and 5-nitro isomers, together with 2-acetyl-4-nitrothiophene (formed by deboronation). Nitration of 3-acetylthiophene-2-boronic acid gives the 5-nitro isomer (74%).[1338] Like the corresponding aldehydes, the acetylthiophene boronic acids are readily deboronated in acetic acid solution. In addition, some nitro derivatives are immediately deboronated in aqueous sodium carbonate.

13. Ketones in Which the Alkyl Side-Chain Contains Another Functional Group

A. Halogeno Ketones

In the main, this section is concerned with the ω-haloalkyl ketones, $ThCO(CH_2)_nX$, which are usually obtained (Table 26) by Friedel-Crafts acylation of a thiophene derivative with a haloacid chloride. α-Halogenation of a ketone has been discussed in Section III.5; compounds prepared by this means are too numerous to be included in Table 26.

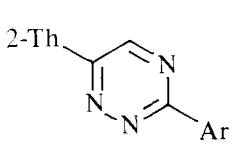
a. REDUCTION

ω-Haloketones are reduced to the corresponding haloalcohols by sodium borohydride[1202,1251] or by aluminum isopropoxide.[1339] Chloroketones undergo Clemmensen reduction with retention of the chlorine atom.[757,876,1031] Chloromethyl ketones are reduced by zinc dust and water to the corresponding methyl ketones.[1114]

b. CYCLIZATION REACTIONS

The formation of macrocyclic β-keto esters by intramolecular alkylation of an activated methylene group with an ω-iodo compound has been discussed in Section III.2.

4-(2-Thienyl)thiazoles are obtained from α-haloketones by the Hantzsch synthesis or modifications thereof.[577,1340–1342] An α-bromoketone (2-ThCOCH_2Br) reacts with an acid hydrazide ($ArCONHNH_2$) in the presence of NaOAc-DMF to give a 6-(2-thienyl)-1,2,4-triazine derivative **133**;[1343] 2-(bromoacetyl)thiophene (2 moles)



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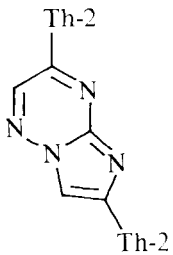

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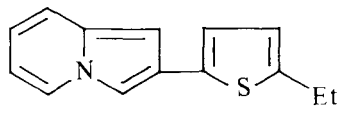

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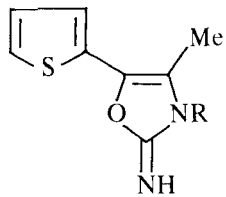
and aminoguanidine (1 mole) react to give the imidazo[1,2-*b*]-*as*-triazine **134**.[1344] Predictably, 2-(bromoacetyl)thiophene reacts with *o*-phenylenediamine to give 2-(2-thienyl)quinoxaline,[1345] and the 2-picolinium salt of its 5-ethyl derivative cyclizes ($NaHCO_3$) to the indolizine **135**.[768]

c. NUCLEOPHILIC SUBSTITUTION REACTIONS

The halogen atom in ω-haloketones is replaced normally by nucleophiles including cyanide,[577,876,878,1025,1036] iodide,[757,1031] acetate and ethoxide,[577] hydroxide (using water),[743] thiophenoxide,[1347] and SCF_3 (using $AgSCF_3$).[1348] The solvolysis of 2-(bromoacetyl)thiophenes apparently proceeds by way of an S_N2 mechanism.[1349]

α-Haloketones give the appropriate α-aminoketone when treated with primary[1203,1256,1350,1351] or secondary amines.[795,1204,1352] The products from the reaction of methylamine with α-bromoethyl 2- or 3-thienyl ketones have been used as precursors to the thiophene analogues of ephedrine and Ψ-ephedrine.[1203,1256] The α-(alkylamino)ketone, 2-ThCOCHMe(NHR), undergoes base-catalyzed reaction with cyanogen bromide to give the 2-iminooxazoline **136**.[1350] The quaternary



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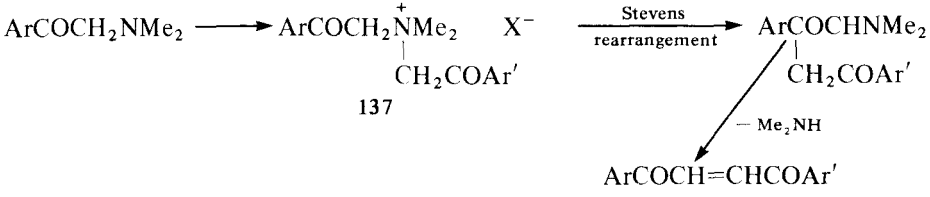
ammonium salt (**137**; Ar and/or Ar′ = a thienyl substituent) undergoes successive Stevens rearrangement and elimination to give an unsaturated 1,4-diketone (Scheme 26).[795,1353]

The conversion of bromomethyl into aminomethyl ketones ($ThCOCH_2Br \rightarrow ThCOCH_2NH_2$) has been achieved by treatment of the hexamine salt with ethanolic hydrogen chloride (Delépine reaction)[1104,1117,1198,1200,1354] or by means of Gabriel's phthalimide method.[713a] Treatment of *N*-acetylated aminomethyl thienyl ketones ($ThCOCH_2NHAc$) with formaldehyde in the presence of a base causes replacement of one[1117,1200] or both[1355,1356] of the hydrogen atoms of the methylene group by $-CH_2OH$; the mono-CH_2OH product is used to prepare thiophene analogues of the antibiotic, chloramphenicol.



Scheme 26

With pyridine, haloalkyl ketones form the expected pyridinium salt,[577,1125] alkaline hydrolysis of that from α-bromoketones gives the corresponding carboxylic acid.[1125]

When treated successively with triphenylphosphine and base, α-bromoketones (2-ThCOCH$_2$Br) form the ylide, 2-ThCOCH=PPh$_3$. This gives the vinyl ketone, 2-ThCOCH=CH$_2$, with formaldehyde,[1351] and the α-substituted products, 2-ThCOCX=PPh$_3$, on reaction with Br$_2$-alcoholic KOH (X = Br)[1357] and cyanogen bromide (X = CN),[1358] respectively. The halomethyl ketones, 2-ThCOCH$_2$X, react with triethyl phosphite to give either the enol phosphate, 2-ThC(=CH$_2$)OPO(OEt)$_2$ (X = Cl), or the ketophosphonate, 2-ThCOCH$_2$PO(OEt)$_2$ (X = I), or a mixture of the two (X = Br).[1359]

With dimethyl selenide, 2-bromoacetylthiophene forms the salt, 2-ThCOCH$_2$-$\overset{+}{\text{S}}$eMe$_2$ Br$^-$; on treatment with base, this gives 1,2,3-tri-(2-thenoyl)cyclopropane.[1360]

Azidomethyl ketones are formed by reaction of bromomethyl ketones with sodium azide.[1361] Azidomethyl 2-thienyl ketone has also been obtained (57%) by treatment of 2-vinylthiophene with Pb(OAc)$_4$–Me$_3$SiN$_3$.[1362]

2-Chloroacetylthiophene forms a Bunte salt with sodium thiosulfate, which on reaction with H$_2$O$_2$–H$_2$SO$_4$ gives the disulfide (2-ThCOCH$_2$S)$_2$.[377]

B. Diazomethyl Ketones

These are obtained by reaction of a thiophene carbonyl chloride with diazomethane[44,1363] or by reaction of the ylide, Ph$_3$P=CHCOTh-2, with 2-azido-3-ethyl-1,3-benzothiazolium tetrafluoroborate.[1364] The same ylide gives the α-diazo compound, 2-ThC(=NCN)CH=N$_2$, when treated with cyanazide.[1365]

Diazomethyl thienyl ketones are transformed into the corresponding thienylacetic acid by the Arndt-Eistert reaction,[44] and into the chloroacetylthiophene by heating them with anhydrous zinc chloride.[1363]

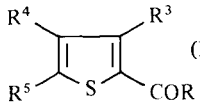
C. Unsaturated Ketones

a. PREPARATION

Ketones containing either an olefinic or acetylenic bond in the acyl group are listed in Table 27. Numerous chalcone analogues, obtained by the Claisen-Schmidt reaction from a methyl thienyl ketone and an aromatic aldehyde (Section II.2; Scheme 1), are excluded from this table.

Friedel-Crafts acylation of a thiophene derivative with an αβ-unsaturated acid chloride proceeds smoothly (Table 27). βγ-Unsaturated ketones are conveniently obtained by treating the unsaturated acid (RCO$_2$H) with tetrachlorosilane, then acylating thiophene with the resulting tetraacyloxysilane [Si(OCOR)$_4$] in the presence of tin(IV) chloride.[1369] The β-chlorovinyl ketones, 2-ThCOCH=CRCl, are readily prepared by treating thiophene-2-carbonyl chloride with an alkyne, RC≡CH, in the presence of aluminum chloride.[1368,1375]

TABLE 27. THIENYL KETONES CONTAINING AN UNSATURATED ACYL GROUP[a]

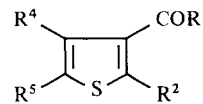
2-Acylthiophenes  (R Contains an Olefinic Double Bond)

R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[b]	References	Melting Point of Derivatives (°C)[c]
$CH=CH_2$	H	H	H	113–117/14		51, 50, 60	H, H, J	746, 1228, 1351	Semi. 135–137 (1228)
$CH=CH_2$	H	H	Me	57–62/0.1		49	I	958	
CH=CHMe	H	H	H	127–129/12		44, 71	A	746, 1366	2,4-DNP 198–199 (1366)
$CMe=CH_2$	H	H	H	112–113/17		79	H	746	
$CMe=CH_2$	H	H	Me	66–68/0.15		45	H	958	
$CMe=CH_2$	H	H	Bu^t	146–148/12		21	H	958	
$CMe=CH_2$	H	H	Cl	130/6		31	H	979	
$CMe=CH_2$	H	H	SMe	Oil		25	H	958	
$CH=CMe_2$	H	H	H	132–137/13		61	A	746	2,4-DNP 137
CH=CHPh	H	H	H		81–82	79, 86	A	746, 1367	
CH=CHPh	SMe	H	H		124	47	A	1321	
CH=CHPh	OMe	H	H		108	84	A	1321	
CH=CHPh	OMe	OMe	H		76	80	A	1321	
CH=CHPh	OH	OH	COCH=CHPh		125	83	G	1321	
$CPh=CH_2$	H	H	H		142.5–143.5	81	H	746	
$CH=CHC_6H_4OMe$-*o*	OMe	H	H		113	63	A	1321	
$CH=CHC_6H_4OMe$-*m*	OMe	H	H		90	72	A	1321	
$CH=CHC_6H_4OMe$-*p*	OMe	H	H		110	70	A	1321	
$CH=CHC_6H_4OMe$-*p*	SMe	H	H		124	58	A	1321	
$CH=CHC_6H_4NO_2$-*m*	H	H	H		145	67	A	1367	
$CH=CHC_6H_4NO_2$-*m*	OMe	H	H		167	60	A	1321	
$CH=CHC_6H_4NO_2$-*m*	SMe	H	H		155	49	A	1321	
$CH=CHC_6H_4NO_2$-*p*	H	H	H		220	72	A	1367	
CH=CHTh-2	OMe	H	H		82	57	A	1321	

CH=CHTh-3	OMe	H	H		70	45	A	1321	
CH=CHCl	H	H	H	154–156.5/23	25.5–27	65	D	1368	Et_3N salt 113–115
$CH=CHSiEt_3$	H	H	H	148–150/3			C	154	
$CH_2CH=CH_2$	H	H	H	104.5–105/3		20	B	1369	2,4-DNP 170–171
$(CH_2)_2CH=CH_2$	H	H	H	123–124/10		30	B	1369	2,4-DNP 136–137
3-Cyclohexen-1-yl	H	H	H	155–156/8		33	B	1369	2,4-DNP 176
2-Acylthiophenes (R Contains a Triple Bond)									
C≡CH	H	H	H		34	77,84	C	151,153	PH 141 (151)
C≡CH	Me	H	H	103–105/1		96	C	151	2,4-DNP 172
C≡CH	H	H	Et		36	90	C	153	
C≡CH	H	H	Br		42	85	C	153	
C≡CMe	H	H	H	110–111/1		78	C	152	2,4-DNP 250–251
C≡CMe	H	H	Et	155–157/5	37–39	75	C	152	2,4-DNP 152–153
C≡CPr	H	H	H	121–122/1		60	C	152	2,4-DNP 204–206
$C≡CBu^n$	H	H	H	136–137/1		67	C	152	2,4-DNP 151–152
$C≡CC_5H_{11}$	H	H	H	152–153/1		80	C	152	2,4-DNP 129–131
C≡CPh	H	H	H		57	75,47	C,E	153,1370	
C≡CPh	H	H	Et		43	81	C	153	
C≡CPh	H	H	Br		91	80	C	153	
$C≡CC_6H_4OMe$-*p*	H	H	H		85	15	E	1370	
C≡CBr	H	H	H		83	61	C	1371	
C≡CBr	H	H	Et		56	56	C	1371	
C≡CSMe	H	H	H			85	C	1372	2,4 DNP 215–217
C≡CSEt	H	H	H			82	C	1372	2,4-DNP 205–207
C≡CSPr	H	H	H			84	C	1372	2,4-DNP 169–171
$C≡CSBu^n$	H	H	H			79	C	1372	2,4-DNP 156–158
C≡CSPh	H	H	H			45	C	1372	
$C≡CSiEt_3$	H	H	H	139–141/3		55	C	154	
$C≡CSiMe_3$	H	H	H	116–118/3		62	C	154	
$C≡CSiMe_2Et$	H	H	H	114–115/2		68	C	154	
$C≡CSiMe_2Et$	H	H	Br	129–131/2		41	C	154	
$(C≡C)_2Me$	H	H	Me		71–72	87	C	1373	2,4-DNP 190–191

TABLE 27. *(Continued)*

R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[b]	References	Melting Point of Derivatives (°C)[c]
$(C{\equiv}C)_2Me$	H	H	Et		38–41	86	C	1373	2,4-DNP 174–176
$(C{\equiv}C)_2Bu^n$	H	H	H	Oil		85	C	1373	2,4-DNP 155–156
$(C{\equiv}C)_2Bu^n$	H	H	Me	Oil		80	C	1373	2,4-DNP 140–141
$(C{\equiv}C)_2Bu^n$	H	H	Et	Oil		82	C	1373	2,4-DNP 144–146
$(C{\equiv}C)_2Ph$	H	H	H		57–58	80	C	1373	2,4-DNP 185–186
$(C{\equiv}C)_2Ph$	H	H	Me		64–66	87	C	1373	2,4-DNP 186–188
$(C{\equiv}C)_2Ph$	H	H	Et		82–84	88	C	1373	2,4-DNP 190–193

3-Acylthiophenes  (R Contains a Double or Triple Bond)

R	R^2	R^4	R^5						
$CMe{=}CH_2$	H	H	H	110–114/14		65	H	746	
$CMe{=}CH_2$	Me	H	Me	107–109/9		69	H	746	
$CMe{=}CH_2$	H	H	Me	93–94/2		27	H	958	
$CMe{=}CH_2$	H	H	Bu^t	94–95/0.8		42	H	958	
$CH{=}CHBu^n$	Me	H	Me			60	F	1374	
C≡CPh	Me	COC≡CPh	Me		105–106	69	C	546	

[a] Excluding chalcone analogues, prepared by the Claisen-Schmidt reaction.

[b] A = Friedel-Crafts acylation; B = acylation with a tetracyloxysilane-$SnCl_4$; C = oxidation of a secondary alcohol; D = acid chloride + ethyne; E = acid chloride + sodium acetylide; F = Bu^nLi on Th–COCH=$CHNMe_2$; G = acid chloride on an acetoxymercuri derivative (reaction accompanied by demethylation of OMe groups in thiophene ring); H = from the Mannich base; I = $NaIO_4$ on ThCOCHSePh(Me); J = Wittig reaction.

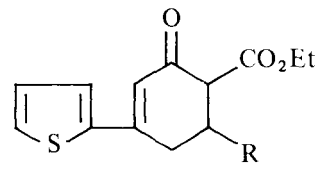
[c] Semi. = semicarbazone; 2-4-DNP = 2,4-dinitrophenylhydrazone; PH = phenylhydrazone.

Vinyl ketones of the type, $ThCOCR{=}CH_2$, are conveniently prepared by thermal elimination of a dialkylamine from a salt of the readily accessible Mannich bases, $ThCOCHRCH_2NR'_2$.[746,958,979,984,1228] There is one example of the formation of a vinyl ketone by treatment of the α-phenylseleno compound, ThCOCHMe(SePh), with sodium metaperiodate.[958] An acetylthiophene may be converted into an αβ-unsaturated ketone, $ThCOCH{=}CHBu^n$, by treating it with the dimethyl acetal of DMF, then allowing the resulting enaminoketone, $ThCOCH{=}CHNMe_2$, to react with *n*-butyllithium.[1374]

Acetylenic ketones ($ThCOC{\equiv}CR$) are most commonly obtained by oxidation of the corresponding secondary alcohol (usually from ThCHO and an acetylenic Grignard reagent) with either manganese dioxide[152-154,546,1371-1373,1376] or Jones reagent.[151]

b. ADDITION REACTIONS

αβ-Unsaturated ketones ($ThCOCH{=}CHR$; R = alkyl or aryl) undergo base-catalyzed addition of HY in the usual way, to give $ThCOCH_2CHR(Y)$[HY = Me_2NH,[1366] PhSH,[1377] H_2S,[1378] Me_2CHNO_2,[1367] or $R'COCH_3$[1379]]. As expected, Michael addition of ethyl acetoacetate proceeds with cyclization to give the cyclohexenone **138**.[172,1380] With 2-aminobenzenethiol, the mercapto group undergoes Michael addition at the β-position, then the amino group cyclises with the keto group, to yield a 1-thia-5-azacycloheptadiene derivative (**139**).[1381] The β-chlorovinyl ketone,



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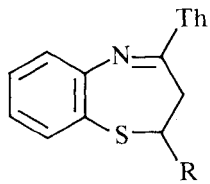

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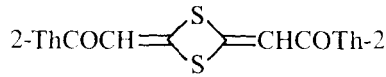

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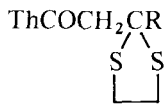

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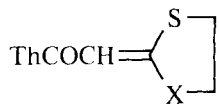

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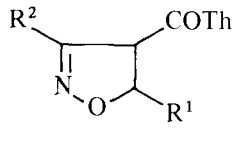
2-ThCOCH=CHCl, reacts predictably with KOH—MeOH, to give the dimethyl acetal, 2-$ThCOCH_2CH(OMe)_2$.[1368] The ββ-dichloro compound, 2-$ThCOCH=CCl_2$, gives the desaurin derivative (**140**) when treated with thiocarbonic or thiocarboxylic acid derivatives.[1382]

αβ-Acetylenic ketones (ThCOC≡CR; R is usually alkyl) give the unsaturated ketones, ThCOCH=CR(Y), by the addition of HY[HY = primary[1370] or secondary amine,[1383] aziridine,[1384] NH_2NH_2 (the product cyclizes to a pyrazole),[152] PhSH,[1385] and HCl or HBr[1375]]. Hydrogen sulfide[1386,1387] or thiourea[1388] give the sulfide, $(ThCOCH=CR)_2S$. With ethane-1,2-thiol, the mercapto group of the primary product undergoes further nucleophilic attack in the β-position to give the cyclic thioacetal **141**.[1389] Acetylenic ketones give pyridines and pyrimidines when treated with ammonia and guanidine, respectively.[151]

Bromoethynyl ketones (ThCOC≡CBr) react with 2 moles of nucleophile: one replaces the bromine atom and the other undergoes addition. For example, thiols (RSH) give $ThCOCH=C(SR)_2$;[1390] H_2S—Et_3N gives the corresponding ββ-dithiol, which then reacts with a second mole of the starting ketone to give the desaurin **140**;[1371] ethane-1,2-thiol and 2-mercaptoethanol give the heterocycles **142** (X = S and O respectively).[1391,1392]

The ylides, $Me_2\overset{+}{S}(=O)\bar{C}H_2$,[1393] $Me_2\overset{+}{S}\bar{C}HCOPh$,[1394] and $Me_2S\overset{+}{e}\bar{C}HCOPh$,[1360] add normally across the double bond of the chalcone analogues, ThCOCH=CHAr, to give the expected thenoylcyclopropane derivatives.

2-Thienyl vinyl ketone undergoes Diels-Alder addition to a conjugated diene.[1395] Unsaturated ketones, $ThCOCH=CHR^1$, undergo cycloaddition reactions with diazomethane[1396] or diphenylnitrilimine ($PhC\equiv NNPh$)[1397] to give the appropriate pyrazoline derivative. 1,3-Cycloaddition of nitrile oxides (R^2CNO) has been shown to give two regioisomeric Δ^2-isoxazoline ketones **143** and **143** (COTh and R^1 interchanged);[1398] earlier, only one regioisomer was isolated from this type of reaction.[1399] The chalcone analogue, 2-ThCOCH=CHPh, undergoes photodimerization to give the diketone **144** (10%).[1400]



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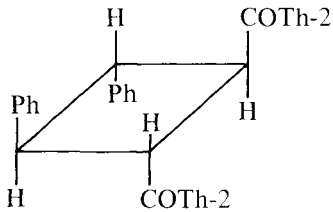

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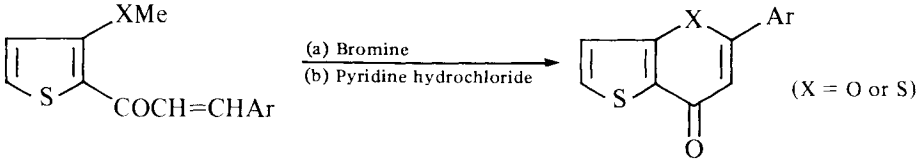
c. CYCLIZATION REACTIONS

The cyclization of unsaturated ketones with PPA to give bicyclic ketones has been discussed in Section III.2.[746,958,979,984] The unsaturated ketones (**145**; X = O or S) are cyclized to thiophene analogues of the flavones by the route shown in Scheme 27.[1321]



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Scheme 27

d. PHYSICAL PROPERTIES

Spectroscopic and other properties of many thiophene analogues of chalcone have been described, especially by Russian workers. In particular, their conformation has been studied by use of IR spectroscopy, dipole moments, and Kerr constants (e.g., References 1401–1403).

D. α-Ketoacids

a. PREPARATION

Thiophene analogues ($ThCOCO_2R$) of phenylglyoxylic acid are widely obtained from oxalic acid derivatives by the following methods: (1) reaction of a dialkyl oxalate with a substituted thienylmagnesium halide[1404–1406] or thienyllithum;[1251, 1407] (2) reaction of the half-amide EtO_2CCONR_2[529] or diamide $(CONR_2)_2$[1408] with a thienyllithium (to give the amide $ThCOCONR_2$); and (3) Friedel-Crafts acylation of a thiophene derivative with the acid chloride $ClCOCO_2R$.[577,1409–1411] Methods involving organometallic reagents often give low yields of product because of predictable side reactions leading to alcohols.

α-Ketoacids may also be obtained by oxidation of acetylthiophenes with nitric acid,[425] potassium permanganate,[84] or selenium dioxide in pyridine.[1412] Further oxidation to a thiophenecarboxylic acid is a competing process with the first two oxidizing agents.

b. SPECTROSCOPY

NMR, IR, and UV methods have been used to establish that 2-$ThCOCO_2H$ exists in the conformation **146**. Conformational preferences of related compounds have been likewise studied.[1413]

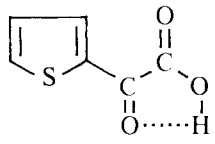

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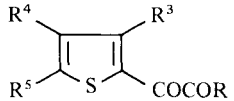
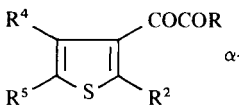
TABLE 28. THIENYL KETONES CONTAINING A 1,2-DICARBONYL SIDE-CHAIN

α–Keto Acid Derivatives (2-Thienyl)



R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b]
OH	H	H	H		85–87	58, –	D	84, 1412	Ox. 144 (1412)
OMe	H	H	H	90–92/0.9		53	E	1410	
OEt	H	H	H	101/3.5		24, 84	A, B	1404, 1407	
OPr	H	H	H	97–99/2		25	A	1404	
OPr^i	H	H	H	97–98/2.5		30	A	1404	
OBu^n	H	H	H	110–112/2.5		35	A	1404	
OBu^i	H	H	H	106–107/2.5		45	A	1404	
$O(CH_2)_6Me$	H	H	H	150–152/2.5		52	A	1404	
NMe_2	H	H	H		67–68	52	C	1408	
OEt	H	H	Cl	100–112/1.0	43–45	78	E	1410	
OMe	H	H	Br	136–137/4		28	A	1405	Acid 121–122
OEt	H	H	Br	151–152/6		44	A	1405	
OPr^n	H	H	Br	136–137/2.5		46	A	1405	
OPr^i	H	H	Br	135–136/4.5		45	A	1405	
OBu^n	H	H	Br	142–143/2		43	A	1405	
OBu^i	H	H	Br	150–151/4		46	A	1405	
$O(CH_2)_4Me$	H	H	Br	170–171/5		38	A	1405	
$O(CH_2)_5Me$	H	H	Br	173–174/3		32	A	1405	
$O(CH_2)_6Me$	H	H	Br	185–186/4		30	A	1405	
OEt	H	H	OMe			56	B	1251	
OH	H	H	NO_2		125	30	D	425	
OEt	H	H	CH_2Ph	115/0.4		17	E	1409	
OEt	H	H	$COCO_2Et$		61–62	48	A	1406	
OPr	H	H	$COCO_2Pr$		70–71	38	A	1406	
OPr^i	H	H	$COCO_2Pr^i$		52–53	40	A	1406	
OBu^n	H	H	$COCO_2Bu^n$		60–61	39	A	1406	

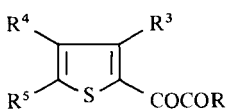
OBu^i	H	H	$COCO_2Bu^i$		63–64	45	A	1406	
$O(CH_2)_4Me$	H	H	$COCO_2(CH_2)_4Me$		59–60	25	A	1406	
$O(CH_2)_2CHMe_2$	H	H	$COCO_2(CH_2)_2CHMe_2$		67–68	29	A	1406	
OEt	H	H	CH_2CO_2Et	201–203/7		80	E	1411	
OEt	H	H	$(CH_2)_3CO_2Me$	217–219/6		78	E	1411	
OEt	H	H	$(CH_2)_4CO_2Me$	225–226/6		66	E	1411	
OEt	H	H	$(CH_2)_5CO_2Me$	237–238/6		72	E	1411	
OEt	H	Cl	Cl		57	30	E	577	Acid 126–127
OEt	Me	H	H	94–95/0.5		66	E	1410	
NEt_2	CHO	H	H		60	78	C	529	Cyclic acetal 78
OH	Me	H	Me		130–135		D	1412	Ox. 162–163.5
OEt	Br	H	Br	135–137/0.5	65–66	75	B	1407	



α-Keto Acid Derivatives (3-Thienyl)

R	R^2	R^4	R^5						
OH	H	H	H		64–65		D	1412	Ox. 145–146
OH	Me	H	Me		85–86.5		D	1412	
OMe	Me	H	Me	95–97/0.5		70	E	1410	
OH	Me	Me	Me		94.5–96.5	85	D	1412	Ox. 127–147
OMe	Cl	H	Cl		58–60	78	E	1410	
OEt	Cl	H	Cl	110/0.8		82	E	1410	
NEt_2	CHO	H	H		68	55	C	529	Cyclic acetal b.p. 175–180/0.3 mm

α-Keto Aldehydes and 1,2-Diketones (2-Thienyl)



R	R^3	R^4	R^5						
H	H	H	H	66–74/15		37	F	1416	Thio. 176.5 (1416), 188–190 (1423)
H	H	H	NO_2		88–89[c]	75	F	1236	Semi. 215–216; Ox. 158–159

TABLE 28. *(Continued)*

R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References	Melting Point of Derivatives (°C)[b]
H	H	NO_2	H		95–96[c]		F	1236	Semi. 217–218; Ox. 146–147
H	H	Cl	Cl		94–95	69	F	577	Semi. 135–137; Thio. 191; Ox. 160
Ph	H	H	H		62–64	93, 78, 44	G, F, I	277, 371, 1419	
2-Thienyl	H	H	H		82–84	12	H	1418	
2-Thienyl	H	H	Me		44–45	28	G	1417	
5-Me-2-Thienyl	H	H	Me		86–87	30	G	1417	
5-Cl-2-Thienyl	H	H	Cl		121–122	41	G	1417	
5-F-2-Thienyl	H	H	F		125–127	34	H	1417	
5-OMe-2-Thienyl	H	H	OMe		140–142	33	J	1417	
5-OPr^i-2-Thienyl	H	H	OPr^i		98–99	17	J	1417	
5-Ad-2-Thienyl[d]	H	H	Ad[d]		260–261	22	H	1417	

α-Keto Aldehydes and 1,2-Diketones (3-Thienyl)

R	R^2	R^4	R^5						
H	H	H	H	95–98/12	86–90[c]	63	F	1414	Semi. (mono) 238–240
H	Me	H	Me		112		F	1415	Semi. (mono) 163; Ox. (mono) 130, (di) 145 and 175
3-Thienyl	H	H	H		75–76	83, 36, 28	G, G, H	139, 1417, 1418	
2-Thienyl	H	H	H		73–75.5	53	F	795	

[a] A = $(CO_2R)_2$ on thienylmagnesium halide; B = $(CO_2Et)_2$ on thienyllithium; C = $(CONR_2)_2$ or EtO_2CCONR_2 on thienyllithium; D = oxidation of COMe to $COCO_2H$; E = Friedel-Crafts acylation with RO_2CCOCl; F = SeO_2 oxidation of $COCH_2$– to COCO–; G = oxidation of an α-ketol; H = $(CO_2Me)_2$ on thienyllithium; I = Tl(III) nitrate on 2-ThCOCH=CHPh; J = Friedel-Crafts acylation with $(COCl)_2$.

[b] Semi. = semicarbazone; Thio. = thiosemicarbazone; Ox. = oxime; Cyclic acetal = 1,3-dioxolane.

[c] Hydrate.

[d] Ad = 1-adamantyl.

E. 1,2-Diketones and α-Ketoaldehydes

a. PREPARATION

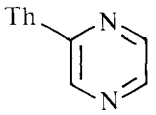
Compounds of the type, ThCOCOR, are generally obtained by selenium dioxide oxidation of an acetylthiophene (R = H)[577,1236,1414-1416] or other ketones containing an α-methylene group.[371,589,795] Oximes, ThCOCH=NOH, are available by α-nitrosation of an acetylthiophene.[1200,1415] Thiophene analogues (ThCOCOAr) of benzil are most commonly prepared by oxidation of the corresponding α-ketol with either ammonium nitrate–copper(II) acetate–aqueous acetic acid[1417] or $CuSO_4$-pyridine.[139,1417] The required α-ketols are obtainable either from the corresponding thiophene carboxaldehyde by means of a benzoin condensation[139,277,1417] or from a thiophene α-ketoaldehyde (ThCOCHO) by means of the Grignard reaction.[1417] Symmetrical benzil analogues (ThCOCOTh) can also be synthesized by treatment of a substituted thienyllithium with dimethyl oxalate[1417,1418] or by Friedel-Crafts acylation of an alkoxythiophene derivative (i.e., activation toward electrophilic substitution) (2 moles) with oxalyl chloride (1 mole).[1417] Two interesting routes to 2-ThCOCOPh are the direct oxidation of the unsaturated ketone 2-ThCOCH=CHPh by means of thallium(III) nitrate in aqueous-acidic 1,2-dimethoxyethane[1419] and hydrolysis of the thioacetal oxime (**35**).[402] 1,2-Dicarbonyl compounds are listed collectively in Table 28.

b. REACTIONS

The morpholine aminal of the α-ketoaldehyde, 2-ThCOCHO, is conveniently converted into the thioacetal 2-$ThCOCH(SR)_2$ by treatment with the appropriate thiol in the presence of $AcOH–H_2SO_4$.[1420]

α-Ketoaldehydes are oxidized (H_2O_2) to the corresponding thiophene carboxylic acid.[1415] The oxime 2-ThCOCH=NOH is reduced by $SnCl_2$–HCl to the ketoamine 2-$ThCOCH_2NH_2$.[1200] Most α-ketoaldehydes and α-diketones (ThCOCOR; R = H or Ar) undergo the benzilic acid rearrangement on treatment with alkali, giving the α-hydroxyacid $ThCR(OH)(CO_2H)$.[277,368,1414,1417] The kinetics of the rearrangement have been investigated.[1421]

The α-ketoaldehydes (ThCOCHO) readily give a quinoxaline on treatment with *o*-phenylenediamine and may be characterized as such.[577,1236,1345,1414,1415] With ethane-1,2-diamine they give the expected dihydropyrazine derivative, which is oxidized by atmospheric oxygen to a thienylpyrazine (**147**).[1422] The thiosemicarbazone, 2-$ThCOCH=NNHCSNR^1R^2$($R^1 = R^2 = H$), predictably undergoes base-



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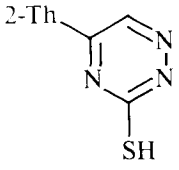

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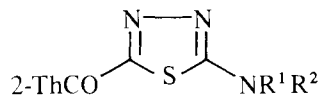

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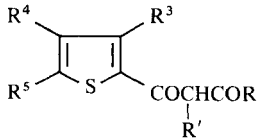
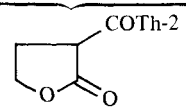
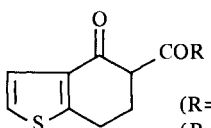
TABLE 29. THIENYL KETONES CONTAINING A 1,3-DICARBONYL SIDE-CHAIN

β–Ketoesters and 1,3-Diketones (2-Thienyl)

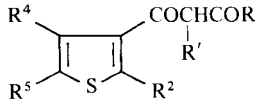


R	R′	R³	R⁴	R⁵	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References
OEt	H	H	H	H	140–143/4	24	30, 69, 58	A, B, D	140, 1426, 795
OMe	Me	H	H	H			90	D	1424
OEt	Cl	H	H	H	130/0.1		88	C	1425
OEt	CN	H	H	H		72–73	83	B	1425
OEt	CO_2Et	H	H	H	145–150/0.1	49	76	B	1425
OEt	H	H	H	Me	140–142/2	47	37, 50	A	140, 1037
OEt	Me	H	H	Me	125–130/1		20	A	1037
OEt	H	H	H	Et	160/3	7	43	A	1037
OEt	Me	H	H	Et	130–140/1		23	A	1037
OEt	H	H	H	$(CH_2)_9Cl$		30.5–31.5	72	G	1031
OEt	H	OH	H	H	118/0.3		47	D	1324
						59	40	A	1460
					175–178/15	88		E	1461
					180/20	45		E	1461
H	H	H	H	H		197	85[b], 49	E, I	1436, 1435

Me	H	H	H	H	128–131/8	31–32	54, 58, 74	E, E, H	1428, 1433, 1432
Et	H	H	H	H	126–129/5		45	E	1428
Pr	H	H	H	H	139–142/4		13	F	1429
Bu^i	H	H	H	H	132–135/5		11	E	1428
Ph	H	H	H	H		78–78.5	48	E	1428
C_6H_4OMe-*p*	H	H	H	H		124–124.5	19	E	1428
C_6H_4Cl-*p*	H	H	H	H		130–131	48	E	1428
Selenophene-2-yl	H	H	H	H		91–92	68	E	1462
Selenophene-3-yl	H	H	H	H		90–91	76	E	1438
Me	H	H	H	$(CH_2)_2CHMe_2$	102–106/0.2		22	E	753
Me	H	H	H	NO_2		122–123.5	62	H	1432
Me	H	H	H	Br		132–133	38	E	753
C≡CPh	H	H	H	H		98–100	22	E	1443
CO_2Et	H	H	H	Me		71–72[c]	87	E	1433
CF_3	Me	H	H	H	116–119/9		72	E	1463
CF_3	Me	H	H	Me	146–148/20		62	E	1463
CF_3	H	H	H	Me	122–124/10	59–60	87	E	1464
CF_3	H	Me	H	H	117–118/10		88	E	1464
CF_3	H	H	H	Cl	117–119/9	40–41	82	E	1464
CF_3	H	H	H	Br	122–124/5	65.5–66	87	E	1464
CF_3	H	H	H	I		73.5–74.5	83	E	1464
C_2F_5	H	H	H	H	92/2.8		68	E	1465
C_3F_7	H	H	H	H	99–102/5		88	E	1464
C_3F_7	H	Me	H	H	104–106/3		86	E	1464
C_3F_7	H	H	H	Me		38.5–39.5	82	E	1464
C_3F_7	H	H	H	Cl	103–104/1.5	45–45.5	86	E	1464
C_3F_7	H	H	H	Br	117–123/3.5	38.5–39	67	E	1464
CF_2Cl	H	H	H	H	120.5/5		49	E	1465
$CFCl_2$	H	H	H	H	100–102/0.4	57.5–58.5	71	E	1466
CF_2OCF_3	H	H	H	H	108–109/2		90	E	753

TABLE 29. (*Continued*)

β–Ketoesters and 1,3-Diketones (3-Thienyl)



R	R'	R^2	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[a]	References
OEt	H	H	H	H	162–175/12		65	B	1426
CF_3	H	Me	H	Me	128–129/10		88	E	1464
CF_3	Me	Me	H	Me	143–145/19	124–125.5	75	E	1463
C_3F_7	H	Me	H	Me	141–143/14		90	E	1464

[a] A = Claisen ester condensation ($ThCO_2Et + R'CH_2CO_2Et$); B = acylation (ThCOCl) of appropriate 1,3-dicarbonyl compound; C = SO_2Cl_2 on β-keto-ester; D = Claisen ester condensation ($ThCOCH_2R'$ + dialkyl carbonate); E = Claisen ester condensation ($ThCOCH_2R'$ + ester); F = ThCOMe + acid anhydride; G = Friedel-Crafts acylation with EtO_2CCH_2COCl; H = acylation (ThCOCl) of copper chelate of acetylacetone, followed by hydrolysis; I = hydrolysis and decarboxylation of 2-$ThCOCH_2COCO_2Et$.

[b] Isolated as the sodio derivative.

[c] Oxime, m.p. 115–116°C (α-C=O).

catalyzed cyclization to the 1,2,4-triazine (**148**)[1416] and undergoes cyclooxidation with $FeCl_3$, to give the 1,3,4-thiadiazole (**149**).[1423] The benzil analogue, 2-ThCOCOPh, gives the expected imidazole derivative when treated with an aromatic aldehyde in the presence of ammonium acetate.[371] The 1,2-diketones, ThCOCOTh, give a terthienyl derivative (**150**) when treated in the Hinsberg reaction with $(MeO_2CCH_2)_2S$ in the presence of sodium methoxide.[795]

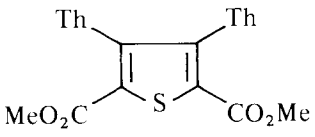
F. β-Ketoesters

a. PREPARATION

β-Ketoesters [$ThCOCH(R)CO_2Et$] (Table 29) are obtained by the classical Claisen condensation from a thiophene carboxylic ester and an aliphatic ester[1037] or from an acylthiophene and a dialkyl carbonate.[795,1324,1424] Alternatively, they may be prepared by acylation of an aliphatic 1,3-dicarbonyl compound with a thiophene carbonyl chloride,[1425] followed by hydrolysis.[1426]

b. CYCLIZATION REACTIONS

The β-ketoesters, $ThCOCH(R)CO_2Et$, give the 1,2-dithiole-3-thiones **151** when treated with P_2S_5.[140,1037,1425] With αβ-dichloroethyl ethyl ether ($ClCH_2CHClOEt$), they give the furan **152** (R = H);[1427] with hydrazine, they give the expected pyrazole-3-one **153**.[1424] Heating ethyl (3-hydroxy-2-thenoyl)acetate gives the 4-hydroxycoumarin analogue (**154**).[1324]



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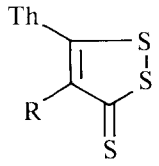

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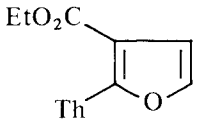

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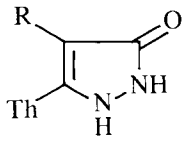

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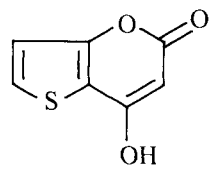

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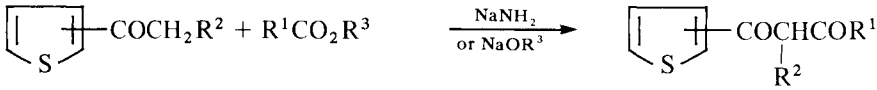
G. 1,3-Diketones

a. PREPARATION

1,3-Diketones (Table 29) are prepared routinely by the Claisen condensation (Scheme 28). A study has been made of the relative reactivities of a number of

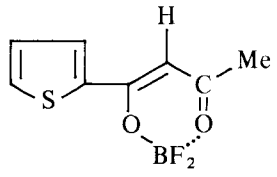


Scheme 28

esters, $R^1CO_2R^3$, in this reaction.[1428] Methyl thienyl ketones have also been acylated with an acid anhydride in the presence of $FeCl_3$ or $ZnCl_2$, but the yields are low.[1429] When 2-acetylthiophene reacts with Ac_2O—BF_3, the initial 1,3-diketone (2-ThCOCH$_2$COMe) reacts further, to give what was termed a "triacetylthiophene".[1430] This compound is now shown to be the boron-containing compound **155**.[1431]

1,3-Diketones are also formed in high yield when the copper chelate of acetylacetone is acylated with thiophene carbonyl chloride and the product is hydrolyzed.[1432]

Use of diethyl oxalate as the acylating ester in Scheme 28 gives the diketoester, ThCOCH$_2$COCO$_2$Et.[1433–1435] This may be hydrolyzed and decarboxylated to provide a convenient alternative source of the β-ketoaldehyde ThCOCH$_2$CHO (as the enol);[1435] such aldehydes are usually obtained as their sodio derivative from the Claisen condensation with an alkyl formate (Scheme 28; $R^1 = H$).[140,1436] Alternatively, the diketoester ThCOCH$_2$COCO$_2$Et may react with a second molecule of ThCOMe to give the tetraketone (ThCOCH$_2$CO)$_2$; with N_2O_4, this gives the pyridazine bis-*N*-oxide (**156**).[1434]



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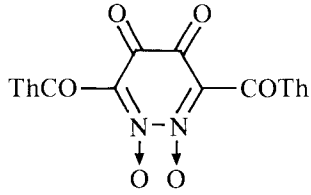

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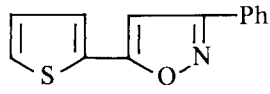
b. CYCLIZATION REACTIONS

1,3-Diketones react unexceptionally with hydrazine to give pyrazoles[1437,1438] and with hydroxylamine to give isoxazoles.[182,1433,1439] Isoxazole (**157**) is the sole product from the reaction of the unsymmetrical diketone 2-ThCOCH$_2$COPh with hydroxylamine.[182,1439] With guanidine, pyrimidines are formed as expected;[753,1192] 1,2-diamines give diazepine derivatives (e.g., **158** from *o*-phenylenediamine).[1440,1441]



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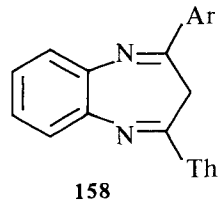

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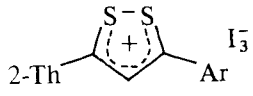

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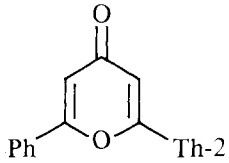

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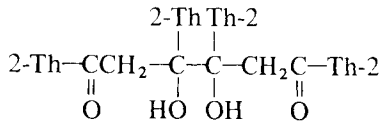
Treating the 1,3-diketones, 2-ThCOCH$_2$COAr, with H_2S—I_2 gives the 3,5-diaryl-1,2-dithiolium triiodides (**159**).[1442] The γ-pyrone (**160**) is formed when the acetylenic 1,3-diketone, PhC≡CCOCH$_2$COTh-2, is heated.[1443]

c. OTHER REACTIONS

The sodio β-ketoaldehyde, 2-ThCOCH=CHO̅ Na^+, undergoes the following reactions: (1) it forms the unsaturated ketoamines, 2-ThCOCH=CHNR^{1}R^2, when treated with R^{1}R^{2}NH;[1436] (2) with phenyl isothiocyanate (and subsequent acidification) it gives 2-ThCOCH(CHO)CS(NHPh), which yields 2-ThCOCH$_2$CS(NHPh) on hydrolysis;[1444] (3) with diethyl phosphorochloridate [(EtO)$_2$P(O)Cl], the expected product [(EtO)$_2$P(O)OCH=CHCOTh-2] spontaneoulsy disproportionates, to give the ether, (2-ThCH=CH)$_2$O.[1445]

Electrolytic reduction of (2-ThCO)$_2$CH$_2$ in THF gives the pinacol **161**.[1446]

1-(2-Thenoyl)-3,3,3-trifluoropropanone, 2-ThCOCH$_2$COCF$_3$, ("thenoyltrifluoroacetone") has enjoyed considerable popularity as a reagent for the separation and



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determination of a wide range of metal ions. Important references to its main uses are listed in References 1447 and 1448. Thenoyltrifluoroacetone reacts smoothly with hydrogen sulfide in ethanolic hydrogen chloride to give the mercaptoketone, 2-ThC(SH)CHCOCF$_3$.[1449,1450]

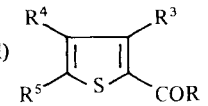
d. PHYSICAL AND SPECTROSCOPIC PROPERTIES

The diketones 2-ThCOCH$_2$COR (R = alkyl or aryl) have been studied by IR[1446] and ^{1}H NMR spectroscopy.[1451–1453] In solution, they exist largely in the enol form.

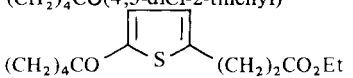
The tautomerism of thenoyltrifluoroacetone has been investigated by IR,[1454] UV,[1455] ^{1}H NMR,[1454,1456] ^{13}C NMR,[1457,1458] and ^{19}F NMR spectroscopy;[1456,1457] its mass spectrum has been recorded.[1459] In dilute solution the molecule is almost entirely enolic. It is postulated that the two possible tautomers [2-ThC(OH)=CHCOCF$_3$ and 2-ThCOCH=C(OH)CF$_3$ may then be in equilbrium.[1455]

TABLE 30. THIENYL KETONES CONTAINING A 1,4- (OR HIGHER) DICARBONYL SIDE-CHAIN[a]

1,4-Dicarbonyl Compounds (2-Thienyl)



R	R^3	R^4	R^5	Boiling Point (°C/mm)	Melting Point (°C)	Yield (%)	Method[b]	References
$(CH_2)_2CO_2Et$	H	H	H	116–118/0.3		45	B	408
$CHMeCH_2CO_2Et$	H	H	H	108/0.5		47	B	408
$(CH_2)_2CO_2H$	H	Cl	Cl		120–121		D	577
$(CH_2)_2COMe$	H	H	H		49–50	80	B	409
$CHPhCH_2COMe$	H	H	H		75	77	B	409
$(CH_2)_2CO(CH_2)_2COMe$	H	H	H		49	43	B	412
$(CH_2)_2COCH{=}CMe_2$	H	H	H	147–149/0.4	61–63	45	B	414
$CH_2CHPhCOPr$	H	H	H	190/0.9		77	B	1469
$CHPhCH_2COPh$	H	H	H		142	90	B	409
$CH_2CHPhCOPh$	H	H	H		130	75	B	1469
$CH(CO_2Et)CH_2COPh$	H	H	H		56	46, 80	B, C	415, 1467
$(CH_2)_2COC_6H_4Me$-*p*	H	H	H		120	82	B	415
$(CH_2)_2COTh$-2	H	H	H		130–131	75, 67, 71	B, E, H	409, 795, 1468
$(CH_2)_2COTh$-2	H	H	Cl		91–92	80	E	795
$CHPhCH_2COTh$-2	H	H	H		145	80	B	409
$(CH_2)_2CO(CH_2)_2COTh$-2	H	H	H		104	51	B	411
$CH(CO_2Et)CH(CO_2Et)COTh$-2	H	H	H		124–127	65	C	795
$(CH_2)_2CO$-(5-Cl-2-thienyl)	H	H	Cl		140.5–141	90	E	795
$(CH_2)_2CO$-(4,5-diCl-2-thienyl)	H	Cl	Cl		188–190	6	A	577
CH=CHCOPh	H	H	H		122–123		G	1353
CH=CHCOTh-2	H	H	H		188–189	60, –	G	795, 1353
CH=CHCOTh-2	H	H	Cl		142–143	69	G	795
CH=CHCO-(5-Cl-2-thienyl)	H	H	Cl		198–199	65	G	795

R	R^2	R^4	R^5				
1,4-Dicarbonyl Compounds (3-Thienyl)							
$(CH_2)_2CO_2H$	Cl	H	Cl	116–117	16	D	577
$(CH_2)_2CO$-(5-Cl-3-thienyl)	H	H	Cl	165–166	29	F	795
$(CH_2)_2CO$-(2,5-diCl-3-thienyl)	Cl	H	Cl	150–151	75	E	795
CH=CHCO(2,5-diCl-3-thienyl)	Cl	H	Cl	166–167	78	G	795
Higher Dicarbonyl Compounds (2-Thienyl)							
R	R^3	R^4	R^5				
$CMe_2(CH_2)_2CO_2H$	H	H	H	191–193/3	89	D	765
$(CH_2)_3CO$-(4,5-diCl-2-thienyl)	H	Cl	Cl	115[c]	40	A	577
$(CF_2)_3COTh$-2	H	H	H	60[d]	37, 61	I(a), I(b)	930, 1471
$(CH_2)_4COTh$-2	H	H	H	126–127	86, 83	A	99, 100
$(CH_2)_4CO$(4,5-diCl-2-thienyl)	H	Cl	Cl	133	82	A	577
	H	H	$(CH_2)_2CO_2Et$	104.5–105[e]	74	A	99
$(CH_2)_5CO$-(4,5-diCl-2-thienyl)	H	Cl	Cl	74–75	42	A	577

[a] Ketoesters prepared by Friedel-Crafts acylation of a thiophene derivative with a monocarboxylic acid chloride are listed in Table 16.

[b] A = Friedel-Crafts acylation of a thiophene derivative (2 moles) with a dicarboxylic acid dichloride (1 mole); B = addition of 2-ThCHO to an activated double bond (Table 5); C = from a β-ketoester by a classical alkylation reaction ($[2\text{-ThCOCHCO}_2Et]^- Na^+ + RX$); D = hydrolysis of the corresponding nitrile: E = reduction ($SnCl_2$–AcOH–HCl) of ThCOCH=CHCOAr; F = reduction (Zn–AcOH) of $ThCOCH_2CHNMe_2COTh$; G = Stevens rearrangement (Scheme 26); H = oxidation of 2-ThC(=CH_2)$OSiMe_3$; I(a) = perfluoroglutaryl dichloride on 2-ThMgBr; I(b) = perfluoroglutaric acid + large excess of 2-ThMgBr.

[c] Thiosemicarbazone, melting point 220–222°C.

[d] 2,4-Dinitrophenylhydrazone (mono), melting point 120°C.

[e] Diacid, melting point 200–202°C.

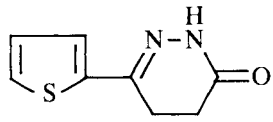
H. 1,4-Dicarbonyl Compounds

a. PREPARATION

Most 1,4-dicarbonyl compounds have been obtained by the addition of a thiophene carboxaldehyde to an activated double bond (Table 5). Others have been prepared by reduction ($SnCl_2$—AcOH—HCl) of the unsaturated 1,4-diketones, ThCOCH=CHCOAr, which are readily available by means of the Stevens rearrangement (Scheme 26).[795,1353] Acetylthiophenes (ThCOMe) are converted into the symmetrical diketones, $ThCO(CH_2)_2COTh$, by reaction with trimethylsilyl chloride and oxidation of the resulting vinyl ether, $Th(=CH_2)OSiMe_3$, with silver oxide.[1468] A few other classical methods for preparing 1,4-diketones are listed as footnotes to Table 30.

b. REACTIONS

Treatment of β-(2-thenoyl)propionic acid with hydrazine gives the expected dihydropyridazinone **162**.[1470] Terthienyls are readily obtained by treatment of the 1,4-diketones, $ThCOCH_2CH_2COTh$, with hydrogen sulfide and ethanolic hydrogen chloride.[795,1468]



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I. 1,5-(and Higher) Dicarbonyl Compounds

The few higher diketones and ketoacids that have been prepared are included in Table 30. Methods of preparation will be evident from the footnotes to this table.

IV. ACKNOWLEDGMENTS

I am indebted to the University of Hull for granting me study leave to enable me to write part of this chapter. I would also like to express my appreciation of the tolerance shown by my family and research students during my prolonged absence from home and laboratory respectively.

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CHAPTER IV

Thiophenecarboxylic Acids and Their Derivatives

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I. PREPARATION OF THIOPHENECARBOXYLIC ACIDS AND THEIR DERIVATIVES

1. General Methods

A. From Organometallic Derivatives

a. LITHIUM DERIVATIVES

The carbonation of thienyllithiums is one of the most versatile and widely used routes to thiophenecarboxylic acids. The intermediates may be obtained either by replacement of hydrogen (transmetalation: method i in the Table of Compounds)

or of halogen or a methylseleno group (method u). The most commonly employed lithiating agents are the alkyllithiums, particularly *n*-butyllithium; others are phenyllithium, lithium diisopropylamide (LDA), and the combination butyllithium–tetramethylethylenediamine (TMEDA). An interesting variation of these agents is lithiated 4-iodopolystyrene, which has been used to produce thiophene-2-carboxylic acid, in fair yields, from both thiophene and 2-bromothiophene.[1] Alternative agents to carbon dioxide that have been used to react with thienyllithiums to produce carboxylic acid derivatives include the bisdiethylamide of perfluoroglutaric acid[2] and *N*,*N*-dimethylchloroformamide,[3] both of which gave the appropriate amides. Ethyl chloroformate reacts similarly to produce ethyl esters,[4,5] whereas phenylisocyanate gave the anilide from a typical thienyllithium.[6]

As a first approximation, the ease of replacement of hydrogen or halogen by lithium (from an alkyllithium) in thiophene derivatives is in the order:

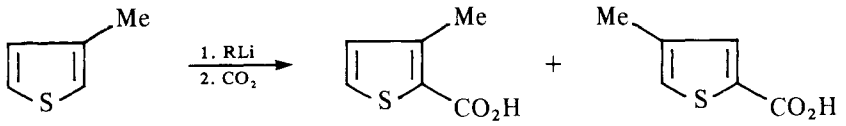
$$\text{I or Br at any position} \gg \alpha\text{-H} \gg \beta\text{-H} > \text{Cl or F at any position}$$

From this order it is apparent that transmetalation will, in general, be best suited for the preparation of thiophene-2-carboxylic acids, and then only if more readily replaced atoms are not also present in the molecule. Halogen–metal exchange, on the other hand, can be used to introduce a carboxyl group at any position.

i. TRANSMETALATION. Thiophene itself gives a good yield of thiophene-2-carboxylic acid on treatment with butyllithium, followed by carbonation;[7] in a competitive experiment involving equimolar quantities of thiophene and furan a mixture of the 2-acids was produced, the thiophene acid being the major component.[8]

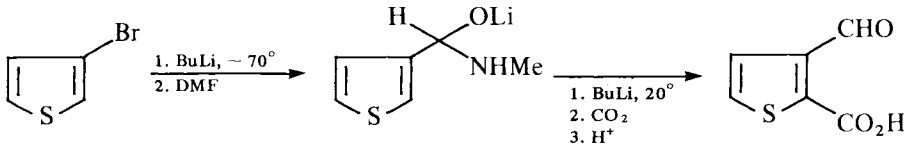
A great variety of 2-monosubstituted thiophenes are lithiated exclusively at C-5 and give good yields of the 5-substituted thiophene-2-carboxylic acid on treatment with solid carbon dioxide. The reaction can be applied to thiophenes with 2-alkyl, -substituted alkyl, -aryl, -heteroaryl, -diarylphosphinyl, -*O*-alkyl, -*O*-aryl, -*S*-alkyl, -*S*-aryl, -sulfono, -dialkylsulfonamido, -chloro, and -fluoro substituents. The carbonyl functions of aldehydes and ketones are generally protected (as ethylene- or diethylacetals or -ketals) before lithiation and carbonation; yields are then generally excellent. On the other hand, 2-cyanothiophene gives only a very poor yield (4%) of 5-cyanothiophene-2-carboxylic acid.[9,10] Amino- and nitrothiophene-2-carboxylic acids have not been prepared by the lithiation route.

The lithiation of 3-monosubstituted thiophenes is rather less straightforward than that of the 2-isomers. For example 3-methylthiophene gives a mixture of 3-



1 2

Scheme 1



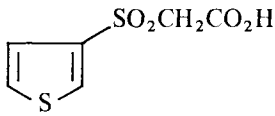
3

Scheme 2

methyl- (**1**) and 4-methylthiophene-2-carboxylic acid (**2**) (Scheme 1); **2** is invariably the major product, but the relative proportions depend on the lithiating agent used. Those studied include phenyllithium and butyllithium,[11] butyllithium-TMEDA in ether at −70°, and LDA.[12] When the lithiation is carried out with butyllithium (with or without TMEDA) in refluxing hexane carbonation produces a quantitative yield of 3-methylthiophene-2,5-dicarboxylic acid.[13] A mixture comparable to that of **1** and **2** is formed from 3-benzylthiophene,[14] but 3-methoxymethylthiophene is lithiated almost exclusively at C-2.[15]

The behavior of 3-arylthiophenes differs considerably from that of 3-alkyl derivatives. 3-Phenyl-[16] and a variety of other 3-arylthiophenes[17] were found to give approximately equal amounts of the 3- and 4-arylthiophene-2-carboxylic acids, whereas 3-(*N*-pyrazolyl)thiophene gave predominantly the 3-pyrazolyl-2-acid.[18]

Some other functional groups at C-3 direct the carboxylation process almost exclusively to C-2; these include methoxy-,[19] *t*-butoxy-,[5,20] fluoro-,[21] diphenylphosphine oxide,[22] and protected ketone groups.[23–25] In the same category as the last examples are the 'one-pot' preparations of 3-formyl-[26] and 3-benzoylthiophene-2-carboxylic acids[27] from 3-bromothiophene. In the former case it is suggested that the intermediate **3** might be involved (Scheme 2). It is interesting to note that, although butyllithium brings about halogen exchange with 3-bromothiophene, phenyllithium fails to react at all at −70°C[28] and at higher temperatures replaces H-2 rather than the bromine atom, which leads to 3-bromothiophene-2-carboxylic acid on carbonation.[28,29] LDA behaves in much the same way, producing 3-bromo-5-methylthiophene-2-carboxylic acid from 4-bromo-2-methylthiophene.[30] In contrast to its 2-isomer, 3-cyanothiophene gives an excellent yield of acid on lithiation-carbonation, the product being 3-cyanothiophene-2-carboxylic acid;[9,10] both these lithiations have been studied by ^{13}C NMR.[31] An *S*-*t*-butyl group at C-3 directs lithiation to C-2 and C-5; at −25°C a mixture of the derived acids is obtained on carbonation,[32] but at 20°C the product is 3-*t*-butylthiothiophene-2,5-dicarboxylic acid.[32,33] 3-Butyl- and 3-methylselenothiophene give mixtures,



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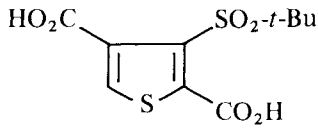

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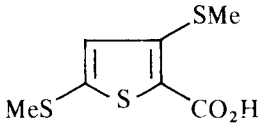

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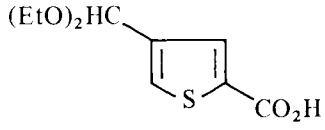

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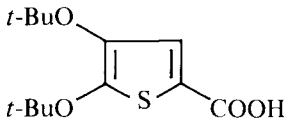

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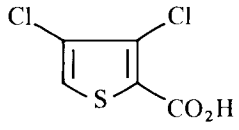

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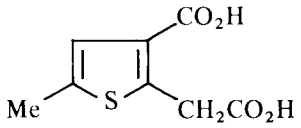
containing a small excess of the 3-alkylseleno- over the 4-alkylselenothiophene-2-carboxylic acid.[34] Reaction of methyl 3-thienylsulfone occurred in the side-chain, to give **4**, but the corresponding *t*-butyl compound (in which side-chain elaboration is precluded) led to a mixture that contained **5** as the major component.[33]

Dialkylthiophenes with a free α-position are lithiated solely at that position. This fact has been put to advantage in the removal (by way of the acid) of a 2,4-[35] and a 2,3-dialkylthiophene[36] from mixtures with the 2,5-dialkyl isomers. Provided that the groups are nonreactive toward alkyllithiums and are not more readily replaced than hydrogen, 2,3-, 2,4-, and 3,4-disubstituted thiophenes with a variety of substituents can be carboxylated α to the sulfur atom. Examples of acids that have been prepared by this means are **6**,[37] **7**,[38] **8**,[3,5] and **9**.[39]

The replacement of the hydrogen atoms at the β-positions in 2,5-disubstituted thiophenes can also be accomplished; generally higher temperatures are required than are necessary for α-hydrogens, and the reaction is not always free of complication. The ease of replacement of a β-hydrogen atom is only marginally greater than that of an α-chlorine, and mixed products were obtained on lithiation-carbonation of 2-chloro-5-methylthiophene.[12] 2,5-Dichlorothiophene, however, gave 2,5-dichlorothiophene-3,4-dicarboxylic acid (in very poor yield) after reaction with butyllithium at room temperature.[40]

The application of the alkyllithium-TMEDA-carbonation sequence to 2,5-dimethylthiophene has been studied by two groups.[12,41] In addition to nuclear carboxylation, reaction takes place to some extent at one of the methyl groups, giving the bisacid **10**. The very low total yields in the reaction were ascribed[41] to ring opening of the intermediate lithium derivatives. The same problem is responsible for the failure of 2-methylthio-5-methylthiophene[42] and of 2,5-dimethoxythiophene[43,44] to provide 3-carboxylic acids. It is of interest that in the



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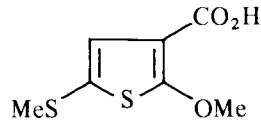

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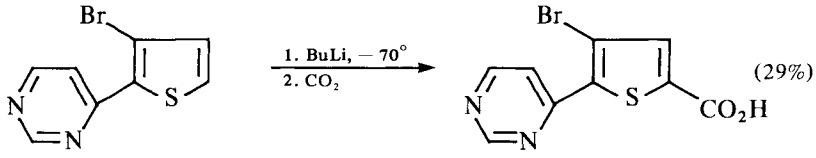
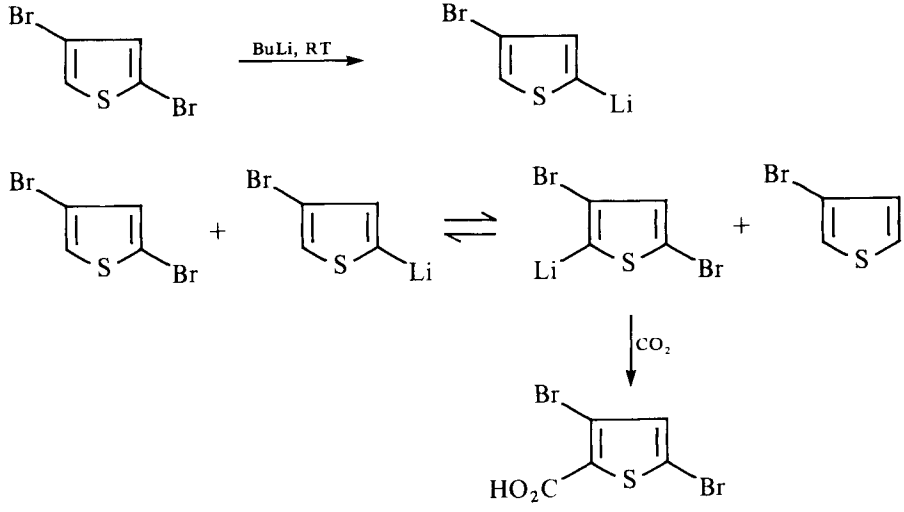


Scheme 3

latter case the acid was obtained, in modest yield, by way of bromine–lithium exchange.[43,44] Curiously, ring opening did not take place to any significant extent with 5-methylthio-2-methoxythiophene, which gave a good yield (64%) of the acid **11**.[45]

ii. HALOGEN-METAL EXCHANGE. A single iodine or bromine atom at any position on a thiophene is an almost guaranteed precursor to a carboxyl group on reaction at low temperature with an alkyllithium, followed by treatment with carbon dioxide. The Tables of Compounds include numerous examples of thiophene-2- and 3-carboxylic acids that have been obtained in this way. The exceptional behavior of 3-bromothiophene with other lithiating agents has already been referred to; another very rare exception to the preference for low temperature halogen exchange is shown in Scheme 3.[46] It has previously been noted that chlorine atoms are very resistant to exchange; their reactivity is somewhat enhanced in tetrachlorothiophene, which can be converted into the 2-[47–49] and 2,5-dicarboxylic acids[50] in excellent yields.

The lithiation-carbonation of polyhalogenothiophenes can be a simple or a complex matter, depending on the nature and location of the halogen atoms. A further important factor is the temperature. At low temperatures rearrangement is uncommon, but at or above room temperature an equilibrium may be established,



Scheme 4

leading to unexpected products. Scheme 4 illustrates such a process. In this reaction lithiation at $-60°C$ gives 4-bromothiophene-2-carboxylic acid, but at room temperature the product is 3,5-dibromothiophene-2-carboxylic acid.[51]

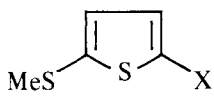
From an examination of numerous results, and from papers in which the subject has been studied closely, e.g., References 52–54, it is possible to make some generalizations about the behavior of dihalogenothiophenes in the low-temperature reaction, as follows:

1. Fluorine atoms are not replaced.
2. Chlorine atoms are very seldom replaced, and from bromochloro- and chloroiodothiophenes chlorothenoic acids are formed.
3. In a 2,3- or 2,4-dibromo or -diiodothiophene the halogen atom at C-2 is exchanged most readily.
4. Some bromoidothiophenes are prone to rearrange, but if this can be prevented (or does not take place) the iodine atom is preferentially exchanged, whether it be at an α- or a β-position.
5. With an excess of alkyllithium both halogen atoms of a dibromo or diiodothiophene can be exchanged.

The presence of other substituents on the ring, for example, carboxyl[55] or methoxyl,[56] does not appear to alter the truth of these observations.

Treatment of 2,3,5-tribromothiophene in the usual way at room temperature gives rise to a mixture of 3,5-dibromo- and 4,5-dibromothiophene-2-carboxylic acids,[51] but only the former is produced at $-70°C$.[57] Tetrabromothiophene suffers exchange of the halogen atoms at C-2 and C-5.[58]

iii. EXCHANGE OF METHYLSELENO (AND OTHER) GROUPS. The methylseleno group is a substitute for halogen in lithiations at thiophene α-positions. Reaction of 2-methylselenothiophene with one equivalent of butyllithium at $-70°C$, and carbonation, gives an excellent yield of thiophene-2-carboxylic acid.[59–62] That the reaction involves exchange of the methylseleno group, rather than hydrogen replacement and reduction, was demonstrated when thiophene itself was recovered unchanged after exposure to identical conditions.[61] With two equivalents of butyllithium both 5-bromo-2-methylselenothiophene and 2-methylselenothiophene gave good yields (78 and 63% respectively) of thiophene-2,5-dicarboxylic acid.[60] It would appear that the methylthio group is considerably less readily exchanged with lithium, but that replacement can occur in certain circumstances. For example, 3,5-dimethylthiophene-2-carboxylic acid has been obtained from 3,5-dimethyl-2-methylthiothiophene;[18] further, it is the 5-methylthio



a. X = Br
b. X = Me
c. X = H
d. X = SeMe

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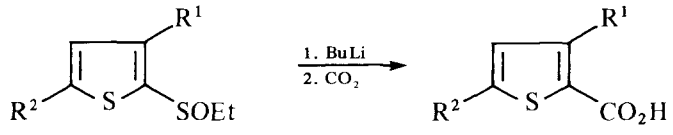

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Scheme 5

group that is replaced from compounds **12a** and **12b**, but X that is lost from **12c** and **12d**.[60]

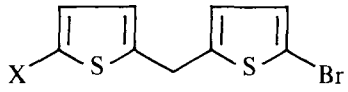
Scheme 5 shows a rather unusual synthesis of some alkyl thiophene-2-carboxylic acids which involved replacement of the sulfoxide group from **13** ($R^1 = R^2 =$ Me, Et; $R^1 =$ H, $R^2 =$ Me, Et).[63]

b. OTHER ALKALI METAL DERIVATIVES

The advent of readily available alkyllithiums has caused a considerable decline in the use of organosodium derivatives for the preparation of thiophenecarboxylic acids in recent years. Thiophene itself is metalated moderately well by the combination of ordinary sodium amalgam–chloroethane[64] or of sodium–mercury sand–bromobenzene,[65] and fair yields of thiophene-2-carboxylic acid were obtained after reaction with carbon dioxide. Naphthylsodium achieves the same result with thiophene; it is interesting that with this agent transmetalation is preferred to halogen exchange, since both 2-chloro- and 2-bromothiophene are converted into the 5-halogenothiophene-2-carboxylic acid.[66] 2,5-Bismetalation of thiophene was achieved by amylsodium, leading to a satisfactory yield (50%) of thiophene-2,5-dicarboxylic acid.[67] In the reaction leading to 4-methylthiophene-2-carboxylic acid (2) from 3-methylthiophene, by treating it (in ether) with an alkyl halide (RBr) and sodium it was found that better yields were obtained when R was butyl than when it was ethyl.[68] The same acid was produced (58%), after carbonation, by the action of phenylsodium on 3-methylthiophene; also formed was 3-methylthiophene-2,5-dicarboxylic acid (11%).[11] A 1:1.84 complex formed between ethylsodium and diethylzinc, which is soluble in organic solvents, metalates thiophene quite effectively and has been used to produce thiophene-2-carboxylic acid.[69] The metalation of thiophene and of 2- and 3-methylthiophene by butylpotassium and butylcaesium has been studied by Benoit and Collignon;[70] the agents were prepared by reaction of dibutylmercury and the alkali metal. When exactly two equivalents of metal were employed, the yields of acids obtained on reaction with carbon dioxide were very low in both cases, caesium giving slightly the better results. With four equivalents of metal the yields were improved very considerably from potassium (e.g., from 4 to 51% in the reaction with thiophene), but much less so for caesium (from 12 up to 18% for the same reaction).

c. GRIGNARD REAGENTS

Because alkyllithiums generally give faster reactions and better yields they have almost completely superseded Grignard reagents as the main means of transforming halogenothiophenes into thiophenecarboxylic acids. However, in the earlier part of

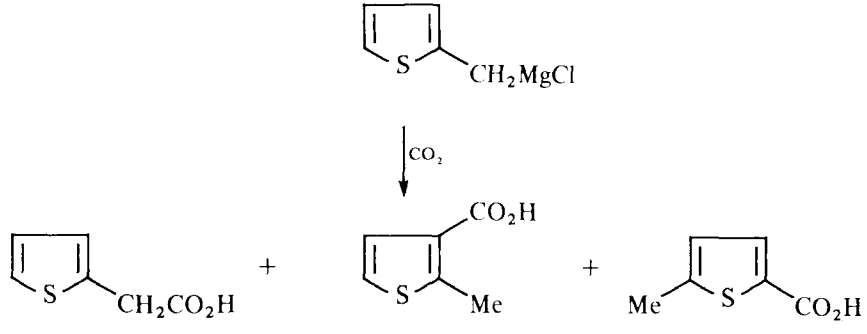


a. X = H, yield of acid 71%
b. X = Br, yield of diacid 84%

14

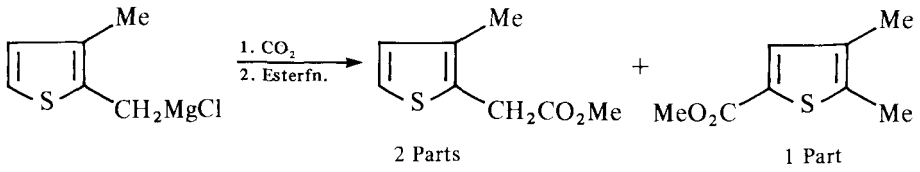
the period covered in this chapter organomagnesium compounds were used frequently for the purpose (method o in the Tables of Compounds). Good yields are obtained from 2-bromo-3-phenyl-[30] and 2-bromo-5-phenylthiophene,[71] but the bromothiophenes themselves, and simple alkylbromothiophenes give only modest returns of acid on reaction with carbon dioxide. Yields are improved in these cases, sometimes considerably, if the entrainment procedure is used that is, if the preparation of the Grignard reagent is carried out in the presence of a large (usually fivefold) excess of an alkyl halide; bromoethane is commonly used for this purpose. The technique has been studied in some detail by Gronowitz[72] and has been applied with success to a range of simple thiophenes, including 2-bromo-5-ethylthiophene,[73] the dithienylmethane derivatives **14a** and **14b**, and 3-bromothiophene,[74] although other reports[75,76] suggest that conversion is still poor in this case. Chlorothiophenes do not generally form Grignard reagents, but an 84% conversion of 2-chlorothiophene was achieved by treating it with a combination of magnesium, bromoethane, and iodine in tetrahydrofuran.[77]

Thiophenecarboxylic acids are formed, in company with thienylacetic acids, in interesting rearrangements of thenylmagnesium halides. 2-Thenylmagnesium chloride, for example, gives a mixture of acids on carbonation[78–81] (Scheme 6). The major product is **15**, and **17** is formed in only very minor amounts. If the solvent is changed from ether to 1,2-dimethoxyethane, **15** becomes the sole product;[81] conversely, replacement of carbon dioxide by ethyl chloroformate gave only **16** (after saponification).[78,79] When the 3-position of a 2-thenylmagnesium halide is blocked, rearrangement still takes place, but now involves the 5-position.[81] Reactions analogous to those just described were also found to take place with 3-thenyl-



15 **16** **17**

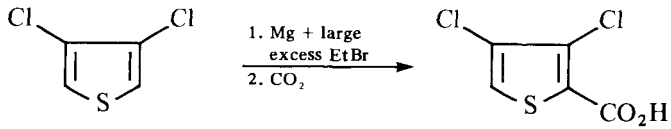
Scheme 6



Scheme 7

magnesium bromide. In this case the rearrangement product is 3-methylthiophene-2-carboxylic acid.[82] Carbonation with $^{14}CO_2$ has been used to prepare labeled thiophenecarboxylic acids from Grignard reagents.[80,83]

The considerations that apply to the reactions of polyhalogenothiophenes with alkyllithiums also hold for their reaction with magnesium. Chlorine atoms are not replaced; 2-bromo-5-chlorothiophene, for example, gave only 5-chlorothiophene-2-carboxylic acid after the normal sequence.[84] An unusual reaction, of the transmetalation type (Scheme 8), emphasizes the resistance of chlorothiophenes to metal exchange.[39] In thiophenes containing bromine atoms at both α- and β-positions it is only the α-halogens that engage in magnesium exchange.[51,76,85] Bromine atoms at β-positions can be exchanged, however; 3,4-dibromo-[76] and 3-bromo-2-chlorothiophene[86] each gave the appropriate halogenothiophene-3-carboxylic acid.



Scheme 8

d. OTHER ORGANOMETALLIC DERIVATIVES

A few attempts to prepare thiophenecarboxylic acids by carbonation of calcium derivatives have been reported. The phenylcalcium iodide–TMEDA complex gave a very poor yield of thiophene-2-carboxylic acid from thiophene,[87] although the result was somewhat better with methylcalcium iodide (34%).[88] In an approach directly analogous to a normal Grignard reaction, 2-iodothiophene, in tetrahydrofuran, was treated with calcium; on carbonation no thiophene-2-carboxylic acid was formed, but the product consisted of a mixture of 5-iodothiophene-2-carboxylic acid and thiophene-2,5-dicarboxylic acid.[89] Compounds of general formula metal–$Al(thienyl)_4$ are obtained quantitatively when thiophene is treated with sodium or potassium aluminum hydride in diglyme; these give low yields of thiophene-2-carboxylic acid on carbonation.[90]

B. Oxidation Reactions

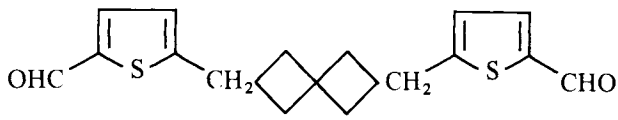
a. OXIDATION OF ALDEHYDES

The oxidation of aldehydes (method p in the Tables of Compounds) has been used very widely for the preparation of thiophenecarboxylic acids of all classes, with the notable exception of aminothiophenecarboxylic acids. The principal difficulty in this last case lies in the instability of simple aminothiophenes. Once stabilized, they can be formylated, and the aldehydes oxidized; 5-acetylaminothiophene-2-aldehyde, for example, gave an almost quantitative yield of the acid on treatment with Fehling's solution,[91] although it was said to be unaffected by silver(I) oxide–sodium hydroxide.[92]

Thiophene aldehydes are generally very accessible and are therefore particularly valuable as intermediates for the synthesis of acids. The formyl group can be introduced into all but the most deactivated nuclei by the Vilsmeier reaction – this is also true of certain of the stable aminothiophene derivatives that have been synthesized in recent years. Thienyllithium derivatives yield aldehydes with dimethylformamide, and the Sommelet reaction represents a third useful direct route to the compounds. None of these methods is of value with nitrothiophenes, but in this case nitration of the aldehyde (or its bisacetoxy derivative) is a reasonable alternative.

By far the most frequently used agent for the oxidation is silver(I) oxide in aqueous sodium hydroxide. The process is capable of giving very high yields (95 to 97% with thiophene-2-aldehyde, for example).[93] This same aldehyde is oxidized very efficiently by silver(II) oxide also,[92] and to some extent by a catalytic process involving silver(I) oxide–copper(II) oxide and air.[94] It is clear that the silver oxide method can be applied to thiophene aldehydes carrying most types of substituents. Alkyl groups are quite unaffected, and examples exist of the successful oxidation of aldehydes carrying cyclopropyl,[95] methoxymethyl,[96,97] phenoxymethyl,[98] acetoxyethyl,[99] carboxy,[100,101] methoxy,[102–104] alkylthio,[42,61,105–107] alkylseleno[34,37], halogeno,[108–111] and protected formyl,[112] and keto[113] groups. When two formyl groups are located on the same ring, oxidation to bisacids takes place without difficulty[114–116] with silver oxide. The same reagent gave excellent yields of bisacids from the aldehydes **18**[95] and **19**.[117]

Agents other than silver oxide have been employed rather infrequently. One of the more interesting combinations is potassium iodide–mercury(II) iodide (the Doevre reagent), which was used to prepare the acid from the naturally occurring junipal (**20**),[118,119] and to oxidize 5-(1-propenyl)thiophene-2-aldehyde;[119] in the former case Jones' reagent was also very effective. Other less commonly used



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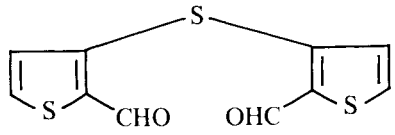

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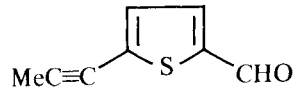

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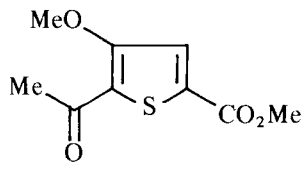
oxidants include nickel peroxide,[120] sodium hypochlorite (which gave thiophene-2,5-dicarboxylic acid from 5-acetylthiophene-2-aldehyde),[113] sodium hypobromite,[121] tetrabutylammonium permanganate,[122] and mixtures of hydrogen peroxide with potassium hydroxide[123] and with sulfuric acid.[124] Some nitroaldehydes are converted into methyl esters by reaction with chlorine or bromine, methanol, and an alkali metal hydroxide, carbonate, or bicarbonate,[125] and into acids by a set of closely related methods in which halogens play the part of oxidants.[126]

For thiophene aldehydes containing oxidation-resistant substituents it is possible to use powerful oxidants for the aldehyde function. Bromo-,[127] chloro-,[128] iodo-,[129] and nitroaldehydes[130,131] have all been converted into the acids by potassium permanganate in acetone. Nitroaldehydes have also given good results on treatment with chromium trioxide[132,133] or acidified dichromates[108,134–137].

b. HYPOHALITE AND RELATED OXIDATIONS OF KETONES

The remarks made earlier about the availability of aldehydes apply almost as well to ketones. Friedel-Crafts acylation is successful even with quite strongly deactivated rings (although it, too, generally fails with nitrothiophenes), and the route to thiophenecarboxylic acids by means of hypohalite oxidation of methyl ketones (method q in the Table of Compounds) has been much used. There seems to be no preferred agent among the accessible alkali metal hypohalites; in one study[138] it was found that sodium hypochlorite gave a better yield than the hypobromite in the preparation of 5-ethylthiophene-2-carboxylic acid from the ketone, but only marginally so (90, as opposed to 85%). Calcium hypochlorite has been used, but no yields were recorded.[139]

The reaction is particularly good for the preparation of thiophene-2-carboxylic acid itself[140,141] and generally gives excellent yields from alkyl-, aryl-, and halogenothenyl methyl ketones. For obvious reasons hypohalite oxidation has not been applied to thiophene compounds containing nuclear hydroxy or mercapto substituents. It was successful with the methoxylated thiophene **21**,[142] but an



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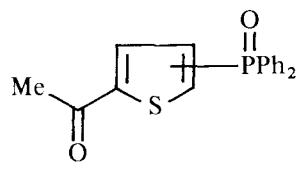

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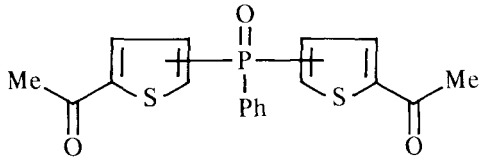
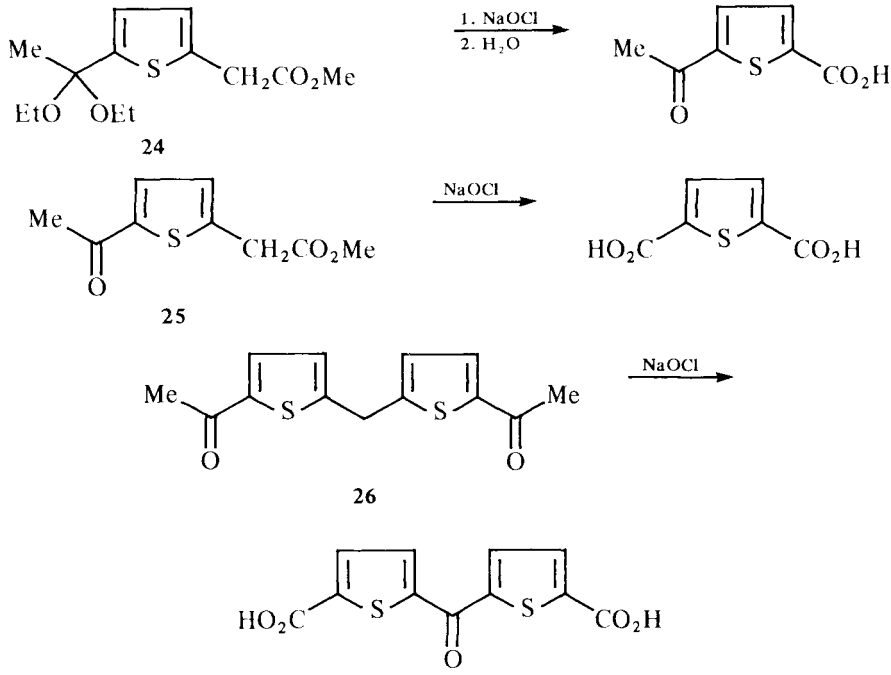


23

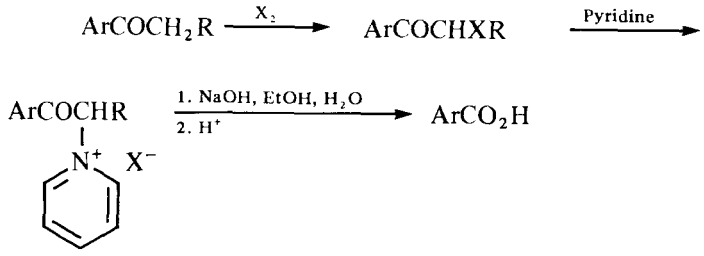
alternative approach (by means of a pyridinium derivative, see later discussion) is preferred when alkylthio or alkylseleno groups are present. The triarylphosphino compounds **22** (substituent at C-4 and at C-5) and **23** (2,2′- and 3,3′-isomers) gave the appropriate acids with sodium hypobromite.[143]

Although in the great majority of cases the oxidation has been applied to methyl 2-thienyl ketones, it can also be successful with 3-thienyl compounds; indeed, the formation of 2,5-dimethylthiophene-3,4-dicarboxylic acid from the bisketone has been described.[144]

A complication occasionally intrudes in methyl thienyl ketones that contain another methylene activated by electron-attracting substituents. Further oxidation may then take place; the reactions, depicted in Scheme 9, of **24**,[145] **25**,[146] and **26**[147] provide examples of this behavior. In connection with the last case it is interesting to note that no oxidation of the dibenzylic position was reported on hypohalite treatment of 5-benzyl-[148,149] or of 5-furylmethyl-2-acetylthiophene.[150]

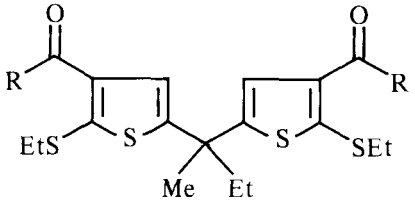


Scheme 9



Scheme 10

The reaction sequence involved in an alternative method of oxidation of ketones is given in Scheme 10 (X = I or Br). In almost every reported case in the thiophene series methyl ketones (R = H) were used, but others are possible, and the formation of thiophene-2-carboxylic acid from a range of alkyl 2-thienyl ketones has been studied.[151] This process has been used chiefly with methyl thenyl ketones carrying alkylthio[105,152] and alkylseleno[34,61] substituents. Yields are usually good (65 to 90%), but the results with **27a** (using either bromine or iodine in the first step) were rather poor and were considerably worse than those obtained from treatment of the bisaldehyde **27b** with silver oxide.[153]



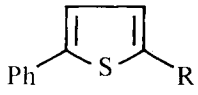
a. R = Me
b. R = H

27

c. VIGOROUS OXIDATION OF SIDE-CHAINS

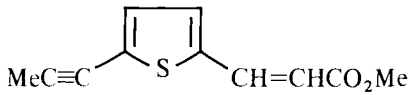
The resistance of a thiophene ring to oxidative degradation is largely a function of the substituents present; in this context, those of an electron-attracting nature tend to stabilize the ring and to allow more vigorous agents to be used. The converse is true of electron-releasing groups, and the method under discussion is almost completely inappropriate for the preparation of amino-, hydroxy-, alkoxy-, mercapto-, and alkylthiothiophenecarboxylic acids.

A second factor to be considered is the ease of oxidation of the carboxyl group precursor. Alkynyl- and alkenylthiophenes generally give fair yields of acid with potassium permanganate in acetone; thus 1-(2-thienyl)propene yielded thiophene-2-carboxylic acid,[119] **28a** and **28b** both gave 5-phenylthiophene-2-carboxylic acid, and **29** gave thiophene-2,5-dicarboxylic acid.[154] Chromium trioxide–sulfuric acid treatment of the nitrothiophenes **30a** and **30b** afforded the corresponding nitrothiophene-2-carboxylic acids.[155]



28

a. R = CH = CHPh
b. R = C≡CC≡CPh



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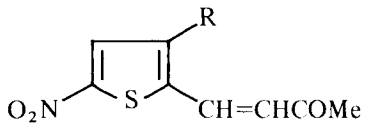


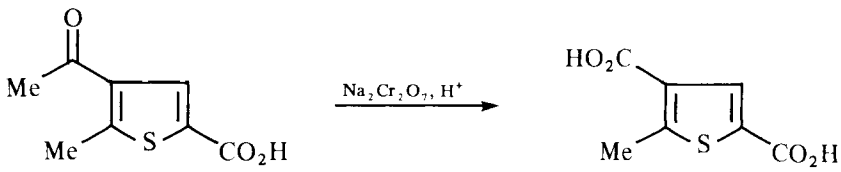
30

a. R = H
b. R = NO_2

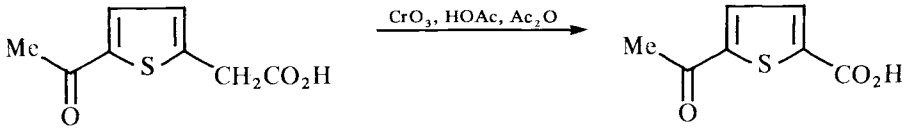
Simple alkylthiophenes give moderate yields of acids on reaction with alkaline potassium permanganate. An interesting insight into the relative reactivities of alkyl groups located at α- and β-positions is given by the oxidation of 2-ethyl-4-methylthiophene, which gave 4-methylthiophene-2-carboxylic acid.[156,157] 2,5-Dimethylthiophene gives the 2,5-diacid on treatment with oxygen in the presence of a cobalt acetate catalyst.[158] The increased stability of the thiophene ring conferred by electron-withdrawing substituents is exemplified by the yields of thiophene-2,5-dicarboxylic acid obtained by alkaline permanganate oxidation of 2,5-dimethylthiophene (40%)[154] and 5-methylthiophene-2-carboxylic acid (82%).[15] Diacids are obtained in similar circumstances from 5-alkenyl-,[119] 5-alkynyl-,[118] 5-alkyl-4-halogeno-,[138] and 3-alkylthiophene-2-carboxylic acids.[159]

In certain circumstances the conditions necessary to convert an acetyl group directly to carboxyl are drastic enough to oxidize alkyl groups also. Not surprisingly the vinyl group of (5-acetyl-2-thienyl)ethylene failed to survive treatment with permanganate[160] during oxidation of the acetyl group. Similarly 2-acetyl-3-methylthiophene gave the 2,3-dicarboxylic acid.[161,162] In other circumstances a methyl group can remain unaffected; for example, the reaction in Scheme 11 gave an 82% yield of the diacid.[163]

A further variation still is possible (Scheme 12). Here an acetyl group remains intact while the acetic acid side-chain is oxidized by chromium trioxide–acetic

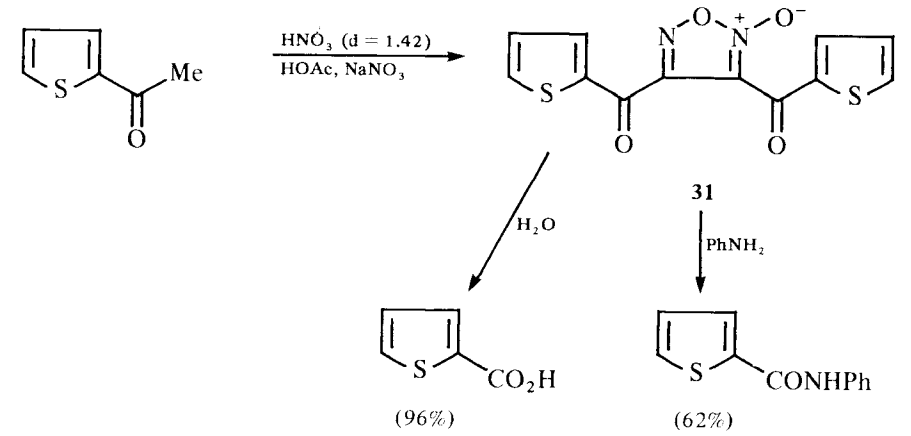


Scheme 11



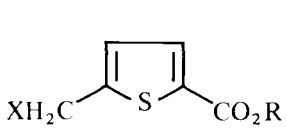
Scheme 12

acid–acetic anhydride,[164] by potassium permanganate,[165] or by air in the presence of sodium hydroxide.[166] Prolonged treatment of 2-acetylthiophene with nitric acid at 100° converts it into the 2-carboxylic acid in good yield.[167] Under other conditions a bis(2-thenoyl)furoxan (**31**) can be obtained; this intermediate can be transformed into the acid or its anilide[168] (Scheme 13). An indirect route from an acetyl to a carboxyl group involves reaction with selenium dioxide, followed by decomposition of the glyoxal with hydrogen peroxide. This process has been applied to 2,5-dimethyl-3-acetylthiophene.[169]



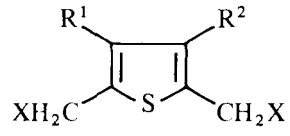
Scheme 13

The chloromethyl group is readily introduced into quite a range of thiophenes by direct substitution, and more compounds in the class are available by electrophilic substitution of a preformed chloromethylthiophene. When neither of these approaches is feasible it may be possible to obtain a halomethyl derivative by side-chain halogenation (for example with *N*-bromosuccinimide) of a methylthiophene. These halomethyl groups and hydroxy, alkoxy, or mercaptomethyl groups obtained from them by nucleophilic substitution are quite useful precursors (through oxidation) of carboxyl functions. Examples may be found of halogeno-,[97,170–173] nitro-[174] and ketothiophene-2-carboxylic acids[163,175] and nitro-[176] and ketothiophene-3-carboxylic acids[177] that have been made by this means. Thiophene-2,5-dicarboxylic acids have been obtained from the 5-substituted-



32

a. X = EtS, R = H
b. X = Cl, R = Et
c. X = MeO, R = H



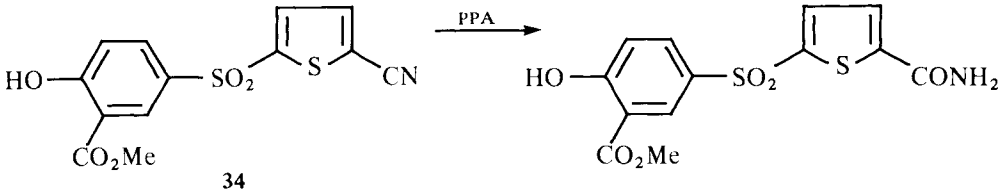
33

a. X = HO, $R^1 = R^2 = H$
b. X = MeO, $R^1 = R^2 = I$
c. X = Cl, $R^1 = H$, $R^2 = Br$

methylthiophene-2-carboxylic acids **32a**,[175] **32b**,[160] and **32c**,[97] and from the 2,5-bis(substituted-methyl)derivatives **33a**,[178] **33b**,[97] and **33c**.[139] Oxidations of the same character have given thiophene-2,3-dicarboxylic acid[15,179] and its 5-chloro derivative,[180] thiophene-2,4-dicarboxylic acid[180] and its 3,5-dibromo derivative,[139] thiophene-2,3,5-tricarboxylic acid,[180,181] and thiophenetetracarboxylic acid.[180]

C. Hydrolysis of Cyanothiophenes

The hydrolysis of cyanothiophenes to either acids or amides is generally an uncomplicated matter. It is of limited utility, in the sense that some of the intermediates in cyanothiophene synthesis (see Section IV.1) could equally be converted directly into the acid, but the sequence halogenothiophene → cyanothiophene → carboxylic acid (or amide) has distinct advantages where substituents are such that halogen–metal interconversion is likely to give poor results; this is especially true for halogenonitrothiophenes. The full hydrolysis of nitriles requires rather drastic conditions. At one extreme they are boiled with concentrated hydrochloric acid, which may account for the rather low yields sometimes reported from cyanothiophenes. Nonetheless, the method can give excellent results [for example, an 84% yield of thiophene-3-carboxylic acid was obtained from the cyano compound[108]], and it has been much used for the preparation of nitrothiophene-2-carboxylic acids.[92,182–186] The alternative conditions are treatment with hot, concentrated alkali solutions; in one case (for 2,3-dicyanothiophene) ethylene glycol was used as solvent, with excellent results.[187] 3,4-Dicyanothiophene also gave a very good yield of diacid, but under milder conditions;[27] thiophene-2,4-dicarboxylic acid has been obtained from the biscyano compound,[188] and the 2,3- and 2,5-diacids from 3- and 5-cyanothiophene-2-carboxylic acid, respectively.[9] The yield in this last case was nearly quantitative. The partial hydrolysis to amides of several cyanothiophenes has been achieved, generally by one of two principal methods. In the first, the cyanothiophene is treated with concentrated sulfuric acid (usually in the cold), then the solution is diluted with water. This technique has been applied to 2-cyanothiophene,[189] 5-nitro-2-cyanothiophene,[190] ethyl 2-amino-5-cyano-4-methylthiophene-3-carboxylate,[191] and 2-amino-4-*t*-butyl-3-cyanothiophene.[192] In the second method, used by Fournari, Guilard, and Person[127] for all the possible isomers of bromocyanothiophenes and iodocyanothiophenes,[129] the cyano com-



Scheme 14

pound is reacted with hydrogen peroxide. Polyphosphoric acid can also be used to achieve partial hydrolysis; it gave a particularly high yield of amide from 2-cyano-3-phenyl-5-phenylaminothiophene[193] and was also effective with the complex compound **34**[194] (Scheme 14).

It should be remembered that iminoethers (which are obtained from cyano compounds) give esters on treatment with water and give amides on heating. Further, reaction of cyano compounds with hydrogen sulphide leads to thioamides. These reactions have been applied to thiophenes; they are dealt with more fully in Sections IV.2. and V.2, respectively.

D. Other Methods

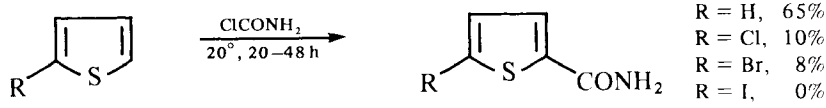
The following is an account of some syntheses that are potentially applicable to all or several of the various classes of thiophenecarboxylic acid, although they may not yet have been widely employed with thiophenes.

a. DIRECT INTRODUCTION OF A CARBOXYL OR SUBSTITUTED CARBOXYL GROUP

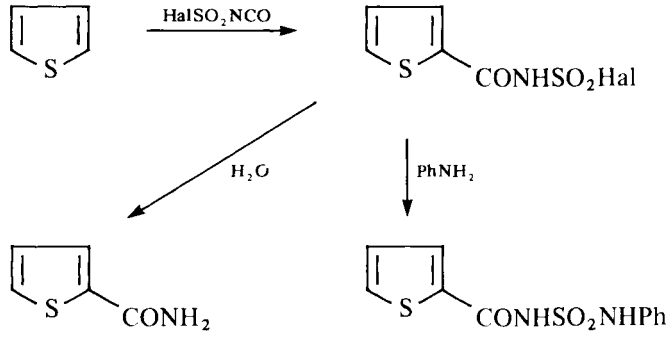
It has been found that the Gattermann synthesis, which involves formation of an amide by reaction of the substrate and carbamoyl chloride, proceeds well with thiophene in the absence of a catalyst and under very mild conditions. Yields with halogenothiophenes are very low, however[195,196] (Scheme 15).

With oxalyl chloride instead of carbamoyl chloride, an extended period of reflux produces the appropriate acid chloride. Yields from thiophene and 2-methylthiophene were good, and those from 2-halogenothiophenes, although still poor (5 to 27%), were better than those listed in Scheme 15.[195,196]

Chloro- and fluorosulphonylisocyanate are sufficiently electrophilic to attack



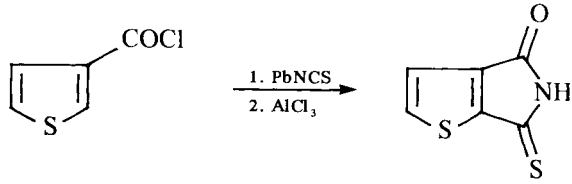
Scheme 15



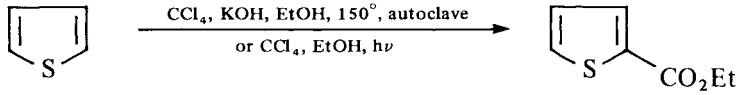
Scheme 16

thiophene in the absence of a catalyst, and the sulphonylamides that result can readily be transformed into the carboxamide or its derivatives[19] (Scheme 16).

Under Friedel-Crafts conditions phenylisocyanate and -isothiocyanate condense with thiophene, giving C_4H_3S–(C = X)NHPh in excellent yields (X = O, 89%; X = S, 92%).[198] Similarly, ethoxycarbonylisocyanate, catalyzed by tin(IV) chloride, yields *N*-ethoxycarbonylthiophene-2-carboxamide from thiophene.[199] An intriguing intramolecular cyclization involving a thenoylisothiocyanate (Scheme 17) has been reported by Cagniant and Merle.[200]

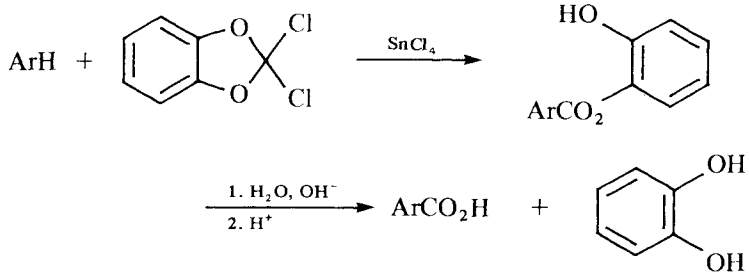


Scheme 17



Scheme 18

Ethyl thiophene-2-carboxylate has been obtained by two methods that employed tetrachloromethane as the source of the carboxyl carbon (Scheme 18). In one,[201] high temperature and pressure were employed, and in the second, UV irradiation;[202] in the latter case it is believed that attack by trichloromethyl radicals is involved.



Scheme 19

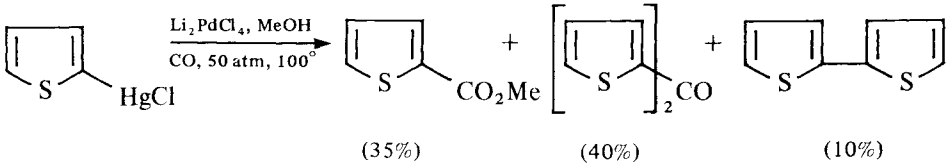
Another reaction of the Friedel-Crafts type that results in the introduction of a carbonyl group employs pyrocatechol dichloromethylene acetal (Scheme 19).

This sequence has been successfully applied to thiophene,[203,204] 2-bromo-3-methylthiophene,[96] methyl thiophene-2-carboxylate,[205] and -3-carboxylate,[206] the products in the last three examples being 5-bromo-4-methylthiophene-2-carboxylic acid, thiophene-2,5-, and -2,4-dicarboxylic acids, respectively. Somewhat in the same category as the last method is the Haller-Bauer reaction, in which a nonenolizable ketone is cleaved under basic conditions to give an acid (Scheme 20).

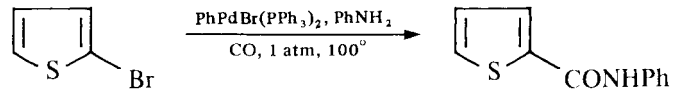
Scheme 20

With thiophene as ArH is was found that the sequence gave very good results when Ar^1 was 2,6-dichlorophenyl[207] and when the cleavage was brought about by a butoxide–water reagent.[208] Thiophene is attacked by a very unusual electrophile, perfluorocyclobutanone, when the two substances are heated together; the product, (1-(2-thienyl)perfluorocyclobutan-1-ol), gives thiophene-2-carboxylic acid when hydrolyzed.[209]

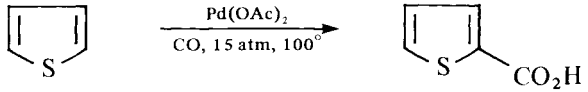
There is a small group of syntheses in which the carboxyl function is introduced into a thiophene ring by direct carbonylation in the presence of a palladium catalyst; the essential features of these processes are shown in Schemes 21,[210] 22,[211–213] and 23.[214]



Scheme 21



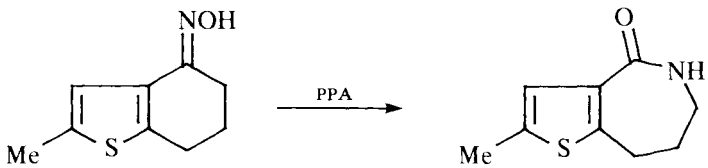
Scheme 22



Scheme 23

b. MISCELLANEOUS PREPARATIONS FROM ALDEHYDES AND KETONES

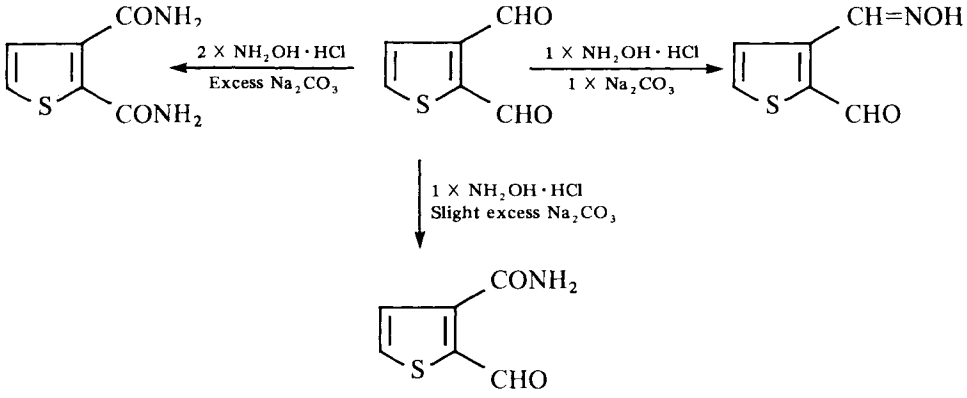
The preparation of thiophenecarboxamides by the Beckmann rearrangement of oximes (method a in the Tables of Compounds) has been reported. Treatment of oxime phenylsulphonates with Grade II or III alumina is a particularly mild means of accomplishing the rearrangement, and it works well with both aryl and alkyl thienyl ketoximes.[215] Generally it seems that much better yields are obtained from aryl thienyl ketoximes, whatever method is used. Very high conversions have been recorded for phenyl thienyl ketoxime[215–218] and for 4-X-phenyl thienyl ketoximes (X = Me, 80%; X = MeO, 88%). An electron-attracting group in the migrating nucleus, on the other hand, causes a sharp reduction in yield (X = Cl, 24%).[216] A particularly interesting use of the Beckmann rearrangement is in the formation of cyclic amides from fused thienocycloalkanoketoximes; it has been used with the methylthienocyclohexanone derivative **35**[219] (Scheme 24) and with thienocycloalkanone oximes lacking further substituents in the thiophene ring.[220] The formation of the related lactones as by-products was reported in the latter case.



35

Scheme 24

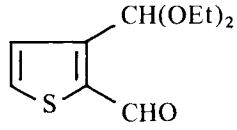
Reports of the rearrangement of thiophene aldoximes are less common. In attempts to prepare oximes of thiophenedialdehydes by treatment with hydroxylamine hydrochloride–sodium carbonate, Bourguignon et al.[221] found that in certain cases, when an excess of sodium carbonate was present, amides and not



Scheme 25

oximes were formed. Scheme 25 summarizes results obtained from thiophene-2,3-dialdehyde.

The rearrangement also took place with 3-cyanothiophene-2-aldoxime, but not with the oximes of **36** or **37a–d.**



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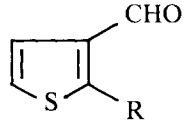


37

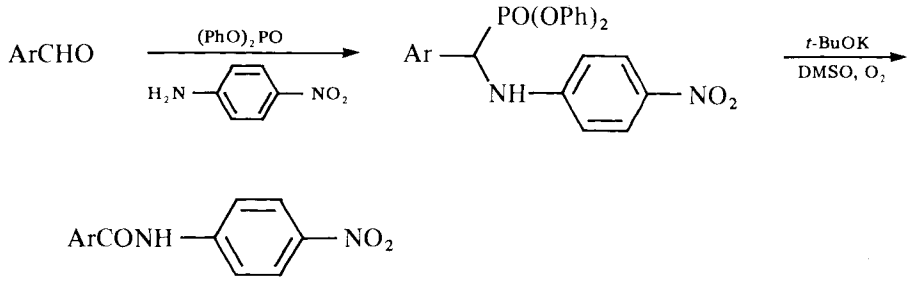
a. R = $CH(OEt)_2$
b. R = CO_2H
c. R = CO_2Me
d. R = $CONH_2$

Although there seems to be no reason for the restriction, the Cannizzaro reaction of aldehydes has only been used to any extent in the thiophene series for the formation of long-chain 5-alkoxythiophene-2-carboxylic acids[222,223] and for alkylthiothiophene-2-[224,225] and -3-carboxylic acids.[63] Yields are generally good.

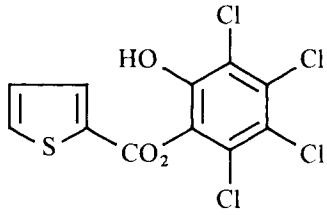
The Schmidt reaction has been employed only very infrequently for the preparation of thiophenecarboxamides. With phenyl 2-thienyl ketone the product was thiophene-2-carboxanilide, but the substituted benzamide was formed from 2,5-dimethyl-3-thienyl phenyl ketone; the change of migrating species was ascribed by the authors to steric rather than electronic factors.[226] Thienocyclohexanones give cyclic amides (see Scheme 24) on reaction with hydrazoic acid.[219,227]

A useful general method for the indirect conversion of aldehydes into amides (Scheme 26) has been applied to thiophene-2-aldehyde and to its 3- and 5-methyl homologues.[228]

Both thiophene-2- and -3-aldehyde yield the related acid chloride when reacted with chlorine in tetrachloromethane.[229] Photolysis of a mixture of thiophene-2-



Scheme 26

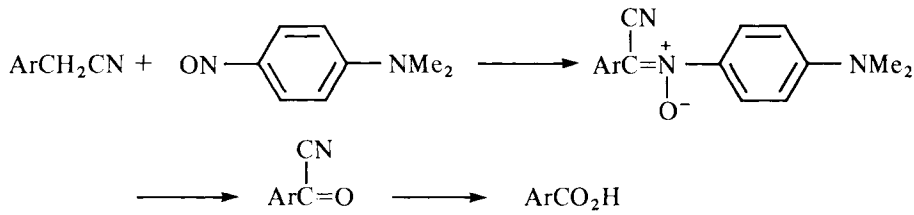


38

aldehyde and orthochloranil afforded the ester **38** (40%) in a free-radical process; no reaction took place in the dark.[230]

c. PREPARATION FROM CYANOMETHYLTHIOPHENES

Cyanomethylthiophenes are readily obtained from accessible halomethylthiophenes; they contain an active methylene group which condenses effectively with 4-nitroso-*N*,*N*-dimethylaniline. The intermediates are hydrolyzed (by way of the thenoylcyanide) to thiophenecarboxylic acids (Scheme 27).



Scheme 27

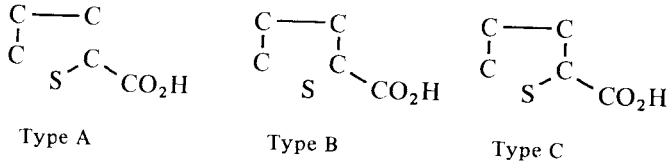
This method has been employed for the synthesis of 5-ethylthiophene-2-carboxylic acid,[73] thiophene-3-carboxylic acid,[200] and its 2,5-diethyl homologue.[231] There seems to be no reason why it should not be a success with any thiophene derivative that can be chloromethylated satisfactorily.

2. Special Methods

A description follows of various synthetic methods that are not general but that are appropriate for the individual classes of thiophenecarboxylic acid.

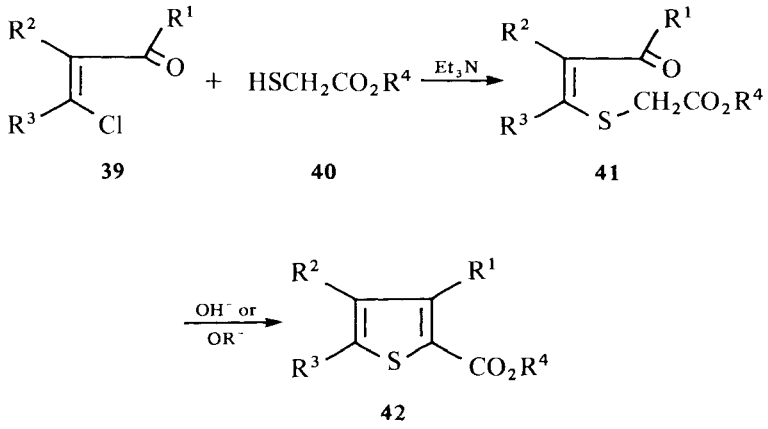
A. Alkyl- and Arylthiophene-2-Carboxylic Acids and Their Derivatives

The structural combinations that have been successful in the preparation of thiophene-2-carboxylic acids by cyclization reactions belong to one of the types A–C shown in Scheme 28.

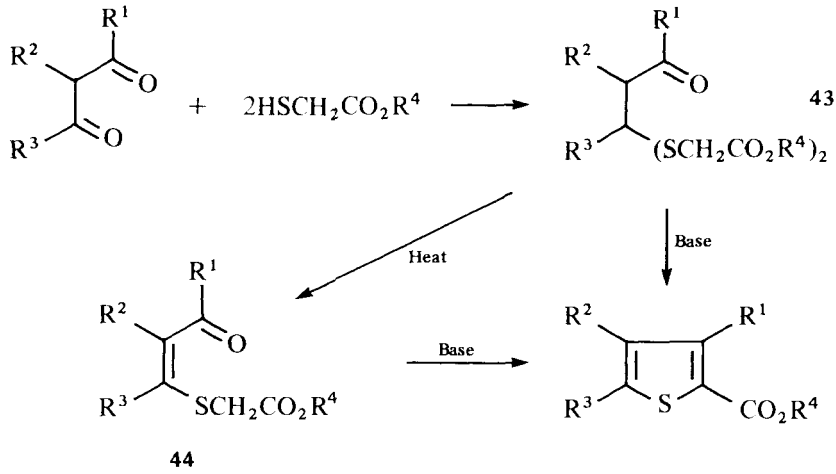


Scheme 28

i. TYPE A. This is most widely used. In the commonest variation a β-chlorovinylaldehyde or -ketone (**39**) and a derivative (generally an ester) (**40**) of thioglycolic acid are combined. In the presence of an organic base the intermediate **41** is often formed, and can be isolated; it, or the mixture of **39** and **40** yield the thiophene-2-carboxylic acid derivative **42** on treatment with alkali or alkoxide in an alcohol solvent (Scheme 29).



Scheme 29

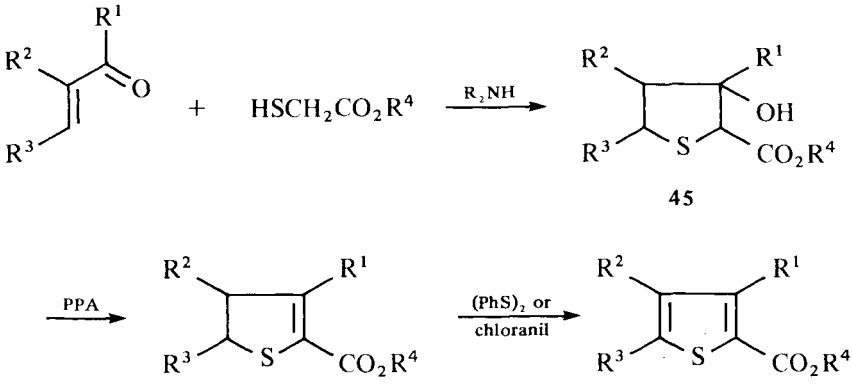


Scheme 30

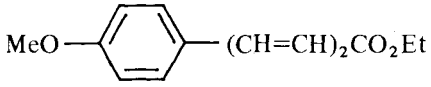
This procedure has been employed for the preparation of a very wide range of alkyl, alkyl aryl, and arylthiophene-2-carboxylic esters.[232–242]

A second variation on the Type A theme, employed by Fiesselmann[243,244] involves the formation of a mercaptole (**43**) from a 1,3-dicarbonyl compound and a thioglycolate, followed by reaction with alkoxide. It is possible to use thioglycolic acid itself in the first step, but the acid group must be esterified before cyclization. If the intermediate **43** is heated, it eliminates alkyl thioglycolate; the alkene (**44**) formed may also be cyclized by base (Scheme 30).

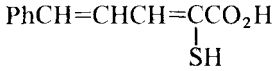
Finally, in this group are the additions of alkyl thioglycolates to $\alpha\beta$-unsaturated ketones in the presence of organic base. The tetrahydrothiophene-3-ols (**45**) so formed are dehydrated with polyphosphoric acid, and thiophene formation is completed by dehydrogenation (Scheme 31).



Scheme 31



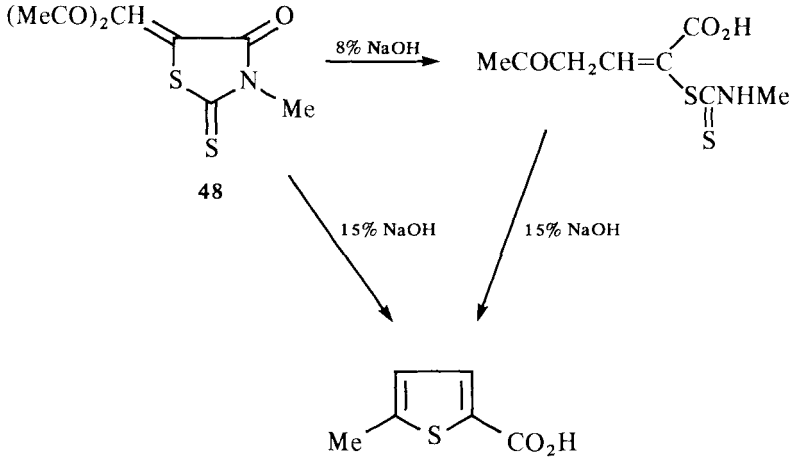
46



47

Yields are usually good, and the route has been applied by Tilak and his co-workers to the preparation of numerous alkyl and arylthiophene-2-carboxylic acid derivatives.[245,246]

ii. TYPES B AND C. Neither of these lines has been much used. A very minor part of the product of the reaction of **46** with sulfur was the 5-arylthiophene-2-carboxylate;[247] 5-phenylbutdiynoic acid gave a fair yield (52%) of 5-phenylthiophene-2-carboxylic acid with hydrogen sulfide.[154] The latter acid was also obtained by oxidative cyclization of 2-mercapto-5-phenylbut-2,4-dienoic acid (**47**).[241,248] An intermediate with the configuration of atoms of a Type C cyclization is involved in the formation of 5-methylthiothiophene-2-carboxylic acid from the rhodanine **48**[249] (Scheme 32).

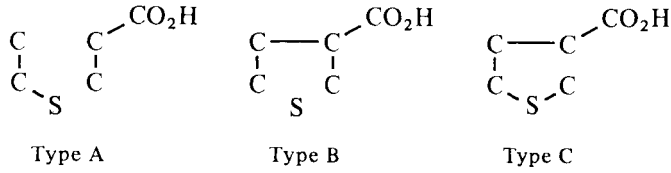


Scheme 32

B. Alkyl- and Arylthiophene-3-Carboxylic Acids and Their Derivatives

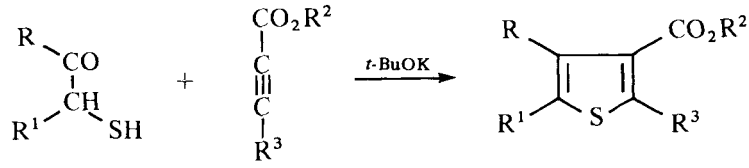
a. CYCLIZATION REACTIONS

Of the various structural subunits that could lead to thiophene-3-carboxylic acids, only those depicted in Scheme 33 have been employed.



Scheme 33

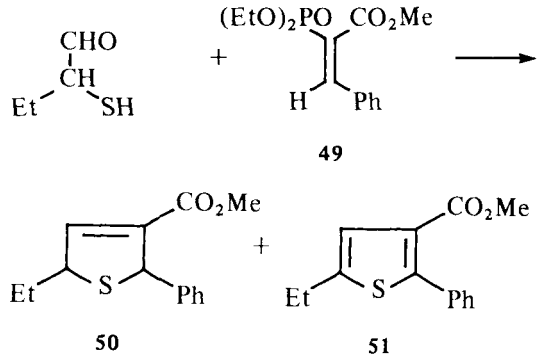
i. TYPE A. The most widely used variation here is the sequence: Michael addition–cyclization of an α-mercaptoaldehyde or -ketone with an acetylenic ester, under the influence of a catalytic quantity of sodium or potassium *t*-butoxide (Scheme 34).



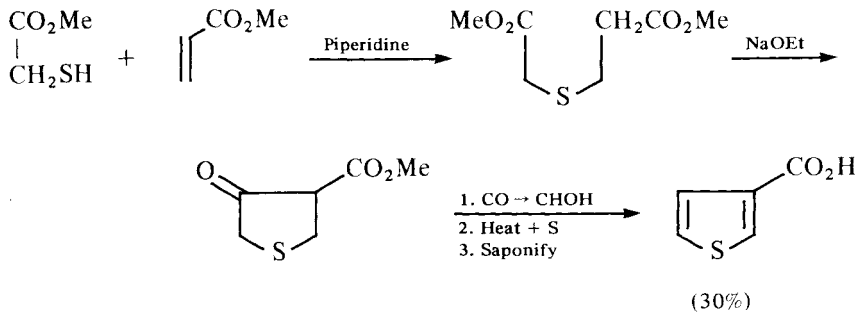
Scheme 34

In the case where R = Me, $R^1 = R^3 = H$, the thiophene (43%) was accompanied by the uncyclized Michael adduct (43% E, 13% Z isomers); further, it was found in this particular case that an equimolar amount of alkoxide gave 2-acetyl-3-hydroxythiophene rather than the ester.[250] This synthesis has been used to prepare a range of alkyl 2-aryl-4-methylthiophene-2-carboxylates.[207,250]

The condensation of vinylphosphonates (e.g., **49**) and α-mercaptoaldehydes or -ketones gave the 2,5-dihydrothiophenes (e.g., **50**) together with the thiophene (e.g., **51**) as by-product (Scheme 35); the identity of **51** was confirmed by synthesis



Scheme 35

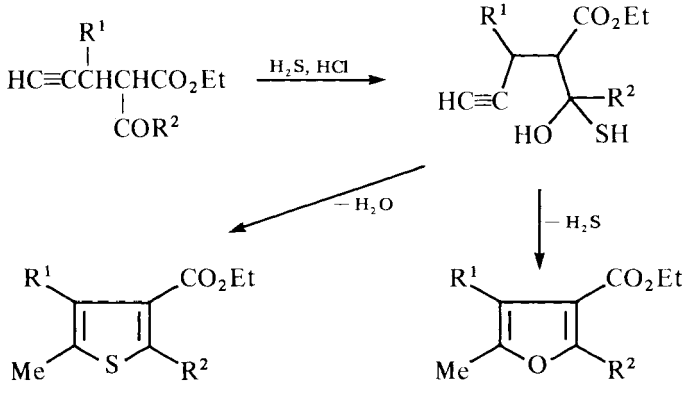


Scheme 36

from 2-mercaptobutyraldehyde and methyl phenylpropiolate.[251] It is suggested that aerial oxidation had taken place to some extent; since 2,5-dihydrothiophenes are readily aromatized, this is a potentially useful general synthesis.

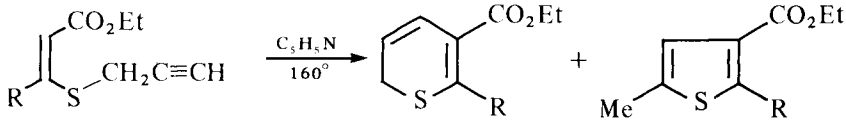
The ($C_2 + C_2S$) combination is also utilized in the reaction sequence shown in Scheme 36.[251] Although the synthesis has several stages, it has the advantage of cheap, readily available starting materials. In addition, the intermediate methyl 4-oxotetrahydrothiophene-3-carboxylate is a particularly versatile one.

ii. TYPE B. One of the very earliest synthetic methods for thiophenes (the Paal synthesis) in which a 1,4-dicarbonyl compound is heated with phosphorus pentasulfide has been used in recent times to prepare ethyl 5-benzylthiophene-3-carboxylate; the product was accompanied by approximately 10% of the thiono-ester.[252] The same starting materials give thiophenes, under much less drastic conditions, on reaction with hydrogen sulfide in ethanol. Duus[253] has used this approach to prepare a number of alkyl and arylthiophene-3-carboxylates, in reasonable yields (46 to 73%). In each case the thiophene was accompanied by 5 to 20% of the 4,5-dihydro derivative. It seems probable that the cyclization step



Scheme 37

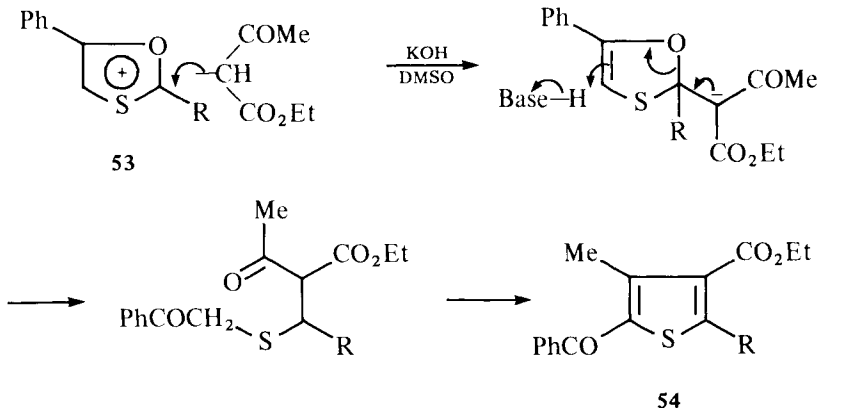
in this reaction entails attack on one carbonyl group by a thioketal or hemiketal formed from the other. A similar process must be involved in the reaction shown in Scheme 37,[254,255] with the difference that the cyclization requires nucleophilic attack on a protonated acetylene. The nucleophile is mostly SH, since the thiophene is the major product.



52 a. R = Me
b. R = Ph

Scheme 38

iii. TYPE C. The reaction of vinylmercaptans, first with base, then with crotyl, allyl, or propargyl halides gave both E and Z isomers of the *S*-alkylation product. When the allyl derivatives (**52a, b**) were heated in pyridine the principal products were the thiopyrans, but small amounts (*ca.* 8%) of the thiophenes were also formed[256] (Scheme 38). The Type C arrangement of atoms is also likely to be involved in the reaction of the thiolium salt **53** (R = substituted indolyl) with the anion of ethyl acetoacetate.[257] A possible mechanism for the formation of the thiophene **54** is presented in Scheme 39.



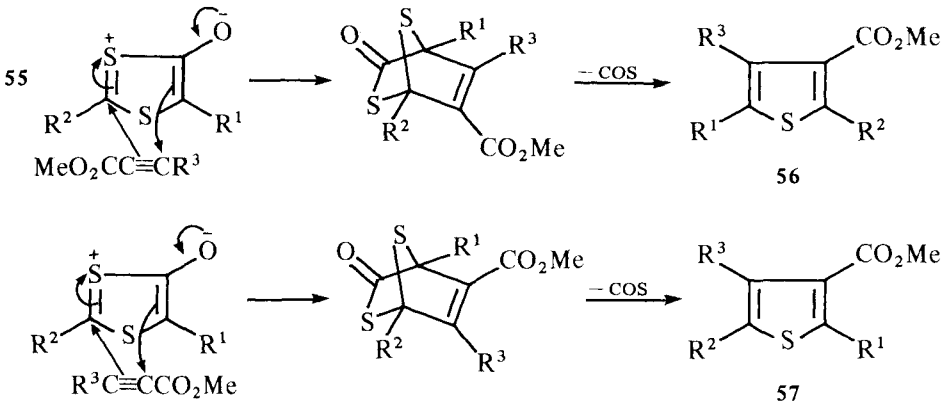
53

54

Scheme 39

b. CYCLOADDITION-EXTRUSION REACTIONS

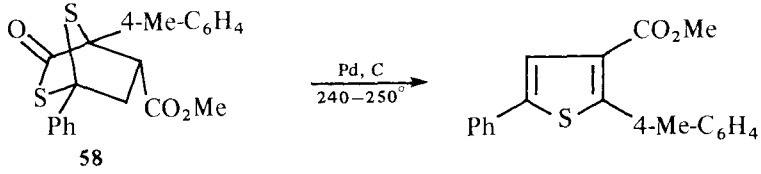
A much more common use of mesoionic intermediates with 1-*S*,3-heteroatoms in the synthesis of thiophenecarboxylic acids is by means of their reaction with dipolarophiles.



Scheme 40

When the dipolarophile is a propiolate, the initial bicyclic adducts extrude a stable fragment to give a thiophene-3-carboxylic acid; when it is a dialkyl acetylene-dicarboxylate, the product is a thiophene-3,4-dicarboxylate. For the monoacids, 1,3-dithiolium salts (**55**) have been used; the reaction sequence can be conveniently represented as in Scheme 40.

The reaction always proceeds in high yield, but only in the cases where a single product is possible is it an uncomplicated synthesis. This is so when $R^1 = R^2 = Ph$, $R^3 = H$[258–260] and when $R^1 = R^2 = R^3 = Ph$.[258,259] When R^1 and R^2 are not the same, the possibility exists of two orientations in the addition. This has been studied in detail by Gotthardt and Weisshuhn;[261] it was found that mixtures of **56** and **57** were obtained from thiolium salts bearing various substituents R^1 and R^2 in their reactions with any of three propialates (R^1 = H, Me, Ph). The addition was apparently regiospecific when methyl acrylate was added to the salt **55** (R^1 = Ph, R^2 = 4-Me-C_6H_4).[262] In this case the adduct (**58**) required dehydrogenation as well as loss of carbonyl sulfide to give the thiophene-3-carboxylate (Scheme 41).

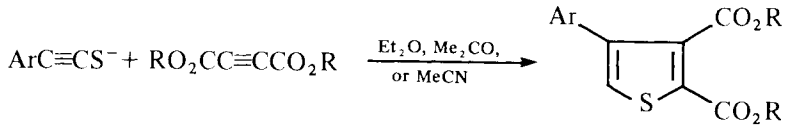


Scheme 41

C. *Thiophenepolycarboxylic Acids and Their Derivatives*

a. THIOPHENE-2,3-DICARBOXYLIC ACIDS

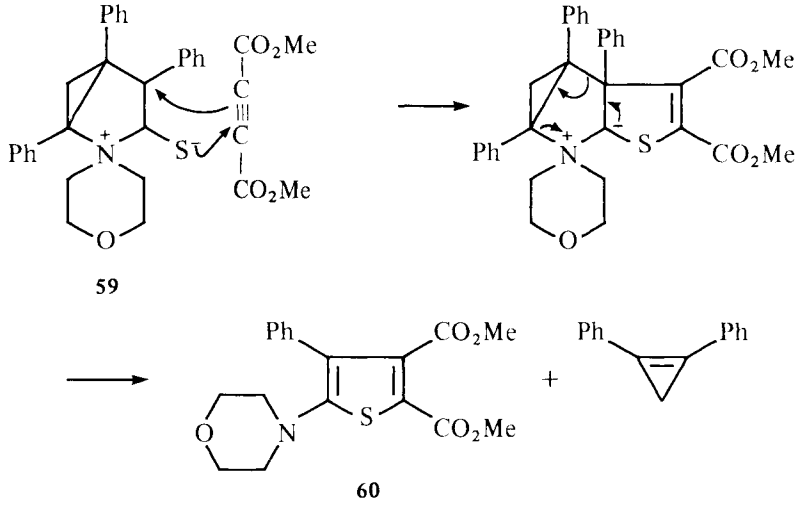
A miscellany of ring syntheses has been used for these acids. In one group the ($C_2 + C_2S$) strategy is used; the simplest employs an arylalkynthiolate and a dialkyl



Scheme 42

acetylene dicarboxylate in the presence of a proton donor of suitable pK_a – acetone and acetonitrile have both been found to be satisfactory[263,264] (Scheme 42).

A complex variation on the (C_2 + C_2S) theme is shown in Scheme 43;[265,266] the *N*-spirodipolar species **59**, formed from diphenylcyclopropenethione and the morpholine enamine of acetophenone, undergoes a cycloaddition with dimethyl acetylenedicarboxylate (DMAD). Elimination of 1,2-diphenylcyclopropene then gives the thiophene (**60**).



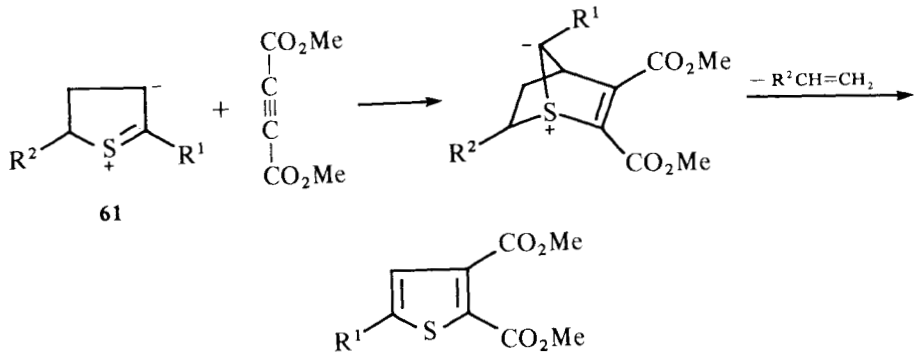
Scheme 43

A [2 + 3] cycloaddition-alkene extrusion process is at the heart of a preparation of the thiophene-2,3-dicarboxylic acid derivatives **62** from the dihydrothiophenes **61** (R^1 = H, Me; R^2 = H, *i*-Pr)[267] (Scheme 44).

Dithiins can undergo extrusion of sulfur to yield thiophenes. It seems likely that a 1,2-dithiin intermediate is involved in the reaction shown in Scheme 45.[268,269]

Nickel polysulphide, NiS_x, reacts with diphenylacetylene to give a square planar Ni(II) complex, **63**. On treatment with dialkyl acetylenedicarboxylates the latter gives a very good yield (80%) of the dialkyl 4,5-diphenylthiophene-2,3-dicarboxylate.[270,271] Once again, a dithiin is probably an intermediate (Scheme 46).

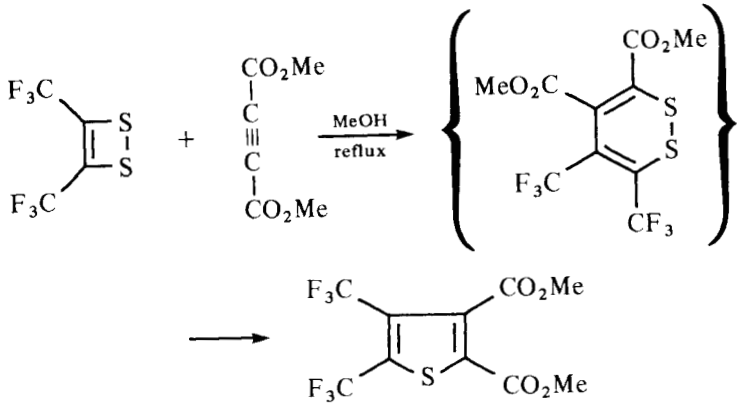
Related to this is the isolation, in poor yield, of dimethyl 4-phenylthiophene-



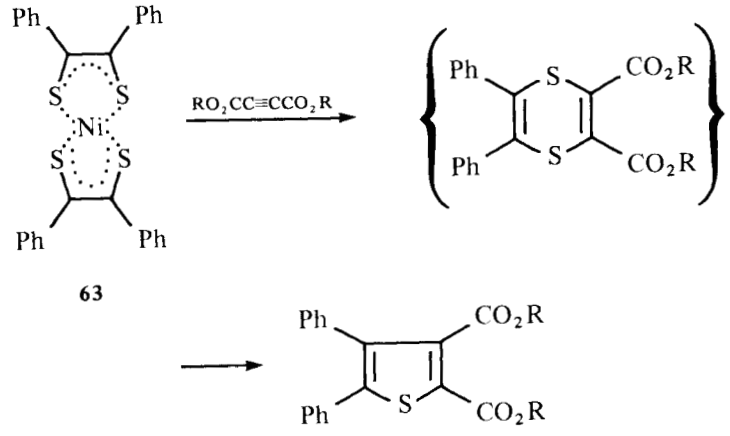
61

62

Scheme 44

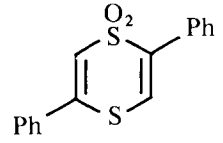


Scheme 45

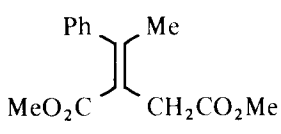


63

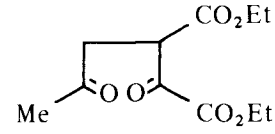
Scheme 46



64



65



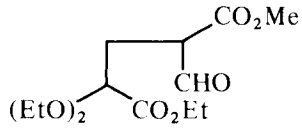
66

2,3-dicarboxylate from thermolysis (in boiling dichlorobenzene) of the thiin sulphone **64** in the presence of DMAD.[272]

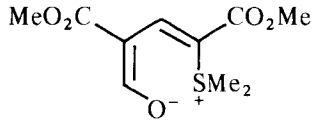
The same product was obtained when the alkene **65** was heated with sulfur;[272] this, and the preparation of 5-methylthiophene-2,3-dicarboxylic acid from the diketone **66** and sulfur,[273] are rare examples of the application of the (C_4 + S) approach to thiophene-2,3-dicarboxylic acids.

b. THIOPHENE-2,4-DICARBOXYLIC ACIDS

These diacids are rather less accessible than their isomers through cyclization reactions. The Paal synthesis has been applied by Jones[274] to the keto aldehyde ketal **67**; the overall yield of thiophene-2,4-dicarboxylic acid was very low. In a more direct approach methyl acrylate was heated at 150 to 200° with sulfur.[180,275]

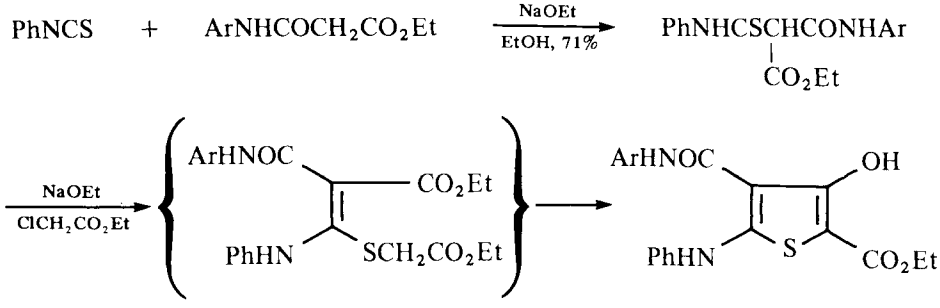


67



68

Although this resulted in a mixture of dimethyl thiophene-2,4- and -2,5-dicarboxylates (separated by chromatography), the route has some attraction in view of the simple nature of the starting material. Also utilizing the (2 x C_2 + S) theme is the combination of methyl propiolate with dimethyl sulphoxide, giving a moderate yield of the zwitterionic species **68**; this, when treated with thionyl chloride, was



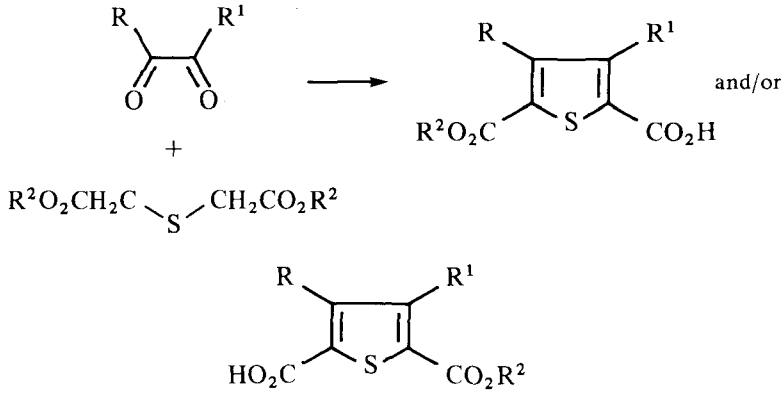
Scheme 47

efficiently converted (91%) into dimethyl thiophene-2,4-dicarboxylate.[276] The conventional sequence of reactions shown in Scheme 47 (Ar = 4-MeO–C_6H_4) is a possible approach to quite a variety of fully substituted thiophene-2,4-dicarboxylic acid derivatives.[277]

The extrusion of sulfur from dithiins has already been mentioned in connection with the preparation of 2,3-diacids; excellent yields of 3,5-diarylthiophene-2,4-dicarboxylates are obtained similarly by the thermolysis of dialkyl 3,6-diaryl-1,4-dithiin-2,5-dicarboxylates.[278,279]

c. THIOPHENE-2,5-DICARBOXYLIC ACIDS

i. CYCLIZATION REACTIONS. The long-established Hinsberg synthesis has been the most used of the various cyclization reactions leading to thiophene-2,5-dicarboxylic acids. The mechanism of the reaction has been studied,[280,281] and it is established that the initial product is a half-ester (Scheme 48). This had

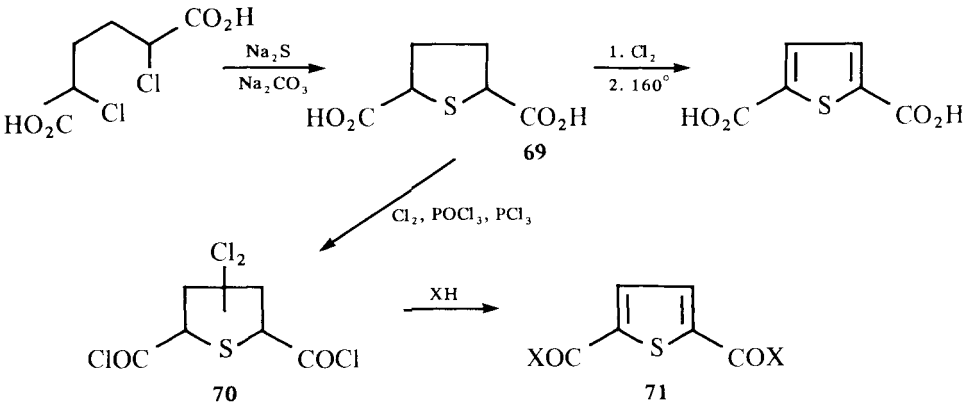


Scheme 48

been overlooked in the past because the usual work-up procedure includes total saponification.

The reaction has been applied to dialkyl diketones,[282–284] diaryl diketones,[285–287] phenylglyoxal,[288] and to some pyruvic acids.[289] The agents used are normally sodium ethoxide-ethanol or potassium *t*-butoxide-*t*-butyl alcohol, but there has been at least one report of the use of the anion of dimethyl sulfoxide.[284]

When 2,5-dichlorohexandioic acid is treated with sodium sulphide–sodium carbonate, the tetrahydrothiophene-2,5-dicarboxylic acid **69** is obtained. Chlorine converts **69** into a dichloro compound which, on heating at approximately 160°, eliminates hydrogen chloride to give thiophene-2,5-dicarboxylic acid.[290,291] In the presence of phosphoryl chloride–phosphorus trichloride the chlorination gives **70**; this yields the diester **71** (X = OMe), the diacid **71**, (X = OH) or the dianilide **71**



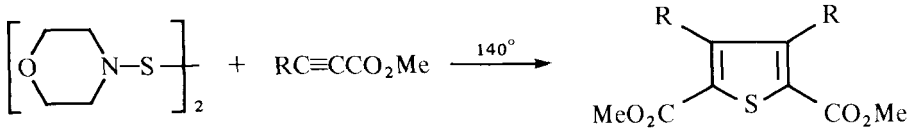
Scheme 49

(X = NHPh) on treatment with methanol, hydrochloric acid, and aniline, respectively[292,293] (Scheme 49).

In a variation, the dimethyl ester of 2,5-dichlorohexandioic acid is cyclized; the chlorination-thermolysis process then gave **71** (X = OMe). This synthesis was carried right through from adipic acid without isolation of any of the intermediates.[294]

A process described in patents[295,296] also uses dialkyl 2,5-dichlorohexandioates for the production of **71** (X = OMe, OPr); the diesters are heated with sulfur in boiling trichlorobenzene until the calculated amount of hydrogen sulfide is evolved.

A remarkably convenient preparation of thiophene-2,5-dicarboxylic acid (by means of the acid chloride) by heating adipic acid with thionyl chloride, has been described.[297,298] Methyl arylpropiolates combine in a head-to-head manner when heated with sulfur in a solvent, to give modest yields of dimethyl 3,4-diarylthiophene-2,5-dicarboxylates, together with 2,4-diarylthiophenes.[299] The intervention of thioketocarbene intermediates is proposed in the reaction of propiolates and the bismorpholino disulfide **72**[300] (Scheme 50).

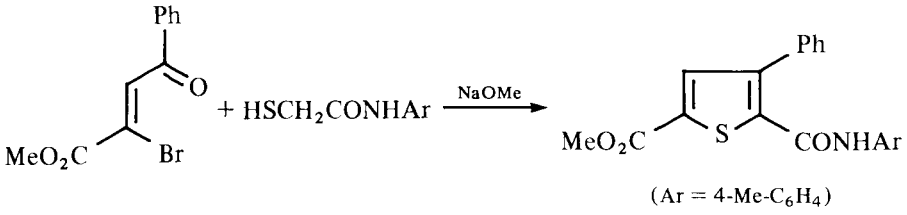


72

R = H, 48%
R = Ph, 67%

Scheme 50

Finally, the β-halogenovinylketone synthesis, so useful for thiophene-2-carboxylic acids, can be adapted to prepare derivatives of the 2,5-dicarboxylic acids. An advantage of the route is that products with different carboxyl functions can be obtained (Scheme 51 illustrates this point).[232]



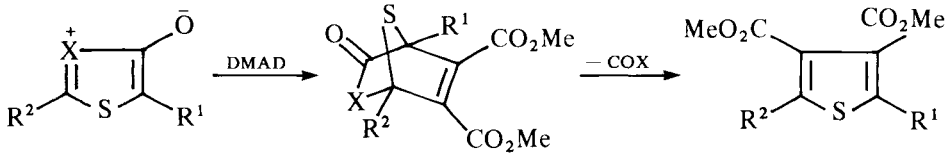
Scheme 51

ii. CARBOXYLATION OF POTASSIUM THIOPHENE-2-CARBOXYLATE AND RELATED PROCESSES. When a mixture of potassium thiophene-2-carboxylate, potassium carbonate, and a catalyst composed of a zinc or cadmium salt is treated with carbon dioxide under rather extreme conditions, thiophene-2,5-dicarboxylic acid is produced, generally in low yield.[301-306] The same product is obtained when 2-thienylmercury chloride is treated in similar fashion.[307] The disproportionation of alkali metal thiophene-2-carboxylates into thiophene and thiophene-2,5-dicarboxylates can be achieved at high temperatures in the presence of cadmium catalysts. On the basis of studies of mixed transcarboxylations, aided by use of labeled compounds, it has been concluded that the reaction proceeds by an intermolecular, ionic mechanism.[308] In another study[309] it was shown that the potassium salt gave twice the yield that was obtained from the sodium salt, and in yet another[310] it was found that addition of aluminum chloride to the cadmium oxide catalyst had a beneficial effect on the yield (which rose from 78 to over 90%).

d. THIOPHENE-3,4-DICARBOXYLIC ACIDS

i. CYCLOADDITION-EXTRUSION REACTIONS. The [3 + 2] cycloaddition of a suitably substituted mesoionic species to DMAD, followed by extrusion of a stable fragment has been used on numerous occasions to prepare esters of thiophene-3,4-dicarboxylic acids. Most of the reactions have a common form, which can be represented as in Scheme 52. A survey of preparations of this type is given in Table 1.

Dipolarophiles other than DMAD can give adducts with these mesoionic



Scheme 52

TABLE 1. PREPARATION OF THIOPHENE-3,4-DICARBOXYLATES BY CYCLIZATION-EXTRUSION (SCHEME 52)

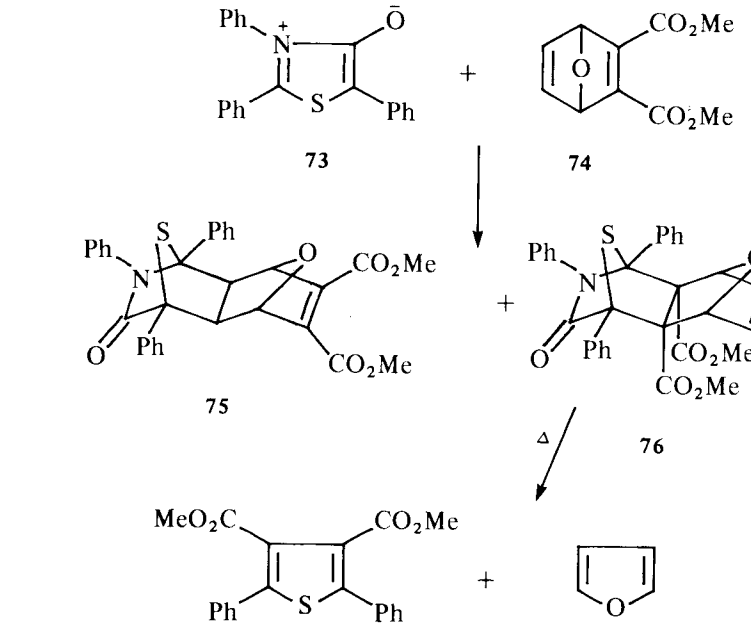
X	R^1	R^2	References
NH	4-Cl—C_6H_4	Ph	311
	4-MeO—C_6H_4	Ph	311
	4-NO_2—C_6H_4	Ph	311
NPh	Ph	Ph	312–314
	Ph	4-MeO—C_6H_4	315
O	Ph	Ph	316, 317
	Ph	4-MeO—C_6H_4	317
	SMe	Ph	316
	SEt	Ph	316
	S-*n*-Bu	Ph	316
	NMe_2	Ph	316
S	H	Ph	318, 319
	Me	Ph	258, 259
	H	4-MeO—C_6H_4	318, 319
	H	4-Cl—C_6H_4	319
	Ph	Ph	258, 259
	Ph	4-Me—C_6H_4	258, 259
	4-Me—C_6H_4	Ph	259
	Ph	4-MeO—C_6H_4	258, 259
	4-MeO—C_6H_4	Ph	259
	Ph	4-Br—C_6H_4	259
	4-Br—C_6H_4	Ph	259
	Ph	4-Me_2N—C_6H_4	259
	4-NO_2—C_6H_4	Ph	259
	Ph	1-Pyrrolidyl	320
	Ph	1-Piperidyl	320
	Ph	1-Morpholyl	320
	Ph	SEt	321, 322
	Ph	$SCH_2CH{=}CH_2$	321, 322

substances. In the interesting reactions shown in Scheme 53 the azathiolium compound **73** and the 1,4-oxidocyclohexadiene **74** gave approximately equal amounts of the alternative addition products **75** and **76**; only the latter was unstable in refluxing toluene, giving furan and dimethyl 2,5-diphenylthiophene-3,4-dicarboxylate.[323,324]

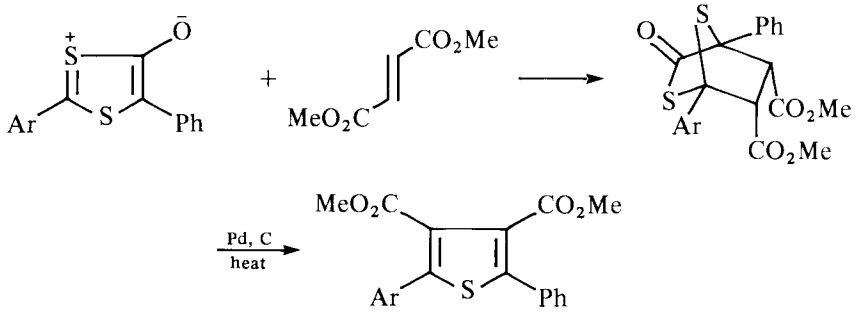
Dimethyl fumarate will also react with mesoionic species of the types just discussed; in this case the adduct is in too low an oxidation state to give a thiophene, but the extrusion process takes place in the usual way under dehydrogenation conditions[325] (Scheme 54; Ar = Ph, 4-MeO–C_6H_4).

ii. OTHER METHODS. Low overall yields of thiophene-3,4-dicarboxylic acid have been obtained by the phosphorus pentasulphide treatment of dimethyl or diethyl 2,3-diformylsuccinates[326,327] or of the mono diethylacetal of the latter ester.[178]

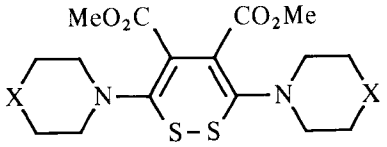
An intriguing partial desulfurization of the 1,2-dithiins **77a**[328] and **77b**[329] with



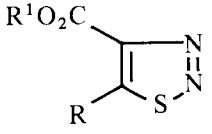
Scheme 53



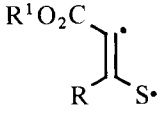
Scheme 54



77 a. X = CH_2
b. X = O



78



79

a. R = Ph, R^1 = Me
b R = H, R^1 = Et
c. R = Me, R^1 = Et

degassed Raney nickel, or copper powder in diglyme, led to the corresponding 2,5-diaminothiophene-3,4-dicarboxylates. Photolysis of the 1,2,3-thiadiazoles **78a**,[330] **78b**, and **78c**[331] gave the 2,5-di-R-thiophene-3,4-dicarboxylates (in low yields) by means of head-to-head union of the diradicals **79a–c**, followed by loss of sulfur.

In a study of the oxidation of 3,4-disubstituted-2,5- and 4,5-dihydrothiophenes by 30% hydrogen peroxide–acetic acid, Takaya et al.[332] found that the product was the thiophene if both substituents at C-3 and C-4 were electron withdrawing. Excellent yields of 3,4-dicarboxy- and 3-cyano-4-carboxythiophenes were obtained by this means. With groups of other character, or when perbenzoic acid was the oxidant, the dihydrothiophene sulfone was formed. The same workers also found that iodosobenzene was equally effective in oxidizing the dihydrocompounds to thiophenes.[333]

e. THIOPHENETRICARBOXYLIC ACIDS

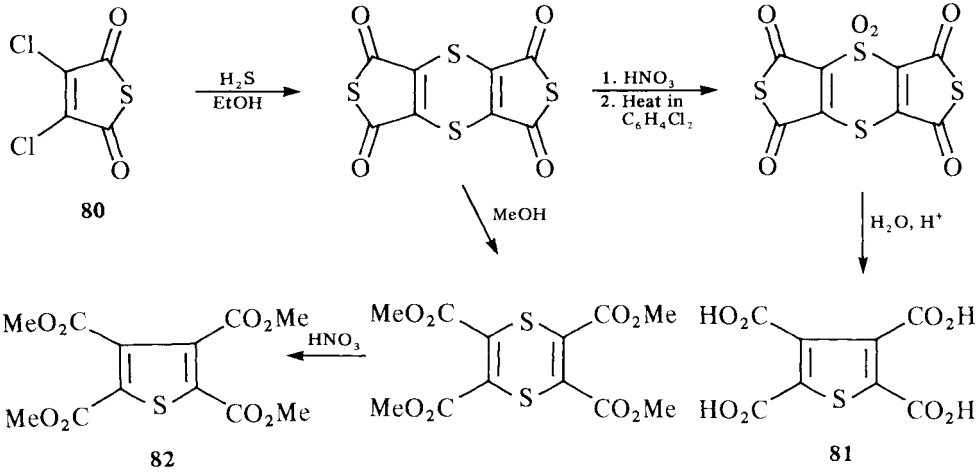
Thiophene-2,3,4- and 2,3,5-tricarboxylic acids have been made by the Paal synthesis from appropriate 1,4-dicarbonyl triesters.[334] The synthesis of the starting materials was not easy, and the overall yields of the thiophene acids were low.

f. THIOPHENETETRACARBOXYLIC ACID

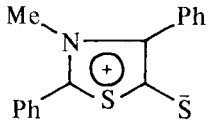
Among the simplest syntheses of tetramethyl thiophenetetracarboxylate is that in which dimethyl maleate (or fumarate) is heated with sulfur at 150 to 200°C.[180,275]

Vigorous oxidation of tetrachlorothiophene gives the anhydride **80**, which has been used as the starting point for the synthesis of the tetracarboxylic acid (**81**) and its tetramethyl ester (**82**)[335,336] (Scheme 55).

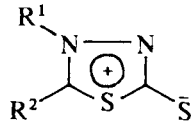
The tetracarboxylic acid has also been prepared in excellent yields by hydrolysis (with concentrated hydrochloric acid) of 2,3,5,6-tetracyano-1,4-dithiin.[337] Yields



Scheme 55



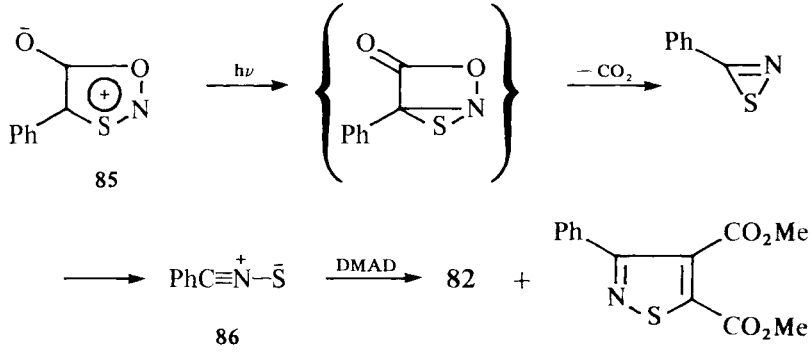
83



84

of **82** of the order of 30% have been obtained when the mesoionic species **83**[338] or **84** (R^1 and R^2 were aryl groups)[339] were heated with DMAD. In the second case the proposed mechanism involved fragmentation of the thiadiazole ring and not cycloaddition to it.

Photolysis of the oxathiazolone **85** gave a mixture of carbon dioxide, sulfur, and benzonitrile. An intermediate, **86**, could be trapped by DMAD, and one of the products was **82**[340] (Scheme 56).

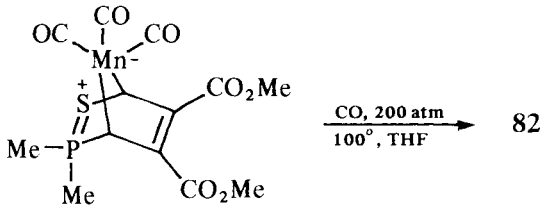


85

86

Scheme 56

If the propiolate in Scheme 50 is replaced by DMAD, the reaction gives a moderate yield (38%) of **82**.[300] This ester is also obtained from DMAD in a high-pressure process in which the alkyne is reacted with carbon monoxide in the presence of a manganese–phosphorus–sulfur catalyst; the complex bicyclic structure **87** is an intermediate[341] (Scheme 57).



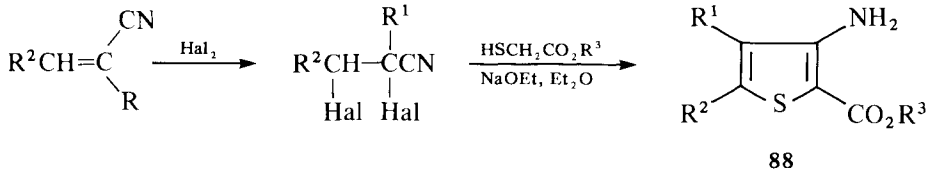
87

Scheme 57

D. *Aminothiophenecarboxylic Acids and Their Derivatives*

a. 3-AMINOTHIOPHENE-2-CARBOXYLIC ACIDS

The synthesis developed by Fiesselmann,[342-344] in which an $\alpha\beta$-dihalogenonitrile is reacted with an alkyl thioglycolate in the presence of base (Scheme 58), provides a simple and attractive route to the stable aminothiophene derivatives **88**.

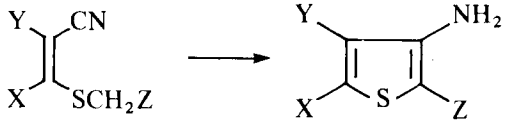


88

Scheme 58

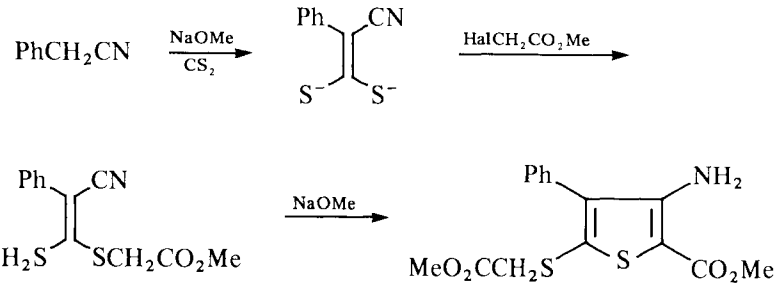
Details of esters that have been made by this route are available in Tables of Compounds 63–67. The cheap 2-chloroacrylonitrile is a very useful alternative to the 2,3-dichloropropionitrile required in the Fiesselmann synthesis of **88** ($R^1 = R^2 = H$), and gives a better yield.[345]

There is a very large group of cyclization reactions leading to thiophenes in which the basic elements of Scheme 59 can be recognized.



89

Scheme 59

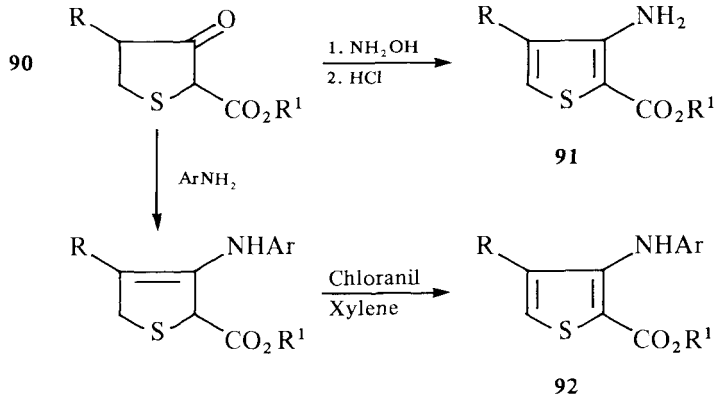


Scheme 60

Although the principle has been applied to numerous combinations of X, Y, and Z, in only a few have X or Y not also been a carboxyl (or cyano) group. Scheme 60[346] shows some typical features of the method.

A rather unusually substituted thiophene was obtained by cyclization of **89** in which X = Me, Y = $PO(OEt)_2$, and Z = COMe.[347]

Oxo esters of general structure **90** are readily available through Dieckmann cyclizations and have been used to a limited extent for the preparation of 3-aminothiophene-2-carboxylates. A low yield of **91** was obtained by oximation of **90** (R = H);[348] 3-arylaminothiophene-2-carboxylates (**92**, R = H, Me) are available through the sequence shown in Scheme 61.[349]

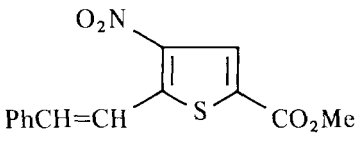


Scheme 61

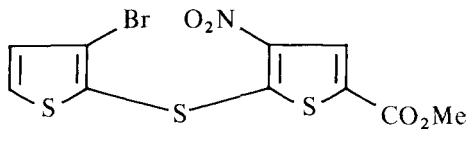
3-Aminothiophene-2-carboxylic acid has been made by reduction of the 3-azido compound with hydrogen sulfide.[350]

b. 4-AMINOTHIOPHENE-2-CARBOXYLIC ACIDS

With the exception of 5-aminothiophene-3-carboxylic acids, 4-aminothiophene carboxylic acids are the least studied of the class. This is a reflection of their inaccessibility. There is no convenient cyclization reaction for them, and the only method that has been used to any extent is the reduction of nitrocompounds made by nitration of 5-substituted thiophene-2-carboxylic acids and their derivatives. A variety of reducing agents has been used. Tin–hydrochloric acid was apparently selective for the nitro group in **93**[351] and in **94**,[352] in spite of the presence of other

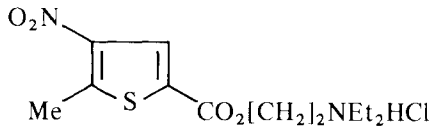


93



94

vulnerable groups. The combination Raney nickel–acetic anhydride gave poor yields of the 4-acetylamino compounds from 4-nitrothiophene-2-carboxylic[353] and 5-alkyl-4-nitrothiophene-2-carboxylic acids.[186] Aluminum flake was effective with methyl 4-nitrothiophene-2-carboxylate,[92] and **95** was reduced catalytically, under pressure. In a rare approach to compounds in this class the oximes of the ketones **96** (R = Me, CH_2Ph) were subjected to the Beckmann rearrangement; the acetylaminothiophenes gave the primary amines when treated with boron trifluoride-methanol.[354]



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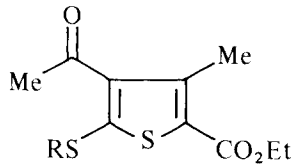
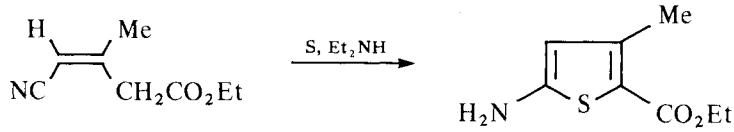


96

c. 5-AMINOTHIOPHENE-2-CARBOXYLIC ACIDS

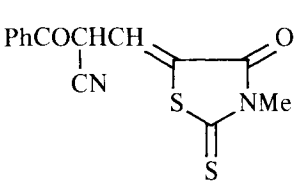
As is the case for their 4-amino counterparts, these aminothiophene acids have most often been obtained by reduction of the nitrothiophene. Aluminum,[355] aluminum amalgam,[183,356] tin(II) chloride–hydrochloric acid,[357] and zinc–hydrochloric acid–methanol[124] have all been used to reduce alkyl 5-nitrothiophene-2-carboxylates. The Raney nickel–acetic anhydride method gave a very much better yield with 5-nitrothiophene-2-carboxylic acid than it did with the 4-nitro isomer;[353] this may reflect greater stability of the 5-amino acid, due to the possibility (not available in the 4-amino compound) of mesomeric interaction between the amino and carboxyl groups. Very few ring-closure syntheses of 5-aminothiophene-2-carboxylic acids have been reported. Thiolation α- to the ester group must take place in the interesting reaction shown in Scheme 62.[358]



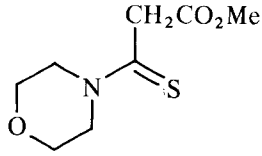
Scheme 62

Hydrolysis of the rhodanine **97** gave a fair yield (53%) of 5-amino-4-benzoylthiophene-2-carboxylic acid; replacement of the benzoyl group in **97** by ethoxycarboxyl gave 5-aminothiophene-2,4-dicarboxylic acid after hydrolysis.[249]

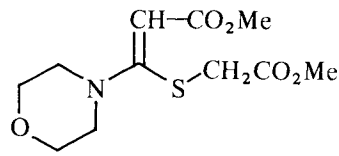
When the half-thioamide–half-ester **98** was treated with sodium hydride–ethyl chloracetate it was converted into the *S*-alkylated substance **99**; further base treatment induced cyclization to ethyl 3-hydroxy-5-(1-morpholino) thiophene-2-carboxylate.[359]



97



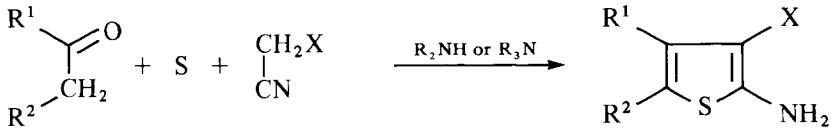
98



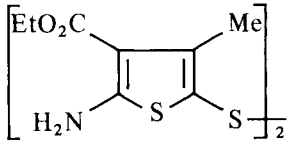
99

d. 2-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS

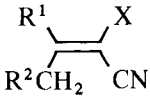
The chemistry of this group of aminothiophenecarboxylic acids has received much attention; this is almost entirely owing to their ready availability through the simple and versatile synthesis introduced by Gewald.[360–363] The components are an aldehyde or ketone with an α-methylene group, a compound of the type XCH_2CN (X is a carboxylic function or a cyano group), and sulfur. In the simplest version the reactants are heated together in ethanol or dimethyliformamide (DMF) in the presence of an organic base (Scheme 63). A complication was noted when acetone was reacted with ethyl cyanoacetate; the product was the disulphide **100** and not ethyl 2-amino-4-methylthiophene-3-carboxylate.[363] Most other methyl ketones give the expected 2-amino-4-substituted derivatives with a free 5-position.



Scheme 63

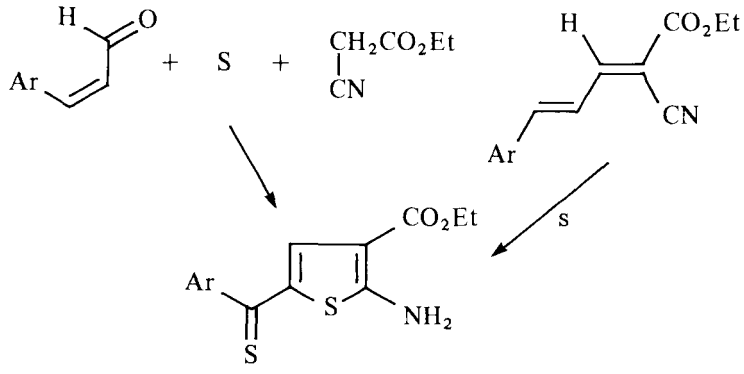


100



101

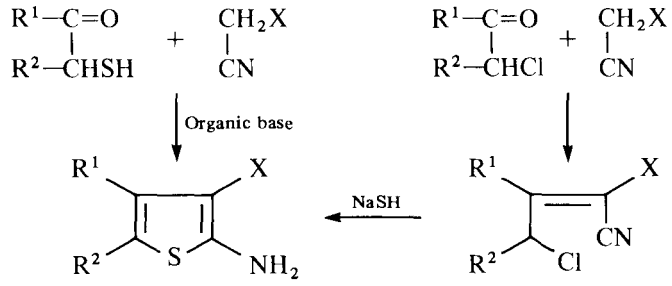
A variation of the synthesis involves the prior condensation of the aldehyde or ketone with the appropriate cyanomethylene compound, usually under the influence of sodium or ammonium acetate. The alkylidene derivative (**101**) is then treated with sulfur and an organic base to complete the 2-aminothiophene preparation.



Scheme 64

Reactions with some of the characteristics of these two syntheses are shown in Scheme 64 (Ar = phenyl and substituted phenyl); here an $\alpha\beta$-unsaturated aldehyde was used in place of the usual carbonyl component.[364,365]

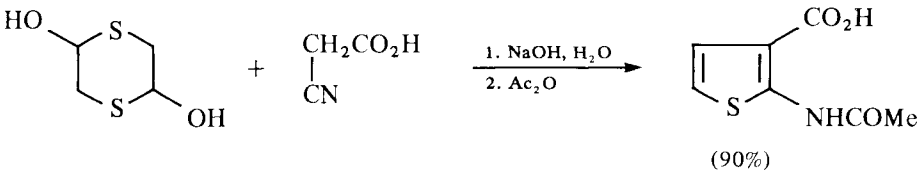
Enamines can replace both aldehydes[366–368] and ketones[369] in the Gewald synthesis. Ketimines have also been employed in place of ketones.[370] Another variation, introduced by Gewald[362] and used by many others, employs an α-mercaptoketone instead of the ketone and sulfur; in a very closely related approach an α-chloroketone is used, and the alkylidene derivative is reacted with sodium hydrosulfide. These syntheses are illustrated in Scheme 65.



Scheme 65

The simplest compounds in the series, that is, those in which $R^1 = R^2 = H$, are made from the mercaptoacetaldehyde dimer. Generally in this context it is esters,[348,371,372] or amides[373,374] that have been made, but it is also possible to obtain a free acid,[375] (Scheme 66).

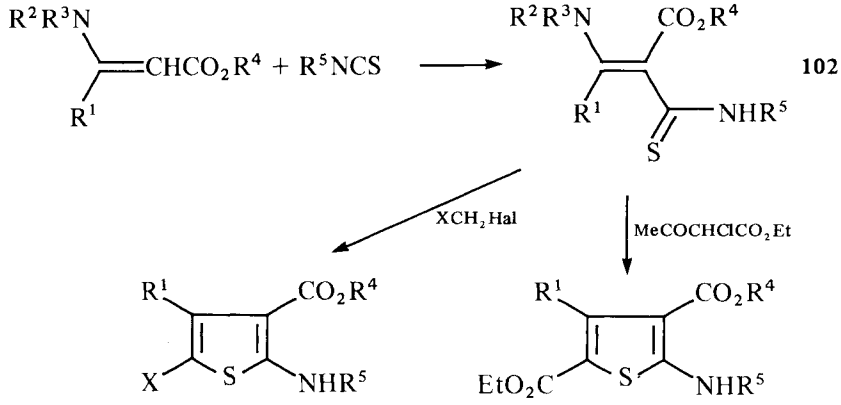
A very large number of variously substituted 2-amino-3-cyanothiophenes and 2-aminothiophene-3-carboxylic acid derivatives have been prepared by one or other



Scheme 66

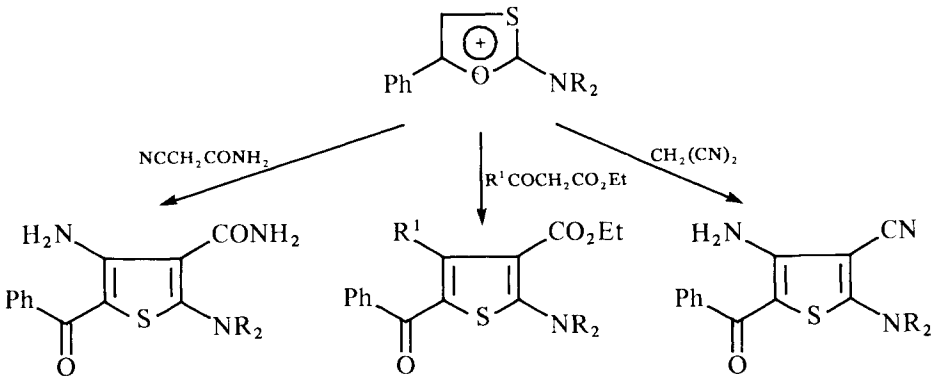
of the foregoing methods; details of many of these substances are to be found in the Tables of Compounds.

The enamines of β-keto esters form the starting point for a versatile synthesis of 2-aminothiophene-3-carboxylic acid derivatives developed by Rajappa and co-workers; the general reaction sequence is outlined in Scheme 67. The group X is electron-attracting, for example, benzoyl[376,377] or nitro,[378] and R^5 can be an alkyl, an aryl, or an acyl group. Note that reaction of the initial adduct **102** with an α-chloro-β-keto ester gives a thiophene-2,4-dicarboxylate.[376,379]



Scheme 67

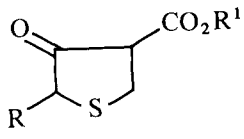
In a novel synthesis of thiophene derivatives, 1,3-oxathiol-2-ylideneimmonium salts are reacted, in the presence of base, with various compounds that contain an active methylene group.[380,381] The products are 2-*t*-amino-5-benzoylthiophenes, and in some there is a 3-cyano or 3-carboxy function. Scheme 68 illustrates some of the possibilities.



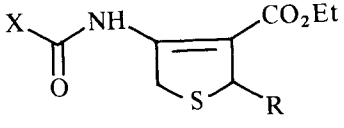
Scheme 68

e. 4-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS

Reactions of the type illustrated in Scheme 61, but starting with 5-substituted-4-oxotetrahydrothiophene-3-carboxylates (**103**) have been much used for the synthesis of the compounds considered in this section. Treatment of the oximes with hydrogen chloride in an alcohol, in ether, or in dioxane has given the fully aromatic amine in cases where R = H,[161] CF_3,[382] CO_2Me,[383] $(CH_2)_4CO_2Me$,[384] alkyl, and phenyl.[385] Normally the enamines obtained from **103** by reaction with primary amines have been dehydrogenated with chloranil,[386–388] but bromination–dehydrobromination is an alternative.[349] The aromatization of 2,5-dihydrothiophenes with iodosobenzene, discussed in Section I.2.C also gives good results with **104** (X = NH_2, OEt; R = H, Me).[333]

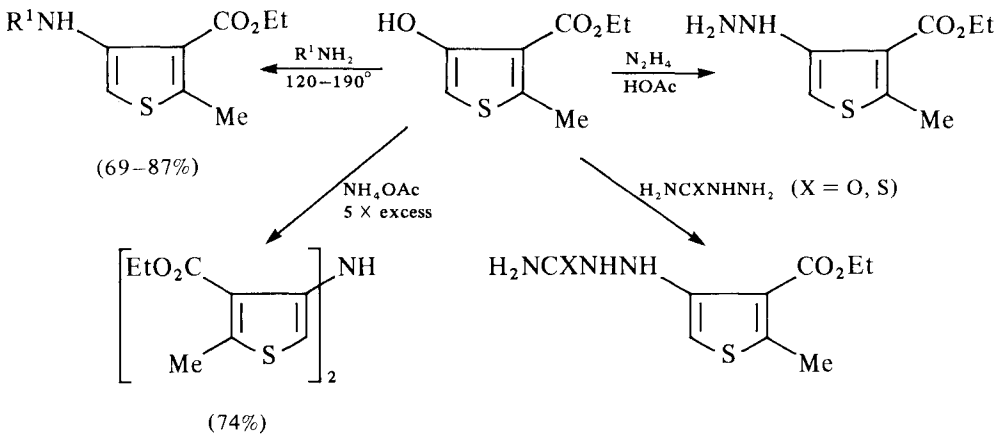


103



104

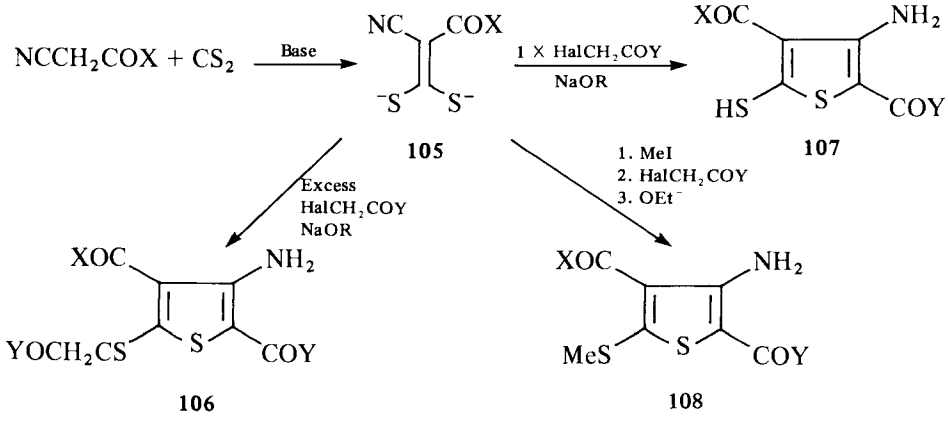
4-Hydroxythiophene-3-carboxylates react as the keto tautomer with primary amino compounds. Ethyl 4-hydroxy-2-methylthiophene-3-carboxylate is typical, and the results of its reactions with ammonium acetate, hydrazine,[389] with alkyl- and arylamines,[390] and with semicarbazides are illustrated in Scheme 69. Good results are also obtained if, instead of an amine, its salt with an organic acid is used.[391]



Scheme 69

f. 3-AMINOTHIOPHENE-2,4-DICARBOXYLIC ACIDS

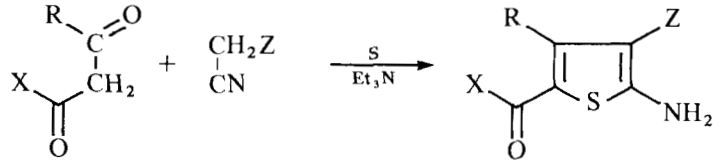
The base-catalyzed combination of carbon disulphide and compounds with an active methylene group (cf. Scheme 60) is applicable to the formation of the title compounds, by way of the enedithiolates **105** (X = OEt, NH_2, etc.). Reaction with an excess of a chloro- or bromoacetic acid ester or amide ($HalCH_2COY$; Y = OEt, NH_2, etc.), then with alkoxide, gives the 3-aminothiophene-2,4-dicarboxylic acid derivative **106**.[8,346] One equivalent of the halogenoacetic acid type leads to **107**, whereas monomethylation before[392,393] or after[394] the cyclization stage gives **108** (Scheme 70).



Scheme 70

g. 5-AMINOTHIOPHENE-2,4-DICARBOXYLIC ACIDS

If the carbonyl component in the Gewald synthesis is a β-keto ester and the other a cyanoacetic acid derivative, the final product is a relative of 5-aminothiophene-2,4-dicarboxylic acid.[191,395–397] The reaction works equally well with malonitrile, in which case a 5-amino-4-cyanothiophene-2-carboxylic acid type is produced. These constructions are summarized in Scheme 71; examples of the various products may be found in the Table of Compounds, Section VI.7 (Table 49).

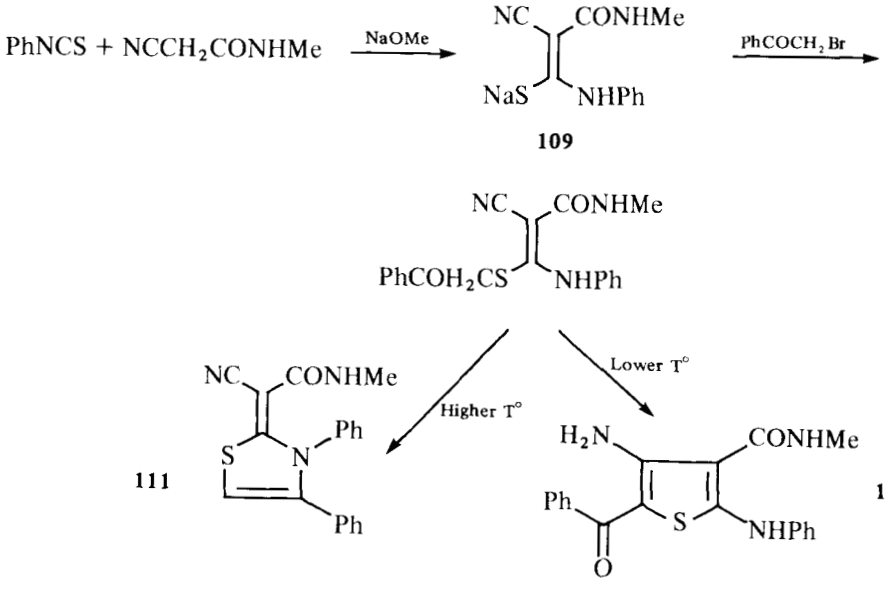


X = OEt, NH_2, etc.
Z = CO_2Et, $CONH_2$, CN

Scheme 71

h. 2,4-DIAMINOTHIOPHENE-3-CARBOXYLIC ACIDS

In an interesting series of patents[398–400] and a paper[401] Laliberte has given an account of the preparation of some 2,4-diaminothiophene-3-carboxamides by a synthesis based on isothiocyanates and cyanoacetamides. The acrylic acid derivatives (e.g., **109**) obtained from them are reacted with a halogenomethyl ketone;



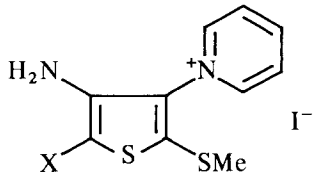
Scheme 72

depending on the temperature and conditions, the product is either a thiophene (e.g., **110**) or a methylenethiazoline (e.g., **111**); Scheme 72 shows a typical reaction sequence.

Gewald[402] used chloracetonitrile in place of the halogenoketone; in this case the initial cyclization products were exclusively thiazolines, which were converted into 2,4-diaminothiophene-3-carboxylates by alkoxides.

j. 3,4-DIAMINOTHIOPHENE-2-CARBOXYLIC ACID

An interesting route to the very rare 3,4-diaminothiophene system is based on the pyridinium salts **112** (X = CO_2Et, $CONH_2$, CN) which are made in the usual way from enedithiolates. Treatment with methylamine causes cleavage of the pyridine ring, and acid hydrolysis completes the formation of the second amino group.[403,404]

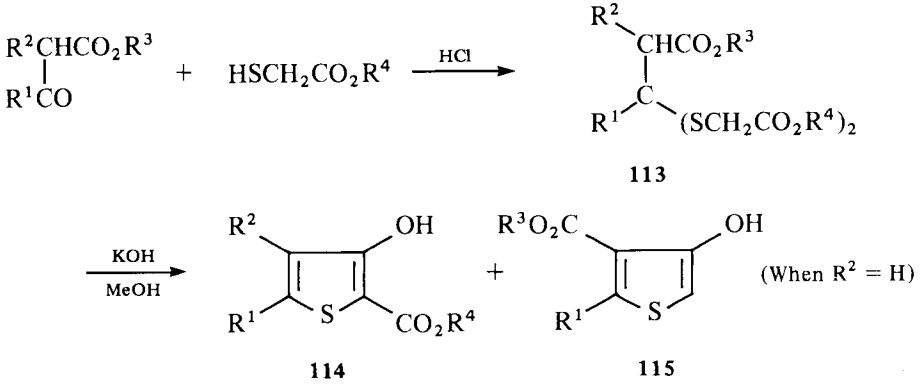


112

E. Hydroxythiophenecarboxylic Acids and Their Derivatives

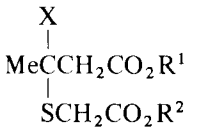
a. 3-HYDROXYTHIOPHENE-2-CARBOXYLIC ACIDS

The thioketals (**113**) formed from β-keto esters and thioglycolates are cyclized by alkali to give 3-hydroxythiophene-2-carboxylates (**114**),[405–407] in good yield (Scheme 73). The 4-hydroxythiophene-3-carboxylate **115** is an alternative product in those cases where R^2 = H; it formed approximately 40% of the cyclized material when R^1 was *i*-propyl or *t*-butyl,[5] but it is not a significant product in other cases.



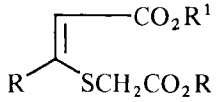
113 **114** **115**

Scheme 73



116

a. X = OH
b. X = SEt



117

Mixed ketals **116a**,[408] and **116b**,[409] yield 3-hydroxy-5-methylthiophene-2-carboxylates under Dieckmann conditions.

Immediate precyclization intermediates of the type **117** are implied in preparations of 3-hydroxythiophene-2-carboxylates from thioglycolates and propiolic esters;[410,411] such intermediates are directly available by combination of a halogenoacetate and an enethiolate.[412,413] A mixture of the cis (80%) and trans (20%) forms of **117**, R = Me, $R^1 = R^2 = Et$, cyclized normally with potassium hydroxide–methanol. When the proportions of stereoisomers were reversed, the reaction failed with this base, but with potassium *t*-butoxide cyclization took the alternative course and gave ethyl 4-hydroxy-2-methylthiophene-3-carboxylate.[413] 2-Alkyl-4-hydroxythiophene-3-carboxylates were also formed, to a minor extent, when potassium *t*-butoxide was used to catalyze the addition of various thioglycolates to propiolic esters to yield mixtures of the stereoisomers of **117**.[250]

The Fiesselmann synthesis described in I.2.D.a leads to 3-hydroxythiophene-2-carboxylates if the starting material is an α,β-dihalogeno ester rather than -nitrile;[344] α-chloroacrylates can also be used.[345]

Oxotetrahydrothiophenecarboxylates (e.g., **90**, **103**) and their enol ethers and enol acetates require only dehydrogenation to give hydroxythiophenecarboxylic acid derivatives. Bromination–dehydrobromination was used by Fiesselmann and Pfeiffer,[408] to obtain **114** (R^1 = Me, R^2 = H, R^4 = Et) from the oxotetrahydrothiophene, and other methods are available, but a recently introduced procedure is the method of choice. In this the cyclic ketone, or one of its enol derivatives, is reacted with sulfuryl chloride in dichloromethane at approximately 0°C. This gives excellent results with **90** (R = H, R^1 = Me) and with the enol acetate and mesylate of the same substance.[414]

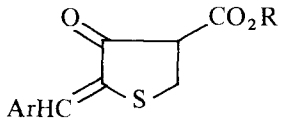
b. 4- AND 5-HYDROXYTHIOPHENE-2-CARBOXYLIC ACIDS

Neither of these types of hydroxythiophene acid is readily available from syntheses that do not involve a preformed thiophene ring.

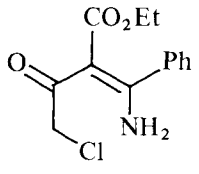
Methyl 5-acetyl-4-hydroxythiophene-2-carboxylate is produced in low yield from mercaptoacetone and DMAD.[142,415] The main preparation of 5-oxygenated-thiophene-2-carboxylic acids is by nucleophilic substitution of halogen. When activating nitro groups are present this is a simple matter, but the replacement of chlorine,[222] or bromine,[416] by long-chain alkoxides from the 5-halogenothiophene-2-carboxylic acids proceeded in poor yield and required long reaction times in high-boiling solvents.

c. 4-HYDROXYTHIOPHENE-3-CARBOXYLIC ACIDS

The aromatization of 4-oxotetrahydrothiophene-3-carboxylates or their enol derivatives by sulfuryl chloride is the most versatile preparation of this group and has been used to obtain numerous 4-hydroxy, -methoxy, and -acetoxy compounds in the class.[417–422] An alternative oxidant, 40% hydrogen peroxide in aqueous ethanol, gave good yields from several ethyl 5-aryl-4-oxotetrahydrothiophene-3-carboxylates.[423,424] Arylidene derivatives of the form **118** are in the correct oxidation state and rearrange to thiophene-3-carboxylates on treatment with acid, but not with aromatic amines.[198]



118

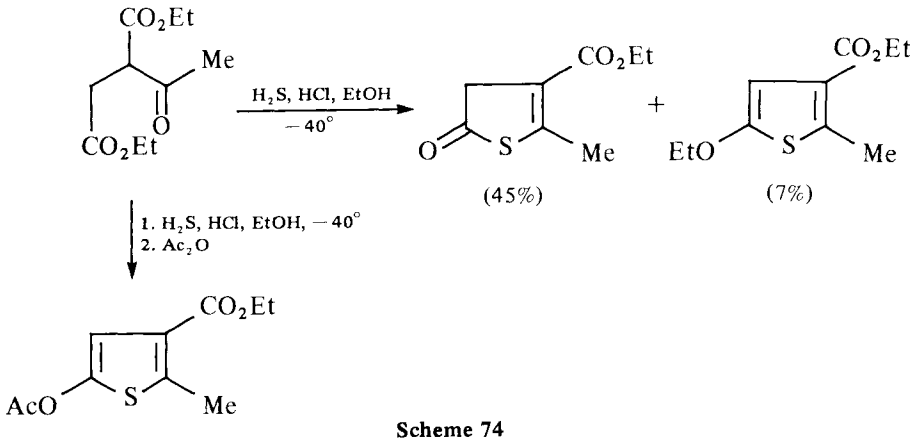


119

Cyclization reactions are of little value for this group. Their formation from propiolates has been mentioned (Section I.2.E.a); they are also produced when the thiolium salts undergo the reaction shown in Scheme 39 with malonate rather than acetoacetate ions.[425,426] The enamine **119** is converted into ethyl 4-hydroxy-2-phenylthiophene-3-carboxylate by sodium hydrosulfide.[411]

d. 5-HYDROXYTHIOPHENE-3-CARBOXYLIC ACIDS

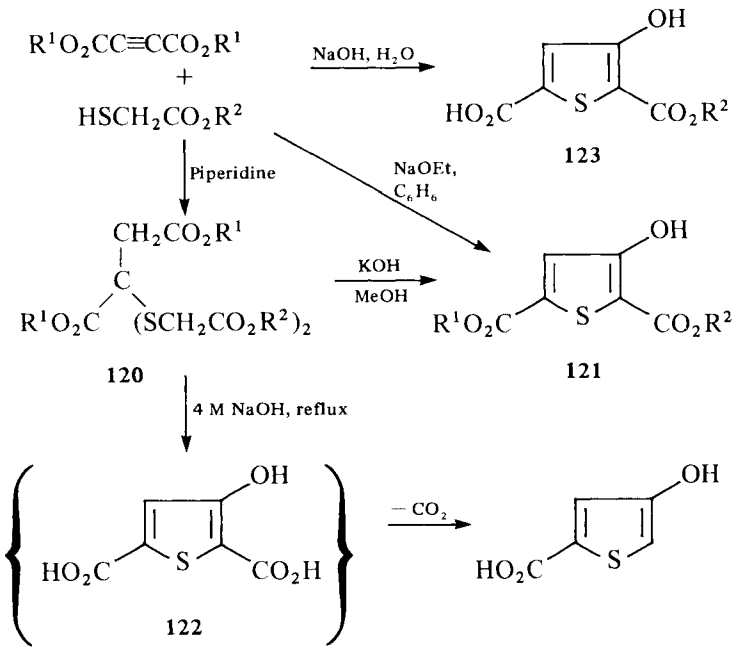
Very few of these compounds are known. The keto is the more stable tautomer, although as is shown in Scheme 74, it is possible to adapt a ring synthesis to obtain an enol acetate as the major product.[427]



Scheme 74

e. 3-HYDROXYTHIOPHENE-2,5-DICARBOXYLIC ACIDS

Fiesselmann and his co-workers have shown that some interesting variations are possible in the reactions of dialkyl acetylenedicarboxylates and thioglycolates. In the presence of piperidine the thioketals **120** are obtained. On treatment with potassium hydroxide–methanol,[428,429] these give dialkyl 3-hydroxythiophene-2,5-dicarboxylates (**121**); vigorous hydrolysis with aqueous sodium hydroxide gives 4-hydroxythiophene-2-carboxylic acid by way of the diacid **122**.[429] Condensation of the acetylenic ester and glycolate induced by sodium ethoxide–benzene leads directly to **121**[430] but aqueous sodium hydroxide produces the half-ester **123**.[415,428] These reactions are summarized in Scheme 75.

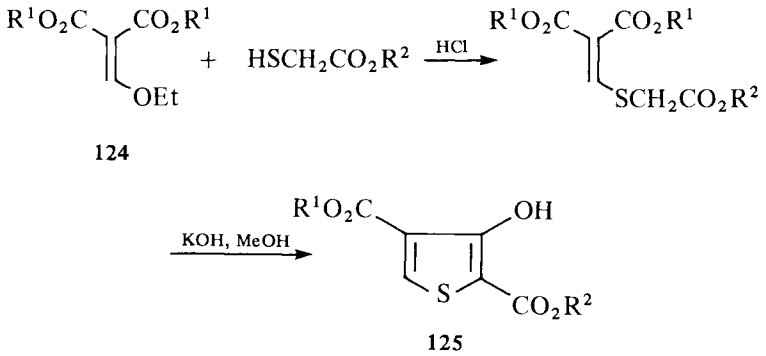


Scheme 75

Fiesselmann's thiophene synthesis from appropriate 1,2-dihalogeno compounds is also applicable here; dimethyl 2,3-dibromosuccinate and methyl thioglycolate form **121** (R^2 = Me) when treated with potassium hydroxide in methanol.[343]

f. 3-HYDROXYTHIOPHENE-2,4-DICARBOXYLIC ACIDS

Enol ethers **124** have been used by Oskay[431] as the starting point for the preparation of a number of mixed esters, **125** (Scheme 76).



Scheme 76

g. DIHYDROXYTHIOPHENECARBOXYLIC ACIDS

The Hinsberg synthesis of 3,4-dihydroxythiophene-2,5-dicarboxylates from thiodiacetates and dialkyl oxalates still has no rival. It has been used to prepare the dimethyl[281] and diethyl esters[411,432–434] and a patent,[435] gives an account of the results of variations in the solvent, in the thiodiacetate, and in the condensing agent used. The *S*-alkylation of a thioamide (**98**) is discussed in Section I.2.D.c. A similar sequence of reactions to those described there has also been applied to dimethyl monothionomalonate (MeO_2CCH_2CSOMe), leading to an excellent yield of 3-hydroxy-5-methoxythiophene-2-carboxylate.[359]

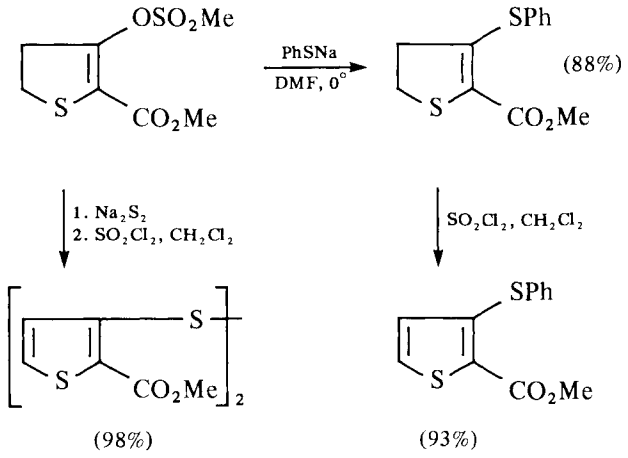
F. Mercaptothiophenecarboxylic Acids and Their Derivatives

The special methods detailed for hydroxythiophenecarboxylic acids and their derivatives are, within limits, applicable also to their sulfur analogues, although many fewer of the latter compounds are known.

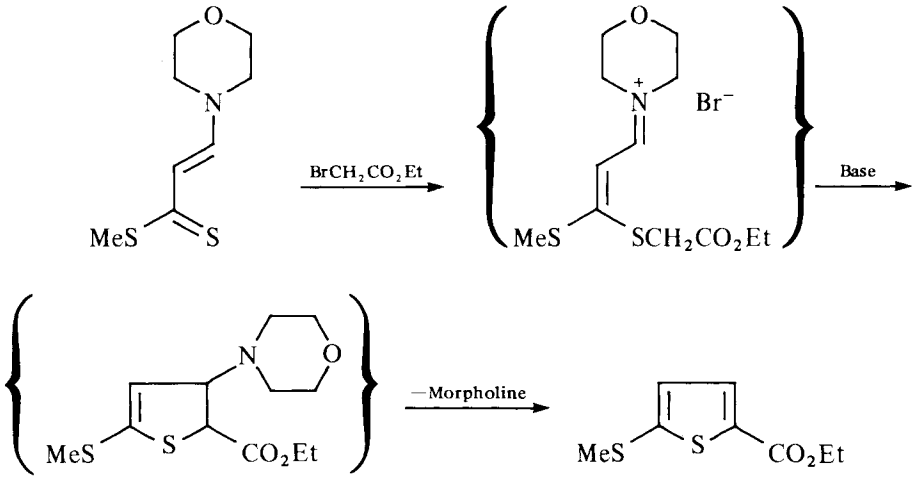
Oxotetrahydrothiophenes are of value here also. Displacement of enolate functions by powerful sulfur nucleophiles, then aromatization, has been used to prepare 3-arylthiothiophene-2-carboxylates[414] and 4-arylthiothiophene-3-carboxylates;[436,437] the reactions of Scheme 77 are typical.

The transformations of enedithiolates illustrated in Scheme 70 can be applied to almost any of the many such compounds that are available by reaction of substances containing an active methylene group with carbon disulfide. The Tables of Compounds contain numerous derivatives of 5-mercaptothiophene-2-carboxylic acid that have been made from enedithiolate intermediates.

The *S*-alkylation-cyclization reactions of thiono esters are mentioned in Section I.2.E.g; when the participating ester group is the full sulfur analogue the product is an alkylthiothiophene[438] (Scheme 78).

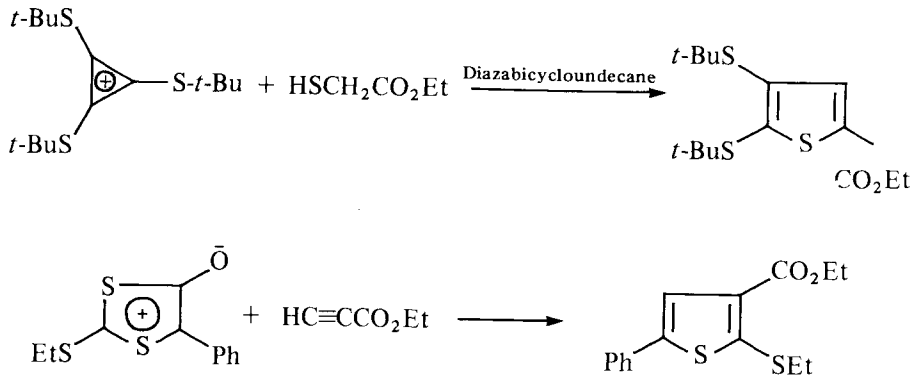


Scheme 77



Scheme 78

Scheme 79 depicts two fascinating preparations of mercaptothiophenecarboxylic acid derivatives, one based on a cyclopropenium salt,[439,440] the other involving the familiar cycloaddition-extrusion theme.[322]



Scheme 79

G. *Halogenothiophenecarboxylic Acids and Their Derivatives*

Apart from the general methods outlined in Section I.1 the main source of halogenothiophenecarboxylic acids is by the introduction of halogen into a preformed thiophenecarboxylic acid.

The halogens themselves are effective for chlorination and bromination, and no catalyst is necessary; reactions are often carried out with acetic acid as solvent. Iodination can be accomplished either by a mixture of iodine and iodic acid or by replacement of an acetoxy- or chloromercury group by a combination of iodine and potassium iodide. The normal directive influence of the carboxyl group is observed. For example, thiophene-3-carboxylic acid is chlorinated and brominated at C-5,[441] but if C-5 is blocked (as in ethyl 5-ethylthiophene-3-carboxylate) the halogen enters at C-2.[442] In the iodine–iodic acid treatment of methyl thiophene-2-carboxylate the main product was the 5-iodo ester, but a small amount of the 4-iodo compound was also formed.[443] On the other hand, ethyl thiophene-2-carboxylate gives the 4-chloro ester with chlorine when aluminum chloride is present ("swamping catalyst effect").[111]

Even though the thiophene ring in its carboxy derivatives is deactivated to electrophilic substitution, it is possible to fully halogenate it: for example, thiophene-3-carboxylic acid, with an excess of bromine at room temperature, gave an 80% yield of 2,4,5-tribromothiophene-3-carboxylic acid after a few hours.[444]

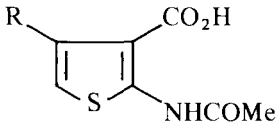
Concentrated solutions of sodium hypochlorite or hypobromite are capable of effecting nuclear halogenation. Thus 2-acetyl-5-ethylthiophene gave the 5-ethyl-4-halogenothiophenecarboxylic acid (in low yield) on oxidation with these agents.[138]

When **103** (R = H, R^1 = Me) is reacted with phosphorus pentachloride both aromatization and chlorination occur, the product being 4-chlorothiophene-3-carboxylic acid chloride;[445] the same reagent replaces the hydroxy group of methyl 3-hydroxythiophene-2-carboxylate.[445–447]

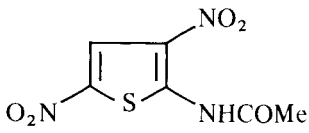
H. Nitrothiophenecarboxylic Acids and Their Derivatives

The nitration of thiophenecarboxylic acids and esters is usually carried out with mixed acid, or with fuming nitric acid in acetic anhydride or in sulfuric acid. Thiophene-2-carboxylic acid gives a mixture of products on nitration. A polarographic study revealed a typical distribution of 31% 4-nitro- and 61% 5-nitrothiophene-2-carboxylic acid; the remainder of the product was 2-nitrothiophene arising by nitro decarboxylation.[448] The results of another study indicate that such nitro decarboxylation involves direct replacement of the carboxyl group, rather than decarboxylation followed by substitution.[449] Esters of thiophene-2-carboxylic acid also give a mixture of the 4- and 5-nitrothiophenecarboxylate. In competitive nitrations methyl furan-2-carboxylate was shown to be much more reactive than its thiophene counterpart, the ratio 5-nitrofuran ester: 5-nitrothiophene ester: 4-nitrothiophene ester was 109: 16.5: 10 in nitration with nitric acid–acetic anhydride, and even more in favor of the furan with acetyl nitrate in sulfuric acid.[450] Under more forcing conditions methyl thiophene-2-carboxylate is dinitrated, giving a mixture of the 3,5- and 4,5-dinitro compounds.[122] 5-Alkylthiophene-2-carboxylic acids and esters are nitrated at C-4;[136,137,186,449,451–453] some decarboxylation of the acid invariably occurs. Nitration of thiophene-3-carboxylic acid[441] and of its amide[454] takes place exclusively at C-5.

Whether or not nitro decarboxylation takes place seems to depend to some extent upon the nitrating agent: other substituents can also have an effect. For example, **126** (R = H) gave **127** with mixed acid at 0°C, but was nitrated without decarboxylation (giving **128**, R = H) by nitric acid in oleum at −10°C. On the other hand, 2-acetylamino-4-methylthiophene-3-carboxylic acid (**126**, R = Me) suffered no decarboxylation on treatment with mixed acid and gave **128** (R = Me).[455] Esters of **126** were nitrated at C-5 without difficulty.[191]



126



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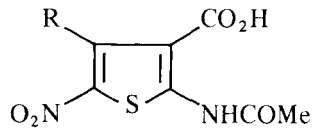
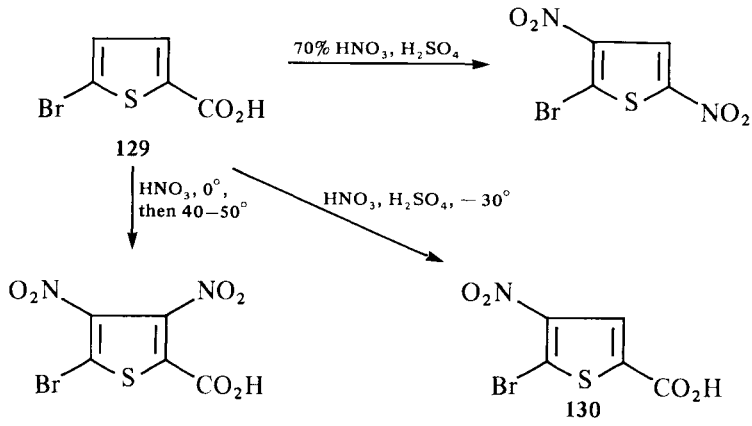


128

The largest group that has been obtained by direct nitration is the halogenonitrothiophenecarboxylic acids (see Tables of Compounds, Sections VI.9 and VI.10). Bromothiophene-2-carboxylic acids are rather prone to decarboxylation during nitration. 4,5-Dibromothiophene-2-carboxylic acid, for example, apparently always gives 2,3-dibromo-5-nitrothiophene;[108,456,457] the same product was obtained from its methyl ester.[456] Reaction of **129** with fuming nitric acid in sulfuric acid gave **130** as the major product,[456] but it is reported that at low temperature the yield of nondecarboxylated material increases significantly.[452] Under suitable conditions nitric acid alone can dinitrate **129**[458] (Scheme 80).

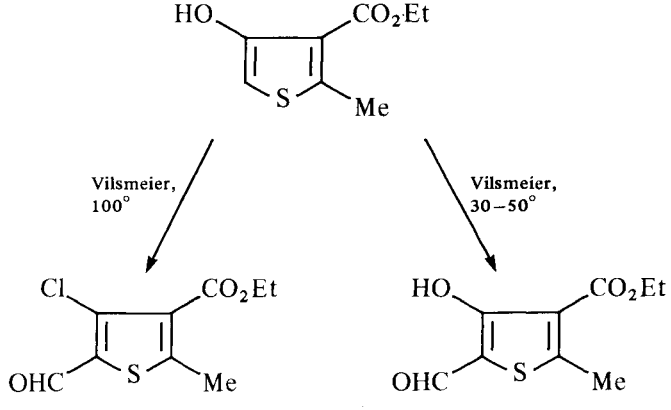


Scheme 80

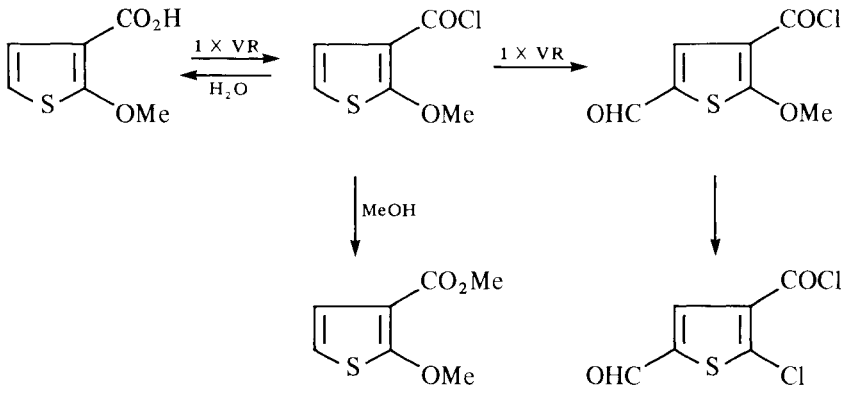
I. Formyl- and Acylthiophenecarboxylic Acids and Their Derivatives

The Vilsmeier reaction fails with simple thiophenecarboxylic acid derivatives, but it is successful if enough electron-releasing groups are present to offset the deactivating effect of the carboxyl group [as is the case of esters of **126** (R = Me), which formylate at C-5].[191,362,395]

Some very interesting results ensue from hydroxy- and methoxythiophenecarboxylic acids. Hydroxyl groups adjacent to the carboxyl function may be replaced by chlorine; this is the case with ethyl 4-hydroxy-2-methylthiophene-3-carboxylate,[354,459,460] although it is possible to avoid the chlorination if the temperature is kept below 50°C.[460] (Scheme 81).



Scheme 81



Scheme 82

Methoxy groups may also be replaced by chlorine. Hallberg and Gronowitz[461] found that two equivalents of the Vilsmeier reagent (VR) converted 2-methoxythiophene-3-carboxylic acid into the 2-chloro-5-formyl compound. It was shown that the first equivalent of reagent produced the acid chloride; this is formylated, and the final stage involves intramolecular replacement of the methoxy group (Scheme 82). Methyl 2-methoxythiophene-3-carboxylate and methylthiothiophene-2-carboxylic acid were formylated without chlorination; the Vilsmeier reaction failed with 3-, 4-, and 5-methoxythiophene-2-carboxylic acids.

The formyl group may be introduced into a wider range of thiophenecarboxylic acids and their derivatives by reaction of a thienyllithium with dimethylformamide. Both 3- and 4-formylthiophene-2-carboxylic acids have been prepared in this way by way of the bromo acids.[101] Reaction of the appropriately lithiated cyanothiophenes in the same way gave low yields of 5-formylthiophene-2-carboxamide and 2-formylthiophene-3-carboxamide,[10] and all the isomeric cyanothiophenealdehydes have been transformed into the methyl and ethyl esters of the formyl acids by means of the imino ethers.[462]

Friedel-Crafts acylation can be successful with deactivated thiophene rings, although yields are often poor. Ethyl thiophene-2-carboxylate gives the 5-acetyl derivative with acetic anhydride–zinc chloride;[463] esters of thiophene-3-carboxylic acid are also acylated at C-5.[464,465] In a reversal of this approach a thiophenedicarboxylic acid anhydride can be used as a monoacylating agent. The reactions of thiophene-3,4-dicarboxylic acid anhydride with benzene–aluminum chloride,[23,466] and with dimethylcadmium,[467] (which gave 4-benzoyl- and 4-acetylthiophene-3-carboxylic acid in 66% and 32% yields, respectively), illustrate the possibilities. It should be noted that many of the cyclizations leading to various thiophenecarboxylic acids give products that also contain a keto group; the reactions in Schemes 68 and 72 are typical.

J. Carboxythiophene Sulfonic Acid Derivatives

There are two principal routes to these compounds. In the first, and longest established, a thiophenecarboxylic acid derivative undergoes electrophilic substitution by chlorosulfonic acid. The product is the thiophene sulfonyl chloride; typical of the compounds made by this method are 5-ethoxycarbonylthiophene-2-sulfonyl chloride,[468] 4-carboxy-5-chlorothiophene-2-sulfonyl chloride,[469] and 2-chloro-5-*N*-methylcarboxamidothiophene-3-sulfonyl chloride.[470] Presumably a copper-catalyzed nucleophilic substitution reaction is involved in the second approach, used by Hromatka and his co-workers. A mixture of sodium bisulphite, sodium hydroxide, and copper(I) chloride at 140°C converts thiophenecarboxylic acids with a chlorine atom adjacent to the carboxylic function into the sulfonic acid by replacement of the chlorine. The reaction has been applied successfully to 3-chlorothiophene-2-[445,447,471] and -4-carboxylic acids,[446,447] and to 2,5-dichlorothiophene-3-carboxylic acid (in which the chlorine atom at C-2 was replaced).[445]

II. REACTIONS OF THIOPHENECARBOXYLIC ACIDS AND THEIR DERIVATIVES

1. Reactions of the Carboxylic Function

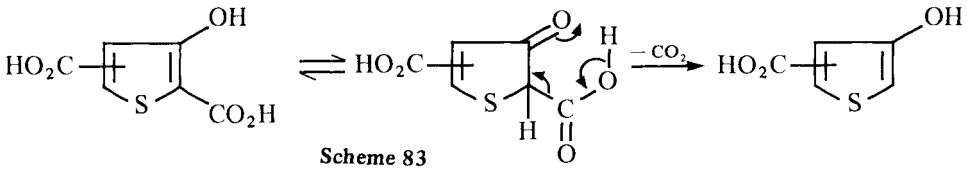
An exceedingly large number of transformations of the acids and their derivatives has been reported in the last 30 years. For the most part in the following account only reactions of particular interest are considered. In addition, mention is made of some reactions that gave products that do not (for want of data, or because they are no longer carboxylic acid derivatives) appear in the Table of Compounds.

A. Thiophenecarboxylic Acids

a. DECARBOXYLATION

Many decarboxylations of thiophenecarboxylic acids have been described. They fall into two classes: those in which the carboxyl group is replaced by hydrogen, and those in which it is replaced by a halogen atom or a nitro group. In the first category the methods used have generally been one of the following:

Method I: Heating the acid alone. This is often effective with hydroxy acids in which the hydroxy group is placed in such a way that the keto tautomer is



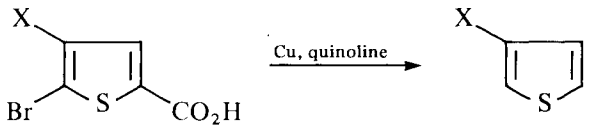
Scheme 83

effectively a β-keto acid. The point is nicely illustrated in the decarboxylation of 3-hydroxythiophene-2,4-[431] and -2,5-dicarboxylic acids[289,410] in which it is the carboxyl group at C-2 that is lost (Scheme 83).

Aminothiophenecarboxylic acids in which the amino and carboxylic groups are neighbors also decarboxylate readily, but the resulting aminothiophenes decompose. Their oxalates, however, decarboxylate readily at very moderate temperatures (35 to 60°C).[472]

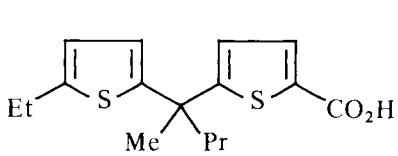
Method II: Heating a salt of the acid. The traditional soda lime treatment is fairly effective, and vacuum thermolysis of barium salts has been used to obtain 2,5-diarylthiophenes from the 3,4-dicarboxylic acids.[259] A study has been made of the thermal decarboxylation of the bishexamine salt of thiophene-2,5-dicarboxylic acid.[473] The pyrolysis of silver salts has been examined; silver thiophene-2-carboxylate gave a poor yield of thiophene, and some bithienyl[474] and the 2,5-dicarboxylate yielded a thiophene silver polymer.[475]

Method III: Heating the acid with copper, copper chromite, or copper bronze in quinoline. This is effective with acids of all classes, but has an interesting additional effect on certain halogeno acids. Bromine atoms at thiophene α-positions are reductively removed during decarboxylation[108,475] (Scheme 84: X = Br and NO_2).

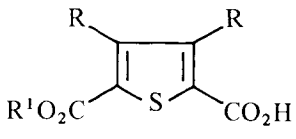


Scheme 84

Chlorine atoms at thiophene α-positions are stable to these conditions. The decarboxylation of the (−)-enantiomer of **131** has been described; chirality was preserved, and the product was the dextro form.



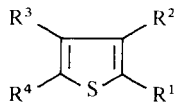
131



132

The half-esters **132** (R = Ph, 4-MeO—C_6H_4), on heating with copper bronze, gave, in addition to the expected products, some of the 3,4-diarylthiophene (arising from loss of the ester group).[281] When the copper salt of 3,4,5-trichlorothiophene-2-carboxylic acid was heated with 4-iodoanisole both decarboxylation and coupling

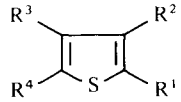
TABLE 2. DECARBOXYLATION OF THIOPHENECARBOXYLIC ACIDS



R^1	R^2	R^3	R^4	Method	Yield (%)	References
CO_2H	SPh	NO_2	H	I	69	477
CO_2H	Me	MeCO	MeS	I	91	354
CO_2H	Ph	Ph	CO_2Et	I	–	280
CO_2H	OH	OH	CO_2Et	I	–	3
CO_2H	OH	OH	CO_2H	I	82	434
NH–COR	CO_2H	–Various–		I	–	478, 479
NHCOR	CO_2H	Various	H	I	–	455
NHtosyl	CO_2H	Me	Me	I	43	480
H	CO_2H	NHAr	H	I	–	349
CO_2H	Et	Me	CO_2H	II	62	282
CO_2H	H	4-NO_2–C_6H_4	CO_2H	III	98	288
CO_2H	OMe	CO_2H	H	III	60	431
CO_2H	H	H	CH_2-5-CO_2H-2-Furyl	III	53	150
CO_2H	*t*-Bu	H	*t*-Bu	III	92	35
CO_2H	H	CH_2SEt	CH_2SEt	III	72	481
CO_2H	H	$-CH_2-S-CH_2-$		III	62	481
CO_2H	3-NO_2–C_6H_4	H	H	III	–	235
CO_2H	4-NO_2–C_6H_4	H	H	III	–	235
Ph	CO_2H	CO_2H	Ph	III	–	312
CO_2H	–Various aryl–		CO_2H	III	–	299
CO_2H	MeO	MeO	CO_2H	III	Good	433
CO_2H	$-O-CH_2-O-$		CO_2Et	III	24	482
CO_2H	H	Cl	Cl	III	68	123
CO_2H	H	NO_2	Et	III	33	453
CO_2H	H	NO_2	Me	III	70	451, 453

CO_2H	H	NO_2	H	III	77	184
CO_2H	H	H	NO_2	III	–	132
CO_2H		—Various alkyl and aryl—		III	Good	236
Me	CO_2H	MeCO	Me	III	54	144
CO_2H	H	H	Ph	IV	44	248
CO_2H	Br	NO_2	H	IV	–	108, 109
CO_2H	H	NO_2	Br	IV	85	109
CO_2H	H	NO_2	Cl	IV	47	483
CO_2H	Me	NO_2	Br	IV	–	110

TABLE 3. HALOGENODECARBOXYLATION OF THIOPHENECARBOXYLIC ACIDS



R^1	R^2	R^3	R^4	Method	Yield (%)	References
CO_2Na	H	H	H	IV	Poor	484
CO_2Na	H	$-CH_2-SO_2-CH_2-$		IV	67–77	284
CO_2Na	H	$-CH_2-NEt-CH_2-$		IV	67–77	284
CO_2Na	*t*-Bu	H	*t*-Bu	IV	67–77	284
CO_2Na	H	CH_2SO_2Et	CH_2SO_2Et	IV	67–77	284
CO_2Na	Me	Me	CO_2Na	IV	88	284
CO_2Na	Ph	Ph	CO_2Na	IV	96	284
CO_2Na	Ph	Ph	CO_2Na	IV	20[a]	485
					70[b]	485
CO_2K	$-O-CH_2-O-$		CO_2Et	IV	31	482
CO_2K	$-O-CH_2-O-$		CO_2K	IV	79	482
CO_2Ag	H	NO_2	Br	V	88	108
CO_2Ag	Br	NO_2	H	V	Low	109
CO_2Ag	H	NO_2	$(CH_2)_3CO_2Me$	V	82	486–488
CO_2Ag	H	NO_2	$(CH_2)_4CO_2Me$	V	54	486–488
CO_2H	OMe	OMe	CO_2H	VI	19	489
CO_2H	$-O-CH_2-O-$		CO_2H	VI	12	482

[a]Replacement of both CO_2Na.
[b]Replacement of one CO_2Na.

occurred, and the mixture of biaryls formed contained some 2,3,4-trichloro-5-(4-methoxyphenyl)thiophene.[48]

Method IV: The acid is treated successively with mercury(II) acetate and sodium chloride solution.

A selection of decarboxylations not mentioned in the foregoing discussion is presented in Table 2.

Reactions in which a carboxyl group is replaced by nitro are discussed in Section I.2.H. Halogenodecarboxylation is also common; it is achieved by one of the methods V to VII.

Method V: The acid (or one of its salts) is treated with bromine. Of interest in connection with this reaction is that 3,5-di-*t*-butylthiophene-2-carboxylic acid was not decarboxylated by bromine unless some hydrogen bromide was also present, and it was concluded that the decarboxylation was actually effected by the latter.[35]

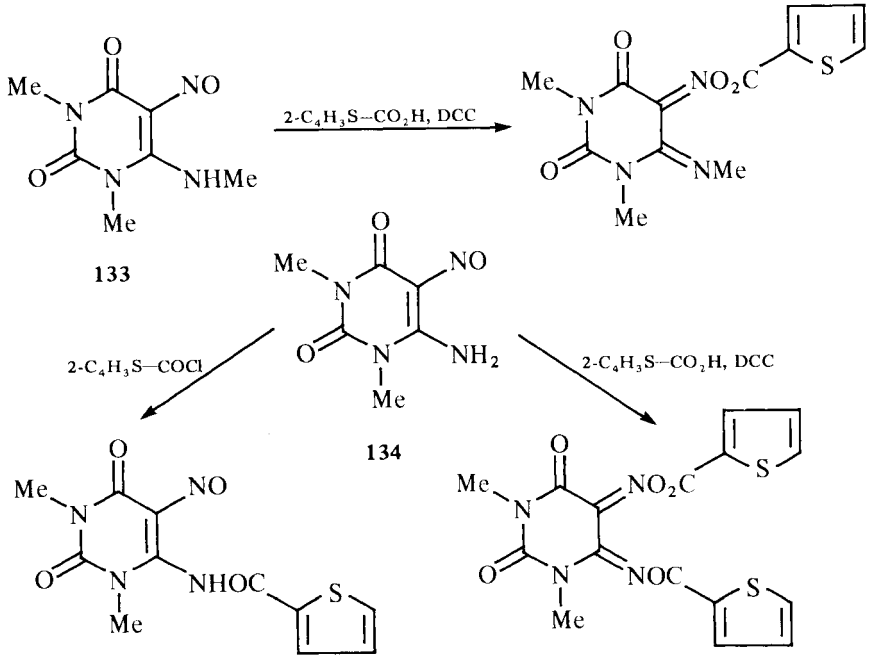
Method VI: The silver salt of the acid is treated with bromine in an inert solvent (the Hunsdiecker reaction).

Method VII: The acid is treated successively with mercury(II) acetate and iodine. Iododecarboxylation can take place in the absence of the mercury salt; treatment of 2,5-dichlorothiophene-3-carboxylic acid with iodine–iodic acid gave some 2,5-dichloro-3,4-diiodothiophene as well as 2,5-dichloro-4-iodothiophene-3-carboxylic acid.[40]

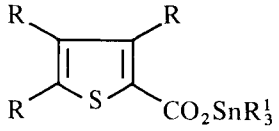
A selection of acids that have been halogenodecarboxylated is presented in Table 3.

b. ESTERIFICATION

All the normal methods of esterification are applicable to thiophenecarboxylic acids. The vinyl ester of thiophene-2-carboxylic has been made by the high-temperature combination of the acid and acetylene in the presence of a zinc oxide[490] or an organozinc or organocadmium catalyst.[491] A safer modification of the process, employing nitrogen as diluent, has been described.[492] A very rapid process of esterification (in which the acid and alcohol are reacted in the presence of 30% hydrogen peroxide and sulfuric acid) has been applied to thiophene-2-carboxylic acid. It gave excellent yields of the *t*-butyl (91%) and the 2-hydroxyethyl (94%) esters.[493,494] Two methods that have the advantage of involving nonacidic conditions have been used. In the first the acid was treated with a mixture of the alcohol and boron trifluoride etherate;[495] in the second, a combination of dimethyl methylphosphonate and triethylamine converted thiophene-2,5-dicarboxylic acid into its dimethyl ester in over 90% yield.[496] Thiophene-2-carboxylic acid forms an oxime ester with the nitrosopyrimidone **133** in the presence of dicyclohexylcarbodiimide (DCC); the product is a member of a new class of activated esters and is a very good acylating agent.[497,498] The primary amine **134** gives the bisacylated product with thiophene-2-carboxylic acid-DCC, and is acylated at the amino group by thiophene-2-carboxylic acid chloride[499] (Scheme 85).

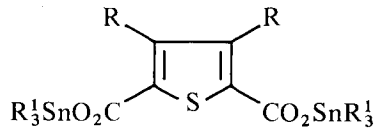


Scheme 85



135

a. R = H, R^1 = Ph
b. R = H, R^1 = Me, Bu
c. R = Br, R^1 = Me, Bu, cyclohexyl, Ph

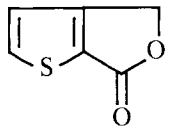


136

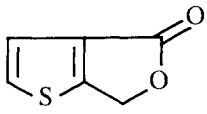
R = H, Br
R^1 = Me, Bu, cyclohexyl, Ph

The interesting esters **135a**,[500] **135b**, **135c**, and **136**[501] have been prepared from the thiophenecarboxylic acid and either a stannane or a trialkyl- or triarylstannol.

Lactones are not uncommon in the thiophene series. The isomers **137** to **139** were made by the action of *p*-toluenesulphonic acid on the hydroxymethyl acids, and by photolysis of thiophene-2,3-dialdehyde (which gave 80% **137**, 20% **138**) and of the 3,4-dialdehyde (which gave **139**).[502]



137



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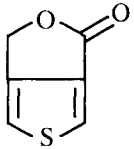
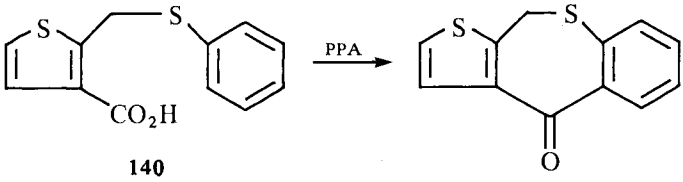


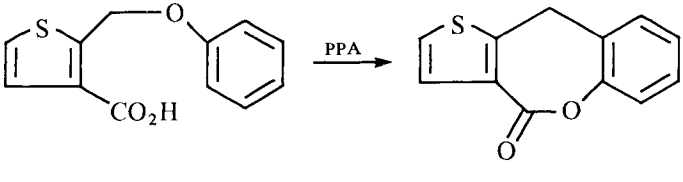
139

c. INTRAMOLECULAR CYCLIZATIONS

There have been numerous descriptions of reactions in which a thiophenecarboxylic acid has been caused to make an electrophilic attack on another ring in the same molecule. The cyclization may involve the acid itself, or the acid chloride; because



140



141 142

Scheme 86

TABLE 4. INTRAMOLECULAR CYCLIZATION OF THIOPHENE-2-CARBOXYLIC ACIDS AND THEIR CHLORIDES

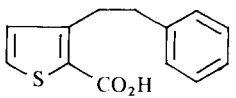
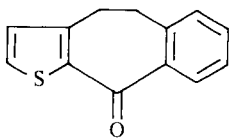
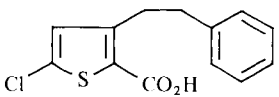
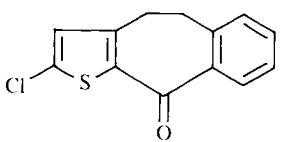
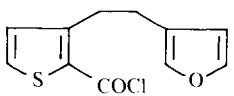
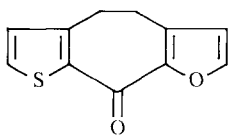
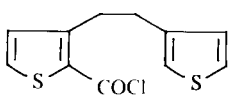
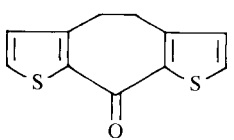
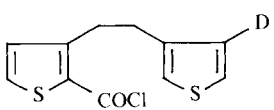
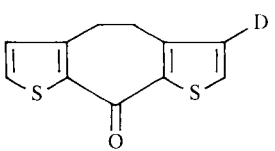
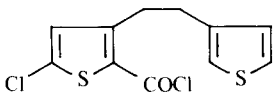
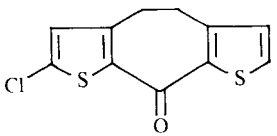
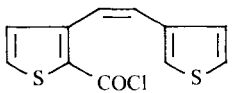
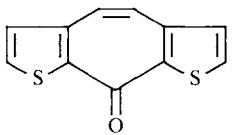
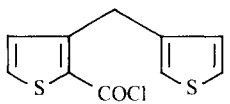
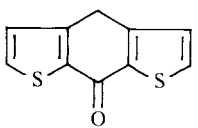
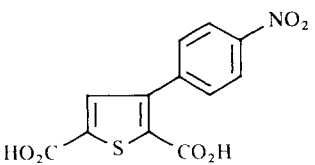
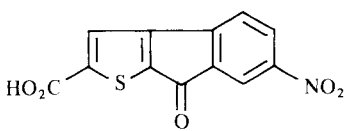
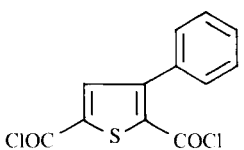
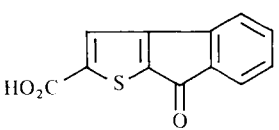
Substrate	Product	Agent	Yield (%)	References
		PPA	–	506
		PPA	58	507
		$SnCl_4$	52	508
		$SnCl_4$	94	509
		$SnCl_4$	94	510

TABLE 4. (*Continued*)

Substrate	Product	Agent	Yield (%)	References
		$SnCl_4$	84	511
		$SnCl_4$	85	512
		$SnCl_4$	26	513
		TFA	42	514
		$AlCl_3$	59	288, 515

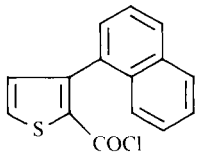
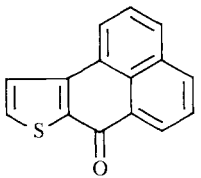
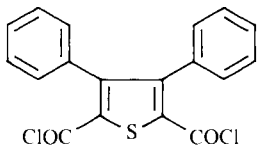
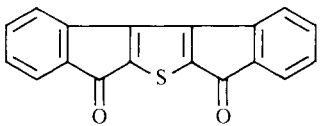
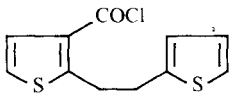
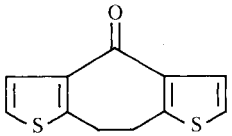
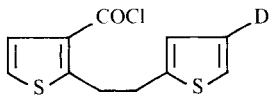
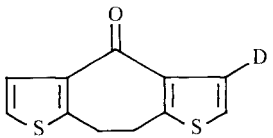
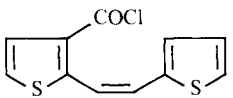
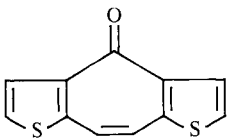
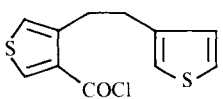
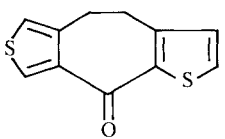
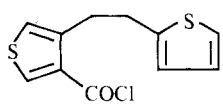
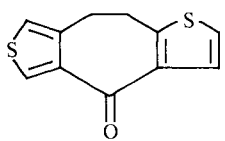
		$AlCl_3$	87	516
		$AlCl_3$	27	517

TABLE 5. INTRAMOLECULAR CYCLIZATION OF THIOPHENE-3-CARBOXYLIC ACIDS AND THEIR CHLORIDES

Substrate	Product	Agent	Yield (%)	References
		$SnCl_4$	93	509
		$SnCl_4$	92	510
		$SnCl_4$	81	512
		$SnCl_4$	Very high	518
		$SnCl_4$	83	518

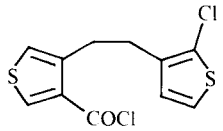
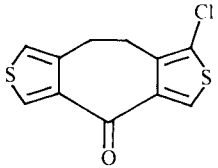
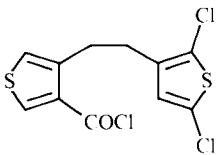
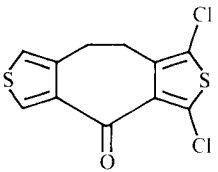
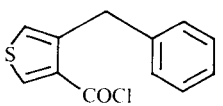
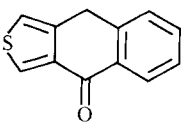
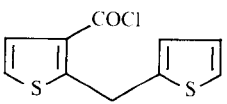
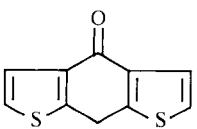
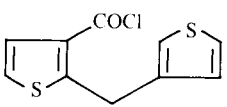
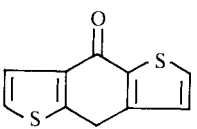
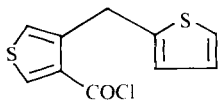
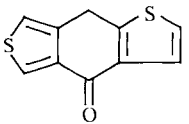
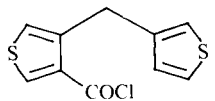
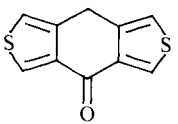
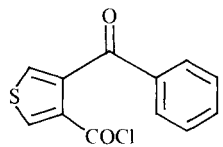
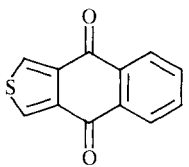
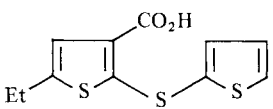
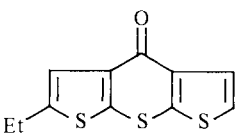
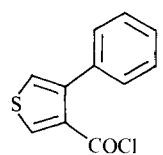
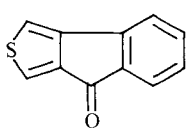
		$SnCl_4$	81	509
		$AlCl_3$	82	509
		$SnCl_4$	82	519
		$SnCl_4$	40	513
		$SnCl_4$	73	513

TABLE 5. (*Continued*)

Substrate	Product	Agent	Yield (%)	References
		$SnCl_4$	58	513
		$SnCl_4$	63	513
		$AlCl_3$	6	466
		PPA	39	442
		$AlCl_3$	91	520

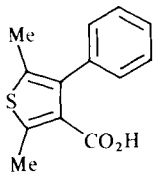
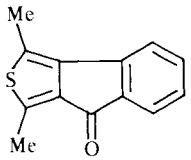
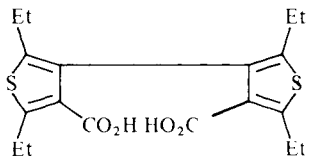
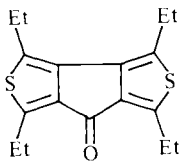
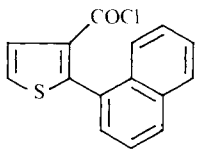
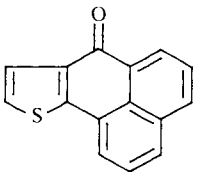
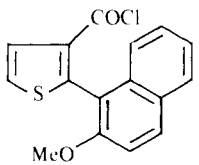
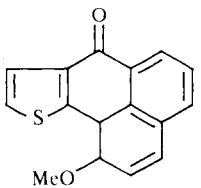
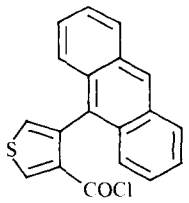
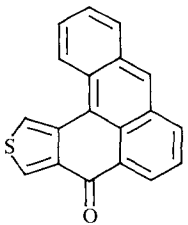
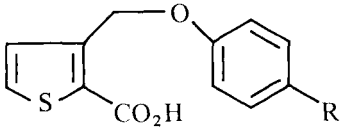
		TFA	55 521
		PPA $MeCOCl\text{-}SnCl_4$	68 78 25
		$AlCl_3$	68 516
		$SnCl_4$	68 522

TABLE 5. (*Continued*)

Substrate	Product	Agent	Yield (%)	References
		$SnCl_4$	56	516



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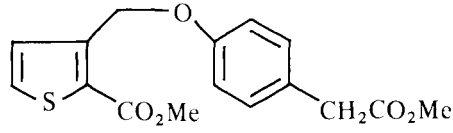
a. R = H
b. R = CH_2CO_2H



144

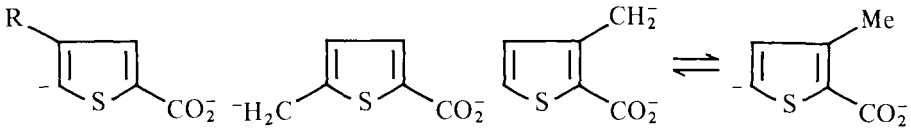
the latter has not been isolated in the great majority of cases these reactions are considered here. In general these ring closures present no surprises, but some interesting rearrangements have been observed by Tagawa and Katsujiro.[503] The phenylthiomethylthiophenecarboxylic acid **140** was cyclized by polyphosphoric acid (PPA) without rearrangement, but the oxygen analogue **141** gave **142** with the same reagent (Scheme 86).

PPA gave the same pattern of results with the corresponding 3-substituted thiophene-2-carboxylic acids. In this case the oxygen analogue **143a** was also treated with thionyl chloride–aluminum chloride and cyclized without rearrangement. Compound **143b** (and its sulfur analogue) were cyclized without complication by the same reagent;[504] it is noteworthy that the ester **144** also gave the cyclic ketone on treatment with phosphorus pentoxide.[505] Details of some other intramolecular cyclizations are collected in Tables 4 and 5.

d. REACTION WITH ORGANOMETALLIC DERIVATIVES

Both thiophene-2-carboxylic acid[523] and 4-methylthiophene-2-carboxylic acid[524] react with LDA to give the dianions (**145**; R = H, Me); these are attacked by electrophiles to give the 5-substituted thiophene-2-carboxylic acid. 5-Methylthiophene also gives a dianion (**146**), which reacts in the expected way with electrophiles; that obtained from 3-methylthiophene-2-carboxylic acid leads to products derived from either **147** or **148**, depending on the electrophile concerned.[524]

LDA attacks thiophene-3-carboxylic acid regiospecifically (at C-2), and the dianion formed undergoes the normal reactions with trimethylsilyl chloride[525] and with a range of alkyl halides and carbonyl compounds.[523] A mixture of phenyl 2-thienyl ketone, 2,2′-dithienyl ketone, and benzophenone is formed when lithium thiophene-2-carboxylate is heated with phenyllithium for a long period;[526] in another account of this reaction (with a much shorter reaction time) diphenyl 2-thienyl carbinol was detected among the products.[527]

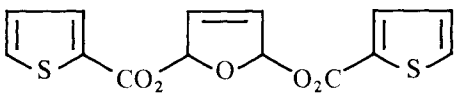


145 146 147 148

e. REDUCTION

The lithium aluminum hydride–aluminum chloride reagent reduces carboxyl groups to methyl; 3-phenylthiophene-2,5-dicarboxylic acid behaved normally in this respect.[288,521] The same reduction can be achieved by reaction of the acid with trichlorosilane, then alkali. This procedure has been applied to thiophene-2- and -3-carboxylic acids[528] and to a half-ester of thiophene-2,5-dicarboxylic acid.[529] Yields are generally poor. Reduction of thiophenecarboxylic acids to hydroxymethyl compounds has seldom been done, presumably because there are more attractive routes to the latter compounds. Various 4-arylaminothiophene-3-carboxylic acids[349] and both 5-chloro- and 5-bromothiophene-3-carboxylic acids[441] have been reduced by lithium aluminum hydride; the halogen atoms failed to survive the reduction in the last two cases.

Birch-style reduction of thiophene-2-carboxylic acid resulted in the formation of 5-mercaptopent-3-enoic acid by ring cleavage;[45] under rather different conditions the 2,5-dihydrothiophene was the major product with lithium in liquid ammonia.[530] Generally this last compound is also the product of the electrolytic reduction of thiophene-2-carboxylic acid salts (with a mercury cathode).[531,532] Electrolysis of the acid itself in dimethylformamide with a platinum electrode led to some interesting results. When furan was present **149** was formed;[533] when it was not the *N*-formylamino ketone **150** was obtained, arising, it is suggested, from the coupling of carboxy and $\cdot CH_2N(CHO)Me$ radicals.[534]



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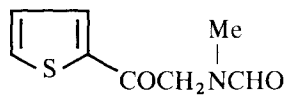


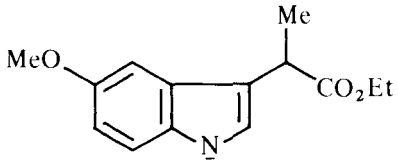
150

B. Thiophenecarboxylic Acid Chlorides

Improved methods for the large scale preparation of thiophene-2-carboxylic acid chloride have been described.[535,536]

a. ACYLATION OF HYDROXY AND AMINO COMPOUNDS

Thiophenecarboxylic acid chlorides of all classes have been used to prepare esters and amides from an exceedingly wide range of hydroxy and amino compounds. Many of the products appear in the Tables of Compounds (methods of preparation 1 and d). The *S*- and *N*-acylation of cysteine[537] and some of its esters[538] have been described; glycine[539] and the esters of various other α-aminoacids[540] have all given *N*-2-thenoyl derivatives. Thiamine phosphate yielded the *S*-acyl derivative with thiophene-2-carboxylic acid chloride.[541] *N*-2-thenoyl derivatives were obtained



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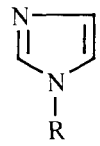

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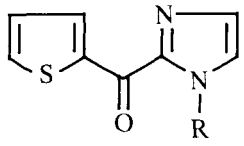
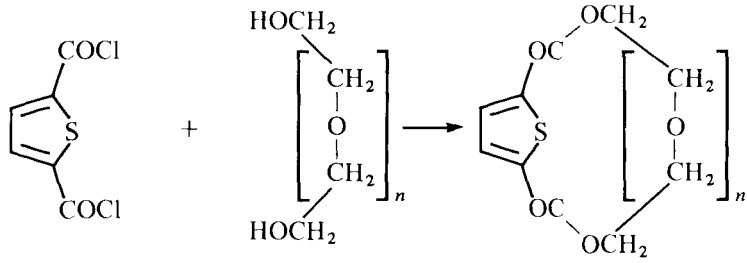


153

from **151**[542] and **152** (R = Me, Et); in the last two cases a rearrangement readily occurred, leading from the *N*(3)-acyl to the 2-acylimidazoles **153**.[543] Variously 5-substituted thiophene-2-carboxylic acid chlorides yielded *t*-butyl peroxy esters on reaction with *t*-butyl hydroperoxide.[544] Both thiophene- and 5-methylthiophene-2-acid chlorides have been used to fully acylate methyl α- and β-D-glycopyranosides.[545] Under appropriate conditions the bis chloride of thiophene-2,5-dicarboxylic acid condensed with the αω diols **154** ($n = 3,4,5$) giving the macrocyclic esters **155**[546] (Scheme 87).

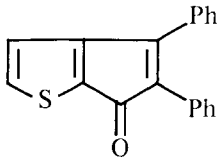


154 155

Scheme 87

b. FRIEDEL-CRAFTS AND RELATED REACTIONS

Thiophenecarboxylic acid chlorides derived from all types of acid behave quite normally as Friedel-Crafts acylating agents. Reactions have been carried out with benzene derivatives too numerous to collect here; biphenyl and fluorene,[547] 2- and 3-methoxybenzo[b]thiophenes[548] and a wide range of other heterocyclic systems have all been substrates for thenoylation. Some less usual syntheses in this category have also been reported. For example, ferrocene gave a mixture of the mono- and diacyl derivatives with thiophene-2-carboxylic acid chloride, and the monoacyl compound with 5-acetylthiophene-2-carboxylic acid chloride.[463] The former chloride, aluminum chloride, and diphenylacetylene produced the thienocyclo-



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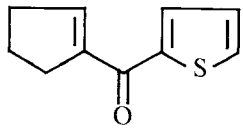

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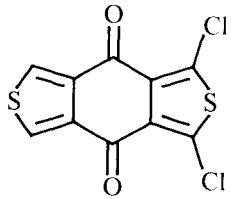


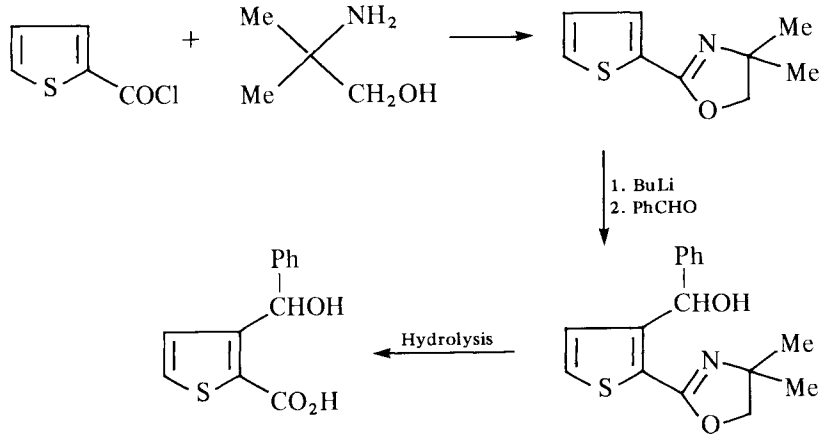
158

pentadienone **156**;[549] the same acyl halide and cyclopentene-antimony chloride reacted no further than the ketone **157**.[550] Aluminum chloride catalyzed the bisacylation of 2,5-dichlorothiophene by thiophene-3,4-dicarboxylic acid chloride, leading to an excellent yield of the quinone **158**.[551] A mixture of products (which included the equivalent of **158**) was obtained from the same bis acid chloride and benzene.[187]

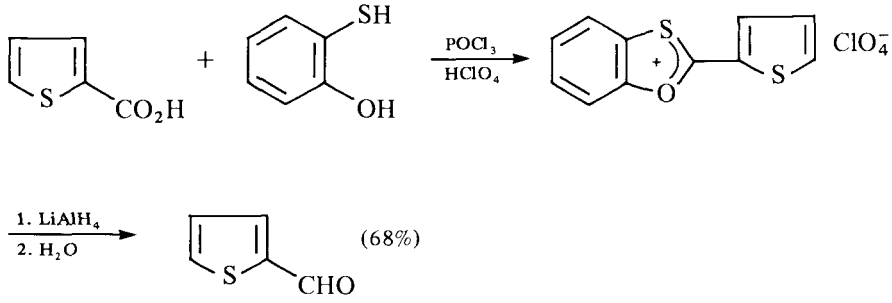
c. FORMATION OF HETEROCYCLIC RINGS

The carboxylic acids, their chlorides, esters, amides, and hydrazides undergo cyclization reactions (mainly with 1,3-difunctional compounds or with ortho disubstituted benzenes) to give heterocyclic rings. For the most part this work is outside the scope of this chapter, but some of the reactions involve modifications to the carboxyl function that allow useful transformations to be carried out. In one of these, thiophene-2-carboxylic acid (by way of the acid chloride) is converted into 4,4-dimethyl-2-(2-thenoyl)oxazoline; this group directs lithiation specifically to the thiophene 3-position[552] (Scheme 88).

The second example is an excellent method for the reduction of a carboxylic acid to an aldehyde, by way of a benzoxathiolium salt. The sequence, depicted in Scheme 89, gave a good yield of thiophene-2-aldehyde from the acid.[553]



Scheme 88

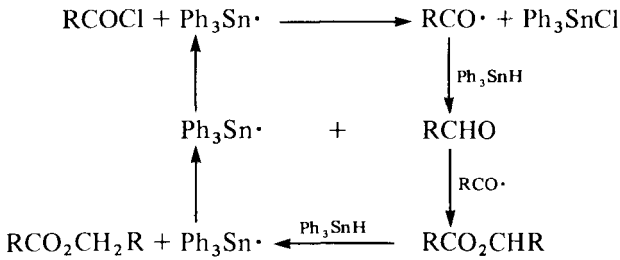


Scheme 89

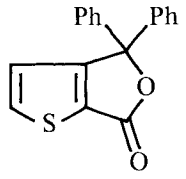
d. MISCELLANEOUS REACTIONS

Replacement of the chlorine atom by a cyano group can be brought about by reaction with sodium cyanide in acetonitrile[554] or under phase-transfer conditions[555] with thallium(I) cyanide[556] or with tributyltin cyanide.[557] Sodium thiosulphate and thiophene-2-carboxylic acid chloride give $C_4H_3S{-}COS_2O_3Na$.[558,559] This salt is itself an acylating agent; in its reaction with vitamin B_1 it caused rupture of the thiazole ring.[560] Exchange of the chlorine atoms by fluorine in a number of bromothiophene acid chlorides was achieved by reacting them with potassium hydrogen difluoride.[561] Diazoketones have been made from thiophene-3-carboxylic acid chloride[562] and from thiophene-2-acid chlorides with 5-phenyl,[71,241] 5-methoxycarbonyl,[563] 5-(2-arylethenyl),[564] and 4-methyl substituents.[565,566] A nearly quantitative yield of bisdiazoketone was obtained from thiophene-2,5-dicarboxylic acid chloride.[567] Reissert compounds were prepared from thiophene-2-carboxylic acid chloride, isoquinoline, and 6,7-dimethoxyisoquinoline.[568]

Scheme 90 (R = 2-thienyl) gives a possible mechanism for the formation of a variety of products (including thiophene-2-aldehyde) from the chloride of thiophene-2-carboxylic acid and triphenylstannane.[569]



Scheme 90



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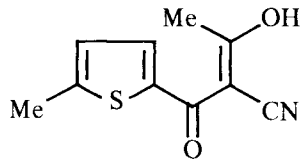


160

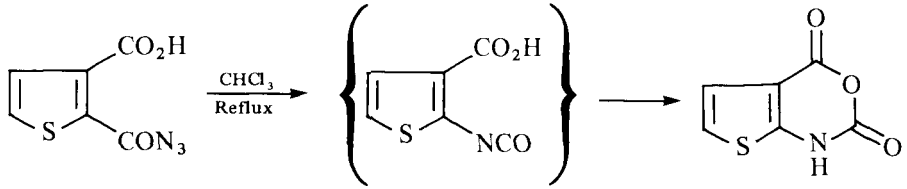
Normal reactions have been observed with other organometallic derivatives, including a Grignard reagent,[570] dimethylcadmium[79,189] and other dialkylcadmiums.[571] In the interaction of 3-benzoylthiophene-2-carboxylic acid chloride and diphenylcadmium the major product was the lactone **159** rather than the 2,3-diketone;[27] the isomeric 2-benzoyl-3-acid derivative behaved analogously.

When the chlorides of both 5-methylthiophene-2-carboxylic acid and thiophene-3-carboxylic acid[572] interacted with the anion of 3-oxobutyronitrile the product was the enol (e.g., **160**); it seems likely that further reaction is prevented by hydrogen bonding.

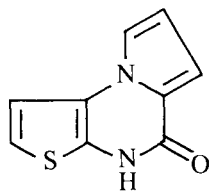
C. Thiophenecarboxylic Acid Azides

Thenoyl azides are available by the usual synthetic procedures, that is, by reaction of the acid chloride (or a mixture of the acid, ethyl chloroformate, and triethylamine), with sodium azide, or by treatment of the acyl hydrazide with nitrous acid. These standard preparations have been successfully used with thiophene-2-acid chloride itself,[573–578] and to some of its alkyl,[161,577] nitro,[124,267] and halogeno derivatives.[579] Thiophene-3-carboxylic azide is similarly accessible.[576,580] In an interesting modification 4-ethoxythiophene-3-carboxylic acid chloride was reacted with trimethylsilylazide in the presence of trace amounts of potassium azide and 18-crown-6; in the absence of these last two the reaction failed.[581] The same thenoyl azide has been obtained from the acyl hydrazide.[422,582] Another alternative is to treat the carboxylic acid with diphenylphosphoric azide. This was very effective with both thiophene-2- and -3-carboxylic acids[583] and with 5-methylthiophene-2-carboxylic acid.[584] In these instances the azide was decomposed in *t*-butyl alcohol, giving the *t*-butyl carbamate; in such reactions thenoyl azides behave quite unexceptionally. It is common to effect the decomposition in a solvent that can react with the isocyanate produced, and simple thenoyl azides lead to the normal products with carboxylic acids, alcohols, and amines. An interesting intramolecular reaction of this type took place with 2-azidocarbonylthiophene-3-carboxylic acid[585] (Scheme 91).

In suitably aryl-substituted thenoyl azides the intermediate can attack the second aromatic ring to give analogues of phenanthridone. The compounds **161**,[586] **162**,[579,586] and **163**[587,588] are typical of those available by this means.



Scheme 91



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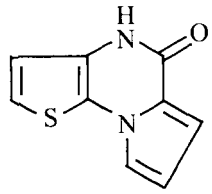

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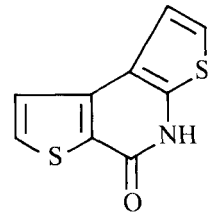

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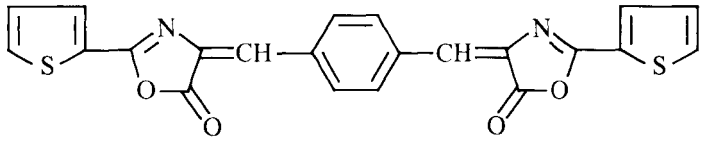
It is also possible for thenoyl azides to undergo replacement of the azido group by nucleophiles, that is to act as acylating agents. This was used in the preparation of the amide from thiophene-2-carboxylic acid azide and 1-amino-2-diethylamino-ethane; in this particular case the acid chloride did not produce the desired product.[573] Arlyamines also reacted with the same thenoyl azide after a long period at room temperature to give arylamides.[578]

D. Thiophenecarboxamides

Thiophenecarboxamides behave as typical aromatic amides. They can be reduced to amines by lithium aluminum hydride[241,589,590] without difficulty; they give thenoylureas with isocyanates[591] and can be acylated at the amino group by acetic anhydride[190] and by aroyl chlorides.[592] Hofmann degradation is successful with thiophene-3-carboxamide[580,593] and with a variety of 2- or 5-mono- or 2,5-dihalogenothiophene-3-carboxamides; because the product aminothiophenes are unstable they are isolated as acyl derivatives. The degradation fails with 5-nitrothiophene-3-carboxamide.[454] On treatment with phosgene, thiophene-2-



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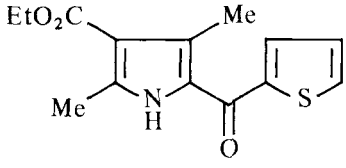

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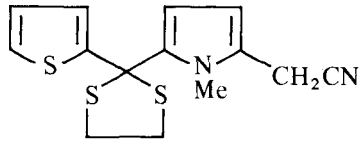
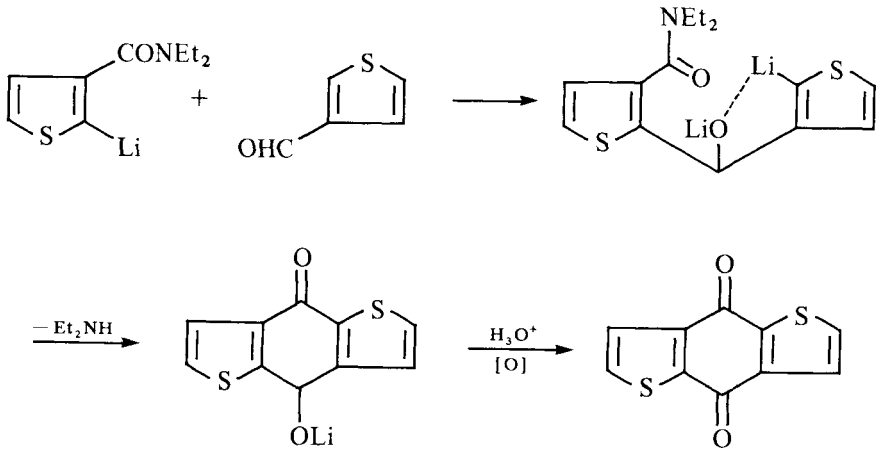


166

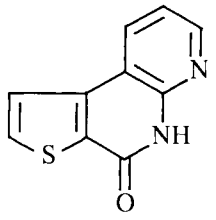
carboxamide[594] and thiophene-2,5-dicarboxamide[595] are converted into the mono- and bisacylthiocyanates, respectively. Thenoylglycine reacts with arylaldehydes to produce azlactones;[596] when benzene-1,4-dialdehyde was employed, the bis-azlactone dye **164** was obtained.[597]

The acylation of electron-rich aromatic nuclei by the combination of a tertiary amide and phosphoryl chloride is well known. *N*,*N*-Dimethylthiophene-2-carboxamide is also effective in this reaction and gave an 86% yield of **165** from the pyrrole.[598] In a similar reaction ethane-1,2-thiol was added to the acylating mixture, so that the thioketal **166** was obtained from 2-cyanomethyl-1-methylpyrrole.[599] The directive influence of the dimethyloxazoline group upon lithiation of the thiophene ring was mentioned in II.1.B.c. The *N*,*N*-diethylcarboxamido group is equally strongly directive; when located at C-3, it directs lithiation of a thiophene to C-2. This is utilized in a fascinating annelation process employing the thiophene-3-carboxamide and a suitable aldehyde with a vacant ortho position (for example, thiophene-3-aldehyde or 1-benzylindole-3-aldehyde). The suggested mechanism, involving "tandem directed metalation," is illustrated in Scheme 92.[600]



Scheme 92

(77%)



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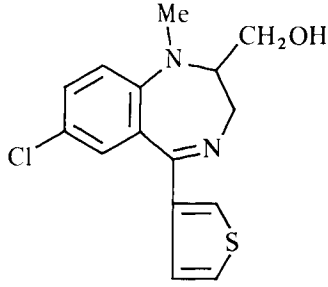
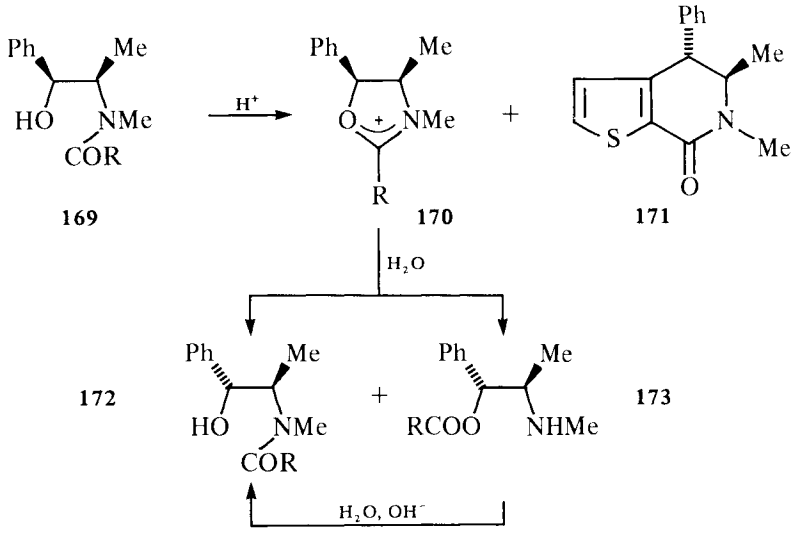


168

Irradiation of the three isomers of *N*-(pyridyl)thiophene-2-carboxamide gave the azaphenanthridone analogues (e.g., **167** from *N*-(2-pyridyl)thiophene-2-carboxamide).[601] Several *N*-(2-thenoyl)-2-phenylethylamines have been cyclized to 3,4-dihydroisoquinolines by phosphoryl chloride. The reaction is successful not only when the benzene ring carries activating methoxy or methylenedioxy groups,[326, 602-604] but also when it is unsubstituted.[605] The 1,4-benzodiazepine **168** was also obtained by cyclization of a thiophenecarboxamide.[606]

Some interesting isomerizations of the amide of (−)ephedrine **169** (R = 2-thienyl) have been reported. When treated with concentrated sulfuric acid, then water, the products were the carbostyril **171** and the *threo*-amide **172** and -ester **173**.[607] Similar observations were made by Maffrand *et al.*[608] (who used polyphosphoric acid for the change), although there is a wide discrepancy in the melting points quoted for **169** by the two groups (78 to 80° and 222°). The results are explicable in terms of the formation of an intermediate oxazolidinium salt (**170**), which can undergo stereospecific ring-opening reactions (Scheme 93).

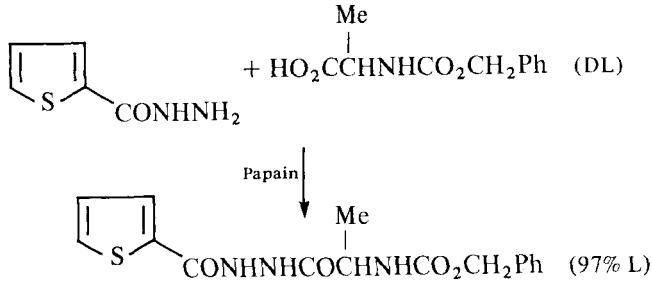


Scheme 93

E. Thiophenecarboxyhydrazides and -hydrazones

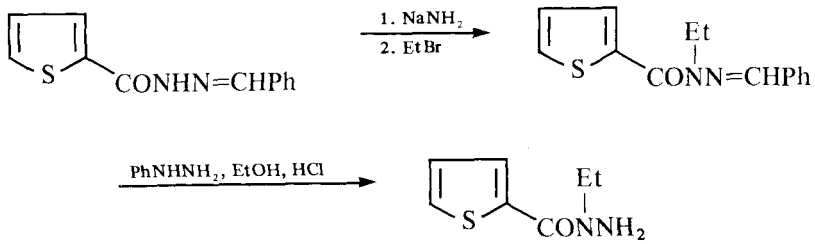
The most commonly reported reaction of thenoylhydrazides is their conversion into heteroarylthiophenes by ring closures involving the acylhydrazide function; these conversions are not considered in this chapter.

Reaction of racemic *N*-benzyloxycarbonyl-α-amino acids with 2-thenoylhydrazine in the presence of papain gives the unsymmetrical hydrazide of one enantiomer in great excess. For example, the product from racemic alanine is 97% of the L-configuration[609] (Scheme 94).



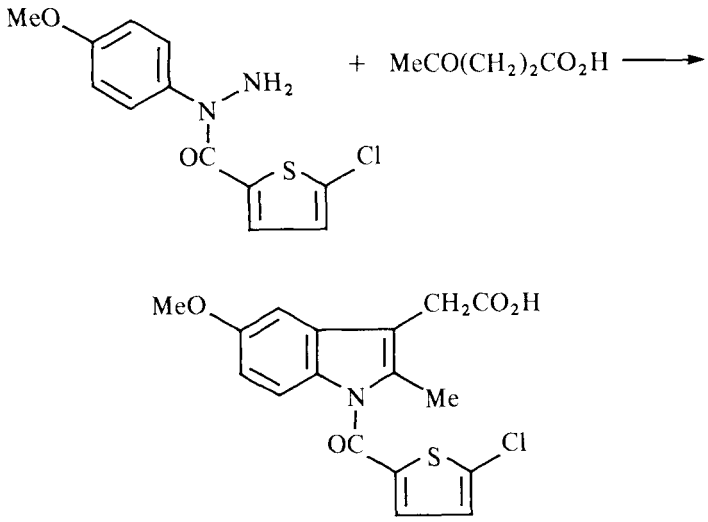
Scheme 94

The proton of the NH group adjacent to the carbonyl function in thenoylhydrazones is sufficiently acidic to be removed by strong bases, and the anion can be alkylated. Cleavage of the azine bond then gives an *N*-alkyl-*N*-thenoylhydrazine[610] (Scheme 95).



Scheme 95

N-Aryl-*N*-thenoylhydrazines undergo the Fischer indole synthesis with ketones and with ketoacids to produce *N*-thenoylindoles;[611–615] the preparation shown in Scheme 96 is typical.



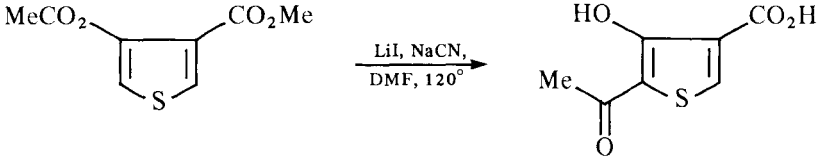
Scheme 96

The azine linkages in various hydrazones made from 2-thenoylhydrazide have been reduced catalytically[616] or by sodium borohydride,[617] yielding the *N*-(2-thenoyl)-*N'*-alkylhydrazine. The hydrazone of chloral and 2-thenoylhydrazide is a useful intermediate; on heating with primary alkyl- or arylamines it is converted into the *N*-alkyl- (or aryl)-thiophene-2-carboxamide.[618] Oxidation of 2-thenoylhydrazide with Gibson's reagent gives *N*,*N'*-bis(2-thenoyl)hydrazide.[619]

F. Thiophenecarboxylic Acid Esters

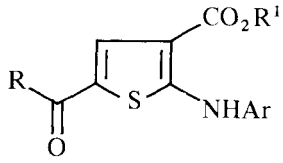
The great majority of thiophenecarboxylates have been obtained in the usual ways from the acid or acid chloride, or by ring closure of ester-bearing intermediates. The less common preparation by reaction of the acid or a salt with an alkyl halide has been used to prepare methyl, 2-*N*,*N*-dialkylaminoethyl,[620] and 1-acyloxyalkyl esters[621] of a range of 4-arylaminothiophene-3-carboxylic acids.

If an ester is treated with iodotrimethylsilane in an aprotic solvent, the trimethylsilyl ester is produced; this, with water, gives a good yield of the acid. This



Scheme 97

mild technique for ester hydrolysis works well with ethyl thiophene-2-carboxylate.[622] Lithium iodide–sodium cyanide in DMF not only brought about ester hydrolysis, but also induced the Fries rearrangement of methyl 4-acetoxythiophene-3-carboxylate[418] (Scheme 97). Treatment of several 5-methyl or -aryl-2-acylaminothiophene-3-carboxylates with lithium iodide in refluxing collidine resulted in both ester hydrolysis and decarboxylation.[584] Esters of structure **174** are very difficult to saponify satisfactorily unless R^1 is *t*-butyl, in which case hydrolysis takes place very readily with trifluoracetic acid at 0°.[376] Ethyl 2-amino- (**175**, R = H) and 2-acetylamino-5-nitrothiophene-2-carboxylate (**175**, R = MeCO) have been transesterified with several different alcohols in the presence of tetra-*n*-butyltitanate as catalyst.[191,395]



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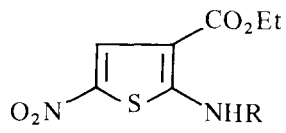
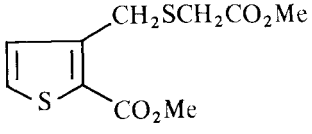


175

The acetonitrile anion reacts in the usual way with ethyl thiophene-2-carboxylate,[572] with a dimethyl 3,4-diarylthiophene-2,5-dicarboxylate,[287] and with the diethyl ester of a thiophene-2,4-dicarboxylic acid.[392] With these diesters the bis α-cyanoketones were formed.

New conditions for the Dieckmann reaction have been applied very successfully to the diester **176**.[623] When the azafluorene **177** was treated with potassium and ethyl thiophene-2-carboxylate, reaction took place at the dibenzylic position rather than at the methyl group, and the product was the enol **178**.[624]



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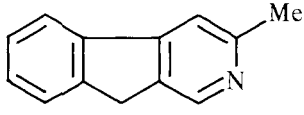

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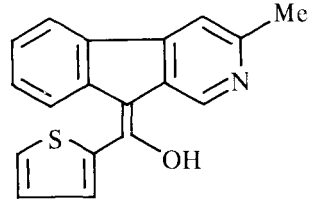
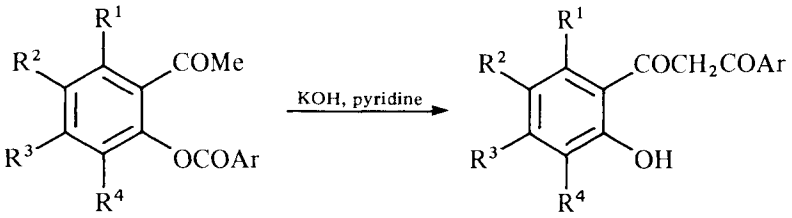


178

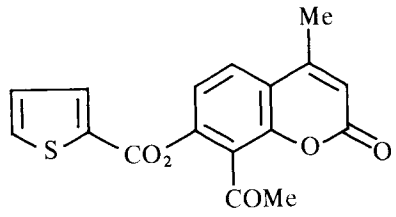
Methyl esters of 3-methylthiophene-2-[625] and of thiophene-2- and -3-carboxylic acids[626] form chromiumtricarbonyl compounds when reacted with suitable chromiumcarbonyls. It is of some interest that in the case of dimethyl 3-phenylthiophene-2,5-dicarboxylate the chromium atom is associated with the benzene and not the thiophene ring.[627]



Scheme 98

A rearrangement of orthoacyloxyacetophenones (the Baker-Venkataraman rearrangement), valuable for the preparation of intermediates for chromone synthesis, takes the general form shown in Scheme 98; R^1—R^4 can be a variety of substituents and can include the fusion of a second ring. The rearrangement has been applied to thiophene-2-carboxylates of orthohydroxy methyl ketones derived from benzene itself,[628] from the methoxybenzenes,[629] from variously substituted benzenes,[630,631] from benzofuran,[632] from a benzoisoxazole,[633] and from chromones (e.g., **179**).[634]

Studies have also been made of the Fries rearrangement of aryl esters of thiophenecarboxylic acids. At 120° neat phenyl thiophene-2-carboxylate gave very poor yields of 2- (10%) and 4-thenoylphenol (5%) when reacted with aluminum chloride.[635] Photolysis of the same ester in hexane gave much improved results, again (unusually), the 2-ketone (33%) being the major product.[636] The rearrangement also takes place with substituted-phenyl thiophene-2-carboxylates (e.g., **180**)[637] and with esters derived from 5-chlorothiophene-2- and thiophene-3-carboxylic acids.[638]



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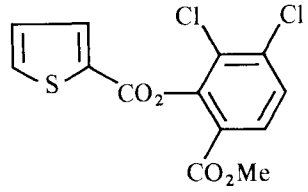


180

The lithium aluminum hydride reduction of 3,4-dimethyl-[639] and 3,4-diphenylthiophene-2,5-dicarboxylates[286] proceeds without complication; in the same reaction of dimethyl 3,4-di(4-methoxyphenyl)thiophene-2,5-dicarboxylate, however, the expected product was accompanied by some 3,4-di(4-hydroxyphenyl) thiophene.[286] As is the case with their acids, simple thiophene-2-carboxylates have rarely been reduced; an exception is the synthesis of 2-hydroxydideuteromethylthiophene by the action of lithium aluminum deuteride on methyl thiophene-2-

carboxylate.[640,641] The reduction of thiophene-3-carboxylates leads to products less accessible by other means; esters with 4-alkoxy-5-aryl-,[424,642] 2-arylthio-5-ethyl-,[442] and 5-(protected ketone)-substitutents[643] have all been reduced to the corresponding 3-hydroxymethylthiophenes.

G. *Thiophenecarboxylic Acid Anhydrides and Dithenoyl Peroxides*

The cyclic anhydrides of thiophenedicarboxylic acids are discussed in Section II.2.A. Very little information about acyclic anhydrides is available. The anhydride of thiophene-3-carboxylic acid has been prepared by the action of acetic anhydride on the acid,[124,644] and that of 5-nitrothiophene-2-carboxylic acid from the sodium salt and the acid chloride.[124] The former anhydride and cyclohexene gave 5-cyclohexylthiophene-3-carboxylic acid and not the acylated cycloalkene when treated with polyphosphoric acid.[644] The thermolysis of 2-thenoic anhydride in the presence of rhodium compounds led to low yields of 2,2′- and 2,3′-bithienyl.[645]

A few dithenoyl peroxides have been described. Their preparation involves treatment of the acid chloride with sodium peroxide or with hydrogen peroxide–sodium carbonate. Details of some of the peroxides are collected in Table 37.

The thermal decomposition of di-2-thenoyl peroxide and its 5-methyl, 5-*t*-butyl, 5-chloro-, and 5-bromo analogues was found to be a first-order reaction, but this was not so with di-(5-nitro-2-thenoyl)peroxide.[646] The decomposition products were carbon dioxide and the original 5-substituted thiophene-2-carboxylic acid. When di-2-thenoyl peroxide is heated in an aromatic solvent, products arise that depend on the nature of the solvent. In halogenobenzenes, phenyl thiophene-2-carboxylate is produced, arising from displacement of halogen by thenoyloxy radicals, whereas in toluene and cumene the side-chains are attacked.[647] In iodobenzene halogen displacement was also noted, but when copper(II) chloride was present, iodophenyl thiophene-2-carboxylates were formed.[648] Similar results were obtained when di-3-thenoyl-peroxide was decomposed in benzene, toluene, and chlorobenzene.[124]

2. Special Reactions of the Various Substituted Thiophenecarboxylic Acids

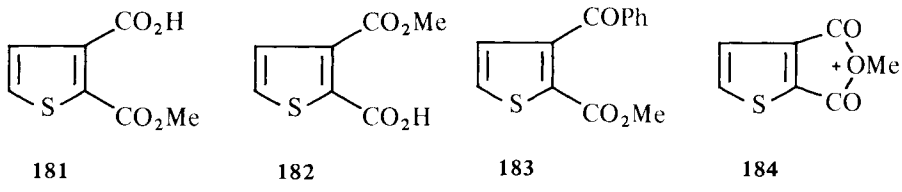
Generally in this section only those reactions that involve *both the substituent and the carboxyl function* are reviewed. Modifications of all the common substituents and of side-chains, electrophilic, nucleophilic, and radical substitution, and desulfurization are all dealt with in other chapters of this work. Many of the products of such reactions are entered into the Tables of Compounds, however.

A. *Thiophenepolycarboxylic Acids*

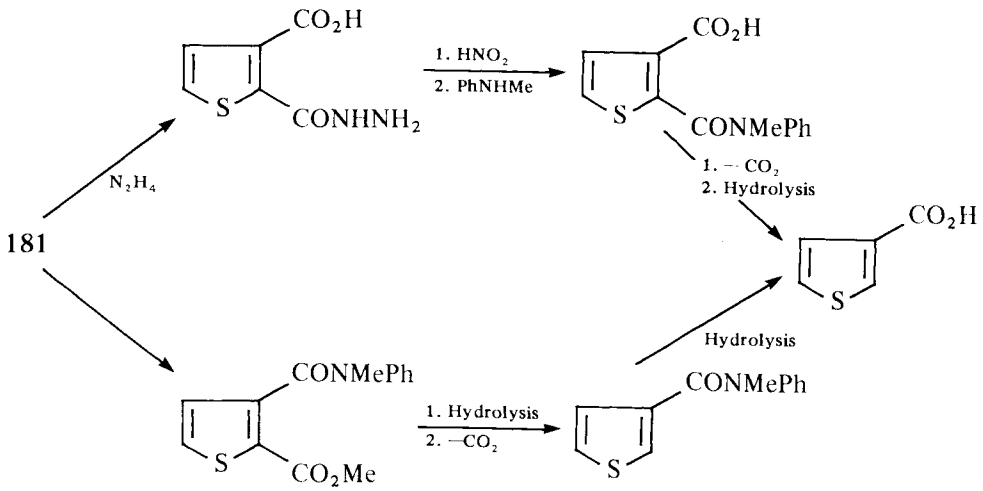
Partial hydrolysis has been achieved of both the dimethyl[649] and diethyl[468] esters of thiophene-2,5-dicarboxylic acid. The presence of one[289,428] or two[411] hydroxy

groups or a methylenedioxy ring[482] does not prevent the reaction. Successful partial hydrolyses have also been carried out of 2,3-[161] and 2,4-[567] diesters; in the former case the group in the 2-position is attacked, but in the latter the structure of the product is unknown. In some cases the half-esters have undergone further reactions, for example, ethyl 5-carboxythiophene-2-carboxylate has been made into its acid chloride and this treated with allylamine;[468] a series of derivatives has been prepared from the analogous 3,4-methylenedioxy half-ester.[482] Baker and his co-workers uncovered a fascinating case of rearrangement in the 2,3-diacid series.[161] The half-esters **181** and **182** were used, being available by the action of methanol on the anhydride and by partial hydrolysis, respectively.

Treatment of **182** with thionyl chloride followed by benzene and aluminum chloride gave **183** instead of the expected product; further, the recovered acid was found to be **181**, not **182**. These reactions were explained in terms of the postulated intermediate **184**, and a similar species was used to interpret results in the half-amide series (Scheme 99).



181 **182** **183** **184**



Scheme 99

In a series of *N,N*-disubstituted methyl 5-carboxamidothiophene-2-carboxylates it was found possible to hydrolyze the ester group selectively;[542] monoesterification of thiophene-3,4-dicarboxylic acid has been achieved,[178] as has monocondensation of diethyl thiophene-2,5-dicarboxylate with the anion of acetonitrile.[649]

Anhydride formation has been observed in both types of diacid with adjacent carboxyl groups, the 2,3-[78,100,159,179,650] and 3,4-[40,101,159] series. The production of imides has been noted,[159,651] as has the preparation of the 3,4-diamide from the corresponding diester, both in the parent compound[652] and in its 2,5-diamino derivative.[653]

The reduction of a 3,4-anhydride to the corresponding dialcohol has been carried out with lithium aluminum hydride[40] and the thermolysis of thiophene-2,3-dicarboxylic anhydride has been investigated with the aid of a trapping agent to detect a fused cyclopropenone (or equivalent species). The results showed that such a species did seem to have been involved.[654] Phthalein and rhodamine dyes have been prepared by substituting thiophene-2,3-dicarboxylic acid for phthalic acid in the usual procedures,[162] and derivatives of the former acid have been used for the synthesis of fused heterocycles. Thus the diethyl ester with hydroxylamine gave a bishydroxamic acid which with benzenesulfonyl chloride afforded a mixture of thieno[2,3-*d*] and [3,2-*d*] pyrimidines in a 1:3 ratio;[15] the same reaction was carried out with diethyl thiophene-3,4-dicarboxylate by the same workers to give a thieno [3,4-*d*]pyrimidine. In another study a thieno [2,3-*d*] pyridazinedione was prepared from 5-methylthiophene-2,3-dicarboxylic acid and hydrazine.[655]

B. Aminothiophenecarboxylic Acids

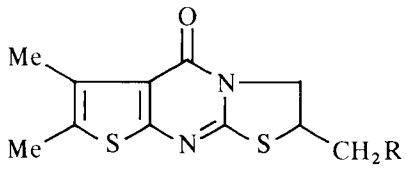
The reactions of these compounds that involve both functional groups are all cyclizations, and a selection of these is presented, mainly in tabular form.

a. COMPOUNDS DERIVED FROM 2-NHR-3-COX-THIOPHENES WITH VARIOUS OTHER SUBSTITUENTS IN THE RING

Material on these compounds is summarized in Tables 6 and 7.

A number of tricyclic compounds containing the thienopyrimidine system has been prepared; thus the appropriate aminothiophene ester with allyl isothiocyanate[679,680] or its dibromo derivative[681] gave the substance **185**, R = H or R = Br respectively.

Another double cyclization, this time with thiocyanatoacetone, yielded the closely related ring system **186**.[682,683] A series of amino esters condensed, under the



185

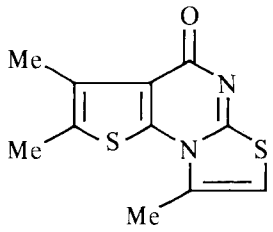


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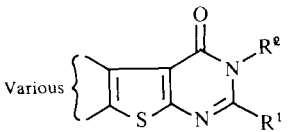
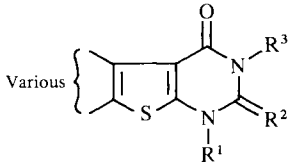
TABLE 6. THIENO-[2,3-*d*]PYRIMIDONES

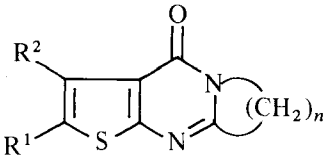


X	R	Reagent(s)	Product(s)	References
OMe	CHO	$MeOH/NH_3$	$R^1 = R^2 = H$	161
OEt	H	Imidates, nitriles, formamide	R^1 = various, $R^2 = H$	656
OMe	H	Imidates	R^1 = various, $R^2 = H$	657
OMe	$COCH_3$	$ArNH_2/POCl_3$	$R^1 = Me$, $R^2 = Ar$	371
OEt	H	$Me_2\overset{+}{N}=CHCl$ then R^3NH_2	$R^1 = H$, $R^2 = R^3$	658
OMe	H	$R^3C(=NH)OEt$	$R^1 = R^3$ = 5-nitrofuryl, $R^2 = H$	659
OEt	COR^3	N_2H_4	$R^1 = R^3$, $R^2 = NH_2$	660
OEt	H	$CH_2=CHCH_2NCS$ then KOH	$R^1 = S^-K^+$, R^2 = allyl	661
OEt	H	PhCONCS then base	$R^1 = S^-K^+$, $R^2 = H$	662
OEt	H	$R^3N=C(OMe)NHR^4$ or $R^3N=C(SMe)NHR^4$	$R^1 = NHR^4$, $R^2 = R^3$	663
NHR^3	$COCH_3$	PPA	$R^1 = Me$, R^2 = various	664
OEt	H	$R^3SC(=\overset{+}{N}R^4R^5)NHR^6$	$R^1 = NR^4R^5$, $R^2 = R^6$	665
NH_2	COR^3	NaOH	$R^1 = R^3$, $R^2 = H$	666
NH_2	$COCO_2Et$	260°	$R^1 = CO_2Et$, $R^2 = H$	667, 668, 669
NHR^3	COR^4	NaOH	$R^1 = R^4$, $R^2 = R^3$	670, 671
NH_2	COAr	Heat	$R^1 = Ar$, $R^2 = H$	672, 673
OEt	COAr	Heat	$R^1 = Ar$, $R^2 = H$	672, 673
OMe	COR^3	$(MeNH)_2PO(OPh)$ 250°	$R^1 = R^2 = Me$	674

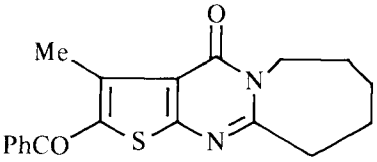
TABLE 7. OTHER THIENO[2,3-*d*]PYRIMIDINES



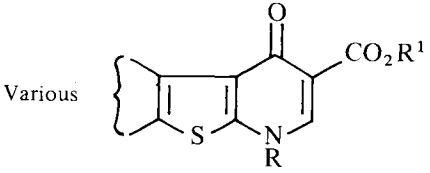
X	R	Reagent(s)	Product(s)	References
OEt	H	R^4NCO/NEt_3 then NaOH	$R^1 = H, R^2 = O, R^3 = R^4$	675
OEt	H	KOCN	$R^1 = R^3 = H, R^2 = O$	676
OEt	H	R^4NCO	$R^1 = H, R^2 = O, R^3 = R^4$	13
OMe	H	$(NH_2)_2CO$	$R^1 = R^3 = H, R^2 = O$	670, 671
NH_2	H	$(NH_2)_2CO$	$R^1 = R^3 = H, R^2 = O$	670, 671
OEt	H	$(NH_2)_2CS$	$R^1 = R^3 = H, R^2 = S$	677
OEt	H	R^4NCS then NaOH	$R^1 = H, R^2 = S, R^3 = R^4$	677
OEt	H	R^4NCS then EtOH/HCl	$R^1 = H, R^2 = S, R^3 = R^4$	678, 679



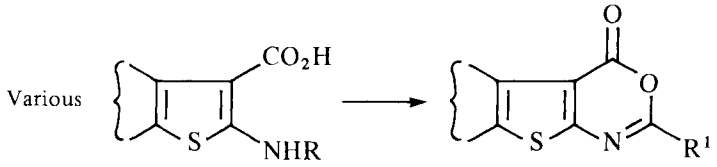
187 $n = 3, 4, 5$



188



189



R = COMe, R^1 = Me, Refs. 664, 686–688
R = H, R^1 = Me, Refs. 664, 688–690
R = COAr, R^1 = Ar, Ref. 685
R = $COCO_2Et$, R^1 = CO_2Et, Refs. 667–669, 691.

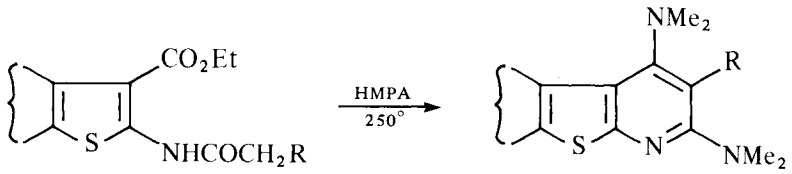
Scheme 100

action of phosphoryl chloride, with a number of lactams to give substances of the general formula **187**,[684] whereas a caprolactam *O*-ether reacted with the appropriate aminothiophenecarboxylic acid to afford **188**.[376]

Many 2-aminothiophene-3-carboxylic acids and their acyl derivatives have been converted into thieno[2,3-*d*] 1,3-oxazinones, usually by means of acetic anhydride, but in one case thionyl chloride in DMF was used[685] (Scheme 100).

The reaction of phosphorus pentasulfide[692] or the valuable new reagent *p*-methoxyphenylthionophosphine sulfide dimer[693] converts an ethyl 2-acylamino-thiophenecarboxylate into the corresponding thioamide or thieno[2,3-*d*] 1,3-thiazinone depending on the conditions; the former reagent will also change the oxazine into the thiazine derivative.

Thieno[2,3-*b*] pyridines of type **189** have been made by the condensation of diethyl ethoxymethylenemalonate with a number of aminothiophene acids or esters followed by cyclization either by heating or by treatment with various reagents.[694–698] Diaminothieno [2,3-*b*] pyridines were prepared by the route shown in Scheme 101.[699]



Scheme 101

Examples of ring systems accessible from 2-aminothiophene-3-carboxylic acid derivatives (themselves usually readily available from the Gewald synthesis) are collected in Table 8.

b. COMPOUNDS DERIVED FROM 3-NHR-2-COX-THIOPHENES WITH VARIOUS OTHER SUBSTITUENTS IN THE RING

Tables 9 and 10 present data for these compounds.

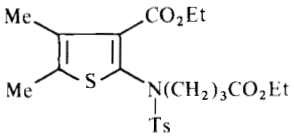
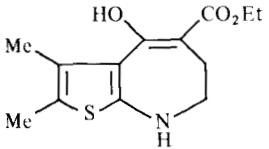
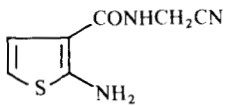
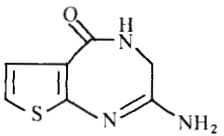
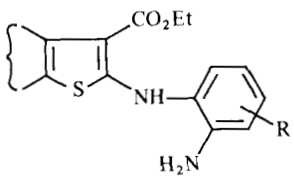
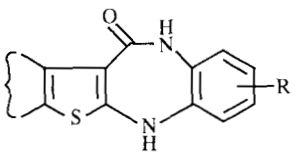
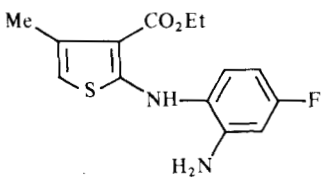
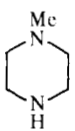
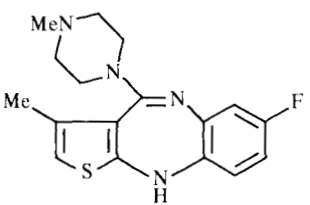
c. COMPOUNDS DERIVED FROM 4-NHR-3-COX-THIOPHENES WITH VARIOUS OTHER SUBSTITUENTS IN THE RING

Tables 11 and 12 summarized data for these compounds.

d. OTHER REACTIONS OF AMINOTHIOPHENECARBOXYLIC ACIDS AND THEIR DERIVATIVES

Selective hydrolysis of 2-acylaminothiophenecarboxylic esters to the corresponding acids has been achieved,[664,686] and in one case the product has been converted into an acyl azide and thence to a carbamate.[719] Methyl 3-formylaminothiophene-2-carboxylate has been converted into the 2-carboxamide by the action of

TABLE 8. OTHER RING SYSTEMS DERIVED FROM 2-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS

Starting Material	Reagent	Product	References
	NaH		700
	NaOMe		373
	$MeSOCH_2^-Na^+$		387, 701
	$TiCl_4$, PhOMe, 		702

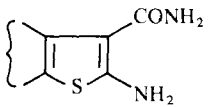
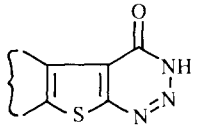
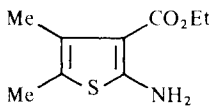
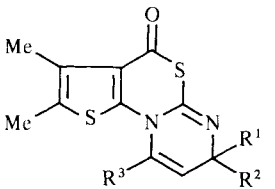
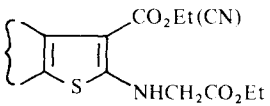
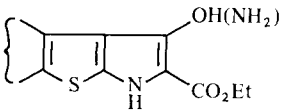
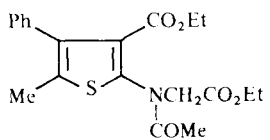
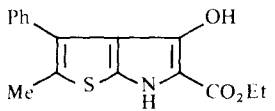
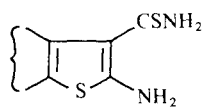
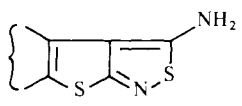
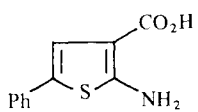
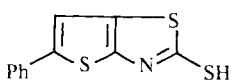
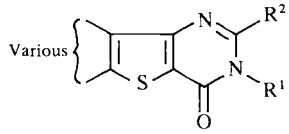
	HNO_2		703
	$R^3COCH_2CR^1R^2NCS$		704
	NaOEt		396
	NaH		705
	I_2/EtOH or H_2O_2		358
	S_2Cl_2 then CS_2/NaOH		706

TABLE 9. THIENO[3,2-*d*]PYRIMIDONES

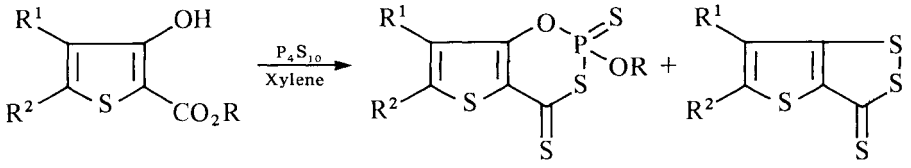


X	R	Reagent(s)	Product(s)	References
OMe	H	Imidates, nitriles formamide	$R^1 = H$, R^2 = various	656
OMe	H	$HCONH_2$	$R^1 = R^2 = H$	707, 708
NH_2	CHO	Heat	$R^1 = R^2 = H$	707
OMe	H	$PhCH_2NH_2/POCl_3$	$R^1 = CH_2Ph$, $R^2 = H$	707
OMe	CHOEt	NH_3	$R^1 = R^2 = H$	346
NH_2	H	$HC(OEt)_3/Ac_2O$	$R^1 = R^2 = H$	346
OMe	H	$R^3C(=NH)OR^4$	$R^1 = H$, $R^2 = R^3$	657
OMe	COMe	$ArNH_2/POCl_3$	$R^1 = Ar$, $R^2 = Me$	371
OH	COMe	$PhNH_2/POCl_3$	$R^1 = Ph$, $R^2 = Me$	687
OMe	CHO	NH_3 or $HCOONH_4$	$R^1 = R^2 = H$	708

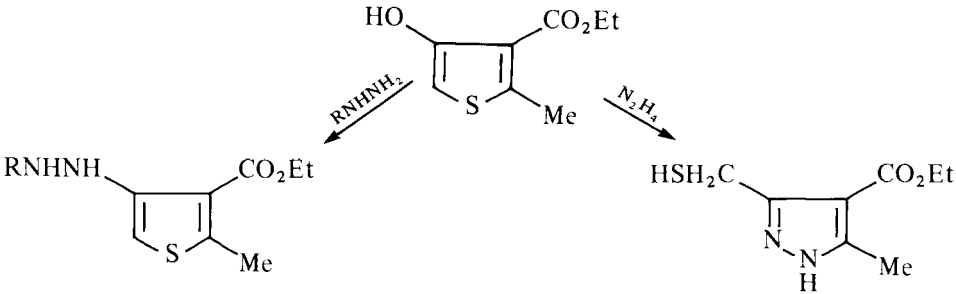
ammonia;[707] the preparation of hydroxynitriles from 2-aminothiophene-3-carboxylic esters by a ring-opening reaction is dealt with in Section IV.1.E.

C. Hydroxy- and Mercaptothiophenecarboxylic Acids

A number of ring-closure reactions has been carried out in this series, an example being shown in Scheme 102.[406, 720]



Scheme 102



R = Me, Ph

Scheme 103

TABLE 10. OTHER RING SYSTEMS DERIVED FROM 3-AMINOTHIOPHENE-2-CARBOXYLIC ACIDS

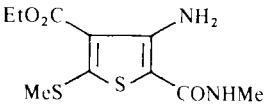
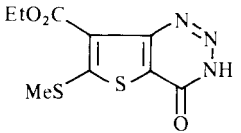
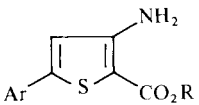
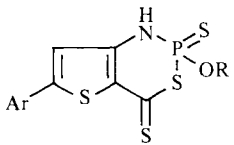
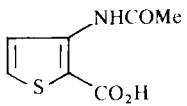
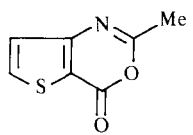
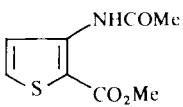
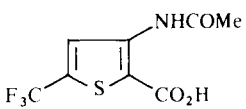
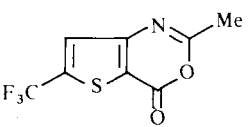
Starting Material	Reagent	Product	References
	HNO_2		394
	P_4S_{10}		709
	Ac_2O		710
	PCl_5		
	Ac_2O		711

TABLE 10. *(Continued)*

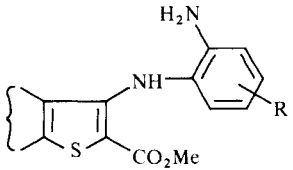
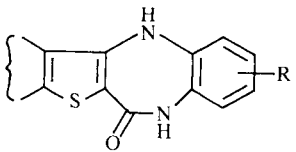
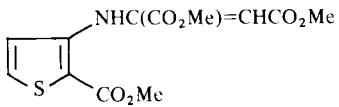
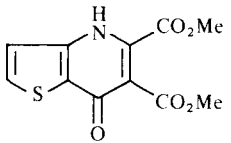
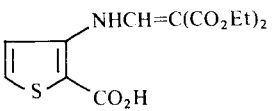
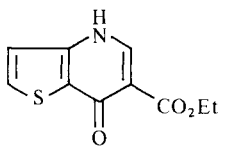
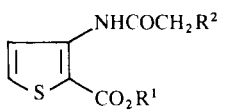
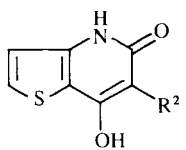
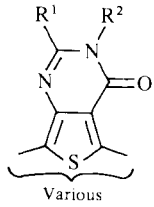
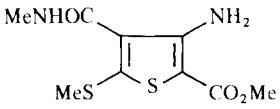
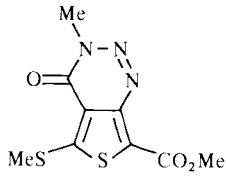
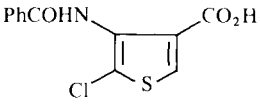
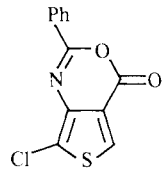
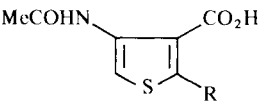
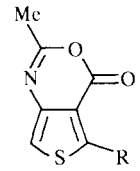
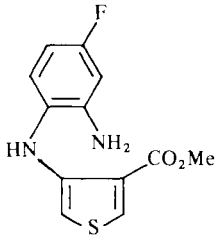
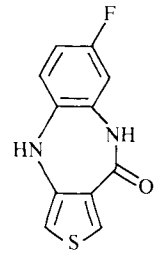
Starting Material	Reagent	Product	References
	$MeSOCH_2^-Na^+$		387
	NaH		712
	Ethyl polyphosphate		712
	NaH		713

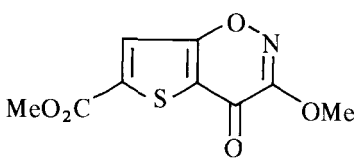
TABLE 11. THIENO[3,4-*d*]PYRIMIDONES



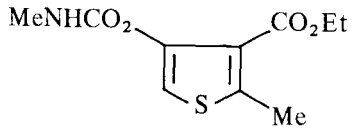
X	R	Reagent(s)	Product(s)	References
NHR^3	H	Ac_2O	$R^1 = Me$, $R^2 = R^3$	400, 401
NH_2	CHO	NaOMe	$R^1 = R^2 = H$	161
OH	$COCH_3$	$ArNH_2/POCl_3$	$R^1 = Me$, $R^2 = Ar$	714
OMe	H	KOCN/HCl	$R^1 = OH$, $R^2 = H$	715

TABLE 12. OTHER RING SYSTEMS DERIVED FROM 4-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS

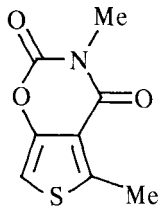
Starting Material	Reagent	Product	References
	HNO_2		394
	PCl_5		716
	Ac_2O		717, 718
	NaH		701



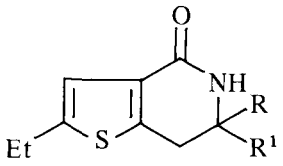
190



191



192

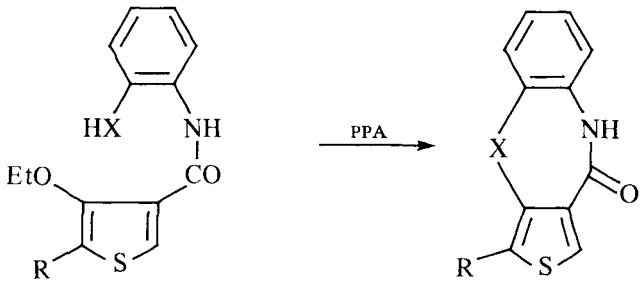


193

An interesting pair of reactions is depicted in Scheme 103; one involves a ring scission followed by reclosure.[721]

Treatment of dimethyl 3-cyanatothiophene-2,5-dicarboxylate with triethylamine yielded **190**[722] whereas the action of potassium hydroxide on **191** afforded the fused oxazine **192** in 69% yield.[675] Fused benzoxazepines[419,420] and benzothiazepines[723] were made by the process of Scheme 104.

Acetylation of methyl 3-hydroxythiophene-2-carboxylate could be readily achieved, but cyclization to a thiophene analogue of 4-hydroxycoumarin could not.[724] 5-Ethyl-2-mercaptothiophene-3-carboxamide was converted into compounds of the type **193** by the action of carbonyl compounds and hydrogen chloride,[725] whereas dimethyl 3,4-dihydroxythiophene-2,5-dicarboxylate underwent an interesting ring cleavage in alkaline solution.[726]

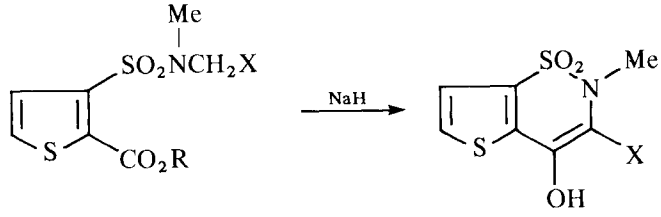


X = O, S

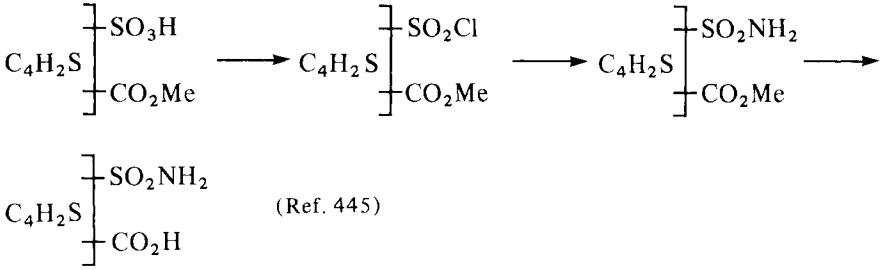
Scheme 104

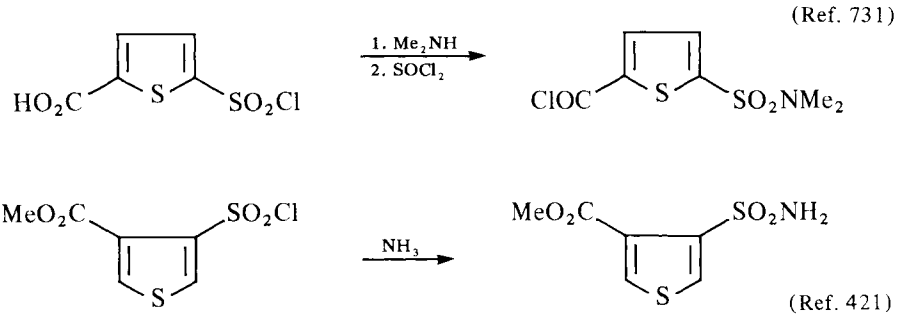
D. *Carboxythiophene Sulfonic Acids*

Again, the majority of reactions of these compounds involving the carboxyl group or its derivatives have been ring closures, usually to thienothiazines or saccharinlike compounds. Scheme 105 summarizes some examples of the former,[446,471,727,728] whereas saccharins have been made from the 2-sulfo-[445,729] and 4-sulfothiophene-3-carboxylic acids[730] and 3-sulfothiophene-2-carboxylic acid.[445] In the course of this work several selective transformations were carried out with thiophenes of various different substitution patterns (Scheme 106).



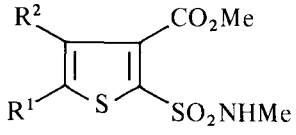
Scheme 105



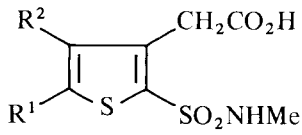


Scheme 106

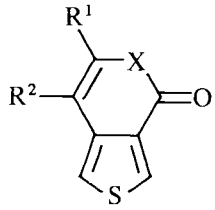
The conversion, by a multistep sequence, of compounds of the general formula **194** into **195** has been described.[732]



194



195



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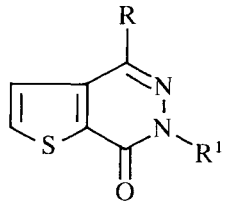


197

E. The Halogenothiophenecarboxylic Acids

Although these acids undergo many reactions, most of them do not involve the carboxyl group and are therefore not considered here. However, the work of Ames and Ribeiro[733] has led to a number of heterocycles; the process involves attack by a carbanion on the halogen atom of 3-bromothiophene-2-carboxylic acid or its 4-bromo-3-isomer. Further reaction then leads to products of, for example, the type **196** (where X = O or NH).

F. The Acyl- and Formylthiophenecarboxylic Acids

Condensation of 3-acylthiophene-2-carboxylic acids with hydrazines leads to thienopyridazines of the type **197**;[24,734] all the three possible vicinal formylthiophenecarboxylic acids have also been so condensed.[24]

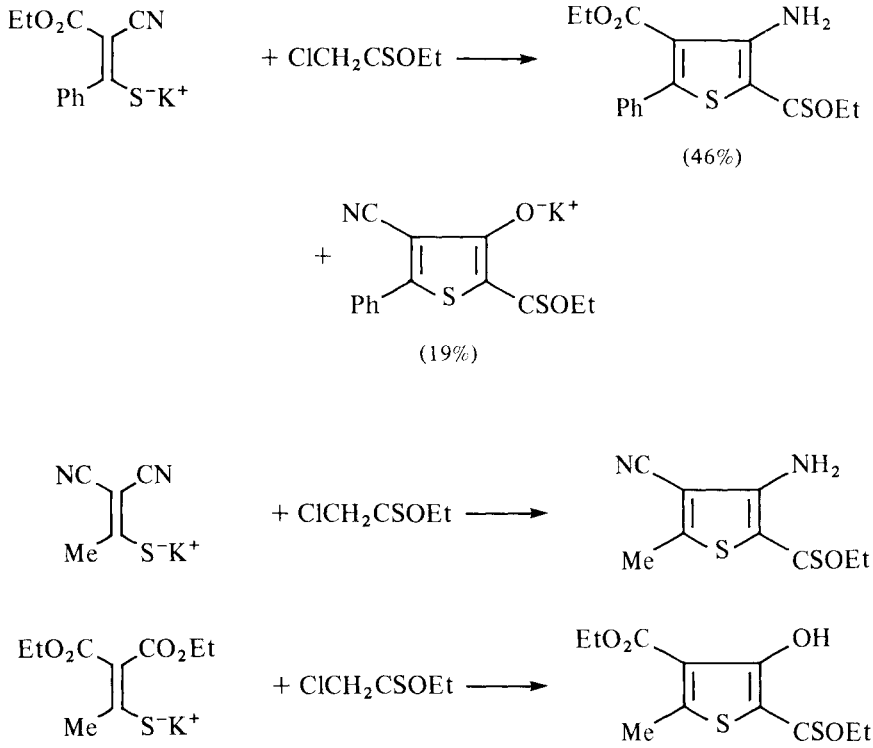
III. SULFUR ANALOGUES OF THIOPHENECARBOXYLIC ACIDS AND THEIR DERIVATIVES

1. Thiophenecarbothioic Acids

Thioamides are readily accessible through the addition of hydrogen sulfide to cyanothiophenes; they are also formed by direct substitution of thiophene with

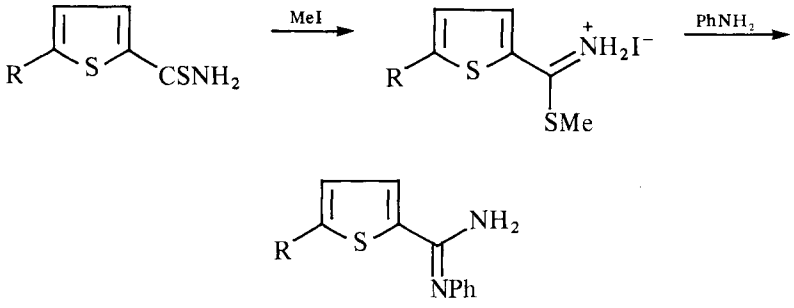
isothiocyanates under Friedel-Crafts conditions. These two subjects are reviewed in Sections IV.2.A. and I.1.D.a, respectively.

Some of the ring syntheses discussed in earlier sections are also adaptable to the preparation of thiophenecarbothioic acids, simply by using thiono analogues of carboxylic components. In this way, for example, cyanothioacetamide has been used in the Gewald synthesis to prepare a number of 2-aminothiophene-3-carbothionoamides.[735] Similarly, the reactions depicted in Scheme 107 yielded thiophene carbothioic esters.[736]

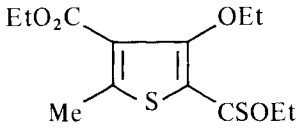


Scheme 107

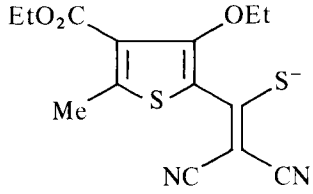
Most of the reported chemistry of thiophenecarbothioic acids has been concerned with the thioamides, in particular, their cyclization to heterarylthiophenes. This is not considered here. Alkylation of thioamides with alkyl halides occurs at the sulfur atom, and the resulting salts readily undergo nucleophilic substitution. The reactions of Scheme 108 are typical (R = H,[737,738]; R = Cl, MeO[737]).



Scheme 108



198



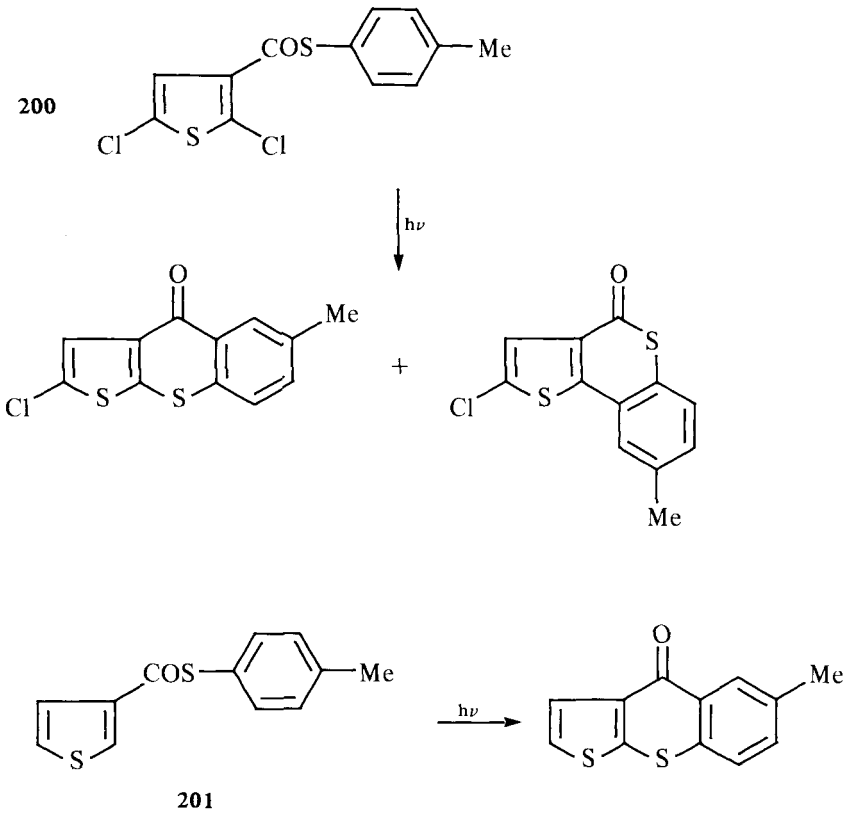
199

An interesting difference in reactivity is revealed by the selective attack of the malondinitrile anion on **198** which gave **199**.[736]

2. Thiophenecarboxythiolic Acids

The very great majority of compounds known in this class are thiolesters, made from thiophenecarboxylic acid chlorides and thiols (see Tables 131 and 133). Methyl thiophene-2-carboxythiolate has been prepared directly from thiophene by the aluminum chloride catalyzed condensation with methyl thiochloroformate.[739] Reaction of 2,2′-dipyridyldisulphide and thiophene-2-carboxylic acid in the presence of triphenylphosphine gave 2-pyridyl thiophene-2-carboxylate; when heated with bis(1,5-cyclopentadiene)nickel this ester gave an excellent yield of 2-thienyl 2-pyridyl ketone.[740] Some 1-carboxyalkyl thioesters have been prepared by direct reaction of thiophene-2-carboxythiolic acid and α-bromoalkanoic acids.[741]

The photolysis of some *S*-aryl esters in the series has produced some very interesting results. The aryl 2,5-dichlorothiophene-3-carboxylate **200** gave two tricyclic products, one arising from S—O cleavage and one in which the S—O bond is intact. Only the product of the former process was formed from the unsubstituted ester **201** (Scheme 109). Similar tricyclic compounds were obtained from analogous *S*-pyridyl esters.[742]



Scheme 109

3. Thiophenecarbodithioic Acids

The principal synthesis of the full sulfur analogue of thiophene-2-carboxylic acid is by interaction of a thienyl Grignard reagent and carbon disulfide.[743-745] An alternative involves the reaction of thiophene-2-aldehyde and ammonium polysulfide; in this case the product was esterified by treatment with chloracetic acid. Although the overall yield of ester was poor, the method succeeded where others had failed.[746] The SCH_2CO_2H group in this ester is easily replaced by nucleophiles; hydrazines have been employed for this substitution.[747,748] Phenyl thiochlorothioformate (PhSC(=S)Cl) and thiophene react together in the presence of stannic chloride to give phenyl thiophene-2-carbodithioate.[749] The acid chloride of thiophene-2-carbodithioic acid is very difficult to prepare in good yield[745] and is very unstable.[750]

IV. CYANOTHIOPHENES

1. Preparation

A. *Reaction of Thienyl Halides with Copper(I) Cyanide*

The Rosenmund–von Braun nitrile synthesis has been widely utilized in the thiophene series; both the solvent and the halogen used have varied. Pyridine is satisfactory in many cases, both with bromo (e.g., reference 751) and, more commonly, iodo (e.g., reference 182) compounds. Quinoline is still probably the most popular solvent giving, for instance, a 75% yield of 3-cyanothiophene from the corresponding bromo compound.[108] *N*-Methylpyrrolidone has been recommended as a solvent for this reaction,[752] but in a comparison it gave a yield of only 46% of 3-cyanothiophene from the bromo compound whereas quinoline afforded 86%.[753] DMF has also been used,[754,755] and hexamethylphosphoramide (HMPA) has been suggested as the solvent of choice for the reaction with iodo compounds, but its high carcinogenicity mitigates against it general use.

Replacement of two halogen atoms simultaneously leads to satisfactory yields of dinitriles,[27,187,756,757] whereas many substituents can be tolerated in the reaction, such as alkyl,[758,759] formyl,[754] diethoxymethyl,[10,760] methoxy,[761,762] methylsulfonyl,[224] arylthio,[194] and benzoyl.[23] In HMPA it is possible to replace the iodine selectively in 2-chloro-5-iodo- and 2-bromo-5-iodothiophene in 91% and 32% yields, respectively.[763]

An interesting vapor-phase modification of the reaction has been described in which a 55% yield of 2-cyanothiophene resulted from 2-chlorothiophene and hydrogen cyanide over a NiO/Al_2O_3 catalyst at 550 to 580°C.[764]

B. *Dehydration of Oximes*

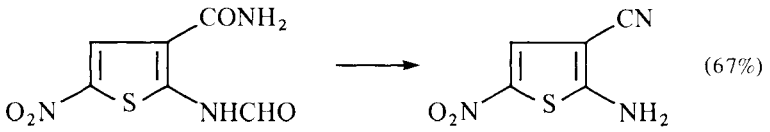
By far the most widely used reagent for this conversion is acetic anhydride; 2- and 3-cyanothiophene can be made this way in 89%[765] and 73% yield,[766] respectively. Again, a wide variety of substituents can be present, such as alkyl,[767,820] bromo,[127,768,769] chloro,[356,737,770] iodo,[129] methoxy,[771] and nitro;[183,185,772] dinitriles can also be made this way.[40]

A mixture of sodium formate and formic acid has been used to dehydrate chlorothiophene[572] and fluorothiophene[21] oximes, whereas *p*-toluenesulphonic acid converted thiophene-2-aldoxime into the nitrile in 48% yield by way of the oxime tosylate.[773] Phosphorus pentachloride found use in the preparation of all six cyanothiophene aldehydes from the corresponding oxime acetals.[10,760] An interesting East German patent describes the reaction of, *inter alia*, thiophene-2-aldoxime with phosphoryl chloride in DMF; under various conditions it is possible to obtain the nitrile (73%), the acid (60%), the amide (61%), and the *N*-formyl

amide (64%).[774] The conversion of 3-azidothiophene-2-aldoxime to the corresponding nitrile (86%) can be achieved with cyanuric chloride,[350] whereas the preparation of 2-cyanothiophene (93%) can be carried out under mild conditions using a carbodiimide and triethylamine in the presence of copper(II) ions.[775] As an alternative to the oxime route, thiophene-2-aldehyde can be converted into the nitrile (70%) by the action of heat on its condensation product with the readily available 4-amino-1,2,4-triazole.[776]

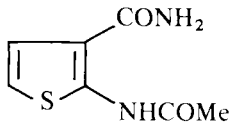
C. *Dehydration of Amides*

The most commonly used reagent is phosphoryl chloride, either alone, in pyridine, or in DMF. The latter reagent affords 2-cyanothiophene from the amide in 95% yield[774] and brings about the conversion shown in Scheme 110.[771]

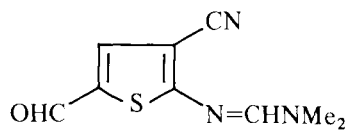


Scheme 110

It induces a simultaneous Vilsmeier reaction and dehydration in the conversion of **202** into **203**, which is an intermediate in the preparation of disperse azo dyes.[777] Phosphoryl chloride in pyridine is used to make 5-methoxy-2-cyanothiophene (75%),[737] whereas the base is omitted in the preparation of some oxygenated mono- and dinitriles.[482,489] Lesser-used reagents include thionyl chloride, which can be utilized for the reaction of Scheme 110, and acetic anhydride which simultaneously acylates and dehydrates 2-aminothiophene-3-carboxamide[379] and its 4-methyl derivative.[688] Phosphorus pentoxide was used to prepare 4-bromo-2-cyanothiophene,[778] and Lehnert[779] has reported the elegant dehydration with titanium(IV) chloride at 0° to give 2-cyanothiophene (88%).



202

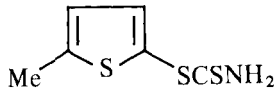


203

Also appropriately considered here are some direct conversions of thiophene-2-carboxylic acid into its nitrile, either by use of the well-established urea/sulphamic acid mixture (30%),[780] or with chlorosulfonyl isocyanate, followed by DMF.[781]

D. By Direct Substitution of Thiophene

Thiophene yields 2-cyanothiophene in 66 to 72% yield on treatment with chlorosulfonyl isocyanate followed by DMF or another amide.[755,782-784] Tin(IV) chloride and thiocyanogen gave a 30% yield of 5-ethyl-2-cyanothiophene from 2-ethylthiophene, but the methyl homologue gave **204**.[785] An intriguing example of the direct introduction of the nitrile group involves the production of 2- and 3-cyano- and 2- and 3-methylthiophene from thiophene and acetonitrile in the vapor phase at 0.05 mm/Hg under the influence of a 13.6-MHz radiofrequency discharge.[786]



204

E. By Cyclization

Many of the cyclization methods described earlier (in Section I.2.D) for the preparation of thiophene carboxylic acids, esters, and other derivatives are adaptable with very minor modifications to the synthesis of nitriles. Thus the Gewald synthesis and its variations using malononitrile[192,362,363,787-790] or other nitriles,[370,396] cycloaddition-extrusion reactions,[257,425,426,791] dehydrogenation of dihydrothiophenes of various types,[386-388,417,421,620,792] the enedithiol synthesis using malononitrile[393,793] or other cyano compounds,[346,393,794,795] and the enethiol process[796-800] have all been used to make thiophenecarbonitriles. A variation of the Hinsberg synthesis using 1,1′-dicyanodimethyl sulfide has been used to make 2,5-dicyano- and 2-carboxamido-5-cyanothiophene,[801] whereas the attack of thioglycolates on cyanoallenes gives good yields of 3-hydroxythiophene-4-carbonitriles.[802]

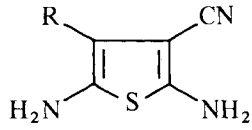
A fascinating reaction involving the alkoxide-induced ring opening of 2-amino-3-ethoxycarbonylthiophenes and their subsequent reclosure has been used to prepare 2-hydroxythiophene-3-carbonitriles[803,804] (Scheme 111).

R^1 = H, COMe, CO_2Et
R^2 = Me, Ph

Scheme 111

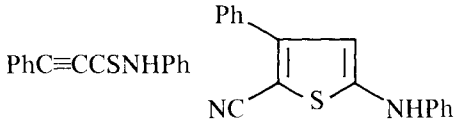
A closely related reaction in which the ester function is replaced by an acyl group has been described.[805]

Polynitriles and a sulfur donor under basic conditions give thiophenes of the structure **205**. Thus tetracyanoethylene with hydrogen sulfide[653,806,807] or carbon disulfide[808] in pyridine gives over 90% yields of **205**, R = NH_2. Tetracyanoethane gives the same product with sodium sulfide[808,809] or with hydrogen sulfide in pyridine,[807] and 1,1,1-tricyano-1-phenylethane (from hydrogen cyanide and β,β-dicyanostyrene) affords **205**, R = Ph.[653,810]

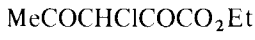


205

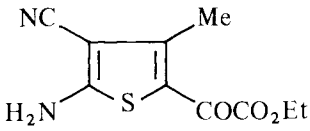
There is a group of cyclizations that involve the C=S group in various environments, for example, the acetylenic thioamide **206** gives **207** with bromoacetonitrile and base,[193] whereas cyanothioacetamide and **208** give **209** in acetic acid and pyridine.[811] The thione group of a dithioester is similarly employed in the conversion of **210** into **211** by the action of bromoacetone and triethylamine.[438] Finally, the thione function of the β-ketoester analogue **212** exists largely in the thioenol form; this can be alkylated with chloroacetonitrile and cyclized to give 5-R-2-cyano-3-hydroxythiophenes.[812]



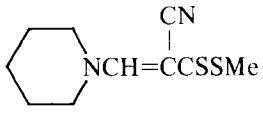
206 **207**



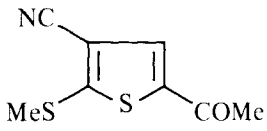
208



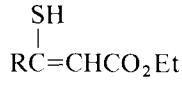
209



210

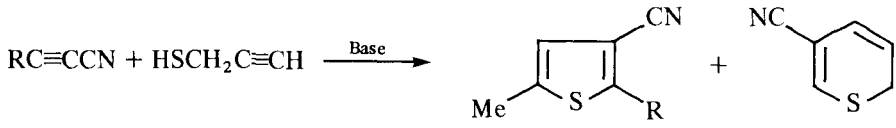


211



212

(R = Me, *i*-Pr, *t*-Bu, Ph)



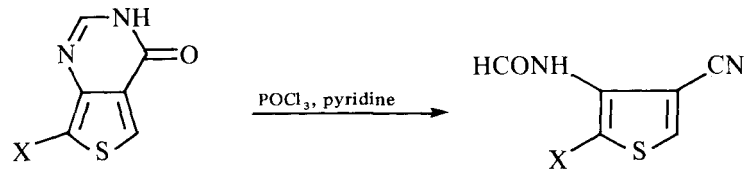
Scheme 112

Hydrocarbon groups of various types can be used in cyclizations yielding cyanothiophenes; an example is the acetylenic linkage (Scheme 112). When R is H there is a substantial amount of the cyanopyran produced, but if R is alkyl good yields are afforded of the cyanothiophenes.[813] An interesting use of alkenes concerns the high-temperature conversion of acrylonitrile and sulfur into 2,4-dicyanothiophene.[188] Even alkanes can be utilized in certain cases, such as the formation of 3-cyano-4-methylthiophene in 14% yield at 300 to 350° from 2,3-dimethylbutane, sulfur, and ammonia.[814]

F. Miscellaneous Syntheses

The ammoxidation of 2-methyl-, 2-ethyl-, or 2-acetylthiophene gives, at best, 36% yields of 2-cyanothiophene,[815] whereas the corresponding reaction in the 3-methyl case affords only a tenth of this amount of product;[816] substitution of sulfur for air in the process does not greatly improve matters.[817] The transformation in the 2-methylthiophene case can also be brought about by nitric oxide over a rhenium catalyst.[818]

A ring-opening reaction that gives a cyanothiophene is shown in Scheme 113.[819]



Scheme 113

2. Reactions

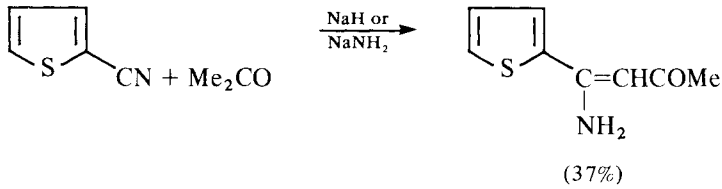
Under this heading only reactions of the cyano group will be reviewed; transformations of the ring (for example, electrophilic substitution) or other substituents (such as the amino group of aminonitriles) are dealt with elsewhere in this treatise.

A. *Nucleophilic Additions to the Cyano Group*

The hydrolysis of nitriles has been covered in Section I.1.C as a method for the preparation of thiophenecarboxylic acids; the interesting partial hydrolyses of 2,5-diamino-3,4-dicyanothiophene[653] and tetracyanothiophene[337] are worthly of note. Likewise, the addition of alcohols is considered in Section V.1, but the application to 5-nitro-2-cyanothiophene of Pinner's method for the direct conversion of a nitrile to an ester should be mentioned.[190]

The addition of hydrogen sulfide to nitriles is probably the most important method for making thioamides, and several examples are found in thiophene chemistry. It has been applied to 5-R-2-cyanothiophenes where R is H, Cl, MeO,[737] NO_2,[377] and Me, Et, Pr,[820] to a 2,5-dicyanothiophene,[482] to a number of derivatives of 2-amino-3-cyanothiophene,[358] and to a series of cyanothiophene acetals.[10] Selenoamides can be made by a similar process,[821,822] and a thioimidate has been produced from 3-cyanothiophene and benzyl mercaptan.[823]

Phenylmagnesium bromide[571,766] and its methyl counterpart[753] react normally with 3-cyanothiophene, as do other species of a carbanion nature. However, 2-cyanothiophene reacts as shown in Scheme 114 with the enolate of acetone, but the reaction fails with the 3-cyano derivative.[824,825]



Scheme 114

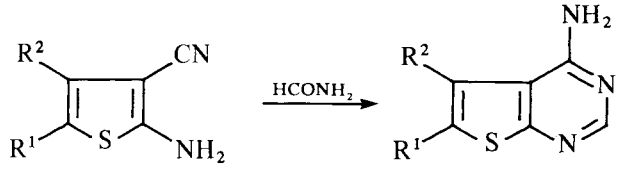
Similar condensations occur with acetonitrile and 2-cyanothiophene,[826] 5-chloro-2-cyano-, or 3-cyanothiophene.[572] A phosphole derivative has also been condensed with 2-cyanothiophene.[827]

Various aromatic and heterocyclic amines have been observed to act as nucleophiles with tetracyanothiophene,[828,829] and the very interesting addition (presumably electrophilic in the first instance followed by a sigmatropic shift) of an allyl borane to 2-cyanothiophene has been noted.[830]

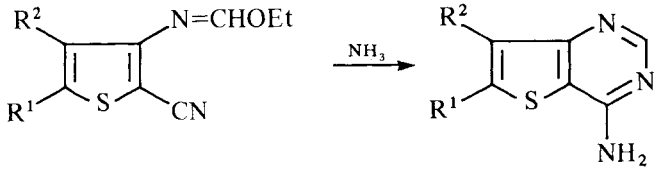
B. *Cyclizations*

Many of these reactions are very similar to those just considered, the initial nucleophilic attack being followed by ring closure. Thus 2-amino-3-cyanothiophenes have furnished thienopyrimidines with formamide (Scheme 115)[789,831] or orthoesters,[832] whereas with formic acid they yield the corresponding oxo derivatives.[670]

Compounds of the latter type can also be made from 2-acetylamino-3-cyanothiophenes with dilute alkali[670] or ethanolic hydrogen chloride.[833] Amino derivatives of an isomeric thienopyrimidine can be prepared by the method shown in Scheme 116.[346]

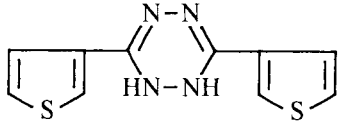


Scheme 115

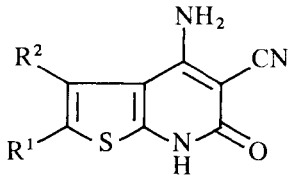


Scheme 116

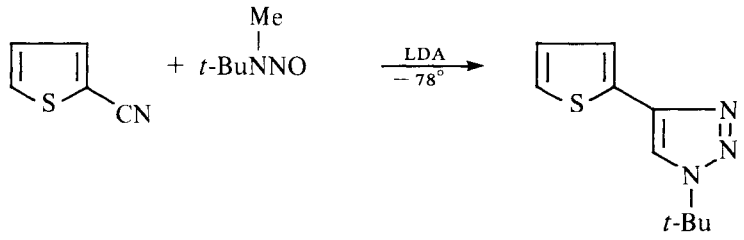
The reaction of cyanothiophenes with hydrazine is normal; the 2-cyano derivative yields 4-amino-3,5-di(2-thienyl)-1,2,4-triazole,[760] whereas 3-cyanothiophene gives the corresponding *N*-aminotriazole with or without the dihydrotetrazine **213** according to the conditions.[738] A 1,2,3-triazole derivative has been made from 2-cyanothiophene (Scheme 117),[834] whereas the reaction of 2-cyano-3-hydroxythiophene[761] and many dicyanothiophenes[738] with hydrogen azide has given the corresponding tetrazoles.



213

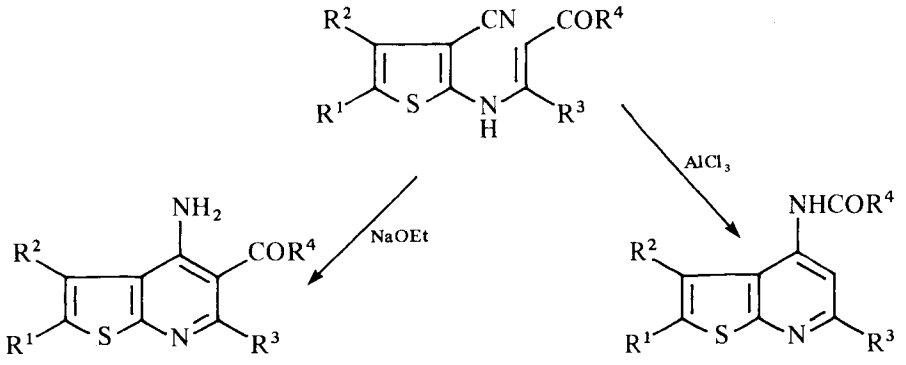


214



(63%)

Scheme 117

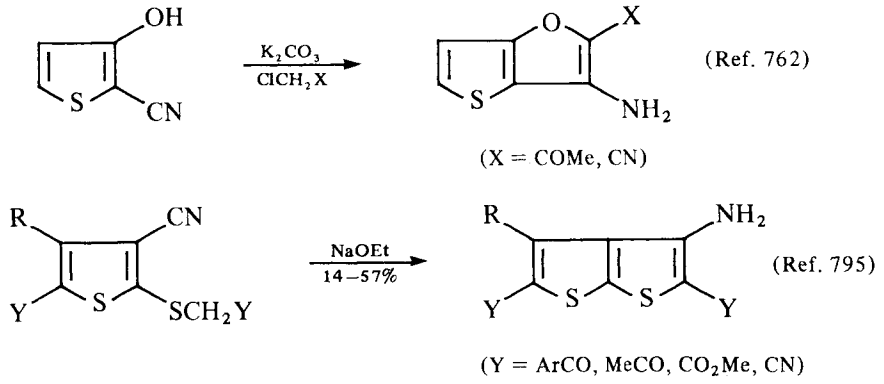


Scheme 118

Scheme 118 depicts two ways of making aminothieno [2,3-b]pyridine derivatives,[835,836] and various 2-aminothiophenes yield the related products of general formula **214** on treatment with sodium ethoxide and ethyl cyanoacetate.[836]

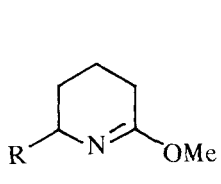
Last in this brief survey of the use of nitrogen nucleophiles in ring closures involving the cyano group, cyclization of 2- or 4-*o*-aminoanilino-3-cyanothiophenes yielded the corresponding aminobenzothienodiazepines.[837,838]

Two examples of the use of a carbon nucleophile in a Thorpe-Ziegler type of cyclization are shown in Scheme 119.

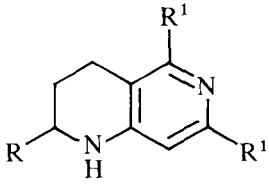


Scheme 119

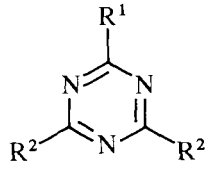
Carbon nucleophiles are also involved in the metal-hydride-mediated condensation of compounds of the type **215** (R = H, Me) with 2-cyanothiophene to give the products **216** (R′ = 2-thienyl).[839]



215



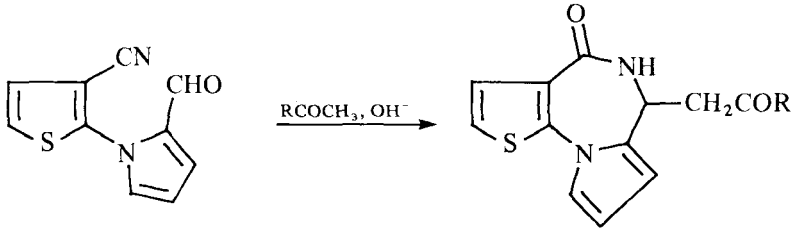
216



217

The cyclotrimerization of 2-cyanothiophene has been studied both in the case of the pure reactant[840] or in the presence of trichloroacetonitrile,[841] to give **217**, $R^1 = R^2$ = 2-thienyl, or **217**, R^1 = 2-thienyl, $R^3 = Cl_3C$, respectively. The formation of **217** ($R^1 = R^2$ = 3-thienyl) has been observed as a by-product in the reaction of 3-bromothiophene with copper(I) cyanide.[842]

Finally, an oxygen nucleophile is involved in the ring closure of Scheme 120.[843]



Scheme 120

C. Reductions

Complete reduction of 2,4-dicyanothiophene to the corresponding diamine could be achieved by hydrogenation,[188] but the attempted partial reduction of a series of dinitriles with lithium aluminum hydride met with only limited success.[10] The same reagent failed with 2-cyano-5-methylsulfonylthiophene,[224] but diisobutylaluminum hydride successfully yielded dialdehydes with many dinitriles,[489,756,757] with the exception of the 2,3-isomer.[757]

V. THIENYL IMIDATES AND RELATED COMPOUNDS

1. Preparation

A. Imidates

The most-often-used preparation of these compounds is the classical treatment of a nitrile with an alcohol and hydrogen chloride; purification of the product by

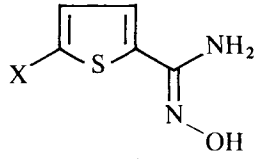
distillation of the free base has been recommended.[844] The method has been applied to 2-cyanothiophene itself[755,845,846] as well as its derivatives,[737] including 3-hydroxy-,[762,847] 5-nitro-, and 5-chloro-2-cyanothiophene.[844] 3-Cyanothiophene[755,846] and various dinitriles can be treated in this way,[462,653,791,848] and often selective reaction at one cyano group is possible.[462] Treatment of 2-cyanothiophene with sodium borohydride in ethanol was shown to lead to the imidate,[791,846] but the reaction failed with the 3-isomer. Another interesting procedure involves the conversion of 4-nitro-2-cyanothiophene into an imidate with methoxide in DMSO followed by acid.[849]

B. Amidines

These are normally made from imidates with ammonia,[755,762,847] ammonium chloride,[462,791,846] or ammonium benzenesulphonate.[462,737,791,846,850] *N*-substituted amidines are available by the use of amines in this reaction,[851–853] as well as by the action of sodamide on thienylidene phenylhydrazones,[854,855] of amines on *N*-ethoxycarbonylthiophene-2-carboxythioamide,[199] and indeed in one case by the catalyzed direct addition of an amine to 2-cyanothiophene.[856]

C. Related Compounds

Amidoximes of the thiophene series have normally been made by the usual method utilizing a nitrile and hydroxylamine,[85,730,857] but *N*-substituted derivatives were prepared from an amine and a hydroxamyl chloride.[506,858] The latter compounds were made by the action of nitrosyl chloride on an oxime, rather than by the usual treatment with chlorine.[506,858] It may be noted in passing that infra red studies of thienyl amidoximes have shown them to exist in the form **218**.[859,860]

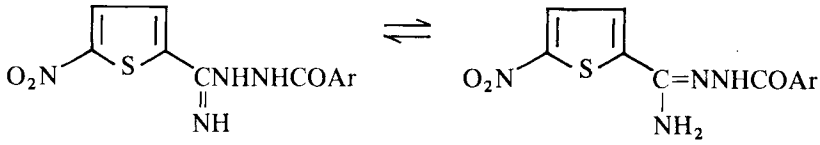


218

2. Reactions

The reactions of these thiophene derivatives are, as expected, unremarkable. They have been used mainly for the preparation of thienyl heterocycles; this topic is beyond the scope of this chapter.

2-Thienylhydroxamyl chloride with triethylamine gives a nitrile oxide which acts as a 1,3-dipole in the usual way with 1,4-naphthoquinone.[861] The standard conversions of imidates into carboxylic esters[462,653,846,851] and amides[462,846,851] have been carried out in the thiophene series. 5-Nitrothienyl-2-amidoxime has been *O*-acylated,[862] whereas acylation of the corresponding amidrazone yields the tautomeric product **219**.[863] A number of aryl isocyanates react with 3-thenamidine in the expected manner.[864,865]



219

VI. TABLES OF COMPOUNDS

The tables cover data from *Chemical Abstracts*, Volumes 44 to 93 inclusive, together with a small amount of material from other sources. They do not, for reasons of space, cover every compound described during that period; the following classes of substance have been excluded:

1. Those for which no physical data appeared in the documents used by the authors (e.g., the entry in *Chemical Abstracts* for a less accessible paper).
2. More complex molecules, for example, the numerous 2-thenoyl derivatives of penams or dyestuffs, that is, where the thiophene ring is merely one of many substituents mentioned.
3. The majority of compounds containing saturated rings fused to the thiophene residue (these are considered to be beyond the scope of this treatise).

It follows that the nonappearance of a compound in the tables does not necessarily mean that it has not been described; it is hoped, however, that perusal of the tables will save a full literature search in the majority of cases.

1. Abbreviations Used in The Tables

*	Percentage yield not recorded but weight of product given
[ ]	Derivative, for example, [*N*-tosyl]

C	^{13}C NMR data
D	Dipole moment data
d	Denotes decomposition after mp or bp, otherwise density
F	^{19}F NMR data
g	Gas-liquid chromatographic data
I	Infrared spectral data
K	pK_a recorded
L	Linear free energy plot
M	Mass spectral data
n	Refractive index recorded
P	^{1}H NMR data
R	Raman spectral data
U	Ultraviolet spectral data
α	Polarimetric data

2. Methods of Synthesis

An attempt has been made to give a broad indication of the methods of synthesis of the compounds listed; the following codes have been used.

a	Rearrangement
b	Hydrolysis/alcoholysis
c	Electrophilic aromatic substitution
d	Acylation/sulfonylation of an amine
e	Reduction
f	Special method
g	Nucleophilic substitution
h	Aminolysis/hydrazinolysis of an ester
i	RH→RLi→RCO_2H
j	ROH→RHal
k	Dehydration (also used to indicate oxime formation etc.)
l	Acylation/sulfonylation of a hydroxy or mercapto group
m	Esterification of an acid
	m1 with a diazoalkane
	m2 with an alcohol and H^+
n	Acyl halide formation from an acid
o	Use of a Grignard reagent
p	Oxidation of an aldehyde
q	Oxidation of a methyl ketone
r	Cyclization

–r	Ring opening
s	Dehydrogenation
t	Alkylation of a hydroxy or mercapto group
	t1 with diazomethane
	t2 with an alcohol and H^+
u	$RX \rightarrow RLi \rightarrow RCO_2H$ $X \neq H$
v	Dealkylation
w	Oxidation (not p or q)
x	Decarboxylation
y	Cannizzaro reaction
z	By-product

3. Further Notes

In certain cases, such as SCN, the position of attachment of a substituent could be ambiguous, and this problem has been avoided by the use of a bond indication, for example, –SCN would show attachment of the group through the sulfur atom.

For the purpose of tabulation all potential hydroxy derivatives of thiophene have been listed as such, irrespective of the actual position of the tautomeric equilibria.

4. Thiophene-2-Carboxylic Acids Containing Alkyl, Alkenyl, Alkynyl, Aryl, Heteroaryl, Cyano, and Isocyano Groups and Their Derivatives

Tables 13 through 37 summarize data for these compounds as follows:

13. Thiophene-2-carboxamide and its *N*-alkyl and substituted-alkyl derivatives
14. Arylamides of thiophene-2-carboxylic acid
15. Heteroarylamides of thiophene-2-carboxylic acid
16. 2-Thenoylhydrazide and its derivatives (excluding hydrazones)
17. 2-Thenoylhydrazones
18. Alkyl and substituted-alkyl esters of thiophene-2-carboxylic acid
19. Aryl and heteroaryl esters of thiophene-2-carboxylic acid
20. Other derivatives of thiophene-2-carboxylic acid
21. 3-Methyl- and substituted-methylthiophene-2-carboxylic acids and their derivatives
22. 3-Alkyl- and substituted-alkyl (other than methyl) thiophene-2-carboxylic acids and their derivatives
23. 4-Alkyl- and substituted-alkylthiophene-2-carboxylic acids and their derivatives

24. 5-Methyl- and substituted-methylthiophene-2-carboxylic acids and their derivatives
25. 5-Alkyl- and substituted-alkyl (other than methyl) thiophene-2-carboxylic acids and their derivatives
26. 5-Alkenyl- and alkynylthiophene-2-carboxylic acids and their derivatives
27. Di- and trialkyl and substituted-alkylthiophene-2-carboxylic acids and their derivatives
28. 3-Aryl- and substituted-arylthiophene-2-carboxylic acids and their derivatives
29. 4-Aryl- and substituted-arylthiophene-2-carboxylic acids and their derivatives
30. 5-Aryl- and substituted-arylthiophene-2-carboxylic acids and their derivatives
31. Diarylthiophene-2-carboxylic acids and their derivatives
32. Heteroarylthiophene-2-carboxylic acids and their derivatives
33. 5-(2-Benzoxazolo)thiophene-2-carboxylic acids and their derivatives
34. Mixed alkyl/arylthiophene-2-carboxylic acids and their derivatives
35. Cyano-substituted thiophene-2-carboxylic acids and their derivatives
36. Esters of 3-isonitrilothiophene-2-carboxylic acids
37. Dithenoylperoxides

5. Thiophene-3-Carboxylic Acids Containing Alkyl, Alkenyl, Aryl, Heteroaryl, and Cyano Groups and Their Derivatives

These compounds are summarized in Tables 38 through 45 as follows:

38. Thiophene-3-carboxylic acid and its derivatives
39. 2-Alkyl- and substituted–alkyl- and alkenylthiophene-3-carboxylic acids and their derivatives
40. 4-Alkyl- and substituted–alkyl- and alkenylthiophene-3-carboxylic acids and their derivatives
41. 5-Alkyl- and substituted-alkylthiophene-3-carboxylic acids and their derivatives
42. Di- and trialkyl and substituted-alkylthiophene-3-carboxylic acids and their derivatives
43. Aryl and heteroarylthiophene-3-carboxylic acids and their derivatives
44. Mixed alkyl and aryl/heteroarylthiophene-3-carboxylic acids and their derivatives
45. Cyanothiophene-3-carboxylic acids and their derivatives

6. Thiophene Di-, Tri-, and Tetracarboxylic Acids Containing Alkyl, Aryl, Heteroaryl, Amino, Cyano, and Hydroxy Groups and Their Derivatives

Note: Hydroxy compounds are listed as such irrespective of tautomerism. These compounds are summarized in Tables 46 through 62:

46. Thiophene-2,3-dicarboxylic acid and its derivatives
47. Substituted thiophene-2,3-dicarboxylic acids and their derivatives
48. Thiophene-2,4-dicarboxylic acid and its derivatives
49. Aminothiophene-2,4-dicarboxylic acids and their derivatives
50. Other substituted thiophene-2,4-dicarboxylic acids and their derivatives
51. Thiophene-2,5-dicarboxylic acid and its derivatives
52. 3,4-Dimethylthiophene-2,5-dicarboxylic acid and its derivatives
53. Aryl and heteroarylthiophene-2,5-dicarboxylic acids and their derivatives
54. 3(4)-Hydroxythiophene-2,5-dicarboxylic acids and their derivatives
55. 3,4-Dihydroxythiophene-2,5-dicarboxylic acid and its derivatives
56. Miscellaneous thiophene-2,5-dicarboxylic acids and their derivatives
57. Thiophene-3,4-dicarboxylic acid and its derivatives
58. Alkyl and arylthiophene-3,5-dicarboxylic acids and their derivatives
59. Miscellaneous thiophene-3,4-dicarboxylic acids and their derivatives
60. Thiophene-2,3,4-tricarboxylic acids and their derivatives
61. Thiophene-2,3,5-tricarboxylic acids and their derivatives
62. Thiophenetetracarboxylic acid and its derivatives

7. Aminothiophenecarboxylic Acids and Their Derivatives

These compounds are summarized by the following tables:

63. 3-Aminothiophene-2-carboxylic acid and its derivatives (excluding ureas)
64. Ureas derived from esters of 3-aminothiophene-2-carboxylic acid
65. 3-Amino-4-methylthiophene-2-carboxylic acid and its derivatives
66. 5-Alkyl, substituted-alkyl, -aryl, and substituted-aryl-3-aminothiophene-2-carboxylic acids and their derivatives
67. Miscellaneous 4,5-disubstituted-3-aminothiophene-2-carboxylic acid derivatives
68. Variously substituted 4-aminothiophene-2-carboxylic acid derivatives
69. 5-Aminothiophene-2-carboxylic acid and its derivatives
70. Derivatives of 5-amino-4-nitrothiophene-2-carboxylic acid
71. Variously substituted 5-aminothiophene-2-carboxylic acid derivatives

72. Derivatives of 2-aminothiophene-3-carboxylic acid
73. 4-Alkyl-2-aminothiophene-3-carboxylic acids and their derivatives
74. 2-Amino-4-aryl and -heteroarylthiophene-3-carboxylic acids and their derivatives
75. 5-Alkyl-2-aminothiophene-3-carboxylic acids and their derivatives
76. 2-Amino-5-aryl and substituted-arylthiophene-3-carboxylic acids and their derivatives
77. Variously 5-substituted-2-aminothiophene-3-carboxylic acids and their derivatives
78. 4,5-Dialkyl- and substituted-alkyl-2-aminothiophene-3-carboxylic acids and their derivatives
79. 4,5-Fused-cycloalkano-2-aminothiophene-3-carboxylic acid derivatives
80. Mixed-alkyl/substituted-alkyl-aryl/substituted-aryl-2-aminothiophene-3-carboxylic acid derivatives
81. Miscellaneous 4,5-disubstituted-2-aminothiophene-3-carboxylic acid derivatives
82. Derivatives of 4-aminothiophene-3-carboxylic acid
83. 2- or 5-Alkyl and substituted-alkyl-4-aminothiophene-3-carboxylic acids and their derivatives
84. Derivatives of 5-acyl-2,4-diaminothiophene-3-carboxylic acids
85. Variously substituted 4-aminothiophene-3-carboxylic acid derivatives

8. Hydroxy- and Mercaptothiophenecarboxylic Acids and Their Derivatives

Note: Hydroxy compounds are listed as such irrespective of tautomerism. These compounds are summarized in Tables 86 through 105 as follows:

86. 3-Hydroxythiophene-2-carboxylic acid and its derivatives
87. Variously substituted 3-hydroxythiophene-2-carboxylic acids and their derivatives
88. 4-Hydroxythiophene-2-carboxylic acids and their derivatives
89. 5-Hydroxythiophene-2-carboxylic acids and their derivatives
90. Various dihydroxythiophenecarboxylic acid derivatives
91. Variously substituted 2-hydroxythiophene-3-carboxylic acids and their derivatives
92. 4-Hydroxythiophene-3-carboxylic acid and its derivatives
93. Variously substituted 4-hydroxythiophene-3-carboxylic acids and their derivatives
94. 2-Substituted 5-hydroxythiophene-3-carboxylic acid derivatives
95. 3-Mercaptothiophene-2-carboxylic acid derivatives

96. 2-Carboxythiophene-3-sulfonic acid and its derivatives
97. 4-Mercapto and 4-sulfothiophene-2-carboxylic acid derivatives
98. Derivatives of 5-mercaptothiophene-2-carboxylic acid and of variously substituted 5-mercaptothiophene-2-carboxylic acids
99. Derivatives of 2-carboxythiophene-5-sulfonic acid
100. 2-Mercaptothiophene-3-carboxylic acids and their derivatives
101. 3-Carboxythiophene-2-sulfonic acids and their derivatives
102. 4-Mercapto and 4-sulfo derivatives of thiophene-3-carboxylic acids
103. 5-Mercapto and 5-sulfo derivatives of thiophene-3-carboxylic acids
104. Miscellaneous bismercapto derivatives of thiophenecarboxylic acids
105. Selenium substitued thiophene-2- and 3-carboxylic acid derivatives

9. Halogeno and Halogenonitrothiophenecarboxylic Acids and Their Derivatives

These compounds are summarized as follows in Tables 106 through 117:

106. Fluorothiophene-2-carboxylic acids and their derivatives
107. Fluorothiophene-3-carboxylic acids and their derivatives
108. Chlorothiophene-2-carboxylic acids and their derivatives (except amides of 3,4,5-trichlorothiophene-2-carboxylic acid)
109. Amides of 3,4,5-trichlorothiophene-2-carboxylic acid
110. Chlorothiophene-3-carboxylic acids and their derivatives
111. Bromothiophene-2-carboxylic acids and their derivatives
112. Bromothiophene-3-carboxylic acids and their derivatives
113. Iodothiophene-2-carboxylic acids and their derivatives
114. Iodothiophene-3-carboxylic acids and their derivatives
115. Thiophenecarboxylic acids and esters with mixed halogens substituents
116. Thiophene-2-carboxylic acids and their derivatives with both halogeno and nitro substituents
117. Thiophene-3-carboxylic acids and their derivatives with both halogeno and nitro substituents

10. Nitrothiophenecarboxylic Acids and Their Derivatives

Tables 118 through 124 summarize these compounds:

118. 3-Nitrothiophene-2-carboxylic acid and related compounds
119. 4-Nitrothiophene-2-carboxylic acid and its derivatives
120. 5-Substituted 4-nitrothiophene-2-carboxylic acids and their derivatives

121. 5-Nitrothiophene-2-carboxylic acid and its derivatives
122. 3- And 4-alkyl-5-nitrothiophene-2-carboxylic acids and their derivatives
123. Dinitrothiophene-2-carboxylic acids and their derivatives
124. Nitrothiophene-3-carboxylic acids and their derivatives

11. Formyl and Acylthiophenecarboxylic Acids

These compounds are summarized in Tables 125 through 130.

125. Various formylthiophene-2-carboxylic acids and their derivatives
126. 3-Acylthiophene-2-carboxylic acids and their derivatives
127. 4-Acylthiophene-2-carboxylic acids and their derivatives
128. 5-Acylthiophene-2-carboxylic acids and their derivatives
129. Various formylthiophene-3-carboxylic acids and their derivatives
130. Various acylthiophene-3-carboxylic acids and their derivatives

12. Sulfur Analogues of Thiophenecarboxylic Acids

Tables 131 through 133 summarize these compounds as follows:

131. Mercaptoesters of thiophene-2-carboxylic acids
132. Thiono and selenono thiophene-2-carboxylic acids and their derivatives
133. Sulfur and selenium analogues of thiophene-3-carboxylic acids

13. Cyanothiophenes

These compounds are summarized by Tables 134 through 154 as follows:

134. 2-Cyanothiophene, its alkyl, substituted alkyl, and alkenyl derivatives
135. Amino, hydroxy, and mercapto-2-cyanothiophenes and related compounds
136. Halogeno, nitro, and nitrohalogeno-2-cyanothiophenes
137. Formyl-2-cyanothiophenes and their derivatives
138. 3-Cyanothiophene and its alkyl, aryl, and heteroaryl derivatives
139. 4-Alkyl-2-amino-3-cyanothiophene derivatives
140. 4,5-Dialkyl- and substituted-alkyl-2-amino-3-cyanothiophenes
141. 4-Aryl and heteroaryl-5-acyl-2-phenylamino-3-cyanothiophenes
142. Miscellaneous 2-amino-3-cyanothiophenes
143. 4-(Substituted amino)-3-cyanothiophenes
144. Miscellaneous 4-amino-3-cyanothiophenes

145. 3-Cyano-2-hydroxythiophenes and related compounds
146. 3-Cyano-4-hydroxythiophenes and related compounds
147. 3-Cyanothiophene thioethers and related compounds
148. Halogeno-, nitro-, and halogenonitro-3-cyanothiophenes
149. Formyl-3-cyanothiophenes and their derivatives
150. 2,4-Dicyanothiophenes and related compounds
151. 2,5-Dicyanothiophenes
152. 3,4-Dicyanothiophenes
153. 2,3-Dicyanothiophenes
154. 2,3,4,5-Tetracyanothiophene

14. Thienyl Imidates and Related Compounds

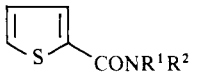
Tables 155 through 159 summarize these compounds as follows:

155. 2-Thienylhydroxamic acids and related compounds
156. 2-Thienyl imidates and their hydrochlorides
157. 2-Thienyl amidines and related compounds
158. 3-Thienylhydroxamic acid derivatives, imidates, and amidines
159. Thienyl bisimidates and bisamidines

15. Symmetric Bithienyls

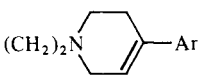
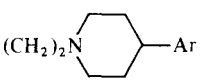
160. Symmetric 2,2′-bithienylcarboxylic acids and their derivatives
161. Symmetric 3,3′-bithienylcarboxylic acids and their derivatives

TABLE 13. THIOPHENE-2-CARBOXAMIDE AND ITS *N*-ALKYL AND SUBSTITUTED-ALKYL DERIVATIVES (R^1, R^2 = H AND SUBSTITUTED ALKYL)

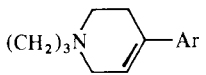


R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	180	a	61	–	774
			b	100	–	774
		–	–	–	U	866
		179	c	65	–	195, 196
		181	b	80	–	197
		175	d	–	I, U	867
		179.5–180.5	d	75	–	591
	CHO	153–153.5	a	64	–	774
	CO_2Et	142–143	c	78	I, P	199
	SO_2F	143–145 d	c	–	–	197
	SO_2Cl	105–110 d	c	–	–	197
	SO_2NHPh	203–205 d	d	–	–	197
	SO_2—(2-NH_2—C_6H_4)	205–206	e	94	–	868
	SO_2—(2-NO_2—C_6H_4)	183–184	d	–	–	868
	Me	110–112	d	95	–	589
		112–114	a	66	–	215
		112	d	–	I, U	867
	CH_2Ph	119.5–120.5	f	–	–	618
		119–120	d	82–98	I	869
	CH_2CO_2H	169–170	d	90	–	540
	CH_2CO_2Me	92–93	d	84	–	540
	CH_2CO_2Et	90–95	d	86	–	870
	Et	75–77	d	76	–	589
	CH_2CH_2Ph	111–112	d	*	–	605
	$(CH_2)_2$—(3,4-di-MeO—C_6H_3)	105	d	*	–	602, 603

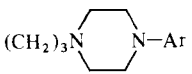
TABLE 13. (*Continued*)

R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	$(CH_2)_2$—(3,4-O—CH_2—O—C_6H_3)	102–103	d	*	–	326, 871
		105	d	*	–	602
	CHMe-(3,4-O—CH_2—O—C_6H_3)	103	d	*	–	602, 603
	$CH_2CH_2CO_2H$	135–136	b	87	–	540
	$CH_2CH_2CO_2Me$	86–87	d	88	–	540
	$CH(CHMe_2)CO_2Me$	77–78	d	86	–	540
	$CH(CH_2CHMe_2)CO_2Me$	98–99	d	56	–	540
	$CH(CH_2$—[4-OH—C_6H_4])CO_2Me	45–46	d	42	–	540
	CH_2CH_2CN	143.5–144	d	85	–	92
	$(CH_2)_2SO_2NH$—(5-*i*-Bu-2-pyrimidyl)	208–210	d	–	–	872
	$CH_2CH_2NMe_2$	150–160/0.3	d	–	–	573
	$CH_2CH_2NMe_2$, picrate	185	–	–	–	573
	$CH_2CH_2NEt_2$, picrate	260 d	–	–	–	573
						
	Ar=Ph	110–112	d	–	–	873
	Hydrochloride	224–227	–	–	–	873
	Ar=4-Cl-C_6H_4	163–165	d	–	–	873
	Hydrochloride	247–250	–	–	–	873
						
	Ar=Ph	132–134	g	–	–	873, 874
	Hydrochloride	241–243	–	–	–	873, 874
	Ar=3-Me-C_6H_4(HCl)	259–262	g	–	–	873
	Ar=4-Me-C_6H_4(HCl)	264–267	g	–	–	873
	Ar=3-CF_3—C_6H_4	148–150	g	–	–	873
	Hydrochloride	242–244	–	–	–	873

Ar=3-MeO—C_6H_4(HCl)	231–233	g	–	–	873
Ar=3-Cl-C_6H_4(HCl)	256–259	g	–	–	873
Ar=4-Cl-C_6H_4(HCl)	259–262	g	–	–	873
CH_2CH_2Br	133–134	d	–	–	874
$CH_2CH=CH_2$	65	d	86	–	875



Ar=Ph	103–105	g	–	–	873
Hydrochloride	193–195	–	–	–	873
Ar=4-Cl-C_6H_4	127–129	g	–	–	873
Hydrochloride	197–199	–	–	–	873



Ar=Ph	117–119	g	–	–	873
Hydrochloride	193–196	–	–	–	873
Ar=4-Cl-C_6H_4	142–144	g	–	–	873
Hydrochloride	226–228	–	–	–	873
$CH_2CH_2CH_2Br$	46–47	d	–	–	873
(R)(S)CHMeCHOHPh	78–80	d	84	–	607
(S)(S)CHMeCHOHPh	111–113	d	82	–	607
n-Bu	67–68	f	*	–	618
t-Bu	147–148	a	40	–	215
CH(CO_2Et)-*n*-Pr	66–67	d	89	–	870
	135–137/0.3				870
CH(CO_2Et)-*n*-Bu	81–82	d	80	–	870
Cyclohexyl	155–156	f	–	–	618
1-Carboxycyclohexyl	212–213	d	90	–	540

TABLE 13. *(Continued)*

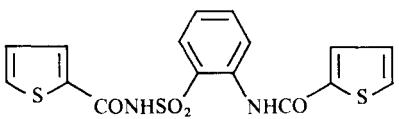
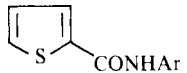
R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	1-Methoxycarbonylcyclohexyl	113–115	d	79	–	540
Me	Me	–	–	–	D	876
		145–148/12–13	d	52	–	3
		45–46	d	70–85	–	877
		142/15				877
		44–45	d	–	N	878
		156–157/12				878
		–	–	–	N	879
	CHMeCHOHPh	222	d	–	I, P, α	608
CH_2Ph	$CH_2CH_2NMe_2$	187–193/0.5	d	44	n	880
Et	Et	51–53	f	75	–	2
		85–94/0.02				2
$-(CH_2)_5-$		66	d	–	I, U	867
H	OH	123	h	–	–	881
Ph	OH	98	d	*	U	882, 883
4-Me-C_6H_4	OH	123	d	*	U	882
H	$CONH_2$	204–205	d	24	P	591
	CONHEt	156–156.5	f	48	–	591
		237–238	d	83	–	884

TABLE 14. ARYLAMIDES OF THIOPHENE-2-CARBOXYLIC ACID



Ar	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Ph	138	f	37	–	557
	144–145	a	49	–	226
	150/0.2				226
	140	d	⩾95	L	885
	139–140	g	63	–	213
	138–139	a	91	–	216
	143–144.5	a	90	–	215
	140	d	–	I, U	867
	139–140	f	63	M	211
3-Me—C_6H_4	107	d	⩾95	L	885
	107	d	–	I, U	867
4-Me—C_6H_4	165	f	52	–	578
	168.5–169.5	a	80	–	216
	169	d	⩾95	L	885
	169	d	–	I, U	867
2,4,6-tri-Me—C_6H_2	164–165	d	–	I	217
3-Cl-2-CH_2OH—C_6H_3	142–143	e	100	–	886
3-CO_2H—C_6H_4	275–280 d	d	34	–	887
4-CO_2H—C_6H_4	260–265 d	d	47	–	887
3-NH_2—C_6H_4	132	d	–	I, U	867
4-NH_2—C_6H_4	165	d	–	I, U	867
3-MeO—C_6H_4	140–141	d	⩾95	L	885
	140–141	d	–	I, U	867
4-MeO—C_6H_4	142–142.5	a	88	–	216
	140	d	⩾95	L	885
	140	d	–	I, U	867
4-$O(CH_2)_2CHMe_2$—C_6H_4	143–144	d	43	–	887

TABLE 14. (*Continued*)

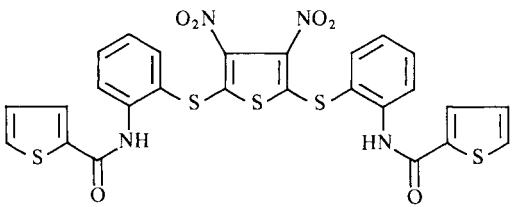
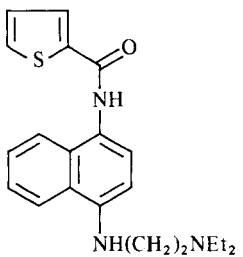
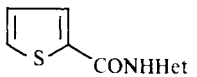
Ar	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
2-MeS—C_6H_4	100	d	*ca* 80	–	880
2-(S-3,5-di-NO_2-2-thienyl)—C_6H_4	184.5–185.5	d	87	–	889
2-($SO_2NHCOPh$)—C_6H_4	233–235	d	86	–	884
3-Cl—C_6H_4	138	d	⩾95	L	885
	138	d	–	I, U	867
4-Cl—C_6H_4	163–164	a	24	–	216
	161	d	⩾95	L	885
	161	d	–	I, U	867
4-Cl—2-PhCO—C_6H_3	159–161	d	82	–	887
3-NO_2—C_6H_4	156	d	–	I, U	867
4-NO_2—C_6H_4	222–224	f	47	–	228
	210	d	–	I, U	867
	257.5–258.5	d	97	–	889
	162–164.5	d	53	–	890

TABLE 15. HETEROARYLAMIDES OF THIOPHENE-2-CARBOXYLIC ACID



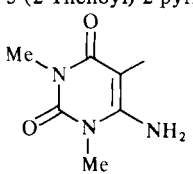
Het	Melting Point (°C)	Preparation	Yield (%)	Notes	References
2-Thienyl	193–195	a	45	–	218
4-OH-2-thiazolyl	212	d	60	–	856
5-Cl-2-thiazolyl	201	d	75	–	856
4-Br-2-thiazolyl	171	j	75	–	856
5-Br-2-thiazolyl	209	d	70	–	856
5-NO_2-2-thiazolyl	255–256	d	–	–	891
4-Me-5-NO_2-2-thiazolyl	249	d	57	–	856
3-Me-4-NO_2-5-isothiazolyl	178	d	65	–	856
2-Pyridyl	112–114	d	37	–	887
5-NO_2-2-pyridyl	206	d	–	–	892
3-Cl-6-pyridazyl	270–275 d	d	58	–	887
2-Pyrimidyl	158–160	d	48	–	887
	160–161	d	35	I, P, M	893
4,6-diMe-2-pyrimidyl	168–169	d	37	I, P, M	893
2-NH_2-4-Me-5-NO-6-pyrimidyl	210–215 d	d	69	–	894
2,5-di-NH_2-4-MeO-6-pyrimidyl	170	e	*	–	894
5-(2-Thenoyl)-2-pyrimidyl	153–154	d	5	I, P, M	893
	280–282	d	*	–	499
		e	*	–	499
6-MeO-8-quinolyl	146–148	f	23	–	895

TABLE 15. *(Continued)*

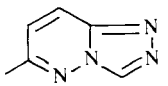
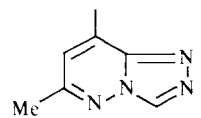
Het	Melting Point (°C)	Preparation	Yield (%)	Notes	References
	224–225	d	40		887
	227–229	d	46	–	887
6-Puryl	248–249.5	d	–	–	590

TABLE 16. 2-THENOYLHYDRAZIDE AND ITS DERIVATIVES (EXCLUDING HYDRAZONES)

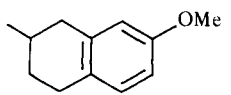
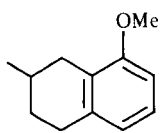
R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	136	h	50	–	896
		138	h	*	–	897
		142–143	h	*	–	898
		165	f	–	–	899
		134–136	h	75	–	609
	CH_2Ph	114–115	e	–	–	616
	i-Pr	110–111	e	–	–	616
	CHEt Ph	145/0.005	e	–	–	616
	Hydrochloride	223–225	–	–	–	616
	$CH_2C(Ph)NNHCO$-2-thienyl	155	f	65	I	900
		127–129	e	72	–	617
		142–144	e	87	–	617
	Ph	180–181	f	62	–	168
	$C(=NH)NH_2$	215–216	d	29	–	901
	Hydrochloride	255–256 d	d	–	–	901
	$COCH_2NHCO_2CH_2Ph$	145–146	k	–	–	609
	$COCHMeCO_2CH_2Ph$	215–216	k	–	α	609
	CO-2-thienyl	276	d	–	–	902

TABLE 16. (*Continued*)

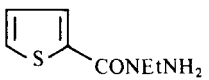
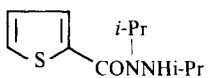
R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	$CONH_2$	215–216	d	80	–	901
	CONHEt	185–186	f	80	–	901
	$CONHCH_2CH{=}CH_2$	164–166	f	62	–	901
	$CONH(CH_2)_{17}Me$	127–129	f	88	–	901
	$CONMe_2$	213–214 d	d	56	–	901
$-COCH_2S-CO-$		172–173	f	–	–	896
H	$CSNH_2$	202–203 d	d	37	–	901
	$CSNHCH_2CH{=}CH_2$	198–199 d	d	75	–	901
	CSNHPh	177	f	95	–	903
	$CSNMe_2$	153–155	d	14	–	901
	$CSNEt_2$	115–116	d	24	–	901
	CSSK	274–276 d	f	–	–	898
		131–133	f	70	–	610
		106–109	d	–	–	904
	Hydrochloride	132–134	–	–	–	904

TABLE 17. 2-THENOYLHYDRAZONES

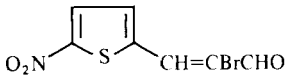
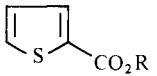
R^1COR^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
CCl_3CHO	160–162	k	–	–	905
i-BuCHO	113–114	k	71	–	906
$C_7H_{15}CHO$	84–85	k	63	–	906
D-Glucose	190–192 d	k	36	–	906
	255	k	94	–	907
4-HO—C_6H_4CHO	>262 d	k	–	–	585
4-HO-3,5-di-Br-C_6H_2CHO	>264 d	k	–	–	585
4-HO-3,5-di-I—C_6H_2CHO	>237 d	k	–	–	585
4-$MeOC_6H_4CHO$	185	k	–	–	585
3,4-di-$MeOC_6H_3CHO$	171	k	–	–	585
3,4-O—CH_2—OC_6H_3CHO	199	k	–	–	585
2-Cl-C_6H_4CHO	186	k	–	–	585
3,4-di-Cl-C_6H_3CHO	219	k	–	–	585
4-$Me_2NC_6H_4CHO$	203	k	–	–	585
5-Acenaphthaldehyde	240	k	–	–	585
3-Pyrenealdehyde	270	k	–	–	585
9-Ethylcarbazole-3-aldehyde	227	k	–	–	585
Me_2CO	108–109	k	–	–	616
	105–106	k	85	–	906
$MeCOC_5H_{11}$	100–101	k	80	–	906
$MeCO(CH_2)_2CO_2H$	175–176	k	–	–	908
$MeCOCO_2H$	200	k	–	–	908
EtCOPh	136–138	k	–	–	616
Cyclohexanone	142–143	k	90	–	906
Tetrachlorocyclopentadienone	207–210	d	79	–	909

TABLE 17. (*Continued*)

R^1COR^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
5-MeO-2-tetralone	159–161	k	53	–	617
7-MeO-2-tetralone	148–150	k	90	–	617
8-MeO-2-tetralone	162–165	k	82	–	617
	175–180/0.6	g	73	–	610

TABLE 18. ALKYL AND SUBSTITUTED-ALKYL ESTERS OF THIOPHENE-2-CARBOXYLIC ACID



R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	40/0.5	–	–	d, n	910
	75.5/7	l	–	d, n	911
	47–50/10	–	–	I	912
	87/10	m2	–	–	871
	91–93/18	–	–	–	913
	–	–	–	I	914, 915, 916, 917
	–	–	–	M	918
	–	–	–	C	919, 920, 921, 922
	–	–	–	C of $AlCl_3$ complex	923, 924
	–	–	–	U	866
5-D derivative	–	–	–	I	916
	–	–	–	P, M	925
CH_2Ph	195–196/24	l	–	n	926
CH_2-2-thienyl	30–32	f	28	U	569
	125–132/0.04	l	80	–	569
Et	45/0.4	m2	78	d, n	910
	71/1	m2	–	n	927
	66.5/2, 117/30	l	98	–	898
	98–99/13	–	–	–	928
	97/14	l	–	d, n, U	911
	114–115/25	f	–	–	905
	210–220/760	f	–	–	899
	–	–	–	D	929
	–	–	–	U	866
	–	–	–	I	914, 916, 917, 930
CH_2CH_2Ph	199–201/18	l	–	n	926

TABLE 18. (*Continued*)

R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
CH_2CH_2-*N*-piperidyl, HCl	181.5–182.5	l	87	–	931
CH_2CH_2-*N*-morpholyl, HCl	209–210.5	l	84	–	931
$CHPhCH_2$-*N*-pyrrolidyl	160–166/0.03	l	11	–	932
CH_2CH_2OH	80–84/8	f	94	–	493,494
n-Pr	51/0.45	m2	75	d, n	910
	88.5/9	l	–	d, n, U	911
	124–125/24	l	–	n	926
i-Pr	36/0.5	m2	31	d, n	910
	110/22	l	–	n	926
$CH_2CH{=}CH_2$	84–87/10	f	–	–	490, 491, 492
$(CH_2)_3$-*N*-piperidyl, HCl	169.5–171	l	89	–	931
$(CH_2)_3$-*N*-morpholyl, HCl	190–190.5	l	86	–	931
$(CH_2)_3$-*N*-(2,5-di-Me-pyrrolyl)	80	l	80	–	933
CH_2CHMe-*N*-piperidyl, HCl	173.5–174.5	l	92	–	931
CH_2CHMe-*N*-morpholyl, HCl	197–198.5	l	85	–	931
CH_2CMe_2NHPr, HCl	165–166	l	–	–	934
CH_2CMe_2NHBu, HCl	175–176	l	24	–	934
$CH_2CMe_2NHC_5H_{11}$, HCl	130–131	l	–	–	934
CHPhCHMeNHMe, HCl	214	b	98	I, P	608
n-Bu	58/0.15	m2	80	d, n	910
	83/1	l	–	d, n	911
	137–138/24	l	–	n	926
i-Bu	43/0.6	m2	60	d, n	910
	129/22	l	–	n	926
t-Bu	63–65/16	f	91	–	493, 494
	–	–	–	I	915, 916, 935
	–	–	–	P, M	925
5-D derivative	–	c	–	I	916, 935
$(CH_2)_4$-*N*-piperidyl, HCl	152.5–154	l	94	–	931

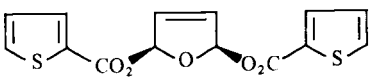
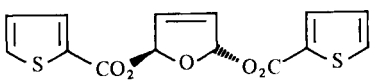
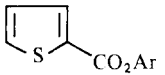
$(CH_2)_4$-*N*-morpholyl, HCl	110–112	l	79	–	931
$(CH_2)_4$-*N*-(2,5-di-Me-pyrrolyl)	232/14	l	*	n	936
CH_2CHEt-*N*-(2,5-di-Me-pyrrolyl)	64	l	–	–	936
n-C_5H_{11}	63/0.13	m2	67	d, n	910
	101.5/4	l	–	d, n	911
	152–153/27	l	–	n	926
i-C_5H_{11}	76/0.7	m2	59	d, n	910
	142–143/22	l	–	n	926
$(CH_2)_5$-*N*-(2,5-di-Me-pyrrolyl)	247–248/14	l	–	n	936
$(CH_2)_5$-*N*-(2-Me-5-Ph-pyrrolyl)	281–282/14	l	–	n	936
4-(*N*-Me-piperidyl), HCl	215.5–216.5	l	53	I	937
CH_2-3-(*N*-Me-piperidyl), HCl	150–153	–	–	–	938
Methiodide	195–196	–	–	–	938
n-C_6H_{13}	125.5/6	l	–	d, n	911
n-C_7H_{15}	133/3	l	–	d, n, U	911
n-$C_{10}H_{21}$	130/0.13	m2	83	d, n	910
	207–208/20	l	–	n	926
Tetrahydrogeranyl	198/22	l	–	n	926
Citronellyl	198–199/20	l	–	n	926
n-$C_{12}H_{25}$	224–225/20	l	–	n	926
n-$C_{14}H_{29}$	245–246/20	l	–	n	926
n-$C_{16}H_{33}$	266–268/22	l	–	n	926
	132.5–133.5	f	*	I, P	533
	149.5–150	f	*	I, P	533

TABLE 19. ARYL AND HETEROARYL ESTERS OF THIOPHENE-2-CARBOXYLIC ACID



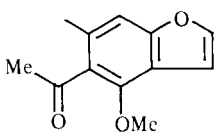
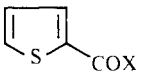
Ar	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Ph	54	l	65	–	635
	54	l	–	–	647
2-Me-C_6H_4	180–181/11	l	54	–	635
3-Me-C_6H_4	61	l	72	–	635
4-Me-C_6H_4	91–92	l	76	–	635
2-HO—C_6H_4	130–132	c	81	–	203
2-MeO-4-$EtCMe_2$—C_6H_3	229–230/13	l	–	n	939
2-MeO-4-Et_2CMe-C_6H_3	235–236/13	l	–	n	939
3,4,5,6-Tetra-Cl-2-OH—C_6	195	f	40	U	230
2-MeCO-3-MeO—C_6H_3	90–91	l	96	–	629
2-MeCO-4-MeO—C_6H_3	75–77	l	95	–	629
2-MeCO-5-MeO—C_6H_3	88–89	l	94	–	629
4-Cl-C_6H_4	84–85.5	l	–	–	647
4-Br-C_6H_4	85	l	–	–	647
4-NO_2—C_6H_4	181	l	–	–	647
2-MeCO—C_6H_4	112–114	l	83	–	629
	115	l	55	–	628
1-Naphthyl	80	l	–	–	647
	275/7	l	52	–	635
2-Naphthyl	112	l	63	–	635
2-Thienyl	54	l	–	–	647
	116–118	l	75	–	632

TABLE 20. OTHER DERIVATIVES OF THIOPHENE-2-CARBOXYLIC ACID



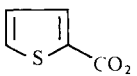
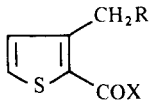
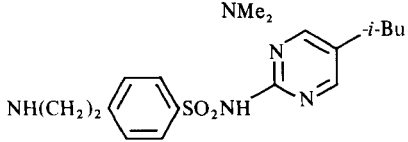
X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
F	75–78/14	g	–	I	561
	–	–	–	F	940
	–	–	70	P	460
Cl	77/10	n	*ca* 100	–	647
	85/14	n	74	–	931
	–	–	–	I	941
	60.5–61.5	f	*	–	647
N_3	35–36	g	73	–	577
		–	80	–	574
—NCO	117/32	d	–	–	942
—CN	52.5	g	50	–	556
	54–55	g	81	I	557
PEt_2	102–103/2	g	58	–	899
P-*n*-Pr_2	122–123/2	g	79	–	899
P-*t*-Bu_2	143–144/2	g	69	–	899
$\overset{+}{P}MeEt_2I^-$	73 d	g	58	–	899
S_2O_3Na	160	g	40	–	558
$OSnPh_3$	111–112	f	32	–	500
S-Benzylisothiouronium salt	184–185	–	–	–	943

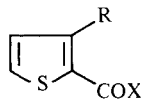
TABLE 21. 3-METHYL- AND SUBSTITUTED-METHYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	OH	147–148	o	64	–	189
		147	b	71	U	246
		141–143	p	86	–	505
		144–145	o	34	–	82
			f	53	–	82
		148	i	19	–	11
		144–145	b	*	–	244
		147	b	71	U	246
		147	q	83	P	944
		–	c	14	P	945
		–	–	–	K	946
	Cl	216–217/760	n	–	I	941
	NMe_2	75–77/0.002	d	67	–	3
		150	d	–	–	872
	NHPh	126	d	95	–	941
		128–30	d	–	–	161
	NH-(4-NO_2—C_6H_4)	171–172	f	40	–	228
	OMe	47–48/0.1	r	*	–	244
		101/12				244
	OEt	84/4	s	68–70	U	246
		108–109/12	r	*	–	244
		93–94/6	m2	60	–	944

Ph	OH	155–155.5	u	56	I, P	14
2-OH–C_6H_4	OH	201–203	b	90	I, P	503
—δ—Lactone—		110–112	v/k	16	I, P	503
3-Thienyl	OH	135–136	u	85	I, P	513
3-CO_2H-2-thienyl	OH	241–242 d	u	48	I, P, U	947
2-CO_2H-3-thienyl	OH	240–241 d	u	61	I, P, U	947
CO_2H	OH	189–191	b	83	I	733
CO_2Et	OH	144–145.5	g	89	I, P	733
CN	OH	135–136	g	79	I, P	733
OH	OH	113	e	–	I	502
		113–114	b	33	P	944
—γ—Lactone—		104	k	–	P	502
OCOMe	OEt	154–156/6	g	93	–	944
OMe	OH	126–127	i	89	I, P	15
OPh	OH	148–151	g/b	67	–	503
O-(3-HO_2CCH_2—C_6H_4)	OH	187–189	g/b	58	–	503
O-(4-HO_2CCH_2—C_6H_4)	OH	222	g	62	–	505
		229–232	g/b	56	–	503
O-(3-HO_2CCHMe-C_6H_4)	OH	192–194	g/b	57	–	503
SCH_2CO_2Me	OMe	148–149/0.5	g	74	–	623
SPh	OH	142–143	g/b	70	–	503
$S(O)_2Ph$	OH	215–216	g	34	P	733
S-(3-$HO_2CCH_2C_6H_4$)	OH	171–173	g/b	71	–	503
S-(4-$HO_2CCH_2C_6H_4$)	OH	187–189	g/b	66	–	503
S-C(=NH)NH_2, HBr	OEt	168–169	g	90	–	944
Cl	OH	163–165	v	21	I, P	503
Br	OMe	118–120/0.5	f	58	I	623
	OEt	138–140/6	f	75	–	944
COMe	OH	127–129	g	90	I, P	733
COPh	OH	199–201	g	42	–	733
$PO(OEt)_2$	OMe	134–138/0.06	g	59	–	948

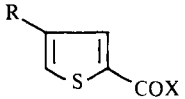
TABLE 22. 3-ALKYL- AND SUBSTITUTED-ALKYL (OTHER THAN METHYL) THIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(R > Me)

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
PhCHOH	OMe	–	ml	–	P	552
PhCH—O—		Oil	k	*	I, P	552
Ph_2C—O—		144–146	f	62	I, P	27
$(MeCO)_2CH$	OH	187–189	g	85	P	733
PhCH=CH	OMe	78–79	f	67	–	948
$PhCH_2CH_2$	OMe	152–154	e	50	–	948
2-Thienyl-CH=CH	OH	219	u	–	P	509
2-Thienyl-CH_2CH_2	OH	176	u	90–95	P	509
			e	90–95		509
3-Thienyl-CH=CH	OH	149–150	u	81	–	512
(4-D-3-Thienyl)—$(CH_2)_2$	OH	176	u	93	P	510
2-Furyl-$(CH_2)_2$	OH	90–91	u	60	P	508
3-Furyl-$(CH_2)_2$	OH	149–150	u	80	P	508
—CH_2CH_2—NH—		123.5–125	a	20	I	220
$HOCH_2CH_2$	OH	–	p/b	*	M	99
—δ—Lactone—		53–54	k	*	M	99
SeCH=CH	OH	165	f	78	P	949
i-Pr	OH	110–111.5	q	–	–	950
	OCH_2CO-(4-Br-C_6H_4)	88–89	–	–	–	950
—CH_2CHMe-NH—		108–109	a	47	I, U	220
		190/2				220
—CH_2CHMe-O—		91–93	f	40	I, P	220
Me_2CHCH_2	OH	84	b	*	–	244
	OMe	78–83/0.1	r	*	–	244
		79/0.5				244
$Me_2CH(OH)CH_2$	OH	–	–	–	P	524
n-C_6H_{13}	OMe	80–90/0.05	f	66	–	524

TABLE 23. 4-ALKYL- AND SUBSTITUTED-ALKYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	OH	119–121	b	94	M, P	951
		116–117	q	94	P	944
		122–124	–	–	K	952
		120–121	w	–	–	156, 157
		119–120	f	21	–	68
		122	i	61–68	–	11
		120–121	i	68	–	28
		–	–	–	K	98, 464, 946
		–	–	–	C	953
		–	–	–	I, C	954
	Cl	112–114/18	n	85	–	566
	OMe	100–103/15	e	90	P	951
	OEt	100–101/7	m2	60	–	944
$PhCH_2$	OH	105–105.5	i	–	I, P	14
HO_2CCH_2	OH	208–210	b	*	K, P	98
		–	–	–	C	953
		–	–	–	I, C	954
$NCCH_2$	OMe	110/0.2	g	75	P	98
$HOCH_2$	OH	124	b	53	P	944
		124	e	–	I	502
		–	–	–	C	953
		–	–	–	I, C	954
		114	b	*	K, P	98
$MeOCH_2$	OH	90–92	p	91	M, P	951

TABLE 23. (*Continued*)

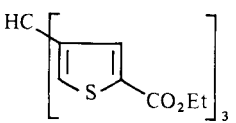
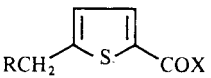
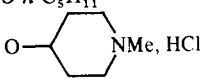
R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
		–	–	–	C	953
		–	–	–	I, C	954
$PhOCH_2$	OH	134–136	g	*	K, P	98
		–	–	–	C	953
		–	–	–	I, C	954
$MeCOOCH_2$	OEt	150–152/5	g	74	–	944
$HSCH_2$	OH	128–130	g	*	K, P	98
		–	–	–	C	953
		–	–	–	I, C	954
$EtSCH_2$	OH	80	b	*	K, C	98
		–	–	–	C	953
		–	–	–	I, C	954
	OMe	115–120/0.4	g	–	–	98
$PhS(O)_2CH_2$	OH	188–190	g	81	K, P	98
		–	–	–	C	953
HBr, $NH_2C(=NH)SCH_2$	OEt	197–198	g	88	–	944
$ClCH_2$	OMe	–	–	–	P	955
$BrCH_2$	OH	172–175	v	93	M, P	951
		–	–	–	K	98
		–	–	–	C	953
		–	–	–	I, C	954
	OMe	65–67	m1	75	M, P	951
	OEt	128–130/3	f	72	–	944
i-Pr	OH	92–93	q	–	–	950
		–	–	–	U	956
		–	–	–	P	957
		–	–	–	K	464
	OCH_2CO—(4-Br-C_6H_4)	80–81.5	–	–	–	950
t-Bu	OH	77	q	60	–	926
		264/0.7	a	20–25	–	958

TABLE 24. 5-METHYL- AND SUBSTITUTED-METHYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



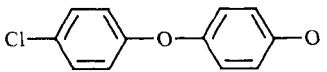
R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	OH	133	b	–	–	181
		137–138	–	–	–	952
		138–139.5	–	–	K	927
		136–138	q	85	–	186
		139–140	i	84	–	767
		132	b	69	–	871
		139–140	–	–	U	959
		135–137	f	59	–	249
		139	r	–	–	236
		–	–	–	P	945
		–	–	–	K	98, 946, 960, 961, 962
		–	–	–	I	963
	Cl	108–110/13	n	99	–	572
		–	–	–	I, P	964
		–	–	–	I	941
	NH_2	163.5–164	d	61	–	951
	NHPh	120–121	d	⩾95	–	965
	NH—(4-NO_2—C_6H_4)	205–207	f	60	–	228
	$NHCONH_2$	218–219	d	15	P	591
	NHCONHPh	230.5–231.5	f	57	–	591
	N_3	54–55	f	76	I	966
		58–60	f	92	–	577
		54–55	f	–	–	967
	OMe	107–108/1.8	e	*	–	181
		77–79/5	m2	71	d, n	968

TABLE 24. *(Continued)*

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
		84/5	e	*	–	871
		96–97/12	m1	–	P, n	767
		–	–	–	I	917
		–	o/m1	–	P	81
	OEt	87/1	–	–	n	927
		87–89/5	m2	82	d, n	968
		100–102/6	m2	60	–	944
		112–114/12	–	–	–	928
	O-n-Pr	95–98/5	m2	80	d, n	968
	O-i-Pr	87–88/5	m2	44	d, n	968
H	*O-n*-Bu	106.5–108.5/5	m2	88	d, n	968
	O-i-Bu	102–105/3	m2	76	d, n	968
	O-n-C_5H_{11}	116–118/5	m2	64	d, n	968
		184.5–185	1	53	I	937
HO_2C	OH	206–207 d	b	–	–	563
	–	–	–	–	K	960
H_2NCO	NH_2	207–208 d	a	20	–	563
Ph	OH	131–132	q	–	–	148
		129–131	i	77	I, P	515
4-CO_2H–C_6H_4	OH	285–286	q	–	–	149
2-Furyl	OH	140–142	q	–	–	150
5-CO_2H-2-furyl	OH	240–242 d	b	–	–	150
5-CO_2Me-2-furyl	OMe	80–81	c	48	–	150
		172–176/0.1				150
2-Thienyl	OH	104–105	i	–	–	969
		105–106	o	71	–	970
5-Me-2-thienyl	OH	128–128.5	i	*	–	971
5-CO_2H-2-thienyl	OH	280 d	o	84	–	970

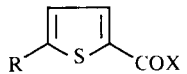
5-CO_2Me-2-thienyl	OMe	74–74.5	–	–	–	970
5-[$(CH_2)_2$OH]-2-thienyl	OH	110.5–111	i	32	–	972
$Me_3N^+Cl^-$	OH	187	b	43	I, U	871, 973
	OMe	177	g	100	–	871, 973
HO	OH	115	b	67	I, U	973
		121	b	70	P	944
		121	e	–	I	502
		121	–	–	–	871
		–	–	–	K	98
MeCOO	OMe	118/0.6	g	99	–	871, 973
	OEt	146–147/4	g	53	–	944
MeO	OH	83–86	p	82	–	97
		76	b	77	I, U	871
		–	–	–	K	973
	OMe	105/2	g	66	–	871, 973
EtO	OH	105–106	q	–	–	139
PhO	OH	129	b	90	I, U	871, 973
		–	–	–	K	98
	OMe	68	g	51	–	871, 973
		185/9				871, 973
(3-CF_3—C_6H_4)O	OH	118	g	–	–	974
(4-*i*-Pr-C_6H_4)O	OH	140	g	–	–	974
(3-*t*-Bu-C_6H_4)O	OH	118	g	–	–	974
(4-*t*-Bu-C_6H_4)O	OH	163	g	–	–	974
(4-Me_2CPh-C_6H_4)O	OH	133	g	–	–	974
(2,6-di-*t*-Bu-C_6H_3)O	OH	105	g	–	–	974
(3,5-di-*t*-Bu-C_6H_3)O	OH	152	g	–	–	974
(4-Ph-C_6H_4)O	OH	208	g	–	–	974
(4-MeO—C_6H_4)O	OH	155	g	–	–	974
(4-*n*-BuO—C_6H_4)O	OH	156	g	–	–	974
(3,5-di-MeO—C_6H_3)O	OH	117	g	–	–	974

TABLE 24. *(Continued)*

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
(3,4-[*O*—CH_2—*O*—]—C_6H_3)O	OH	174	g	–	–	974
	OH	199	g	–	–	974
(4-MeS—C_6H_4)O	OH	163	g	–	–	974
(2-MeSO—C_6H_4)O	OH	167	g	–	–	974
(4-$MeSO_2$—C_6H_4)O	OH	208	g	–	–	974
(4-F—C_6H_4)O	OH	143	g	–	–	974
(3-Cl-C_6H_4)O	OH	115	g	–	–	974
(4-Cl-C_6H_4)O	OH	162	g	–	–	974
(4-Cl-2-Me-C_6H_3)O	OH	156	g	–	–	974
(2,4-di-Cl-C_6H_3)O	OH	167	g	–	–	974
(2,6-di-Cl-C_6H_3)O	OH	194	g	–	–	974
(4-Br-C_6H_4)O	OH	160	g	–	–	974
(4-MeCO—C_6H_4)O	OH	192	g	–	–	974
(4-PhCO—C_6H_4)O	OH	189	g	–	–	974
HS	OH	135–136	b	85	I, U	871, 973
		225–226 d	b	60	–	944
		–	–	–	K	98
EtS	OH	79–80	i	53	–	175
$EtSO_2$	OH	168–169	w	–	–	175
$PhSO_2$	OH	173	b	81	I, U	871
		–	–	–	K	973
	OMe	115	g	87	–	871, 973
(4-*t*-Bu-C_6H_4)S	OH	122	g	–	–	974
(4-MeS—C_6H_4)S	OH	118	g	–	–	974
(4-Cl-C_6H_4)S	OH	123	g	–	–	974
HBr, $H_2NC(=NH)S$	OH	180–181	g	83	–	944
HCl, $H_2NC(=NH)S$	OMe	181	g	74	–	973

Cl	OMe	93/0.2	c	*	–	160
		103/0.5	c	72	–	871
		–	–	–	P	955
Br	OEt	140–142/4	f	83	–	944
$Br^{-}Ph_3P^{+}$	OH	273	g	*	–	975

TABLE 25. 5-ALKYL- AND SUBSTITUTED-ALKYL (OTHER THAN METHYL) THIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(R > Me)

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Et	OH	70	i	92	–	453
		67–68	q, e	–	–	175
		69	o	91	–	73
		66–69	q	78	–	186
		69	b	73	I, U	973
		69	q	90	–	138
		–	–	–	K	960, 961
	Cl	119/14	n	–	n	73
	NH_2	140	d	–	–	73
	N_3	70/0.1	f	85	–	577
	OMe	120/12	e	45	–	871, 973
	OEt	114/20	l	–	–	73
$PhCH_2CH_2$	OH	122	q	68	–	976
$4\text{-}CO_2H\text{—}C_6H_4\text{—}(CH_2)_2$	OH	294–295	q	–	–	149
$HOCH_2CH_2$	OH	–	–	–	K	960
$MeOCH_2CH_2$	OH	–	–	–	K	960
$PhOCH_2CH_2$	OH	–	–	–	K	960
$HSCH_2CH_2$	OH	–	–	–	K	960
$PhS(O)_2CH_2CH_2$	OH	–	–	–	K	960
$Cl^-Me_3\dot{N}CH_2CH_2$	OH	–	–	–	K	960
$MeCOCH_2CH_2$	OMe	180/1	f	60	I, M, P	141
$CH_3CH(OH)$	OEt	–	e	–	P	465
$CH_3CH(4\text{-}NO_2\text{—}C_6H_4\text{—}COO)$	OEt	91.5–92	l	–	P	465
CH_3CHCl	OMe	135/8	c	35	–	871, 973
n-Pr	OH	–	–	–	K	960

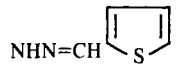
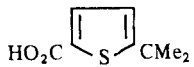
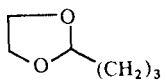
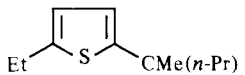
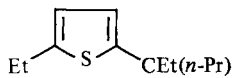
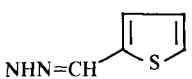
		173	k	–	–	585
i-Pr	OH	81	q	82	–	977
		81	c	30	–	978
Cyclopropyl	OH	113–114.5	o	45	I, P, U	979
		–	–	–	P	957
$Ph(CH_2)_3$	OH	73	q	–	–	976
$4\text{-}CO_2H\text{—}C_6H_4\text{—}(CH_2)_3$	OH	242	q	*	–	976
	OH	275–277 d	q	62	–	980
$Me_2C(OH)$	OH	116–118	f	61	–	524
$HO_2C(CH_2)_3$	OH	193–194.5	q	*	–	452
		194	q	–	–	149
		193–194.5	q	*	–	486
$MeO_2C(CH_2)_3$	OH	79.5–81	w	47	–	487
		79.5–81	p	–	–	486
	OEt	142–147/0.1	f	69	–	524
$MeCO(CH_2)_3$	OMe	160/1	f	30	I, M, P	141
i-Bu	OH	47	p	>90	–	981
		45–46	q	83	–	186
t-Bu	OH	127–128	p	32	–	977
		128–128.5	q	90	–	982
		126.5–128	i	68	–	983
		101	i	–	–	961
	Cl	120–122/13	n	–	n	982
	NH_2	148	d	–	–	982
	OCH_2Ph	226–227/29	l	–	n	926
	OEt	150–151/20	l	–	n	926
		174.5–175/17	r	47	n	239

TABLE 25. *(Continued)*

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	$O(CH_2)_2Ph$	238–239/31	l	–	n	926
	$O(CH_2)_2NEt_2$	198/13	l	–	n	982
	Hydrochloride	118	–	–	–	982
	O-*i*-C_5H_{11}	174–175/20	l	–	n	926
$Ph(CH_2)_4$	OH	116–117	q	63	–	976
4-HO_2C–C_6H_4–$(CH_2)_4$	OH	265	q	74	–	976
$HO_2C(CH_2)_4$	OH	170–172	b	–	–	751
$EtO_2C(CH_2)_4$	OEt	155–168/12	–	–	–	751
	OH	Oil	w	59	I, α	476
	S-benzylisothiouronium salt	154–155	–	–	–	476
	OH	80–81	p	88	I, U, α	984
	S-benzylisothiouronium salt	148–149	–	–	–	984
n-C_6H_{13}	OMe	80–88/0.05	f	65	–	524
Et_2CHCH_2	OH	37	p	74	–	981
$EtMe_2CCH_2$	OH	106	p	60	–	981
n-C_9H_{19}	OH	75–76	i	–	U	985
	OMe	Oil	m2	–	U	985
	–	–	–	–	M	986
n-$C_{10}H_{21}$	OH	84–85	q	91	–	987
1-Adamantyl	OH	266–268 d	i	70	I	988
	OMe	112.5–113	m1	–	I, P	988
		112–113	f	55	P	122
n-$C_{11}H_{23}$		105	k	–	–	585
n-$C_{13}H_{27}$	OH	91–92	i	85	I, M, P, U	985

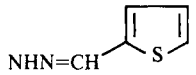
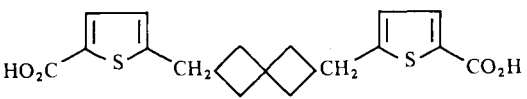
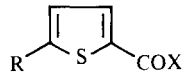
	OMe	36–37	m2	97	I, M, P, U	985
		–	–		M	986
n-$C_{14}H_{29}$		106	k	–	–	585
n-$C_{15}H_{31}$	OMe	46–47	m2	–	U	985
		–	–	–	M	986
n-$C_{17}H_{35}$	OH	95–96	i	–	U	985
	OMe	49.5–50	m2	–	U	985
		–	–	–	M	986
n-$C_{18}H_{37}$	OH	102–103	q	86	–	987
n-$C_{19}H_{39}$	OH	98.5–100	i	–	U	985
	OMe	–	m2	–	U	985
		250 d	p	76	I, P	95

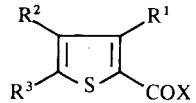
TABLE 26. 5-ALKENYL- AND ALKYNYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(R = alkenyl or alkynyl)

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
MeC≡C	OH	180	p	*	U	118
		176.5–177.5	i	37	U	989
		179–180	p	–	–	119
		175–177	w	70	–	154
			p	78	–	154
	OMe	62	m1	*	–	118
PhC≡C	OH	205–206	i	63	–	990
MeCH=CH	OH	138–139	p	45	–	119
MeCH=CCl	OH	169–170	c	–	P	467
EtCH=CCl	OH	139–140	c	–	I, M, P, U	467
$MeCHOHCH_2CH=CH$	OMe	160/1	f	10	I, M, P	141
2-Furyl-CH=CH–C≡C	OEt	150–152/760	g	55	–	991
2-Thienyl-CH=CH–C≡C	OEt	110	g	43	–	991
$Ph(CH=CH)_2$	OMe	130–131	r	Good	U	240
		130–132	r	*	–	237
2-Naphthyl$(CH=CH)_2$	OMe	129–131	r	*	–	237
PhCH=CH	OMe	103	r	Good	U	240
		102–103	r	*	–	237
	OEt	105–107	r	*	–	237
4-Me-C_6H_4–CH=CH	OMe	145	r	Good	U	240
4-HO–$C_6H_4CH=CH$	OMe	199	r	Good	U	240
4-MeO–$C_6H_4CH=CH$	OMe	120–121	r	Good	U	240
2-Cl-$C_6H_4CH=CH$	OMe	89–91	r	Good	U	240
4-Cl-$C_6H_4CH=CH$	OMe	149	r	Good	U	240
4-NO_2–$C_6H_4CH=CH$	OH	278–279	p	70	P	564
2-Naphthyl-CH=CH	OMe	129–131	r	Good	U	240

TABLE 27. DI- AND TRIALKYL AND SUBSTITUTED-ALKYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



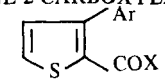
R¹	R²	R³	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	Me	H	OH	184–186	b	–	–	281
				188–189	i	–	U	159
				187–188	b	*	–	244
				–	–	–	K	961
			OMe	34	r	*	–	244
				–	–	–	I	916
			OEt	98–102/0.02	x	*	n	281
				100–105/0.5	s	80	P	246
				–	–	–	I	915, 916
			O-*t*-Bu	50–52	f	81	–	281
				100–105/0.04				281
				–	–	–	I	915, 916, 992
Et	Me	H	OH	111–112	b	*	–	244
			OMe	87–88/0.05	r	*	–	244
Me	H	Me	OH	173–174	p	–	–	159
				169–170	u	–	–	42
				171	b	*	–	243
				171.5–172.5	u	14	–	63
				–	–	–	P	945
			NH_2	115–116	–	–	–	63
			NHPh	98–101	f	–	–	993
			NH–(2-F–C_6H_4)	73–74	f	–	–	993
			OMe	115–119/12	r	*	–	243
$(CH_2)_2$–(4-Cl-C_6H_4)	H	Me	OH	179–180	i	90	P	507
Me	H	$Me_2C(OH)$	OH	119–120	f	60	P	524

TABLE 27. (*Continued*)

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
		n-C_5H_{11}	OMe	83–85/0.05	f	71	–	524
Et	H	Et	OH	85–85.5	q	–	–	63
t-Bu	H	t-Bu	OH	197–198	i	58	–	35
H	Me	Me	OH	210–212	i	*	U	159
				213	p, w	–	–	994
				186	r	–	–	236
		$HOCH_2$	OMe	65–66	b	70	–	995
				67.5–68	e	34	P, U	995
		$MeCOOCH_2$	OMe	122/0.3	g	90	P, U	995
		$ClCH_2$	OMe	38–39.5	c	27	P, U	995
					j	33		995
	$PhNHCH_2$	Me	OMe	105–106	g	50	P, U	995
	$ClCH_2$	Me	OMe	51–52	c	*	–	181
				108/0.7				181
				59–60	c	30	P, U	996
				104–117/0.6				996
	$HSCH_2$	$HSCH_2$	OMe	139–146/0.1	g	60	P, U	481
				182–184/0.9				481
	$EtSOCH_2$	$EtSOCH_2$	OMe	139–140	w	84	I, P, U	284
	$ClCH_2$	$ClCH_2$	OMe	72–72.5	c	85	P, U	481
				77–78	c	*	–	139
				–	–	–	P	955
		$BrCH_2$	OMe	87–88	f	*	–	181
	Me	Et	OH	113	r	–	–	236
	Et	Et	OH	130–130.5	i	1.3	P	36
	Me	n-C_9H_{19}	OMe	–	e	–	U	985
	$ClCH_2$	n-C_9H_{19}	OMe	44–45	c	–	U	985
				–	–	–	M	986
	Me	n-$C_{13}H_{27}$	OH	97–98	b	–	U	985

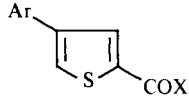
		n-$C_{13}H_{27}$	OMe	42–43.5	e	–	U	985
				–	–	–	M	986
	$ClCH_2$	n-$C_{13}H_{27}$	OMe	54–55	c	87	I, M, P, U	985
				–	–	–	M	986
	Me	n-$C_{15}H_{31}$	OH	–	b	–	U	985
			OMe	45–46	e	–	U	985
				–	–	–	M	986
	$ClCH_2$	n-$C_{15}H_{31}$	OMe	60–61	c	–	U	985
				–	–	–	M	986
	Me	n-$C_{17}H_{35}$	OH	–	b	–	U	985
			OMe	50–51	e	–	U	985
				–	–	–	M	986
	$ClCH_2$	n-$C_{17}H_{35}$	OMe	62–64	c	–	U	985
				–	–	–	M	986
	Me	n-$C_{19}H_{39}$	OH	104–105	b	–	U	985
			OMe	57–58	e	–	U	985
				–	–	–	M	986
H	$ClCH_2$	n-$C_{19}H_{39}$	OMe	67.5–68	c	–	U	985
				–	–	–	M	986
Me	Me	Me	OH	209	b	–	–	243
			OMe	53	r	–	–	243
	$ClCH_2$	$ClCH_2$	OMe	98.5–99	c	82	P, U	997
CH_2Cl	Me	$ClCH_2$	OMe	84–84.5	c	8	P, U	995

TABLE 28. 3-ARYL- AND SUBSTITUTED-ARYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



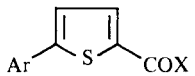
Ar	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Ph	OH	207	b	90	U	246
		113	r	–	–	236
		200–202	–	–	–	17
		205–207	u	82	N	16
			e	–		16
		112–113	b	–	–	238
		113	r	–	–	236
		201–204	o	88	P	997
		205–206	b	*	–	244
	OMe	120–121	m1	–	–	17
		123	r	60	–	234
		119–120	m1	–	P	16
		123	r	50	–	238
		119	r	*	–	244
	OEt	60	s	50	P, U	246
		61.5	r	56	–	238
4-Me-C_6H_4	OH	175	b	*	–	244
	OMe	148–150/0.1	r	*	–	244
2-CO_2Me-C_6H_4	OMe	95–97	f	–	–	17
4-MeO—C_6H_4	OH	170–171	b	*	–	244
	OMe	102	r	*	–	244
4-Cl-C_6H_4	OH	229 d	b	–	–	238
	OMe	98–99	r	50	–	238
		98–99	r	–	–	234
4-Br-C_6H_4	OH	223	b	–	–	238
	OMe	108–110	m1	–	P	17
		109–110	r	–	–	234
		109–110	r	55	–	238
	OEt	80–81	r	70	–	238
3-NO_2—C_6H_4	OMe	132–134	r	–	–	235
4-NO_2—C_6H_4	OMe	163–164	r	–	–	235
1-Naphthyl	OH	187.5–188	i	84	I, P	516

TABLE 29. 4-ARYL- AND SUBSTITUTED-ARYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



Ar	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Ph	OH	166–168	u	–	–	17
		168–170	u	85	N	16
			i	–		16
		187–188	i	94	–	241
	OMe	95–97	m1	–	–	17
		92–93	m1	–	P	16
	OEt	50–51	r	52	–	241
4-Br-C_6H_4	OH	238–240	u	*	–	17
	OMe	85–87	m1	–	P	17

TABLE 30. 5-ARYL- AND SUBSTITUTED-ARYLTHIOPHENE–2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



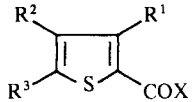
Ar	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Ph	OH	187–188	r	95	–	241
			r	47	–	241
		189–190	b	–	–	124
		189	r	75	–	236
		188–189	b	–	–	238
		184	w	*	–	154
		183–184	r	52	–	154
		187–188	r	61	U	248
		182	p	–	–	998
		186–188	o	81	–	71
		–	–	–	K	961
	NH_2	197–198	–	–	–	248
		200–201	d	66	–	241
	NMe_2	113–114	d	96	–	241
	N-Pyrrolidyl	132–133	d	82	–	241
	N-Piperidyl	102–103	d	98	–	241
		102–103	d	–	–	248
	N-morpholyl	122–123	d	98	–	241
	$NHNH_2$	164–165	h	63	–	241
		165.5–166.5	h	–	–	999–1002
	OMe	97–98	f	85	–	124
		98	r	*	–	237
		98	r	Good	U	240
	OEt	27–28	r	48	–	241
		29	r	40	–	233

		29	r	30	–	238
		145/0.4				238
4-Me-C_6H_4	OH	216	r	–	–	236
		217–218	i	78	–	241
		217	q	–	–	1003
	NH_2	214–215	d	69	–	241
	NMe_2	136–137	d	91	–	241
	N-Pyrrolidyl	156–157	d	76	–	241
4-Me-C_6H_4	*N*-Piperidyl	132–133	d	79	–	241
	N-Morpholyl	134–135	d	86	–	241
	$NHNH_2$	175–176	h	65	–	241
	OMe	112	r	Good	U	240
	OEt	91	r	Good	U	240
4-Ph-C_6H_4	OMe	196–197	r	Good	U	240
4-(5′-HO_2C-2′-thienyl)-C_6H_4	OH	>300	i	80	I	1004
4-(5′-MeO_2C-2′-thienyl)-C_6H_4	OMe	>270	m1	–	I, P	1004
4-MeO_2C—C_6H_4	OMe	161–162	r	Good	U	240
4-MeO—C_6H_4	OEt	77	r	2	I	247
4-Cl-C_6H_4	OH	260	b	–	–	238
		249	r	–	–	236
		254	i	81	–	241
		254	q	–	–	1003
	NH_2	207–208	d	72	–	241
	NMe_2	140–141	d	87	–	241
	N-Pyrrolidyl	189–190	d	72	–	241
	N-Piperidyl	109–110	d	97	–	241
	N-Morpholyl	147–148	d	97	–	241
	$NHNH_2$	179–180	h	71	–	241
	OEt	83	r	60	–	238
		83	r	56	–	233
4-Br-C_6H_4	OH	263	b	–	–	238
		251	r	–	–	236
		263–264	i	86	–	241

TABLE 30. (*Continued*)

Ar	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	NH_2	209–211	d	62	–	241
	NMe_2	136–137	d	93	–	241
	N-Pyrrolidyl	189–190	d	90	–	241
	N-Piperidyl	79–80	d	92	–	241
	N-Morpholyl	160–161	d	89	–	241
	OEt	80	r	75	–	238
		79–80	r	74	–	233
4-NO_2–C_6H_4	OMe	194–196	r	Good	U	240
2-Naphthyl	OMe	136	r	Good	U	240

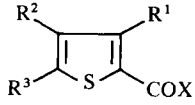
TABLE 31. DIARYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



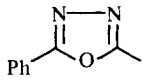
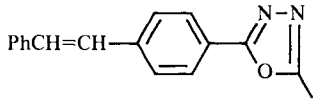
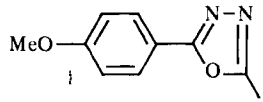
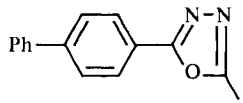
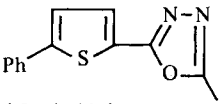
(Two of R^1–R^3 = aryl or substituted aryl)

R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	Ph	Ph	OH	261	r	–	–	236
				260–261	b	–	–	238
			OEt	78–78.5	r	30	–	238
				77.5	r	38	–	233
Ph	H	Ph	OH	225	r/b	*	–	232
			OEt	81–82	s	78	–	245
				81–82	s	78	U	246
	Ph	H	OH	225–225.5	b	–	–	485
				223–224	b	–	–	238
			OMe	144	r	–	–	234
				145–146	x	83	–	485
				144–145	r	40	–	238
				–	–	–	I	915, 916, 992
			OEt	65	s	70	P, U	246
				74–75	x	53	–	280
				–	–	–	I	915, 916, 992
			O-*t*-Bu	–	–	–	I	915, 916, 992
4-MeO–C_6H_4	4-MeO–C_6H_4	H	OH	205–215 d	b	72	P	281
			OMe	126	x	*	P, M	281
				–	–	–	I	916, 992
			OEt	83–84	x	*	–	281
				–	–	–	I	915, 916, 992
			O-*t*-Bu	123–125	f	*	M	281
				–	–	–	I	916, 992

TABLE 32. HETEROARYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVA

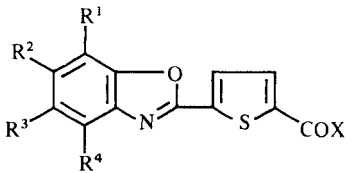


(One of R^1–R^3 = heteroaryl)

R^1	R^2	R^3	X
1-Pyrrolyl	H	H	OH
			OMe
1-Pyrazolyl	H	H	OH
2-Thienyl	H	H	OEt
H	2-Benzothiazolyl	H	OMe
	H	1-Pyrazolyl	OH
		2-Thienyl	OH
		5-Me-2-thienyl	OH
		5-Et-2-thienyl	OH
		5-Br-2-thienyl	OH
		5-I-2-thienyl	OH
		5-NO_2-2-thienyl	OH
		5-MeCO-2-thienyl	OH
		5-MeCO-2-thienyl	OMe
			$NHNH_2$
H	H		OMe
			$NHNH_2$
			OMe
			OMe
			OMe
		4-Pyrimidyl	OH

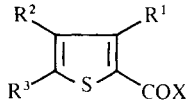
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
185	b	–	I, P	579
130/4	f	–	I, P	579
214–214.5	i	71	I, M, P	18
130–135/0.007	f	–	–	246
150–151	d/k	93	–	1005
240–241	i	43	I, M, P	18
184	–	–	K	1006
205	q	–	K	1006
185	–	–	K	1006
262	–	–	K	1006
258	–	–	K	1006
258	c	–	K	1006
286	b	–	K	1006
188	c	–	K	1006
228–229.5	h		–	1001, 1002
227.5–228.5	f	82	–	1001
241–242	h	–	–	1007
178.5–179	k	69	–	1007
211.5–212	k	82	–	1007
246–247	f	81	–	999
260–285 d	u	50	–	46

TABLE 33. 5-(2-BENZOXAZOLO)THIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	R^4	X	Melting Point (°C)	Yield (%)	References
H	H	H	H	OH	245–246	95	1005, 1008
				Cl	163–164	84	999, 1001, 1002
				NHPh	239.5	81	1005, 1008
				$NHNH_2$	250–251	89	1005, 1008
				OMe	145–145.5	90	1005, 1008
Me	H	H	H	OMe	129.5–130	78	1005, 1008
	H	Me	H	OMe	127	75	1005, 1008
H	Me	H	H	OMe	123.5–124.5	46	1005, 1008
		Me	H	OMe	156	69	1005, 1008
	H	Me	H	$NHNH_2$	221	78	1005, 1008
				OMe	132.5–133	73	1005, 1008
		$PhCH_2$	H	OMe	125–125.5	86	1005, 1008
		Et	H	OMe	97–97.5	59	1005, 1008
		Pr	H	OMe	84–84.5	84	1005, 1008
		i-Pr	H	OMe	87–87.5	51	1005, 1008
		t-Bu	H	Cl	176–178	–	81, 1003
				OMe	129.5–130	75	1005, 1008
		$PhMe_2C$	H	OMe	126.5–127.5	46	1005, 1008
		t-$BuCH_2Me_2C$	H	OMe	135.5–136	63	1005, 1008
		Cyclohexyl	H	OMe	146	72	1005, 1008
		Ph	H	OMe	189–189.5	84	1005, 1008
		MeO_2C	H	OMe	237.5	89	1005, 1008
		MeO	H	OMe	137.5–138	94	1005, 1008
		Cl	H	OMe	167.5–168	84	1005, 1008
		H	Me	OMe	108–108.5	77	1005, 1008

TABLE 34. MIXED ALKYL/ARYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



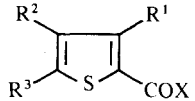
(One of R^1—R^3 = aryl, other alkyls)

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	Me	Ph	OH	149–150	b	97	–	241
				151–152	b	–	–	238
				147	r	–	–	236
				151	b	–	–	239
			OEt	45–46	r	75	–	241
				44	r	45	–	238
				152/0.6				238
				203/1.5	r	65	n	239
				44	r	42	–	233
		4-Br-C_6H_4	OH	184–185	b	94	–	241
			OEt	67–68	r	67	–	241
		3-NO_2—C_6H_4	OH	262–263	b	90	–	241
			OEt	114–115	r	47	–	241
		4-NO_2—C_6H_4	OH	249–250	b	90	–	241
			OEt	133–134	r	72	–	241
	Ph	Me	OH	188–189	b	99	–	241
			NH_2	171–172	d	83	–	241
			NHMe	158–159	d	87	–	241
			NMe_2	69–70	d	84	–	241
			OEt	140–142/0.15	r	59	–	241
Me	H	Ph	OH	190	b	80	–	246
				189	r	–	–	236
				185	r	*	–	232
			NHPh	174	r	–	–	232
			NH—(4-Me-C_6H_4)	156	r	–	–	232

TABLE 34. *(Continued)*

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
			OMe	36	r	–	–	234
			OEt	48	s	60	U	245, 246
Ph	H	Me	OH	192	b	–	–	243
			OMe	100	r	–	–	243
	Me	H	OH	167–168	b	*	–	244
			OMe	137/0.05	r	*	–	244

TABLE 35. CYANO-SUBSTITUTED THIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(One of R^1–R^3 = CN)

R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
—CN	H	H	OH	205	i	–	–	10
				195–199	i	80	I, P	9
			NH_2	179	–	–	–	221
H	NC—	H	NH_2	176	a	–	–	462
Me	NC—	Me	OMe	94–95	a	20	I, P	805
		Ph	OEt	132	a	–	–	805
		NH_2	OMe	220	r	–	–	397
			OEt	209	r	60–65	I	396
				210 d	r	63	–	833
Me	NC—	MeCONH	OEt	236	d	90–95	I	396
				232	d	60	–	833
		EtO_2CCH_2NH	OEt	76	g	65	I, P	396
CH_2CO_2Et	NC—	NH_2	OEt	137	r	70–75	I, P	396
		MeCONH	OEt	194	d	90–95	I	396
		EtO_2CCH_2NH	OEt	103	g	65	I, P	396
Pr	NC—	NH_2	OEt	180	r	–	–	397
Me	NC—	OH	OEt	86–90	a	78	–	804
				86–90	a	82	I, P	805
				86–90	a	76	I	803
Ph	NC—	4-Me-C_6H_4—NH	OEt	198–199	a	67	–	1009
		4-Cl-C_6H_4—NH	OEt	219–220	a	58	–	1009
		MeS	OMe	98–100	r	45	I	795
4-MeO—C_6H_4	NC—	MeS	OMe	150–151	r	36	I	795
4-Cl-C_6H_4	NC—	PhNH	OEt	203–204	a	63	–	1009
4-Cl-C_6H_4	NC—	MeS	OMe	148–149	r	53	I	795

TABLE 35. *(Continued)*

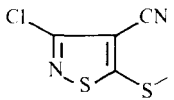
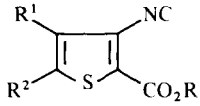
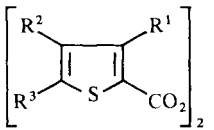
R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
3,4-di-Cl-C_6H_3	NC—	MeS	OMe	144–146	r	45	I	795
4-Br-C_6H_4	NC—	MeS	OMe	149–150	r	60	I	795
2-Thienyl	NC—	MeS	OMe	135–136	r	21	I	795
Ph	NC—	MeO_2CCH_2S	OMe	101–102	r	25	I	795
			OEt	100.5–101.5	r	14	–	794
4-Cl-C_6H_4	NC—	MeO_2CCH_2S	OMe	112–114	r	47	I	795
4-Br-C_6H_4	NC—	MeO_2CCH_2S	OMe	123–126	r	42	I	795
NH_2	NC—	Me	OEt	140	r	–	–	800
			OEt	172–173	r	54	I, P, U	354
		PhNH	OEt	212–213	a	71	U	402
		MeS	NH_2	233–235	r	78	–	394
			NHMe	153–155	r	71	–	394
		EtO_2CCH_2S	OEt	142–145	r	87	I	150
OH	NC—	Me	OEt	150	r	82	I	1010
		MeS	OMe	164–166	r	30	P	393
H	NC—	Cl	OEt	70–71	k	93	–	354
	H	NC—	OH	190–192	z	4	I, P	9
			OH	199	i	–	–	10
			NH_2	190	a	–	–	462
			OMe	79	b	–	I	462
			OEt	Liq.	b	–	I	462
Me	Me	NC—	NH_2	192	r	65	I, M, P	801
Ph	Me	NC—	NH_2	–	r	65	I, P	801
	Ph	NC—	NH_2	264–265	r	85	I, P	801
O—CH_2—O		NC—	OEt	97	k	82	I	482

TABLE 36. ESTERS OF 3-ISONITRILOTHIOPHENE-2-CARBOXYLIC ACIDS



R^1	R^2	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	Me	65–66	k	–	–	1011, 1012
	Me	Me	82–83	k	–	–	1011, 1012
	Ph	Me	125–126	k	–	–	1011, 1012
Me	H	Me	107–108	k	–	–	1011, 1012
		Et	76–77	k	–	–	1011, 1012
		Pr	90–92/0.005	k	–	–	1011, 1012
	Me	Me	84–85	k	–	–	1011, 1012
Et	Me	Me	38–39	k	–	–	1011, 1012
Ph	Me	Me	105–107	k	–	–	1011, 1012

TABLE 37. DITHENOYLPEROXIDES



And other

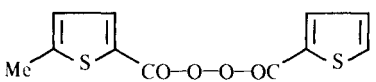
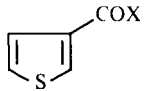
R^1	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	H	103 d	1	60–65	–	647
			100–101	1	40	–	646
		Me	104	1	35	–	646
	Me	H	113	1	54	–	646
	H	*t*-Bu	93	1	24	–	646
		Cl	110	1	48	–	646
		Br	130	1	44	–	646
	Br	H	126	1	23	–	646
I	H	H	110.5–111 d	1	75	–	29
H	H	O_2N	120–122	1	34	–	646
			121–121.5 d	1	80	–	124
			78–80	1	22	–	646

TABLE 38. THIOPHENE-3-CARBOXYLIC ACID AND ITS DERIVATIVES



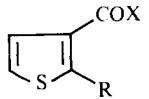
X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	136–137	b	84	–	108
	136–137.5	o	41	–	179
	136	–	–	K	927
	–	–	–	K	962, 1013
	–	–	–	K, P	1014
	–	–	–	P	1015
	–	–	–	C	919
	–	–	–	I	52
	–	–	–	U	220, 866, 956, 1016
	–	–	–	M	1017
Cl	50–52	n	62	–	179
	50–52	–	–	–	108
	52–52.5	n	100	–	124
	204/748	n	–	–	1018
F	–	f	–	P	940
NH_2	178–179	f	–	–	1019
	178–179	d	–	–	454
	–	–	–	I, U	1020
	–	–	–	U	866
NHMe	115–117	d	13	–	179
	114–116	d	–	I, U	1020
	114–116	d	–	–	1021
NMe_2	89–90/0.5	d	45	–	179
	45	d	–	I, U	1021
	44–45	d	70–85	–	877

TABLE 38. *(Continued)*

X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	45–46	d	–	P	878
	107–108/0.8				878
	–	–	–	U	1020
NHPh	141–142	–	–	–	108
	141	d	–	–	1018
	–	–	–	I, U	1020
NH-(3-Me-C_6H_4)	126	d	–	–	1018
	–	–	–	I, U	1020
NH-(4-Me-C_6H_4)	163	d	–	–	1018
	–	–	–	I, U	1020
NH-(3-MeO—C_6H_4)	138	d	–	–	1018
	–	–	–	I, U	1020
NH-(4-MeO—C_6H_4)	159	d	–	–	1022
	–	–	–	I, U	1020
NH-(3-Cl-C_6H_4)	132	d	–	–	1018
	–	–	–	I, U	1020
NH-(4-Cl-C_6H_4)	178	d	–	–	1018
	–	–	–	I, U	1020
NH-(3-NO_2—C_6H_4)	172	d	–	–	1018
	–	–	–	I, U	1020
NH-(4-NO_2-C_6H_4)	210	–	–	–	1022
	–	–	–	I, U	1020
NH-(4-OH-2-thiazolyl)	218	d	65	–	856
NH-(5-Cl-2-thiazolyl)	219	d	70	–	856
NH-(5-Br-2-thiazolyl)	227	d	80	–	856
NH-(5-NO_2-2-thiazolyl)	259	d	90	–	856
NH-(5-$CSNH_2$-2-thiazolyl)	269	d	70	–	856
$NHNH_2$	122–123	h	50	–	906
NHNH-*i*-Pr	123	e	–	–	616

—NCS	76/0.3	g	72	–	1023
OMe	–	–	–	I	1013
	–	–	–	P	1024, 1025
	–	–	–	C	922
	–	–	–	U	866, 1026
OCH_2Ph	140–142/1	l	–	I	124
OEt	82/2.3	m2	–	n	927
	97–98/12	–	–	–	928
OPh	57	l	–	I	124
O-(3-Me-C_6H_4)	60–61.5	l	–	I	124
O-(4-Me-C_6H_4)	90–91	l	–	I	124
O-(2-MeO—C_6H_4)	71	l	–	–	1027
O-(3-Cl-C_6H_4)	70–71	l	–	I	124
O-(4-Cl-C_6H_4)	77.5–78	l	–	I	124
O-2-Thienyl	47–47.5	l	–	I	124
O-CO-3-thienyl	53–56	g	90	–	644
	55.5–56	k	–	–	124
O-*O*-CO-3-thienyl	120	g	52	–	646
	121–122 d	g	62	I	124

TABLE 39. 2-ALKYL- AND SUBSTITUTED-ALKYL- AND ALKENYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(R = alkyl, substituted alkyl, or alkenyl)

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	OH	115–117	o	72	–	78
		116–117	b	96	K	1013
		115–116	u	77	P	37
		–	–	–	K	1014
	Cl	98–100/16	n	92	–	79
	OMe	87/12	m1	87	I	1013
		–	–	–	U	1026
CH_2Ph	OH	123–125	z	20	I, P	503
CH_2-2-thienyl	OH	122.5–123.5	u	81	I	513
CH_2-3-thienyl	OH	132–133.5	u	83	I	513
CH_2-2-thienyl-3-CO_2H	OH	257–258	u	54	P	172
CH_2-2-MeO-1-naphthyl	OH	176.2–177	u	83	I, P	522
CH_2OH	OH	108	e	–	I	502
CH_2——O——		96	k	–	P	502
Ph_2C——O——		118–119	g	62	I, P, U	27
CH_2OH	OMe	61–62	m2	85	I, P	503
CH_2OMe	OMe	66/1	m2	7	I, P	503
CH_2OPh	OMe	163–165	g	79	–	503
CH_2O-(3-CO_2Me-2-CH_2 thienyl)	OMe	111–112	z	3	I, P	503
CH_2SPh	OMe	135–136	g	78	–	503
CH_2S-(3-CH_2CO_2H—C_6H_4)	OH	146–148	g	67	–	503
CH_2Cl	OMe	80–81	j	83	I	503
CH=CH-2-thienyl	OH	109–110	u	High	–	512
CH=CH-2-thienyl	OH	182	u	90	P	509
$(CH_2)_2$-2-NH_2—C_6H_4	ONa	295 d	b	75	–	1028

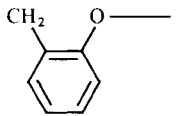
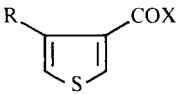
$(CH_2)_2$-2-furyl	OH	91.6–92.2	u	77	P	508
$(CH_2)_2$-2-thienyl	OH	134	u	90–95	P	509
$(CH_2)_2$-2-(4-D-thienyl)	OH	135	u	90	P	510
$(CH_2)_3NH_2$	OH	206–207	b	–	–	219
Hydrochloride		212.5–214 d	–	–	–	219
$(CH_2)_3$———NH———		132–133	a	63	I, U	220
CH_2CHMe———NH———		122.5–124.5	a	60	I, P	220
		99–100	v/k	38	I, M, P	503

TABLE 40. 4-ALKYL- AND SUBSTITUTED–ALKYL- AND ALKENYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

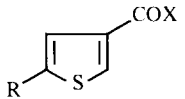


(R = alkyl, substituted alkyl, or alkenyl)

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	OMe	50/0.001	r	43	I, P, U	250
			–	–	I	917
$PhCH_2$	OH	143.5–144	u	85	I, P	519
2-Thienyl-CH_2	OH	136–137	u	69	I, P	513
3-Thienyl-CH_2	OH	138–139	u	84	I, P	513
Ph_2CH	OH	170	c	41	I	466
$HOCH_2$	OH	167	e	–	I	502
CH_2———O———		115	k	–	P	502
CH_2CO———O———		157–158	k	*	I, P	733
Ph_2C———O———		159–161	c	29	I, P	466
PhCHOH	OH	124–124.5	e	80	I, P	466
$PhCH_2CH_2$	OH	146–147	e	*	P	733
2-Thienyl-CH_2CH_2	OH	136	u	82	P	518
3-Thienyl-CH_2CH_2	OH	164	u	80	P	518
2-HO—C_6H_4—CH_2CH_2	OH	159–160.5	e	*	P	733
2-PhCOO—C_6H_4—CH_2CH_2	OH	130–131	e	*	P	733
$PhCH(OH)CH_2$	OH	169–171	e	*	P	733
2-Cl-3-thienyl-CH=CH	OH	204	u	90–95	P	509
2-Cl-3-thienyl-CH_2CH_2	OH	140	e	>95	P	509
2,5-di-Cl-3-thienyl-CH=CH	OH	215–216	f	85	P	509
2,5-di-Cl-3-thienyl-CH_2CH_2	OH	121	e	>95	P	509
HO_2CCH_2	OH	210–213	b	*	–	733
H_2NCOCH_2	OH	193–194	h	*	–	733
$MeNHCOCH_2$	OH	162–164	h	*	–	733
EtO_2CCH_2	OH	159.5–161	g	95	P	733

$(EtO_2C)_2CH$	OEt	124–125.5	g	31	–	733
$EtO_2C(PhSO_2)CH$	OH	201–203.5	g	52	–	733
PhNHCO(PhCO)CH	OH	190–191	g	63	–	733
$NCCH_2$	OH	171–172.5	g	*	P	733
$MeCOCH_2$	OH	153–154	g	*	I, P	733
$(MeCO)_2CH$	OH	198–199	g	*	P	733
$PhCOCH_2$	OH	212–214	g	67	P	733
2-$PhCH_2O$–C_6H_4–$COCH_2$	OH	126–128	g	75	P	733

TABLE 41. 5-ALKYL- AND SUBSTITUTED- ALKYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

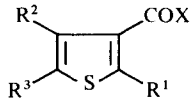


(R = alkyl or substituted alkyl)

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	OH	130–131	b	94	–	1029
		128–130	b	–	C, I, K	98
		–	–	–	C	953
		–	–	–	K	1013
	OMe	–	–	–	I	1013
	OEt	74–75/2	e	45	–	1029
		105–107/15	e	49	–	98
$PhCH_2$	OEt	137–141/0.04	r	32	P	252
$HOCH_2$	OH	135–136	b	–	K	98
		132	e	–	I	502
		–	–	–	C	953
		–	–	–	C, I	954
$MeOCH_2$	OH	73–74	g/b	*	K	98
		–	–	–	C, I	1030
		–	–	–	C	953
$PhOCH_2$	OH	124	g	–	K	98
		–	–	–	C, I	1030
		–	–	–	C	953
$HSCH_2$	OH	106–107	g	–	K	98
		–	–	–	C, I	1030
		–	–	–	C	953
$EtSCH_2$	OH	99–101	g	–	K	98
		–	–	–	C, I	1030
		–	–	–	C	953

$PhSO_2CH_2$	OH	197–199	g	–	K	98
	–	–	–	C	953
$ClCH_2$	OMe	–	–	–	P	955
$BrCH_2$	OH	170–173	v/j	100	K	98
	–	–	–	C, I	954
Et	OH	58–59	e	*	K	464
	66–67	b	88	–	1029
	OEt	96–97/3	–	–	–	464
	86/0.1	e	44	P	442
	79–80/1	e	42	–	1029
$CH_3CH(OH)$	OEt	–	e	–	P	465
$CH_3CH(O—CO\text{-}4\text{-}NO_2—C_6H_4)$	OEt	116	l	–	P	465
Cyclohexyl	OH	176	f	39	P	644

TABLE 42. DI- AND TRIALKYL- AND SUBSTITUTED-ALKYLTHIOPHENE-3-

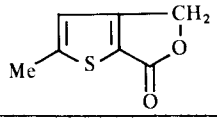


(At least two of R^1—R^3 are alkyl or substituted alkyl)

R^1	R^2	R^3	X
Me	Me	H	OH
			OMe
			OEt
	H	Me	OH
			Cl
			NH_2
			NHPh
			OMe
			OEt
		HO_2CCH_2	OH
		t-Bu	OH
CH_2CO_2H	H	Me	OH
n-Pr	H	Me	OH
			OEt
		n-Pr	OH
i-Pr	H	Me	OH
$(CH_2)_3NH_2$ Hydrochloride	H	Me	OH
$CHEt_2$	H	Me	OEt
Et	H	Et	OH
			Cl
			NH_2
			OEt
t-Bu	H	*t*-Bu	OH
			Cl
H	Me	Me	OH
			OEt
			$O(CH_2)_3\overset{+}{N}HMe_2\bar{C}l$

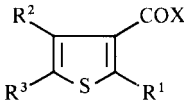
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
165–166	i	*	U	159
–	–	–	I	917
48/0.001	r	25	I, P, U	250
117–118	q	–	K	1013
115–119	b	85	–	255
117–118	u	76	–	1031
120–120.5	–	–	U	1032
115–116	q	Good	–	1033
119.5	p	–	–	1034
116–117	q	–	–	1035
117	w	–	–	169
103–105/12	n	–	–	1035
136.5–137	d	68	U	1032
135	–	–	–	1034
139.5–140	d	–	–	226
108/8	m1	–	I	1013
97/4	–	–	U	1032
97/4	m1	87	n	1036
114–116/12	r	57	P	253
98–99/5	m2	86	–	144
108–109/8	r	69	–	254
119–121/13	r	69	P	255
224–226	q	52	I, P	41
131–132	o	62	–	1033
219	i	–	–	12
217–219	i	–	–	41
95–96	b	86	–	255
135–142/14	r	80	P	255
126–127	q	–	–	148
187–188/16				148
88–89	b	–	–	255
228–229	–	–	–	219
212–213	—r	–	–	219
Liquid	z	6	P	255
83	u	83	P	36
65	f, q	–	–	231
125/9.5	n	–	n	231
116	d	–	–	231
123/12	l	–	n	231
168–169	q	50	–	1033
129–130/7	n	90	–	1037
149–150	b	89	–	1029
144–145	i	*	U	159
100–100.5/4	e	58	–	1029
168–169	l	90	–	1029

TABLE 42. *(Continued)*

R^1	R^2	R^3	X
		$MeCOO(CH_2)_2$	OEt
Me	Me	Me	OH
			OEt
			

Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
147–150/3	e	25	–	1029
167–168	o	31	U	159
131–133/14	r	52	I, P, n	253
178	k	–	–	12

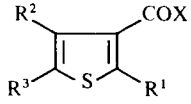
TABLE 43. ARYL- AND HETEROARYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Ph	H	H	OH	234–236	p	–	–	1038
			OMe	78–79	r	94	I, M, P	1039
				79–80 (±)	m1	–	–	1038
2-Me-6-NO_2—C_6H_3	H	H	OH	183–186 (–)	f	9	–	1040
				185–187	f	–	α	1040
2-Me-6-NO_2—C_6H_3	H	H	NH_2	164–165	d	–	–	1040
			OMe	109–110	m1	–	–	1040
1-Naphthyl	H	H	OH	223–225	u	74	I, P	516
H	Ph	H	OH	206–208	u	84	I, P	520
			Cl	–	n	–	I	520
			OMe	48–49	f	83	–	1038
	1-Naphthyl	H	OH	210–212	u	76	I, P	516
	9-Phenanthryl	H	OH	285–287	u	77	I, P	516
	H	Ph	OMe	91–92	f	72	–	1038
Ph	H	Ph	OH	200–201.5	b	85	I	259
			OMe	86–89	r	54	I, P	1039
				153–161/0.001	r	83	I	258, 259
			OEt	53–55	r	82	I, P	260
C_6H_4-4-OMe	H	Ph	OMe	145.5–147	r	81	I, P	261
Ph	Ph	Ph	OH	245–246.5	b	95	I	259
			OMe	138–139	r	82	I	258, 259
C_6H_4-4-OMe	Ph	Ph	OMe	112–113.5	r	67	I, P, U	261

Ph	Ph	4-MeO—C_6H_4	OMe	117–118	r	–	I, P, U	261
1-Pyrrolyl	H	H	OH	145–146	f	–	–	1041
				178	b	–	P	579
			N_3	80	f	74	I	586
				–	–	–	I	579
			OEt	219/40	f	72	–	1041
	—$(CH_2)_3$—		OH	200–200.5	f	96	–	1041
			OEt	209/13	f	71	–	1041
	—$(CH_2)_4$—		OH	174–175	f	97	–	1041
			OEt	217/18	f	60	–	1041
1-Pyrazolyl	H	H	OH	227–227.5	i	61	I, M, P	18
3-(1,2,4-Triazolyl)	H	H	OH	260–270 d	f	18	I	1042
H	4-(3,5-di-Me-isoxazolyl)	H	OH	206–208	f	*	P	733
	4-(3,5-di-Me-pyrazolyl)	H	OH	229–231	f	*	P	733
2-Thienyl	H	H	OH	168–169	o	41	–	25
				167–168	f	90	I, P	1043

TABLE 44. MIXED ALKYL- AND ARYL/HETEROARYLTHIOPHENE-3-CARBOXYLIC



R^1	R^2	R^3	X
Me	Ph	H	OH
			OEt
	H	Ph	OH
			Cl
			OEt
		4-Br-C_6H_4	OEt
Ph	Me	H	OH
			Cl
			OMe
			OEt
C_6H_4-2-Cl	Me	H	OH
			Cl
			OEt
C_6H_4-4-Cl	Me	H	OH
			Cl
			OEt
C_6H_4-4-NO_2	Me	H	OEt
C_6H_3-2,6-di-Cl	Me	H	OH
			Cl
			OEt
Ph	H	Me	OH
			OMe
			OEt
		Et	OMe
Me	Me	Ph	OEt
	Ph	Me	OH
			OEt
	4-CO_2H–C_6H_4	Me	OH
Me	2-Me-6-NO_2–C_6H_3	Me	OH
			NH_2
			OMe
t-Bu	Ph	*t*-Bu	OH

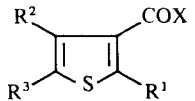
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
179.5–180.5	u	73	P	1044
–	–	–	I	917
185–187	b	–	–	1045
77–78	–	–	–	1045
45	r	48	I, P	253
44.5–45.5	b	–	–	1045
73–75	b	–	–	1045
183–184	b	–	–	1040
184.5–186.5	i	80	P	1044
128–131/0.5	n	–	–	1046
128–130/0.8	r	–	–	1046
45–46	r	31	I, P, U	250
139–140	b	–	–	1046
126–128/0.8	n	–	–	1046
133–145/1	r	–	–	1046
154–155	b	–	–	1046
120–128/0.2	n	–	–	1046
156–166/1.2	r	–	–	1046
127	r	22	I, P, U	250
181–182	b	–	–	1046
130–151/0.5	n	–	–	1046
135–146/0.6	r	–	–	1046
163–165	b	86	–	255
–	z	9	P	256
104/0.3	r	46	I, P, n	253
36–41	r	65	P	254, 255
129–130/2				254, 255
140–150/0.23	r	–	I, M, P	1047
128/0.09	r	73	I, P, n	253
130–131	u	82	P	1044
	q	89		1044
103–105	q	75	–	288
128	b	–	–	255
36–42	r	23	–	255
180	q	98	–	288
(+)209	–	–	–	1048
(–)208–210	–	–	α	1048
(±)211–212	–	–	–	1048
211–212	f	30	–	1036
212–212.5	–	–	U	1032
177–178	d	80	–	1036
177.5	–	–	U	1032
58–59	m1	46	–	1036
58.5	–	–	U	1032
214(subl.)	u	98	P	1044

TABLE 44. *(Continued)*

R^1	R^2	R^3	X
Ph	$-(CH_2)_4-$		OMe
	Me	Me	OEt
		Ph	OMe
2-Thienyl	H	Me	OH
			OEt
4-(3,5-di-Me-1,2,4-triazolyl)	Me	H	OH
4-(3-CH_2CN-5-Me-1,2-4-triazolyl)	Me	H	OH
4-(3-Ph-5-Me-1,2,4-triazolyl)	Me	H	OH
4-(3-$PhCH_2$-5-Me-1,2,4-triazolyl)	Me	H	OH
4-(4'-Pyridyl-5-Me-1,2,4-triazolyl)	Me	H	OH
1-Pyrrolyl	Me	Me	OH
			OEt
1-(2-CH_2NMe_2-Pyrrolyl)	Me	Me	OEt
Me	4-Pyrimidyl	Me	OH
Et	(2,5-di-Et-3-thienyl)	Et	OH

Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
62–64	r	–	I, M, P	1047
117/0.09	r	48	I, P, n	1049
105–107	r	83	I, P	261
157–158	b	–	–	255
Liquid	z	2	P	255
238–239	f	52	–	664
231–232	f	36	–	664
229–231	f	30	–	664
199–200	f	48	–	664
295–296	f	50	–	664
162–163	f	97	–	1041
192/18	f	70	–	1041
193–194/12	c	32	–	1041
162–163	u	60	P	1044
170/0.01	u	71	P	25

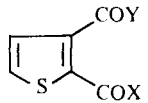
TABLE 45. CYANOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(One of R^1—R^3 is CN)

R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
—CN	H	H	OH	191–193	u	50	K, P	1014
			NH_2	174	a	70–80	–	221
			OMe	59.5–60.5	m1	–	U	1020
H	NC—	H	NH_2	197	a	–	–	462
			OMe	87	b	–	I	462
			OEt	100	b	–	I	462
				96–97	w	88	–	332
Me	NC—	H	OEt	82–83	w	92	–	332
	H_2N	NC—	OEt	186	r	95	I	1010
NH_2	Me	NC—	OH	165–167	b	–	–	370
			NH_2	235–237	r	55	–	370
			OMe	183–185	r	83	–	370
			OEt	200–202	r	70	–	370
NHPh	H_2N	NC—	OEt	134–136	r	69	I, U	402
SCH_2CH_2CN	H_2N	NC—	OMe	168	r	70	–	1050

TABLE 46. THIOPHENE-2,3-DICARBOXYLIC ACID AND ITS DERIVATIVES

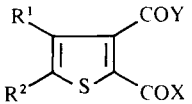


X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	OH	287–288	b	67–83	I, P	27
		268–270 d	p	80	I, U	101
		268–270	w	21	–	179
		270	w	86	–	15
		268–270	w	14–43	–	161, 162
		270–272	u	72	–	1051
		270	i/u	7	–	650
		270–272 d	p	69	–	100
		270 d	b	74	–	383
		264–267	b	26	–	9
		270	b	75	–	1023
		272–274	w	–	–	78
		277–278 d	b	–	–	159
——O——		137–138	k	50	–	179
		140–141	k	–	–	78, 100, 101, 650
		141–143	–	–	–	159
——NH——		200–201	b	76	I	9
OH	NH_2	258	–	–	–	221
NH_2	OH	255	–	–	–	221
	NH_2	232	–	–	–	221
$NHNH_2$	OH	329–331 d	h	78	–	161
NHN=CHPh	OH	220–221	f	93	–	161
N_3	OH	100 exp	f	*	–	161
NPhMe	OH	169–170	f	71	–	161
OMe	OH	119–121	–r	37	–	161

TABLE 46. *(Continued)*

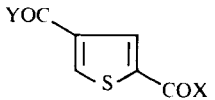
X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	OMe	103–105	b	–	–	161
OMe	NPhMe	90–92	d	71	–	161
NPhMe	OMe	113–115	d	58	–	161
OMe	OMe	33–34	e	68	–	383
		110/0.05				383
		32–33	m1	–	U	159
		34–35	m1	–	I, U	101
		58	m1	–	–	944
OEt	OEt	109/0.015	m2	86	P	15

TABLE 47. SUBSTITUTED THIOPHENE-2,3-DICARBOXYLIC ACIDS AND THEIR DERIVATIVES



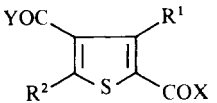
R^1	R^2	X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	Me	OH	OH	218	r	24	–	273
		OMe	OMe	124–128/2	m2	–	–	273
	Ph	OMe	OMe	91–93	r	19	I, P	272
Ph	H	OMe	OMe	93–95	r	–	I, P	272
	Ph	OMe	OMe	98	r	–	–	270
				92	r	84	–	271
		OEt	OEt	85	r	82	–	271
	N-Morpholino	OMe	OMe	143–144	r	71	I, M, P, U	266
					r	67	I, U	265
F_3C	F_3C	OMe	OMe	49	r	*	I, P	268, 269
				76–78/0.5				268, 269
H	O_2N	OH	OH	162	p	*	–	137
		NH_2	NH_2	274 d	h	*	–	137
		OMe	OMe	65–67	m1	*	–	137
H_2N	H	OMe	OMe	60–61	a	77	–	383
PhCONH	H	OMe	OMe	102–103	d	–	–	383
PhCH=N	H	OMe	OMe	108–110	f	–	–	383
N-Pyrrolidyl	H	OMe	OMe	130–132	g	45	–	799

TABLE 48. THIOPHENE-2,4-DICARBOXYLIC ACID AND ITS DERIVATIVES



X	Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OH	HO	304–305 d	p	65	I, U	101
		>300	r	45	–	274
		299–301 d	u	80	–	443
		316	b	–	–	188
		280	b	–	P	98
OMe	MeO	120–121	m1	60	–	115
		121	m	–	–	944
		120	f	60–80	–	462
		118	c/m2	75	P	206
		119.5–120	m1	–	–	1052
		123–124	w	–	U	1053
		123	m2	Excellent	–	274
		120	r	91	I, P	276
		119–120	m1	–	I, U	101
OEt	EtO	37	f	60–80	–	462
O-(4-MeO–C_6H_4)	4-MeO–C_6H_4–O	185	l	–	–	1054

TABLE 49. AMINOTHIOPHENE-2,4-DICARBOXYLIC ACIDS AND THEIR DERIVATIVES

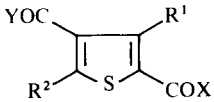


R^1	R^2	X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H_2N	OH	HO	180–186 d	f	90	I	249
		OMe	MeO	165–167	m1	61	–	249
		OEt	EtO	107–108	r	34	–	368
	MeCONH	OMe	MeO	172–173	h	80	I	249
Me	H_2N	NHPh	EtO	174–176	r	–	–	191, 395
				180–181	r	30	–	1055
		OMe	EtO	110	r	*	–	397
		OEt	EtO	108	r	*	–	397
				–	–	–	I	917
				109	r	77	I, P	805
				108–109	r	32	U	361
				126–127	r	75	–	686
	MeCONH	OEt	EtO	132	d	–	–	361
	PhCONH	OEt	EtO	165–167	r	*	P	1056
	4-Cl-C_6H_4—CO—NH	OEt	EtO	218–220	d	*	–	672
	2,4-di-Cl-C_6H_3—CO—NH	OEt	EtO	178–180	d	*	–	672
	EtO_2CNH	OEt	EtO	92–94	d	*	–	672
	EtO_2CCH_2NH	OEt	EtO	87–88	g	65	I, P	396
	$EtO_2CCH_2N(COMe)$	OEt	EtO	98	d	95	I, P	396
	PhNH	OEt	EtO	115–116	r/s	*	P	1056
	3-CH_3—C_6H_4—NH	OEt	HO	186–189	b	*	–	376
			t-BuO	124–127	r	*	P	376
	2,3-di-Me-C_6H_3NH	OEt	EtO	105–106	r/s	*	P	1056
	H_2NNH	OEt	EtO	150	e	75	I, U	1057
	MeCONHNH	OEt	EtO	184–185	d	73	–	1057

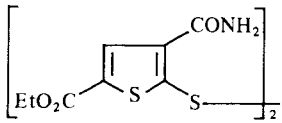
TABLE 49. *(Continued)*

R^1	R^2	X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	$Me_2C{=}NNH$	OEt	EtO	122	f	–	–	1057
	$EtO_2CCH_2C(Me){=}NNH$	OEt	EtO	97–98	f	–	–	1057
	4-NO_2—C_6H_4—$CH{=}NNH$	OEt	EtO	220	f	–	–	1057
CH_2CO_2Et	H_2N	OEt	EtO	115–116	r	55–60	I, P	396
	MeCONH	OEt	EtO	100	d	–	–	396
	EtO_2CCH_2NH	OEt	EtO	108	g	70	I, P	396
	$EtO_2CCH_2N(COMe)$	OEt	EtO	265/15	d	90	I, P	396
OH	PhNH	OEt	4-MeO—C_6H_4—NH	133–135	r	62	–	277
NH_2	Me	OEt	EtO	73	r	65	I	1010
NH_2	MeS	NH_2	MeNH	240–242	r	65	–	394
		NHMe	H_2N	238–240	r	66	–	394
		OMe	H_2N	225–227 d	r	59	I	346
			MeNH	147–149	r	58	–	394
		NH_2	EtO	189–192	r	42	–	394
		OEt	H_2N	183–185	r	64	–	394
		OMe	MeO	136–138	r	27	P	393
		OEt	EtO	137	r	*	–	287
		OEt	$C_{11}H_{23}CONH$	111	d	*	–	287
	MeO_2CCH_2S	OEt	H_2N	205 d	r	33	I	346
	EtO_2CCH_2S	OEt	H_2N	143	r	–	I	346
	MeO_2CCH_2S	OMe	MeO	154–156	r	40	I	346
	H_2N	OEt	EtO	149–151	r	21	I, U	787

TABLE 50. OTHER SUBSTITUTED THIOPHENE-2,4-DICARBOXYLIC ACIDS AND

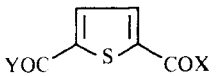


R^1	R^2	X	Y
Me	H	OH	HO
		OEt	EtO
		$O(CH_2)_2NEt_2$, HCl	HCl, $Et_2N(CH_2)_2O$
		$O(CH_2)_3NMe_2$, HCl	HCl, $Me_2N(CH_2)_3O$
H	Me	OH	HO
		OMe	MeO
Ph	Ph	OH	HO
		NHPh	PhNH
		OMe	MeO
		OEt	EtO
		O-*i*-Pr	*i*-Pr-O
		OMe/OH	HO/MeO
		OEt/OH	HO/EtO
3-(2-CH_2OH-4-CO_2H-thienyl)	H	OH	HO
OH	H	OMe	MeO
		OMe	EtO
		OEt	MeO
		OEt	EtO
OMe	H	OH	HO
		OMe	MeO
		OMe	EtO
		OEt	MeO
		OEt	EtO
OCOMe	H	OMe	MeO
OCOPh	H	OMe	MeO
H	HS	OEt	H_2N
H	*t*-$BuSO_2$	OH	HO
		OMe	MeO
		NH_2	H_2N
OMe	HS	NH_2	H_2N
OH	MeO_2CCH_2S	OMe	MeO
H	Cl	OEt	H_2N
Br	H	OH	HO
		OMe	MeO
Br	Br	OH	HO
		OMe	MeO
Cl	Me	OH	EtO
H	O_2N	OMe	MeO



Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
250	b	89	–	1029
33–33.5	e	61	–	1029
208–209	l	95	–	1029
214–216	l	94	–	1029
278–279	q	–	–	144
d > 250	w	*	–	181
275–276	p	*	I, U	116
280–283	w	82	–	163
85–86	m1	98	–	144, 163, 181
–	–	–	I	1058
250	b	*	–	278
200–202	f	58	–	278
94	f	82	–	278
68	f	74	–	278
72–73	f	44	–	278
181	b	51	–	278
170	b	36	–	278
215–216	y	69	P, U, α	55
115	r	*ca* 60	–	431
90	r	61	–	431
104	r	*ca* 60	–	431
30	r	*ca* 60	–	431
246 d	b	95	–	431
172/14	t1	High	–	431
180/12	t1	High	–	431
169/14	t1	High	–	431
185/12	t1	High	–	431
77–78	l	–	–	431
106	x	–	–	431
217–218 d	g	93	I, M	354
>200	i	68	–	1052
94–95	–	–	–	1052
225–226 d	–	–	–	1052
174–176	r	56	I	1059
149–152	r	–	I	346
213–214	w	84	–	354
305–310 d	u	64	P	55
129–131	m2	86	P	55
–	–	–	P	1025
264–265	w	–	–	171
76–77	–	–	–	171
159–160	p	81	–	459
56–59	c	15	–	249
238 d	w	89	M	354

TABLE 51. *THIOPHENE*-2,5-DICARBOXYLIC ACID AND ITS DERIVATIVES



X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	HO	354–358	w	40	–	154
		ca 335–340	w	*	–	118
		325 d	p	67	I, U	101
		ca 320	r	39	–	291
		320	r/s	*	–	290
		358.5	w	75	I, K	178
		325–330	p	78	U	1060
		318–320	b	95	–	9
		–	–	–	K	473, 961
Cl	Cl	45–46	n	*	–	567
NH_2	H_2N	331	d	–	–	595
NHPh	PhNH	316.5–318	f	–	–	292, 293
$NHNH_2$	H_2NNH	258–260	d, h	–	–	902
		262–263	h	70	–	434
NHNHCO-2-thienyl	2-Thienyl-CONHNH	>300	d, h	–	–	902
–NCO	OCN–	125–128/1	k	–	–	595
OH	MeO	187–190	b	*	–	648
		192	w	*	U	118
	EtO	140–142	b	83	–	468
Cl	EtO	132–135/10	n	80	–	468
$NHCH_2CH{=}CH_2$	EtO	117–118	g	92	–	468
$NHCH_2CH(OMe)CH_2HgOCOMe$	EtO	99–101	f	76	–	468
OMe	MeO	149	f	60–80	–	462
		148.5–149	m	92	–	496
		149	r	48	I, M, P	300

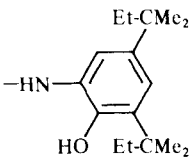
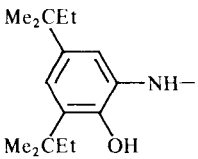
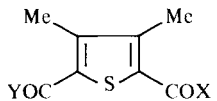
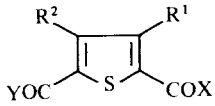
		150–150.5	m	74	–	178
		147–148	m1	–	I, U	101
		148–149	m1	87	–	154
		146–147	m1	*	U	118
	MeO	149–150	m1	91	–	113
		145	f	40	–	210
		144–146	w	–	M, P	1061
	EtO	–	–	–	I	917
OEt	EtO	53	f	60–80	–	462
		–	–	–	I	917
O-(4-MeO–C_6H_4)	4-MeO–C_6H_4–O	160	1	–	–	1054
–O–CH_2–(CH_2–O–CH_2)$_3$–CH_2–O–		111–113	1	17	–	546
–O–CH_2–(CH_2–O–CH_2)$_4$–CH_2–O–		96–97	1	18	–	546
–O–CH_2–(CH_2–O–CH_2)$_5$–CH_2–O–		63–64.5	1	14	–	546
		238–240	1	–	–	1062

TABLE 52. 3,4-DIMETHYLTHIOPHENE-2,5-DICARBOXYLIC ACID AND ITS DERIVATIVES



X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	HO	324–327 d	b	83	–	1063
Cl	Cl	67–73	n	–	–	1063
OH	MeO	235–236.5	r	43	–	284
		230–231.5	r	51	–	283
	EtO	231–232.5	r	50	U	283
OMe	MeO	171.5–172.5	m1	93	–	1063
		170–171	m2	77	P, U	283
$O(CH_2)_2NEt_2, HBr$	$HBr, Et_2N(CH_2)_2O$	212.5–214 d	–	–	–	1063
$O(CH_2)_2\overset{+}{N}MeEt_2I^-$	$I^-Et_2\overset{+}{N}Me(CH_2)_2O$	202.5–203.5	f	81	–	1063
OMe	EtO	93–94	m1	–	–	283
OEt	EtO	79–80	m2	*	–	281
O-*t*-Bu	*t*-BuO	167–168	m2	78	–	281

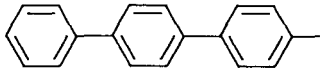
TABLE 53. ARYL- AND HETEROARYLTHIOPHENE-2,5-DICARBOXYLIC ACIDS AND



R^1	R^2	X
Ph	H	OH
		Cl
		NH(4-Me-C_6H_4)
		OMe
		OEt
C_6H_4-4-NO_2	H	OH
		OMe
C_6H_4-4-Me	H	OH
		OMe
1-Naphthyl	H	OH
		OMe
Ph	Ph	OH
		Cl
		OH
		OH
		OMe
		OMe
		OEt
		$O(CH_2)_2NMe_2$
		$O(CH_2)_2\overset{+}{N}Me_3\bar{I}$
		$O(CH_2)_2NEt_2$
		Hydrobromide
		Picrate
		$O(CH_2)_2\overset{+}{N}MeEt_2\bar{I}$
		$O(CH_2)_2\overset{+}{N}(CH_2Ph)Et_2\bar{B}r$
		$O(CH_2)_3\overset{+}{N}MeEt_2\bar{I}$
		$O(CH_2)_3\overset{+}{N}MeEt_2\bar{C}l$
		$O(CH_2)_4\overset{+}{N}MeEt_2\bar{I}$
		O-*t*-Bu
C_6H_4-4-Me	4-Me-C_6H_4	OH
Ph	4-$C_{12}H_{25}$—C_6H_4	OH
		OMe
C_6H_4-2-Cl	2-Cl-C_6H_4	OH
C_6H_4-3-Cl	3-Cl-C_6H_4	OH
C_6H_4-4-Cl	4-Cl-C_6H_4	OH
C_6H_4-4-MeO	4-MeO—C_6H_4	OH

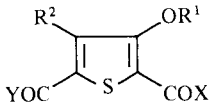
Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
HO	296–297 d	r	57	I, P, U	515
	297	r	48	–	288
	295	b	–	–	232
Cl	138	n	81	I	288
HO	219	b	–	–	232
MeO	156	r	–	–	232
MeO	110	r	*	–	232
	100	m2	92	–	288
EtO	59–60	s	68	U	246
HO	244	b	80	–	288
MeO	181	c	20	–	288
HO	279	b	–	–	232
MeO	112	r	*	–	232
HO	300	b	–	–	232
MeO	151	r	*	–	232
HO	341	r/b	34	U	299
Cl	121–122	n	90	I	517
	123–124	n	73	–	1063
EtO	224–225	r	93	U	280
t-BuO	210–220 d	r	*	–	281
MeO	187–188	m1	–	–	286
	187–188	–	–	I	280
EtO	146–147	m1	80	–	280
EtO	141	r	67	I, M, P	300
$Me_2N(CH_2)_2O$	67–69	l	65	–	1063
$\bar{I}Me_3\overset{+}{N}(CH_2)_2O$	250 d	g	72	–	1063
$Et_2N(CH_2)_2O$	76.5–77	l	66	–	1063
Hydrobromide	185.5–186.5	f	–	–	1063
Picrate	175.5–177	f	–	–	1063
$\bar{I}Et_2\overset{+}{N}Me(CH_2)_2O$	212–213	g	97	–	1063
$\bar{B}rEt_2\overset{+}{N}(CH_2Ph)(CH_2)_2O$	191 d	g	83	–	1063
$\bar{I}Et_2Me\overset{+}{N}(CH_2)_3O$	206–220 d	g	*	–	1064
$\bar{C}lEt_2\overset{+}{N}Me(CH_2)_3O$	192–194	g	*	–	1064
$\bar{I}Et_2\overset{+}{N}Me(CH_2)_4O$	197–199	g	–	–	1064
t-BuO	172–174	m	67	–	281
HO	–	r/b	31	U	299
HO	230–235	r	*	–	287
MeO	94	m2	*	–	287
HO	334–335	r/b	35	U	299
HO	313–314	r/b	30	U	299
HO	–	r/b	40	U	299
	299–300	r	59	–	1065
HO	269–270	r	75	–	286

TABLE 53. *(Continued)*

R^1	R^2	X
		OH
		OH
		OMe
C_6H_3-3,4-OCH_2O	3,4-OCH_2O—C_6H_3	OH
C_6H_3-3,4-di-MeO	3,4-di-MeO—C_6H_3	OH
2-Furyl	2-Furyl	Cl
		OMe
		$O(CH_2)_2NEt_2$, HBr
		$O(CH_2)_2\overset{+}{N}MeEt_2\bar{I}$
5-NO_2-2-furyl	5-NO_2-2-furyl	OH
		Cl
		OMe
		$O(CH_2)_2NEt_2$
		$O(CH_2)_2\overset{+}{N}MeEt_2\bar{I}$
1-Naphthyl	4-Biphenylyl	OH
		OMe
Ph	4′-$C_{12}H_{25}$-4-biphenylyl	OMe
1-Naphthyl	4′-$C_{12}H_{25}$-4-biphenylyl	OMe
Ph		OH
		OMe

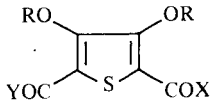
Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
	273–274	b	75	U	281
	277–278	r/b	28	U	299
MeO	220–225 d	r	*	I, P	281
EtO	192–194 d	r	*	–	281
MeO	194–195	r, m1	–	–	286
HO	304–305	r/b	36	U	299
HO	250–251	r/b	32	–	299
Cl	90.5–91.5	n	91	–	1063
MeO	129	m1	90	–	1063
$Et_2N(CH_2)_2O,HBr$	179.5–181	–	–	–	1063
$\bar{I}Et_2\overset{+}{N}Me(CH_2)_2O$	177.5–179	g	90	–	1063
HO	258 d	b	*	–	1063
Cl	92.5–95	n	–	–	1063
MeO	182–184	c	–	–	1063
$Et_2N(CH_2)_2O$	42–47	l	47	–	1063
$\bar{I}Et_2\overset{+}{N}Me(CH_2)_2O$	192–195 d	g	87	–	1063
HO	300	r	–	–	287
MeO	185	m2	–	–	287
MeO	101	m2	–	–	287
MeO	103	m2	–	–	287
HO	>300	r	–	–	287
MeO	185	r	–	–	287

TABLE 54. 3(4)-HYDROXYTHIOPHENE-2,5-DICARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	X	Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	OH	HO	194 d	b	–	–	428
				190 d	b	*	–	415
		OMe	HO	189	r	65	–	429
					b	94	–	428
		NHPh	MeO	236	r	*	–	343
		OMe	MeO	111	r	65–94	–	343, 428–430
				–	–	–	M	1066
				–	–	–	P	1067
				–	–	–	I, P	5
		OEt	EtO	69	r	88	–	428, 429
Me	H	OH	HO	221	b	80	–	410
		OMe	MeO	120	t	–	I, U	142
				118	t	84	–	410
$(CH_2)_3Br$	H	OMe	MeO	88–89	–	–	–	1068
$(CH_2)_3N$ NPh, 2HCl	H	OMe	MeO	181	g	–	–	1068
$(CH_2)_3N$ N-2Me-C_6H_4, 2HCl	H	OMe	MeO	162	g	–	–	1068
COMe	H	OMe	MeO	76	l	78	–	410
—CN	H	OMe	MeO	77	f	39	I	722
$CONH_2$	H	OMe	MeO	155	b	87	I	722
H	Me	OMe	HO	206	b	*	U	289
		OEt	HO	233	b	*	U	289
		OMe	MeO	87	r	*	U	289
	Ph	OEt	EtO	82	r	75	I, U	289

TABLE 55. 3,4-DIHYDROXYTHIOPHENE-2,5-DICARBOXYLIC ACID AND ITS DERIVATIVES

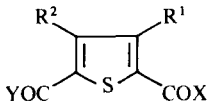


R	X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	OH	HO	192 d	b	81	–	434
	$NHNH_2$	H_2NNH	290 d	z	21	I	482
	OMe	MeO	177	r	–	U, K	432
			174	–	–	U	726
MeCO	OMe	MeO	105.5–106.5	–	–	–	726
H	OEt	EtO	142–143	r	–	I, P	1069
			134.5–135	r	79	–	433
			134	r	72	I	1070
			135–136	r	90	–	434
			–	–	–	I, P, U	3
MeCO	OEt	EtO	80.5–81.2	d	–	–	433
PhCO	OEt	EtO	96.5–97.5	d	–	–	433
H	O-*n*-Pr	*n*-PrO	96–97	r	71	–	435
	O-*i*-Pr	*i*-PrO	113–114	r	53	–	435
	O-*n*-C_5H_{11}	*n*-$C_5H_{11}O$	71–72	r	56	–	435
Me	OH	HO	>260 d	b	92	–	433
	Cl	Cl	94	n	–	–	489
	NH_2	H_2N	247	d	70	–	489
	OEt	EtO	52–53	m1	95	U	433
Et	OH	HO	245–250	b	64	–	434
	OEt	EtO	150–160/0.6	g	30	–	434
$PhCH_2$	OH	HO	205–206	b	80	U	281
	OMe	MeO	104–106	g	*	M, U	281
$-CH_2-$	OH	HO	253 d	b	97	I	482
	NH_2	H_2N	224–225 d	d	83	I	482

TABLE 55. (*Continued*)

R	X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	NMePh	PhMeN	142–143	d	79	I	482
	N-Piperidino	*N*-Piperidino	138–139	d	87	I	482
	$NHNH_2$	H_2NNH	228 d	h	79	I	482
	N_3	N_3	105 d	g	87	I	482
	OH	MeO	217 d	b	54	I	482
	OH	EtO	193	b	80	I	482
	NH_2	EtO	171	d	85	I	482
	OMe	MeO	163	m1	95	I	482
	OMe	EtO	–	m1	–	I	482
	OEt	EtO	123	g	74	I, P	1070
			185–195/1.8				1070
$-(CH_2)_2-$	OH	HO	323 d	b	73	–	434

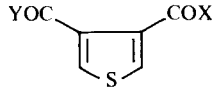
TABLE 56. MISCELLANEOUS THIOPHENE-2,5-DICARBOXYLIC ACIDS AND THEIR DERIVATIVES



(R¹— (R¹, R² are various substituents)

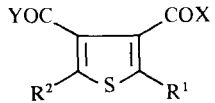
R¹	R²	X	Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	H	OH	HO	278	u	75	–	11
				266	b	–	–	232
		OMe	MeO	84	r	*	–	232
1-Adamantyl	H	OMe	MeO	131–132	f	25	P	1071
CH=C(CO_2H)-*i*-Pr	H	OH	HO	256–259	w	*	U	1072
		OMe	MeO	84–86	m1	*	I, P, U	1072
CH_2Br	$BrCH_2$	OMe	MeO	124.5–126	f	71	P, U	283
—CN	NC—	NH_2	H_2N	>300	b	80	I, U	32
CH_2SEt	$EtSCH_2$	OH	HO	235–240	b	–	–	283
		OMe	HO	137–139	z	–	–	283
		OMe	MeO	79.5–80.5	g	55	P, U	283
S-*t*-Bu	H	OH	HO	275–285 d	i	80	P	32
		OMe	MeO	77–79	–	–	–	32
SO_2-*t*-Bu	H	OH	HO	230 d	p	75	–	1052
		OMe	MeO	127–128	w	*	P	32
				127–128	–	–	–	1052
Cl	H	OH	HO	259	w	37	–	138
Cl	Cl	OH	HO	330–331	u	90	–	50
Br	H	OH	HO	261–262	w	–	–	171
				269	w	13	–	138
		OMe	MeO	128–129	w/m	–	–	171
Br	Br	OH	HO	>300	w	–	–	171
				317	p	50	–	1073
		OMe	MeO	166–167	w/m	–	–	171
I	I	OH	HO	300	w	71	–	97
		OMe	MeO	177.5–178.5	m1	*	–	97

TABLE 57. THIOPHENE-3,4-DICARBOXYLIC ACID AND ITS DERIVATIVES



X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	HO	225–229	u	40	–	15
		227–229	b	79	–	187
		230–231	u	*	U	159
		225–226	r/b	35	–	1074
		225.5–226.5	r/b	20	I, K	178
		225–227	b	*	–	332
			s	68–97	–	332
		223–225	p	100	I, U	101
——O——		141–143	k	67	–	333
		145–146	k	86	–	159
		149–150	k	–	–	101
——NH——		293–294	f	–	–	159
NH_2	H_2N	237–239	h	98	–	652
OH	MeO	115.5–116.5	g	–	K	178
		108–110	r	70	–	333
OMe	MeO	60	f	60–80	–	462
		59–60	m1	–	–	159
		60–61	m2	87	–	1074
		60–61	m2	82	–	178
		59–60	s	10–23	–	332
		58–60	m1	–	I, U	101
OEt	EtO	Liquid	f	60–80	–	462
		136–142/1	m	77	P	15
		118–130/1	r	–	–	327
		156–157/8	m2	87	–	1074

TABLE 58. ALKYL- AND ARYLTHIOPHENE-3,4-DICARBOXYLIC ACIDS AND THEIR DERIVATIVES

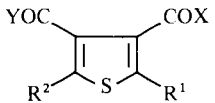


R^1	R^2	X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	H	OH	HO	204–205	s	83–90	–	332
		OMe	MeO	123–124/3	s	13	–	332
					m1	–	n	332
Me	Me	OH	HO	201–202	q	–	–	144
		$NHNH_2$	H_2NNH	247–249	h	75	–	906
		OMe	MeO	63–64	m1	–	–	144
		–	–	–	–	–	I	1058
		OEt	EtO	73–74	f	3	M	331
Me	Ph	OMe	MeO	78.5–79.5	r	67	I	258, 259
Ph	H	OMe	MeO	70–71	r	40	I, M, P, U	272, 318, 319
C_6H_4-4-MeO	H	OMe	MeO	100–101	r	47	I, M, P, U	318, 319
C_6H_4-4-Cl	H	OMe	MeO	80–82	r	44	I, M, P, U	319
Ph	Ph	OH	HO	190–191.5	b	99	I	259
				200	b	–	I, M	312
		OMe	MeO	167–169	r	84	–	324
				166–167.5	r	98	I, P	259
					r	97	–	314
				166–168	r	11	–	316
				167–168	r	90	U	313
				165–166	f	*	–	330
				167–168	r	90	I, M, P, U	312
				165–167	r	54	–	325
				165–167	r	58	I, P	317
				166–167.5	r	99	–	258
				167.5–168	u/m1	27	–	29

TABLE 58. (*Continued*)

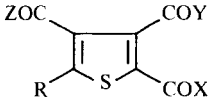
R^1	R^2	X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Ph	4-Me-C_6H_4	OMe	MeO	97–98	r	89	I, P	259
				93–94.5	r	86	I	259
				89–90	r	65	–	258
Ph	4-Br-C_6H_4	OMe	MeO	107–108	r	91	I, P	259
Ph	4-MeO—C_6H_4	OH	HO	192–194 d	b	–	–	259
Ph		OMe	MeO	110.5–111.5	r	93	I, P	258, 259
				107–109	r	80	–	315
				109–110.5	r	28	–	325
				160–165/10^{-4}	r	90	M	317
Ph	4-Me_2N—C_6H_4	OMe	MeO	115–116	r	88	I, P, U	259
Ph	4-NO_2—C_6H_4	OMe	MeO	173–174	r	70	I, P, U	259

TABLE 59. MISCELLANEOUS THIOPHENE-3,4-DICARBOXYLIC ACIDS AND THEIR DERIVATIVES



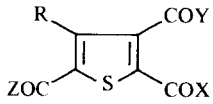
R^1	R^2	X	Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Cl	Cl	OH	HO	205–206	u	65	–	40
		——O——		142–143	k	72	I	40
Ph	Me_2N	OMe	MeO	108–109	r	69	I, M, P, U	316
	N-Pyrrolidino	OMe	MeO	142–143	r	93	I, P, U	320
	N-Piperidino	OMe	MeO	115–116	r	80	I, P, U	320
	N-Morpholino	OMe	MeO	136–137	r	87	I, U	320
N-Morpholino	*N*-Morpholino	OMe	MeO	131	f	40	I	329
Et	EtS	OH	HO	212.5–213.5	p	88	–	42
		——O——		79–80.5	k	*	–	42
Ph	MeS	OH	HO	235–237	b	100	I, M, P, U	316
		OMe	MeO	130–131	r	67	I, M, P, U	316
	EtS	OMe	MeO	120–121	r	88	I, P	321, 322
				117–119	r	63	I, M, P, U	316
	n-PrS	OMe	MeO	74–76	r	46	I, M, P, U	316
	CH_2=$CHCH_2S$	OMe	MeO	113–114	r	37	I, M, P	321, 322
SMe	MeS	OH	HO	230–231.5	p	–	–	106
		OMe	MeO	119–119.5	m1	–	–	1075
SOMe	MeS	OH	HO	209.5–210	p	70	–	1075
		OMe	MeO	82.5–83.5	m1	–	–	1075

TABLE 60. THIOPHENE-2,3,4-TRICARBOXYLIC ACIDS AND THEIR DERIVATIVES



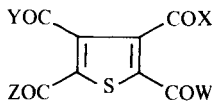
R	X	Y	Z	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	OH	OH	HO	247–249	r	34	–	334
	OMe	OMe	MeO	87–87.5	m2	80	–	334
Me_2N	OMe	OMe	MeO	89–91	r	16	I, M, P, U	316

TABLE 61. THIOPHENE-2,3,5-TRICARBOXYLIC ACIDS AND THEIR DERIVATIVES



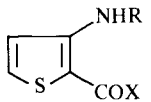
R	X	Y	Z	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	OH	OH	HO	215–216	w	*	U	1072
				214–216	r	18	–	334
				>200 d	w	*	–	181
	OMe	OMe	MeO	85–86	m	–	–	181
				82.5–83	m	–	–	334
				82–83	m1	*	U	1072
H_2N	OMe	NH_2	MeO	127–129	r	50	I	346

TABLE 62. THIOPHENETETRACARBOXYLIC ACID AND ITS DERIVATIVES



W	X	Y	Z	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OH	OH	HO	HO	254–260 d	w	*	–	335, 336
				260–261	b	–	–	1076
				253 d	b	53	–	337
				–	f	83	–	337
OMe	OMe	MeO	MeO	125	r	38	I, P, U	300
				124.5–125.5	r	8	I, P	340
				124–125	r	32	I	338
				125–126	f	*	–	336
NH_2	—O—		H_2N	300	b	87	I	337
	NH_2	H_2N	H_2N	233–234	b	71	–	337
—S—		—S—		228–231 d	f	*	–	336

TABLE 63. 3-AMINOTHIOPHENE-2-CARBOXYLIC ACID AND ITS DERIVATIVES (EXCLUDING UREAS)

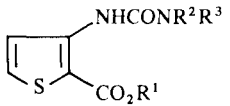


X	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	H	83 d	b	96	–	343, 1077
		82	e	61	I, P	350
[Diazonium chloride]		150	f	85	–	1078
	$CH{=}C(CO_2Et)_2$	98–101	g	41	I, P	712
N_3	COMe	96–98 d	–r	25	–	719
OMe	H	64–65	r	43	P	371
		65.5	r	72	–	343, 1077
		100–102/0.1				343, 1077
		63–64	r	68	–	345
	CHO	82	d	80	I	707
		82	d	–	I	708
		subl 150/0.2				708
		92–93	–	–	–	1012
	COMe	96.8–97.2	d	91	P	371
		100	–	–	–	343, 1077
		93–95	d	–	–	348
	COPh	103	–	–	–	343, 1077
	$COCH_2COMe$	127–128	f	88	I, P	722
	$COCH_2CO_2Et$	58.5–59.5	f	85	I, P	713
	CO_2Et	84–86	f	–	–	1079
	CO_2Ph	118–120	d	*	–	348
	$CH{=}C(CO_2Et)_2$	68–70	g	68	P	713
	$C(CO_2Me){=}CHCO_2Me$	93–94	f	78	I, P	712
	C_6H_4-2-NH_2	102	e	–	–	387
	C_6H_3-2-NH_2-4F	111–113	e	95	–	701

TABLE 63. *(Continued)*

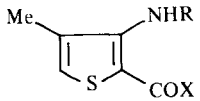
X	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
	C_6H_4-2-NO_2	184	g	–	–	387
	C_6H_3-4-F-2-NO_2	174–175	g	36	I, P	701
	C_6H_3-4-Cl-2-NO_2	207–208	g	–	–	387
	7-Cl-4-quinolyl	226	g	*	–	1080
	NH_2	69–71	f	88	I, P	1081
	NH_2,HCl	194–196	e	56	I, P	1081
	NHCOMe	143–145	d	–	I, P	1081
	N=CHPh	69–70	k	50	I, P	1081
	N=CH-(5-NO_2-2-furyl)	194–196	k	90	I, P	1081
	NH–CH=C(CO_2Et)$_2$	118–120	f	73	I, P	1081
OMe	N=C(Me)CH_2CO_2Me	75–76	k	66	I, P	1081
OEt	H	42–43	r	44	–	343, 1077
		109–112/0.3				343, 1077
		96–98/0.2	r	–	–	348
	CHO	39	d	80	I	707
	$COCH_2COMe$	90–92	f	89	I, P	713
	$COCH_2CO_2Et$	58–60	f	88	I, P	713
	$COCHMeCO_2Et$	Oil	f	73	I, P	713
	COCHMeCONH-(2-CO_2Et-3-thienyl)	109–111	z	–	I, P	713
	$COCH_2CN$	149–150	f	81	I, P	713
	CH=C(CO_2Et)$_2$	111–113	f	77	I, P	713
O-i-Pr	H	120–130/0.1	r	–	–	348
O-n-Bu	H	122–132/0.1	r	–	–	348

TABLE 64. UREAS DERIVED FROM ESTERS OF 3-AMINOTHIOPHENE-2-CARBOXYLIC ACID



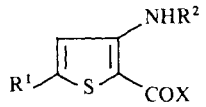
R^1	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	H	Me	117–118.5	f	–	–	1079
			145–146	f	*	–	348
		Et	108–110	f	–	–	348
		n-Pr	105–106	f	–	–	348
		i-Pr	120–121	f	–	–	348
		n-Bu	76–78	f	–	–	348
		t-Bu	126–127.5	h	–	–	348
		n-C_5H_{11}	67–68	h	–	–	348
		Cyclohexyl	157–159	h	–	–	348
		3-(2-CO_2Me-thienyl)	200–202	f	Small	–	161
		$CH_2CH{=}CH_2$	102–103	h	–	–	348
	Me	Me	129.5–131.5	f	–	–	1079
		Ph	129	f	29	–	1082
	—$(CH_2)_4$—		164	f	56	–	1082
	—$(CH_2)_5$—		103	f	66	–	1082
	—$(CH_2)_2NMe(CH_2)_2$—		118	f	60	–	1082
	—$(CH_2)_2NPh(CH_2)_2$—		158	f	85	–	1082
	—$(CH_2)_2O(CH_2)_2$—		139	f	72	–	1082
Et	H	Me	129–130	f	–	–	348
n-Bu	H	Me	122–123	f	–	–	348

TABLE 65. 3-AMINO-4-METHYLTHIOPHENE-2-CARBOXYLIC ACID AND ITS DERIVATIVES



X	R	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OH	H	123	b	83	–	344, 1077
	2,6-di-Cl-C_6H_3	157–158	b	–	–	349
OMe	H	84–85	r	–	–	344, 1077
	H, HCl	78	r	63	–	344, 1077
	CHO	132–134	d	–	–	1012
	COMe	118	–	–	–	344, 1077
	COPh	105	–	–	–	344
	$COCH_2NH$-*i*-Pr, HCl	98–99	g	–	–	1083
	$COCH_2$N-pyrrolidyl, HCl	182–183	g	–	–	1083
	$COCH_2$N-piperidyl, HCl	188	g	–	–	1083
	COCHMeNH-*i*-Pr, HCl	117–118	g	–	–	1083
	COCHMeNHBu, HCl	178–180	g	–	–	1083
	COCHMeNHBu, H_3PO_4	193–194	g	–	–	1083
	$COCHMeNHCH_2CH{=}CH_2$, HCl	170–171	g	–	–	1083
	$COCHMeNEt_2$, HCl	178–180	g	–	–	1083
	$COCH_2CH_2NHPr$, HCl	200–202	g	–	–	1083
	$COCH_2CH_2NHBu$, HCl	174–175	g	–	–	1083
	$COCH_2CH_2NEt_2$, HCl	101–102	g	–	–	1083
	$COCH_2CH_2$N-pyrrolidyl, HCl	138–139	g	–	–	1083
	$COCH_2CH_2$N-morpholyl, HCl	152–153	g	–	–	1083
	2,6-di-Cl-C_6H_3	110–112	s	–	–	349
	CONHBu, HCl	154–156	g	–	–	1083
	$CONHCH_2NHEt$, HCl	157–158	g	–	–	1083
OEt	CHO	88–89	d	–	–	1012
	$COCH_2NHBu$, HCl	130–134	g	–	–	1083
	$COCH_2NEt_2$, HCl	130–133	g	–	–	1083
OPr	CHO	81–82	d	–	–	1083

TABLE 66. 5-ALKYL-, SUBSTITUTED-ALKYL-, -ARYL-, AND SUBSTITUTED-ARYL-3-AMINOTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

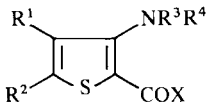


X	R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	Me	H	>85 d	b	91	–	343, 1077
OMe	Me	H	72	r	85	–	343, 1077
		CHO	104–105	d	–	–	1012
		COMe	90	–	–	–	343, 1077
		COPh	145.5–146.5	–	–	–	343, 1077
		NH_2	101–102	f	80	I, P	1081
		NH_2, HCl	205–206	e	43	I, P	1081
		N=CH-2-(5-NO_2-furyl)	196–198	k	83	I, P	1081
		N=C(Me)CH_2CO_2Me	70–71	k	91	I, P	1081
OEt	Me	H	59–60	r	41	–	343
			120–124/0.3				343
OH	CF_3	COMe	223	b	*	–	711
OEt	CF_3	H	33–35	a	*	P	382
			110–115/1.5				382
		COMe	68–70	d	*	–	711
		COPh	114–115	d	*	P	382
OH	Ph	H	>94 d	b	94	–	343, 1077
OMe	Ph	H	150–151	r	66	–	343, 1077
		CHO	112–113	d	–	–	1012
		COMe	124–125	–	–	–	343, 1077
		COPh	165–166	–	–	–	343, 1077
		NH_2, HCl	213–214	e	43	I, P	1081
		N=CH-2-(5-NO_2-furyl)	188–190	k	87	I, P	1081

TABLE 66. *(Continued)*

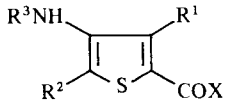
X	R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
		$N{=}C(Me)CH_2CO_2Me$	103–105	k	27	I, P	1081
		$PS(OMe)_2$	118	f	–	P	709
OEt	Ph	H	104–105	r	55	–	343, 1077
OMe	4-Me-C_6H_4	H	124	r	40–70	–	709
	4-MeO–C_6H_4	H	185	r	40–70	–	709
OEt	4-Me-C_6H_4	H	115	r	40–70	–	709
	4-MeO–C_6H_4	H	174	r	40–70	–	709

TABLE 67. MISCELLANEOUS 4,5-DISUBSTITUTED-3-AMINOTHIOPHENE-2-CARBOXYLIC ACID DERIVATIVES



X	R^1	R^2	R^3	R^4	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	Me	Me	H	H	86 d	b	*ca* 100	–	344
OMe	Me	Me	H	H	154	r	27	–	344
				CHO	123–124	d	–	–	1012
				COMe	115	–	–	–	344
	Et	Me	H	CHO	116–117	d	–	–	1012
	Ph	Me	H	CHO	122–124	d	–	–	1012
NH_2	Ph	H_2NCOCH_2S	H	H	195–197 d	r	82	I	346
OMe	Ph	H_2NCOCH_2S	H	H	170–172	r	65	I	346
		MeO_2CCH_2S	H	H	57–59	r	94	I	346
			=CHOEt		86–87	f	76	I	346
			=N-(2-OH-1-naphthyl)		168	c	79	–	346
OEt	$PO(OEt)_2$	Me	H	H	131–132/0.01	r	56	I, P	347
NH_2	NH_2	MeS	H	H	116	r	86	I, P, U	403, 404
				H, HCl	228	–r	86	I, U	404
OEt	NH_2	MeS	H	H	78	r	82	I, P, U	403, 404
			=CHPh		69	k	55	I, P, U	404
NH_2	$\overset{+}{N}$-pyridyl I^-	MeS	H	H	273	r	77	I, U	404
					248	r	88	–	403
OEt	$\overset{+}{N}$-pyridyl I^-	MeS	H	H	241	r	95	I, U	404
					203	r	82	–	403

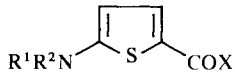
TABLE 68. VARIOUSLY SUBSTITUTED 4-AMINOTHIOPHENE-2-CARBOXYLIC ACID DERIVATIVES



X	R^1	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OH	H	H	MeCO	273–274 d	e/d	10	–	186, 353
			Tosyl	214–215	d	67	–	92
$NH(CH_2)_2CN$	H	H	H	177–178	e	49	–	92
			i-Pr	137–138	e	28	–	92
			Tosyl	176.5–177.5	d	68	–	92
$NH(CH_2)_2C(=NH)NH_2$, HCl	H	H	*i*-Pr	208.5–209.5	f	43	–	92
OMe	H	H	MeCO	135–136	m1	–	–	186, 353
OEt	H	H	MeCO	116–117	–	–	–	353
			[*N*,*N*-di-tosyl]	137–138	e/d	51	–	92
OH	H	Me	H, HCl	252–253 d	b	–	–	186
			MeCO	270–271 d	e/d	28	–	186
$NH(CH_2)_2CN$	H	Me	H	170–171	e	73	–	135
			4-NO_2–C_6H_4–CO	242–245	d	93	–	135
$NH(CH_2)_2C(=NH)NH_2$, HCl	H	Me	4-NO_2–C_6H_4–CO	251–253	f	48	–	135
			$CONH_2$	248–252	f	41	–	135
OCH_2Ph	H	Me	H	49–51	e	95	–	135
$OCH_2CH_2NEt_2$, HCl	H	Me	H	159.5–161	e	72	–	449
OH	H	Et	H, HCl	257–258 d	b	–	–	186
			MeCO	231–232 d	e/d	14	–	186
		i-Bu	H	170–171 d	f	–	–	186
			H, HCl	209–210	b	–	–	186
			MeCO	210–211	e/d	–	–	186
OMe	H	PhCH=CH	MeCO	203–203.5	d	–	–	351
	Me	Me	$BuNHCH_2CO$, HCl	234	g	–	–	1083
			Et_2NCH_2CO, HCl	112–114	g	–	–	1083

	H	3-Thienyl-S	CH_2=CHCO	118–119.5	z	14	I, P	352
			$ClCH_2CH_2CO$	131–131.5	d	75	–	352
		2-(3-Br-thienyl)S	H	–	e	50	P	352
			$ClCH_2CH_2CO$	153–153.5	d	75	–	352
		3-(2-Br-thienyl)S	$ClCH_2CH_2CO$	139.5–140	c	80	–	352
OEt	Me	HS	MeCO	127–128	v	77	I, M, P	354
		MeS	H	77–78	b	88	I, M, P	354
			MeCO	155–156	a	93	I, M, P	354
		$PhCH_2S$	MeCO	114–115	a	83	I, M, P	354

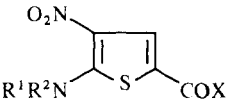
TABLE 69. 5-AMINOTHIOPHENE-2-CARBOXYLIC ACID AND ITS DERIVATIVES



X	R^1	R^2
OH	H	MeCO
		Tosyl
$NH(CH_2)_2CN$	H	H
		i-Pr
	=CMe_2	
	H	PhCO
		4-NO_2—C_6H_4—CO
		2-(5-NO_2-thienyl)CO
	Tosyl	Tosyl
$NH(CH_2)_2C(=NH)NH_2$, HCl	H	H
		i-Pr
		PhCO
		4-NO_2—C_6H_4
		2-(5-NO_2-thienyl)CO
OMe	H	H
		H, HCl
		MeCO
		PhCO
OMe	=CHPh	
	H	NH_2, HCl
		N=CPh_2
OEt	H	H
		MeCO
		EtO_2CCO
	Tosyl	Tosyl
	1-(2-OH-naphthyl)N=	
	2-(5-MeCONH-thienyl)N=	
	2-(5-MeCONH-furyl)N=	

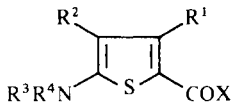
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
272	b	–	–	356
230–232 d	e/d	61	–	353
271–272	p	100	–	91
169–170	e/d	64	–	1084
124–125 d	b	88	I	92
150–152	e	74	–	92
149–151	e	85	–	135
117–118.5	e/g	30	–	92
206–207	k	*	–	92
283–285 d	d	84	–	135
256–257	d	99	–	135
275–276 d	d	93	–	135
189–190	d	19	–	92
213–215	f	18	–	92
210–212	f	26	–	92
275–277 d	f	54	–	135
295–300	f	55	–	135
284–287 d	f	62	–	135
81	e	–	–	356
81	e	*	–	183
85.5–86	f	90	I	124
86–89	–	–	D	1085
181–184 d	e	60	–	124
172	d	–	–	356
171–171.5	m1	–	–	353
172–173	d	–	–	124
173–174	–	–	–	183
192	d	–	–	356
107.5–108.5	k	–	–	124
>183 d	e	–	–	124
169.5–170	k	–	–	124
160–170/4	e	–	–	357
161–162	m	–	–	353
161–162	d	60	–	357
140–142	d	44	–	1086
167–168	e/d	59	–	92
165–165.5	c	–	–	1087
248 d	c	–	U	1087
191–192 d	c	–	U	1087

TABLE 70. DERIVATIVES OF 5-AMINO-4-NITROTHIOPHENE-2-CARBOXYLIC ACID



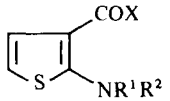
X	R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OH	H	NH_2	210–211 d	g	84	–	1088, 1089
		$Me_2C{=}N$	207–208 d	k	–	–	1089
		PhCH=N	276–278 d	k	–	–	1089
		PhMeC=N	243–244 d	k	–	–	1089
NH_2	$-(CH_2)_5-$		216	g	*ca* 100	U	110
OMe	H	Me	152	f	–	–	1090
		Ph	157	f	95	–	1090
		MeCO	200–201	c	74	–	1084
	$-(CH_2)_5-$		92	g	*ca* 100	U	110
	H	NH_2	171.5 d	g	100	–	1088, 1089
		PhNH	168 d	g	39	–	1090
		PhCH=N	222 d	k	–	–	1089
		PhMeC=N	176 d	k	–	–	1089
		$EtO_2CCH_2C(Me){=}N$	107	k	–	–	1089
		2,4-di-NO_2–C_6H_3–$NH(CH{=}CH)_2CH_2CH{=}N$	188	–r	76	–	1091
	Me	NH_2	91	g	65	–	1090
		PhCH=N	211	k	–	–	1090
	Ph	NH_2	186	z	31	–	1090
		PhCH=N	164	k	–	–	1090
	=NPh		147	f	59	–	1090
OEt	H	NH_2	147	g	91	–	1088, 1089
		$Me_2C{=}N$	119–120	k	–	–	1089
		PhCH=N	205	k	–	–	1089
		PhC(Me)=N	172	k	–	–	1089
		$EtO_2CCH_2C(Me){=}N$	135.5	k	–	–	1089
		4-NO_2–C_6H_4–$C(CH_2CO_2Et){=}N$	161–162	k	–	–	1089

TABLE 71. VARIOUSLY SUBSTITUTED 5-AMINOTHIOPHENE-2-CARBOXYLIC ACID DERIVATIVES



X	R^1	R^2	R^3	R^4	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OEt	Me	H	H	H, HCl	160–165	r	68	–	358
		H	H	PhCO	199–200	d	73	U	358
NH_2	Ph	H	H	Ph	175	b	95	I	193
OMe	H	MeCONH	H	MeCO	230–232	e/d	56	–	1084
OEt	Me	*t*-BuNH	H	*t*-Bu	111–113	f	80	P	1092
		NCS–	H	H	190–192	e	81	U	358
NH_2	Me	NO_2	$-(CH_2)_5-$		178	g	*ca* 100	U	110
OMe	Me	NO_2	$-(CH_2)_5-$		92	g	*ca* 100	U	110
OEt	Me	MeCO	H	Me	117–120	r	*	P	376
OH	H	PhCO	H	H	200–207 d	f	53	I	249
				Me	205–210	–r	*	–	1093
				$ClCH_2CO$	248–253	d	*	–	1093
OMe	H	PhCO	H	H	164–165	m1	*	–	1093
				Me	153–154	–r	*	–	1093
				H_2NCH_2CO	183–186	g	*	–	1093
				$HOCH_2CO$	203–210	g	*	–	1093
				$ClCH_2CO$	165–167	d	*	–	1093
				ICH_2CO	144–145	g	*	–	1093
OEt	OH	H	$-(CH_2)_2O(CH_2)_2-$		115–116	r	61	I, P, U	359
	OMe	H	$-(CH_2)_2O(CH_2)_2-$		119–120	m1	91	I	359
NHPh	N(Ph)*i*-Pr	H	Ph	*i*-Pr	143	c	83	I, P	1094
NH-(3,4-di-Cl-C_6H_3)	N(Ph)*i*-Pr	H	Ph	*i*-Pr	112–113	c	36	–	1094

TABLE 72. DERIVATIVES OF 2-AMINOTHIOPHENE-3-CARBOXYLIC ACID



X	R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	H	$CH{=}C(CO_2Et)_2$	164	v	96	–	696
			167–169	b	–	–	695
			268	f	60	I, P	379
			191–193	f	50	–	161
			244	r/d	75	–	375, 455
		COMe	216–217	r/d	90	–	375, 455
		$COCH_2Ph$	185–190 d	b	38	–	719
		$CONH_2$	184–185 d	f	56	–	161
		$CO(CH_2)_2CO_2H$	200–202 d	r/d	85	–	375
NH_2	H	H	153–155	r	–	–	672
			161	r	60	I	379
			158–160	r	–	–	703
		CHO	150	d	–	–	670
		COMe	217	d	95	I, P	671
			223	d	–	I, P	379
			220–222	d	–	–	777
		COPh	212–214	d	*	–	672
			207	d	86	I, P	671
			186	d	–	–	379
		CO-(4-MeO—C_6H_4)	219–221	d	*	–	672
		CO-2-pyrrolyl	315	d	87	I, P	1095
		CO-2-furyl	220	d	56	I, P	1095
		CO-2-thienyl	208	d	55	I, P	671
		CO-2-pyridyl	270	d	60	I, P	671
		$COCO_2Et$	186–187	d	–	I, P	668, 669, 691

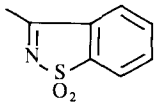
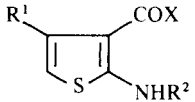
			267–269	g	*	–	1096
NHCOEt	H	COEt	155	d	–	I, P	379
$NHCH_2CN$	H	H	135–137	r	44	P	373
N_3	H	COMe	135–138 d	f	52	–	719
		$COCH_2Ph$	114–116 d	f	67	I	719
OMe	H	H	78–79	r	58	P	371
			77–78	r	46	I, U	362
		CH_2CONEt_2	107–109	b	76	–	1097
		$CH{=}C(CO_2Et)_2$	137–138	f	–	–	695
		CHO	119–121	d	45	–	1097
			89–90	m1	83	–	161
			118–120	d	27	–	674
			180/0.2				674
		COMe	97–98	d	92	P	371
			98	d	–	–	362
		$COCH_2Ph$	90–92	d	73	–	719
		$COCH_2$-4-EtO—C_6H_4	97–98	d	81	–	1097
		CO_2Ph	126–127	f	*	–	348
		CONHMe	164–166	f	*	–	348
		CONH-*n*-Pr	156–158	f	–	–	348
		CONH-*i*-Pr	171–172	f	–	–	348
		$CONHCH_2CH{=}CH_2$	125–126.5	f	–	–	348
		CONH-*n*-Bu	138.5–140	f	–	–	348
		CONH-*t*-Bu	158–159	f	–	–	348
		CONH-cyclohexyl	158–160	f	–	–	348
OEt	H	H	46–48	r	–	–	348, 372
			–	–	–	U	1098
		COMe	–	–	–	I	917
		4-F-2-NO_2—C_6H_3	125	g	–	–	387
		$C(CO_2Me){=}CHCO_2Me$	Oil	f	25	I, P, U	1099

TABLE 72. *(Continued)*

X	R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
		CONHMe	134–135	f	–	–	348
		CONHEt	104–106	f	–	–	348
O-*n*-Pr	H	H	105–120/0.2	r	–	–	348, 372
		CONHMe	138–140	f	–	–	348
O-*i*-Pr	H	H	84–88	r	–	–	348, 372
		CONHMe	169–170	f	–	–	348
O-*n*-Bu	H	H	122–124/0.1	r	–	–	348, 372
		CONHMe	122–124	f	–	–	348
O-*t*-Bu	H	H	–	–	–	I	917
		$CH{=}C(CO_2Et)_2$	108	f	80	–	696
O-*n*-C_5H_{11}	H	H	100–125/0.1–0.2	r	–	–	348, 372
		CONHMe	123–125	f	–	–	348
O-Cyclohexyl	H	H	89–90	r	–	–	348, 372
		CONHMe	143–144	f	–	–	348
OH	Me	COMe	165–168	b	87	–	719
N_3	Me	COMe	103–105 d	f	77	–	719
OMe	Me	COMe	92–93	g	74	–	719
OH	CH_2CONEt_2	$COCH_2$-4-EtO—C_6H_4	117–119	b	74	P	1097
OMe	CH_2CONEt_2	CHO	82–83	b	58	–	1097
		$COCH_2$-4-EtO—C_6H_4	91–93	d	90	I, P	1097
N_3	CH_2CONEt_2	$COCH_2$-4-EtO—C_6H_4	86–88 d	f	90	–	1097

TABLE 73. 4-ALKYL-2-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



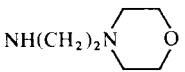
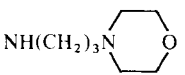
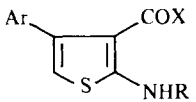
X	R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OH	Me	H	118–120	b	85	–	472
			118–120	b	57	I	688
		COMe	234	r/d	81	–	375, 455
			214–215	b	81	I	688
			214–215	b	81	–	664
NH_2	Me	H	176–178	r	53	I, U	362
		$COCO_2Et$	196–198	d	–	–	667, 668, 669
$NH(CH_2)_2O$-*i*-Pr	Me	COMe	149	f	66	I	664, 688
	Me	COMe	121	f	85	I	664, 688
	Me	COMe	174	f	72	I, P	664, 688
$NHCO_2Et$	Me	COMe	162	f	60	–	664, 688
OMe	Me	H	110–111	r	75	I, U	362
			111–113	r	–	–	348
		COMe	109–111	d	–	–	362
OEt	Me	H	85	r	88	–	13
			77–78	r	78	–	688
		4-F-2-NO_2—C_6H_3	125–127	g	27	–	702
	Me	COMe	74	d	98	–	688
		CSNHMe	80–81	z	*	–	677

TABLE 73. *(Continued)*

X	R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
	i-Pr	H	62	r	–	–	192
		COMe	62	d	–	–	192
		COEt	39	d	–	–	192
		CO-*i*-Pr	34	d	–	–	192
		CO-*t*-Bu	67	d	–	–	192
OEt	*i*-Bu	H	65	r	–	–	192
NH_2	*t*-Bu	H	145	b	*	–	192
		COMe	251	d	*	–	192
		CO-*i*-Pr	226	d	*	–	192
		CO-*t*-Bu	221	d	–	–	192
OMe	Cyclohexyl	H	88–92	r	–	I, U	363

TABLE 74. 2-AMINO-4-ARYL- AND -HETEROARYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

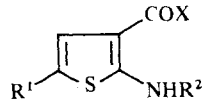


Ar	X	R	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Ph	OH	COMe	223–224	r	67	–	686
		CO-(4-Cl-C_6H_4)	128–129	–	66	I	685
	$NHNH_2$	COPh	157–158	f	90	–	685
	OMe	H	137–139	r	–	–	674
		COMe	124–127	d	–	–	674
	OEt	H	98	r	62	I	361
			93–94	r	80	–	686
			98	r	70	I, U	1100
			99	r	75	–	13
			96	r	–	–	192
			98	r	76	–	1101
			–	–	–	P	1102
		CH_2CO_2H	178–179.5	b	90	I, P	705
		$(CH_2)_3CO_2Et$[N-benzoyl]	81–83	g	46	–	700
		CH_2CO_2Et[N-tosyl]	82–85	g	81	I	705
		COMe	90–91	r	90	–	686
			93	d	–	–	192
		COMe	95	d	70	P	1101
		$COCH_2Ph$	108	d	86	–	1101
		$COCH_2Cl$	101	d	82	–	1101
		$COCH_2$N-piperidyl	125	g	76	P	1101
		$COCH_2$N-morpholyl	165	g	69	P	1101
		COEt	68	d	–	–	192
		COCH=CHPh	150	d	76	–	1101
		CO-*i*-Pr	92	d	–	–	192
		CO-*t*-Bu	112	d	–	–	192

TABLE 74. (*Continued*)

Ar	X	R	Melting Point (°C)	Preparation	Yield (%)	Notes	References
		COPh	160	d	65	–	1101
			158–159	d	99	–	700
		CO-(4-Cl-C_6H_4)	173	d	71	–	1101
		$COCO_2Et$	102–105	d	71	–	1086
		Tosyl	97–99	d	64	–	705
		CSNH-4-MeO–C_6H_4	164–168	f	60–70	–	678
		CSNH-4-EtO–C_6H_4	149–151	f	60–70	–	678
		CSNH-4-*n*-PrO–C_6H_4	168–170	f	60–70	–	678
		CSNH-4-*n*-BuO–C_6H_4	175–176	f	60–70	–	678
4-Me-C_6H_4	OEt	H	104–105	r	75	–	1103
		CSNH-4-MeO–C_6H_4	192–194	f	60–70	–	678
		CSNH-4-EtO–C_6H_4	168–170	f	60–70	–	678
		CSNH-4-*n*-Pr-O–C_6H_4	145–146	f	60–70	–	678
2,4-di-Me-C_6H_3	OEt	H	81–82	r	72	–	1103
2,5-di-Me-C_6H_3	OEt	H	84.5–85.5	r	22	–	1103
4-MeO–C_6H_4	OEt	H	75.5–76	r	69	–	1103
2,4-di-MeO–C_6H_3	OEt	H	95–96	r	61	–	1103
3,4-di-MeO–C_6H_3	OEt	H	143–144	r	93	–	1103
3,4,5-tri-MeO–C_6H_2	OEt	H	115–116	r	75	I, P, U	1100
		COPh	145–148	d	100	–	700
4-F–C_6H_4	NH_2	H	150–151	r	–	–	369
	OEt	H	97–98	r	68	I, P, U	1100
4-Cl-C_6H_4	NH_2	H	159–160	r	–	–	369
	OEt	CSNH-4-MeO–C_6H_4	196–198	f	60–70	–	678
		CSNH-4-EtO–C_6H_4	149–150	f	60–70	–	678
		CSNH-4-*n*-PrO–C_6H_4	166–169	f	60–70	–	678
4-NO_2–C_6H_4	OEt	COPh	169–172	d	95	–	700
		$(CH_2)_3CO_2Et$[N-benzoyl]	83–84	g	46	–	700
2-Thienyl	OEt	H	77–78	r	33	–	686
		COMe	72–73	d	99	–	686
		COPh	222–223	–	75	I	685

TABLE 75. 5-ALKYL-2-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	X	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	OH	COMe	194–196	f	2	I, M, P, U	699
		CO-*i*-Pr	160–162	z	23	–	584
		$CH{=}C(CO_2Et)_2$	180	v	99	–	696
	NH_2	H	138–140	r	–	–	703
	NMe_2	COMe	147–148	f	1	P	699
	$NHNH_2$	COPh	226–226.5	f	68	I	685
	OMe	2-NH_2-4-F—C_6H_3	116–118	e	–	–	387
		4-F-2-NO_2—C_6H_3	147–151	g	–	–	387
		COMe	94–95	d	–	–	674
		$COCH_2Ph$	107–109	d	98	–	584
		CO-*i*-Pr	63–65	d	88	–	584
		CO-cyclopropyl	121–123	d	46	–	584
		COPh	170	d	–	–	674
		NH_2	121	e	55	I, U	1057
	OEt	H	46	r	42	I	361
			159–161/19				361
		COMe	75–76	d	78	P	699
			–	–	–	I	917
		CO-*n*-Pr	33	d	88	P	699
		CONHMe	118–119	f	76	–	675
		CONHPh	140	f	81	–	675
	O-*t*-Bu	$CH{=}C(CO_2Et)_2$	115	r	67	–	696
Et	OH	H	97 d	b	87	–	442
		n-C_6H_{13} [N—CO-*i*-Pr]	98–101	b	–	–	584
		2-NO_2—C_6H_4	189–191	b	100	–	387, 701

TABLE 75. (*Continued*)

R^1	X	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
		4-F-2-NO_2—C_6H_3	198–200	b	–	–	387
		COMe	174–175	d	87	–	686
		COPh	201–202	d	56	I	685
	NHPh	COMe	158–159	f	72	–	687
	$NHNH_2$	COPh	200.5–201.5	f	63	I	685
	OMe	H	62	r	–	–	674
		CH_2CONEt_2	67–69	b	56	–	1097
		4-MeO—C_6H_4	160–163	g	17	I, M, P	701
		4-MeO-2-NO_2—C_6H_3	125–127	g	–	–	387
		4-Me_2NSO_2-2-NO_2—C_6H_3	166–168	g	–	–	387
		CHO	92	d	86	–	1097
		COMe	58	d	–	–	674
Et	OEt	H	73	r	75	I, U	361
			67–68	r	46	–	368
			–	–	–	I	917
		$COCH_2COMe$	–	–	–	I	917
		5-Me-2-NO_2—C_6H_3	55–57	g	–	–	387
		4-CF_3-2-NO_2—C_6H_3	102	g	–	–	387
		2-CF_3-6-NO_2—C_6H_3	72–73	g	–	–	387
		4-CHF_2-2-NO_2—C_6H_3	88–90	g	–	–	387
		2-NH_2—C_6H_4	50–52	e	88	I, P, U	387, 701
		2,4-di-NH_2—C_6H_3	152–155	e	–	–	387
		2-NH_2-4-F—C_6H_3	80–83	e	84	I, P, U	701
			82–84	e	–	–	387
		2-NH_2-5-F—C_6H_3	100–101	e	–	–	387
		2-NH_2-3,5-di-F—C_6H_2	106	e	–	–	387
		2-NH_2-4-Cl-C_6H_3	119–121	e	–	–	387
		2-NH_2-4-NO_2—C_6H_3	174–176	e	–	–	387
		4-F-2-NO_2—C_6H_3	90	g	30–35	I, P, U	387, 701

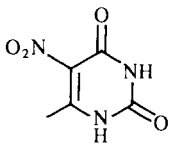
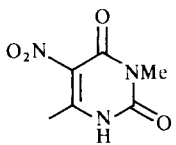
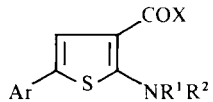
5-F-2-NO_2—C_6H_3	87–88	g	–	–	387
2,5-di-F-4-NO_2—C_6H_2	186	g	*	C, P, U	701
3,5-di-F-2-NO_2—C_6H_2	74–75	g	35	I, P, U	387, 701
4,5-di-F-2-NO_2—C_6H_2	105	g	*	C, P, U	387, 701
4-Cl-2-NO_2—C_6H_4	75–76	g	–	–	387
2-Cl-6-NO_2—C_6H_4	67–70	g	–	–	387
4-Br-2-NO_2—C_6H_4	76–78	g	–	–	387
4-MeO-2-NO_2—C_6H_4	125–127	g	33	I, P, U	701
2-NO_2—C_6H_4	66–68	g	32	I, P, U	387, 701
2,4-di-NO_2—C_6H_3	148	g	50	I, P, U	387, 701
	228	g	–	M	1104
	205 d	g	60	M	1104
CHO	31	d	86	I, P	693
COMe	55.5	d	86	I, P	693
	54–55	d	90	–	686
COEt	42.5	d	85	I, P	693
CO-*i*-Pr	40	d	83	I, P	693
CO-*t*-Bu	84	d	78	I, P	693
COPh	84	d	86	I, P	693
N=C(CN)CO_2Et	92	k	–	M, U	1104
N=C(COMe)CO_2Et	70	k	*	M	1104
C(=S)H	61	f	99	I, P	693
C(=S)Me	96	f	85	I, P	693

TABLE 75. *(Continued)*

R^1	X	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
		C(=S)Et	44	f	86	I, P	693
		C(=S)*i*-Pr	57	f	89	I, P	693
		C(=S)*t*-Bu	91	f	9	I, P	693
		C(=S)Ph	108	f	22	I, P	693
i-Pr	OEt	H	104–110/0.08	r	40	I, P, U, n	699
		COMe	54–55	d	89	P	699

TABLE 76. 2-AMINO-5-ARYL- AND SUBSTITUTED-ARYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



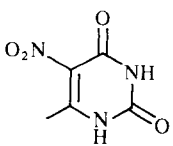
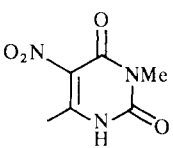
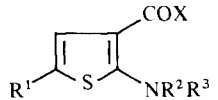
Ar	X	R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Ph	OH	H	H	188–190	b	90	–	472
	NH_2	H	H	220–222 d	r	45	I, U	1100
				218–220	r	45	–	361
			$COCO_2Et$	198–200	d	–	–	667–669
	OMe	H	H	182–185	r	–	–	674
			4-F-2-NO_2—C_6H_3	150	g	–	–	387
			COMe	136–137	d	–	–	674
			CO-cyclohexyl	121–122	d	–	–	584
			COPh	190	d	*	–	584
		—$(CH_2)_5$—		65–67	r	66	I, M, P	261
	OEt	H	H	124	r	74	I, P	805
				123–124	r	75	I	361
			COMe	103–106	d	81	P	699
				275	g	–	M	1104
				165 d	g	–	–	1104
			NH_2	119	e	20	I, U	1057

TABLE 76. *(Continued)*

Ar	X	R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
			NHCOMe	196–198	e/d	55	–	1057
			$N{=}C(CN)CO_2Et$	174	k	100	M	1104
			N=C(COMe)COMe	193	k	100	M, U	1104
			$N{=}C(COMe)CO_2Et$	128–130	k	100	M	1104
			CSNHPh	202–203	f	*	M	1104
4-Me-C_6H_4	NH_2	H	H	228–230	r	–	–	369
2-F—C_6H_4	NH_2	H	H	170–171	r	–	–	369
4-F—C_6H_4	OH	H	H	172–174	b	–	–	369
	NH_2	H	H	227–230	r	40	–	369
			COMe	230–233	d	90	–	369
	NHMe	H	H	168 d	r	40	–	369
	OEt	H	H	98–99	r	–	–	369
3-Cl-C_6H_4	NH_2	H	H	190–192	r	–	–	369
	OEt	H	H	110–111	r	–	–	369
4-Cl-C_6H_4	NH_2	H	H	255–257	r	–	–	369

TABLE 77. VARIOUSLY 5-SUBSTITUTED-2-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

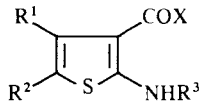


R^1	X	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Cl	OMe	H	COMe	109.5–110.5	c	85	P	371
Br	OH	H	$CH{=}C(CO_2Et)_2$	191–193	c	–	–	695
	OMe	H	CHO	156	c	60	I, P	379
I	OH	H	$CH{=}C(CO_2Et)_2$	195–197	c	–	–	695
	OMe	H	CHO	165	c	50	I, P	379
			COMe	139–141	c	*	–	362
NO_2	OH	H	H	>310	c/b	–	–	191, 395
			COMe	238–240	c	80	–	455
	NH_2	H	H	266–268	c	–	–	395
			CHO	266–268	c	–	–	191
		$-(CH_2)_5-$		155	g	*ca* 100	U	1105
	OMe	H	H	227	b	–	–	191, 395
		$-(CH_2)_5-$		71	g	*ca* 100	U	1105
	OEt	H	H	240–242	b	–	–	191, 395
			COMe	144	c	–	–	191, 395
	$O(CH_2)_2OMe$	H	COMe	112–113	b	–	–	191, 395
	O-*n*-Bu	H	H	136–139	b	–	–	191, 395
	O-*i*-Bu	H	H	138	b	–	–	191, 395
	O-*n*-C_7H_{15}	H	H	86–89	b	–	–	191, 395
PhCO	OEt	H	H	150	f	74	I, P	364, 365, 690
PhC(=NOH)	OEt	H	H	169	f	83	I, P	690
4-Me-C_6H_4—CO	OEt	H	H	164	f	84	I, P	690
4-Me-C_6H_4—C(=NOH)	OEt	H	H	192	f	76	I, P	690
4-MeO—C_6H_4—C(=NOH)	OEt	H	H	168	f	45	I, P	690
PhCS	OH	H	H	258	b	73	I	690

TABLE 77. *(Continued)*

R^1	X	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
	OEt	H	H	179	f	38	I, P	364
				179	r	64	I, P	365
			COMe	167	d	72	I, P	690
4-Me-C_6H_4CS	OH	H	H	261	b	71	I	690
4-Me-C_6H_4—CS	OEt	H	H	190	r	33	I, P	364, 365
			COMe	174	d	69	I, P	690
4-MeO—C_6H_4—CS	OH	H	H	260	b	64	I	690
	OEt	H	H	157	r	48	I, P	364, 365
			COMe	176	d	71	I, P	690

TABLE 78. 4,5-DIALKYL- AND -SUBSTITUTED-ALKYL-2-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



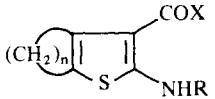
R^1	R^2	X	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	Me	OH	COMe	205–206	b	79	–	686
			COPh	191–194	b	93	–	692
			Tosyl	188–189	b	74	–	480
		NH_2	H	178–180	r	–	–	703
			CH_2CO_2H	203–204	b	64	I, P	705
			CO-(4-MeO—C_6H_4)	219–220	d	*	–	672
		$NHNH_2$	COPh	184–185	f	85	–	685
		OMe	H	123–125	r	45	I, U	362
		OEt	H	92	r	–	–	192
				92	r	60	I, P	805
				85–86	r	55	–	686
				91–92	r	50	–	360, 361
				–	–	–	P	1102
			CH_2CO_2H	158–160	b	80	I, R	705
			CH_2CO_2Et	62–64	b	86	I	705
			CH_2CO_2Et[N-tosyl]	89–96	g	92	I	705
			$(CH_2)_3CO_2H$[N-tosyl]	141–143 d	b	78	–	700
			$(CH_2)_3CO_2Et$[N-tosyl]	70–73	g	92	–	700
			$CH{=}\overset{+}{N}Me_2\bar{C}l$	147–150	f	95	–	658
			$C(SH){=}NCH_2CH{=}CH_2$	134	f	78	–	680
			COMe	98	d	*	–	192
				96–97	d	99	–	686
			$COCH_2Cl$	152–154	d	*	–	672, 673
			$COCH_2NH_2$	101–104	d	*	–	672

TABLE 78. *(Continued)*

R^1	R^2	X	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
			$COCH_2NHMe$	102–105	d	*	–	672
			$COCH_2NMe_2$	79–81	d	85	–	673
			$COCH_2$N-piperidyl	118–121	d	83	–	673
			$COCH_2$N-morpholyl	114–116	d	88	–	673
			$COCH_2N(CH_2CH_2OH)_2$	108–110	d	57	–	673
			$COCH_2$N-phthalimidyl	204–205	d	*	–	672
			COEt	73	d	–	–	192
			CO-*i*-Pr	46	d	–	–	192
			CO-*t*-Bu	81	d	–	–	192
			COPh	148–149	d	88	–	692
			CO-3-pyridyl	125–127	d	79	–	673
			CO-4-pyridyl	154–155	d	76	–	673
			CO_2Et	70–72	d	79	–	673
			$COCO_2Et$	87–89	d	82	–	1086
			CSPh	112–114	f	15	–	692
			CSNHMe	182–184	f	80	–	679
			$CSNHCH_2Ph$	146–148	f	65	–	679
			CSNHEt	164–166	f	82	–	679
			$CSNHCH_2CH{=}CH_2$	133–135	f	70	–	679
			CSNH-*n*-Bu	128–130	f	67	–	679
			CSNH-*n*-C_6H_{13}	92–94	f	78	–	679
			CSNH-cyclohexyl	179–181	f	75	–	679
			CSNHPh	169–172	f	74	–	679
			CSNH-2-Me-C_6H_4	164–165	f	70	–	679
			CSNH-4-Me-C_6H_4	169–171	f	80	–	679
			CSNH-4-MeO–C_6H_4	161–164	f	60–70	–	678
			CSNH-4-EtO–C_6H_4	165–168	f	60–70	–	678
			CSNH-4-*n*-PrO–C_6H_4	166–168	f	60–70	–	678

			CSNH-4-*n*-BuO—C_6H_4	180–181	f	60–70	–	678
			$CSS^-Et_3\overset{+}{N}H$	105–107	f	56	I	1106
			N=CHPh	123.5–124.5	e/k	44	–	1107
			Tosyl	91–93	d	88	–	705
				91.5–92.5	d	–	–	480
			SO_2-(4-NO_2—C_6H_4)	127.5–128	d	25	–	480
Me	HO_2CCH_2	OEt	H	145–148	r	30	I, U	1055
	HC(CN)=CMe	OMe	H	172	r	36	I, U	361
	$PhCH_2$	NH_2	H	150–152	r	*	–	1108
	C_5H_{11}	NH_2	$COCO_2Et$	153–154	d	–	–	667, 668
	$MeCH=CMeCH_2$	NH_2	$COCO_2Et$	199–200	d	–	–	667–669
	C_6H_{13}	NH_2	$COCO_2Et$	147–149	d	–	–	667–669
	$MeO_2C(CH_2)_2$	OEt	H	64–65	r	77	–	1103
Et	Me	OMe	H	153–155/11	r	50	–	361
		OEt	CH_2CO_2Et[N-tosyl]	86–89	g	68	I	705
			Tosyl	81–85	g	89	–	705

TABLE 79. 4,5-FUSED-CYCLOALKANO-2-AMINOTHIOPHENE-3-CARBOXYLIC ACID DERIVATIVES



n	X	R	Melting Point (°C)	Preparation	Yield (%)	Notes	References
3	OH	$CH{=}C(CO_2Et)_2$	194	v	100	–	696
	OEt	H	91	r	52	–	361
		COMe	96–99	d	89	P	699
		CSNHEt	200–202	f	72	–	679
		CSNHPh	183–185	f	65	–	679
		CSNH-4-Me-C_6H_4	198–200	f	60	–	679
	O-t-Bu	$CH{=}C(CO_2Et)_2$	111	r	56	–	696
4	NH_2	H	189–190	r	71	I, U	361
		CO-4-NH_2—C_6H_4	288–289	d	*	–	672
		CO-4-MeO—C_6H_4	115–116	d	*	–	672
		CO-4-Cl-C_6H_4	230–231	d	*	–	672
		CO-4-NO_2—C_6H_4	241–242	d	*	–	672
		$COCO_2Et$	204–205	d	44	I	667, 668
			204–205	d	49	I, P	669
			204–205	d	–	I, P	691
	NHMe	H	192–193	r	*	–	677, 703
	NH-*n*-Pr	COMe	179	f	34	–	664
	$NH(CH_2)_3NEt_2$	COMe	136	f	52	–	664
	$NH(CH_2)_2$N-pyrrolidyl	COMe	176	f	95	–	664
	$NH(CH_2)_2$N-morpholyl	COMe	185	f	89	–	664
	$NH(CH_2)_3$N-morpholyl	COMe	174	f	80	–	664
	$NHCO_2Et$	COMe	177	f	85	–	664
	OEt	H	115	r	92	C, I, P	805
			115	r	91	–	361
			115	r	80	I, U	362

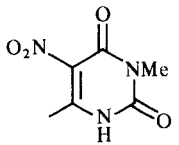
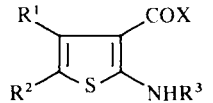
		–	–	I	917
	195–196	g	80	M	1104
$COCH_2Cl$	115–117	d	92	–	673
	115–117	d	*	–	672
$COCH_2NH_2$	121–124	d	*	–	672
$COCH_2NHMe$	99–102	d	*	–	672
$COCH_2NMe_2$	94–95	d	84	–	673
$COCH_2$N-piperidyl	100–102	d	81	–	673
$COCH_2$N-morpholyl	108–110	d	83	–	673
$COCH_2$N-phthalimidyl	194–196	d	*	–	672
$CO(CH_2)_2Cl$	83–85	d	*	–	672
COPh	173–174	d	85	–	673
CO-(2-CO_2H—C_6H_4)	173–176	d	*	–	672
CO-4-NO_2—C_6H_4	182	d	*	–	1104
CO-3,4,5-tri-MeO—C_6H_2	102	d	*	M	1104
CO-3-pyridyl	160–162	d	79	–	673
CO-4-pyridyl	182–183	d	*	–	672
CO_2Et	67–68	d	84	–	673
CSNHMe	170–175	d	100	–	1104
	193–195	f	80	–	679
	190–193	f	*	I	677
$CSNHCH_2Ph$	136–138	f	87	–	679
CSNHEt	161–164	f	82	–	679
$CSNHCH_2CH{=}CH_2$	154–156	f	85	–	679
CSNH-*n*-C_6H_{13}	87–89	f	73	–	679
CSNHPh	184–187	f	82	–	679
	188	f	–	M	1104
CSNH-3-Me-C_6H_4	176–178	f	84	–	679
CSNH-4-Me-C_6H_4	165–167	f	80	–	679
$CSS^-Et_3\overset{+}{N}H$	101–103	f	56	I	1106

TABLE 79. *(Continued)*

n	X	R	Melting Point (°C)	Preparation	Yield (%)	Notes	References
		$N{=}C(CN)CO_2Et$	112	k	57	M	1104
		$N{=}C(COMe)COMe$	88	k	*	M	1104
		$N{=}C(COMe)CO_2Et$	110	k	60	M	1104
5	OEt	$CSNHCH_2Ph$	129–131	f	70	–	679
		$CSNHCH_2CH{=}CH_2$	114–116	f	76	–	679
		$CSNH\text{-}4\text{-}Me\text{-}C_6H_4$	149–151	f	70	–	679

TABLE 80. MIXED-ALKYL/SUBSTITUTED ALKYL-ARYL/SUBSTITUTED-ARYL-2-AMINOTHIOPHENE-3-CARBOXYLIC ACID DERIVATIVES



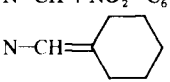
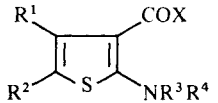
R^1	R^2	X	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	Ph	NH_2	H	184–185	r	58	–	361
			$COCO_2Et$	175–176	d	–	–	667–669
		OEt	H	93	r	*	–	192
				95	r	38	I	361
Ph	Me	OEt	H	97	r	97	–	13
				94–95	r	70	I, P, U	1100
				93	r	50	–	361
				–	–	–	P	1102
			Me	168–170	e	55	–	1109
			CH_2CO_2H	133–135	b	75–95	I	705
			CH_2CO_2Et[N-tosyl]	110–112	g	56	I	705
			$(CH_2)_3CO_2Et$[N-tosyl]	70–72	g	91	–	700
			N=CHPh	166–167.5	e/k	71	–	1107
			N=CHPh[N'-COMe]	167–168	d	40	–	1107
			N=CH-4-NO_2—C_6H_4	166–167	e/k	42	–	1107
				94–95	e/k	65	–	1107
			Tosyl	104–110	d	66	–	705
Ph	Me_2NCH_2, HCl	OEt	H	220–222 d	c	72	–	1110
2-Me-C_6H_4	Me_2NCH_2, HCl	OEt	H	>220 d	c	55	–	1110
4-Me-C_6H_4	Me_2NCH_2, HCl	OEt	H	200–202 d	c	66	–	1110
4-Et-C_6H_4	Me_2NCH_2, HCl	OEt	H	212–214 d	c	42	–	1110
2,4-di-Me-C_6H_3	Me_2NCH_2, HCl	OEt	H	214–216 d	c	66	–	1110

TABLE 80. *(Continued)*

R^1	R^2	X	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
4-MeO—C_6H_4	Et_2NCH_2, HCl	OEt	H	>193 d	c	63	–	1110
2,4-di-MeO—C_6H_3	Me_2NCH_2, HCl	OEt	H	>200 d	c	71	–	1110
	Et_2NCH_2, HCl	OEt	H	202–204 d	c	46	–	1110
2,5-di-MeO—C_6H_3	Me_2NCH_2, HCl	OEt	H	194–195 d	c	80	–	1110
	Et_2NCH_2, HCl	OEt	H	206–208 d	c	75	–	1110
Ph	4-F—C_6H_4	NH_2	H	205–207	r	–	–	369

TABLE 81. MISCELLANEOUS 4,5-DISUBSTITUTED-2-AMINOTHIOPHENE-3-CARBOXYLIC ACID DERIVATIVES

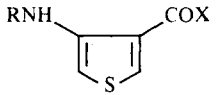


R^1	R^2	X	R^3	R^4	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	Br	OH	H	$CH{=}C(CO_2Et)_2$	129–131	c	–	–	695
	I	OH	H	$CH{=}C(CO_2Et)_2$	163–164	c	–	–	695
		OMe	H	COMe	140–142	c	*	–	362
I	I	OMe	H	COMe	197–199	c	–	–	362
Me	NO	NH_2	H	H_2SO_4	200–205 d	c	–	–	703
	NO_2	OMe	H	COMe	176–178	c	*	–	362
		OEt	H	H	204	c	–	–	191, 395
				Me	188–190	r	*	P, M	378
				Ph	117–119	r	46	P, M	378
				4-MeO—C_6H_4	111–113	r	*	M	378
	CHO	OMe	H	COMe	190–192	c	*	–	362
		OEt	H	COMe	174–176	c	–	–	191, 395
	HON=CH	OEt	H	COMe	214	k	–	–	191
	MeCO	OMe	H	H	161	r	31	I, U	361
				COMe	149–151	d	–	–	361
					149–151	c	*	–	362
		OEt	H	H	161	r	88	I, P	805
					158	r	55–60	I, P	396
				COMe	149	d	–	–	396
				CH_2CO_2Et	82–83	g	75	I, P	396
			COMe	CH_2CO_2Et	90	d	90	I, P	396
	PhCO	OH	H	H	196–197 d	b	*	–	689
				Ph	174–175 d	b	*	–	376
				3-CF_3—C_6H_4	183–184 d	v	*	–	376
				2,3-di-Me-C_6H_3	206	v	*	–	376

TABLE 81. *(Continued)*

R^1	R^2	X	R^3	R^4	Melting Point (°C)	Preparation	Yield (%)	Notes	References
		N-Morpholyl	H	COMe	226–228	—r	*	–	376
		OEt	H	Ph	139–141	r	*	P	377
			H	COPh	184–186	r	*	I, P, U	377
			Me	Me	79–81	r	75	I, P, U	381
			$-(CH_2)_5-$		73–75	r	68	I, P, U	381
		O-t-Bu	H	3-CF_3—C_6H_4	161–162	r	*	–	376
				2,3-di-Me-C_6H_3	101–102	r	*	–	376
Ph	PhCO	OEt	Me	Me	Oil	r	65	I, P, U	381
			$-(CH_2)_5-$		84–86	r	60	I, P, U	380, 381
Me	HgCl	OMe	H	COMe	*ca* 300 d	c	–	–	362

TABLE 82. DERIVATIVES OF 4-AMINOTHIOPHENE-3-CARBOXYLIC ACIDS

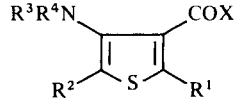


X	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	Ph	170 d	b	*	–	386
	Ph[N—COPh]	185–186	d	*	–	386
	3-CF_3—C_6H_4	178	b	*	–	620
	4-*i*-Pr-C_6H_4	159	b	55	–	620
	2,3-di-Me-C_6H_3	142	b	–	–	620
	3,4-di-Me-C_6H_3	151	b	62	–	620
	2,6-di-Me-C_6H_3	169	b	47	–	620
	2,4,6-tri-Me-C_6H_2	177	b	58	–	620
	4-EtO-3-Me-C_6H_3	149	b	54	–	620
	2,6-di-Cl-4-EtO—C_6H_2	225	b	49	–	620
	2,4,6-tri-Cl-4-EtO—C_6H	225	b	52	–	620
	2-Cl-C_6H_4	198	b	68	–	620
	2-Cl-3-Me-C_6H_3	184	b	57	–	620
	2-Cl-5-Me-C_6H_3	165	b	61	–	620
	2-Cl-6-Me-C_6H_3	177	b	49	–	620
	2,3-di-Cl-C_6H_3	264	b	68	–	620
	2,6-di-Cl-C_6H_3	194	b	–	–	620
	2,4-di-Cl-3-Me-C_6H_2	246	b	56	–	620
	2,4-di-Cl-6-Me-C_6H_2	264	b	42	–	620
	2,4,6-tri-Cl-C_6H_2	224	b	45	–	620
	2,4,6-tri-Cl-3-Me-C_6H	223	b	49	–	620
	MeCO	207–208	b	97	–	717
	$ClCH_2CO$	185–187	b	*	–	716
	PhCO	215–216	b	96	–	717
	EtO_2C	152–154	b	73	–	1111

TABLE 82. *(Continued)*

X	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
NH_2	2-Cl-3-Me-C_6H_3	133	b	*	–	620
	CHO	197–198	h	71	–	161
OMe	H, HCl	203–205 d	f	57	–	161
	Ph	163–164/0.5	s	–	–	386
	Ph[N—COMe]	126	d	*	–	386
	Ph[N—COPh]	122–123	d	*	–	386
	2-NH_2—C_6H_4	120–122	s	82–96	–	387, 388
	4-MeO-2-NO_2—C_6H_3	170–171	s	76	–	388
	2,6-di-F—C_6H_3	90–92	s	–	–	349
	4-F-2-NO_2—C_6H_3	164	g	10	P	387, 701
	3-Cl-2-Me-C_6H_3	80–82	s	–	–	349
	3,4-di-Cl-5-NH_2—C_6H_2	162–163	s	67	–	388
	2,6-di-Cl-C_6H_3	140/0.01	s	–	–	349
	2,6-di-Cl-3-Me-C_6H_2	80–82	s	–	–	349
	3,4-di-Cl-6-NO_2—C_6H_2	162–163	s	–	–	387
	4-CF_3-2-NO_2—C_6H_3	175	s	–	–	387
	CHO	94–96	d	71	–	161
	MeCO	67	d	91	–	717
	$ClCH_2CO$	105–106	d	*	–	716
	PhCO	91–92	d	79	–	717
	MeNHCO	168–170	f	–	–	348
OEt	2,6-di-Cl-C_6H_4	68	g	*	–	620
	H_2NCO	171–172	s	61	–	333
	EtO_2C	34–35	s	72	–	333
		114–115/0.1				333
$O(CH_2)_2NEt_2$, HCl	2-Cl-C_6H_4	154	g	–	–	620
	2,6-di-Cl-C_6H_3	198	g	*	–	620
$O(CH_2)_2$N-piperidyl, HCl	2,6-di-Cl-C_6H_3	248	g	–	–	620

TABLE 83. 2- OR 5-ALKYL- AND SUBSTITUTED-ALKYL-4-AMINOTHIOPHENE-3-

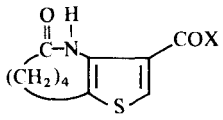


(R^1 or R^2 = H)

R^1	R^2	X	R^3	R^4
H	Me	OH	H	H
		OMe	H	H, HCl
				2-Cl-C_6H_4
				2,6-di-Cl-C_6H_3
				CHO
				Et_2NCH_2CO, HCl
				$BuNHCH_2CO$, HCl
				H_2NCO
	Et	OMe	H	H, HCl
	n-Pr	OH	H	H
		OMe	H	H, HCl
	i-Pr	OH	H	H
		OMe	H	H, HCl
	$(CH_2)_4CO_2H$	OMe	H	H
	$(CH_2)_4CO_2Me$	OMe	H	H
Me	H	OEt	H	Me
				$PhCH_2$
				n-Bu
				Ph
				4-Me-C_6H_4
				4-MeO—C_6H_4
				H_2NCO
				EtO_2C
				NH_2
				NHCHO
				NHCOMe
				NHCOPh
				H_2NCONH
				H_2NCSNH
			MeCO	MeCONH
			4-Cl-C_6H_4—CO	MeCONH
CF_3	H	OH	H	MeCO
		OEt	H	H
				MeCO
				PhCO
$(CH_2)_3OCH_2Ph$	H	$NHNH_2$	H	PhCO
		N_3	H	PhCO
		OEt	H	PhCO
$(CH_2)_3OPh$	H	$NHNH_2$	H	PhCO
		N_3	H	PhCO
		OEt	H	PhCO
$(CH_2)_4CO_2H$	H	$NHNH_2$	H	PhCO
		N_3	H	PhCO
		OEt	H	PhCO

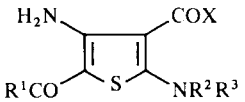
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
163–164	b	*	–	385
191–192	a	*	–	385
64–65	s	–	–	349
86	s	–	–	349
125–126	d	–	–	1012
163–164	g	–	–	1083
142–143	g	–	–	1083
194–195	f	*	–	385
161	a	*	–	385
144–145	b	*	–	385
180–181	a	*	–	385
117–118	b	*	–	385
185 d	a	*	–	385
131–132	z	13	–	384
50–52	a	83	–	384
37–38	f	86	I	390
25–26	f	69	I	390
133–134/1	f	69	I	390
54–55	f	83	I	390
83.5–84	f	81	I	390
90–90.5	f	87	I	390
185–186	s	53	–	333
78–79	s	73	–	333
69–70	f	–	I, U	389
–	f	–	P	1112
–	f	–	P	1112
–	f	–	P	1112
–	f	–	P	1112
–	f	–	P	1112
128–129	d	74	I, P	1112
129.5–130.5	d	60	I	1112
188–189	b	*	–	718
33–35	a	*	P	382
110–115/1.5				382
95–96	d	*	–	718
114–115	d	*	–	382
116–117	–	–	–	1113
62–64	–	–	–	1113
65–66	–	–	–	1113
186.5–187.5	–	–	–	1113
108–109	–	–	–	1113
97–98	–	–	–	1113
140–141	h	90	–	1113
99–100 d	f	–	–	1113
126.5–127.5	d	81	–	1113

TABLE 83. *(Continued)*

R^1	R^2	X	R^3	R^4
			X = OH	
			X = OMe	
			$X = NHNH_2$	

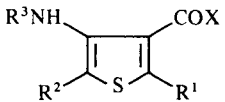
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
215–217	b	96	–	384
167–168	r	96	–	384
191–192	h	100	–	384

TABLE 84. DERIVATIVES OF 5-ACYL-2,4-DIAMINOTHIOPHENE-3-CARBOXYLIC ACIDS



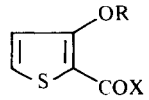
R^1	X	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	NHMe	H	Me	221–223 d	r	30	I, U	398, 400, 401
	NHPh	H	Ph	223–225 d	r	30	I, U	398, 401
	OEt	H	CH_2Ph	130	r	20	I, U	398, 401
			t-Bu	88–90	r	40	I, U	398, 401
			Cyclohexyl	80–82	r	40	I, U	398, 401
Ph	NH_2	Me	Me	216–217	r	17	I, P, U	381
			$-(CH_2)_5-$	219–220	r	–	I, P, U	381
	NHMe	H	Me	220–222 d	r	40	I, U	398, 400, 401
			$CH_2CH=CH_2$	127–128 d	r	30	I, U	398, 401
			Ph	207–209 d	r	75	I, U	398, 400, 401
			Ph[4-N—COMe]	182–184	d	55	I, U	398, 401
			3-NO_2—C_6H_4	259–260 d	r	45	I, U	398, 401
	N-Piperidyl	H	Ph	243–245	r	–	–	398, 400
	NHPh	H	Ph	228–230 d	r	70	I, U	398, 401
			3-NO_2—C_6H_4	213–215 d	r	60	I, U	398, 401
	$NHNMe_2$	H	Ph	232–234 d	r	60	I, U	398, 400, 401
	NHN-morpholyl	H	Ph	243–245 d	r	80	I, U	401
	OEt	H	Ph	138–139	r	60	I, U	398, 401
4-Cl-C_6H_4	NHMe	H	Ph	233–235 d	r	30	I, U	398, 401
4-Biphenylyl	NHMe	H	Ph	251–253 d	r	60	I, U	398, 401
	NHPh	H	Ph	256–258 d	r	70	I, U	398, 401

TABLE 85. VARIOUSLY SUBSTITUTED 4-AMINOTHIOPHENE-3-CARBOXYLIC ACID DERIVATIVES



R^1	R^2	X	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	Ph	OH	H	201–202	b	*	–	385
			MeCO	182–183	b	*	–	385
		OMe	H, HCl	181–182	a	*	–	385
			MeCO	117–118	d	*	–	385
NHPh	Me	$NHNMe_2$	H	197–200	r	–	I	399
		NH-*N*-piperidyl	H	275–277	r	–	I	399
$N(COCF_3)Ph$	Me	NH-*N*-piperidyl	CF_3CO	221–224	–	–	–	399
NHPh	Ph	$NHNMe_2$	H	191–193	r	–	I	399
SMe	MeCO	NH_2	H	180–181	r	53	–	394
	PhCO	NH_2	H	186–188	r	59	–	394
H	Cl	OH	MeCO	203–205	c	*	–	716
			PhCO	187–189	c	*	–	716

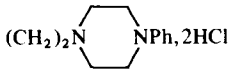
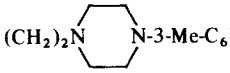
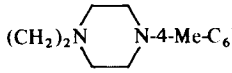
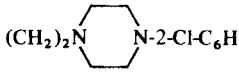
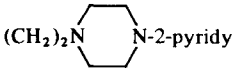
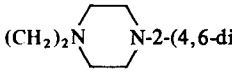
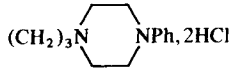
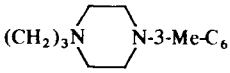
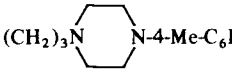
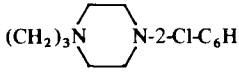
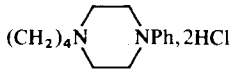
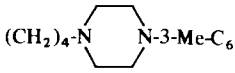
TABLE 86. 3-HYDROXYTHIOPHENE-2-CARBOXYLIC ACID AND ITS DERIVATIVES



X	R
OH	H
	Me
	CH_2OMe
	CH_2OEt
	$(CH_2)_2OMe$
	$(CH_2)_2OEt$
	t-Bu
Cl	Me
NH_2	H
NHPh	Me
$NH(CH_2)_2$-4-C_6H_4—SO_2NH-2-(5-*i*-Bu-pyrimidyl)	Me
	CH_2OMe
	CH_2OEt
	$(CH_2)_2OMe$
	$(CH_2)_2OEt$
	Et
$NH(CH_2)_2$-4-C_6H_4—SO_2NH-2-(5-*n*-Pr-pyrimidyl)	Et
$NMe(CH_2)_2$-4-C_6H_4—SO_2NH-2-(5-*i*-Bu-pyrimidyl)	Et
$NH(CH_2)_2$-4-C_6H_4—SO_2NH-2-(4-Me-5-EtS-pyrimidyl)	Me
OMe	H
	Me
	$(CH_2)_2Br$

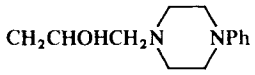
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
108	b	35	–	410
102–110	w	62	P	1114
178.5–179.5	i, g	–	–	19
175–176	–	–	–	1115
–	–	–	K	946
102–103	–	–	–	1116
88–90	–	–	–	1116
86–88	–	–	–	1116
78–80	–	–	–	1116
89–91	i	–	–	20
110/4	–	–	L	1117
85	n	90	–	103
196	b	81	–	761, 762
85	d	–	L	1117
180–181	d	–	–	872
151–153	h	76	–	1116
153–154	h	*	–	1116
66–69	d	68	–	1116
112–113	d	52	–	1116
170	d	–	–	872
158–159	d	–	–	872
142	d	–	–	872
162–164	d	33	–	1118
43	r	–	–	343
96–97/0.5				343
68–73/0.4	s	70–98	I, P	421
43	r	72	–	345
102–106/15				345
42–43	s	82		414
68–73/0.4				414
40	r	28	–	410
108/13				410
45	–	–		1068
45/0.001	r	8	I, P, U	250
100–102/14	–	–	P	1114
–	–	–	I, P	5
–	–	–	M	1066
54	t1	–	–	410
54–55	–	–	–	19
74–75	–	–	–	1068

TABLE 86. (*Continued*)

X	R
	
	
	
	
	
	
	$(CH_2)_3Br$
	
	
	
	
	CH_2cyclopropyl
	$(CH_2)_4Br$
	
	

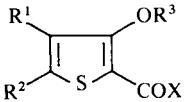
Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
196.5	g	–	–	1068
174	g	–	–	1068
175–176	m	*	–	1068
189	g	–	–	1068
191.5	g	–	–	1068
216	g	–	–	1068
238–239	g	–	–	1068
80	–	–	–	1068
147–150/0.1				1068
176	g	–	–	1068
180.5	g	–	–	1068
187	g	–	–	1068
187	g	–	–	1068
71.5–72.5	t	*	–	1068
155–158/0.1				1068
59–60	–	–	–	1068
194	g	–	–	1068
181	g	–	–	1068

TABLE 86. *(Continued)*

X	R
	
	COMe
	SO_2Me
OEt	H
OEt	*t*-Bu

Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
125–126	—r	–	–	1068
84–86/0.03	s	79	–	414, 421
118–120/3	l	80	–	724
Oil	s	83	–	414, 421
109/16	r	–	–	410
65/0.1	r	–	–	343
63–65/0.4	v	90	I, P	5
110/11	r	30	–	411
–	–	–	I, P	1119
–	–	–	K	1120
–	–	–	M	1066
96–98/0.3	i	75	I, P	5
–	–	–	P	1119

TABLE 87. VARIOUSLY SUBSTITUTED 3-HYDROXYTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	Me	H	OH	122	r	53	–	409
			NH_2	217	r	–	–	343
			NHPh	204	r	–	–	343
			OMe	67–70/0.3	s	75	–	414, 421
				51	r	–	–	343, 409
				95–96/0.2				343, 409
				53	r	75	–	405
				53	r	75	P	407
				–	–	–	I, P	5
				–	–	–	M	1066
		—CN	OMe	93–93.5	g	–	I	722
		$CONH_2$	OMe	133	b	–	–	722
		H	OEt	71/0.2	r	80	–	405
				71/0.2	r	27	–	408
				72/0.2	r	55	P	407, 413
				–	–	–	K	1120
	i-Pr	H	OEt	87/0.5	r	47	–	411
				–	–	–	I, P	5
	t-Bu	H	OEt	105/0.4	r	77	–	411
				–	–	–	I, P	5
	Ph	H	OMe	98	r	70	P	343, 405, 407
				–	–	–	I, P	5
				–	–	–	M	1066
			OEt	68	r	36	–	411
				125/0.2				411

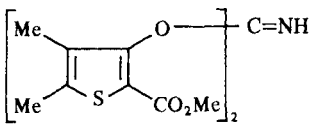
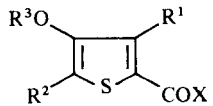
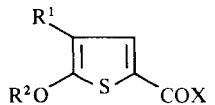
				68	r	30	–	410
				68	r	70	P	407
				69	r	–	–	405, 412
				–	–	–	K	1120
		COMe	OEt	95	–	–	–	412
	1-Naphthyl	H	OMe	67	r	–	–	411
			OEt	–	–	–	I, P	5
				–	–	–	K	1120
	4-Biphenylyl	H	OEt	136	r	43	–	411
				–	–	–	K	1120
Me	H	H	OMe	60/0.05	r	40–60	–	406
			OEt	54/0.08	r	40–60	–	406
	Me	H	OMe	50	r	–	–	406
		–CN	OMe	63	g	–	–	722
		$CONH_2$	OMe	126	b	–	–	722
		H	OEt	43	r	–	–	406
				77/0.1				406
Et	Me	H	OEt	43–44	r	81	–	405
				97–98/0.1				405
H	NO_2	H	OMe	110–111	c	*	–	1121
			OEt	98–99	c	–	–	1121
NO_2	H	H	OMe	89–90	c	*	–	1121
			OEt	89–91	c	–	–	1121
				172.5	f	–	–	722

TABLE 88. 4-HYDROXYTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



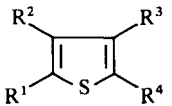
R¹	R²	R³	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	H	OH	210	x	72	M, P	1067
				202	b/x	81	–	410
				185 d	r	–	–	429
				204	–	–	P	1114
		Me	OH	166–168	g	–	–	19
		MeCO	OH	118	l	74	–	1067
			Cl	120–140/12	n	80	M, P	1067
		H	NH_2	134–135	b	–	–	1122
			NMe_2	148–149	b	–	–	1122
			NHPh	186–188	f	–	–	1122
			OMe	86–87	m2	–	–	1122
				89.5–90.5	m1	86	P	1114
		Me	OMe	38–39	m + t	73	–	1114
	Me	H	OEt	80–82	i	87	I, P	5
				131–133/0.4				5
				–	–	–	P	1066
		t-Bu	OEt	96–97/0.3	g	66	–	5
Me	H	H	OH	184	b/x	–	–	289
H	MeCO	Me	OMe	93–94	g	–	I, P, U	142
		H	OEt	87–88	r	23	I, U	415

TABLE 89. 5-HYDROXYTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



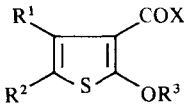
R^1	R^2	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	OEt	66–67.5	v	89	P	4
			95–97/0.1				4
			–	–	–	M	1066
	Me	OH	162–163 d	i	61	U	1123
			–	–	–	K	946, 961, 962
			–	–	–	U	1124
		Cl	158/30	n	*	–	737
			–	–	–	I	941
		NH_2	163	d	90	–	737
		NHPh	141–143	–	–	–	965
	t-Bu	OH	114–116	i	75	–	4
		OEt	90–92/0.1	g	46	–	4
	$C_{14}H_{29}$	OH	95–96	g	10	–	222, 416
NO_2	4-NO_2—C_6H_4—O	NH_2	194	g	–	–	1125
		OMe	116	g	–	–	1125

TABLE 90. VARIOUS DIHYDROXYTHIOPHENECARBOXYLIC ACID DERIVATIVES



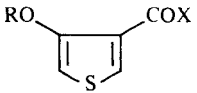
R^1	R^2	R^3	R^4	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
A. 2-Carboxylic Acids								
H	HO	OH	CO_2Et	77–78	b/y	–	I, P, U	3
				–	–	–	C	1069
	—O—CH_2—O—		CO_2H	204	b	75	I	482
			CO_2Et	69	x	24	I	482
MeO	H	OH	CO_2Me	71–73	r	90	I, P, U	359
			CO_2Et	32–33	r	86	P	359
		OMe	CO_2Me	67–68	t1	100	I, P, U	359
			CO_2Et	42–45	t1	–	–	359
HO	HO	H	CO_2Et	45–47	v	83	P	5
				95–110/0.1				5
				–	–	–	I, P, U	3
t-BuO	*t*-BuO	H	CO_2Et	39–40	g	51	–	5
				115–125/0.3				5
Br	—O—CH_2—O—		CO_2H	195 d	b	100	I	482
			CO_2Et	92–93	c/x	–	I	482
B. 3-Carboxylic Acids								
H	HO	CO_2Et	OH	–	–	–	I, P, U	3
Me	HO	CO_2Et	OH	–	r	–	I, P, U	3
MeO	H	CO_2H	OMe	138–139	u	45	I, P	43
	Me	CO_2H	OMe	150 d	u	56	I, P, M	44

TABLE 91. VARIOUSLY SUBSTITUTED 2-HYDROXYTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	H	OEt	44–46/0.08	v	73	I, P	1119
		Me	OH	174–175	u	–	P	461
				–	–	–	K	1014
			Cl	70–75 d	n	97	P	461
			OMe	133–137/14	f	81	P	461
				–	–	–	U	1026
		t-Bu	OEt	75–77/0.08	u	81	P	1119
	Me	Me	OH	147–149	p	*	–	102
				147–148	i	50	U	1123
				146–148	o	70	P	1126
	MeS	Me	OH	153–154	p	65	P	104
			OMe	58–60	m1	90	I, P	104
				136–138/0.3				104
	Cl	Me	OH	170 d	u	61	I, P	56
	CHO	Me	OMe	153–154	f	60	P	461
Me	NO	H	NH_2	240 d	f	*	–	703
		COMe	NH_2	183–185	l	*	–	703

TABLE 92. 4-HYDROXYTHIOPHENE-3-CARBOXYLIC ACID AND ITS DERIVATIVES



X	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	H	145–145.5	v	94	I, M, P, U	418
		124–125	x	–	–	431
	Me	106–107.5	b	98	I, M, P, U	418
	Et	106–107.5	b	94	I, M, P, U	418
	MeCO	173–175.5	l	38	I, M, P, U	418
	PhCO	37–38	l	–	–	431
Cl	Et	125–127/0.35	n	82	I, P	723
NH_2	Me	122.5–123	h	89	I, M, P, U	418
	Et	170–171.5	h	92	I, M, P, U	418, 422
NH-(2-HO–C_6H_4)	Et	230–231	d	70	M, P, U	723
NH-(2-HS–C_6H_4)	Et	73.5–74.5	f	100	M, P	723
NH-(2-MeS–C_6H_4)	Et	83–84.5	d	50	M, P	723
N_3	Et	63–65 d	f	93	I, P	418
$NHNH_2$	Et	104.5–105.5	h	97	I, M, P, U	418
OMe	H	48.5–49.5	b	91	I, M, P, U	418, 422
		79/0.35				418, 422
		76–84/0.1	s	–	–	417, 421
		40–43	s	76	–	417
	Me	66–67	s	93	I, P	417, 421
		68–70	tl	32	I, M, P, U	418
	MeCO	56–58	s	91	–	417, 421
		66.5–67.5	s	89	I, M, P, U	418, 422
		104–106/0.5				418, 422
	$(EtO)_2PO$	124–126/0.2	s	98	–	421
OEt	H	55/0.01	r	8	I, P, U	250
			–	–	K	1120

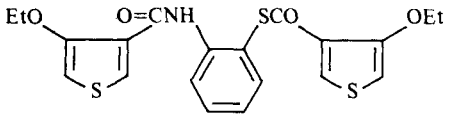
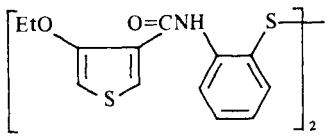
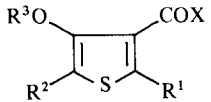
Me	73–75/0.2	s	54	–	333
Et	92–98/0.1	t2	78	I, M, P, U	418, 422
	136–138	d	48	M, P	723
	139–141	f	86	M, P	723

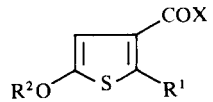
TABLE 93. VARIOUSLY SUBSTITUTED 4-HYDROXYTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	X	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	OEt	H	–	–	–	I	917
	$PhCH_2$	NH-(4-Me-C_6H_4)	H	175–177	a	67	I, P, U	198
			Me	66–68	t1	–	I, P, U	198
		NH-(4-Br-C_6H_4)	H	163–165	a	62	I, P, U	198
			Me	78–80	t1	–	I, P, U	198
		NH-(6-Me-2-pyridyl)	H	166–168	a/h	55	I, P, U	198
			Me	114–116	t1	–	I, P, U	198
		OMe	H	55–57	a	78	I, P, U	198
			PhCO	103–104	a	89	I, P, U	198
	4-Cl-C_6H_4—CH_2	NH-(4-Cl-C_6H_4)	H	179–181	a	64	I, P, U	198
			Me	124–126	a	62	I, P, U	198
		OMe	H	61–63	a	70	I, P, U	198
			PhCO	99–101	l	–	I, P, U	198
	Ph	OEt	H	84–86	s	90	–	424
			Me	55–57	t	92	–	424
				144/0.09				424
Me	H	OMe	H	67–70/0.03	s	75	–	417, 421
		OEt	H	65	r	7	I, P, U	250
				66–68	–	–	I, P	5
				–	–	–	I	917
				–	–	–	K	1120
				–	r	–	P	407, 413
				–	–	–	M	1066
			MeNHCO	111	f	76–94	–	675
			PhNHCO	123	f	61–79	–	675

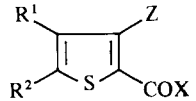
i-Pr	H	OEt	H	–	–	–	I, P	5
t-Bu	H	OEt	H	–	–	–	I, P	5
Ph	H	OH	H	161 d	b	83	–	411
		OEt	H	68	r	8	I, P, U	250
				113/0.001				250
				67–68	r	68	–	411
				–	–	–	I, P	5
				–	–	–	K	1120
				–	–	–	M	1066
				–	–	–	P	407
H	Cl	OH	Et	127.5–129	c	81	I, M, P, U	418
		Cl	Et	95–97/"iV"	n	*	–	422
		NH_2	Et	139–139.5	h	*	–	422
	Br	OH	Et	137–139	c	80	I, M, P, U	418
Me	NO_2	OH	H	102–103	c	59	–	459
H	MeCO	OH	H	256–258	f	70	I, M, P, U	418
			MeCO	179.5–181	l	85	I, M, P, U	418
		OMe	H	120–121	m1	82	I, M, P, U	418
Me	CHO	OEt	H	132–133	f	78	I, P	460
	PhCO	OEt	H	57–58	c	41	I	460
Ph	PhCO	OMe	H	114–116	f	42	I, U	425, 426
4-MeO–C_6H_4	4-Cl-C_6H_4–CO	OMe	H	119–122	f	20	U	425
				119–120	–	–	I, U	426

TABLE 94. 2-SUBSTITUTED 5-HYDROXYTHIOPHENE-3-CARBOXYLIC ACID DERIVATIVES



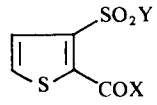
R^1	X	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	OEt	H	82/0.2	r	45	I, P	427
		Et	88–90/0.2	t2	92	I, P	427
		MeCO	62	l	–	I, P	427
	OEt	Me	–	t2	65	Mixture composition by pmr	427
	OMe	Me	–		35		
Cl	OH	Me	152–153	u	57	I, P	56

TABLE 95. 3-MERCAPTOTHIOPHENE-2-CARBOXYLIC ACID DERIVATIVES



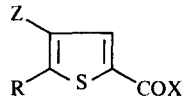
R^1	R^2	X	Z	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	OH	SMe	201–202	i	*	–	1127
				–	–	–	K	946
			SOMe	172	w	–	K, L	946
			SO_2Me	180	w	–	K, L	946
			SEt	146–147.5 d	–	80	–	1128
			S-*t*-Bu	72.5–74.5	i	50	–	32
			S-3-thienyl	203–205 d	u	33	–	117
			S-(2-CO_2H-3-thienyl)	216–218 d	p	96	–	117
		Cl	SMe	143/0.4	–	–	L	1117
			SOMe	68	–	–	L	1117
				151/0.4				1117
			SO_2Me	160/0.3	–	–	L	1117
		NHPh	SMe	86	d	–	L	1117
			SOMe	122	d	–	L	1117
			SO_2Me	164	d	–	L	1117
		OMe	SMe	75	–	–	L	1129
			SOMe	112	–	–	L	1129
			SO_2Me	109	–	–	L	1129
			SPh	63–66	s	70–98	–	421
			S-(2-CO_2Me-3-thienyl)	173–173.5	t1	–	–	117
			S_2-(2-CO_2Me-3-thienyl)	141–145	s	98	–	414
NO_2	H	NH_2	SPh	147	g	*ca* 100	U	1130
		OMe	SPh	132	g	*ca* 100	U	1130

TABLE 96. 2-CARBOXYTHIOPHENE-3-SULFONIC ACID AND ITS DERIVATIVES



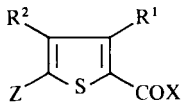
X	Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
OH	OH	107–110	g	76–85	–	445
	NH_2	203–205	b	95	–	445
	NH-t-Bu	161–163	i	50	–	445
Cl	Cl	42–43	n	97	–	445
—NH—		220–222	r	75	–	445
OMe	Cl	60–63	l	92	–	445
	NH_2	121–122	d	80	–	445
	NHMe	115–122	d	–	–	471

TABLE 97. 4-MERCAPTO- AND 4-SULFOTHIOPHENE-2-CARBOXYLIC ACID DERIVATIVES



R	X	Z	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	OH	*t*-BuS	116–118	i	6	–	32
		$MeSO_2$	194–198	w	–	–	1131
NO_2	NH_2	PhS	272	g	–	–	778
	OMe	PhS	105	g	–	–	778
	OEt	PhS	105	g	–	–	778
Cl	H	H_2NSO_2	270	b	74	–	470
	NHMe	$ClSO_2$	132	c	48	–	470
		H_2NSO_2	242–244	d	55	–	470

TABLE 98. DERIVATIVES OF 5-MERCAPTOTHIOPHENE-2-CARBOXYLIC ACID AND OF VARIOUSLY SUBSTITUTED 5-MERCAPTOTHIOPHENE-2-CARBOXYLIC ACIDS



R^1	R^2	X	Z	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	OH	MeS	106	y	62	–	224
				106	i	87	–	1132
				103–104	p	–	–	106
				106–107	u	67–78	–	60
				102–103	i	73	–	60
				–	–	–	K	946
				–	–	–	U	1124
			$MeSO_2$	198.5–201	w	–	–	1132
				201–202	b	80	–	224
				–	–	–	K	946
			EtS	67–68	y	80–90	–	225
				66.5–67	i	77	–	1132
			n-PrS	130.5–132	y	80–90	–	225
			n-BuS	97.5–98.5	y	80–90	–	225
			i-BuS	139–140	y	80–90	–	225
			t-BuS	116.5–118	i	88	P	32
			n-$C_5H_{11}S$	77–78	y	80–90	–	225
			i-$C_5H_{11}S$	69.5–70.5	y	80–90	–	225
			n-$C_6H_{13}S$	80.5–81.5	y	80–90	–	225
			n-$C_7H_{15}S$	86–87.5	y	80–90	–	225
			n-$C_{14}H_{29}S$	84–86	g	46	I, P, U	416
			$PhSO_2$	205–207.5	i	60	–	1133
			4-Me-C_6H_4–SO_2	222–223	p	–	–	1134
		OMe	$MeSO_2$	118	m1	97	–	224

TABLE 98. (*Continued*)

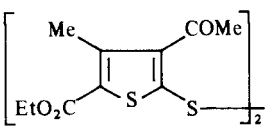
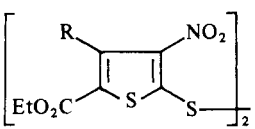
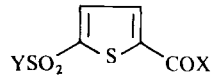
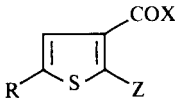
R^1	R^2	X	Z	Melting Point (°C)	Preparation	Yield (%)	Notes	References
	CHO	OEt	NCS–	104–105	g	52	I, M, P	354
		OH	EtS	148–149	i	68	–	38
	CH=NOH	OH	HS	108–109	g	79	I, M, P	354
Me	MeCO	OH	MeS	220–221	b	95	I, M, P	354
		OEt	HS	61–62	r	47	I, M, P	354
			MeS	75–76	r	52	I, M, P	354
			$PhCH_2S$	60–61	r	49	I, M, P	354
	MeC=NOH	OEt	MeS	115–116	f	86	I, M, P	354
			$PhCH_2S$	Oil	f	93	I, M, P	354
	MeC=NOCOMe	OEt	MeS	51–52	l	76	I, M, P	354
	MeC=NOCO(4-MeO—C_6H_4)	OEt	MeS	116–117	l	84	I, M, P	354
	MeC=NOCO(4-NO_2—C_6H_4)	OEt	MeS	122–123	l	86	I, M, P	354
H	NO_2	OMe	3-Br-2-thienyl-S	172–173.5	g	60	–	352
		NH_2	$PhSO_2$	224	g	–	–	1125
		OMe	$PhSO_2$	123	g	–	–	1125
				177–178	w	95	I, M, P	354
			R = H	189–191	r	76	I, M, P	1135
			R = Me	153–155	r	81	I, M, P	1135
			R = Ph	140–143	r	68	I, M, P	1135

TABLE 99. DERIVATIVES OF 2-CARBOXYTHIOPHENE-5-SULFONIC ACID



X	Y	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	Cl	132–133	–	–	–	1136
	NH_2	198–200	d	65	–	1136
	EtNH	129–131	d	92	–	1136
	n-PrNH	164–166	d	60	–	1136
	n-BuNH	157–158	d	75	–	1136
	i-BuNH	177–179	d	96	–	1136
	t-BuNH	158–160	d	74	–	1136
	PhNH	170–172	d	65	–	1136
	Me_2N	164–166	d	90	–	1136
		178	d	–	–	731
	Et_2N	128–130	i	82	I	1137
	N-Pyrrolidyl	176–178	d	42	–	1136
	N-Morpholyl	205	d	90	–	1136
	H_2NNH	165	d	55	–	1136
OEt	Cl	180–185/15	c	40	–	468
	CH_2=$CHCH_2NH$	150–152	d	71	–	468

TABLE 100. 2-MERCAPTOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R	X	Z	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	OH	SMe	152–154	u	86	I, K	1014
		SOMe	210–211	w	61	K, P	1014
		SO_2Me	188	w	39	K, P	1014
	OMe	SMe	–	m1	–	U	1026
		SOMe	81.5–82.5	m1	–	U	1026
		SO_2Me	102–103	m1	–	U	1026
Me	OH	SMe	193.5	i	27	–	1132
				q	63	–	1132
			193–193.5	i	–	–	63
		SO_2Me	161	w	–	Hydrate	63
	NH_2	SO_2Me	190	d	–	–	63
Et	OH	SH	119–121	e	–	–	1138
		SMe	146–147	q	74	–	105
				w	89	–	105
		SEt	126	u	–	–	63
			127.5–128	q	66	–	152
				u	7	–	1132
			126.5–127	t	–	–	63
			127–127.5	u	62	–	1139
			126.5–128	p	–	–	107
		SCH_2CO_2H	202–203	g	76	–	63
			202–203	p	–	–	105
		S-2-Thienyl	142.5–144.5	b	81	P, U	442
	NH_2	SH	98–100	e	76	–	1140
		SEt	65–65.5	d	27	–	1140

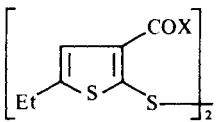
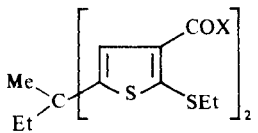
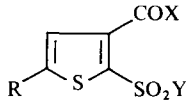
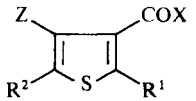
				h	100	–	1140
		SCO(4-NO_2—C_6H_4)	147–148.5	l	69	–	1140
	$N(COPh)_2$	SCOPh	139–140	d + l	–	–	1140
	OMe	SH	116–118 d/3	m2	–	–	1140
	OMe	SMe	44–45	t1	82	–	105
		SEt	133–134/3	t2	86	–	1140
		SCO(4-NO_2—C_6H_4)	152.5–153.5	l	–	–	1140
	OEt	SH	136–140 d/4	e	–	–	1140
		SPh	154–157/13	g	69	P, U	442
		S-2-Thienyl	174–178/40	g	71	P, U	442
Ph	OMe	SEt	67–68	r	28	I, P	322
NO_2	NH_2	SO_2Ph	180–181	g	–	–	1141
	OMe	SO_2Ph	106–107	g	–	–	1141
CHO	OH	SMe	250–260 d	f	69	P	461
	OMe	SMe	120–121	f	58	P	461
		X = OH	210–211 d	w	–	–	1138
		$X = NH_2$	180–181	z	–	–	1140
		X = OH	204.5–206	q	36	–	153
		X = OMe	63–64	m1	–	–	153

TABLE 101. 3-CARBOXYTHIOPHENE-2-SULFONIC ACIDS AND THEIR DERIVATIVES



R	X	Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	OH	OH	118–121	e	80	–	445
		NH_2	202–204	b	95	–	445
		NEt_2	147–149	i	44	I, P	1137
	OMe	Cl	51–54	n	91	–	445
		NH_2	131–133	d	66	–	445
Me	OH	NH-*t*-Bu	178	i	82	I, P	729
Me_3Si	OH	NMe_2	119–121 d	i	10	I, P	1137

TABLE 102. 4-MERCAPTO- AND 4-SULFO DERIVATIVES OF THIOPHENE-3-CARBOXYLIC ACIDS



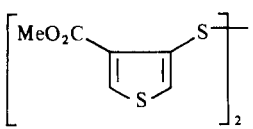
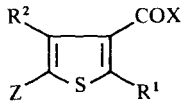
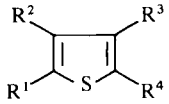
R^1	R^2	X	Z	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	OH	MeS	159.5–160	u	87	–	983
			$MeSO_2$	217–219	w	81	–	19
		OMe	MeS	76.5–78	m1	83	–	983
				158/11				983
			MeCOS	92–95	s	75	–	417
	NO_2	NH_2	PhS	173	g	–	U	1130
		OMe	PhS	81	g	–	U	1130
Me	CHO	OEt	HS	74–75	g	82	I, M, P	354
	CH=NOH	OEt	HS	145–146	k	88	M, P	354
H	H	OH	HO_3S	154	g	80	–	445, 447
			H_2NSO_2	215–216	b	95	–	445
		Cl	$ClSO_2$	78–79	n	96	–	445
		NH_2	H_2NSO_2	218–219	d	–	–	445
		OMe	$ClSO_2$	71	n	94	–	445, 447
				70–72	f	92	–	436
			H_2NSO_2	128	d	85	–	445
				92–95	s	98	–	437

TABLE 103. 5-MERCAPTO AND 5-SULFO DERIVATIVES OF THIOPHENE-3-CARBOXYLIC ACIDS



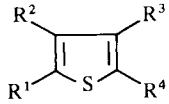
R^1	R^2	X	Z	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	OH	MeS	78–80	u	84	–	983
		OMe	MeS	134–136/9	m1	–	–	983
Me	CHO	OH	MeS	217–218 d	i	55	–	42
		OMe	MeS	138–139	m1	–	I, P	42
Et	CHO	OH	EtS	158–159	i	38	–	42
		OMe	EtS	130–140 d/10	z	*	n	42
Cl	H	OH	$ClSO_2$	148–150	c	53	–	469
			N-pyrrolidyl-SO_2	236–238	c	75	–	469
			N-3,5-di-Me-piperidyl-SO_2	220–221	c	69	–	469

TABLE 104. MISCELLANEOUS BISMERCAPTO DERIVATIVES OF THIOPHENECARBOXYLIC ACIDS



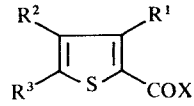
R^1	R^2	R^3	R^4	Melting Point (°C)	Preparation	Yield (%)	Notes	References
MeS	H	SMe	CO_2H	160–161.5	i	75	P	37
	$HOCH_2$	CO_2H	SMe	201–202 d	p	82	–	1075
	CHO	CO_2H	SMe	204 d	z	"A little"	–	1075
		CO_2Me	SMe	173–173.5	m1	–	–	1075
	CH=NOH	CO_2H	SMe	184.5–185.5	k	–	–	1075
EtS	CHO	CO_2H	SEt	167.5–168.5	w	–	–	1075

TABLE 105. SELENIUM SUBSTITUTED THIOPHENE-2- AND 3-CARBOXYLIC ACID DERIVATIVES



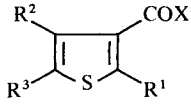
R^1	R^2	R^3	R^4	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	SeBu	CO_2H	103.5–104.5	p	75	–	34
					q	47	–	34
			CO_2Et	34–35	m2	–	–	34
				145/11				34
	BuSe	H	CO_2H	45–46	p	63	–	34
				145–153/1				34
			CO_2Et	129–131/2	m2	–	n	34
		CO_2H	H	110–111	u	64	–	1137
Me	H	CO_2H	SeMe	188–189	p, q	–	–	61
MeSe	H	H	CO_2H	–	–	–	U	1124

TABLE 106. FLUOROTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
F	H	H	OH	175–176	i	75	P	21
	F	H	OH	122–123	u	63	–	21
				–	–	–	P	1142
				–	–	–	F	1143
			OMe	77–78/10	m2	69	n	21
				–	–	–	P	1142
				–	–	–	F	1143
	H	F	OH	145.5–146.5	u	77	–	21
				139–141	i	*	K	542
				–	–	–	F	1143
				–	–	–	K	962
				–	–	–	P	1142
			OMe	78–79/15	m2	61	n	21
					–	–	F	1143
					–	–	P	1142

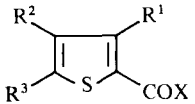
TABLE 107. FLUOROTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(One of R^1–R^3 = F)

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
F	H	H	OH	147.5–148.5	u	75	K, P	1014
			OMe	–	–	–	U	1026
H	H	F	OH	160–161	u	72	–	21
				–	–	–	F	1143
				–	–	–	P	1142
			OMe	80–81/15	m2	59	n	21
				–	–	–	F	1143
				–	–	–	P	1142

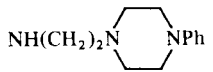
TABLE 108. CHLOROTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES (EXCEPT AMIDES OF 3,4,5-TRICHLOROTHIOPHENE-2-CARBOXYLIC ACID)



(One or more of R^1–R^3 = Cl)

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Cl	H	H	OH	186	j	40	–	445
				183–185	p	–	–	123
				185–186	j	–	–	447, 471
H	Cl	H	OH	131–132	p	100	P, U	111
			OEt	60–62/0.025	c	48	P, U	111
		Et	OH	143	q	37	–	138
	H	Cl	OH	152	b	40	–	183
				153	f	32	–	66
				148	c	20	–	196
				147	b	–	–	195
				146–146.5	–	–	K	952
				152–153	w	–	–	97
				145–146	–	–	K	927
				153–153.5	o	–	–	84
				154	q	–	–	342
				150–151	w	–	–	170
				–	–	–	K	946, 961, 962
				–	–	–	U	220, 956
			Cl	220–225/760	n	100	–	547
				–	–	–	I, P	964
				–	–	–	I	941
			NH_2	178	a	–	I	858
				176	–	–	–	183
				166–68	c	10	–	195, 196

TABLE 108. *(Continued)*

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
				177	b/z	–	–	356
				176	a	–	–	183
			NHMe	168	a	27	I	342
				121–122	a	50	I, P	220
				162–164	h	–	–	873
			Hydrochloride	245–247	–	–	–	873
			NHPh	154	a	75	–	218
				149–151	d	95	–	965
			$NH(4\text{-}MeCONHC_6H_4)$	288	d	100	–	547
			$NH(2\text{-}MeSC_6H_4)$	74	d	*ca* 80	–	888
			$NHNH_2$	151 d	h	–	–	585
			NHN=CHPh	189	k	–	–	585
			N_3	20–30	f	98	–	577
			$NHCONH_2$	218.5–219.5	d	11	P	591
			OMe	15	b	–	–	356
				16.5–18	b	–	–	483
				95–97/7				483
				15	b	–	–	183
				145–147/95				183
			OEt	75/0.3	m2	–	n	927
				234–236/760	l	–	–	585
				68–70/0.25	–	–	L	928
	Me	Cl	OH	199–201	i	89	I, M, P	354
			OEt	86–88/0.2	l	94	–	354
	Br_2CH	Cl	OEt	146–148/0.2	f	94	–	354
CH=CHPh	H	Cl	OH	214–215	u	82	P	507
CH_2CH_2Ph	H	Cl	OH	107–108	e	81	P	507

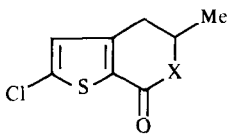
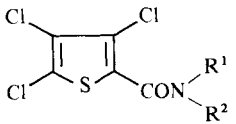
H	CHO	Cl	OEt	122–126/3	b	90	I, M, P	354
	CH=NOH	Cl	OEt	159–160	k	92	I, M, P; E isomer	354
Cl	Cl	H	OH	186–187	i	82	–	39
				187–188	p	100	–	123
	H	Cl	OH	191	p	65	–	128
					y	79	–	128
				186–187	p	100	–	123
H	Cl	Cl	OH	194–196	q	82	–	123
				196–197	w	36	–	173
			Cl	116/13	n	59	–	1144
			NH_2	165	d	81	–	1145
			NH-*n*-Bu	83	d	91	–	1145
			$NH(CH_2)_2OH$	153	d	66	–	1145
			NHPh	181	d	90	–	1145
			NH-2-naphthyl	191	d	85	–	1145
			OMe	60	l	75	–	1145
Cl	Cl	Cl	OH	225	w	30	–	770
				230–231	u	99	–	48, 49
				230	o	60	–	1146
			Cl	124–125/10	n	92	–	1147, 1148
				109–119/0.7–1.1	n	87	–	1146
			$NHNMe_2$	122	d	–	–	1146
			X = O	102–103	z	30	I, P	133
			X = NH	123.5–125	z	52	I, P, U	220

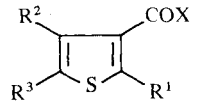
TABLE 109. AMIDES OF 3,4,5-TRICHLOROTHIOPHENE-2-CARBOXYLIC ACID



R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	175	d	93	–	1146, 1147
	Me	97–99	d	55	–	1146, 1147
	s-Bu	72–75	d	62	–	1146, 1147
Me	Me	150–155/3.5	d	61	–	1146, 1147
	n-Pr	150–158/3–4	d	79	n	1146, 1147
	i-Pr	146–154/4–5	d	89	n	1146, 1147
	$(CH_2)_2CN$	85	d	81	–	1146, 1147
	$(CH_2)_3OMe$	174/0.5	d	83	–	1146, 1147
	n-Bu	173–180/4.3–4.6	d	90	n	1146, 1147
	s-Bu	167–172/3.5–3.8	d	86	n	1146, 1147
	i-Bu	152–156/0.5	d	86	n	1146, 1147
Et	Et	37–38	d	90	n	1146, 1147
		118–121/0.2				1146, 1147
	n-Bu	167–170/0.7	d	88	n	1146, 1147
$CH_2CH=CH_2$	$CH_2CH=CH_2$	–	d	62	n	1146
$(CH_2)_2CN$	$(CH_2)_2CN$	135	d	74	–	1146, 1147
$(CH_2)_2CN$	Cyclohexyl	88	d	62	–	1146, 1147
H	Ph	156–158	d	80	–	1146, 1147
	3-CF_3—C_6H_4	131–135	d	67	–	1146, 1147
	2-MeO-5-NO_2—C_6H_3	276	d	91	–	1146, 1147
	2-F—C_6H_4	132–133	d	81	–	1146, 1147
	4-F—C_6H_4	164–167	d	83	–	1146, 1147
	2-Cl-5-CF_3—C_6H_3	149–153	d	69	–	1146, 1147
	4-Cl-3-NO_2—C_6H_3	230	d	87	–	1146, 1147

2,5-di-Cl-C_6H_3	215	d	73	–	1146, 1147
3,4-di-Cl-C_6H_3	181	d	89	–	1146, 1147
2,3,5-tri-Cl-C_6H_2	224	d	82	–	1146, 1147
2-Br-5-CF_3—C_6H_3	181	d	74	–	1146, 1147
2-NO_2—C_6H_4	183–184	d	61	–	1146, 1147
3-NO_2—C_6H_4	208	d	98	–	1146, 1147
2-Naphthyl	157–158	d	78	–	1146, 1147
2-Thiazolyl	246	d	92	–	1146, 1147
5-NO_2-2-thiazolyl	186	d	65	–	1146, 1147
—$(CH_2)_5$—	150–160/0.07	d	89	–	1146, 1147
—$(CH_2)_2O(CH_2)_2$—	99	d	80	–	1146, 1147
—CHEt-$(CH_2)_2$—$CHEtCH_2$—	165–175/0.2	d	82	–	1146, 1147
—CO—O—$(CH_2)_2$—	171–174	d	80	–	1146, 1147
—CO—O—CHMe-CH_2—	144	d	66	–	1146, 1147
—CS—O—CMe_2—CO—	130	d	33		1146, 1147

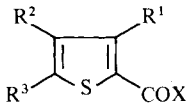
TABLE 110. CHLOROTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(At least one of R^1–R^3 = Cl)

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Cl	H	H	OH	161–163	o	87	P	86
				162–163	u	58	P	54
				162–163	u	68	–	469
				–	–	–	K, P	1014
			NH_2	120–121	d	Good	–	454
			OMe	107–112/15	c	59	P	461
				–	–	–	U	1026
	H	Me	OH	165–168	u	36	P	1126
		CHO	OH	200–202	f	71	P	461
			OMe	96–97	f	65	P	461
H	Cl	H	OH	164	b	23	–	445
				164	j	–	–	447
Me	Cl	H	OH	204–205	b	65	–	459
			OEt	93–94/1	x	68	n	459
		Me	OH	192–194	c	–	P	41
n-Pr	Cl	Me	OH	135–136	u	67	P	41
Me	Cl	CHO	OEt	62–63	c	66	–	459
				62–63	f	53	I, M, P	354
				62–63	f	50	P, U	460
H	H	Cl	OH	163–164	u	47	P	54
				156–157	c	40	–	441
			NH_2	135–136	d	–	–	441
			NHPh	170–171	d	–	–	441
CH_2Cl	H	Cl	OMe	–	–	–	P	955
5-Me-2-MeS–C_6H_3	H	Cl	OH	146–149	–r	26	I, M, P	742
Cl	H	Cl	OH	146–147	u	89	–	40
				147–148	c	*	–	441
			NH_2	115–116	d	Good	–	454

TABLE 111. BROMOTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(At least one of R^1—R^3 = Br)

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Br	H	H	OH	197–198	p	50–60	–	127
				197–197.5	q	49	–	1149
				188–190	p	*	–	108, 109
				193–195	u	70	–	57
				194–195	u	85	–	1051
				190–193	u	38	–	15
				195–197	u	72	–	28
				194–195	w	–	–	171
				–	u	70	I	52
				–	–	–	K	916
				–	–	–	I	51
			Cl	66–68	n	98	I, P, U	1043
				135–137/13				1043
				135–136/13	n	–	I	941
			NH_2	103	w	*ca* 50	–	127
			NHPh	74–75	d	95	–	941
			OMe	47–49	m2	*	–	17
				50	l	50	L	1129
				–	–	–	I	916
			OEt	–	–	–	I	916
			O-t-Bu	–	–	–	I	916
		Me	OH	205–206	i	56	P	30
			NMe_2	128–130/0.5	d	48	P	30
	Me	Me	OH	222–224	u	79	P	1150
			OMe	64–65	m1	78	P	1150

TABLE 111. *(Continued)*

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	Br	H	OH	123	w	50–60	–	127
				122–122.5	p	94	–	115
				120–125	w	88	–	151
				121–122	q	82	–	1149
				122–124	u	69	I	51
				122–123	e	*	–	1151
				113–114	q	*	–	109
				122–123.5	–	–	–	983
				–	–	–	K	946
				–	–	–	M	1017
				–	–	–	U	956
H	Br	H	F	25/0.1	g	–	I, M, P	561
			Cl	82–84/0.4	n	–	I, M, P	561
			NH_2	153–154	w	*ca* 50	–	127
				148–150	–	–	–	51
			OMe	113–115/9	m1	81	n	983
				–	–	–	I	916
			OEt	–	–	–	I	916
			O-*t*-Bu	–	–	–	I	916
		Me	OH	197–200	u	75	P	30
				198.5–199.5	p	–	–	61
				197–199	c	–	U	959
			NMe_2	144–145/1	d	74	I, P	30
		Et	OH	160	q	13	–	138
		t-Bu	OH	198–200	c	72	–	1044
		4-Pyrimidyl	OH	260 d	u	29	P	46
Me	Br	Ph	OH	260.5–262	u	85	–	1044
Ph	Br	Me	OH	256–258	u	73	–	1044
CHO	Br	H	OH	152–154	f	34	P	1152
H	H	Br	OH	142	p	50–60	–	127

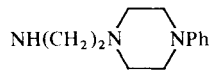
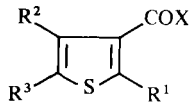
				141–142	z	*	–	1151
				137	f	30	–	66
				140–141	o	–	–	84
				141–142	w	–	–	97, 171
				141–142	–	–	K	952
				115–117	d	27	–	196
				–	–	–	K	473, 946, 961
				–	–	–	M	1017
				–	–	–	U	956
			F	42–45/0.1	g	–	I, M, P	561
			Cl	72–74/0.5	n	*	I, P	561
				126/14	n	–	I	941
				–	–	–	I, P	964
			NH_2	164	w	*ca* 50	–	127
				158–159	f	8	–	196
				165–167	h	–	–	873
			NHPh	119	d	95	–	941
			2-NH(5-NO_2-thiazolyl)	224	d	–	–	892
			$NHNH_2$	144 d	h	–	–	585
			NHN=CHPh	201	k	–	–	585
			N(*i*-Pr)NHi-Pr	118–120	d	–	–	904
			NHN(COMe)-2,4-di-Br-C_6H_3	104.5–105	f	84	I, M	1153
			OMe	–	–	–	I	916
			OEt	134–136/30	l	–	–	585
				87–89/16	–	–	–	928
			O-*t*-Bu	–	–	–	I	916
H	Me	Br	OMe	–	m1	93	P	951
Me	H	Br	OH	168	p	–	–	110
			NH_2	109	d	–	–	110
Ph	Ph	Br	OH	263 d	c/x	70	–	485

TABLE 111. *(Continued)*

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Br	Br	H	OH	203–204	w	–	–	171
				201–203	u	*	I	85
				–	u	34	I	52
			OMe	137–137.5	m2	72	P	1154
				–	–	–	P	1025
	H	Br	OH	210–212	u	28	I	51
				210–212	u	36	I	57
				211–212	w	–	–	171
				–	–	–	I	52
			F	90–92/5	g	–	I, M, P	561
			Cl	126–128/0.1	n	–	I, M, P	561
			OMe	–	–	–	I	916
			OEt	–	–	–	I	916
			O-t-Bu	–	–	–	I	916
H	Br	Br	OH	225.5–228	p	79	–	115
				227–228	q	27	–	1149
				–	–	–	I	57
				–	–	–	M	1017
			Cl	36–38	n	80	–	889
			OMe	81–82	m2	78	–	457
				–	–	–	I	916
			OEt	–	–	–	I	916
			O-t-Bu	–	–	–	I	916
Br	Br	Br	OH	–	–	–	M	1017
			OMe	–	–	–	I	916
				–	–	–	P	1025
			OEt	–	–	–	I	916
			O-t-Bu	–	–	–	I	916

TABLE 112. BROMOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



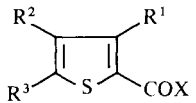
(Any or all of R^1–R^3 = Br)

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Br	H	H	OH	176–178	o	81	P	86
				180	p	50–60	–	127
				178–179	u	46	P	53
				–	–	–	K, P	1014
			NH_2	142	w	*ca* 50	–	127
				135–137	d	Good	–	454
			OMe	114–115/4	m1	–	–	1040, 1155
				–	–	–	U	1026
		Et	OEt	114/40	c	91	P	442
H	Br	H	OH	159	p	50–60	–	127
				157–159	u	*	I	85
				153–156	u/z	17	–	15
				158–159	–	–	–	983
				–	u	80	I	52
				–	–	–	M	1017
			NH_2	146	w	*ca* 50	–	127
				136–138	–	–	–	85
			OMe	48.5–50	m1	84	–	983
				126–128/10				983
Me	Br	Me	Cl	75–76/0.05	–	–	–	1046
			OMe	138–139/8	m1	–	n	1156
H	H	Br	OH	139	p	*	–	127
				117–118	c	69	–	441
				–	–	–	K	464
			NH_2	146	w	*ca* 50	–	127

TABLE 112. *(Continued)*

R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
				100–101	d	–	–	441
			NHPh	142–143	d	–	–	441
Ph	Me	Br	OH	165–166	c	–	–	1046
			Cl	145/0.4	n	–	–	1046
Br	H	Br	OH	178	p	50–60	–	127
				175–176	c	*	–	441
				176–177	w	–	–	171
				–	–	–	M	1017
			NH_2	140–141	w	*ca* 50	–	127
				147–148	d	Good	–	454
			OMe	61–62	m2	–	–	1157
				60–61	m2	–	–	457
			OEt	94–96	l	–	U	1157
H	Br	Br	OH	192–194	c	*	–	85
			NH_2	166–168	–	–	–	85
			OMe	–	–	–	P	1025
Br	Br	Br	OH	202–204	c	*	–	85
				203–205	c	80	–	444

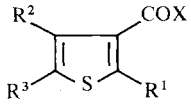
TABLE 113. IODOTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(Any or all of R^1–R^3 = 1)

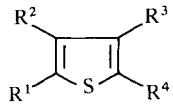
R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
I	H	H	OH	199–201	u	45	P	54
				197.5–198	u	63	–	29
				200	p	60	–	129
			Cl	74.5–75	n	76	–	29
				96	–	–	–	1117
				96/1				1117
			NH_2	140	w	62	–	129
			NHPh	106	d	–	L	1117
			OMe	54	l	–	L	1129
H	I		5-CO_2Me-2-thienyl	OMe	127.5–129	c	65	–	443
		H	OH	116	p	50	–	129
				115–117	u	53	P	443
			NH_2	170	w	72	–	129
			OMe	41.5–43	m1	90	I, P	443
	H	I	OH	133–134	c	*	–	97
				135	p	60	–	129
				132–133	q	30	–	452
				133	f	5	–	196
				132–134	b	80	P	443
				133	f	–	–	89
				–	–	–	U	956
			Cl	–	–	–	I	941
			NH_2	182	w	55	–	129
			OMe	88–89	c	40	I, P	443
			OCH_2CO-4-Br-C_6H_4	145	–	–	–	89
I	I	H	OMe	–	–	–	P	1025
		I	OH	240–243 d	o	–	–	76
			OMe	–	–	–	P	1025

TABLE 114. IODOTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



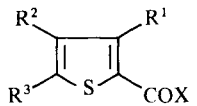
R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
I	H	H	OH	178	p	58	–	129
				178–179	–	–	K, P	1014
			NH_2	160	w	60	–	129
			OMe	–	–	–	I	1026
H	I	H	OH	170	p	51	–	129
			NH_2	184	w	54	–	129
Me	I	Me	OH	199	u	72	–	40
			OMe	33.5–34.5	c	60	–	1036
Ph	I	Ph	OH	210–211	–	–	–	29
			OMe	89.5–90	m1	24	–	29
H	H	I	OH	145	p	45	–	129
			NH_2	162	w	61	–	129

TABLE 115. THIOPHENECARBOXYLIC ACIDS AND ESTERS WITH MIXED HALOGEN SUBSTITUENTS



R^1	R^2	R^3	R^4	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Cl	H	Br	CO_2H	198–199	u	67	–	54
	Br	H	CO_2H	206–207	u	62	–	54
I	Br	CO_2H	H	204–206	c	84	P	55
		CO_2Me	H	89–91	m1	–	P	55
				–	–	–	P	1025
Cl	I	CO_2H	Cl	163–164	c	21	–	40
I	Br	CO_2H	I	244–246	c	89	I	55
		CO_2Me	I	90–92	m1	–	P	55
				–	–	–	P	1025

TABLE 116. THIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES WITH BOTH HALOGENO AND NITRO SUBSTITUENTS



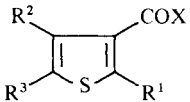
(One of R^1—R^3 = NO_2 and one = halogeno)

R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	NO_2	Cl	OH	156.5–157.5	b	*	–	483
				156–157	c	58	–	452
			NH_2	209	c	–	–	1125
			OMe	84.5–86	c	53	–	1036
				83–84	c	*	–	483
			OEt	47–48	c	40–50	–	1089
		Br	OH	172–173	c	37	–	456
				172–173	b	–	–	108
				172–173	c	70	–	452
			NHPh	212–213	d	82	–	1158
			NH-4-Cl-C_6H_4	235–237	d	–	–	1158
			NH-4-NO_2—C_6H_4	250–252	d	–	–	1158
			OMe	99	–	–	–	110
				98.5–102	c	72	–	108
				–	–	–	I	916
				–	–	–	U	956
			OEt	87	c	–	–	769
					–	–	I	916
			O-t-Bu	54.5–55	–	–	I	916
			O-2-Cl-C_6H_4	143.5–144.5	1	–	–	1158
			O-4-Cl-C_6H_4	99–102	1	75	–	1158
			O-2,4-di-Cl-C_6H_3	144–145	1	54	–	1158
			O-2-NO_2—C_6H_4	158–162	1	–	–	1158
			O-4-NO_2—C_6H_4	168–170	1	–	–	1158
		I	OH	199–200	–	–	–	452

TABLE 116. (*Continued*)

R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
			NH_2	237	c	–	–	1125
Me	NO_2	Br	OH	215	b	–	–	110
			NH_2	166	c	–	–	110
			OMe	105	m	–	–	110
Br	NO_2	H	OH	209–210	p	–	–	133
				214–215	p	*	–	109
				214–215	p	44	–	108
			NH_2	204–205	d	–	–	1130
			OMe	101–102	m	*	–	133
NO_2	NO_2	Br	OH	135–136	c	–	–	458
H	Br	NO_2	OH	177	b	–	–	778
			NH_2	187	d	–	–	778
Br	H	NO_2	OH	170–172	p	–	–	133

TABLE 117. THIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES WITH BOTH HALOGENO AND NITRO SUBSTITUENTS



(At least one of R^1—R^3 = NO_2 and one = halogeno)

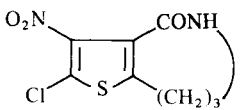
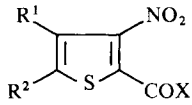
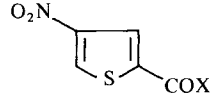
R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	Cl	NO_2	OEt	81–82	c	87	–	459
$(CH_2)_3NH_2$	NO_2	Cl	OH	192–194 d	f	–	–	227
		Hydrochloride		204–206 d	b	–	–	227
Br	H	NO_2	OH	160	b	–	–	1105
			NH_2	212	d	–	–	1105
			OMe	89	c	–	–	1105
H	Br	NO_2	OH	236–238	c	*	–	85
			NH_2	188–190	–	–	–	85
$(CH_2)_2CO_2H$	NO_2	Br	OH	206–207	w	*	–	1159
$(CH_2)_3NH_2$, HCl	NO_2	Br	OH	209–210	b	–	–	1159
$(CH_2)_3NHCOMe$	NO_2	Br	OH	210–211 d	d	–	–	1159
				186–187	c	79	–	227

TABLE 118. 3-NITROTHIOPHENE-2-CARBOXYLIC ACID AND RELATED COMPOUNDS



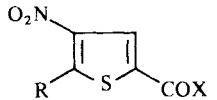
R^1	R^2	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	OH	137	w	–	–	1160
		OMe	50–51	c	*	P	122
	1-Adamantyl	OMe	131–132	f	45	P	122

TABLE 119. 4-NITROTHIOPHENE-2-CARBOXYLIC ACID AND ITS DERIVATIVES



X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	154–155	b	–	–	108
	150–154	b	*	–	134
	152	b	100	–	183, 184
	154	b	57	–	92
	153–154	–	–	K	952
	150–152	b	35	–	186
	–	–	–	K	464, 946
	–	–	–	U	956
NH_2	149–151.5	d	*	–	137
$NH(CH_2)_2CN$	208–208.5	d	90	–	92
$NH(CH_2)_2C(=NH)NH_2$, HCl	240–241	f	80	–	92
OMe	98–100	p	*	P	122
	98–99	m2	–	–	1161
	101	p	83	–	125
	99–100	e	–	–	133
	100–101	m2	38	–	108
	99–100	m	75	–	134
	–	–	–	P	1025
OEt	60–62	f	50	I	1162
	75/0.05				1162
	58–58.5	m	69	–	92
O-(2-MeCO—C_6H_4)	120	l	87	–	628

TABLE 120. 5-SUBSTITUTED 4-NITROTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

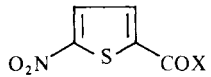


R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
Me	OH	179–180	c	*	–	137
		179–180	c	66	–	186
		180–181	c	46	–	451
		180.5–181.5	c	61	–	449
		181–181.5	c	76	–	452
		181	c	51	–	1162
	Cl	45.5–47.5	n	62	–	449
		124–127/3				449
	NH_2	223–224	d	*	–	137
	$NH(CH_2)_2CN$	168–171	d	88	–	135
	OMe	75–76	f	50	P	122
		25–30/0.09	m2	99	–	1162
		–	–	–	U	956
	OCH_2Ph	48–50	l	56	–	135
	OEt	158–161/10	–	–	–	449
		93–99/0.005	m2	80	–	1162
		122/1.6	m2	81	I	1163
	$O(CH_2)_2NEt_2$, HCl	172.5–174	l	72	–	449
	$O(CH_2)_3N$-*n*-Bu_2, HCl	93–95	l	62	–	449
Et	OH	156–157	c	45	–	186
i-Bu	OH	118–119.5	c	–	–	186
EtO_2CCOCH_2	OEt	143–144	f	59	I	1163
$HO_2C(CH_2)_3$	OH	158–160	c	58	–	452
$MeO_2C(CH_2)_3$	OH	95–96.5	p	56	–	486, 487
$MeO_2C(CH_2)_4$	OH	37–38.5	p	76	–	486, 487

TABLE 120. (*Continued*)

R	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
1-Adamantyl	OMe	101–103	f	47–55	P	122
PhCH≡CH	OMe	106–107	k	86	P, U	1164
4-Me_2N–C_6H_4–CH=CH	OMe	175–176	k	66	I	1162
4-Me-C_6H_4–CH≡CH	OMe	146–147	k	37	–	1162
2-MeO–C_6H_4–CH≡CH	OMe	166–168	k	72	–	1162
3-MeO–C_6H_4–CH≡CH	OMe	118–119	k	67	–	1162
4-MeO–C_6H_4–CH≡CH	OMe	139–140	k	88	P, U	1164
2,4,6-tri-MeO–C_6H_2–CH≡CH	OMe	224–226	k	70	–	1162
2-Cl-C_6H_4–CH=CH	OMe	175–176	k	72	–	1162
4-Cl-C_6H_4–CH=CH	OMe	147–148	k	89	P, U	1164
2-Thienyl-CH≡CH	OH	230–235	b	84	I	453
	OMe	135.8–138	k	85	–	453
		139–140	k	59	P, U	1165
3-Thienyl-CH=CH	OMe	139–140	k	74	P, U	1165
5-Cl-3-thienyl-CH=CH	OMe	177–178	k	91	P, U	1165
4-Pyridyl-CH=CH	OMe	168–170	k	30	–	1162
$Ph(CH=CH)_2$	OMe	156–157	k	9	P, U	1165
CHO	OH	172–174	b	98	I	1162
4-Me_2N–C_6H_4–N=CH	OH	186–187 d	k	70	I, M	1162
CHO	OMe	47–49	g	91	I	1162
		110/0.001				1162
PhN=CH	OMe	129–130	k	85	I, M	1162
4-Me_2N–C_6H_4–N=CH	OMe	175–176	k	88	I	1162
4-Me_2N–C_6H_4–N(O)=CH	OMe	230 d	k	–	I, M	1162
CHO	OEt	35–36	g	46	I, M	1162
		90/0.01				1162
4-Me_2N–C_6H_4–N(O)=CH	OEt	209 d	k	–	I, M	1162
3,5-di-Me-1-pyrazolyl	OH	214	k	94	–	1089
3-Me-5-Ph-1-pyrazolyl	OMe	107	k	62	–	1089
5-CO_2Me-3-NO_2-2-thienyl-Hg	OMe	202	f	49	–	1089

TABLE 121. 5-NITROTHIOPHENE-2-CARBOXYLIC ACID AND ITS DERIVATIVES



X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
OH	156	q	23	–	131
	157–158	p	98	–	135
	160.5–161.5	w	70	–	519
	157–158	p	–	–	132
	149	w	–	–	737
	155	b	Excellent	–	185
	158	b	55	–	92
	157	b	*	–	183
	156–159	w	–	–	1166
	158	w	–	–	155
	–	–	–	D	1085
	–	–	–	K, P	962
	–	–	–	P	927, 946, 952, 1167
	–	–	–	U	956
Cl	51–52	n	90	–	519
	90–91/0.4				519
	52–53	–	–	–	183
	144/14				183
	–	–	–	I	941
	–	–	–	I, P	964
	–	–	–	P	1167
NH_2	185–187	b	–	–	190
	188.5–190	d	*	–	137
NHCOMe	196–197	d	–	–	190
$NHCONH_2$	216–218	d	67	–	182
$NHCSNH_2$	205–206	d	64	–	182

TABLE 121. *(Continued)*

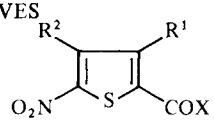
X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
$NHCH_2Ph$	117–118	d	95	–	182
	127–128	d	–	–	190
$NHCH_2$-(2-thienyl)	116–118	d	–	–	190
$NHCH_2CO_2Et$	122–124	d	42	–	182
	119–120	d	82	–	870
$NH(CH_2)_2NEt_2$, HCl	200–202	d	60	–	182
$NH(CH_2)_2OH$	148	d	–	–	190
NHCHMe-(5-NO_2-2-thienyl)	159–160	d	–	–	190
NHCHMe-(3,5-di-NO_2-2-thienyl)	188–189	d	–	–	190
$NHCH(CH_2Ph)CO_2Et$	150–151	–	83	–	870
$NHCH(CH_2OH)CO_2Et$	126–127	–	68	–	870
$NH(CH_2)_2$-(3,4-di-MeO-C_6H_3)	139–140	d	*	–	604
$NHCH(CH_2OH)CHOH$-(4-NO_2–C_6H_4)	152–156	d	–	–	190
$NHCH_2CH{=}CH_2$	113–114	d	85	–	182
$NH(CH_2)_2CN$	133–134	d	76	–	135
	133–134	d	78	–	92
$NH(CH_2)_2C(=NH)NH_2$, HCl	209–210	f	79	–	92
$NHCHMe(CH_2)_3NEt_2$	99–101	d	*	–	1168
Hydrochloride	133–134	–	–	–	1168
N-pyrrolidyl	179–180	d	75	–	182
N-piperidyl	94–95	d	75	–	182
N-morpholyl	89–90	d	80	–	182
N,N'-Et-piperazyl, HCl	262–264	d	56	–	182
NHPh	189–191	d	–	–	190, 965
NH-(4-$CN(CH_2)_2NH$–CO–C_6H_4)	260–263 d	d	75	–	98
NH-(3-Br–C_6H_4)	232–234	d	89	–	182
NH-(3-NO_2–C_6H_4)	204–205	d	80	–	182
NH-(4-NO_2–C_6H_4)	274–275	d	90	–	182
NH-2-thiazolyl	> 330	d	80	–	182

	ca 300 d	d	*	–	1168
	> 300	d	–	–	190
NH-(4-Me-2-thiazolyl)	260–262	–	–	–	356
NH-(5-NO_2-2-thiazolyl)	218	–	–	–	356
NH-2-pyridyl	198–200	d	65	–	182
	201–202	d	–	–	190
NH-(3-Me-2-pyridyl)	222–224	d	–	–	356
NH-(4-Me-2-pyridyl)	208	–	–	–	356
NH-(3-CO_2H-6-pyridyl)	290–300 d	d	*	–	1168
NH-2-pyrimidyl	207.5–208	d	*	–	1168
NH-(4-Me-2-pyrimidyl)	197–198	d	–	–	190
$NHNH_2$	164	–	–	–	908
N_3	61–62	f	70	–	966, 967
	62	g	97	I, P	1167
	61–63	g	93	I	124
OCO-(5-NO_2-2-thienyl)	134–135.5	g	–	I	124
OMe	74–75	m2	*	–	124, 130, 183, 1084
	76	m	97	–	125
	78–79	m1	85	P	122
	75–76	–	–	D	1085
	–	–	–	I	916, 917
OCH_2Ph	86–87	l	*	–	183
	90–91	l	–	I	124
OEt	63–64	–	–	–	928
	124/0.15				928
	64	c	76	–	92
	–	–	–	I	916
$O(CH_2)_2Cl$	185–190/12	l	–	–	1169
$O(CH_2)_2OMe$	185–190/12	l	–	–	1169
$O(CH_2)_2CN$	80–82	l	–	–	1169
O–*n*–Pr	155–158/12	l	–	–	1169
O–*n*–Bu	176–178/12	l	–	–	1169

TABLE 121. *(Continued)*

X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
O-*t*-Bu	97–98	m	–	I	916
O-*n*-C_5H_{11}	179–183/12	l	–	–	1169
OPh	93–94	l	–	I	124
O-(2-Me–C_6H_4)	57–58	l	–	I	124
O-(3-Me–C_6H_4)	62.5–63.5	l	–	I	124
O-(4-Me–C_6H_4)	93–94	l	–	I	124
O-(3-Cl–C_6H_4)	92–93	l	–	I	124
O-(4-Cl–C_6H_4)	99.5–100.5	l	–	I	124
O-(2-MeCO–C_6H_4)	95	l	60	–	628

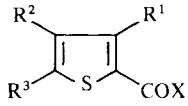
TABLE 122. 3- AND 4-ALKYL-5-NITROTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



($R^1 = R^2$ = alkyl)

R^1	R^2	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	H	OH	183	p	*	–	137
		NH_2	164–166	d	*	–	137
H	Me	OH	181–182	p	*	–	137
		NH_2	169–170	d	*	–	137
		OMe	89–90	f	35	P	122

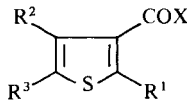
TABLE 123. DINITROTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(Two of R^1–R^3 = NO_2)

R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
NO_2	NO_2	H	OMe	86–88	c	14	P	122
	H	NO_2	OH	–	w	–	–	155
			NH_2	146	d	76	–	190
			NHCOMe	139	d	–	–	190
			OMe	61–62	c	–	–	190
				Oil	c	56	P	122
	Me	NO_2	OMe	63–64	f	35	P	122
H	NO_2	NO_2	OMe	57–58	c	*	P	122

TABLE 124. NITROTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(One of R^1–$R^3 = NO_2$)

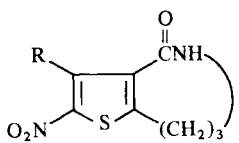
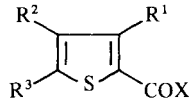
R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
NO_2	H	H	OH	156–157	w	*	–	176
			NH_2	184–185	d	–	–	176
Ph	NO_2	Ph	OEt	90–92	c	70	I, P	260
H	H	NO_2	OH	147	w	*	–	176
				145–146	c	*	–	441
				–	–	–	K	464
			NH_2	163–164	d	*	–	137
				166–167	c	67	–	454
				162–163	d	–	–	176, 441
			NHPh	179–180	d	–	–	441
Me	$EtO_2CCH(CN)$	NO_2	OEt	90–91	g	55	–	1170
								
		R = H		168–169	c	78	–	227
		R = Me		185–186	c	72	–	227

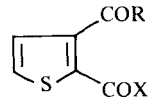
TABLE 125. VARIOUS FORMYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(At least one of R^1–R^3 = CHO or a derivative of CHO)

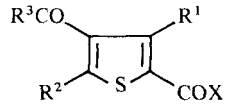
R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
CHO	H	H	OH	130–131	u	44	–	26
				130–131	i	78	I, P	100
				–	f	75	I, P, U	101
			NH_2	172	–	–	–	221
			OMe	56	b	–	I	462
				61–62	m	68	I, P	100
				140–141/20				100
				–	–	–	I, P, U	101
			OEt	Oil	b	–	I	462
CH=NOH	H	H	OH	210	k	75–95	–	221
			NH_2	225	k	75–95	–	221
			OMe	125	–	–	–	221
H	CHO	H	OH	156–159	f	Low	I, P, U	101
			OMe	61	b	–	I	462
			OEt	45	b	–	I	462
	H	CHO	OH	166–167	i	60	–	1171
				168–169	i	*	–	113
				165–166	w	65	–	944
				171–172	i	78	I, P, U	101
			NH_2	187	f	10	–	10
			OMe	88–89	m2	–	I, P, U	101
				82	m2	–	I	462
			OEt	59	b	–	I	462
CHO	CHO	H	OH	154	p	50–70	P	112
	H	CHO	OH	183	p	50–70	P	112

TABLE 126. 3-ACYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



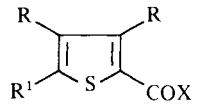
R	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	OH	148	–	–	X-ray structure	1172
		151	i	*	I	24
Ph	OH	154–155	i	70	I, P, U	27
		146–148	b	87	–	161
		148	i	43	–	23
	Cl	–	n	–	I, P	27
	OMe	126–128	a	38	–	161
5-CO_2H-2-thienyl	OH	198–203	i	93	P	25

TABLE 127. 4-ACYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	Me	Me	OH	174.5–175.5	w	71	–	163
	H	2-HO–C_6H_4	OH	161–163	f	44	–	1173
			OMe	79–80	m1	57	P	1173
		2-HO-6-MeO–C_6H_3	OH	202	f	80	–	1173
			OMe	125–126	m1	60	P	1173
Me	H	Me	OH	188–189	–	–	–	244
			OEt	89	–	–	–	244

TABLE 128. 5-ACYLTHIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(R^1 = acyl or acyl derivative)

R	R^1	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	MeCO	OH	203.5–204.5	w	35	–	175
			213	i	70	–	6
			203–206	b	68	–	463
			204–205	i	–	–	1174
			205–206	p	–	–	54
			203–204	–	–	–	643
			–	–	–	K	761
	MeC=NOH	OH	236	–	–	–	175
	MeC=NNH-(2,4-di-NO_2-C_6H_3)	OH	283	–	–	–	6
	MeCO	Cl	77–79	n	90	–	463
		NH_2	226–228	d	93	I, P	1175
		NHPh	206–207	b	90	–	6
	$MeC(OCH_2)_2$	NHPh	127.5–128	f	65	–	6
	MeCO	OMe	137–138	m2	–	–	1174
		OEt	49–51	c	8	–	463
			110/0.3				463
			54–54.5	m2	56	–	465
			53.5–54.5	m	74	–	643
	$MeC(OEt)_2$	OEt	124–125/0.7	f	80	n	643
	EtCO	OH	184–185	p	97	–	113
	$BrCH_2CO$	NH_2	188–189 d	f	81	I, P	1175
		OMe	122–123	f	91	–	1174

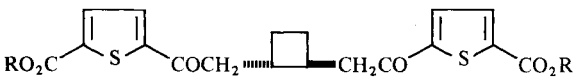
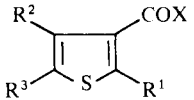
	$CNCH_2CO$	OH	204–207 d	b	–	–	648
		OMe	143–145	f	*	–	648
		$NHCO(3\text{-}CH(OCH_2)_2\text{-}C_6H_4)$	208–210	d	–	–	648
	$5\text{-}CO_2H\text{-}2\text{-thienyl-CO}$	OH	>300	w	21	–	147
	$5\text{-}CO_2Me\text{-}2\text{-thienyl-CO}$	OMe	210	f	36	I, P	210
	$5\text{-}CO_2Et\text{-}2\text{-thienyl-CO}$	OEt	136–137	g	37	–	147
Ph	PhCO	OH	186.5	b	–	–	485
		OMe	185–187	–	–	–	485
		R = H	250–252	f	60	I, M, P	1061
		R = Me	170–171	–	–	I, M, P	1061

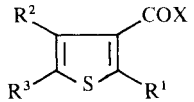
TABLE 129. VARIOUS FORMYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(At least one of R^1—R^3 = formyl or a formyl derivative)

R^1	R^2	R^3	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
CHO	H	H	OH	130–132	u	75	I, P, U	101
CH=NNH-(4-NO_2-C_6H_4)	H	H	OH	319	k	90	–	24
CH=NNHCOPh	H	H	OH	256	k	75	–	24
CH=NNH-tos	H	H	OH	242	k	80	–	24
CHO	H	H	NH_2	190	f	10	–	10
				178	–	–	–	221
			OMe	67	b	–	I	462
				68–70	m	61	I, P, U	101
			OEt	Oil	m	–	I	462
		Et	OH	129–131	i	23	P	42
H	CHO	H	OH	136–138	u	75	I, P, U	101
			OMe	57	m2	–	I	462
				55–57	m	62	I, P, U	101
			OEt	69	m2	–	I	462
	H	CHO	OH	185–187	u	86	I, P, U	101
			OMe	114–116	m2	73	I, P, U	101
				116	m2	–	I	462
			OEt	51	m2	–	I	462
CHO	H	CHO	OH	197	p	50–70	P	112

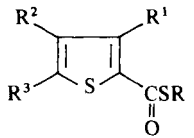
TABLE 130. VARIOUS ACYLTHIOPHENE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



(One of R^1—R^3 = acyl or a derivative of acyl)

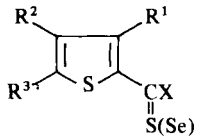
R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
COMe	H	H	OH	108	–	–	X-ray structure	1172
				108	u	56	–	23
COPh	H	H	OH	121–122	u	58	I, P, U	27
				104	p	30–44	–	23
H	MeCO	H	OH	185	–	–	X-ray structure	1172
				185	f	32	–	23
Me	MeCO	Me	OH	155–156	b	–	–	144
			OEt	130–132/4	c	55	–	144
				–	–	–	I	1058
H	PhCO	H	OH	132	c	63	–	1172
			Cl	Oil	n	–	I	466
	H	MeCO	OH	199–200	w	96	–	177
				200–201	u	65	–	643
			OEt	79.5–80.5	c	25	–	465
				140–144/5				465
				69–70	m	91	–	643
				150–152/6	c	*	–	464
		$MeC(OEt)_2$	OEt	98–100/0.2	f	75	–	643
		$MeC{=}NNHCONH_2$	OEt	245–246	–	–	–	464
Me	H	MeCO	OH	167–168	u	76	P	41
1-Me-2-Ph-3-indolyl	Me	PhCO	OEt	154	–r/r	50–80	I, U	257

TABLE 131. MERCAPTOESTERS OF THIOPHENE-2-CARBOXYLIC ACIDS



R^1	R^2	R^3	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	H	Me	125–126/19	c	–	–	739
			C_6H_4-4-Me	56–59	l	45	I, M, P	742
OMe	H	Me	Me	112	w	–	I, P	406
H	Br	Br	C_6H_4-4-Me	153–154	l	83	I, M, P	742
Br	H	H	Ph	60	l	37	I, M, P	742
			C_6H_4-4-Me	81–82	l	77	I, M, P	742
			2-pyridyl	94–96	l	81	I, M, P	742
			4-pyridyl	80–82	l	17	I, M, P	742
	Br	H	C_6H_4-4-Me	144–146	l	67	I, M, P	742
H	H	4-MeO–C_6H_4–C(=O)S	C_6H_4-4-MeO	133	l	–	Liq. cryst.	1054
	4-MeO–C_6H_4–C(=O)S	H	C_6H_4-4-MeO	181	l	–	Liq. cryst.	1054

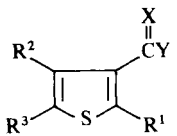
TABLE 132. THIONO AND SELENO THIOPHENE-2-CARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	X	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	H	Cl	82 d/1.5	n	7	U	750
				65–68/0.5	f	40–50	U	745
			NH_2	108	f	–	–	737
				110–111	f	–	D	1176
				107–109	f	30	I, P	199
			NH_2, MeI	206	g	–	–	737
				204	g	85	–	738
			NMe_2	138/9	f	75–85	–	877
			N-piperidyl	89	d	–	–	750
			$NHCO_2Et$	107–108	c	81	I, P	199
			NHCONHPh	225–226 d	f	33	I, P	199
			$NHCONHSO_2Me$	234	f	19	I	1177
			$NHCONHSO_2Ph$	204	f	56	I	1177
			$NHCONHSO_2(4\text{-}Me\text{-}C_6H_4)$	199	f	64	I	1177
			$NHCONHSO_2(4\text{-}Cl\text{-}C_6H_4)$	207	f	43	I	1177
			$NHNH_2$	156	f	–	–	1178
				155–156	f	60	–	747
			$NHN{=}CH\text{-}(4\text{-}NHCOMe\text{-}C_6H_4)$	205	k	–	–	747
			NHN=CH-2-thienyl	138	k	–	–	747
			$NHNMe_2$	94–95	f	63	–	748
			$NHNEt_2$, HCl	155–156	f	45	–	748
			OEt	115–116/9	f	73	–	1179
			SMe	120/1	g	50	–	743

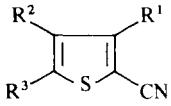
				158/12	o/g	68	–	744
				–	–	–	U	1180
			SCH_2CO_2H	123–124	g	26	–	746
			SPh	Oil	c	84	U	749
		Me	NH_2	170–172	f	90	–	820
		Et	NH_2	143	f	82	–	820
		Pr	NH_2	128–130	f	90	–	820
		$(CH_2)_3NCS$	$NH(CH_2)_3$-2-thienyl	71–72	c	20	I	1181
		MeO	NH_2	153	f	–	–	737
			NH_2, MeI	195	g	–	–	737
		Cl	NH_2	192	f	–	–	737
			NH_2, MeI	195	g	–	–	737
		NO_2	NH_2	188–189	f	90	–	1182
		$(EtO)_2CH$	NH_2	83	f	57	–	10
$CH(OEt)_2$	H	H	NH_2	75	f	62	–	10
NH_2	CO_2Et	Ph	OEt	89	r	46	I, P	736
OMe	H	Me	SMe	80	–r	–	P	406
OH	CO_2Et	Me	OEt	64	r	37	I	736
OEt	CO_2Et	Me	OEt	82	g	–	I	736
OH	CN	Ph	OEt	260	r	19	I	736
OEt	CN	Ph	OEt	100	g	–	I	736
NH_2	CN	Me	OEt	155	r	58	I	736
$-O-CH_2-O-$		NH_2CS	NH_2	203 d	f	100	I	482
N(*i*-Pr)Ph	H	Ph(i-Pr)N	NH-(4-NO_2-C_6H_4)	175–176	c	79	–	1094
			NH-(3,4-di-Cl-C_6H_3)	155–156	c	82	–	1094
$NHPS(OMe)_2$	H	Ph	SMe	94	–r	–	P	709
NHPS(OMe) (OEt)	H	Ph	SMe	88	–r	–	–	709
2-Thienyl-C(=Se)NH_2				105	f	48	P	822

TABLE 133. SULFUR AND SELENIUM ANALOGUES OF THIOPHENE-3-CARBOXYLIC ACIDS



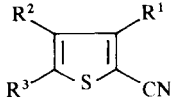
H	R^2	R^3	X	Y	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	H	$\overset{+}{N}H_2\bar{I}$	SMe	163	g	82	–	738
			Se	NH_2	108	f	42	P	822
			O	SPh	65	l	86	I, M, P	742
				S-(4-Me–C_6H_4)	70–71	l	88	I, M, P	742
				S-(2-Pyridyl)	48–49	l	81	I, M, P	742
				S-(4-Pyridyl)	107–108	l	80	I, M, P	742
		CH_2Ph	S	OEt	–	z	10	P	252
	Br	H	O	S-(4-Me–C_6H_4)	82–84	l	44	I, M, P	742
$CH(OEt)_2$	H	H	S	NH_2	73	f	54	–	10
NH_2	H	H	S	NH_2	119–121	f	84	I, U	358
					120–124	r	88	–	735
	Me	H	S	NH_2	115–118	f	61	–	358
		Me	S	NH_2	135–138	r	*	–	735
	$-(CH_2)_4-$		S	NH_2	156–158	f	88	U	358
					154–156	r	80	–	735
	Et	Me	S	NH_2	126–128	r	44	–	735
Cl	H	Cl	O	S-(4-Me–C_6H_4)	85–86	l	85	I, M, P	742

TABLE 134. 2-CYANOTHIOPHENE, ITS ALKYL, SUBSTITUTED ALKYL AND ALKENYL DERIVATIVES



R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	H	81/16	k	73–95	–	774
			192/760	f	48	–	773
			92–94/27	g	85	I, P	763
			88/19	c	–	–	782
			77–78/14	c	–	–	781
			88–90/21	g	*	–	1183
			89/20	k	88	n	184
			72/12	k	89	g	765,1184
			77–78/14	c	66	–	783
			196/760	k	–	U	1185
			–	–	–	d, n, U	911
			–	–	–	P	1186
			–	–	–	I	930
			–	–	–	D	1187,1188
			–	–	–	C	919
Me	H	H	90–91/16	g	84	I, P	763
H	H	Me	87/10	g	*	n	1189
			87–90/10	g	73	n	758,759
			87/10	g	*	–	1190
			91–93/15	k	89	P	767
		Et	85–87/8	c	30	–	785
			102–103/12	k	–	–	820
		n-Pr	99–100/12	k	–	–	820
		OHCCH=CH	128–129	k	*	–	1189,1190
			128–130	k	43	–	758
		OHCCBr=CH	153–155	f	*	–	1190
		$O_2NCH=CH$	181–182	k	63–77	–	758,759
		$O_2NCBr=CH$	151–153	f	75	–	758,759
		$EtO_2C(CH_2)_4$	147–150/1	g	–	–	751

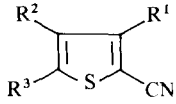
TABLE 135. AMINO-, HYDROXY-, AND MERCAPTO-2-CYANOTHIOPHENES AND RELATED COMPOUNDS



R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
NH_2	H	H	47.5–50	e	95	I, P	350
H	H	NHCOMe	161–163	k	–	–	183
Me	H	NH_2	71–73	x	–	–	370
Ph	H	NHPh	161	r	83	I, P	193
H	NO_2	*N*-Piperidyl	118	g	*ca* 100	U	110
Me	NO_2	*N*-Piperidyl	105	g	*ca* 100	U	110
NH_2	$(EtO)_2PO$	Me	84–85	r	42	I, P	347
	Ph	$NCCH_2S$	146–148	r	81	I	346
N=CHOEt	Ph	$NCCH_2S$	99–101	f	76	–	346
N_3	H	H	77.5–79	f	86	I, P	350
NH_2	$C_5H_5\overset{+}{N}I^-$	MeS	300	r	87	I, U	404
			257	r	86	–	403
	NH_2	MeS	90	f	89	I, P, U	404
			90	a	89	–	403
Hydrochloride			208	– r/b	92	I, U	404
NH_2	PhCH=N	MeS	132	k	97	I, P, U	404
	4-Cl–C_6H_4–CH=N	MeS	178	k	82	I, P, U	404
	4-NO_2–C_6H_4–CH=N	MeS	210	k	87	I, P, U	404
	3-NO_2–C_6H_4–CH=N	MeS	175	k	92	I, P, U	404
	2-NO_2–C_6H_4–CH=N	MeS	227	k	76	I, P, U	404
	4-MeO–C_6H_4–CH=N	MeS	186	k	94	I, P, U	404
	3,4-OCH_2O–C_6H_3–CH=N	MeS	161	k	61	I, P, U	404
	PhCH=CHCH=N	MeS	178	k	83	I, U	404
	$PhCH_2NH$	MeS	80	e	92	I, P, U	404
	$PhCH_2(CH_3CO)N$	MeS	200	d	91	I, P, U	404

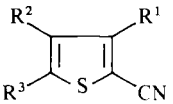
	3-NO_2–$C_6H_4CH_2(CH_3CO)N$	MeS	224	d	77	I, U	404
	4-MeO–$C_6H_4CH_2(CH_3CO)N$	MeS	183	d	85	I, P, U	404
	MeCONH	MeS	209–211	d	98	I, U	404
	PhCONH	MeS	223	d	73	I, U	404
	TsNH	MeS	183	d	62	–	404
	PhNHCSNH	MeS	260	f	95	I, P	404
NHCOMe	MeCONH	MeS	243	d	93	I, P	404
NHCOPh	PhCONH	MeS	232	d/k	89	I, P	404
NH_2	2-Cl–C_6H_4–CO	PhNH	210–212	r	48	I, M	799
OH	H	H	88–92	s	76	–	421
			117	v	62	K	761
OMe	H	H	72–74/0.12	s	91	–	421
			105/1	g	*	–	761
			73/0.16	s	91	–	414
$OCH_2CH(O)CH_2$	H	H	127–130/0.2	g	50	–	1191
H	H	MeO	12	k	75	–	737
			122/14				737
			–	k	–	I, P, n	771
	NO_2	MeO	130–131	c	25	I, M, P, U	771
			–	–	–	P, U	849
OH	H	Me	137	r	78	I, P, U	812
OMe	H	Me	32–33	g	64	P	812
OH	H	*i*-Pr	67–68	r	57	I, P, U	812
OMe	H	*i*-Pr	–	g	65	P	812
OH	H	*t*-Bu	95–96	r	32	I, P, U	812
OMe	H	*t*-Bu	liq	g	79	P	812
OH	H	Ph	182–184	r	50	I, P, U	812
OMe	H	Ph	129–130	g	56	P	812
H	NO_2	4-NO_2-C_6H_4-O	144	g	–	–	1125
	PhS	NO_2	170	g	–	–	778
	H	$MeSO_2$	137–137.5	g	59	–	224
	NO_2	$PhSO_2$	183	g	–	–	1125

TABLE 136. HALOGENO-, NITRO-, AND NITROHALOGENO-2-CYANOTHIOPHENES



R^1	R^2	R^3	Melting Point (°C) Boiling Pont (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	F	H	51–52	k	69	–	21
			–	–	–	P	1142
	H	F	80/30	k	80	n	21
		Cl	93–94/17	g	91	I, P	763
			80/14	k	70	–	737
			15	k	–	–	183, 356
			90–92/15				183, 356
			–	–	–	I, P	990
Cl	Cl	Cl	60	k	94	–	770
Br	H	H	50	k	70	–	127
H	Br	H	45	c	71	P	1186
			45	k	68	–	127
			48–49	k	–	–	778
			–	–	–	P	1186
	H	Br	114–117/15	g	32	I, P	763
			124/34	k	75	–	127
			100–102/6	k	–	–	769
	Br	Br	117	z	–	P	1186
I	H	H	54	k	53	–	129
H	I	H	74	k	75	–	129
	H	I	56	k	50	–	129
	NO_2	H	102	k	–	–	1192
			102–103	k	–	–	185
			102	c	*	–	184
			102	k	80	–	183
			101–102	c	25	–	92
			–	–	–	M, P	765
			–	–	–	P, U	849
			–	–	–	P	1193
	H	NO_2	44	k	–	–	185
			45	c	*	–	184
			44	k	*	–	183
			41–43	c	17	–	92
			45	k	78	–	851
			–	–	–	M, P	765
NO_2	H	H	–	–	–	M, P	765
			–	–	–	U	956
H	NO_2	Cl	117	c	–	–	1125
	Br	NO_2	85	c	–	–	778
Me	NO_2	Br	95	c	–	–	110
H	NO_2	I	173	c	–	–	1125

TABLE 137. FORMYL-2-CYANOTHIOPHENES AND THEIR DERIVATIVES



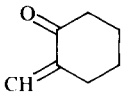
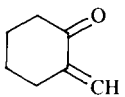
R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
CHO	H	H	78	g	65	P	10
			84	–	–	–	221
CH=NOH	H	H	100	–	–	–	221
$CH=NNH_2$	H	H	140	k	–	–	10
CH=NNHPh	H	H	159	k	77	–	10
$CH=C(CN)_2$	H	H	150	k	84	–	10
	H	H	92	f	35	–	10
$CH(OEt)_2$	H	H	110/0.5	g	77	–	10
H	CHO	H	77	g	60	P	10
		H	132	f	29	–	10
	$CH(OEt)_2$	H	115/1	g	80	–	10
	H	CHO	89	g	69	P	10
			94	g	30	–	754
			130–135/1.2				754
			93–94	w	*	–	1189
			96–97	w	51	–	758, 759
			93–94	b	*	–	1190

TABLE 137. *(Continued)*

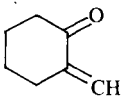
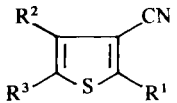
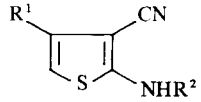
R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
			105	f	38	–	10
		$CH(OEt)_2$	118/1	g	88	–	10
		$CH(OCOCH_3)_2$	77–78	w	*	–	1189, 1190
		$NH_2N{=}CH$	90	k	–	–	10
		4-HO–$C_6H_4NHN{=}CH$	165	k	–	–	881
		$H_2NC(=S)NHN{=}CH$	234 d	k	91	–	754
		$NH_2N{=}CH$	90	k	–	–	10
Me	H	CHO	100–103/1.5	g	–	–	754
		$NH_2C(=S)NHN{=}CH$	207 d	k	–	–	754
H	Me	CHO	86–88	g	–	–	754
		$NH_2C(=S)NHN{=}CH$	228 d	k	–	–	754

TABLE 138. 3-CYANOTHIOPHENE AND ITS ALKYL, ARYL, AND HETEROARYL DERIVATIVES



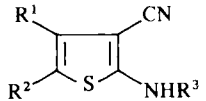
R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	H	58–59/3	k	73	–	766
			100–102/30	g	75	–	108
			203–205/760	k	–	n	845
			77/10	g	85	g	765, 1184
			104–105/32	g	86	I	753
			–	–	–	C	919
			–	–	–	U	956
Me	H	H	98–102/13	g	89	–	1013
H	Me	H	34.7–35.1	f	14	I, M	814
	H	Me	40/0.001	r	40	n	813
Me	H	Me	50/0.001	r	66	n	813
Et	H	Me	45/0.001	r	60	n	813
Pr	H	Me	76/0.001	r	68	n	813
Bu	H	Me	71/0.001	r	60	n	813
Ph	Me	Me	38–40	a	42	–	805
N-Pyrrolyl	H	H	150/4	f	–	I, P	1194
H	–NC	Me	107–108	k	–	–	1012

TABLE 139. 4-ALKYL-2-AMINO-3-CYANOTHIOPHENE DERIVATIVES



R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Me	H	119–120	r	73	I	362
	COMe	–	k	38	I	688
i-Pr	H	70	r	–	–	192
	COMe	140	d	–	–	192
	$COCF_3$	155	d	–	–	192
	COEt	137	d	–	–	192
	$CONH_2$	190–192	f	–	–	1195
	CONHMe	179–181	f	*	–	192
		177–178	f	–	–	1195
	$CONMe_2$	113–116	f	–	–	1195
Cyclopropyl	CONHMe	169–172	f	–	–	1195
	$CONMe_2$	171–172	f	–	–	1195
	CONHEt	174–180	f	–	–	1195
	CONH-*t*-Bu	227–230	f	–	–	1195
n-Bu	CONHMe	149–152	f	–	–	1195
s-Bu	CONHEt	104–106	f	–	–	1195
t-Bu	H	92	r	*	–	192
		91–92	r	48	I	363
	COMe	160	d	–	–	192
	$COCF_3$	156	d	–	–	192
	$COCH_2Cl$	126	d	–	–	192
	COEt	157	d	–	–	192
	CO-*i*-Pr	136	d	–	–	192
	CO-*t*-Bu	173	d	–	–	192
	COPh	130	d	*	–	192
	CONHMe	220	f	–	–	192
		212–214	f	–	I	1195
	CONHPr	154–158	f	–	–	1195
	$CONHCH_2CH{=}CH_2$	150	f	–	–	192
	CONH-*n*-Bu	157	f	–	–	192
	CONHPh	202	f	–	–	192
	CONH-3-Cl–C_6H_4	240	f	–	–	192
	CONH-2,4-di-Cl–C_6H_3	238	f	–	–	192
	CONH-3,4-di-Cl–C_6H_3	271	f	–	–	192
	$CONMe_2$	140	f	*	–	192
	$CONEt_2$	120–125	f	–	I	1195
	CO_2Me	114	d	–	–	192
	CO_2Ph	125	d	–	–	192
Cyclohexyl	CONHMe	225–226	f	–	–	1195

TABLE 140. 4,5-DIALKYL- AND SUBSTITUTED-ALKYL-2-AMINO-3-CYANOTHIOPHENES



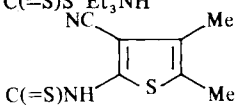
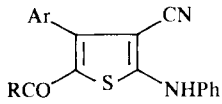
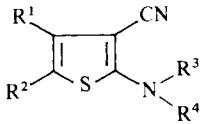
R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mmHg)	Preparation	Yield (%)	Notes	References
Me	Me	H	141–142	r	70	–	362
			–	r	42	I, U	361
		Ts	170–171	d	63	–	705
		Me	132–133	f	88–95	I, P	1109
		CH_2CO_2H	188–189	e	68–81	I, P	705
		CH_2CO_2Me	84.5–85.5	e	59–87	I, P	705
		CH_2CH_2OH	114–115	e	90	I, P	705
		$COCO_2Et$	85–87	d	71	–	1086
		$CH_2CH_2CO_2n$-Bu	Oil	e	68	I	705
		CMe=CHCOMe	117–122	k	–	U	836
		$CMe{=}CHCO_2Et$	73–75	f	91	M, P	835
		$C(=S)S^-Et_3\overset{+}{N}H$	241–242	f	28	I	1106
			>300	f	27	I	1106
Et	Me	H	155–159/16	r	51	–	362
Me	$PhCH_2$	H	150–154	r	17	–	788
$PhCH_2$	Me	H	151–153	r	34	–	788
Me	3,4-di-Cl–C_6H_3–CH_2	H	203–204	r	18	–	788
	$PhCH_2CH_2$	H	131–132	r	29	–	788
	4,5-di-Cl–C_6H_3–CH_2CH_2	H	169–172	r	24	–	788

TABLE 141. 4-ARYL- AND HETEROARYL-5-ACYL-2-PHENYLAMINO-3-CYANOTHIOPHENES



Ar	R	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Ph	Me	217–218	r	75	I	795, 798
	Ph	231–232	r	65–79	I	795, 798
	4-Me–C_6H_4	223–224	r	66	–	798
	4-Cl–C_6H_4	221–223	r	95	I	795, 798
	4-Br–C_6H_4	229–230	r	95	I	795, 798
	4-NO_2–C_6H_4	262–264	r	21	I	795, 798
4-Me–C_6H_4	Ph	225–226	r	71	–	798
4-Cl–C_6H_4	4-Cl–C_6H_4	230–231	r	79	–	798
4-Br–C_6H_4	Me	277–278	r	64	–	798
	Ph	213–215	r	91	–	798
4-MeO–C_6H_4	Ph	194–195	r	62	–	798
	4-Cl–C_6H_4	219–220	r	65	–	798
2-Furyl	Me	285–286	r	88	–	798
2-Thienyl	Me	245–247	r	89	–	798

TABLE 142. MISCELLANEOUS 2-AMINO-3-CYANOTHIOPHENES

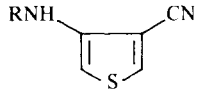


R^1	R^2	R^3	R^4	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	H	H	104–105	r	55	I, U	362
			COMe	194	k	80	I, P	379
			$COCH_2Cl$	176	d	70	I	379
			$COCO_2Et$	88	d	70	I	379
			COPh	171	d	60	I	379
			CMe=CHCOMe	143–145	k	75	P, U	836
Me	Me	COMe	CH_2CO_2H	153.5–154.5	e	67	I, P	705
		COMe	CH_2CO_2Me	111–112	e	70	I, P	705
			CH_2CONEt_2	68.5–69.5	e	67	I, P	705
		=CHOEt		58.5–59.5	f	88–98	I, P	1109
Ph	H	H	H	100–102	r	75	–	362
Me	Ph	H	H	165	r	45–55	I	396
			COMe	225	d	90–95	I	396
4-Cl–C_6H_4	Me	H	H	157–158	r	95	–	788
	Et	H	H	198–202	r	86	–	788
$PhCH_2$	Ph	H	H	140–142	r	98	–	788
Ph	Ph	H	H	194–196	r	95	–	788
	NH_2	H	H	100–105	r	64	U	653, 810
OH	PhCO	Me	Me	156–158	r	50	I, P, U	381
		$-(CH_2)_5-$		168–170	r	50	I, U	381
t-Bu	Cl	H	H	Oil	c	*	–	1195
			CONHMe	215–217	f	–	–	1195
H	NO_2	$-(CH_2)_5-$		155	g	*ca* 100	U	1105
	NO_2	H	CHO	216–218	c	–	–	191, 395

Table 142. (*Continued*)

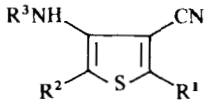
R^1	R^2	R^3	R^4	Melting Point (°C)	Preparation	Yield (%)	Notes	References
Ph	NO_2	H	Ph	204–206	r	71	–	798
H	CHO	H	H	–	c/b	–	I	777
		$=CHNMe_2$		192–193	k	–	–	777
PhCH=CH	MeCO	H	Ph	258–259	r	29	–	798
Ph	PhCO	H	$CH_2CH=CH_2$	208–210	r	50	–	798
		$-(CH_2)_5-$		163–164	r	69	I, U	381

TABLE 143. 4-(SUBSTITUTED AMINO)-3-CYANOTHIOPHENES



R	Melting Point (°C)	Preparation	Yield (%)	Notes	References
CHO	168	—r	45	I, P	819
Ph	88–89	s	*	–	386
4-*i*-Pr-C_6H_4	124	s	–	–	620
3-CF_3–C_6H_4	70	s	*	–	620
2,3-di-Me–C_6H_4	77	s	–	–	620
2,6-di-Me–C_6H_3	104	s	–	–	620
3,4-di-Me–C_6H_3	78	s	–	–	620
2,4,6-tri-Me–C_6H_2	114	s	–	–	620
2-Cl–C_6H_4	69	s	–	–	620
2,3-di-Cl–C_6H_3	162	s	–	–	620
2,6-di-Cl–C_6H_3	105–108	s	75	–	417, 421
	107	s	–	–	620
2-Cl-3-Me–C_6H_3	125	s	–	–	620
2-Cl-5-Me–C_6H_3	112	s	–	–	620
2-Cl-6-Me–C_6H_3	96	s	–	–	620
2,4,6-tri-Cl–C_6H_2	135	s	–	–	620
2,4-di-Cl-3-Me–C_6H_2	124	s	–	–	620
2,4-di-Cl-5-Me–C_6H_2	157	s	–	–	620
2,4,6-tri-Cl-3-Me–C_6H	118	s	–	–	620
2,6-di-Cl-4-EtO–C_6H_2	113	s	–	–	620
2,6-di-Cl-4-EtO-3-Me–C_6H	136	s	–	–	620
4-EtO–C_6H_4	126	s	–	–	620
4-Cl-2-NO_2–C_6H_3	214	s	–	–	387
	213–214	s	80	–	388
4-MeO-2-NO_2–C_6H_3	149–150	s	63	–	388
2-NO_2-4-MeS–C_6H_3	167–169	s	55	–	388
2-NO_2-4-CF_3–C_6H_3	156–157	s	35	–	388

TABLE 144. MISCELLANEOUS 4-AMINO-3-CYANOTHIOPHENES



R¹	R²	R³	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	Br	CHO	163	–r/k	40	I, P	819
	Me	CHO	122–123	d	–	–	1012
		2-NO_2–C_6H_4	127–128	s	21	–	388
NH_2	Me	PhCO	199	r	70	–	789
		4-Me–C_6H_4–CO	232	r	63	–	789
		4-Cl–C_6H_4–CO	226	r	60	–	789
		2,6-di-Cl–C_6H_3–CO	312	r	68	–	789
Ph	MeCO	H	171	r	–	–	800
Me	PhCO	H	153	r	–	–	800
NMe_2	PhCO	H	213–215	r	95	I, P, U	381
N-Piperidyl	PhCO	H	155–156	r	86	I, P, U	381
		Me	149–151	g	–	P	1196
		$MeNHCOCH_2$	171–173	a	*	P	1196
		Me	233–234	d	*	P, U	1196
		$ClCH_2CO$	165–166	d	99	P	1196
		ICH_2CO	171–172	g	*	P	1196
OH	PhCO	H	270 d	r	64	I, U	797
SCH_2CO(4-Br–C_6H_4)	4-Br–C_6H_4–CO	H	201–202	r	75	P	393
Ph	PhCO	H	220–221	r	90	I, U	426
C_6H_4-4-NMe_2	PhCO	H	210–211	r	90	I, U	426
Ph	4-Br–C_6H_4–CO	H	250–252	r	100	I, U	426

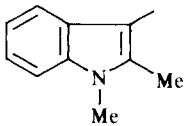
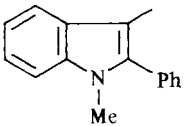
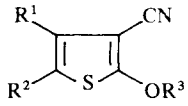
C_6H_4-4-MeO	PhCO	H	177–179	r	75	I, U	426
	4-Cl–C_6H_4–CO	H	198–199	r	100	I, U	426
	PhCO	H	220	–r/r	72	I, U	257
	PhCO	H	218	–r/r	50–80	I, U	257

TABLE 145. 3-CYANO-2-HYDROXYTHIOPHENES AND RELATED COMPOUNDS



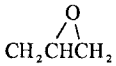
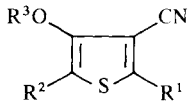
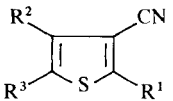
R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mmHg)	Preparation	Yield (%)	Notes	References
Me	H	H	48–54	a	59	P	803
			49–54	a	63	–	804
			115–120/0.03	g	60	–	1191
	Me	H	165/1.5	a	96	C, I, M, P	805
H	Ph	H	172 d	a	76	I, P	805
Ph	H	H	110–113	a	66	P	803
			110–113	f	65	–	804
		Me	91–93	g	40	P, U	803
		COMe	74–76	d	82	U	803
H	NO_2	Me	147.5–148	g	25	I, M, P, U	771
Me	MeCO	H	214–215	a	86	I, P	805
			211–215	a	55	P, U	803
	EtO_2C	H	86–90	a	76	I	803

TABLE 146. 3-CYANO-4-HYDROXYTHIOPHENES AND RELATED COMPOUNDS



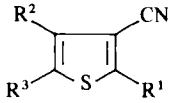
R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mmHg)	Preparation	Yield (%)	Notes	References
H	H	H	Oil	s	77	–	421
		$MeSO_2$	52–55	s	88–90	–	417, 421
i-Pr	H	H	130/0.5	r	89	P, n	802
		Me	100–102/0.4	t1	80	I, P, n	802
		MeNHCO	46	f	26	I, P	802
		Me_2NCO	132–133/0.5	d	71	I, P, n	802
i-Pr	Me	H	111/0.1	r	65	n	802
		Me_2NCO	197/13	d	62	–	802
s-Bu	H	H	134/0.5	r	90	n	802
		Me_2NCO	126–127/0.1	d	55	–	802
	Me	H	121/0.3	r	75	n	802
	EtO_2CCH_2	H	155/0.1	r	75	n	802
Ph	PhCO	H	163–164	–r/r	65	I, U	425, 426
	4-Br–C_6H_4–CO	H	193–194	–r/r	72	I, U	426
			193–194	–r/r	88	U	425
C_6H_4-4-Me_2N	PhCO	H	199–201	f	95	I, U	426
			199–201	f	100	U	425
C_6H_4-4-MeO	PhCO	H	149–150	–r/r	45	I, U	426
	4-Cl–C_6H_4–CO	H	195–198	–r/r	90	I, U	426

TABLE 147. 3-CYANOTHIOPHENE THIOETHERS AND RELATED COMPOUNDS



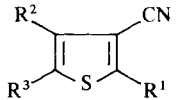
R^1	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
SMe	Ph	MeCO	109–111	r	51	I	795
		PhCO	143–144	r	37	I	795
	4-MeO–C_6H_4	MeCO	127–129	r	30	I	795
	4-Cl–C_6H_4	MeCO	126.5–127	r	54	I	795
	3,4-di-Cl–C_6H_3	MeCO	147–149	r	54	I	795
	4-Br–C_6H_4	MeCO	140.5–142	r	33	I	795
	Ph	4-NO_2–C_6H_4	184–186	r	36	I	795
	2-Furyl	MeCO	113–114	r	63	I	795
	2-Thienyl	MeCO	106–108	r	37	I	795
SCH_2COPh	Ph	PhCO	153–154	r	20	I	795
SCH_2COMe	2,4-di-Cl–C_6H_3	MeCO	156–158	r	26	I	795
SCH_2CO–C_6H_4-4-NO_2	Ph	4-NO_2–C_6H_4	211–213	r	74	I	795
SO_2Ph	H	NO_2	175	g	–	–	1141
H	PhS	H	32–34	s	90	–	417, 421
		NO_2	125	g	*ca* 100	U	1130

TABLE 148. HALOGENO-, NITRO- AND HALOGENONITRO-3-CYANOTHIOPHENES



R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mmHg)	Preparation	Yield (%)	Notes	References
H	H	F	66–68/11	k	65	g, n	21
			–	–	–	I, R	1197
			–	–	–	P	1142
Br	H	H	130/22	k	50	–	127
H	Br	H	56	k	62	–	127
	H	Br	33	k	45	–	127
Br	H	Br	76	k	48	–	127
I	H	H	57	k	80	–	129
H	I	H	54	k	70	–	129
	H	I	65	k	89	–	129
NO_2	H	H	–	–	–	M, P	765
			–	–	–	U	956
H	NO_2	H	–	–	–	M, P	765
	H	NO_2	120	k	–	–	1192
			122–122.5	c	–	I, M, P, U	771
			–	–	–	P, U	849
			–	–	–	P	1193
Br	H	NO_2	119–120	c	–	–	771
			123	c	–	–	1105
H	Br	NO_2	178	c	–	–	1130

TABLE 149. FORMYL-3-CYANOTHIOPHENES AND THEIR DERIVATIVES



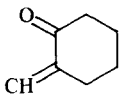
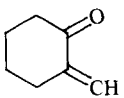
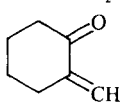
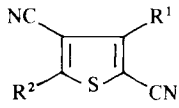
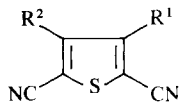
R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
CHO	H	H	85	g/b	58	P	10
			88	–	–	–	221
$CH{=}NNH_2$	H	H	138	k	–	–	10
	H	H	83	f	33	–	10
$CH(OEt)_2$	H	H	105/0.5	g	87	–	10
			100/0.5	–	–	–	221
H	CHO	H	138	g/b	67	P	10
	$CH{=}NNH_2$	H	86–88	k	–	–	10
		H	112	f	37	–	10
	$CH(OEt)_2$	H	120/1	g	90	–	10
	H	CHO	84	g/b	73	P	10
		$CH{=}NNH_2$	109	k	–	–	10
			129	f	40	–	10
		$CH(OEt)_2$	125/0.7	g	73	–	10

TABLE 150. 2,4-DICYANOTHIOPHENES AND RELATED COMPOUNDS



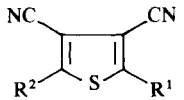
R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	163–164	r	–	–	188
		164	g	61	I, P	756, 757
Me	NH_2	206–208	k	52	–	666
		220–222	r	65	–	370
NH_2	Me	221	r	–	–	800
Ph	NH_2	230–231	60	–	–	370
NH_2	NH_2	250	r	75	C, I	790
		252–254	r	85	I, U	787
	PhCH=N	253–256	k	88	I	787
	PhNH	222–224	r	75	I, U	402
OH	Me	180–185 d	r	40	I	1010
Ph	MeS	199–200	r	45	I	795
	$PhCH_2S$	150–152	r	30	–	795
C_6H_4-4-MeO	MeS	186–187	r	20	I	795
C_6H_4-4-Cl	MeS	209–210	r	37	I	795
C_6H_3-3,4-di-Cl	MeS	186–187	r	20	I	795
C_6H_4-4-Br	MeS	206–207	r	41	I	795
2-Furyl	MeS	203–204	r	23	I	795
2-Thienyl	MeS	194–195	r	35	I	795

TABLE 151. 2,5-DICYANOTHIOPHENES



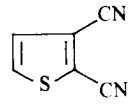
R^1	R^2	Melting Point (°C) Boiling Point (°C/mm Hg)	Preparation	Yield (%)	Notes	References
H	H	205	g	46	I, P	756, 757
		–	–	–	D	1198
Me	H	73–74	g	83	I, P	763
		137–138/16				763
OH	Me	180–183	r	67	I, M, P	801
	Ph	195–199	r	68	I, M, P	801
OMe	MeO	132	k	90	–	489
O–CH_2–O		170	k	54	I	482
Cl	Cl	128	k	74	–	768
Br	Br	138–139	k	76	–	768

TABLE 152. 3,4-DICYANOTHIOPHENES



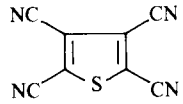
R^1	R^2	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	H	171	g	71	I, P	756, 757
		169–170	g	75	I, P	187
Ph	Ph	181–182	r	95	I	313
N-Pyrrolyl	*N*-Pyrrolyl	164–165	f	22	–	1199
NH_2	NH_2	240–244	r	30	I	787
		subl >250 d	r	79–85	–	756, 807
		240–244 d	r	92	I	653, 808
	PhCH=N	255–257	k	–	–	1200
	$Me_2NCH=N$	210–213	f	75	–	1200
NHCOMe	MeCONH	>300	d	86	–	653, 808
NHCOPh	PhCONH	>300	d	82	–	653, 808
$N=CHNMe_2$	$Me_2NCH=N$	229–230.5	f	76	–	1200
N=CHPh	PhCH=N	297–298	k	94	U	808
N=CH-(4-NO_2–C_6H_4)	4-NO_2–C_6H_4–CH=N	>300	k	92	U	808
N=CH-(2-OH–C_6H_4)	2-OH–C_6H_4–CH=N	>300	k	91	U	808
NSO	NSO	–	f	45	C, I	1201
NH_2	NSO	–	f	36	I	1201
Cl	Cl	139–140	k	58	I	40

TABLE 153. 2,3-DICYANOTHIOPHENE



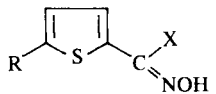
Melting Point (°C)	Preparation	Yield (%)	Notes	References
150	g	63	I, P	756, 757
150	–	–	–	221
115–122	g	58	I, P	27
103–105	g	73	I, P	763

TABLE 154. 2,3,4,5-TETRACYANOTHIOPHENE



Melting Point (°C)	Preparation	Yield (%)	Notes	References
198	f	80	–	1076
198	f	70	I, U	337
198	f	–	–	1202
188–192	f	–	–	1203
–	–	–	X-ray structure	567
–	–	–	I, R	1204

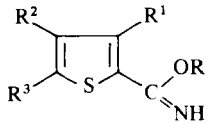
TABLE 155. 2-THIENYLHYDROXAMIC ACIDS AND RELATED COMPOUNDS



(Or tautomers)

R	X	Melting Point (°C)	Preparation	Yield (%)	Notes	References
H	NH_2	90	f	68	P	857
		180	f	–	–	85
		–	–	–	I	859, 860
	NHPh	90–93	g	75	–	858
	NH-(4-Me–C_6H_4)	170 d	g	67	–	858
	Cl	102	f	44	–	858
MeO	NH_2	105	f	–	–	737
		–	–	–	I	859, 860
Cl	NH_2	133	f	–	–	737
	NHPh	132–134	g	70	–	858
	Cl	127–128	f	–	–	858
NO_2	NH_2	182	f	–	–	737
		–	–	–	I	859, 860
$CH(OEt)_2$	NH_2	80–82	f	82	–	857
2-Thienyl-CO–N(OH)R	R=3-Me–C_6H_4	80	d	76	I, U	1205
	R=4-Cl–C_6H_4	143	d	80	I, U	1205

TABLE 156. 2-THIENYL IMIDATES AND THEIR HYDROCHLORIDES



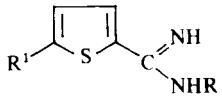
R^1	R^2	R^3	R	Melting Point (°C) Boiling Point (°C/mmHg)	Yield (%)	Hydrochloride (M.p. °C)	Notes	References
H	H	H	Me	99/15	–	100	I, P	846
				93/15	50	170 d	–	850
				95/13	–	173	–	737
			Et	105/15	–	125	I, P	846
				–	91	126–128	P	755
				101/11	–	128	–	737
				–	80	124–126 d	–	845
		–CN	Me	91	–	–	I	462
			Et	51	–	–	I	462
–CN	H	H	Me	65–68	–	–	I	462
OH	H	H	Me	–	78	134	–	848
H	H	MeO	Me	–	–	179	–	737
			Et	152/12	–	160	–	737
		Cl	Me	113/13	–	175 d	–	850
				113/12	–	175	–	737
			Et	122/13	–	174 d	–	737, 850
				122/13	80	–	–	844
	NO_2	H	Me	105	90	177	–	737
				105	–	180 d	–	850
				–	–	–	I, M, P, U	849
			Et	108	90	180	–	737, 850
	H	NO_2	Me	91	78	–	*	851
				75	90	170 d	–	737, 850
			Et	93–95	73		*	851

TABLE 156. *(Continued)*

R^1	R^2	R^3	R	Melting Point (°C) Boiling Point (°C/mm Hg)	Yield (%)	Hydrochloride (M.P. °C)	Notes	References
				99	90	–	–	844, 850
				104	–	152	–	737
			n-Pr	58–60	80	–	*	851
			i-Pr	47–49	70	–	*	851
			n-Bu	68–70	88	–	*	851
			n-C_5H_{11}	44–48	80	–	*	851
			n-C_8H_{17}	47–48	91	–	*	851
		CHO	Me	70	–	–	I, P	462
			Et	49	–	–	I, P	462
	CHO	H	Me	123	–	–	I, P	462
			Et	123	–	–	I, P	462

*Hydrochloride converted into amide on heating.

TABLE 157. 2-THIENYL AMIDINES AND RELATED COMPOUNDS



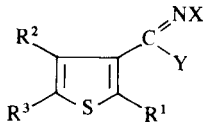
(And/or tautomer)

				Salt		
R^1	R	Melting Point (°C)	Notes	Acid	Melting Point (°C)	References
H	H	–	–	$PhSO_3H$	110	737, 846, 850
		–	–	HCl	176	846
		109–111	P	HCl	177–178	755
	—CN	230–232	–	–	–	848
	Ph	139	–	HI	191	738
		143–144	I, P	–	–	199
		144–145	–	–	–	854
		–	–	HI	197	737
	CO_2Et	153.5–154.5	I, P	–	–	199
	2-F–C_6H_4	125	–	–	–	855
	2-Cl–C_6H_4	157	–	–	–	855
	2-Thiazolyl	159	70	–	–	856
NC—	H	–	–	$PhSO_3H$	228	462
HO	H	–	–	HCl	>300	761
MeO	H	–	–	$PhSO_3H$	180	737
	Ph	–	–	HI	199	737
Cl	H	–	–	$PhSO_3H$	196	737
	Ph	–	–	HI	174	737
NO_2	H	216–219	–	–	–	851
		–	–	$PhSO_3H$	237	737, 850
	Me	150–155	–	HCl	201–204	851

TABLE 157. (*Continued*)

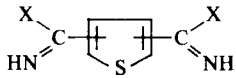
R[1]	R	Melting Point (°C)	Notes	Salt		References
				Acid	Melting Point (°C)	
	Et	117–118	–	HCl	225–229	851
	n-Pr	144–146	–	HCl	218–220	851
	$CH_2CH{=}CH_2$	175–177	–	–	–	851
	n-Bu	171–175	–	–	–	851
	2-Glucosyl	205–206	–	–	–	851
	$NHCONH_2$	280–288	–	–	–	851
2-Thienyl-C(=NCO_2Et)-N-morpholyl		85.5–87	I, P	–	–	199
2-Thienyl-C(=NCO_2Et)-NHPh		101–102	I, P	–	–	199
2-Thienyl-C(=N–C_6H_4-4-Cl)-NHMe		119–121	I	–	–	1206
4-NO_2-2-thienyl-C(=NH)NH_2		–	–	$PhSO_3H$	217	737, 850

TABLE 158. 3-THIENYLHYDROXAMIC ACID DERIVATIVES, IMIDATES, AND AMIDINES



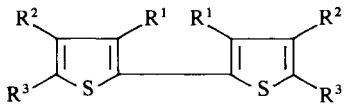
							Salt		
R^1	R^2	R^3	X	Y	Melting Point (°C)	Notes	Acid	Melting Point (°C)	References
H	H	H	OH	NH_2	85	P	–	–	857
$CH(OEt)_2$	H	H	OH	NH_2	92	–	–	–	857
H	H	$CH(OEt)_2$	OH	NH_2	69	–	–	–	857
		H	CN	NH_2	204–206	–	–	–	848
			H	OMe	Liquid	I, P	HCl	110	846
				OEt	Liquid	I, P	HCl	129	846
					–	P	HCl	126–129	755
–CN	H	H	H	OMe	65–68	I	–	–	462
H	–CN	H	H	OMe	82	I	–	–	462
				OEt	85	I	–	–	462
	H	–CN	H	OMe	105	I	–	–	462
		CHO	H	OMe	71	I, P	–	–	462
				OEt	40	I, P	–	–	462
		H	H	NH_2	–	–	HCl	180	846
					107–108	P	HCl	177–178	755
					–	–	$PhSO_3H$	149–152	846
				NHPh	125	–	HI	180	738
H	–CN	H	H	NH_2	–	–	$PhSO_3H$	198–203	462

TABLE 159. THIENYL BISIMIDATES AND BISAMIDINES



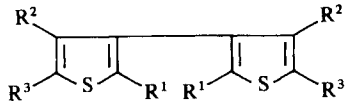
Locations on Ring	X	Melting Point (°C)	Notes	Bis Salt		References
				Acid	Melting Point (°C)	
2, 4	OMe	62	P	HCl	105–108	462
	OEt	98	P	HCl	121	462
2, 5	OMe	68	P	HCl	Indefinite	462
	OEt	69	P	HCl	Indefinite	462
3, 4	OMe	Liquid	P	HCl	Indefinite	462
	OEt	–	–	HCl	106–110	462
2, 4	NH_2	–	–	HCl	>300	462
		–	–	$PhSO_3H$	229	462
2, 5	NH_2	–	–	HCl	>300	462
		–	–	$PhSO_3H$	232	462
3, 4	NH_2	–	–	HCl	>300	462
		–	–	$PhSO_3H$	235	462

TABLE 160. SYMMETRICAL 2,2′-BITHIENYLCARBOXYLIC ACIDS AND THEIR DERIVATIVES



R^1	R^2	R^3	Melting Point (°C) Boiling Point (°C/mmHg)	Preparation	Yield (%)	Notes	References
CO_2H	H	H	175–185 d	b	90	–	1040
			278–281	p	41	–	25
CO_2Me	H	H	145–147	f	24	–	1040
H	CO_2H	H	289–291 d	u	70	P	1207
	CO_2Me	H	150–151	m1	–	–	1207
Me	CO_2Et	NH_2	176	r	40	I	396
		NHCOMe	194	d	–	–	396
NH_2	CO_2Et	Me	144–145	z	15	I, U	1112
NHCOMe	CO_2Et	Me	270–271	d	73	I	1112
H	H	CO_2H	>350	i	72	–	443
		CO_2Me	208–210	l	85	–	443
			180/1	z	14	I, M, P	141
NO_2	H	CO_2Me	168–169.5	f	53	–	1036

TABLE 161. SYMMETRICAL 3,3'-BITHIENYLCARBOXYLIC ACIDS AND THEIR DERIVATIVES

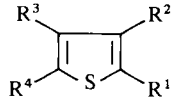


R^1	R^2	R^3	Melting Point (°C)	Preparation	Yield (%)	Notes	References
CO_2Me	H	H	193–195	f	–	–	17
			–	–	–	P	1025
CO_2H	H	Me	258–260 d	u	83	–	1208
	Me	H	254–257	i	45	U	959
	Br	H	295 d	u	59	P	1154
CO_2Me	Br	H	160–162	f	12	P	1154
			–	–	–	P	1025
CO_2H	Br	Me	(±)-303–308 d	–	72	P	1208
			(±)311–313 d	c	78	U	959
			(–)301–304 d	–	–	α	959
			(+)302–305 d	–	–	α	959
CO_2Me	Br	Me	(+), (–) –178–180	m1	–	α	1208
	I	H	–	–	–	P	1025
CO_2H	NO_2	H	283–285	b	75	–	133
CO_2Me	NO_2	H	164–165	f	73	–	133
			–	–	–	P	1025
CO_2H	CO_2H	H	(±)310–315 d	b	70	P	55
			(+)310 d	–	–	α, C, U	55
			(–) –	–	–	α	55
CO_2Me	CO_2Me	H	–	–	–	P	1025
H	CO_2H	H	275–280	u	80	P	1207
	CO_2Me	H	147–148	m1	–	–	1207
Me	CO_2H	Me	295–305	b	–	–	1156
	CO_2Me	Me	48–48.5	f	–	–	1156
			50–51.5	f	35	–	1036
Et	CO_2H	Et	183–186	u	60	α, P	36
				q	40		36
I	CO_2H	H	237–239	c	51	P	55
	CO_2Me	H	156–159	m1	–	P	55
			–	–	–	P	1025
NO_2	CO_2Me	H	–	–	–	P	1025
CHO	CO_2H	H	(±)225–229	u	91	P	55
			(+)225–229	–	–	α, C, U	55
	CO_2Me	H	(±)164–167	m1	–	P	55
			(+)112–113	m1	–	α, C, U	55
H	H	CO_2Me	–	–	–	P	1025
Br	Br	CO_2H	275 d	u	60	–	1154
		CO_2Me	167–168	m1	–	P	1154
			–	–	–	P	1025
I	I	CO_2Me	–	–	–	P	1025

VII. APPENDIX: PHYSICAL PROPERTIES OF THIOPHENECARBOXYLIC ACIDS AND THEIR DERIVATIVES

Since the physical properties of thiophenes in general are dealt with elsewhere in this treatise, we cover this topic briefly in the form of tables. Entries in the latter usually refer to groups of substances; information on individuals should be sought in the Tables of Compounds.

In the tables that follow, these conventions are used:

1. The pattern is 

2. Unspecified R's are H.
3. Individual compounds are separated by a semicolon.

TABLE 162. UV SPECTROSCOPY

Compound(s) Studied	Comments	References
$R^1 = COX; R^2 = COY$	X=OH, NH_2, OMe, OEt; Y=OH, Me, Et, NH_2	866
$R^1 = CO_2H; R^2 = CO_2H$	–	1016
$R^1 = CO_2H$	–	1209
$R^1 = CONXY$	Also IR	867
$R^4 = XCH_2, R^1 = CO_2Me;$	A group of compounds studied where X	985
$R^4 = XCH_2, R^2 = CH_2Cl,$	includes some chains between C_8 and C_{18}	
$R^1 = CO_2Me; R^4 = XCH_2,$		
$R^2 = Me, R^1 = CO_2Me$		
$R^1 = CONXY; R^2 = CONXY$	Investigation of protonation by UV	1021
$R^3 = X, R^1 = CO_2H; R^1 = NO_2,$	X = H, *i*-Pr, Br, NO_2	956
$R^3 = CN; R^2 = NO_2,$		
$R^1 = CN; R^4 = Y, R^1 = CO_2H;$	Y = Cl, Br, I, NO_2	
$R^4 = Z, R^3 = NO_2, R^1 = CO_2Me$	Z = Br, Me	
$R^4 = MeX, R^1 = CO_2H$	X = O, S, Se	1124
$R^4 = X, R^1 = CONH_2$	Investigation of protonation by UV	1210
$R^2 = CONXY$	Many compounds studied; also IR	1020
$R^1 = CN$	–	1185
$R^1 = CN$	TCNE complex	1211
$R^1 = R^4 = NH_2, R^3 = Ph, R^2 = CN$	–	653, 810
$R^1 = R^4 = XCH{=}N, R^2 = R^3 = CN$	–	808
$R^1 = CSSMe$	Comparison with MO predictions	1253
$R^1 = CSSPh$	Also polarography	749

TABLE 163. IR SPECTROSCOPY[a]

Compound(s) Studied	Comments	References
$R^1 = CO_2H; R^2 = CO_2H$	Conjugation of C=O examined (stronger in 2 than 3)	444
$R^1 = CO_2Me; R^1 = CO_2Et$	Detailed analysis of the 800–2000 cm^{-1} region	914
$R^1 = COX; R^2 = COX$	X=OH, NH_2,OAr. 2 and 3 isomers can be distinguished	1212
$R^1 = CO_2H; R^1 = CO_2Et$	–	930
$R^1 = CO_2^- Na^+$	Assignment of fundamental vibrations; also Raman	1213
$R^1 = CONXY$	–	867
$R^1 = CO_2H$	C=O stretch of monomer and dimer	1214
$R^1 = CO_2H; R^1 = CO_2Me$	–	1215
$R^2 = X, R^1 = COCl; R^4 = X, R^1 = COCl$	LFER between $ArCOCl/PhNH_2$ reaction and C=O stretch	1216, 1217
$R^3 = CH_2X, R^1 = CO_2H; R^4 = CH_2X, R^2 = CO_2H$	Correlation investigated between C=O stretch and σ constants	954
$R^2 = CO_2Me; R^3 = CO_2Me; R^4 = Me,$	–	1058
$R^3 = R^1 = CO_2Me; R^4 = R^1 = Me,$		
$R^2 = R^3 = CO_2Me; R^4 = R^1 = Me,$		
$R^3 = COMe, R^2 = CO_2Et$		
$R^4 = Me, R^2 = CO_2H$	Assignment of bands	963
$R^2 = COX$	X = NH_2, OH, OMe	1218
$R^2 = CONXY$	Also UV	1020
Many compounds with $R^2 = OH$	Investigation of tautomerism by IR and NMR	5
Various 2- and 3-esters containing NH_2,OH,NO_2 and second ester groups	Study of C=O stretch, H-bonding and bond orders. Includes MO calculations	253
$R^1 = CN$	–	930
$R^4 = Cl, R^1 = CN$	Also Raman	990
$R^4 = F, R^2 = CN$	Also Raman	1197
$R^1–R^4 = CN$	Also Raman	1204
$R^1–R^4 = CN$, as radical	–	1219
$R^1–R^4 = CN$, as anion radical	–	1220

[a]*Note*: IR spectra have been widely used in conformational studies, see Table 170.

TABLE 164. NMR SPECTROSCOPY[a]

Compound(s) Studied	Comments	References
$R^1 = CO_2H; R^2 = CO_2H$	–	1015
$R^1 = CO_2Me; R^2 = CO_2Me$	Analysis of CMR spectra	922
Protonated $R^1 = CO_2H$	–	1221
Deuterated $R^1 = CO_2H$, etc.	–	925, 1222
$R^1 = CO_2Me$	CMR of $AlCl_3$ complexes	923, 924
$R^1 = CO_2H; R^2 = CO_2H; R^1 = CN; R^2 = CN$	CMR	919
$R^1 = CO_2Me$	CMR	920, 921, 1223
$R^4 = XCH_2$, $R^1 = CO_2Me$; $R^4 = XCH_2$, $R^3 = ClCH_2$,	X = some chains between C_8 and C_{18}	985
$R^1 = CO_2Me$; $R^4 = XCH_2$, $R^3 = Me$, $R^1 = CO_2Me$	Also UV	
$R^3 = XCH_2$, $R^1 = CO_2H$; $R^4 = XCH_2$, $R^2 = CO_2H$	Correlation between σ constants of the X and CMR of the CO_2H	953, 954
$R^1 = CO_2X$	Lanthanide shift work on esters	1224
$R^4 = F$, $R^1 = CO_2X$; $R^3 = F$, $R^2 = CO_2X$; $R^4 = F$, $R^2 = CO_2X$	^{19}F NMR. X=H, Me. MO calculations	1143
$R^4 = F$, $R^1 = CO_2X$; $R^3 = F$, $R^1 = CO_2X$;	Also ^{19}F NMR	1142
$R^4 = F$, $R^2 = CO_2X$, $R^3 = F$, $R^1 = CN$; $R^4 = F$, $R^2 = CN$		
$R^1 = CONXY; R^2 = CONXY$	Site of protonation studied by CMR	1021
$R^1 = COF$	Also ^{19}F NMR and CNDO/2 calculations	940, 1225
Many compounds with $R^2 = OH$	Tautomerism study by NMR and IR	5
$R^1 = CN$	Effect of complexing with $AlCl_3$ and $HSbCl_6$	1186
3,3′-Bithienyls	Structural determination by NMR	1025

[a]NMR spectra have been widely used in conformational studies, see Table 170. Spectra are PMR unless otherwise specified.

TABLE 165. MASS SPECTROMETRY

Compound(s) Studied	Comments	References
$R^1 = CO_2H$; $R^2 = CO_2H$; also their mono-, di-, and tribromo derivatives; $R^1 = NH_2$, $R^2 = CO_2Et$, $R^3 = OH$		1017
$R^1 = CO_2Me$	Compound present in coffee aroma	918
$R^4 = D$, $R^1 = COX$	X = OH, O-*t*-Bu, OMe	925
$R^4 = XCH_2$, $R^1 = CO_2Me$; $R^4 = XCH_2$, $R^3 = ClCH_2$, $R^1 = CO_2Me$; $R^4 = XCH_2$, $R^3 = Me$, $R^1 = CO_2Me$	X = some chains between C_8 and C_{18}	986
$R^1 = NHX$, $R^2 = CO_2Y$	X = Substituted nitrophenyl; Y = Me, Et	1226
$R^4 = HO$, $R^1 = CO_2Et$; $R^4 = Me$, $R^3 = OH$, $R^1 = CO_2Et$; $R^1 = X$, $R^2 = CO_2Et$, $R^3 = OH$	X = Me, Ph	1066
$R^2 = CN$, $R^3 = Me$	–	814
R^1–$R^4 = CN$	Negative ion MS	1227

TABLE 166. pK_a DETERMINATIONS[a]

Compound(s) Studied	Comments	References
$R^1 = CO_2H$	Correlation with rate of hydrolysis of $R^1 = CO_2Et$	1228
$R^1 = CO_2H$	–	1214
$R^1 = CO_2H$	Potentiometric measurement	1229
$R^1 = CO_2H$	Variation of pK_a with temperature	1209
$R^1 = CO_2H$	Effect of change of solvent	582
$R^1 = CO_2H$; $R^2 = CO_2H$	Correlation with rate of hydrolysis of $R^1 = CO_2Et$ and $R^2 = CO_2Et$	1230
$R^4 = X$, $R^1 = CO_2H$; $R^3 = Y$, $R^1 = CO_2H$	X = H, Br, Cl, Me, NO_2; Y = Me, NO_2. Used for LFER	952
$R^1 = CO_2H$; $R^4 = Br$, $R^1 = CO_2H$; $R^4 = R^1 = CO_2H$	pK_a in 80% methyl cellosolve	473
$R^4 = XCH_2$, $R^1 = CO_2H$	X = H, Me, OH, SH, OMe, OPh, SO_2Ph, $\overset{+}{N}Me_3$	960, 1231
$R^4 = X$, $R^1 = CO_2H$	X = Me, Et, MeO, H, Cl, Br, MeCO, CO_2H, *t*-Bu, Ph. Used for LFER	961
$R^4 = X$, $R^1 = CO_2H$; $R^2 = CO_2H$	X = H, Me, Cl, NO_2, F, MeO. Used for LFER	962
$R^2 = X$, $R^1 = CO_2H$; $R^4 = Y$, $R^1 = CO_2H$; $R^3 = Z$, $R^1 = CO_2H$	X = MeO, Me, MeS, H, I, Br, MeSO, $MeSO_2$; Y = MeO Me, MeS, I, Br, $MeSO_2$, Et, Cl, NO_2; Z = Me, Br, NO_2	946
$R^4 = XCH_2$, $R^1 = CO_2H$; $R^3 = XCH_2$, $R^1 = CO_2H$; $R^4 = XCH_2$, $R^2 = CO_2H$	X = H, Br, HO, MeO, PhO, HS, EtS, $PhSO_2$, HO_2C	98
$R^1 = CONH_2$	Also metal complex formation constants	1232
$R^1 = X$, $R^2 = CO_2H$	X = I, Cl, Br	706
$R^1 = X$, $R^2 = CO_2H$	X = Me, CN, F, Cl, Br, I, SMe, SOMe, SO_2Me	1014
$R^2 = CO_2H$; $R^4 = R^1 = Me$, $R^2 = CO_2H$; $R^1 = Me$, $R^2 = CO_2H$; $R^4 = Me$, $R^2 = CO_2H$	–	1013
$R^2 = R^3 = CO_2H$; $R^2 = CO_2H$, $R^3 = CO_2Me$; $R^4 = R^1 = CO_2H$	–	178
$R^4 = X$, $R^2 = OH$, $R^1 = CO_2Et$; $R^1 = Y$, $R^2 = CO_2Et$, $R^3 = OH$	X = H, Me, Ph, 1-naphthyl, 1-biphenylyl; Y = H, Me, Ph	1120

[a]See also Table 167.

TABLE 167. LINEAR FREE ENERGY RELATIONSHIPS (LFER)

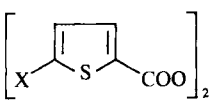
Compound(s) Studied	Comments	References
$R^3 = X$, $R^1 = CO_2H$; $R^3 = X$, $R^1 = CO_2Et$; $R^4 = Y$, $R^2 = CO_2H$; $R^4 = Y$, $R^2 = CO_2Et$	X = Me, *i*-Pr, Br, NO_2; *Y* = Et, Br, NO_2 Ester hydrolysis	464
$R^4 = X$, $R^1 = CO_2H$; $R^4 = X$, $R^1 = CO_2Et$	Esterification and ester hydrolysis	1233
Substituted $R^1 = CO_2Et$ and $R^2 = CO_2Et$	Acid- and base-induced hydrolysis	928
$R^2 = X$, $R^1 = CO_2Me$	X = H, Me, I, Br, OMe, SMe, SO_2Me, SOMe. Hydrolysis examined	1129
$R^4 = X$, $R^2 = CO_2Et$	X = Et, Cl, NO_2. Ester hydrolysis	927
$R^2 = CO_2H$, $R^3 = CO_2Me$; $R^2 = R^3 = CO_2Me$; $R^4 = R^1 = CO_2Me$	Ester hydrolysis	178
$R^1 = COCl$	Kinetics of reaction with substituted anilines	885
Substituted $R^1 = COCl$	Kinetics of reaction with substituted anilines	965
$R^2 = Y$, $R^1 = COCl$	Reaction with aniline	1117
$R^2 = X$, $R^1 = COCl$; $R^4 = X$, $R^1 = COCl$	Reaction with aniline and correlation with C=O stretch	1216
$R^3 = XCH_2$, $R^1 = CO_2H$; $R^4 = XCH_2$, $R^2 = CO_2H$	IR and CMR correlations	954
$R^1 = CONHPh$; $R^2 = CONHPh$	Alkaline hydrolysis studied	1234
$R^4 = X$, $R^1 = CONH_2$	X = H, Me, MeO, Br, Cl, I, NO_2. Protonation studied by UV	1210
	X = H, Me, *t*-Bu, Hal, NO_2. Thermal decomposition investigated	646

TABLE 168. DIPOLE MOMENTS

Compound(s) Studied	Comments	References
$R^1 = CO_2H$; $R^1 = CO_2Et$	–	929
$R^4 = NO_2$, $R^1 = CO_2Me$; $R^4 = NO_2$, $R^1 = CO_2H$; $R^4 = NH_2$, $R^1 = CO_2Me$	–	1085
$R^1 = CN$	–	1187, 1188, 1198

TABLE 169. X-RAY STUDIES

Compound(s) Studied	Comments	References
$R^1 = CO_2H$	Structural investigation	1235–1239
$R^1 = CO_2H$	Absorption of X-radiation	1240
$R^2 = CO_2H$	Structural investigation	1241, 1242
$R^2 = COMe$, $R^1 = CO_2H$; $R^1 = COMe$, $R^2 = CO_2H$; $R^3 = MeCO$, $R^2 = CO_2H$	Structural investigation	1172
R^1–$R^4 = CN$	Structural investigation	567

TABLE 170. CONFORMATIONAL STUDIES

Compound(s) Studied	Comments	References
$R^1 = CO_2X$	Also 3,4-dialkyl and diaryl esters. IR analysis, D compounds used	915, 935 992
$R^1 = COX$	X = F, Cl. Also halogenated halides. IR and NMR used	561
$R^1 = COX$	X = OH, Cl. NMR investigation	1243
$R^1 = COCl$	Dipole moment, IR and Kerr constants used	1244
$R^1 = COCl$	EHMO study	1245
$R^1 = COCl$; $R^4 = X$, $R^1 = COCl$	NMR and IR studies	964
substituted $R^1 = CO_2X$	X = Me, Et, *t*-Bu. IR investigation	916
$R^2 = CO_2Me$	NMR investigation and CNDO/2 calculations	1024
$R^1 = CONMe_2$; $R^2 = CONMe_2$	Thermodynamic parameters of rotation determined	877
$R^1 = CONMe_2$; $R^2 = CONMe_2$	Investigation of rotational barriers	878, 1021
$R^1 = CONMe_2$	Lanthanide shift investigation	879
$R^1 = CONMe_2$	Dipole moment investigation	876
R^4–$R^2 = Br$, $R^1 = CO_2Et$; $R^2 = R^4 = Br$, $R^1 = COF$	IR study	1246
$R^1 = CSNH_2$	Dipole moments used	1176

TABLE 171. TAUTOMERISM

Compound(s) Studied	Comments	References
$R^1 = OH$ and $R^2 = OH$ derivatives	–	1119
$R^2 = OH$ derivatives	IR and NMR used	5
$R^2 = OH$ derivatives	NMR used	1114
$R^2 = OH$ derivatives	IR, UV, and NMR used	3
$R^4 = X$, $R^2 = OH$, $R^1 = CN$	–	812
$R^2 = CHO$, $R^1 = CO_2H$	Ring-chain tautomerism study	100
Many formyl acids	Ring-chain tautomerism study	101

TABLE 172. KINETIC MEASUREMENTS

Compound(s) Studied	Comments	References
$R^4 = X$, $R^1 = CO_2H$	Kinetics of azide formation	966
$R^4 = X$, $R^1 = CON_3$	Curtius rearrangement	967
$R^2 = CON_3$	Thermal decomposition	1247
$R^1 = COCl$	Solvolysis studies	1248, 1249
$R^2 = Me$, $R^1 = COCl$; $R^2 = Br$, $R^1 = COCl$	Relation between rate of reaction with aniline and C=O stretch	1250
$R^1 = COCl$; $R^2 = COCl$	Reaction with aniline	1251
$R^2 = Br$, $R^1 = COCl$; $R^2 = Me$	Reaction with aniline	941, 1217
$R^1 = COCl$; $R^4 = Br$, $R^1 = COCl$; $R^4 = Me$, $R^1 = COCl$		
$R^1 = CO_2Et$	Rate changes of hydrolyses in various solvents	1252
$R^4 = R^1 = CO_2Et$, $R^3 = R^4 = OH$	Reaction with butylamine	1069

TABLE 173. MISCELLANEOUS INVESTIGATIONS

Compound(s) Studied	Comments	Reference
$R^1 = CN$; $R^2 = CN$	Ab initio MO calculations	1254
$R^1 = CO_2Et$	Chromatography on Raney cobalt	1255
$R^1 = CO_2H$; R^4 = 2-thienyl, $R^1 = CO_2H$	TLC	1256
$R^1 = CO_2Et$	GLC on polyester stationary phases	1257
$R^4 = R^1 = CO_2H$	Paper chromatography	1258
$R^1 = CO_2X$	X = C_1–C_7. Densities, n_D, UV	911
$R^1 = CO_2H$	Effects of electron irradiation	1259
$R^1 = CO_2Me$; $R^1 = CN$	Ionization potentials	1260
$R^1 = COCl$	Kerr constants	1244
$R^1 = R^4 = CO{-}X{-}C_6H_4{-}OMe$	Liquid crystals	1049, 1054, 1261
$R^1 = R^3 = CO{-}X{-}C_6H_4{-}OMe$		
$R^1 = CO_2H$	Magnetic circular dichroism	1262
$R^2 = CN$	Microwave spectra	581, 1263
$R^4 = NO_2$, $R^1 = CO_2H$; $R^3 = NO_2$, $R^1 = CO_2H$	Polarography	1264
$R^4 = NO_2$, $R^1 = CN$; $R^3 = NO_2$, $R^1 = CO_2H$	Polarography	185, 448
$R^1 = CSSMe$	Relationship studied between energy of LUMO and half-wave potential	1266
$R^1 = CSSPh$	Polarography	749
$R^4 = F$, $R^2 = CN$	Raman spectrum	1197
$R^4 = Cl$, $R^2 = CN$	Raman spectrum	990
R^1–$R^4 = CN$	Raman spectrum	1204
$R^1 = CO_2H$	Vaporization data	1265

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CHAPTER V

Side-Chain Reactivity of Thiophenes. Thenyl Derivatives

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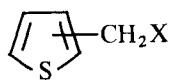
I. INTRODUCTION

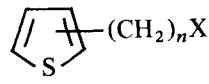
1. General

This chapter on side-chain reactivity of thiophenes covers literature starting from Hartough's Volume,[1] published in 1952, that includes references up to 1949. Articles published before 1949 are not cited (except when needed for comparison purposes), and compounds reported in Hartough's book that have not received further attention are not listed in the Tables of Compounds.

This chapter surveys the literature to December 1981 and deals with the synthesis, the spectroscopic and the physicochemical properties, and the reactivity of thenyl derivatives **1** and of the linear-chain analogues **2**.



1



2

The chemistry of cephalosporins, a new class of thiophene acetamides which has been extensively and intensively investigated in the past few years, is reported separately in Section VII. Kinetic rate data and comparison with side-chain reactivity of other five-membered heterocyclic compounds are also discussed in a separate section. The properties of thenyl radicals and radical reactions are briefly discussed in the introduction.

2. Thenyl Radicals

The electron spin resonance spectra of 2- and 3-thenyl radicals have been investigated[2-4] and the nonequivalence of the methylene protons pointed out.[2]

A survey of general principles and findings on the pyrolytic formation of arenes includes studies on the pyrolytic fragmentation of thenyl radicals[5,6] and on the rearrangement without fragmentation of 2-thenyl into 3-thenyl radical.[5]

The reactions of nitrothienylmethyl and ethyl chlorides and acetates with $LiCMe_2NO_2$ proceed by a ionic-substitution process involving initial nucleophilic attack on the thiophene ring.[7] The 5-nitro derivatives react to give complex mixtures of products which arise from $S_{RN}1$, S_N2, elimination, electron transfer, and radical-coupling processes.

II. HALOMETHYL DERIVATIVES

1. Synthesis

A. Synthesis of Chloromethylthiophenes

The main method for the synthesis of 2-chloromethylthiophenes is chloromethylation of thiophene and its derivatives by formaldehyde and HCl or by chloromethyl ether[8] (see Table 1).

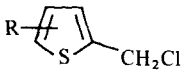
The structure of the compounds formed from thiophene and 2-methylthiophene under conditions of chloromethylation in the presence of zinc chloride has been investigated.[44]

Thenyl chlorides can also be conveniently prepared by treating thenyl alcohols with $SOCl_2$ in the presence of a base such as triethylamine[12-14] or pyridine[23] and by reactions with PCl_3,[32] PCl_5 and $ZnCl_2$.[16]

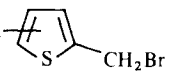
The synthesis of 3-chloromethyl-5-acylthiophenes from 2-acylthiophenes has been reported,[45] but few details on the reaction conditions are available.

B. Synthesis of Bromomethylthiophenes

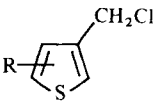
Tables 2 and 4, in which the methods of preparation of bromomethylthiophenes are reported, show that these compounds are mainly synthesized by bromination

TABLE 1. SYNTHESIS OF 2-CHLOROMETHYLTHIOPHENES 

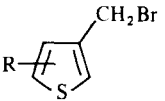
R_3	R_4	R_5	Conditions	Yield (%)	Reference
H	H	H	Thiophene, HCHO, HCl (gas)	47	9
			Thiophene, trioxane, conc. HCl, HCl (gas)	50	10
			Thiophene, HCHO, HCl	65	11
			Thiophene, chloromethyl ether, AcOH, light	46	8
			2-Thenyl alcohol, $SOCl_2$, Et_3N	85	12
Me	H	H	3-Methyl-2-thenyl alcohol, $SOCl_2$	79	13
Br	H	H	3-Bromo-2-thenyl alcohol, $SOCl_2$, Et_3N	75	14
			3-Bromothiophene, HCHO, HCl	72	15
I	H	H	3-Iodo-2-thenyl alcohol, $SOCl_2$, Et_3N	81	14
NO_2	H	H	3-Nitro-2-thenyl alcohol, PCl_5, $CHCl_3$	59	16
Cl	H	H	Chloromethylation	10	17
H	NO_2	H	3-Nitrothiophene, trioxane, $ZnCl_2$, CCl_4, HCl	48	16
H	H	Me	5-Methyl-2-thenyl alcohol, $SOCl_2$	71	18
H	H	Et	2-Ethylthiophene, $MeOCH_2Cl$, AcOH	21	19
H	H	*t*-Bu	Chloromethylation	52	17
H	H	C≡CSMe	5-C≡CSMe-2-thenyl alcohol, $SOCl_2$, Et_3N	100	20
H	H	Cl	2-Chlorothiophene, HCl, HCHO	54	21
H	H	Br	Chloromethylation of 2-Bromothiophene	70–80	22
H	H	NO_2	5-Nitro-2-thenyl alcohol, $ZnCl_2$, HCl	68	16
CH_2Cl	Me	COOMe	3-Methyl-2-thiophene carboxylate, $MeOCH_2Cl$, $ZnCl_2$	82	23

TABLE 2. SYNTHESIS OF 2-BROMOMETHYL THIOPHENES 

R_3	R_4	R_5	Conditions	Yield (%)	Reference
H	H	H	2-Methylthiophene, NBS, peroxide	84	24
			2-Thenyl alcohol, PBr_3	90	25
			2-Methylthiophene, NBS, Bz_2O_2, CCl_4	69	26
CH_2Br	H	H	2,3-bis(hydroxymethyl)thiophene, PBr_3	99	27
Ph	H	H	Methyl analogue, NBS, peroxide	95	28
Br	H	H	NBS on methyl compound	86	17
NO_2	H	H	3-Nitro-2-methylthiophene, NBS, peroxide	51	29
Ph	H	Br	2-Methyl analogue, NBS, peroxide	97	28
Br	H	Br	NBS on methyl compound	61	17
H	H	COOEt	5-COOEt-2-methylthiophene, NBS, benzoylperoxide	83	30

TABLE 3. SYNTHESIS OF 3-CHLOROMETHYL THIOPHENES 

R_2	R_4	R_5	Conditions	Yield (%)	Reference
H	H	H	3-Methylthiophene, *N*-chlorosuccinimide, peroxide	2	31
			3-Thenyl alcohol, $SOCl_2$, Et_3N	85	12
Me	H	H	2-Methyl-3-thenyl alcohol, PCl_3	–	32
Me	H	Me	2,5-Dimethyl thiophene, AcOH, $MeOCH_2Cl$	41	33
Cl	H	Cl	Chloromethylation	11	17
H	Br	H	4-Bromo-3-thenyl alcohol, $SOCl_2$, Et_3N	78	14
H	I	H	4-Iodo-3-thenyl alcohol, $SOCl_2$, Et_3N	86	14
H	OMe	Ph	4-Methoxy-5-phenyl-3-thenyl alcohol, $SOCl_2$	76	34
H	CH_2Cl	H	3,4-Bishydroxymethylthiophene, $SOCl_2$, piperidine	65	23
Cl	CH_2Cl	Cl	Chloromethylation of 2,5-dichlorothiophene, $MeOCH_2Cl$, $SnCl_4$	74	35

TABLE 4. SYNTHESIS OF 3-BROMOMETHYL THIOPHENES 

R_2	R_4	R_5		Yield (%)	Reference
H	H	H	3-Methylthiophene, NBS, ABN	71	36
			3-Methylthiophene, NBS, peroxide	–	37
			3-Methylthiophene, NBS, peroxide	90	24
			3-Methylthiophene, NBS, CCl_4, IR initiation	75	38
Ph	H	H	Methyl analogue, NBS, peroxide	98	28
Cl	H	H	2-Chloro-3-methylthiophene, NBS, peroxide	75	39
Br	H	H	2-Bromo-3-methylthiophene, NBS, peroxide	65	39
			2-Bromo-3-methylthiophene, NBS, ABN	–	40
NO_2	H	H	2-Nitro-3-methylthiophene, NBS, peroxide	60	29
			2-Nitro-3-thenyl alcohol, HBr	71	41
Ph	H	Br	Methyl analogue, NBS, peroxide	98	28
Cl	H	Cl	2,5-Dichloro-3-methylthiophene, NBS, peroxide	69	39
H	Br	H	3-Methyl-4-Bromothiophene, NBS, ABN	60	40
H	H	COOEt	5-COOEt-3-methylthiophene, NBS, peroxide	76	30
COOMe	CH_2Br	COOMe	3,4-Dimethyl analogue, NBS, peroxide	71	42
Br	CH_2Br	Br	3,4-Dimethyl analogue, NBS, peroxide	80	43

of methylthiophenes with *N*-bromosuccinimide (NBS) in the presence of a peroxide or of azobisisobutyronitrile (ABN) as initiators.

Bromomethylthiophenes are also obtained by brominating alkylthiophenes in the presence of azobisisobutyronitrile and light[46] or by IR initiation[38] (Table 4).

Hydroxymethylthiophenes can be converted in almost quantitative yield into the corresponding bromomethyl analogues by reaction with PBr_3.[25,27]

C. Synthesis of Iodomethylthiophenes

Owing to the sensitivity of thenyl iodides to air and light (iodine formation), very scarce data are available on these derivatives.

2-Thenyl iodide is prepared from 2-thenyl chloride and sodium iodide in dry acetone,[47] but the strongly lachrimatory product was used as such in a subsequent step without isolation or characterization. 4,5-Dichloro-2-thenyl iodide, similarly obtained in 95% yield from the corresponding thenyl chloride, is a solid, melting at 48°C.[48]

2,5-Dichloro-3,4-bischloromethylthiophene, treated with NaI, gives 70% 2,5-dichloro-3,4-bisiodomethylthiophene.[23]

2-(Chloroalkyl)-5-(carbethoxyacetyl)thiophene refluxed with sodium iodide in acetone or methyl ethyl ketone gives 2-(iodoalkyl)-5-(carbethoxyacetyl)thiophene in high yields.[49,50]

D. Synthesis of Thenyl Grignard Reagents and Lithio Derivatives

A modified cyclic reactor giving Grignard reagents from active halides was first used to prepare 3-thenylmagnesium bromide from 3-thenyl bromide in 91% yield.[51] This reactor is now widely used for the synthesis of Grignard reagents.[52–54]

Side-chain metalation of 2,5-dimethylthiophene can be achieved by action of BuLi/TMEDA (tetramethylenediamine).[55]

2. Spectroscopic and Physicochemical Properties

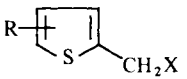
2-Chloromethylthiophene is lachrimatory and a skin irritant;[56] and explosion when stored at room temperature has been reported.[57]

IR, NMR, and mass spectra of 2-chloromethylthiophene are available,[11] together with the vertical ionization energies of π_3 and π_2 molecular orbitals determined from the photoelectron spectrum: these energies are 8.89 and 9.49 eV respectively.[58]

The electric moment of 2-thenyl chloride (1.58 D) is in exact agreement with that calculated on the basis of vector addition using the group moment values in the corresponding benzene derivatives, showing the resemblance of this compound to benzyl chloride.[59]

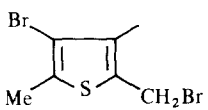
PMR spectra of 2- and 3-halomethylthiophenes are recorded in Tables 5 and 6 respectively.

TABLE 5. ^{1}H NMR SHIFTS OF 2-HALOMETHYLTHIOPHENES[a]



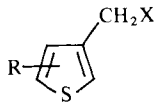
Solvent	X	R_3	R_4	R_5	Thiophene Ring H_3	H_4	H_5	CH_2	Others	Coupling Constants (Hz) J_{34}	J_{45}	J_{35}	$J_{CH_2\text{-}H_3}$	References
a	Cl	H	H	H		6.81[b]		4.53						60
c					6.77	6.77	7.20	4.69						61
c								4.74					0.7	62
d					6.86	6.86	6.96	4.56						11
c	Cl	Br	H	H		6.91	7.26	4.70			5.4			62
e	Cl	I	H	H		7.10	7.53	4.87			5.3			14
c	Cl	NO_2	H	H		7.60	7.26	5.16			5.5			62,63
c	Cl	Br	Br	H			7.34	4.72						62
c	Cl	CH_2Cl	H	CHO		7.66		4.63, 4.83						62
c	Cl	CH_2Cl	H	COMe		7.53		4.99, 4.77						62
c	Cl	CH_2Cl	H	COOMe		7.63		4.57, 4.77						62
c	Cl	COOMe	H	Cl		7.20		5.08						62
c	Cl	Br	H	CH_2Cl		6.89		4.65						62
c	Cl	Br	H	Br		6.90		4.63						62
c	Cl	NO_2	H	NO_2		7.32		5.25						62
a						8.43		5.41						60
c	Cl	H	COOMe	H	7.49		7.95	4.70				1.3	0.6	62
c	Cl	H	NO_2	H	7.61		8.24	4.74				1.75	0.8	62,63
f					7.62		8.27	4.74				1.68	0.81	7
c	Cl	H	H	Me	6.75	6.47		4.63		3.4			1.0	62
c	Cl	H	H	CH_2Cl	6.88	6.88		4.69						62
c	Cl	H	H	CHO	7.20	7.63		4.79		3.7			0.65	62
c	Cl	H	H	COMe	7.06	7.48		4.73		3.8			0.65	62
c	Cl	H	H	COOMe	7.02	7.56		4.72		4.0			0.65	62
c	Cl	H	H	COPh	7.08	7.75		4.75		3.6				62
c	Cl	H	H	2-COC_4H_3S				4.74						62

TABLE 5. *(Continued)*

Solvent	X	R_3	R_4	R_5	Thiophene Ring H_3	H_4	H_5	CH_2	Others	Coupling Constants (Hz) J_{34}	J_{45}	J_{35}	$J_{CH_2\text{-}H_3}$	References
c	Cl	H	H	C≡CSMe	6.96	6.96		4.67	2.44					20
c	Cl	H	H	Cl	6.81	6.71		4.63		3.6			0.85	62
a					6.63	6.51		4.49		3.7			0.7	60
c	Cl	H	H	Br	6.67	6.86		4.64		3.9			0.75	62
a					6.55	6.70		4.51		3.7			0.7	60
c	Cl	H	CH_2Cl	Br	6.96			4.43, 4.62					0.8	62
c	Cl	H	H	NO_2	7.03	7.72.		4.73		4.1			0.7	62, 63
a					7.08	7.73		4.84		4.1			0.8	60
f					7.05	7.79		4.74		4.23			0.90	7
c	Cl	CH_2Cl	Me	COOMe				4.73	2.56, 3.83, 4.53					23
c	Cl	Br	CH_2Cl	Br				4.51, 4.67						62
c	Cl	Br	Br	CH_2Cl				4.73						62
c	Cl	Br	Br	Br				4.69						62
a	Br	H	H	H		6.88[b]		4.49						60
f	Br	CH_2Br	H	H		7.28[g]	7.00[g]	4.71, 4.50			6.0			27
c	Br	Ph	H	H		6.93	7.26		7.2–7.5		5.0			28
h	Br	NO_2	H	H		7.52	7.20	4.97			5.5			64
a						7.51	7.20	4.96			5.5			60
c	Br	Ph	H	Br		6.90		4.55	7.5–7.2					28
e	Br	H	COOH	H	7.58		8.26	4.94						65
a	Br	H	H	Br	6.68	6.68		4.49						60
i	Br		Br	Me				4.34	2.43					66

[a]Letter codes, either under "Solvent" or as italic superscripts have the following designations:
a, Cyclohexane; b, mean shift of thiophene ring protons; c, CCl_4; d, neat; e, acetone-d_6; f, $CDCl_3$; g, alternative assignments; h, acetone, i, CS_2.

TABLE 6. ^{1}NMR SHIFTS OF 3-HALOMETHYLTHIOPHENES[a]



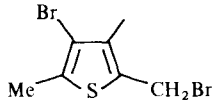
					Thiophene Ring					Coupling Constants (Hz)				
Solvent	X	R_2	R_4	R_5	H_2	H_4	H_5	CH_2	Others	J_{24}	J_{25}	J_{45}	$J_{CH_2-H_2}$	Reference
a	Cl	COOH	H	H		7.27	7.82	5.07				5		67
b	Cl	Me	H	Me		6.53		4.37						62
						6.55		4.35	2.30					33
b	Cl	Me	H	CHO		7.65		4.52						62
b	Cl	Me	H	COMe		7.50		4.48						62
b	Cl	Cl	H	Cl				4.43						62
a	Cl	SPh	H	Et		6.89		4.58	1.28, 2.78, 7.4					68
b	Cl	H	CH_2Cl	H	7.28		7.28	4.66						23
c	Cl	H	I	H	7.31		7.41	4.53			3.0			14
a	Cl	H	H	CHO	7.79	7.30		4.63		1.6				69
b	Cl	H	H	COMe	7.53	7.62		4.55		1.5			0.75	62
b	Cl	H	H	COPh				4.54						62
b	Cl	H	H	2-COC_4H_3S				4.56						62
b	Cl	H	H	COOMe	7.44	7.70		4.53		1.5			0.6	62
b	Cl	Me	CH_2Cl	Me				4.53						62
a	Cl	*t*-Bu	CH_2Cl	*t*-Bu				4.80		1.45				70
b	Cl	Cl	CH_2Cl	Cl				4.65						62
b	Cl	Br	CH_2Cl	Br				4.63						62
a	Cl	Cl	CH_2OH	Cl				4.61	4.63, 7.56					71
b	Cl	Cl	CH_2OSO_2Me	Cl				4.57	2.07, 5.16					71
d	Br	H	H	H		7.00[e]		4.33						60
b								4.38						35
b	Br	Ph	H	H		7.01	7.19		7.25, 7.55			5.5		28
d	Br	NO_2	H	H		7.10	7.40	4.79				5.1		60
b	Br	Ph	H	Br		7.06		4.32	7.35, 7.5					28

TABLE 6. *(Continued)*

Solvent	X	R_2	R_4	R_5	Thiophene Ring			CH_2	Others	Coupling Constants (Hz)				Reference
					H_2	H_4	H_5			J_{24}	J_{25}	J_{45}	$J_{CH_2-H_2}$	
a	Br	H	CH_2Br	H	7.23		7.23	4.48						70
a	Br	H	Br	H	7.32		7.20	4.43			3.4		0.5	40
a	Br	H	H	COOH	7.90	7.60		4.50						65
a					7.89	7.58		4.50		1.6				69
c					7.83	7.83		4.66						65
a	Br	H	H	COOMe	7.79	7.48			3.89	1.6				69
f	Br	COOMe	CH_2Br	COOMe				5.02	3.95					42
a	Br	Br	CH_2Br	Br				4.55						43
b	I	Cl	CH_2I	Cl				4.38						23

[a]Letter codes, either under "Solvent" or as italic superscripts have the following designations: a, $CDCl_3$; b, CCl_4; c, acetone-d_6; d, cyclohexane; e, mean shifts of ring protons; f, $CHCl_3$.

TABLE 7. ULTRAVIOLET ABSORPTION OF HALOMETHYLTHIOPHENES

R_2	R_3	R_4	R_5	λ_{max}	ϵ	Reference
CH_2Cl	CH_2Cl	Me	COOMe	218	14,200	23
				270	13,400	
H	CH_2Cl	CH_2Cl	H	230	5,200	23
Cl	CH_2Cl	CH_2OH	Cl	251	5,900	71
Cl	CH_2Cl	CH_2OSO_2Me	Cl	257	5,700	71
CH_2Br	CH_2Br	H	H	225	8,800	27
				250	10,000	
CH_2Br		Br	Me	245[a]	13,500	66
COOMe	CH_2Br	CH_2Br	COOMe	234	19,900	42
				282.5	12,100	
Br	CH_2Br	CH_2Br	Br	231	19,300	43
Cl	CH_2I	CH_2I	Cl	242	21,400	23

[a] (R)–(+) form.

Following previous work on the proton magnetic resonance of thenyl derivatives,[60] Sone and Takahashi[62] studied the ^1H NMR spectra of a series of chloromethylthiophenes. The chemical shifts of the methylene protons range from δ 4.63 to 5.25 ppm for monosubstituted 2-thenyl chlorides and from δ 4.37 to 4.56 ppm for monosubstituted 3-thenyl chlorides. These shifts are useful for establishing the positions of the methylene groups in related compounds. The ring protons coupling constants and the long-range coupling constants for the methylene protons allow the determination of the substituent's position in the thiophene ring.

Carbon-13 NMR spectra of 5-chloromethyl-3-thiophenecarboxylic acid and of 4-bromomethyl-2-thiophenecarboxylic acid have been reported.[72,73]

Ultraviolet absorptions of halomethylthiophenes are recorded in Table 7, whereas infrared data[11,27] are very scarce.

3. Chemical Reactivity

A. Reactivity of Halomethylthiophenes

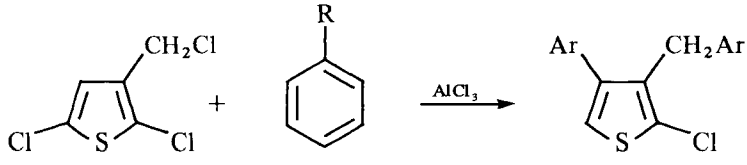
The kinetics of the solvolysis reactions of halomethylthiophenes has been investigated.[74] Reduction of 2-thenyl chloride over Pd-black gives 42% 2-methylthiophene.[75]

2-Chloromethylthiophene, treated with hexamethylenetetramine, undergoes the Sommelet reaction to give 2-thiophenecarboxaldehyde[76] in 51% yield; analogous reaction of 3-thenylbromide gives 3-thiophenealdehyde.[61]

In the reaction of 2-thenyl chloride with ammonia bis(di-2-thenylamino)methane is detected as a minor product,[77] whereas the reaction with liquid ammonia gives primary, secondary, and tertiary amines.[78]

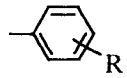
Thenyl halides are convenient starting materials for the synthesis of other thenyl derivatives: thenyl chlorides, first treated with PR_3, form thenylphosphonium salts,[79] and 3-thenyl bromide in a two-steps synthesis (by way of the cyanide) gives 3-thiopheneacetic acid.[37]

An unusual Friedel-Crafts reaction of 2,5-dichloro-3-chloromethyl thiophene with benzene and alkylbenzenes, in which the chlorine atom in the 5-position is removed with the introduction of an aryl group into the neighboring 4-position, leads to 4-aryl-3-arylmethyl-2-chlorothiophenes **5** as the major products.[80] Reaction of 3,4-bis(chloromethyl)-2,5-dimethylthiophene with aqueous ethanolic sodium sulfide affords 35% 4,6-dimethyl-1 H,3H-thieno[3,4-c] thiophene and a dimerization product.[81]



3 **4** **5**

R = H, CH_3, C_2H_5

Ar = 

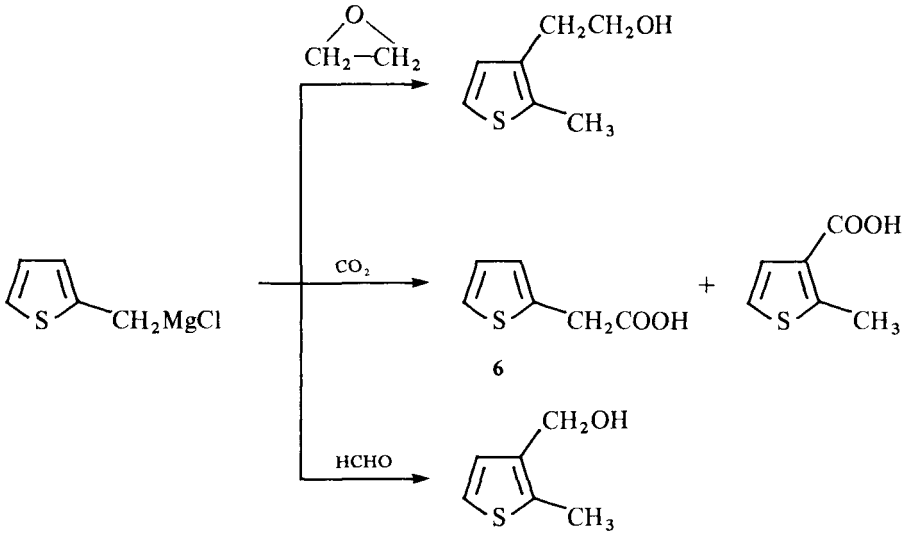
The synthesis and the reactions of dialkylethynyl (2-thienylmethyl) silanes have been studied.[82]

Halomethylthiophenes are reported in patents to be used as starting materials for the synthesis of a wide variety of compounds, most of which have pharmacological applications;[83–88] the exact formulas of the products, their physical properties, and the detailed synthetic procedures, however, are not available from *Chemical Abstracts.*

B. Reactivity of Grignard Reagents

The reaction of 2-thenylmagnesium bromide with carbon dioxide, formaldehyde, and ethylene oxide gives 3-substituted 2-methylthiophenes by rearrangement, the normal product **6** being isolated only in the case of carbon dioxide.[32]

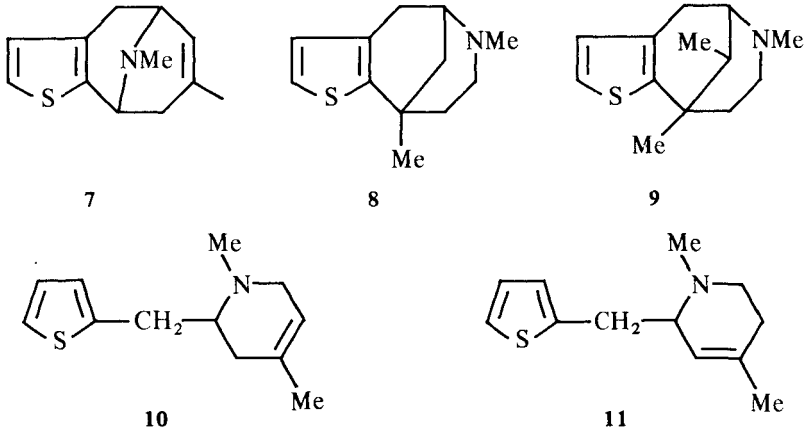
2-Thenylmagnesium chloride reacts with carbon dioxide ^{14}C to produce 64% of the normal product 2-thienylacetic acid and 30% of 2-methyl-3-thenoic acid,[52] whereas 3-thenylmagnesium bromide reacts with carbon dioxide to produce 23% of 3-thiopheneacetic acid together with the abnormal product 3-methyl-2-thenoic acid.[51]



The reaction of 2-thenylmagnesium chloride with carbon dioxide and ethylene oxide produces significant amounts of 5-substituted ("para") products, as well as 3-substituted ("ortho") and normal addition products.[53] Blocking the ortho position in 3-methyl-2-thenylmagnesium chloride results in an increased proportion of para product.[53]

Thenylmagnesium halides are used for the synthesis of 2-(2- and 3-thenyl)-tetrahydropyridines.[89–91]

Reaction of 3-thenylmagnesium bromide with pyridinium iodides followed by *in situ* reduction gives compounds **7**,[92] **8**,[93,94] and **9**;[95] derivatives **10** and **11** can be prepared analogously.[96]



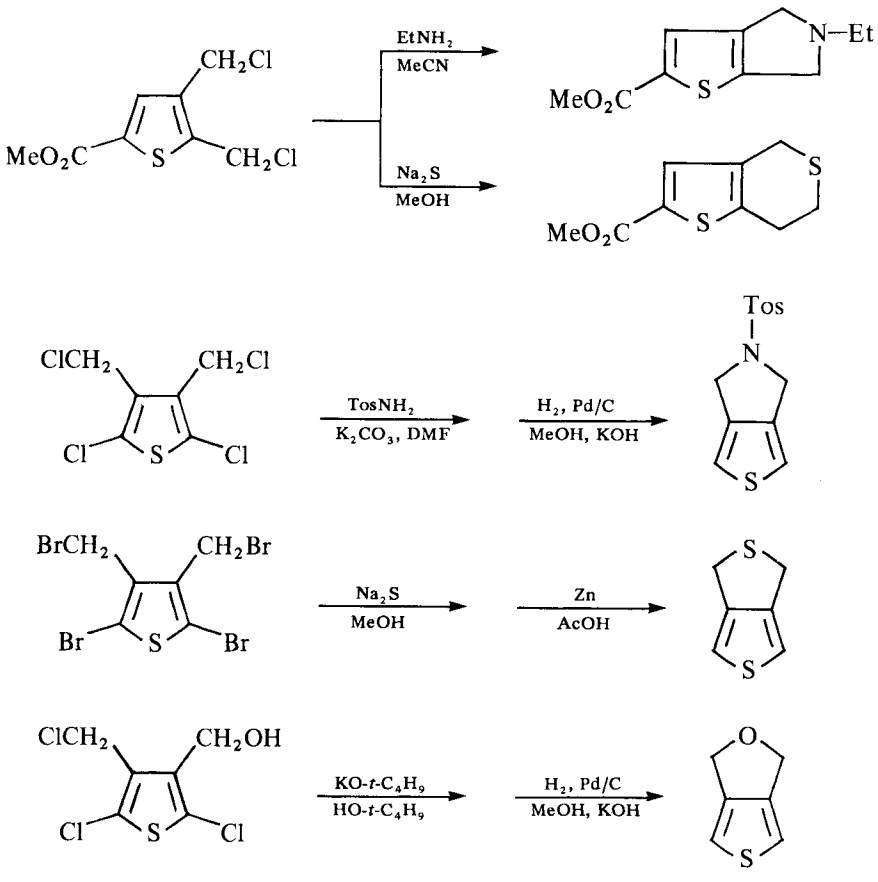
Condensation of 2-thenylmagnesium chloride with 1,3,4-trimethylpyridinium iodide affords 1,3,4-trimethyl-2-(2-thenyl)-1,2-dihydropyridine, an intermediate for the synthesis of rigid bridged thienomorphans.[97]

C. *Cyclization Reactions*

2,3-Bis(bromomethyl)thiophene reacts with Na_2S to give 4,6-dihydrothieno[3,4-b]-thiophene **12**.[27]

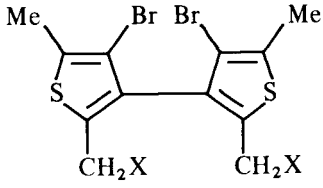
12

Scheme 1 summarizes part of the extensive studies by Wynberg and Zwanenburg regarding the cyclization of bichloromethyl derivatives to give heterocyclic rings fused to the thiophene nucleus in 2,3-[98,99] or in 3,4-positions.[23,71]

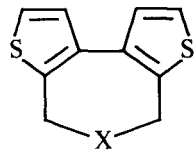


Scheme 1

The stereochemistry of 3,3′-bithienyls **13** and **14** and their reactions to give oxepin **15** and thiepin **16** have been studied.[66]



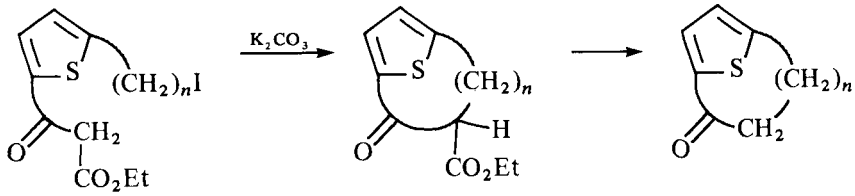
X = OH **13**
Br **14**



X = O **15**
S **16**

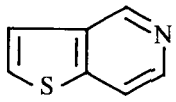
The introduction of the isoprene skeleton into the methyl group of 2-chloromethylthiophene, 2-chloromethylfuran, and chloromethylbenzenes can be achieved by a three-step sequence involving a solvent-assisted Claisen-Cope rearrangement.[100]

Intramolecular cyclizations of an activated methylene group with a iodomethylene group in the presence of alkali metal carbonates have been widely investigated[49,50,101–103] and reviewed.[104]

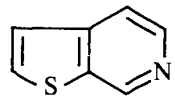


n = 5, 7, 9, 11

Thenyl halides are starting materials for the synthesis of thieno[2,3-c]pyridines **17** and **18**,[105] and of their tetrahydro derivatives.[106]



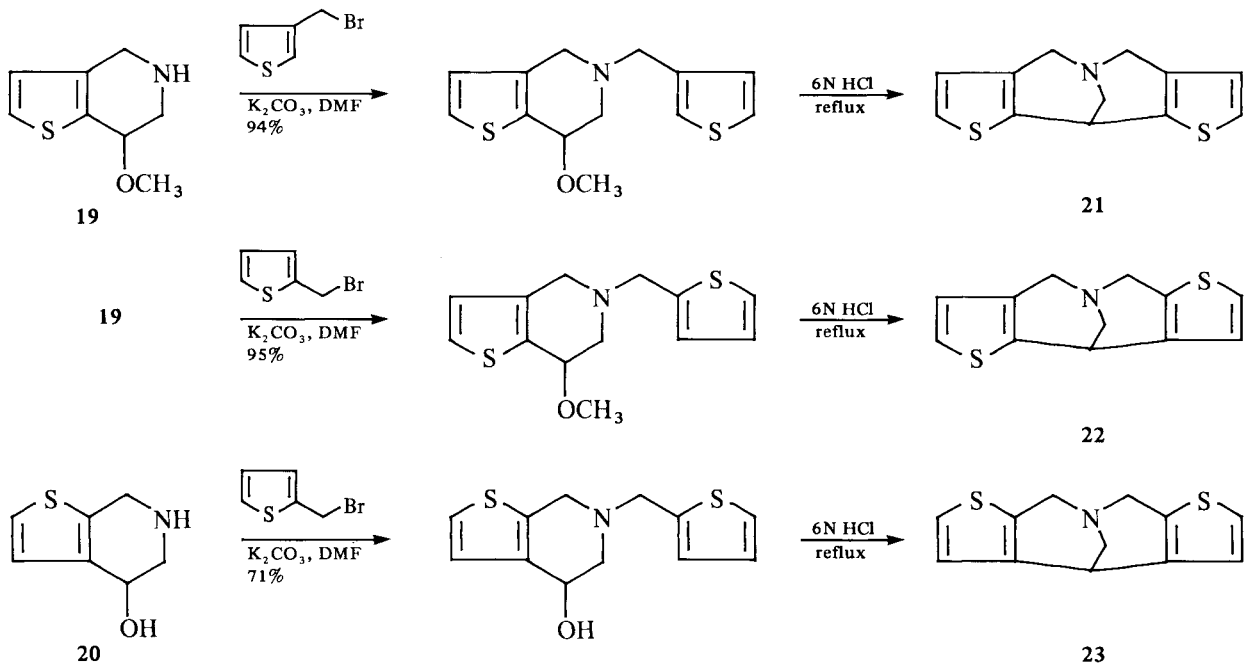
17



18

A series of thienomorphans can be prepared reacting 3-thenyl bromide and pyridines by an application of the Grewe morphinian synthesis.[107] 2- And 3-thenyl bromides are reacted with methoxy- and hydroxytetrahydrothienopyridines **19** and **20** to give, by a double cyclization, thiophene-condensed azabicyclo derivatives **21**, **22**, and **23** (Scheme 2).[108]

Chloromethyl thiophenes are also starting materials for the synthesis of spiro[cyclohexane-cyclopentathiophenes][109] and of 4- and 7-spiro-substituted benzo[b]thiophene derivatives.[110]


Br
S
NH
S
OCH3
K2CO3, DMF
94%
N
S
S
OCH3
6N HCl
reflux
N
S
S
19
21
19
Br
S
K2CO3, DMF
95%
N
S
S
OCH3
6N HCl
reflux
N
S
S
22
S
NH
OH
20
Br
S
K2CO3, DMF
71%
S
N
S
OH
6N HCl
reflux
S
N
S
23

Scheme 2

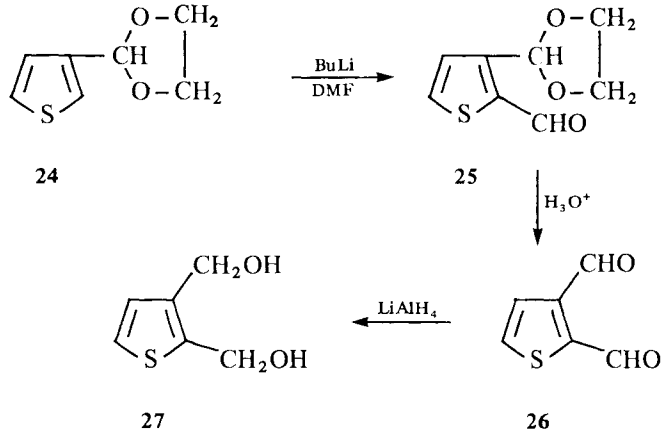
III. HYDROXYMETHYL AND THIOMETHYL DERIVATIVES

1. Synthesis

A general method for the synthesis of thenyl alcohols in high yields is the reduction of the corresponding aldehydes. This reduction can be achieved by using $NaBH_4$,[12-14,111] $LiAlH_4$,[112] Bu_2SnH_2,[113] iso Bu_3Al,[114] Zn,[115,116] thiourea dioxide,[117] Fe and $NiCl_2$ in acetic acid.[18]

Thenyl alcohols and thenyl acetates can alternatively be prepared from halomethylthiophenes by reaction with sodium or potassium acetates. Thenyl acetates are converted into alcohols in alkaline[18,41] or acidic[16] media.

Thenyl ethers are obtained from the reaction of halomethyl thiophenes with methoxide, ethoxide, and phenoxide ions (Tables 8 and 9).



24 25 27 26

Scheme 3

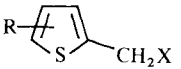
2,3-Bis(hydroxymethyl)thiophene **27** can be prepared (Scheme 3) by formylating 3-thiophenealdehyde ethylene acetal **24** to the 2-formyl derivative **25** which, after hydrolysis, affords 2,3-thiophenedicarboxaldehyde **26**; the dialdehyde **26**, treated with lithium aluminum hydride, gives 2,3-bis(hydroxymethyl)thiophene **27**.[27]

Thiophenemethanethiols are not very stable compounds. However, in some cases it is possible to convert thenylisothiouronium halides (obtained from thenyl halides and thiourea) into thiophenemethanethiols by treatment with NaOH.[65,126,127]

Thenyl sulfides and thiocyanates are prepared from halomethylthiophenes by nucleophilic substitution with RS^-;[65,98,128,129] and SCN^-[64,120,130] respectively.

Thenyl sulfoxides and sulfones are obtained by oxidation of the corresponding sulfides.[98,128,129]

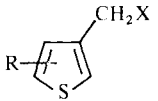
The synthesis of 2-thenyl isothiocyanate from 2-thenylamine has been reported.[131]

TABLE 8. SYNTHESIS OF 2-HYDROXYMETHYLTHIOPHENES AND DERIVATIVES 

X	R_3	R_4	R_5	Conditions	Yield (%)	Reference
OH	H	H	H	2-Thiophenealdehyde, $NaBH_4$	96	12
				2-Thiophenealdehyde, Bu_2SnH_2, 30°	90	113
				2-Thiophenealdehyde, $LiAlH_4$, NaOH	90	112
				2-Thiophenealdehyde, thiourea dioxide	65–83	117
				2-Thiophenealdehyde, Zn, AcOH–H_2O	–	115
				2-Thiophenealdehyde, Zn, NaOH, EtOH	–	116
				2-Thiophenealdehyde, iso Bu_3Al	–	114
				2-Thenyl chloride, AcONa	77	18
				2-Thenyl acetate, KOH, EtOH	49	18
OH	Me	H	H	3-Thenylmagnesium bromide, HCHO	70	51
				3-Methyl-2-thiophenealdehyde, $NaBH_4$	52	13
OH	CH_2OH	H	H	2,3-Dicarboxaldehyde, $LiAlH_4$	85	27
OH	Br	H	H	3-Bromo-2-formylthiophene, $NaBH_4$	80	14
OH	I	H	H	3-Iodo-2-formylthiophene, $NaBH_4$	78	14
OH	NO_2	H	H	3-Nitro-2-thenyl acetate, H_2SO_4	90	16
OH	H	COOH	H	2-Chloromethyl-4-carboxylate, AcONa AcOH	–	65
OH	H	NO_2	H	4-Nitro-2-thenyl acetate, H_2SO_4	63	16
OH	H	H	Me	5-Methyl-2-thiophenealdehyde, Fe AcOH, $NiCl_2$	56	18
				5-Methyl-2-thenyl chloride, AcONa	58	18
OH	H	H	COOH	5-COOEt-2-thenyl acetate hydrolysis	70	30
OH	H	H	C≡CSMe	Thiophene 2-C=CSMe, BuLi, CH_2O	65	20
OH	H	H	Cl	5-Cl-2-thenyl chloride, AcONa	64	18
OH	H	H	I	2-Thenyl alcohol, I_2, HgO	69	118
OH	H	H	OMe	5-OMe-2-thiophenealdehyde, $NaBH_4$, NaOH	75	111
OH	H	H	NO_2	5-Nitro-2-thenyl acetate, H_2SO_4	63	16
CH_2OH	H	H	H	2-Thienylacetic acid, $LiAlH_4$		53

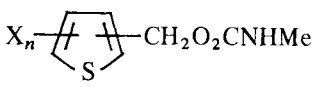
CH_2OH	H	H	Me	5-Methyl-2-thiophene magnesium bromide, ethylene oxide	–	53
$(CH_2)_2OH$	H	H	H	β-(2-thienyl)propanoic acid, $LiAlH_4$	–	53
OMe	H	H	H	2-Thenyl chloride, MeOH, KOH, 75°	78	119
OMe	CH_2OMe	H	H	2,3-Bis(bromomethyl), MeOH	36	27
OMe	H	COOH	H	4-Carboxylate-2-thenyl chloride MeONa	–	65
OMe	H	H	Cl	5-Chloro-2-thenyl chloride, AcONa	26	18
OEt	H	H	Cl	5-Chloro-2-thenyl chloride, EtONa	47	120
$OC_5H_{11}n$	H	H	H	2-Thenyl chloride, n-$C_5H_{11}OH$, Na	69	120
OPh	H	COOH	H	4-Carboxylate-2-thenyl chloride, PhONa	–	65
OAc	H	H	H	2-Thenyl chloride, AcONa, Et_3N	69	18
OAc	NO_2	H	H	Acetolysis of 3-NO_2-2-thenyl bromide	–	29
OAc	H	NO_2	H	4-NO_2-2-thenyl chloride, AcONa, Ac_2O	38	16
OAc	H	H	COOEt	5-COOEt-2-thenyl bromide, AcOK, AcOH	53	30
OAc	H	H	Cl	5-Chloro-2-thenyl chloride, AcOK	86	120
OAc	H	H	NO_2	Nitration of 2-thenyl acetate, HNO_3 in Ac_2O	21	16
OCOEt	H	H	H	2-Thenyl chloride, EtCOOK	65	120
OCOPh	H	H	H	2-Thenyl chloride, PhCOONa	60	120
$OCO(2C_4H_3S)$	H	H	H	2-Thenyl alcohol, 2-thenoyl chloride, pyridine	80	121

TABLE 9. SYNTHESIS OF 3-HYDROXYMETHYLTHIOPHENE AND DERIVATIVES



X	R_2	R_4	R_5	Conditions	Yield (%)	Reference
OH	H	H	H	Acetate, NaOH	58	41
				Reductive dehalogenation by $LiAlH_4$ of halogenated 3-thiophene carboxylic acids	30–35	122
				3-Thiophenealdehyde, $NaBH_4$	94	12
OH	Me	H	H	2-Thenylmagnesium chloride HCHO, N_2	49	32
OH	Br	H	H	2-Bromo-3-formylthiophene, $NaBH_4$	71	14
OH	I	H	H	2-Iodo-3-formylthiophene, $NaBH_4$	76	14
OH	NO_2	H	H	2-Nitro-3-thenylacetate, NaOH	86	41
				2-Nitro-3-thenyl bromide, sodium formate	–	29
OH	Me	H	Me	2,5-diMe, 3-thiophenealdehyde *i*-PrOH, aluminium isopropoxide	65	123
OH	H	CH_2OH	H	2,5-dichloro analogue, Pd/C, H_2 MeOH, KOH	44	23
OH	H	Br	H	4-Bromo-3-formylthiophene, $NaBH_4$	78	14
OH	H	I	H	4-Iodo-3-formylthiophene, $NaBH_4$	81	14
OH	H	OMe	Ph	Ethyl carboxylate, dihydrobis-(2-methoxy ethoxy)aluminate	72	34
OH	H	H	COOH	Hydrolysis of 5-COOEt-3-thenyl acetate	53	30
				Bromomethyl analogue, NaOH	76	65
OH	Cl	CH_2OH	Cl	Bischloromethyl analogue, H_2O	70	23
				Dimesylate analogue, Na_2CO_3, H_2O, dioxane	87	71
OH	Cl	CH_2Cl	Cl	Mesylate analogue, $NaHCO_3$, H_2O, dioxane	82	71
CH_2OH	H	H	H	3-Thienylacetic acid, $LiAlH_4$	79	51
OMe	H	H	H	3-Thenyl bromide, MeONa	38	124
OMe	CHO	H	H	Metalation of methyl thenyl ether, condensation with DMF	89	125
					54	124

OMe	COOH	H	H	3-Methoxymethyl thiophene lithiation and carbonylation	89	125
OMe	$C(Ph)_2OH$	H	H	Metalation of methyl thenyl ether, condensation with Ph_2CO	46	124
OMe	SMe	H	H	Metalation of methyl thenyl ether, condensation with dimethyl disulfide	61	124
OPh	H	H	COOH	4-Chloromethyl-2-thiophene aldehyde PhONa, MeOH	16	65
OAc	H	H	H	3-Chloromethyl thiophene, NaOAc	58	41
OAc	NO_2	H	H	Nitration of 3-thenyl acetate	30	41
OAc	H	H	COOEt	$3\text{-}CH_2Br$ analogues, AcOK, AcOH	74	30
OAc	H	H	NO_2	Nitration of 3-thenyl acetate	--	41
OSO_2Me	Cl	CH_2Cl	Cl	2,5-Dichloro-3,4-bis-(chloromethyl) thiophene, $AgOSO_2Me$, MeCN	25	71
OSO_2Me	Cl	CH_2OSO_2Me	Cl	Bischloromethyl analogue, $AgOSO_2Me$, MeCN	71	71



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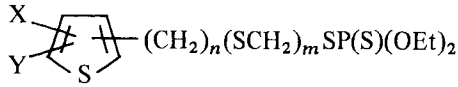


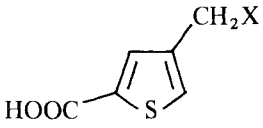
29

The synthesis of 2-thenyl-*N*-methyl carbamates of general formula **28**, which possess insecticidal activity, and of thiomethyl derivatives of general formula **29** are reported in patents.[132]

2. Spectroscopic and Physicochemical Properties

A. Dissociation Constants

Apparent dissociation constants in 80% methyl cellosolve of halomethyl, hydroxymethyl, and thiomethyl carboxylic acids **30** to **32** have been determined (Table 10) to study the transmission of inductive effect in the thiophene series.[65,133] The *pK* values are correlated with σ_I constants, the slope being -0.77 for the acids **30** and -0.50 for the acids **31**. The interpretation of transfer of inductive effect across the thiophene nucleus involves participation of π electrons.[65]



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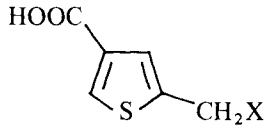

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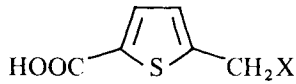


32

B. Nuclear Magnetic Resonance

Proton and ^{13}C NMR shifts of hydroxymethylthiophenes and their derivatives are recorded in Tables 11 to 14.

TABLE 10. DISSOCIATION CONSTANTS OF THE ACIDS **30**, **31**, AND **32**

Substituent X		**30**	**31**	**32**
H		6.08	6.58	6.16
Br		5.68	5.75	–
OH		5.87	6.48	5.95
OCH_3		5.84	6.41	5.85
OC_6H_5		5.70	6.37	5.79
SH		5.90	6.47	5.89
SC_2H_5		5.92	6.49	–
$SO_2C_6H_5$		5.64	6.28	5.63
COOH	pK_1	5.83	5.95	–
	pK_2	6.95	6.99	–

Substituent chemical shifts (SCS) for 3, 4, and 5 protons of 2-hydroxymethylthiophene relative to the α and β protons of thiophene are -0.19, -0.22, and -0.19 respectively,[141] whereas SCS for 2, 3, 4, and 5 carbons in the same compound are 20.4, -2.2, -0.1, and -0.3.[140] Direct and long-range CH-coupling constants[140] are in good agreement with those reported for other monosubstituted thiophenes.

When the effects of substituents on ^{13}C shifts of compounds in series **30** are compared with those in series **31** by plotting against each other the shifts for the corresponding carbons from the two series, the best correlation ($r = 0.999$, slope $\approx$ 1) is obtained for the methylene chemical shifts.[72] A significant correlation is also found between carboxyl carbon shifts in series **31** and σ_I constants for X substituents.[73]

Extensive studies on the effects of substituents on ^1H[134] and ^{13}C chemical shifts[140-142] of monosubstituted furans, thiophenes, selenophenes, and tellurophenes showed that the ease of transmission of the 2-substituent resonance effects to the 5-hydrogen and 5-carbon increase in the series furan < thiophene < selenophene < tellurophene and that good correlations of 5-proton shifts versus 5-carbon shifts are found in all four systems.[134]

C. *Mass Spectrometry*

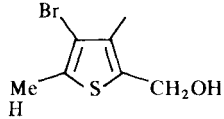
The mass spectral behavior of hydroxymethylthiophenes and derivatives have been scarcely investigated. Mass spectral data are available for 2(2-thiophene)ethanol[11] and for thiophenecarboxylic acids (**30** to **32**).[65]

D. *Infrared Spectroscopy*

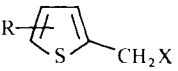
The infrared frequencies of hydroxymethylthiophenes and derivatives are recorded in Table 15.

The infrared carbonyl-stretching frequencies of compounds in series **30** and **31** are reported in Table 16.[72] In CCl_4 two absorption bands occur, the higher wave number assigned to the C=O stretching of the free carboxylic acid groups, and the lower wave number ascribed to the carbonyl stretching of carboxyls bonded by an intermolecular hydrogen bond of the type C=O . . . HO. In chloroform solution only one band occurs, hydrogen bonding between the carboxylic groups and chloroform molecules being preferred to self-association of the acids. The infrared carbonyl-stretching frequencies of **30** and **31** show reasonable correlations with σ_I constants for X substituents. Summarizing the results of equilibrium and spectroscopic studies on the transmission of substituent effects in series **30** and **31**, all of the data can be explained in terms of differences in the relative coplanarity of the systems **30** and **31** and the consequences on the π inductive effect.[72]

TABLE 11. ^{1}H NMR SHIFTS OF 2-HYDROXYMETHYL- AND 2-THIOMETHYLTHIO-

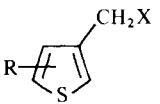
					Thiophene Ring	
Solvent	X	R_3	R_4	R_5	H_3	H_4
a	OH	H	H	H		6.83[b]
c					6.91	6.88
d	OH	CH_2OH	H	H		6.94
e	OH	COOMe	H	H		7.43
f	OH	Br	H	H		6.94
f	OH	I	H	H		7.03
a	OH	NO_2	H	H		7.55
g	OH		Br	Me		
c	OH	H	COOH	H	7.33	
a	OH	H	H	C≡CSMe	6.73[h]	6.99[h]
a	OH	H	H	NO_2	7.06	7.83
i	CH_2OH	H	H	H		6.70–7.10[b]
i	CH_2OH	H	H	Me	6.50	6.39
i	$(CH_2)_2OH$	H	H	H		6.63–7.03[b]
a	OMe	H	H	H		6.85[b]
e	OMe	CH_2OMe	H	H		7.04
e	OMe	COOMe	H	H		7.41
c	OMe	H	COOH	H	7.38	
a	OMe	H	H	Br	6.53	6.75
c	OPh	H	COOH	H	7.54	
a	OAc	H	H	H		6.98[b]
i	OAc	NO_2	H	H		7.53[h]
e	OAc	H	NO_2	H	7.63	
i					7.56	
a	OAc	H	H	Br	6.70	6.83
a	OAc	H	H	NO_2	6.95	7.66
i					7.02	7.72
e					7.03	7.81
c	SH	H	COOH	H	7.36	
i	SEt	CH_2SEt	H	H		6.86
i	SEt	CH_2SEt	H	COOMe		7.56
c	SEt	H	COOH	H	7.35	
i	SCH_2COOH	H	H	H		7.00[b]
a	SCN	H	H	H		6.88[b]
a	SCN	NO_2	H	H		7.60
a	SCN	H	H	CH_2SCN	6.93	6.93
a	SCN	H	H	NO_2	7.24	6.88
a	NCS	H	H	H		
a	NCS	H	H	Br	6.64	6.80
c	SO_2Ph	H	COOH	H	7.28	
e	$SO_2C_6H_4pMe$	H	H	H		6.70–7.75[b]

[a] Letter codes, either under "Solvent" or as italic superscripts, have the following designations: a, cyclohexane; b, multiplet for thiophene ring protons; c, acetone-d_6; d, $CDCl_3$ + CF_3COOH;

PHENES AND DERIVATIVES[a] R- 

			Coupling Constants (Hz)					
H_5	CH_2	Others	$J_{3,4}$	$J_{4,5}$	$J_{3,5}$	$J_{CH_2-H_3}$	$J_{CH_2-CH_2}$	Reference
	4.56							60
7.21	4.67		3.40	5.14	1.11			134
7.15	4.58, 4.47	5.27		5.0				27
7.13	4.97	3.88		5.5				67
7.38	4.79			5.4				14
7.38	4.76			5.4				14
7.35				5.4				60
	4.18	2.38						66
8.10	4.80							65
	4.58	2.44, 3.36						20
	5.03		4.1					60
	3.70	2.95, 3.08					6.5	53
	3.63	2.37, 2.82, 3.31	4				6.5	53
	3.57	1.70–2.10, 2.85, 3.47						53
	4.43							60
7.27	4.55, 4.64	6.61, 6.65		5.0				27
7.16	4.98	3.51, 3.84		5.5				67
8.16	4.61	3.34						65
	4.35	3.21	3.7			0.9		60
8.20	5.32	6.84–7.40						65
	5.13							60
7.24[h]	5.59	2.15		5.8				16
8.28	5.23	2.16				0.81		7
8.21	5.19	2.09			1.6	0.7		16
	5.05	1.98	3.9			0.7		60
	5.13	2.08	3.9					60
	5.19	2.09	4.0			0.7		16
	5.26	2.16	4.17			0.84		7
8.08	4.02	2.50						65
7.01	3.66, 3.85	1.21, 2.22–2.64						98
	3.67, 3.87	1.24, 2.27, 2.72						98
8.11	4.00	1.23, 2.54						65
	4.00	3.05, 11.8						135
	4.10							60
7.61	4.88							60
	4.29							60
	4.58		4.1					60
	4.55							60
	4.64		3.8			0.7		60
8.17	4.82	7.50–7.86						65
	4.30	2.39, 6.70–7.75						136

TABLE 12. ^{1}H NMR SHIFTS of 3-HYDROXYMETHYLTHIOPHENES AND DERIVATIVES[a]

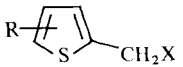


	Product				Thiophene Ring					Coupling Constants (Hz)				
Solvent	X	R_2	R_4	R_5	H_2	H_4	H_5	CH_2	Others	J_{24}	J_{25}	J_{45}	J_{CH_2-H}	Reference
a	OH	Br	H	H		7.05	7.38	4.57				5.4		14
a	OH	I	H	H		7.01	7.63	4.56				5.4		14
b	OH	$S(2C_4H_3S)$	H	Et		6.75		4.70	2.00, 2.71, 6.89, 7.08, 7.22					68
c	OH	H	CH_2OH	H	7.29		7.29	4.63	4.33					23
c	OH	H	Br	H	7.41		7.46	4.62			3.3		0.9[d]	14
a	OH	H	I	H	7.36		7.60	4.60			3.3		0.9[e]	14
c	OH	H	H	COOH	7.76	7.61		4.66						65
f	OH	Cl	CH_2OH	Cl				4.49	4.90				5.5[g]	137
b								4.58	3.64					23, 71
b								4.55	3.16					138
b	OH	Cl	CH_2Cl	Cl				4.63	4.61, 7.56					71
b	OMe	H	H	H		6.95–7.40[h]		4.40	3.34					125
i						7.00[h]		4.31						60
b						6.97–7.35[h]		4.45	3.37					124
j	OMe	CHO	H	H		6.92–7.37[h]		4.60	3.32, 7.99					124
b	OMe	COOH	H	H		7.31	7.64	4.86	3.46, 10.8			5.2		125
j	OMe	CPh_2OH	H	H		6.88–7.46[h]		4.00	3.08, 5.47					124
j	OMe	SMe	H	H		6.75–6.98[h]		4.29	2.27, 3.17					124
b	OMe	H	H	CHO	7.75	7.65		4.48	3.40, 9.90	1.6				69
c	OMe	H	H	COOH	7.73	7.64		4.45	3.34					65
b					7.82	7.51		4.47	3.42	1.5				69
c	OPh	H	H	COOH	7.85	7.80		5.14	6.84–7.40					65
j	OAc	Cl	CH_2OAc	Cl				5.00	2.00					137

j	OSO_2Me	Cl	CH_2Cl	Cl				5.16	2.97, 4.57			71
b	OSO_2Me	Cl	OSO_2Me	Cl				5.25	3.08			71
c	SH	H	H	COOH	7.78	7.60		3.81	2.29			65
c	SEt	H	H	COOH	7.75	7.58		3.78	1.20, 2.46			65
j	SCH_2COOH	H	H	H		7.18[h]		3.85	3.03, 11.9			135
j	SCH_2COOH	Me	H	Me		6.58[h]		3.65	3.0, 3.33, 11.6			135
j	SCN	H	H	H		7.09[h]		3.95				60
j	SCN	NO_2	H	H		7.25	7.85	4.66			5.5	60
c	SO_2Ph	H	H	COOH		7.50–7.80[h]		4.60	7.50–7.80			65

[a] Letter codes, either under "Solvent" or as italic superscipt, have the following designations: a, acetone-d_6 + CF_3COOH; b, $CDCl_3$; c, acetone-d_6; d, $J_{CH_2-H_2}$; e, $J_{CH_2-H_5}$; f, DMF; g, J_{CH_2-OH}; h, multiplet for thiophene ring protons; i, cyclohexane; j, CCl_4.

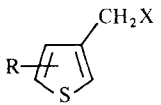
TABLE 13. ^{13}C NMR SHIFTS OF 2-HYDROXYMETHYLTHIOPHENES AND DERIVATIVES[a]



Solvent	X	R_3	R_4	R_5	C_2	C_3	C_4	C_5	CH_2	COOH	Others	Reference
a	OH	H	H	H	146.8	123.8	127.4	125.4	59.2			139
b					146.0	125.1	127.2	125.3	59.5			140
a	OH	H	COOH	H	147.28	124.86	134.21	132.13	58.84	164.47		73
c					147.3	123.8	133.3	131.8	58.1	163.2		72
a	OMe	H	COOH	H	142.69	127.18	132.83	135.39	68.96	168.23		73
					141.9	126.2	133.3	133.0	57.2	163.0		72
a	OPh	H	COOH	H	140.31	127.05	134.20	132.95	64.29	163.90	114.82, 121.22 129.42, 157.93	73
c					140.4	127.0	133.4	133.4	63.9	163.0	157.4(1′), 114.7(2′) 129.3(3′), 120.9(4′)	72
a	SH	H	COOH	H	145.99	125.97	134.32	132.08	22.83	164.12		73
c					146.0	125.2	133.3	132.0	22.2	163.0		72
a	SEt	H	COOH	H	143.75	126.75	134.20	132.55	30.02	164.77	14.23, 25.45	73
c					143.5	126.0	133.3	132.3	29.0	163.0	14.3, 24.8	72
a	SO_2Ph	H	COOH	H	137.92	121.15	134.59	134.59	56.34	163.76	128.54, 129.41 130.67, 134.29	73
c					137.5	138.9	133.3[d]	134.6	55.2	162.7	130.3(1′), 127.8[e](2′) 128.9[e](3′), 133.7[d](4′)	72

[a]Letter codes, either under "Solvent" or as italic superscripts, have the following designations: a, $CDCl_3$; b, acetone-d_6; c, DMSO-d_6; d, e, alternative assignments.

TABLE 14. ^{13}NMR SHIFTS OF 3-HYDROXYMETHYL THIOPHENES AND DERIVATIVES



Solvent	X	R_2	R_4	R_5	C_2	C_3	C_4	C_5	CH_2	COOH	Others	Reference
a	OH	H	H	COOH	128.23	144.77	133.05	135.19	59.32	163.85		73
b					127.8	144.5	132.4	134.2	58.5	162.5		72
a	OMe	H	H	COOH	130.33	140.59	134.05	135.00	69.61	165.10	58.14	73
b					129.8	140.0	132.7	134.5	57.4	162.4	68.6	72
a	OPh	H	H	COOH	129.80	139.19	132.98	136.01	65.25	163.83	115.06, 121.39, 129.78 158.71	73
b					130.4	138.6	132.7	134.7	64.3	162.3	157.7(1'), 114.5(2'), 129.1(3'), 120.5(4')	72
a	SH	H	H	COOH	128.73	142.69	133.85	135.63	23.11	163.87		73
b					128.7	142.7	133.5	134.4	22.2	162.4		72
a	SEt	H	H	COOH	131.14	140.99	136.23	133.55	30.26	168.21	14.40, 25.68	73
b					129.4	139.9	133.8	134.4	29.1	162.5	14.4, 25.0	72
a	SO_2Ph	H	H	COOH	133.60	138.32	134.89	135.75	56.79	163.31	128.47, 129.37, 129.18 134.19	73
b					133.6	137.9	134.5	134.3	55.5	162.2	129.1(1'), 127.6(2') 128.9(3'), 133.7(4')	72

a, $CDCl_3$; b, DMSO-d_6.

TABLE 15. INFRARED FREQUENCIES OF HYDROXYMETHYLTHIOPHENES

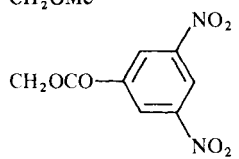
Product						
R_2	R_3	R_4	R_5	ν_{OH}	Others	Reference
CH_2OH	CH_2OH	H	H	3200		27
CH_2OH	Br	H	H	3320		14
CH_2OH	I	H	H	3270		14
CH_2OH	H	H	C≡CSMe	3100–3500	2150	20
CH_2OH	H	H	NO_2	3420	1340, 1495	143
CH_2OH	H	H	I	3300	796, 1010	118
CH_2OMe	CH_2OMe	H	H		1080	27
Br	CH_2OH	H	H	3340		14
I	CH_2OH	H	H	3330		14
H	CH_2OH	Br	H	3280		14
H	CH_2OH	I	H	3270		14
Cl	CH_2OH	CH_2OH	Cl	3350		71
Cl	CH_2OH	CH_2Cl	Cl	3300		71
H	CH_2OMe	H	H		1100	124
COOH	CH_2OMe	H	H		1675, 2200–3300	125
H		H	H		708, 720, 765, 775 815, 829, 853, 910, 960	144
Cl	CH_2OSO_2Me	CH_2Cl	Cl		1175, 1360	71
Cl	CH_2OSO_2Me	CH_2OSO_2Me	Cl		1190, 1350	71

TABLE 16. C=O STRETCHING VIBRATION FREQUENCIES (cm^{-1}) FOR COMPOUNDS IN SERIES **30** AND **31**[a]

	Series **30**			Series **31**		
	CCl_4		$CHCl_3$	CCl_4		$CHCl_3$
X	ν(C=O) Free	ν(C=O) Bound	ν(C=O) Bound	ν(C=O) Free	ν(C=O) Bound	ν(C=O) Bound
H	1733	1681	1694	1738	1692	1702
OH	1734	1683	1699	1739	1694	1711
OMe	1734	1682	1702	1739	1690	1706
SH	1734	1682	1698	1739	1690	1705
OPh	1734	1683	1699	1741	1691	1706
COOH			1712			1718
SEt	1734	1682	1697	1738	1686	1705
Br	1737	1685	1701	1742	1693	1708
SO_3Ph			1702			1708

[a] From Ref. 72.

E. Ultraviolet Spectroscopy

Ultraviolet absorptions of hydroxymethyl-, thiomethylthiophenes, and derivatives are recorded in Table 17.

F. Other Properties

2-Hydroxymethylthiophene has radiation-protective effects on mice irradiated with lethal doses of X-rays[146] and protective effect against hyperbaric oxygen pressures.[147]

2-Hydroxymethylthiophene[148] and thenyl xanthates[149] are efficient as corrosion inhibitors.

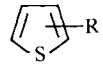
2-Thenyl alcohol, 2-thenyl acetate, and 2-thenyl formate have been identified in coffee aroma by gas-chromatography/mass spectrometry;[150] thenylmethyl sulfide has been used as coffee-flavoring agent.[151]

3. Chemical Reactivity

A. Oxidation and Reduction

2-Thenyl alcohol is oxidized to 2-thiophenecarboxaldehyde by liquid-phase catalytic oxidation[152] by $AgCO_3$ absorbed on celite (2 hours, 94% yield)[153] by 2,2′-bipyridinium chlorochromate (3 hours, 79% yield)[154] and with $K_2S_2O_4$ (43%).[155]

TABLE 17. ULTRAVIOLET ABSORPTION OF HYDROXYMETHYL- AND THIOMETHYLTHIOPHENES



R_2	R_3	R_4	R_5	λ_{max}	ϵ	Reference
CH_2OH	CH_2OH	H	H	246	4,250	27
				241	4,950	
CH_2OH	H	H	$C{\equiv}C(2C_4H_3S)$	340	13,200	145
				335	14,150	
				328	17,100	
				318	20,500	
				313	19,700	
				307	17,950	
				303	16,600	
				257	11,150	
CH_2OH	H	H	I	254	4.01[a]	118
CH_2OH		Br	Me	247[b]	14,000	66
CH_2OAc	H	H	$C{\equiv}C(2C_4H_3S)$	341	12,600	145
				335	13,350	
				328	15,900	
				319	19,200	
				316	18,200	
				310	16,700	
				303	15,300	
				257	10,400	
H	CH_2OH	CH_2OH	H	236	5,300	23
				239	5,300	
Cl	CH_2OH	CH_2OH	Cl	248	6,700	23, 71
Cl	CH_2OH	CH_2Cl	Cl	251	5,900	71
Cl	CH_2OSO_2Me	CH_2Cl	Cl	257	5,700	71
Cl	CH_2OSO_2Me	CH_2OSO_2Me	Cl	256	5,800	71
CH_2SEt	CH_2SEt	H	H	240.5	8,300	98
CH_2SEt	CH_2SEt	H	COOMe	257	7,400	98
				289	9,000	

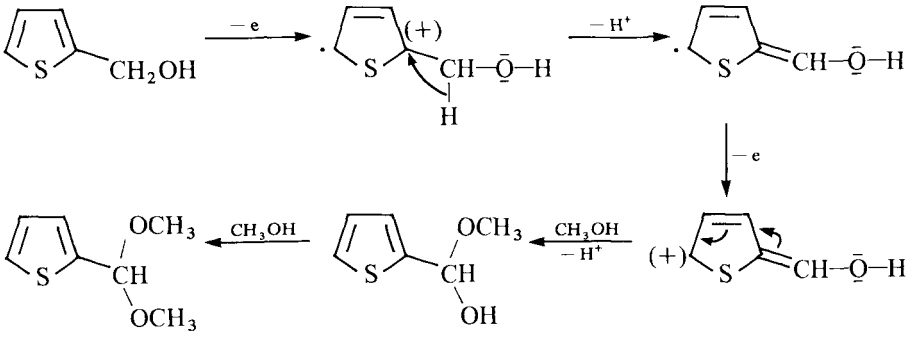
[a] Log ϵ.
[b] (R)—(+) form.

During the oxidation of 2-thenyl alcohol in methanol, using sulfuric acid as electrolyte, the dimethyl acetal of 2-thiophenecarboxyaldehyde is formed as the main product.[112]

The proposed mechanism for this oxidation, depicted in Scheme 4, involves the abstraction of electron from the α position of the ring, followed by the loss of a proton from the CH_2OH group.

A general method for the oxidation of heteroaromatic alcohols to carbonyl compounds by OC—Me_2SO can successfully be applied for the oxidation of 2-thiophenemethanol.[156]

Oxidation of ethyl thenyl sulfides with hydrogen peroxide in acetic acid (peracetic acid) gives the sulfones in high yields,[129] sulfoxides being absent or present



Scheme 4

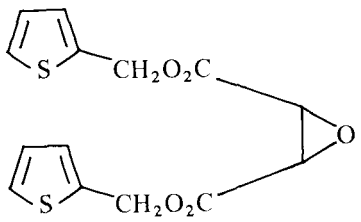
in traces in the reaction products. Thenyl sulfoxides and sulfones are obtained under different oxidation conditions;[128] in fact it is well known that the reaction products, as well as the mechanism and the rate of oxidation, are largely affected by the nature of the oxidant.[157-166]

Reductions of 2-thiophenemethanol using $Co(CO)_8$ and $CoCO_3$[167] and of 2-thenylcarbanilate with Pd-black[75] lead to 2-methylthiophene in 24% and 94% yields respectively.

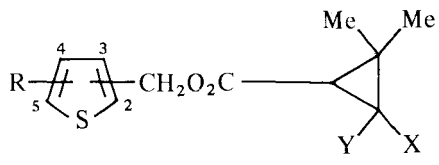
B. Other Reactions

2-Thenyl alcohol reacts with 2-thenoyl chloride to give 80% 2-thenylthenoate;[121] thenyl sodium alcoholate, reacted with $(p\text{-}MeC_6H_4SO_2)_2O$, affords the corresponding tosylate.[168] (2-Thienyl)alkanols, treated with lithium and terbutyl alcohol in liquid ammonia, provide aliphatic keto alcohols in high yields.[169]

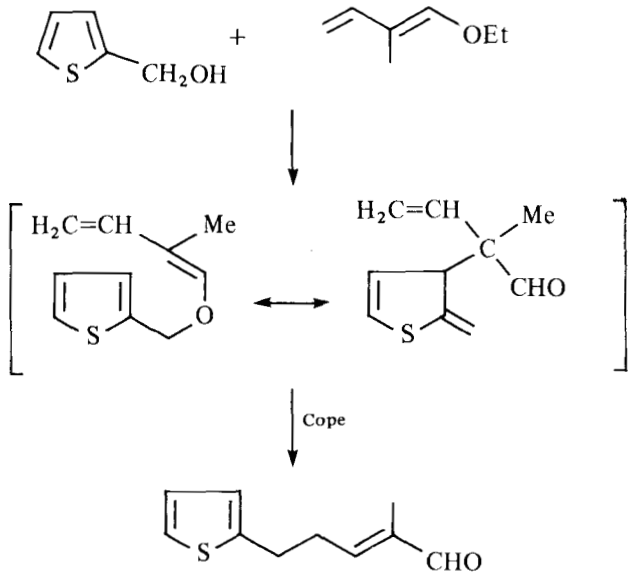
2-Thiophene methanol reacted with $(COOH)_2$ forms 4-hydroxythiopyran, which can be oxidized with $KMnO_4$ to thiopyrone,[170] whereas the alcohol reacted with epoxysuccinic acid gives epoxysuccinic diester **33**.[171] Substituted thenyl alcohols can be reacted with 2,2-dimethyl-3-X,Y-cyclopropane-1-carbonylchlorides[172,173] or derivatives of chrysanthemum carboxylic acid[174-177] to give a series of compounds of general formula **34**, useful as insecticides.



33



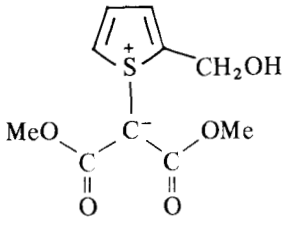
34



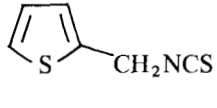
Scheme 5

The double bond in the thiophene ring of 2-thiophenemethanol can participate in a Claisen-Cope type rearrangement,[178] as shown in Scheme 5.

The thiophenium ylide **35** is obtained in 92% yield by rhodium(II)-catalyzed addition of dimethyldiazomalonate to 2-thenyl alcohol.[179]



35



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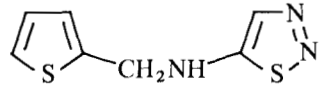
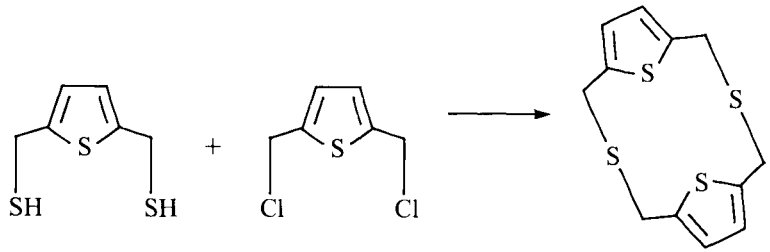


38

Thenyl thiocyanate was shown by NMR to undergo thermal isomerization (150°, 2 hours) to isothiocyanate **36**.[180] Isothiocyanate **36** and L-cysteine HCl in dimethylformamide give **37**;[181] cyclization of **36** with diazomethane affords 1,2,3-thiadiazole **38**.[182]



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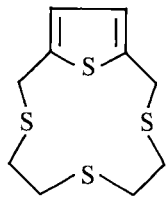


40

The synthesis of the heterophanes **39**[183] and **40**[184] is accomplished by reaction of 2,5-bis(mercaptomethyl)thiophene with 2,5-bis(chloromethyl)thiophene and 1,5-dibromo-3-thiopentane under high-dilution conditions.[104]

IV. AMINOMETHYL AND PHOSPHOMETHYL DERIVATIVES

1. Synthesis

A. Aminomethylthiophenes

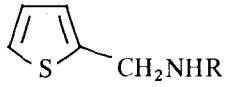
Aminomethylthiophenes can be synthesized in high yields by one of the three standard methods listed in Hartough's volume:[1] (1) reduction of oximes, (2) the aminomethylation reaction, and (3) reaction of thenyl halides with amines.

2-Thenylamine is obtained in 62% yield by reduction of 2-carbaldoxime,[185] in 40% yield by aminomethylation of thiophene,[186] and in 41% yield by reacting 2-thenyl chloride with urotropin in $CHCl_3$.[187] The synthesis of 3-thenylamine from *N*-(3-thenyl)phtalimide, hydrazine hydrate under reflux with HCl, and subsequent treatment with NaOH has been reported in a patent.[188]

5-Substituted 2-thenyl amines and 2-substituted 3-thenyl amines can be prepared in high yields by treatment of unsubstituted amines with butyllithium and an appropriate reagent for the introduction of the desired functional group in the 5-position of the ring;[124] 5-chloro-2-thenyl amines are obtained by chlorination of 2-thenyl amines with sulfuryl chloride.[189]

The synthesis of aminomethyl thiophenes **41**,[190-192] **42**,[193] **43**,[194] **44**,[195] **45**,[196] **46**,[197] **47**,[198] and of other derivatives such as 5-phenyltetrazole,[199] thenyl

piperazines,[200,201] imidazolines,[202] benzomorphans,[203,204] morphines and norcodeines,[205,206] ethanomorphinans,[207,208] benzothiazepines,[209] thiacarbocyanine halide dyes,[210] and other derivatives[83,211–213] with pharmacological or insecticidal activity has been reported; however, details on the synthetic procedure and on the physicochemical properties of these compounds are not available.



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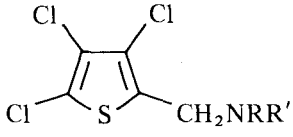
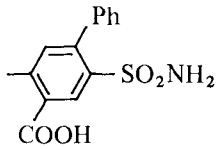
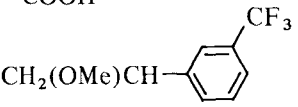


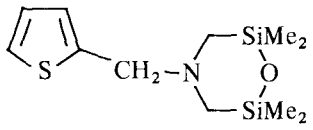
44

42 R =



43 R =





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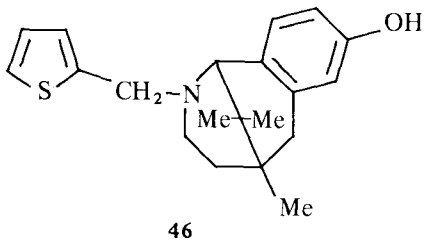

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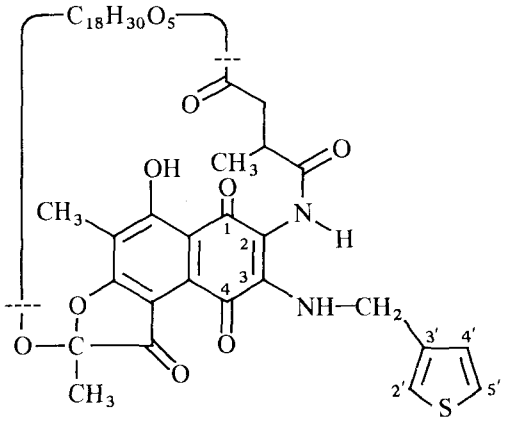


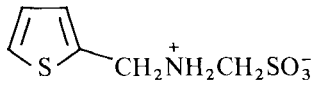
47

2-Thenylaminosulfonic acid **48** is prepared by reaction of thiophene and formaldehyde with aminomethyl sulfonic acid.[214]

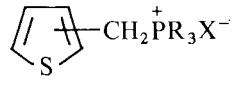
B. Phosphomethylthiophenes

Thenyltriarylphosphonium halides **49** are synthesized by reaction of thenyl halides with triarylphosphines. By this method 2-thenyltriphenylphosphonium chloride is obtained in quantitative yield,[215] the 2-bromide in 95%,[26] the 2- and 3-bromides in 79% and 71%[216] yields respectively. Thenyltriphenylphosphonium chlorides with substituents in the thiophene ring can similarly be prepared in high yields;[14] diphenylbenzyl and diphenyl-2-furylmethyl phosphonium bromides are obtained with about 40% yields.[217]

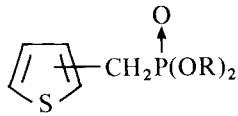
Diethyl phosphonates **50** are prepared by heating thenyl halides with an excess triethylphosphite under nitrogen (Arbuzov reaction);[30,218,219] 2-thenylphosphonic acid is obtained by hydrolyzing the dibutyl ester with HCl.[220]



48



49



50

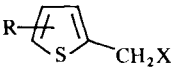
2. Spectroscopic and Physicochemical Properties

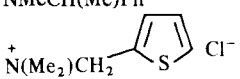
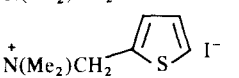
A. Dissociation Constants

In 1 *M* electrolytes (KNO_3 or KCl) the acid dissociation constant of 2-thenylamine (pK_a 8.92) is intermediate between that of benzylamide (9.46) and 2-furfurylamine (8.89),[221] in agreement with the electron-withdrawing effect of the heteroatoms. The acid dissociation constant of 2-thenylamine in 50% aqueous dioxane at 30° (8.25) is 0.33 pK_a units lower than that of benzylamine; the complex formation constants with Cu(II), Ni(II), Co(II), Zu(II), Cd(II), and Ag(I) have been reported.[222]

B. Nuclear Magnetic Resonance

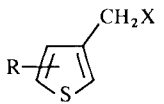
The proton NMR shifts of 2- and 3-aminomethylthiophenes are recorded in Tables 18 and 19 respectively. Table 20 lists the ^1H and ^{31}P NMR shifts of phosphomethyl derivatives. The greater electron-withdrawing effect of 2-thenyl relative to 3-thenyl is indicated by ^{31}P NMR shifts, the phosphorus in 2-thenyltriphenylphosphonium bromide being shielded relative to that of the 3-isomer.[216,217]

TABLE 18. ^{1}NMR SHIFTS OF 2-AMINOMETHYLTHIOPHENES AND DERIVATIVES[a] R- 

Solvent	X	R_3	R_4	R_5	Thiophene Ring H_3	H_4	H_5	CH_2	Others	Reference
a	NH_2	H	H	H		6.81[b]		3.80		60
c	NHPh	H	H	H		6.41–7.17[b]		4.36	3.74, 6.41–7.17	61
c	NHMe	H	H	H	6.74	6.74	7.01	3.83	2.39	47
c	NMe_2	H	H	H	6.77	6.77	7.04	3.53	2.16	47
c	NMe_2[d]	Me	H	H		6.65	6.98	3.54	2.15, 2.21	223
e	NMe_2	CPh_2OH	H	Me		6.05			2.12, 7.25–7.57	124
e	NMe_2	H	H	Me	6.6	6.6		3.52	2.24, 2.40	124
e	NMe_2	H	H	CHO	7.05	7.65		3.66	2.26, 9.84	124
c	NMe_2	H	H	$SiMe_3$	6.80–6.98[b]			3.54	1.28, 2.72	124
c		H	H	H	6.85	6.85	7.12	3.68	1.16, 1.69	224
c	$NMeCH_2C_6H_4$*o*Me	H	H	H	6.77	6.77	7.00	3.65	2.15, 2.33, 3.43, 7.00	225
c	$NMeCH_2C_6H_4$pMe	H	H	H	6.80	6.80	7.06	3.66[f]	2.04, 2.29, 3.79[f], 7.06	225
c	$NMeCH_2CH_2Ph$	H	H	H	6.74	6.74	7.04		2.26, 2.67	225
c	NMeCH(Me)Ph	H	H	H	6.70	6.70	7.14	3.59	1.35, 2.16, 3.59, 6.70	225
g		H	H	H	7.65	7.28	7.28	4.74	3.03	47
g		H	H	H	7.48	7.11	7.11	5.38	3.26	47
h	$NEtCH_2Ph$	H	H	H	6.70	6.70	7.10	3.63[f]	1.00, 2.45, 3.46[f], 7.10	225

[a] Letter codes, either under "Solvent" or as italic superscripts, have the following designations: a, cyclohexane; b, thiophene ring protons; c, CCl_4; d, $J_{45} = 5$ Hz; e, $CDCl_3$; g, D_2O; f, alternative assignments; h, CS_2.

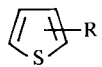
TABLE 19. ^{1}NMR SHIFTS OF 3-AMINOMETHYLTHIOPHENES AND DERIVATIVES[a]

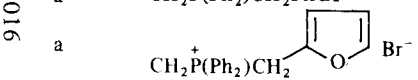


Solvent	X	R_2	R_4	R_5	Thiophene Ring H_2	Thiophene Ring H_4	Thiophene Ring H_5	CH_2	NH	Others	Reference
a	NH_2	1-Pyrryl	H	H		7.08	7.30	3.53	2.5	6.20, 6.96	226
b	NHEt	Cl	CH_2NHEt	Cl				3.65	1.62	1.07, 2.60	23
a	NHCHO	1-Pyrryl	H	H		6.95	7.35	4.15	8.4	6.25, 7.0, 8.05	226
a	NHCOMe	1-Pyrryl	H	H		6.98	7.30	4.12	8.3	1.83	226
a	NHCOEt	1-Pyrryl	H	H		6.96	7.33	4.13	8.2	1.02, 2.11	226
a	NHCOPh	1-Pyrryl	H	H		7.01	7.30	4.35	9.0	7.50, 7.86	226
a	$NHCOC_7H_7$	1-Pyrryl	H	H		7.03	7.36	4.38	8.9	2.38, 7.21, 7.78	226
a	$NHCO(\alpha C_4H_3S)$	1-Pyrryl	H	H		6.96	7.28	4.28	8.9	7.0, 7.7	226
c	NMe_2	H	H	H		7.00–7.37[d]		3.42		2.17	124
c	NMe_2	CHO	H	H		6.87	7.35	3.56		2.15, 8.15	124
c	NMe_2	COPh	H	H		7.15–7.80[d]		3.6		2.12, 7.15–7.80	124
b	NMe_2	Cl	H	H		6.85–6.97[d]		3.32		2.15	124
b	NMe_2	Br	H	H		6.92–7.17[d]		3.32		2.16	124

[a] Letter codes, either under "Solvent" or as italic superscripts, have the following designations: a, dimethylsulfoxide-d_6; b, CCl_4; c, $CDCl_3$; d, thiophene ring protons.

TABLE 20. ^{1}H AND ^{31}P NMR SHIFTS OF PHOSPHOMETHYLTHIOPHENES[a]



Solvent	R_2	R_3	R_4	R_5	Thiophene Ring H_2	H_3	H_4	H_5	CH_2	Others	^{31}P	$^{2}J_{PCH}$	Reference
a	$CH_2\overset{+}{P}Ph_3Br^-$	H	H	H			7.6[b]		4.81		−18.25	12.96	216
a	$CH_2\overset{+}{P}(Ph_2)CH_2Ph\,Br^-$	H	H	H			6.6–6.80[b]		4.37	4.22		12.7, 13.5	217
a		H	H	H			6.2–7.6[b]		4.35	4.55		12.7, 12.9	217
c	$CH_2PO(OEt)_2$	H	H	H			6.82–7.3[b]		3.35	1.3, 3.82, 4.32	−21	21	227
c						6.92	6.92	7.10	3.35	1.26, 4.04			228
a	H	$CH_2\overset{+}{P}Ph_3Br^-$	H	H			6.65–7.6[b]		4.66	7.6	−19.75	13.02	216
c	H	$CH_2PO(OEt)_2$	H	H			7.0–7.4[b]		3.22	1.22, 4.06			228

[a] Letter codes, either under "Solvent" or as italic superscripts, have the following designations: a, CF_3COOH; b, thiophene ring protons; c, $CDCl_3$.

C. *Mass Spectrometry*

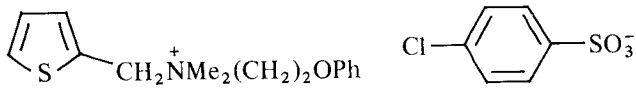
The products of the Stevens and Sommelet rearrangements of thenylammonium ions were identified by mass spectrometry;[47] the mass spectra of thenylammonium salts[47] and of *N*-(2-thenyl) aziridine[224] have been discussed.

D. *Infrared Spectroscopy*

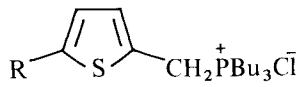
The NH-stretching frequencies of 2-thenylamine occur at 3426 and 3310 cm^{-1} and the NH bending at 1640 and 1550 cm^{-1}.[229] The infrared frequencies of *N,N*-dimethyl-5-substituted-2-thenylamines have been reported[124] together with those of 3-*N,N*-dimethylthenylamine[124] and of 2-(1-pyrryl)-3-thenylamine.[226]

E. *Other Properties*

Thenium closylate **51** shows anthelmintic efficacy, which is increased by synergistic effect when combined with piperazine phosphate.[230] Yields of snap beans were found to be increased by application of growth regulators **52**.[231] The influence of aromatic rings and their substituents on the mutagenic activity of nitrogen mustards has also been investigated.[232,233]



51



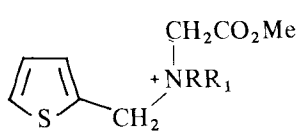
R = Cl, Br

52

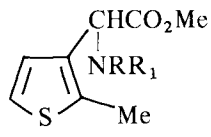
3. Chemical Reactivity

A. *Rearrangements*

Cations **53** rearrange to give almost entirely Sommelet products **54**;[234] other ammonium derivatives such as **55** are thermally cleaved and rearranged to **56** in aqueous KOH in 27% yield.[235]



53



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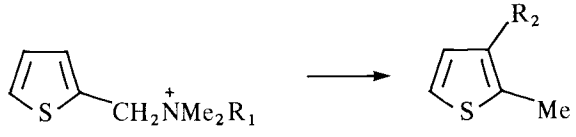
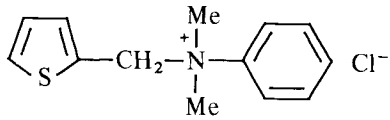


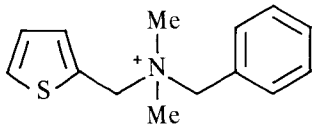
55 56

$R_1 = CH(OBu)CH_2Br, CH{=}CMe_2$ $R_2 = CH_2CO_2Bu, CMe_2CHO$

Giumanini et al.[11,236] have shown that the base-induced rearrangements of *N*-(2-thenyl)-*N,N*-dimethylanilinium chloride **57** give the Sommelet amine, the Stevens amines, as well as the Hofmann-Martius amines in low overall yield; fusion of **57** with potassium hydroxide produces a marked increase of the yield of rearranged amines. Further studies on the base-induced [1,2]- and [3,2]-rearrangements of *N*-(2-thenyl)-*N*-benzyldimethylammonium ion **58**[225] demonstrate that ionization of the thenyl methylene group of **58** to the corresponding ylid **59** is the prevalent process. The general expected trends of product changes with change in base are observed, *n*-butyllithium and potassium hydroxide being the most effective in performing the Stevens rearrangement and sodamide in liquid ammonia the best reagent to obtain a Sommelet product in high yield.



57



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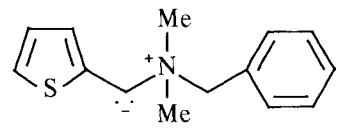
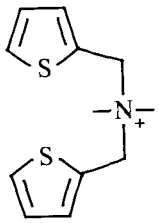
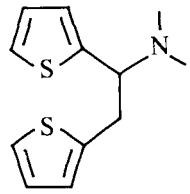


59

The presence of 2-thenyl groups as substituents on nitrogen in the ammonium salts **60** gives base-initiated rearrangements producing high yields of amines **61** and **62**.[47] The absence of other rearrangement products and the good linear fit of log (ratio **61**/**62**) versus 1/T is independent of concentration, base, or solvent system, can be taken as indicative of a common ylide precursor **63** analogous to **59**, but subsequently different reaction routes in the Stevens and Sommelet rearrangement processes.[47]



60



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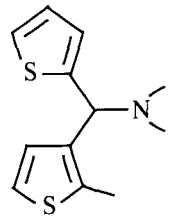

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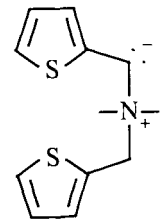
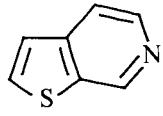


63

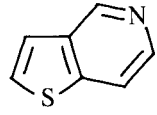
Sommelet-Hauser and Stevens rearrangements of other thenyl quaternary ammonium salts have been investigated.[237]

B. Reactions Leading to the Formation of Cycles

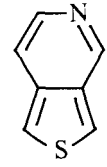
Thienylethyl amines are used in Bischler-Nepieralski reactions as precursors of thienopyridines **64** to **66**, which can be regarded as sulphur analogues of isoquinolines.[238] 2-(3-Thienyl)ethylamine is used as starting material for the synthesis of benzo[g] thieno[2,3-a] quinolizines.[239]



64

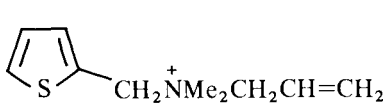


65



66

Thermal cyclizations of **67** and **69** give **68** and **70** in good yields.[240]



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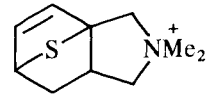

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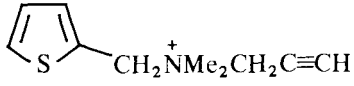

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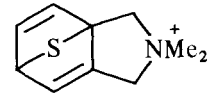
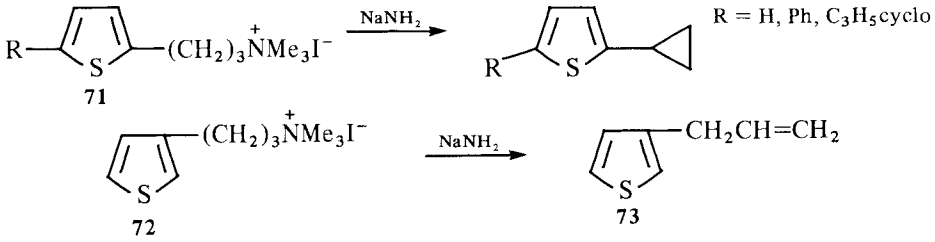


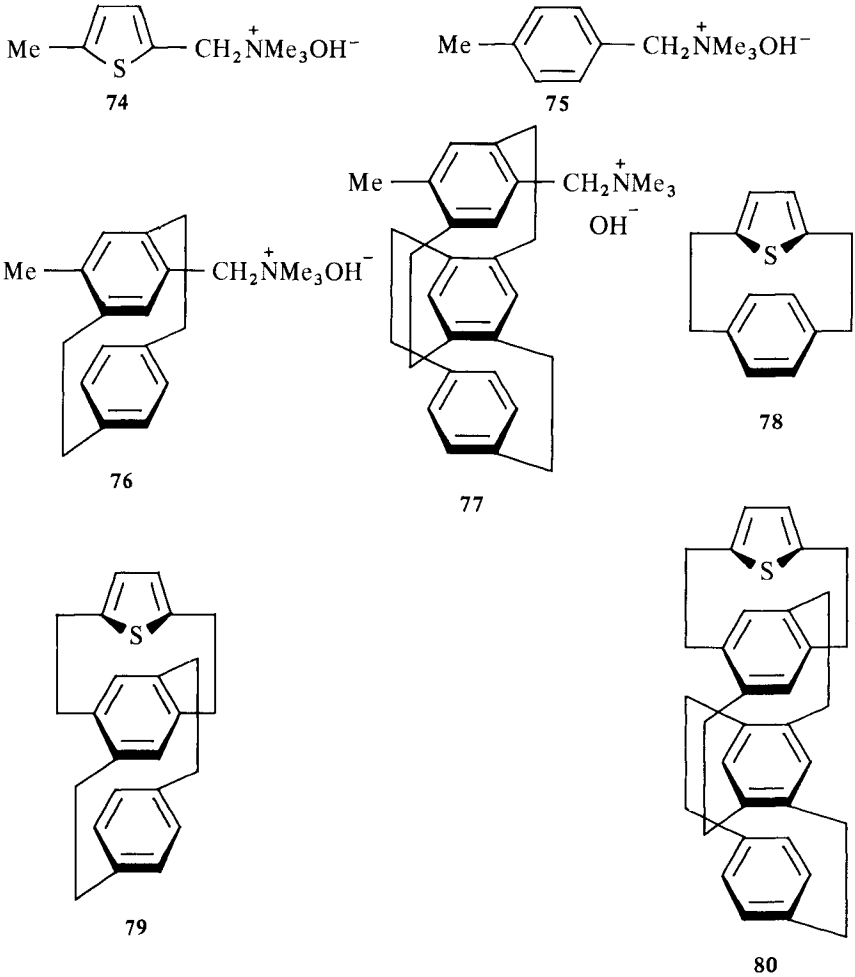
70

Sodium amide induced cyclization of the propylammonium iodides **71** gives 2-cyclopropyl thiophenes in high yields, whereas the analogous 3-thienyl ammonium iodide **72** gives mainly the E2 elimination product **73**, demonstrating the difference in acidity of α-methylene groups in 2- and 3-thenyl derivatives.[241]



71 72 73

Reaction of the ammonium hydroxide **74** with ammonium hydroxides **75, 76,** and **77** give multilayered paracyclothiophenophanes **78** to **80.**[242] Other series of multilayered paracyclothiophenophanes[243] and anthracenoheterophanes[244] can be synthesized by the cross-breeding Hofmann elimination method from a mixture of 5-methylthenyltrimethyl ammonium hydroxide and other quaternary ammonium hydroxides.

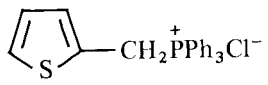


74 75 76 77 78 79 80

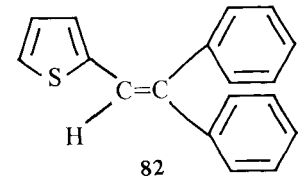
C. *Wittig Reactions*

Wittig reactions of thenyl phosphonium halides are widely used for the introduction of the ethylene group in the side-chain of thiophene.

Thenyltriphenyl phosphonium chloride **81**, treated with sodium ethoxide under nitrogen and reacted with aroyl chlorides, gives (α-aroyl-α-2-thienylmethylene) triphenylphosphoranes.[245] Similarly, **81** reacts in typical Witting reactions with benzophenone and sodium ethoxide under nitrogen to give 68% 1,1-diphenyl-2-(2-thienyl)ethylene **82**,[246] with 5-(3-pyridyl)furfural to give **83**,[247] with a series of aldehydes to give 2-thienylethylenes **84** with mothproofing activity,[248] and with ferrocenyl polyenals to give polyenes.[215] The Wittig reaction between orthobromothenyl triphenylphosphoranes and orthobromoformylthiophenes gives all six *cis*-1,2-(orthobromothienyl) ethenes, which, after halogen–metal exchange with butyllithium followed by reaction with cupric chloride, yield all six benzodithiophenes analogous to phenantrene.[14]



81



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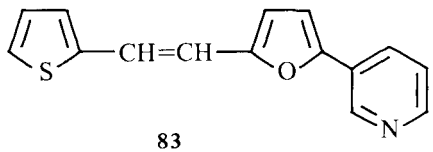
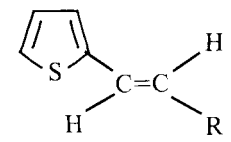


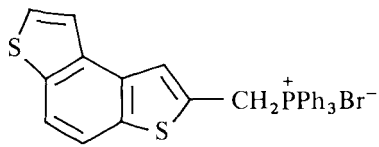
83



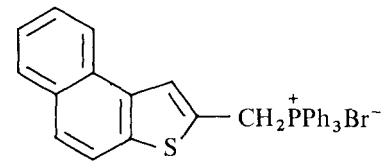
84

R = Substituted phenyl, 1- and 2-naphtyl, benzo[b]-thien-2-yl.

2-Thenyltriphenylphosphonium halides with fused aromatic rings at 4,5 positions **85** and **86** can be used as precursors for the synthesis of heterohelicenes **87** and **88**.[249]



85



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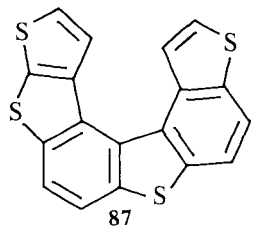
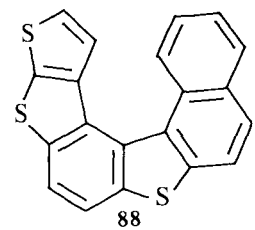
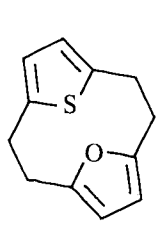


87

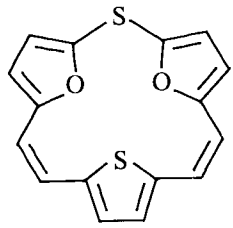


88

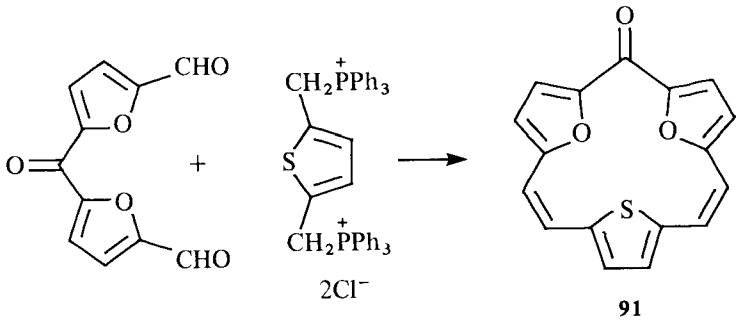
The formation of rings **89** to **91** containing 2,5 thiopheno subunits has been reviewed.[104] Annulenone **91** is prepared in 80% yield by reaction of bis(5-formyl-2-furyl)ketone with the 2,5-thiophene bis-Wittig reagent.[250,251] The heteroannulene **90** is analogously obtained from the thiophene 2,5 bis-Wittig reagent and the appropriate diformyl compound.[252]



89

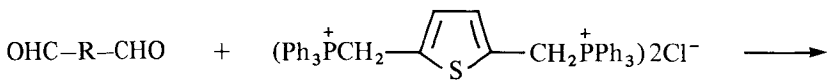


90



91

Polymers and oligomers of general formula **93** are prepared by Wittig reaction from 2,5-bis(triphenylphosphoniummethyl) thiophene dihalides **92**.[253,254]



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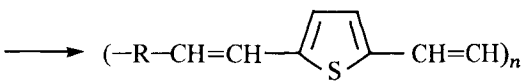
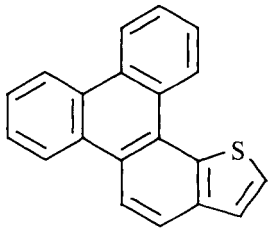
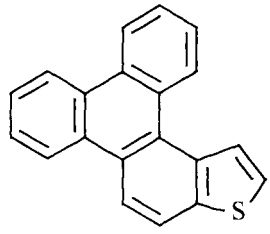


93

2- and 3-Thenylphosphonates react with phenanthrene-9-carboxaldehyde to give vinylthiophenes which can be photocyclized to triphenyleno[b]thiophenes **94** and **95**.[255] Similarly, diethylthenyl phosphonates react with naphtaldehyde to yield naphtylvinylthiophenes, which, irradiated in the presence of iodine, give phenantro-[b]thiophenes.[228]

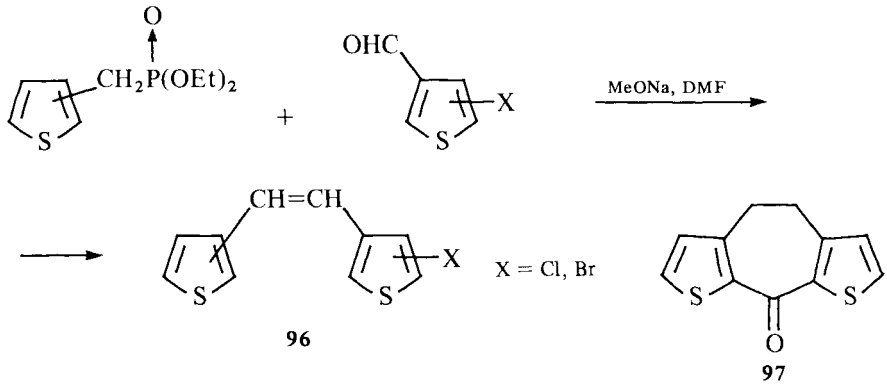


94



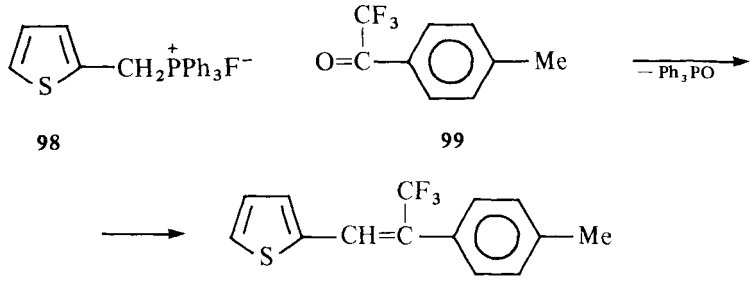
95

Thenyl phosphonates react with halo-substituted thiophene carboxaldehydes in the presence of sodium methoxide to yield halo-substituted di(thienyl)-ethenes **96** (in a phosphonate carbanion modification of the Wittig olefin synthesis) which are hydrogenated to the corresponding ethanes, subsequently lithiated, carbonylated, and cyclized into tricyclic ketones such as **97**.[40] Other modifications of the classical Wittig reaction have been reported. So in the reaction of **81** with aldehydes, the latter may be replaced by sodium α-hydroxysulfonates with the advantage of higher yields and purer products.[256]



96 97

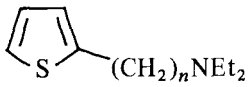
A phase-transfer catalyzed Wittig reaction without base addition is achieved by reacting 2-thenylphosphonium fluoride **98** (prepared *in situ* from the corresponding chloride with potassium fluoride in acetonitrile at 70° in the presence of dibenzo-18-crown-6 as phase-transfer catalyst) with trifluoroacetyl ketone **99**, a compound that gives the haloform reaction in basic solutions.[257]



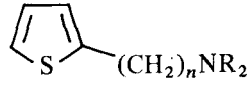
98 99

D. *Other Reactions*

The Dem'yanov reaction with 2-thenylamine yields mainly 2-thenyl alcohol.[258] Carbonyl compounds are formed in the oxidation of 2-thienylmethylammonium bromides with dimethyl sulfoxide.[259]



100 $n = 2–6$



101 $n = 1–6$ R = Me, Et

$MeCH_2CH_2CO(CH_2)_nNR_2$

102

2-(ω-Diethylaminoalkyl)thiophenes **100** can be hydrogenated by $Et_3SiH–CF_3CO_2H$ to the corresponding thiophanes.[260]

Ring cleavage of the thiophenes **101** with $Li–Me_3COH–NH_3$ gives **102**.[261]

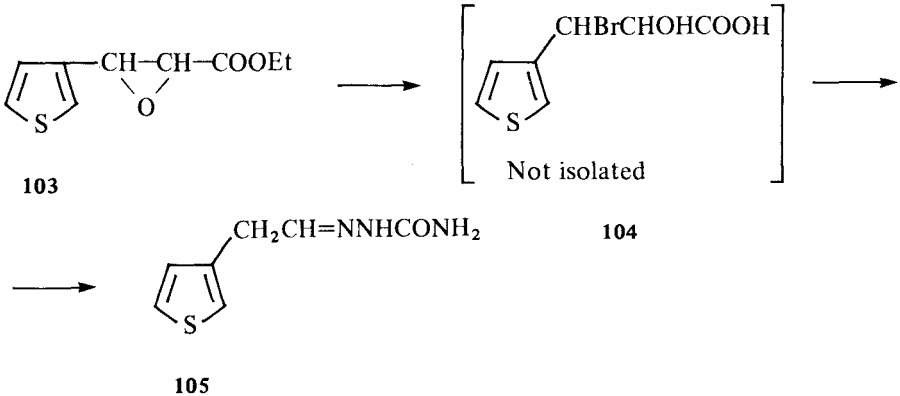
V. THENYL ALDEHYDES AND KETONES

1. Synthesis

The conditions for the synthesis of 2-thenyl aldehydes and ketones are summarized in Table 21.

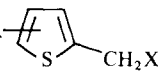
A. *Thenyl Aldehydes*

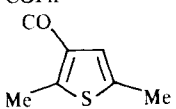
Mason and Nord[263] prepared 2-thienylacetaldehyde from methyl-2-(2-thienylvinyl)-carbamate; Pappalardo[268] obtained it from the acid hydrolysis of 1-(2′-thienyl) 2-(*N*-acetylamino)ethylene; and Winterfeld[262] synthesized it in high yield from the acetal.



103 **104** **105**

Scheme 6

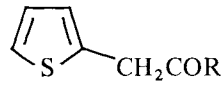
TABLE 21. SYNTHESIS OF 2-THENYL ALDEHYDES AND KETONES 

X	R_3	R_4	R_5	Conditions	Yield (%)	Reference
CHO	H	H	H	From the acetal	95	262
				Me-2-(2-thienylvinyl)carbamate, EtOH $(COOH)_2 \cdot 2H_2O$	19	263
CHO	H	H	Cl	Me-2-(5-chloro-2-thienylvinyl)carbamate, $(COOH)_2 \cdot 2H_2O$, EtOH	24	263
COMe	H	H	H	Thiophene-2-acetyl chloride, Me_2Cd		53
				2-Thiopheneacetic acid, AcOH	70	8
				Decarboxylation of β-(2-thienyl)α-Me-glycidic acid	87	8
				Darzens condensation of 2-thiophene aldehyde with ethyl 2-bromo ester, saponification, and decarboxylation	71	264
				Thiophene, $MeOCH_2 \cdot$		265
COEt	H	H	H	Darzens condensation of 2-thiophene aldehyde with bromo ester, saponification, and decarboxylation	61	264
CO-*n*-Pr	H	H	H	Darzens condensation of 2-thiophene aldehyde with bromo ester, saponification, and decarboxylation	69	264
CO-*i*-Pr	H	H	H	Darzens condensation of 2-thiophene aldehyde with bromo ester, saponification, and decarboxylation	60	264
CO-*n*-Bu	H	H	H	Darzens condensation of 2-thiophene aldehyde with bromo ester, saponification, and decarboxylation	41	264
CO-*i*-Bu	H	H	H	Darzens condensation of 2-thiophene aldehyde with bromo ester, saponification, and decarboxylation	58	264
CO-*t*-Bu	H	H	H	Darzens condensation of 2-thiophene aldehyde with bromo ester, saponification, and decarboxylation	82	264
CO-*n*-C_5H_{11}	H	H	H	Darzens condensation of 2-thiophene aldehyde with bromo ester, saponification, and decarboxylation	66	264
COPh	H	H	H	Thiophene, $Rh_2(OAc)_4$, diazoacetophenone, N_2	23	266
	H	H	Cl	Thiophene-5-chloro-2-acetyl chloride, 2,5-dimethyl thiophene, $SnCl_4$, C_6H_6	73	267

3-Thienylacetaldehyde semicarbazone **105** is obtained from ethyl-β-3-thienyl-α,β-epoxypropionate **103** by way of the bromhydrin **104**, according to Scheme 6.[269]

B. Thenyl Ketones

2-Thenyl methyl ketone was prepared in high yields by Cagniant both from 2-thiopheneacetic acid, following the procedure used for the synthesis of benzyl methyl ketone, and from decarboxylation of β-(2′-thienyl)α-methyl glycidic acid.[8] Similarly, a series of 1-(2-thienyl)2-alkanones **106** can be synthesized in high yield by the Darzens glycidic ester condensation of 2-thiophenecarboxaldehyde and the appropriate ethyl-2-bromoester, followed by saponification and decarboxylation.[264] The reverse addition of lithium aluminum hydride to nitroolefins, a general method for the synthesis of carbonyl compounds, can be adopted for preparing 2-thienyl-acetone.[270]



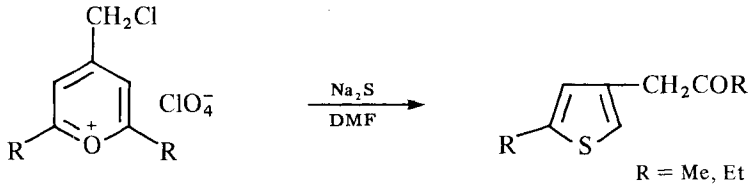
106

R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *s*-Bu, *n*-C_5H_{11}

A new synthetic route to thenyl ketones has been provided by Bunnett and Gloor,[271] who found that acetone enolate ion undergoes photostimulated reaction with chloro- and bromothiophenes in liquid ammonia to give thenyl methyl ketones and dithienyl acetones. These substitutions, which are believed to occur by the $S_{RN}1$ mechanism, turn out to be particularly useful for the preparation of 3-substituted thiophenes.

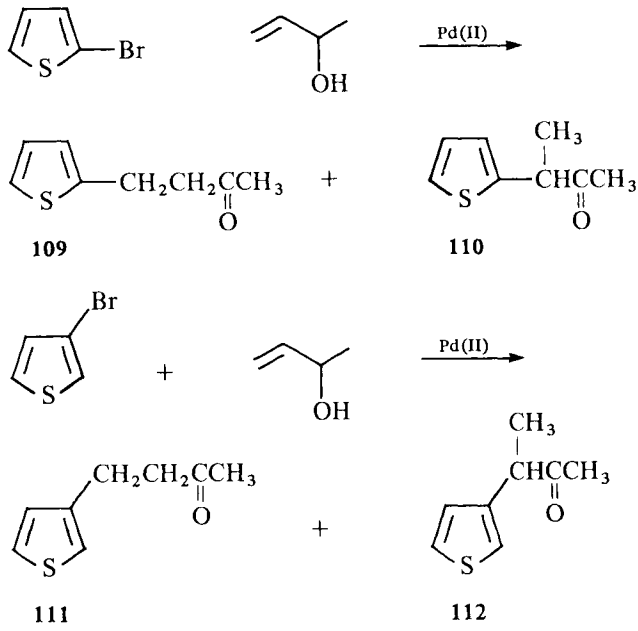
A recent patent[272] reports a new method for the synthesis of 3-thenyl alkyl ketones **108**, obtained by treating pyrylium salts **107** with Na_2S in boiling dimethylformamide (Scheme 7).

The palladium-catalyzed thienylation of allylic alcohols with 2- and 3-bromothiophenes affords 3-(2′- or 3′-thienyl)aldehydes or ketones **109** and **111**,[273,274] the thienylation at the 3-position of allylic alcohols taking place preferentially



107 **108**

Scheme 7



Scheme 8

over the thienylation at the 2-position (Scheme 8). The formation 3-alkyl-substituted thiophenes **111** and **112** probably occurs through a 3-thienylpalladium complex. 3-Bromothiophene is found to be two or three times less reactive than 2-bromothiophene.

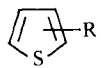
3-Acetonylthiophen and 3-phenacylthiophen 2- or 4-carboxylic acids can be prepared by condensation of bromothiophencarboxylic acids with the appropriate carbanions.[275]

2. Spectroscopic and Physicochemical Properties

^{1}H NMR shifts of thenyl ketones are recorded in Table 22, and infrared frequencies of thenyl aldehydes and ketones in Table 23. The UV spectrum of 2-thiopheneacetaldehyde shows a maximum at 232 nm (ϵ = 8300).[262] The fragmentation peaks in the mass spectra of 2- and 3-thenyl methyl ketones have been reported.[271]

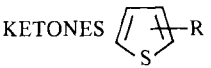
3. Reactivity

Thenyl aldehydes and ketones undergo the typical reactions of aldehydes and ketones; so Wolf-Kishner reduction of 4-phenacylthiophen-3-carboxylic acid affords 4-phenethyl 3-carboxylic acid.[275] It is worth mentioning the use of 2-thiophene acetaldehyde as a catalyst for homo- and copolymerization of vinyl compounds, in particular for cross-linking of polyesters with styrene.[277]

TABLE 22. ^{1}H NMR SHIFTS OF THENYL KETONES 

Solvent	R_2	R_3	R_4	R_5	H_2	H_3	H_4	H_5	CH_2	Others	Coupling Constants (Hz) J_{24}	J_{25}	J_{45}	Reference
a	CH_2COMe	H	H	H			6.70–7.07[b]		3.78	2.08				53
c	CH_2COPh	H	H	H		6.78	6.78	7.03	4.27	7.45, 7.85				266
d	H	CH_2COMe	H	H	7.0		6.88	7.17	3.58	1.97	1.6	3.0	4.8	271
c	COOH	CH_2COMe	H	H			7.00	7.55	4.17	2.22			5.0	275
e	H	CH_2COMe	COOH	H	8.13			7.09	3.91	2.19, 7.09		4.0		275
f	H	CH_2COPh	COOH	H	8.25			7.35	4.62	7.6, 8.0		4.0		275

[a] Letter codes, either under "Solvent" or italic superscripts, have the following designations: a, CCl_4; b, multiplet for thiophene ring protons; c, $CDCl_3$; d, neat; e, $CDCl_3$-DMSO-d_6; f, DMSO-d_6.

TABLE 23. INFRARED FREQUENCIES FOR THENYL ALDEHYDES AND KETONES 

R_2	R_3	R_4	R_5	$\nu_{C=O}$	Others	Reference
CH_2CHO	H	H	H	1740	2730, 855	262
$(CH_2)_2CHO$	H	H	H	1725	3120, 1440, 700	274
$CH_2CHMeCHO$	H	H	H	1720	3090, 1440, 695	274
H	$(CH_2)_2CHO$	H	H	1720	3100, 1460, 775	274
CH_2COMe	H	H	H	1715	3115, 3080, 3000, 2920, 1715, 1415, 1350, 1220, 1155, 1040, 855, 698	271
CH_2COPh	H	H	H	1680	3015, 1595, 1580, 1440, 1320, 1280	266
$(CH_2)_2COMe$	H	H	H	1723	1585, 1540, 1411, 1358	276
$(CH_2)_2COMe$	H	H	Me	1712	3070, 1360, 800	274
$(CH_2)_2COMe$	H	H	CH_2CO_2Me	1740, 1720	3075, 1440, 807	274
$(CH_2)_2COMe$	H	H	COMe	1713, 1660	3080, 1440, 810	274
$(CH_2)_2COMe$	H	H	CO_2Me	1710	3080, 1460, 750	274
$(CH_2)_2COEt$	H	H	H	1710	3100, 1440, 695	274
$(CH_2)_2CO$-*i*-Pr	H	H	H	1700	3100, 1440, 690	274
$(CH_2)_2COPh$	H	H	H	1680	3110, 3050, 752, 708, 692	274
$(CH_2)_2COMe$	H	H	H	1710	3100, 1445, 700	274
$(CH_2)_2COMe$	H	H	CO_2Me	1705	2990, 1465, 1095, 750	274
H	CH_2COMe	H	H	1710	3100, 3000, 2925, 1420, 1385, 1350, 1315, 1240, 1215, 1160, 834, 767, 710, 690, 630	271
COOH	CH_2COMe	H	H	1720	1665	275
H	CH_2COMe	COOH	H	1720	3100, 1675	275
H	CH_2COMe	H	H	1710	3100, 1410, 770	274
H	$(CH_2)_2COEt$	H	H	1710	3090, 1450, 775	274
H	$(CH_2)_2CO$-*i*-Pr	H	H	1710	3100, 1470, 775	274
H	$(CH_2)_2COPh$	H	H	1680	3105, 3050, 776, 744, 695	274

VI. THIOPHENEACETIC ACIDS AND THEIR DERIVATIVES

1. Synthesis

A. Thiopheneacetic acids

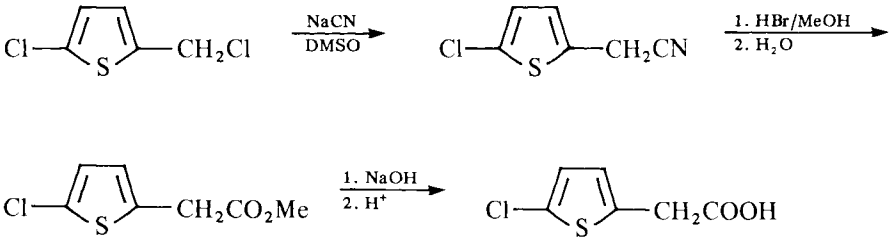
The reaction conditions and the yields for the synthesis of 2-thiopheneacetic acid are reported in Table 24.

The most widely adopted synthetic methods are as follows:

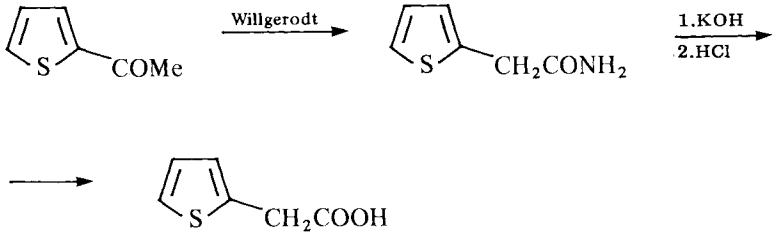
1. *Conversion of acetonitriles into thiopheneacetic acid esters.* This method is illustrated in Scheme 9, which reports the three-step synthesis of 5-chloro-2-thiopheneacetic acid.[12]
2. *Hydrolysis of the amides prepared by the Willgerodt Reaction.* Thiophene acetamide, synthesized by the Willgerodt reaction, can be hydrolyzed to the corresponding acetic acid (Scheme 10).[282,291,292]
3. *Conversion of thiophenealdehydes into the acetic acid esters by formaldehyde dimethylmercaptal 5-oxide, followed by hydrolysis.* A novel synthetic route to 2-thiopheneacetic acid (Scheme 11) involves reaction of 2-thiophenecarboxaldehyde with formaldehyde dimethylmercaptal S-oxide (FAMSO) **113** and conversion of the resulting condensation product **114** into the acetate **115**; hydrolysis of **115** gives 2-thiopheneactic acid **116**.[293]
4. *Catalytic carbonylation of chloromethylthiophene.* 2-Thiopheneacetic acid has recently been prepared by carbonylating 2-chloromethylthiophene using as a catalyst a Fe–Mn alloy with a cobalt salt, a sulfide promoter, and an inorganic base[284–286] or $NaCo(CO)_4$.[287]

TABLE 24. SYNTHESIS OF 2-THIOPHENEACETIC ACID

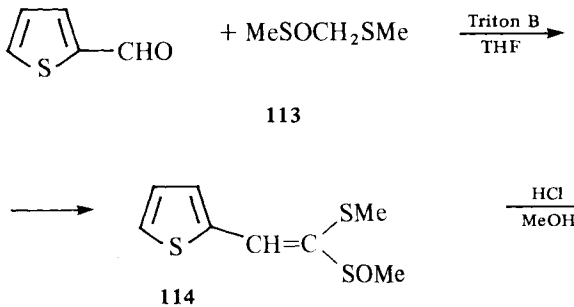
Conditions	Yield (%)	Reference
2-Thiopheneacetonitrile, KOH	65	8
2-Thiopheneacetonitrile, KOH, EtOH	77	278
Hydrolysis of the ethyl ester	81	279
Hydrolysis of the methyl ester	94	280, 281
2-Thiopheneacetamide, KOH	42	282
Thiophene, FAMSO, EtOH, Br, reflux, 2 hours, KOH, MeOH	79–84	283
2-Thenyl chloride, Fe-Mn alloy, $CoCl_2 . 6H_2O$, Na_2S, $Na_2S_2O_3$, MeOH, CuO	72	284–286
2-Thenyl chloride, CO, aq. MeOH, CaO, $NaCo(CO)_4$, saponification	70	287
2-Thiophenemagnesium chloride, CO_2	29	288
Thiophene-2-COCOOEt, N_2H_4, KOH	88	289
Thiophene, $BrCH_2COOH$, EtOH, 20 hours, 50°, pressure, UV light	35	290



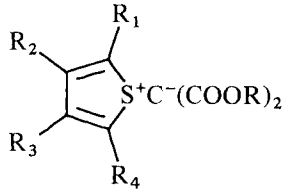
Scheme 9



Scheme 10



Scheme 11



117

Other methods adopted for the synthesis of thiophenacetic acids are the hydrazinolysis of the esters[289] and the reaction of thiophene with $BrCH_2COOH$ under UV irradiation;[290] the thiophenium ylides **117** have also been reported to be useful intermediates in the preparation of 2-thiopheneacetic acid.[294] 2-Thienyl-α,α-d_2-acetic acid is obtained in 71% yield by deuterating and hydrolyzing 2-thiopheneacetonitrile.[69]

The methods of preparation, the physical properties, and the uses of 2-thiopheneacetic acid have been reviewed.[293,295]

3-Thiopheneacetic acid is conveniently prepared by hydrolysis of the nitrile,[37,296] whereas its 2-methyl[32] and 2,5-dimethyl[123] derivatives can be obtained by hydrolysis of the corresponding amides, synthesized by the Willgerodt reaction.

ω-Thienylalkanoic acids are prepared from halomethyl thiophenes by conventional chain elongation reactions.[288,297]

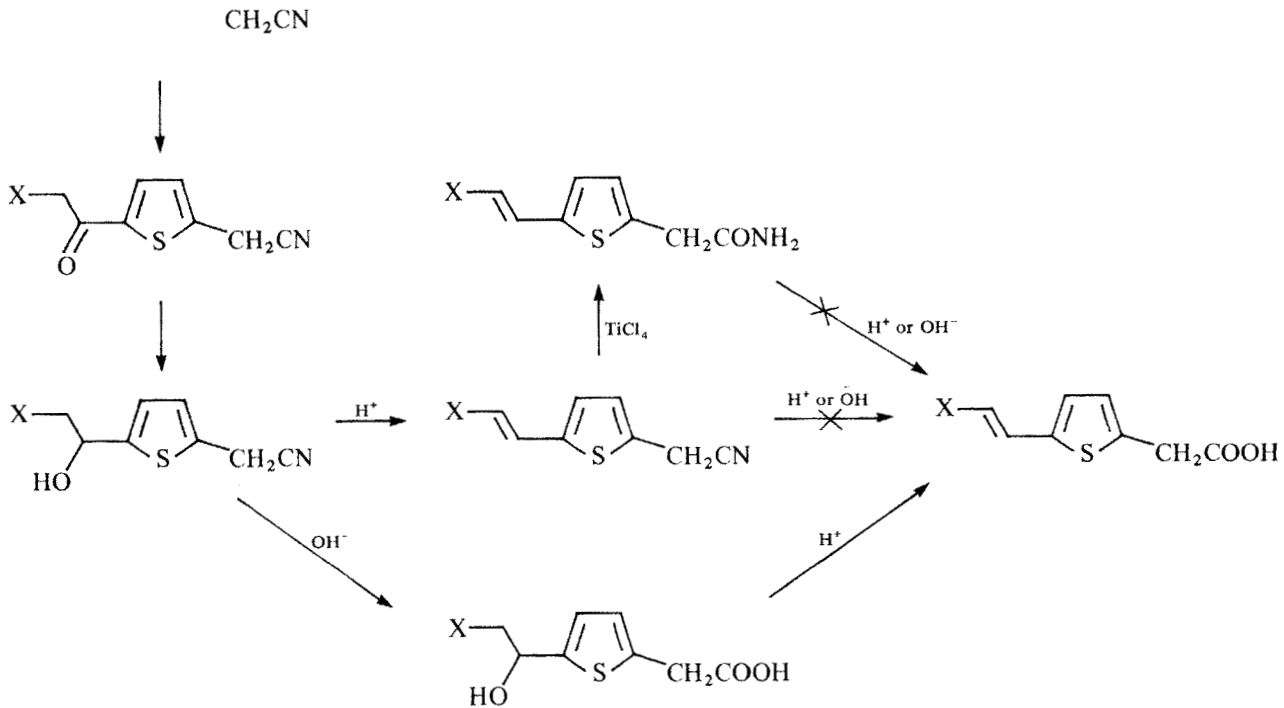
The reduction of thenylalkanoic acids to the corresponding thenyl derivatives is widely adopted; recent patents reported the use, as reducing agents, of N_2H_4[289] and of cobalt polysulfide under pressure.[298] The synthesis of long-chain ω-(2-thienyl)alkanoic acids can also be achieved by alkylating thiophene with the appropriate dibromo alkane to give either the nitrile or the malonate, which are then hydrolyzed (and the malonate decarboxylated) to the corresponding carboxylic acids.[50,299]

The synthesis of thiopheneacetic acids substituted in the thiophene ring can be achieved by conventional methods using appropriately substituted compounds as starting materials or introducing the substituent directly into thiopheneacetic acids, for example, by acetylation.[21] Brief discussions of typical or novel examples of synthesis of substituted thiopheneacetic acids follow.

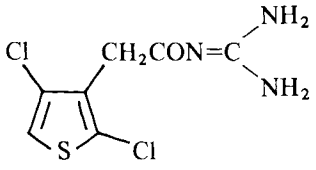
A series of 2- and 4-carboxythiophen acetic acids and derivatives are prepared by reaction of the sodium salts of 3-bromothiophen-2- and 4-bromothiophen-3-carboxylic acids with carbanions in the presence of copper and copper(II) acetate, which give condensation products by displacement of bromide ion (often with simultaneous deacylation);[275] by this method ethylacetoacetate gives the monoethyl esters of 2- and 4-carboxythiophen-3-acetic acids.

5-Aminomethyl-2-thiophene acetic acid is synthesized by a five-step synthesis starting from 2-thienylethynyl thioether.[20]

The preparation of a series of 5-substituted 2-thienylacetic acid derivatives (Scheme 12) has been described and their inhibitory activity of platelet aggregation tested.[300]



Scheme 12



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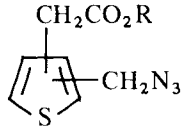

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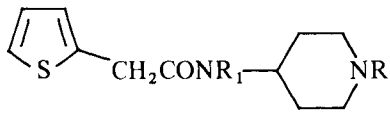

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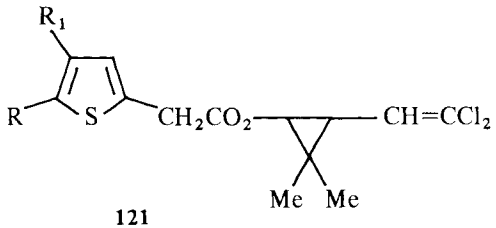

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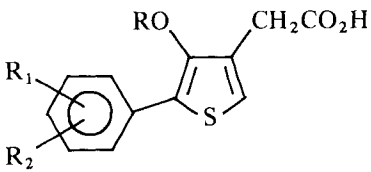

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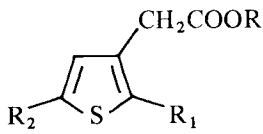

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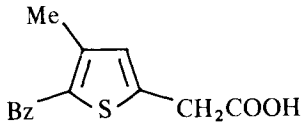
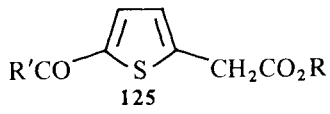


123

The synthesis of thiopheneacetic acids and derivatives **118** to **128** with pharmacological or insecticidal activity has been reported in patents: **118**,[301] **119**,[302] **120**,[303] **121**,[304] **122**,[305] **123**,[306] **124**,[307] **125**,[308] **126**,[309] **127**,[310] **128**.[311] Patents also report the synthesis of thiopheneacetic acid ester,[312–315] 2-thienylbutyric acid,[316] 3-thiopheneacetonitrile,[317] 5-phenyl-2-thiopheneacetic acid,[318] and 5-cyclohexyl-2-thiopheneacetic acid.[319]



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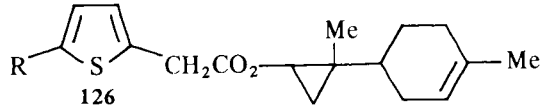
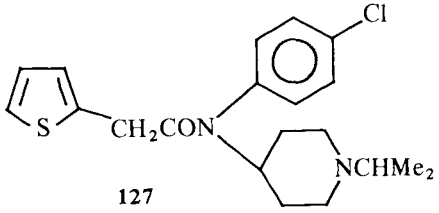


126

R = CH_2Ph, allyl



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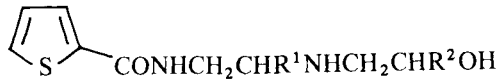

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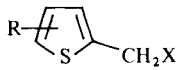
B. Thiopheneacetic Acid Derivatives

The synthetic conditions and the yields for the synthesis of 2- and 3-thiopheneacetic acid derivatives are reported in Tables 25 and 26 respectively.

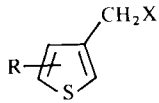
Thiopheneacetonitriles are mainly prepared by reaction of the corresponding halomethyl derivatives with cyanides under various reaction conditions (Table 26).

TABLE 25. SYNTHESIS OF 2-THIOPHENEACETIC ACID DERIVATIVES



X	Conditions	Yield (%)	Reference
CN	From 2-chloromethylthiophene	89	12
	2-Chloromethylthiophene, NaCN	81	9
	2-Chloromethylthiophene, KCN	80	8
	2-Chloromethylthiophene, NaCN	60	320
	2-Chloromethylthiophene, NaCN	70	321
	Thiophene-2-$CH_2C(CO_2H)$=NOH, Ac_2O	87	278
COOMe	2-Thiopheneacetic acid, MeOH, HCl	82	282
	2-Thiopheneacetic acid, MeOH, *p*-toluensulfonic acid		21
	2-Thiophenecarboxylic acid, diazomethane		53
	2-Acetylthiophene, $BF_3 \cdot OEt_2$, $Pb(OAc)_4$, MeOH, 11 hours	83	280
	α-Thienyldiazomethyl ketone, MeOH, Ag_2O		320
COOEt	2-Thienylacetonitrile, EtOH, HCl	66	9
	2-Thienylacetonitrile, EtOH, H_2SO_4	68	322
	2-Chloromethylthiophene, CO, EtOH, NaOEt, $Co_2(CO)_8$	75	323
	1-(Methylsulfinyl)-1-(methylthio)-2-(2-thienyl)ethylene, HCl, EtOH	80	324
	α-Thienyldiazomethyl ketone, EtOH, Ag_2O	68	320
	Ethyl-2-thenylglyoxylate, 200°, hydrogen 135 atm, 4 hours, Re_2S_7	77	325
COCl	Acid, thionyl chloride		8, 326
	Acid, C_6H_6–H_2O azeotropic distillation, $SOCl_2$	92	327, 328
$CONH_2$	2-Thienylmethyl ketone, Willgerodt reaction	43–53	292
	2-Thienylmethyl ketone, Willgerodt reaction	68	282
	2-Thiopheneacetonitrile, H_2O_2, KOH	35	278

TABLE 26. SYNTHESIS OF 3-THIOPHENEACETIC ACID DERIVATIVES



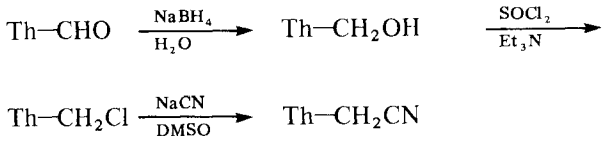
X	Conditions	Yield (%)	Reference
CN	3-Chloromethylthiophene, CN^-	81	12
	3-Chloromethylthiophene, KCN, Me_2CO	82	296
	3-Bromomethylthiophene, KCN, reflux, 3 hours	76	238
	From 3-methylthiophene by way of bromomethyl derivative and CN^-	65	35
	Bromomethylthiophene, CCl_4, NaCN in H_2O, three-phase catalyst		329
	3-Bromothiophene, $^-CH_2CN$, UV light	30–40	330
	Dechlorination of 2,5-dichloro-3-thiopheneacetonitrile with H over $Pd/CaCO_3$		331
COOMe	Cyclization of 5-chloro-3-chloromethyl-penta-2,4-dienoate		332
COOEt	CHCOOEt, HCl, EtOH	23	266, 333
		quant.	334
COCl	From 3-thiopheneacetic acid		296
$CONH_2$	Willgerodt reaction of 3-methyl ketone	5–13	291

Scheme 13, reporting the three-step synthesis of thiopheneacetonitrile[12] illustrates well a few typical reactions of thenyl derivatives discussed in this chapter.

It has recently been reported that thiopheneacetonitriles can also be prepared by reacting methylthiophenes with ClCN in the gas phase.[335]

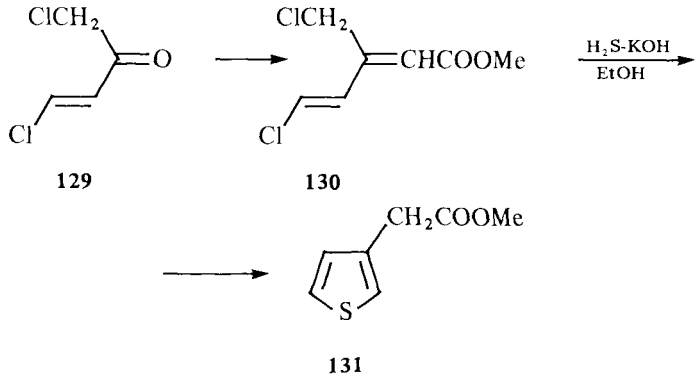
Thiopheneacetic acid esters are prepared mainly by esterification of the acids. The Willgerodt-Kindler reaction for the conversion of aryl methyl ketones into phenylacetic acids has also been adopted for the synthesis of thienylacetates. Recently, an improved method involving the use of lead(IV) acetate under mild conditions allowed the conversion of 2-acetylthiophene into methyl-2-thienylacetate at room temperature in high yield.[280]

Ethyl-2-thiophene acetate can be prepared[324] starting from 2-thiophenecarboxaldehyde and the sulfoxide **113**, following a reaction sequence analogous to that depicted in Scheme 11 for the synthesis of the methyl ester.



Th = 2-thienyl, 3-thienyl

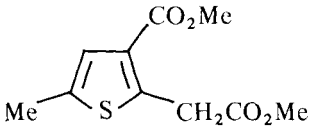
Scheme 13



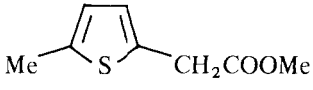
Scheme 14

The 3-methyl ester **131** has been prepared by reacting the chloroketone **129** with methyltriphenylphosphoranylidene acetate to give methyl-5-chloro-3-chloromethylpenta-2,4-dienoate **130**, which was cyclized to **131** (Scheme 14).[332]

Thiopheneacetic acid esters **132** and **133** were formed in the attempted synthesis of dilithio derivatives from 2,5-dimethylthiophene.[336]



132

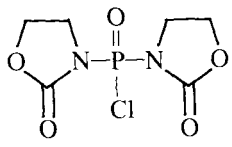


133

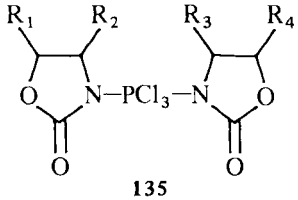
Thiopheneacetic acid chlorides are obtained by conventional treatment of the acids with thionyl chloride. The distillation of 2-thienylacetyl chloride from reaction mixtures has been reported to be improved by using as an additive silicone fluid SWS-101, which remains liquid at the distillation temperature.[337]

Thiopheneacetamides are mainly synthesized by the Willgerodt reaction,[282,291,492] but other methods such as treatment of 2-thiopheneacetonitrile with hydrogen peroxide[278] and reaction of 2-thiopheneacetyl chloride with ammonia[8] have been reported.

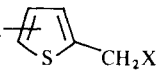
A new reagent, *N*-*N*-bis[2-oxo-3-oxazolidinyl] phosphorodiamidic chloride **134**, has recently been used to obtain 2-thiopheneacetic acid anilides in almost quantitative yields;[338] adducts of the type **135** can be used as activators for the carboxyl group in amidation and esterification reactions.[339]



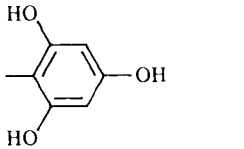
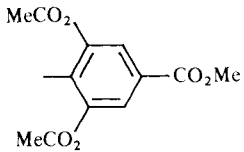
134



135

TABLE 27. ^{1}NMR SHIFTS OF 2-THIOPHENEACETIC ACIDS AND DERIVATIVES 

Solvent	X	R_3	R_4	R_5	Thiophene Ring H_3	Thiophene Ring H_4	Thiophene Ring H_5	CH_2	Others	Reference
a	COOH	COOH	H	Me		7.04[b]		4.06	2.38	342
c	COOH	H	COOH	H	7.36		8.11	3.92		65
a	COOH	H	COOH	Me	7.17			3.78	2.67	342
d	COOH	Me	Me	Me				3.67	2.00, 2.30, 11.0	342
e	COOH	H	H	CH_2NH_2	7.08	7.08		4.02[f]	4.61[f], 7.08	20
a	COOH	H	H	CH_2NPhtal.	6.92	6.92		3.78[g]	4.93[g], 7.90	20
d	COOH	H	H	CH_2NHCO_2-*t*-Bu	6.79	6.79		3.81[h]	1.46, 4.41[h], 8.47	20
d	COOH	H	H	$CH(OH)CH_2C_6H_5$				3.80		300
a	COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-F				3.74		300
a	COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-Cl				3.72		300
d	COOH	H	H	$CH(OH)CH_2C_6H_4$-*m*-Cl				3.83		300
a	COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-Br				3.74		300
d	COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-OMe				3.80		300
d	COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-isoBu				3.83		300
a	COOH	H	H	$CH{=}CHC_6H_5$				3.83		300
a	COOH	H	H	$CH{=}CHC_6H_4$-*p*-F				3.84		300
a	COOH	H	H	$CH{=}CHC_6H_4$-*p*-Cl				3.84		300
a	COOH	H	H	$CH{=}CHC_6H_4$-*m*-Cl				3.83		300
a	COOH	H	H	$CH{=}CHC_6H_4$-*p*-Br				3.83		300
a	COOH	H	H	$CH{=}CHC_6H_4$-*p*-OMe				3.73		300
a	COOH	H	H	$CH{=}CHC_6H_4$-*p*-isoBu				3.80		300
i	CN	H	H	H		6.85[j]		3.66		60
d	CN	H	H	$CH{=}CHC_6H_4$-*p*-isoBu				3.90		300
d	CN	H	H	$CH{=}CHC_6H_4$-*p*-NO_2				3.96		300
i	CN[k]	H	H	I	6.64	7.01		3.78		60

l	CN	H	H		7.29	6.95	4.02	8.41, 8.30, 6.10	343
l	CN	H	H		7.10	7.10	4.19	7.06	343
d	CN	H	H	$COCH_2C_6H_5$			3.93	4.16	300
d	CN	H	H	$COCH_2C_6H_4$-*p*-F			3.91	4.13	300
d	CN	H	H	$COCH_2C_6H_4$-*p*-Cl			3.26	4.26	300
d	CN	H	H	$COCH_2C_6H_4$-*m*-Cl			3.90	4.13	300
d	CN	H	H	$COCH_2C_6H_4$-*p*-Br			3.93	4.11	300
d	CN	H	H	$COCH_2C_6H_4$-*p*-OMe			3.90	4.06	300
d	CN	H	H	$COCH_2C_6H_4$-*p*-*iso* Bu			3.90	4.13	300
d	CN	H	H	$COCH_2C_6H_4$-*p*-NO_2			3.96	4.30	300
d	CN	H	H	$CH{=}CHC_6H_5$			3.86		300
d	CN	H	H	$CH{=}CHC_6H_4$-*p*-F			3.83		300
d	CN	H	H	$CH{=}CHC_6H_4$-*p*-Cl			3.90		300
d	CN	H	H	$CH{=}CHC_6H_4$-*m*-Cl			3.83		300
d	CN	H	H	$CH{=}CHC_6H_4$-*p*-Br			3.83		300
d	CN	H	H	$CH{=}CHC_6H_4$-*p*-OMe			3.83		300
m	COOMe	H	H	H		6.71[j]	3.70	3.60	53
d						6.84–7.32[j]	3.81	3.70	344
d	COOMe	H	H	Me		6.45–6.95[j]	3.73	2.44, 3.70	344
d	COOMe	H	H	Ph		7.0–7.7[j]	3.70	3.78, 7.0, 7.7	344
d	COOMe	H	H	C_6H_4-*p*-OMe		6.70–7.58[j]	3.70	3.77, 6.58, 6.70	344
d	COOMe	H	H	OMe	5.98–6.20[j], 6.67–6.81[j]		3.70–3.89	3.70–3.89, 3.85	344
d	COOEt	H	H	Me	6.60	7.40	3.70	1.28, 2.40, 4.13	345

Letter codes, either under "Solvent" or as italic superscripts, have the following designations; a, DMSO-d_6; b, $J_{H_4-SMe} = 1.1$ Hz; c, acetone-d_6; d, $CDCl_3$; e, CF_3COOH; f–h, alternative assignments; i, multiplet for thiophene ring protons; l, acetone; k, $J_{34} = 3.7$ Hz; $J_{CH_2-H_3} = 1.0$ Hz.

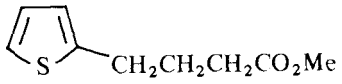
2. Spectroscopic and Physicochemical Properties

The dissociation constant of 2-thiopheneacetic acid in water at 25° is 3.89,[340] and its apparent dissociation constant in 80% methyl cellosolve is 5.96.[341]

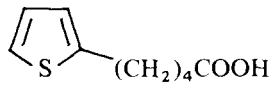
Tables 27 and 28 report ^{1}H NMR chemical shifts of 2- and 3-thiopheneacetic acids and their derivatives. ^{13}C NMR shifts of 4-carboxy-2-thiopheneacetic acid and 5-carboxy-3-thiopheneacetic acids have been reported.[72,73]

Mass spectroscopic studies on γ-2-thienylmethylbutyrate **136** and analogous γ-aryl derivatives showed that the ratio $[M^+\text{-OMe}]/[M^+]$ decreases sharply as the ionization potential of the γ-substituent is decreased.[347]

The infrared frequencies of thiopheneacetic acids and their derivatives are recorded in Table 29. The carbonyl frequencies range from 1650 to 1745 cm^{-1} and the CN frequencies from 2220 to 2260 cm^{-1}.



136



137

The UV spectrum of 2-thiopheneacetic acid shows a maximum at 235 nm ($\epsilon = 3900$) and that of the 3-isomer at 234 nm ($\epsilon = 3400$).[349,350]

The mode of action of 5-(2-thienyl)valeric acid **137** on biotin biosynthesis has been investigated.[351]

3. Reactivity

A. Thiopheneacetic Acids and Esters

The alkaline hydrolysis of thiopheneacetic acids has been investigated and compared with the analogous reactions of other arylacetic acids.[352]

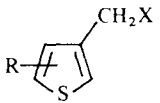
Air oxidation of 2-acetyl-5-thiopheneacetic acid in the presence of sodium hydroxide yields 65% 5-carboxy-2-acetylthiophene;[353] reduction of the esters of ω-(2-thienyl)alkanoic acids with $LiAlH_4$ followed by decomposition of the reaction mass with H_2SO_4 gives ω-(2-thienyl)alkanols.[354]

2- and 3-thienylbenzothiophenes **138** are synthesized in 65% and 70% yields respectively by reacting thiopheneacetic acids with the benzothiophene ozonation products.[355]

Condensation of ethyl-2-thienylacetate with diethylethoxymethylenemalonate gives the phenol **139** in 12% yield.[356]

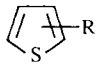
Methyl-3-thienylacetate mixed with bromocyclohexane and added to a mixture of NaH in dimethylformamide at −5° gives 83% of the alkylated derivative **140**,[357] and treated with $BrCH_2C{\equiv}CH$ in the presence of NaH gives 63% of the ester **141**.[358]

TABLE 28. ^{1}H NMR SHIFTS OF 3-THIOPHENEACETIC ACIDS AND DERIVATIVES



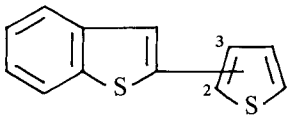
Solvent	X	R_2	R_4	R_5	Thiophene Ring H_2	Thiophene Ring H_4	Thiophene Ring H_5	CH_2	Others	Reference
a	COOH	H	H	H		7.04[b]		3.58		60
c	COOH	Br	H	Br		7.05		3.6	7.7	346
c	COOH	S(2C$_4$H$_3$S)	H	Et		6.60		3.75	1.20, 2.68, 6.56, 7.01, 7.14	68
d	COOH	H	H	COOH	7.78	7.62		3.73		65
e	COOH	Me	Me	Me				3.37	1.95, 2.23	342
c	COOH	Me	CH_2COOH	*t*-Bu				3.65, 3.45	1.40, 2.30	70
f	COOH	*t*-Bu	CH_2COOH	*t*-Bu				3.7	1.40	70
a	CN	H	H	H				3.51	7.05	60
c	CN[g]	COOH	H	H		7.29	7.67	4.17	8.12	275
c	CN	SPh	H	Et		6.90		3.55	1.29, 2.80, 7.15	68
c	CN	S(2C$_4$H$_3$S)	H	Et		6.80		3.80	1.26, 2.76, 6.90, 7.12, 7.28	68
e	CN[h]	H	COOH	H	7.6		8.35	4.18		275
c	CN	H	CH_2CN	H	7.35		7.35	3.70		70
d	CN[i]	H	H	COOMe	7.69	7.48		3.75	3.89	65
c	CN	*t*-Bu	CH_2CN	*t*-Bu				3.80	1.42	70
c	COOMe	*t*-Bu	CH_2COOMe	*t*-Bu				3.70	1.50, 3.65	70
c	COOEt	H	H	H	6.95	6.95	7.05	5.70	1.15, 4.05	266
c	COOEt[j]	COOH	H	H		7.05	7.45	4.07	1.24, 4.15	275
f	COOEt[k]	H	COOH	H	7.19		8.20	3.90	1.23, 4.12	275
c	COOEt	H	CH_2COOEt	H	7.15		7.15	3.60	1.25, 4.15	70
f	$CONH_2$	*t*-Bu	CH_2CONH_2	*t*-Bu				3.6	1.4, 6.6	70

Letter codes, either under "Solvent" or as italic superscripts, have the following designations: a, cyclohexane; b, mean shift of ring protons; c, $CDCl_3$; d, acetone-d_6; e, DMSO-d_6; f, $CDCl_3$-DMSO-d_6; g, $J_{45} = 6$ Hz; h, $J_{25} = 4$ Hz; i, $J_{24} = 1.6$ Hz; j, $J_{45} = 5$ Hz; k, $J_{25} = 3$ Hz.

TABLE 29. INFRARED FREQUENCIES OF THIOPHENEACETIC ACIDS AND DERIVATIVES 

R_2	R_3	R_4	R_5	ν_{CO}	ν_{CN}	Others	Reference
CH_2COOH	COOH	H	Me	1700 1640			342
CH_2COOH	H	COOH	Me	1700 1640			342
CH_2COOH	Me	Me	Me	1710			342
CH_2COOH	H	H	$CH{=}CHC_6H_5$	1690			300
CH_2COOH	H	H	$CH{=}CHC_6H_4$-*p*-F	1685			300
CH_2COOH	H	H	$CH{=}CHC_6H_4$-*p*-Cl	1690			300
CH_2COOH	H	H	$CH{=}CHC_6H_4$-*m*-Cl	1680			300
CH_2COOH	H	H	$CH{=}CHC_6H_4$-*p*-Br	1690			300
CH_2COOH	H	H	$CH{=}CHC_6H_4$-*p*-OMe	1680			300
CH_2COOH	H	H	$CH{=}CHC_6H_4$-*p*-isoBu	1680			300
CH_2COOH	H	H	$CH(OH)CH_2C_6H_5$	1680			300
CH_2COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-F	1670			300
CH_2COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-Cl	1670			300
CH_2COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-Br	1675			300
CH_2COOH	H	H	$CH(OH)CH_2C_6H_4$-*m*-Cl	1680			300
CH_2COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-OMe	1680			300
CH_2COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-isoBu	1680			300
CH_2COOH	H	H	$CH_2NPhtal$	1720 1695			20
CH_2COOH	H	H	CH_2NHCO_2-*t*-Bu	1710 1645		3300	20
CH_2CN	H	H	H		2258		348
CH_2CN	CH_2CN	H	H		2250		70
CH_2CN	H	H	$CH{=}CHC_6H_5$		2220		300
CH_2CN	H	H	$CH{=}CHC_6H_4$-*p*-F		2240		300
CH_2CN	H	H	$CH{=}CHC_6H_4$-*p*-Cl		2230		300
CH_2CN	H	H	$CH{=}CHC_6H_4$-*m*-Cl		2230		300
CH_2CN	H	H	$CH{=}CHC_6H_4$-*p*-Br		2240		300
CH_2CN	H	H	$CH{=}CHC_6H_4$-*p*-OMe		2220		300

CH_2CN	H	H	$CH{=}CHC_6H_4$-*p*-isoBu		2220		300
CH_2CN	H	H	$CH{=}CHC_6H_4$-*p*-NO_2		2220		300
CH_2CN	H	H	$COCH_2C_6H_5$	1660	2230		300
CH_2CN	H	H	$COCH_2C_6H_4$-*p*-F	1650	2240		300
CH_2CN	H	H	$COCH_2C_6H_4$-*p*-Cl	1660	2240		300
CH_2CN	H	H	$COCH_2C_6H_4$-*m*-Cl	1650	2240		300
CH_2CN	H	H	$COCH_2C_6H_4$-*p*-Br	1650	2240		300
CH_2CN	H	H	$COCH_2C_6H_4$-*p*-OMe	1660	2240		300
CH_2CN	H	H	$COCH_2C_6H_4$-*p*-isoBu	1650	2240		300
CH_2CN	H	H	$COCH_2C_6H_4$-*p*-NO_2	1660	2240		300
CH_2COOEt	CH_2COOEt	H	H	1745		3120, 2290	70
CH_2COOEt	H	H	Me	1695		2950, 2920, 2870, 1740, 1580, 1185, 1040	345
$CH_2CONHPh$	H	H	H	1660			338
$CH_2CONHC_6H_4$-*o*-Me	H	H	H	1660			338
H	$(CH_2)_2COOH$	H	H			940, 926, 908, 858, 827, 787, 743, 708, 685, 645, 585, 561, 498	144
COOH	CH_2COOH	H	H	1700 1665			275
Br	CH_2COOH	H	Br	1710		3200–2900	346
SPh	CH_2COOH	H	Et	1714		3180, 1582, 1480, 1227, 923	68
Me	CH_2COOH	Me	Me	1705			342
t-Bu	CH_2COOH	CH_2COOH	*t*-Bu	1700		3500–2500	70
Cl	CH_2COOH	CH_2CONH_2	Cl	1715, 1640		3450, 3350, 3240	70
COOH	CH_2CN	H	H		2260		275
SPh	CH_2CN	H	Et		2253	1580, 1542, 1478, 830, 736, 683	68
H	CH_2CN	CH_2CN	H		2250		70
t-Bu	CH_2CN	CH_2CN	*t*-Bu		2250 2240		70
Me	CH_2COOMe	CH_2COOMe	*t*-Bu	1740			70
t-Bu	CH_2COOMe	CH_2COOMe	*t*-Bu	1750			70
COOH	CH_2COOEt	H	H	1735, 1660			275
H	CH_2COOEt	CH_2COOEt	H	1745		3120, 2990	70
t-Bu	CH_2CONH_2	CH_2CONH_2	*t*-Bu	1680		3480, 3460, 3350, 3200	70



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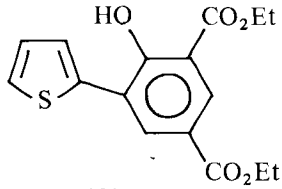

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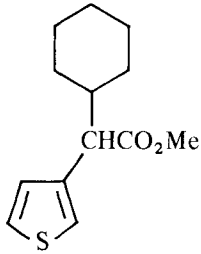

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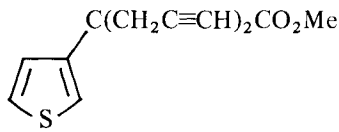
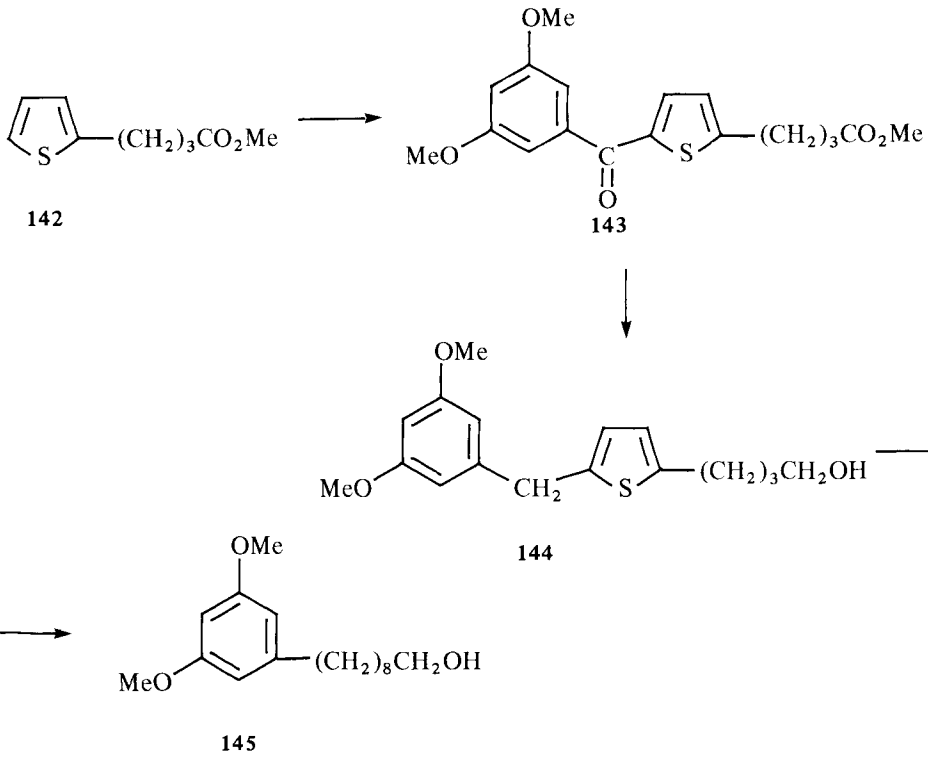


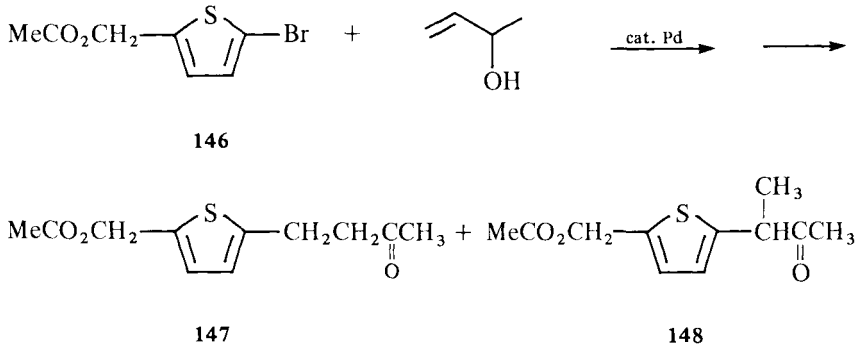
141

4-(2-Thienyl)butyrate **142** reacts with 3,5-dimethoxybenzoyl chloride in the presence of stannic chloride to yield the 5-(3,5-dimethoxybenzoyl) derivative **143**, which can be converted into the benzyl analogue **144** by treatment with lithium aluminum hydride–aluminum chloride. Compound **144** heated with Raney nickel gives the resorcinol dimethyl ether **145**.[359]



142 143 144 145

Scheme 15

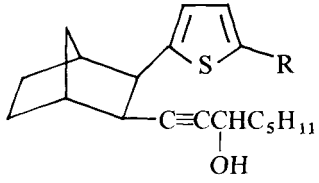


146 **147** **148**

Scheme 16

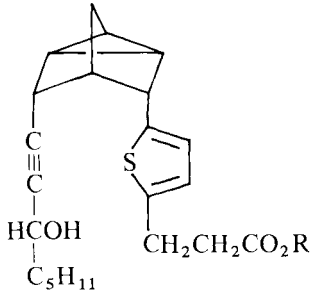
The palladium-catalyzed reaction of methyl 5-bromo-2-thienyl acetate **146** (Scheme 16) with α-methylallyl alcohol gives β-thienyl ketone **147** almost selectively, together with small amounts of α-thienyl ketone **148**.[360] Reduction to give methyl(2-thienyl)acetate is suppressed by using dimethylformamide as a solvent, potassium carbonate as a base, and keeping the reaction temperature at 100°.

Thiophene-containing prostaglandin endoperoxide analogues **149** and **151** (Scheme 17) are available by addition of thienylpalladium species to bicyclic olefins and subsequent treatment with alkenyl or alkynyl organometallics;[361] saponification yields the corresponding carboxylic acids **150** and **152**.



$R = CH_2CH_2CO_2CH_3$ **149**

$CH_2CH_2CO_2H$ **150**



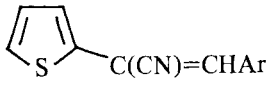
$R = CH_3$ **151**

H **152**

Scheme 17

B. Thiopheneacetonitriles

The reactivity of thiopheneacetonitriles is mainly due to the active methylene group in these compounds.



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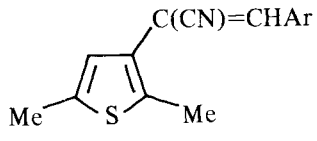

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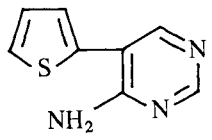

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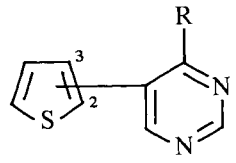


156 R = H
157 NH_2
158 OH
159 Cl

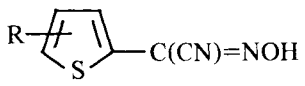
Condensation of 2-thenylcyanide and 2,5-dimethyl-3-thiopheneacetonitrile with aromatic aldehydes gives acrylonitriles **153**[362] and **154**[363] respectively.

The reaction of *s*-triazine with the active methylene group of 2-thiopheneacetonitrile leads to the aminopyrimidine **155** in 53% yield;[364] the postulated reaction path is supported by isolation of the intermediate for the analogous reactions of cyclopentenyl and cyclohexenyl acetonitriles.

Thienylpyrimidines **156** are prepared by condensing 2- or 3-thiopheneacetonitrile with $HCONH_2$–NH_3, hydrolyzing **157**, chlorinating **158**, and hydrogenating **159**.[365] Condensation of 2-thiopheneacetonitrile with ethylphenylpropiolate has also been studied.[366]

Carbethoxylation of 2-thiopheneacetonitrile gives 2-thienylcyanoacetate.[367] 2-Thienylacetonitriles, treated with 2-substituted 4-nitrosophenols in the presence of EtONa give α-(thienyl)-α-(*p*-hydroxyphenylimino)acetonitriles.[368]

Reaction of thenylcyanides with BuONO–Na gives the oximes **160** used as insecticides.[369] Thenylcyanides are also converted in high yields into propenenitriles **161**, which, on nitrous deamination, give propynenitriles **162**.[370]



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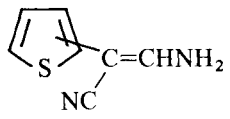

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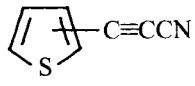

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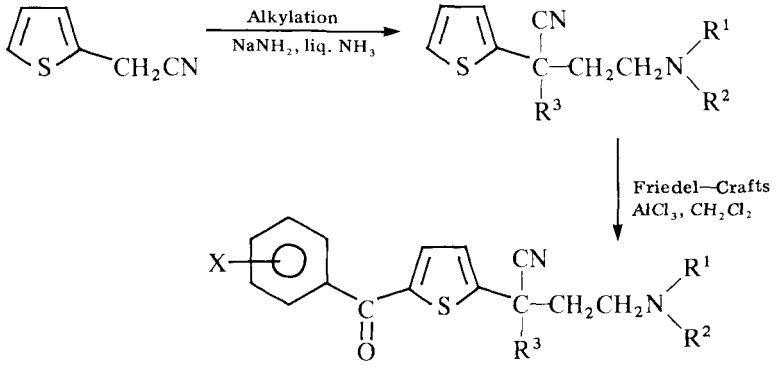


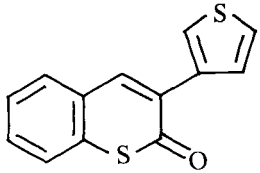
163

Scheme 18

Scheme 18 shows the two-step conversion of 2-thienylacetonitrile into thienylalkanenitriles **163**, which possess spasmolytic activity.[371]

3-Thiopheneacetonitrile reacts with 2-*t*-butylthiobenzaldehyde to give a cyanostyrene which, on heating with polyphosphoric acid, gives 37% thiocoumarine **164**.[372] Vilsmeier-Haack formylation of 3-thenylcyanide gives the pyridine **165** in 34% yield with no trace of formylated pyridine.[373]

New reactivity patterns of 3-thiopheneacetonitrile recently reported in patents include successive condensation with MeCOEt, hydride reduction, hydrolysis, conversion to the acid chloride and amidation to give **166**,[374] alkylation to **167** by treatment with $NaNH_2$ and cyclohexyl bromide,[375] and reaction with ClCN at 650° leading to 3-thienylmalononitrile in 50% yield.[376]



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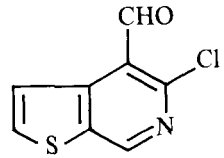

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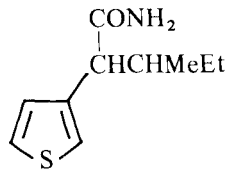

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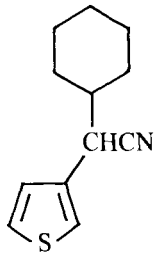
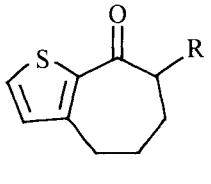


167

C. *Cyclizations*

Cyclization reactions of thiopheneacetic acids and their derivatives have received considerable attention by several research groups.

Cagniant and co-workers, who were able to increase the number of carbons in the side-chain of thiopheneacetic acids by applying the malonic synthesis to chloromethyl derivatives,[377] obtained cyclic ketones **168**, **169**,[378] **170**,[379] **171**,[380] **172**, and **173**[381] by cyclization of the appropriate thiopheneacetic acids and derivatives.



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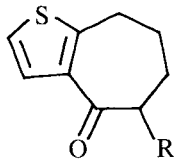

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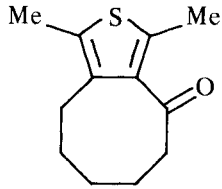

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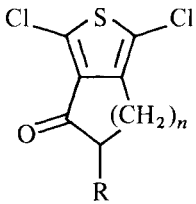

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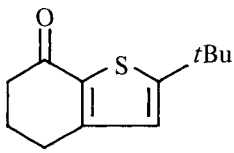

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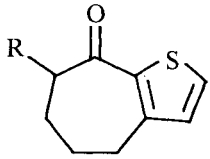
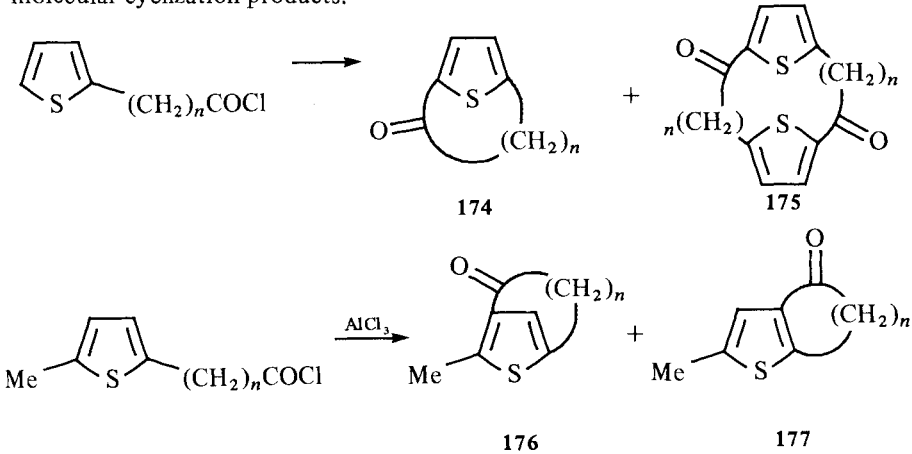


173

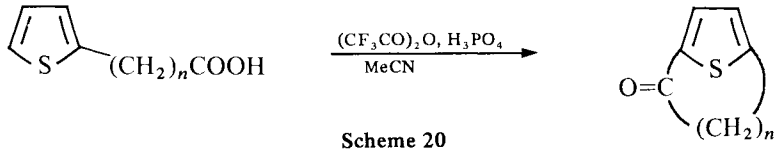
Extensive studies by Gol'dfarb and co-workers[382–385] have shown that in the Friedel-Crafts acylation of terminal 2-thienyl straight-chain acyl chlorides both monomeric **174** (intramolecular) and dimeric **175** (intermolecular) products are formed (Scheme 19). The addition of silica gel (or alumina) in these Friedel-Crafts acylations and utilizing high-dilution conditions favors the formation of intramolecular cyclization products.



174 **175**

176 **177**

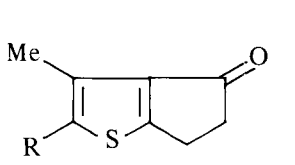
Scheme 19



Scheme 20

5-Methyl derivatives cyclize at the 3- or 4-positions to give **176** and **177**. Further details on the formation of macrocycles by Friedel-Crafts acylation and by cyclization of thiopheneacetic acids are provided in a recent comprehensive review.[104]

The intramolecular acylation of long-chain ω-(2-thienyl)alkanoic acids in acetonitrile solution in the presence of trifluoroacetic anhydride and of catalytic amounts of H_3PO_4 (Scheme 20) has been studied by Illuminati, Mandolini, and co-workers,[299,386,387] who obtained kinetic rate data and effective molarities (EM) for use in structure activity correlations. This extensive quantitative investigation of ring-closure reactions over a wide spectrum of ring sizes provides new insights into the factors controlling the formation of ring molecules. The effect of decreasing the length of the connecting α-oxopolymethylene chain upon the free energy of activation can be attributed mainly to ring-strain. Below the nine-membered chain length, the ring-formation rate was estimated to be very low, and steric hindrance of solvation in the transition state was suggested on the basis of the EM analysis.[386]



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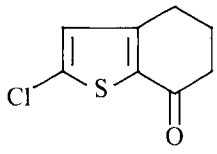

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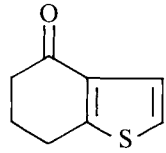

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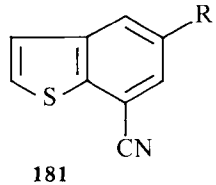

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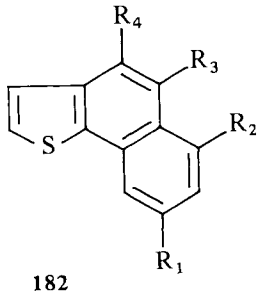

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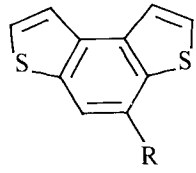
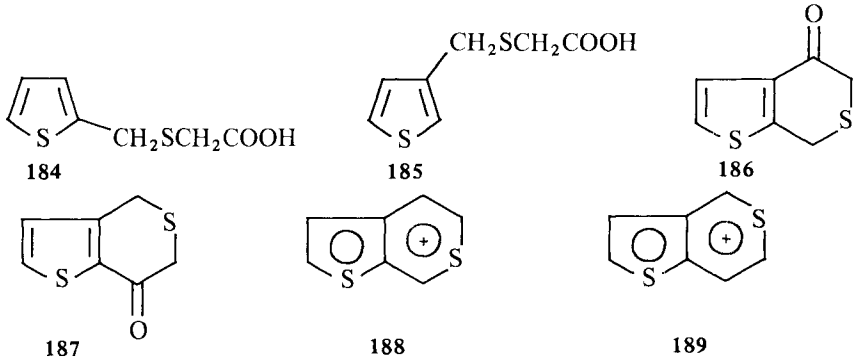


183

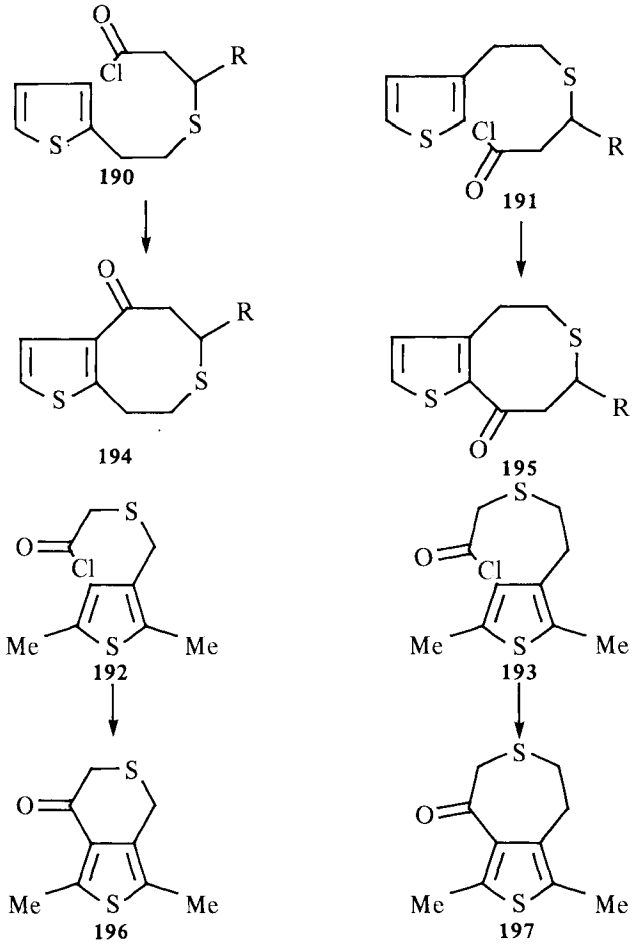
Cyclization reactions led to the formation of cyclic ketones **178**,[388,389] **179**[390] and **180**,[391] benzothiophenes **181**,[392] and dibenzothiophene;[393] photooxidative cyclizations afforded naphtothiophenes **182**[394,395] and benzodithiophenes **183**[396] with antimalarial activity.



184 185 186

187 188 189

Cyclization of thenylthioacetic acids provides heterocyclic compounds containing a sulfur atom in the ring formed in the cyclization process. So thenylthioacetic acids **184** and **185** cyclize to dithiatetrahydroindenes **186** and **187**[126,397]

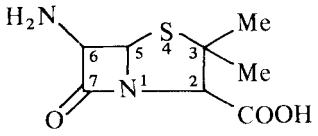


Scheme 21

and are convenient precursors for the synthesis of thienothiapyrylium cations **188** and **189**,[398] whereas acid chlorides **190**, **191**,[399] **192**,[400] and **193**[401] cyclize to give **194**, **195**, **196**, and **197**, respectively (Scheme 21).

VII. CEPHALOSPORINS

Amides derived from 6-aminopenicillanic acid **198** and from 7-aminocephalosporanic acid **199** have been widely investigated in the last three decades owing to their antibiotic activity. Two cephalosporins containing the thiopheneacetamido group are commercial: cephaloridine **200** and cephalothin **201**.



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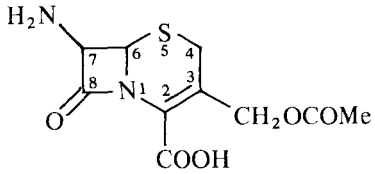

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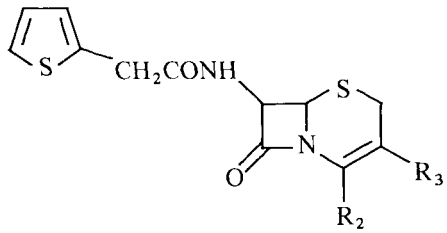
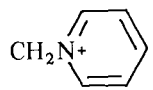
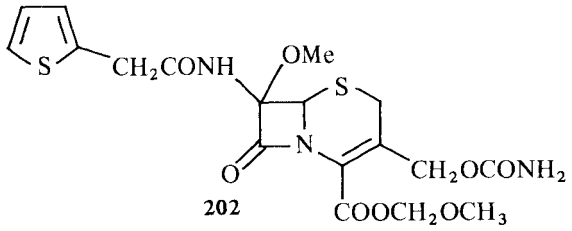


	R_2	R_3
200 Cephaloridine	COO^-	
201 Cephalothin	COOH	CH_2OCOMe

The antibacterial activity, pharmacology, toxicology, and clinical aspects of cephalosporin antibiotics, which are discussed in comprehensive reviews[402,403] and in textbooks,[404,405] are out of the scope of the present chapter. The chemistry and the physicochemical properties of these compounds have also been reviewed[402,403,406] and reported in textbooks[404] and encyclopedias.[407] The present section is limited to the citation of a few references regarding recent advances (i.e., after 1975) on the synthesis and on the reactivity, whereas melting points and spectral data are collected in tables. Thiopheneacetamido cephalosporins for which neither physical nor spectral properties are available, are reported in the Tables of Compounds.

1. Synthesis

Cephalothin **201** has recently been prepared in 50% yield by reaction of 2-thienylacetic acid with 7-aminocephalosporanic acid, catalyzed by immobilized penicillin amidase in acetate buffer.[408] A novel method for the mild acylation of base- and acid-sensitive amides in the presence of neutral scavengers (i.e., partially hydrated molecular sieves) allowed the synthesis of the methoxymethyl ester of cefoxitin **202**.[409] The synthesis and the reactions of 7-hydrazinocephalosporanates **203** have been investigated.[410] Thio-β-lactam cephalosporins are obtained by treating the corresponding oxo derivatives with excess boron sulfide in an inert solvent;[411]



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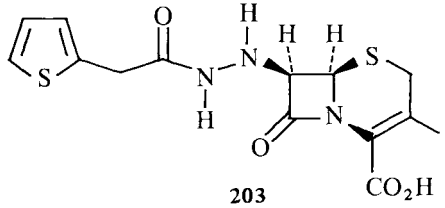
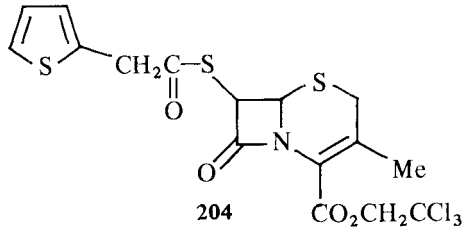
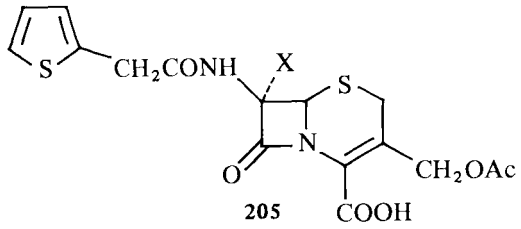


203

the synthesis of the thiol ester **204** has also been reported.[412] A novel method for the introduction of substituents into the C-7 position of cephalosporines allows the synthesis of 7-substituted cephalothins **205**.[413]



204



205

X = OC_2H_5, $OCH_2CH_2CH_3$, OCH_2CN, $OCH_2CH_2OCH_3$, SCH_3, CN, $CH(COOC_2H_5)_2$, N_3

The syntheses of thiopheneacetamido penicillins[414-418] and cephalosporins[419-454] have been reported, but the exact formulas and the physical properties are not available.

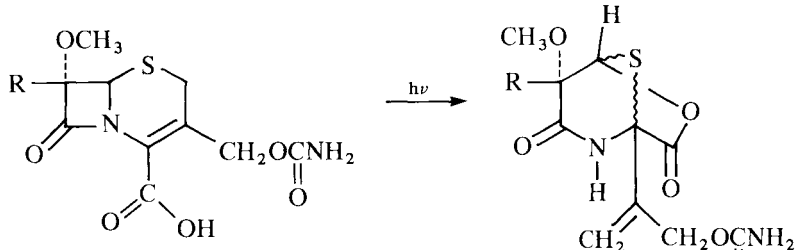
2. Spectroscopic and Physicochemical Properties

Melting points, ^{1}H NMR, infrared, ultraviolet, and mass spectra data of thiopheneacetamido cephalosporins are collected in Tables 30 to 33. The spectral behavior and other properties of sodium cephalothin are well known.[406] ^{13}C NMR spectra of free acids and esters of cephaloridine and cephalothin in various solvents have recently been reported.[480]

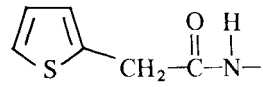
3. Reactivity

The hydrolysis of cephalothin **201** and cephaloridin **200** in strongly acid medium at 100° has been studied,[481] and a spectrophotometric method for their detection[482] developed. The kinetics of aminolysis of cephalosporins has been investigated and related to the allergic properties of these compounds.[483] The stability of sodium cephalothin in large-volume parenteral solution and the distribution coefficients in biphasic systems BuOAc–H_2O and $CHCl_3$–H_2O[484] were also studied. The metabolism of orally administered cephalothin-^{14}C was investigated in the rat.[485,486]

Photolysis of cefoxitin **206** yields 50% **207** which was characterized by mass, ^{1}H NMR, ^{13}C NMR, infrared, and ultraviolet spectroscopy.[487]



206 **207**

R = 

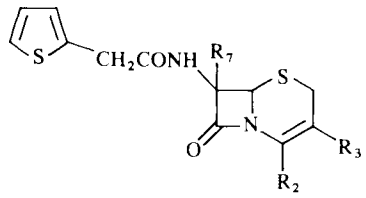
VIII. KINETIC DATA AND COMPARISON WITH SIDE-CHAIN REACTIVITY OF OTHER FIVE-MEMBERED HETEROCYCLES

First-order rate constants and activations energies for the solvolysis of chloromethyl furans, thiophenes, and selenophenes **208** to **213** have been measured.[74]

TABLE 30. MELTING POINTS AND SPECTRAL DATA FOR CEPHALOSPORINS OF

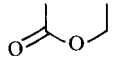
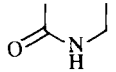
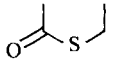
R_2	R_3	R_7	Melting Point (°C)	NMR Solvent	NMR δ (CH_2CONH)
CH_2OH	CH_2OAc	H	172–173		
CHO	CH_2CHN_2	H	183–185	b	
COOH	CH_2OAc	H	70–72		
COOH	Me	H	230–232		
COOH	$CH{=}CHCO_2H$	H	139–141		
COOH	$CH{=}CHCO_2Et$	H	191–193		
COOH	Cl	H	114–120	c	3.84
COOH	Br	H		b	3.78
COOH	OMe	H	168–171	b	3.76
COOH[d]	CH_2OAc[d]	H[d]		c	3.78
COOH	Me	OMe			
COOH	Me	SMe	107–110		
COOH	CH_2OCONH_2	OMe		f	4.00
COO^-	$CH_2SC(NH_2){=}\overset{+}{N}H_2$	H	194 dec.		
COO^-	$CH_2SC(S)COEt$	H	154 dec.		
CO_2Na	SSO_2ONa	H	196–198 dec.	g	4.09
COOMe	Me	H	180–182		
COOMe	CHO	H	167–170	f	3.95
COOMe	CH_2OAc	H			
COOMe	CH_2OH	H		f	3.92
COOMe		H	200–205	c	3.85[h] 3.97[h]
COOMe	CH_2N_3	H			
$COOCHPh_2$	CH_2OCONH_2	OMe		c	3.78
$COOCH_2Ph$	$CH_2SC(S)OEt$	H	150–152		
$COOCH_2Ph$	CH_2SCOPh	H	150–151		
$COOCH_2C_6H_4$-*p*-OMe	Me	H	160	c	3.82
$COOCH_2C_6H_4$-*p*-NO_2	Me	H	217	b	3.80
$COOCH_2C_6H_4$-*p*-NO_2	OH	H	148–158 dec.	c	3.87
$COOCH_2C_6H_4$-*p*-NO_2	OMe	H	171–172		
			171–175	c	3.85
$COOCH_2C_6H_4$-*p*-NO_2	$OCOCH_2(2C_4H_3S)$	H	105–126 dec.	c	3.81
$COOCH_2C_6H_4$-*p*-NO_2	OCOMe	H	150–178 dec.	c	3.81
$COOCH_2C_6H_4$-*p*-NO_2	Cl	H	164–166	c	3.83

GENERAL FORMULA[a]

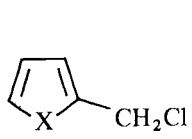


Infrared		UV			
Units		λ_{max}	ϵ	m/e	Reference
a	3.00, 5.59, 5.70, 6.00				455
a	4.80				455
a	5.70, 5.80, 6.06				455
a	5.73, 6.04				455
		317	20,800		456
		320	20,000		456
					457
					457
					457
e	1795, 1735, 1680, 1640	316	5,950		458
a	3.0, 5.60, 5.80, 5.95			512, 497, 415	459
a	5.64, 5.83, 5.90				459
					460
					461
					461
					462
a	5.66, 5.80, 5.90, 6.00			366, 335, 196, 186, 172, 154, 129, 97	455
a	3.06, 5.59, 5.81, 6.00, 6.23, 6.53	233	10,550		463
		296	10,750		
		340	Shoulder		
a	5.73, 6.00			424, 364, 244, 184, 97	455
a	2.75, 3.00, 5.60, 5.82, 6.00, 6.51	235	13,500		463
		260	7,180		
a	2.97, 5.60, 5.77, 6.04, 6.20, 6.50	236	12,600		463
		260	7,370		
e	2100, 1793, 1734, 1690, 1646, 1512				464
e	3500–3200, 1780, 1725				460
					461
					461
					461
					461
		238	16,850		457, 465
		268	14,750		465
					457
					457
					457
					457, 465

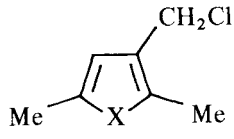
TABLE 30. (*Continued*)

R_2	R_3	R_7	Melting Point (°C)	NMR Solvent	NMR δ (CH_2CONH)
$COOCH_2C_6H_4$-*p*-NO_2	Br	H		b	3.79
$COOCMe_3$	CH_2Ph	H	153		
$COOCMe_3$	Me	OMe	158–160		
$COOCMe_3$	Me	SMe	143–144		
COCl	Me	H	179 dec.		
COCl	CH_2OAc	H	117–118 dec.		
COOAc	Et	H	200–202	c	
COOAc	CH_2CHN_2	H	169–174	b	
COOAc	CH_2CH_2OMe	H	189–190	c	
COOAc	CH_2CH_2OAc	H	164–166		
COOAc	CH_2CH_2Cl	H	194–197	b	
		H	228–230 dec. 235–238 dec. 210	f	3.88
		H			
		H		b	3.87

[a] Letter codes, under columns for "Solvent", "Units", or as italic superscripts, have the following designations: a, $\mu(\lambda_{max})$; b, DMSO-d_6; c, $CDCl_3$; d, 4-CO derivative; e, $\nu(cm^{-1})$; f, DMF-d_7,



X = O **208**
Se **209**
S **210**



X = O **211**
Se **212**
S **213**

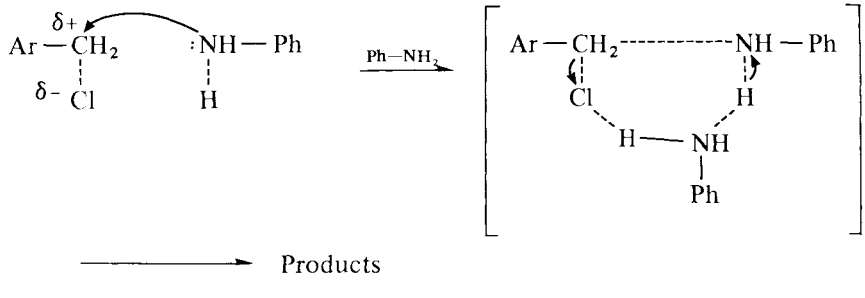
3-Chloromethyl-2,5-dimethyl derivatives **211** to **213** react faster than the corresponding 2-chloromethyl analogues **208** to **210**, whereas the reactivity of the heterocyclic groups decrease in the order furan > selenophene > thiophene.

Arcoria and co-workers have studied the kinetics of the reactions of 2-furfuryl, 2-thenyl, and benzyl chlorides[61] with aniline in acetonitrile and in benzene and of 2-chloromethylselenophene with aniline in acetonitrile.[488] The reactions are third order overall, first order with respect to the chloromethyl compound and second order with respect to aniline. The rate-determining contribution of the second aniline molecule implies a base catalysis where aniline acts as a bifunctional

Infrared		UV			
Units		λ_{max}	ϵ	m/e	Reference
					457
					466
a	5.66, 5.80, 5.88				459
a	5.72, 5.88, 5.95				459
a	5.63, 5.71, 6.04				455
a	5.73, 5.70, 6.09				455
a	5.60, 5.75, 5.90, 6.00				455
a	4.74				455
				424	455
a	5.60, 5.73, 5.88, 6.00			452	455
a	5.62, 5.73, 5.88, 6.00			428	455
					467
a	3.10, 3.25, 5.56, 5.69, 6.00, 6.35	236 260	12,800 7,020		463
e	1794, 1778–1763, 1742, 1666, 1523				468
e	1799, 1701, 1657, 1538				464
					461

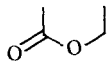
g, D_2O; h, alternative assignments possible.

catalyst favoring both the N–H and C–Cl bond breaking (Scheme 22). The preceding hypothesis is supported by kinetic experiments for the reaction of benzyl chloride with orthophenylendiamine, a nucleophile where both amino groups can interact with the substrate exerting an intramolecular catalysis; this reaction, in fact, turns out to be first order with respect to the amine.[489] Third-order rate constants for the reactions in acetonitrile show the following reactivity order: 2-furyl > 2-thienyl > selenophene-2-yl > phenyl; the highly negative activation



Scheme 22

TABLE 31. MELTING POINTS AND SPECTRAL DATA FOR CEPHALOSPORINS OF

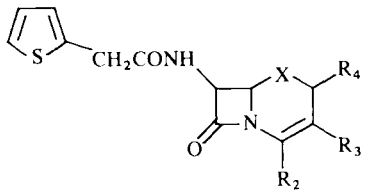
X	R_2	R_3	R_4	Melting Point (°C)	NMR Solvent
CH_2	COOH	CH_2COAc	H		a
CH_2	COOH	Me	OAc	169–170	a
CH_2	COONa	CH_2COAc	H		d
CH_2	COOMe	CH_2OAc	H		
CH_2	CO_2-*t*-Bu	CH_2OAc	$OCO_2CH_2CCl_3$	131.5–132	e
CH_2	CO_2-*t*-Bu	CH_2OAc	OH	145.5–147	a
CH_2	CO_2-*t*-Bu	CH_2OAc	=O[f]	178–179	e
CH_2			H	210	
O	COOH	CH_2COAc	H		
O	COONa	CH_2COAc	H		d
SO[g]	H	CH_2OAc	H	176–177	h
SO[j]	H	CH_2OAc	H	~100	h
SO[g]	COO(9-fluorenyl)	CH_2OAc	H	229–230	h
SO[j]	COO(9-fluorenyl)	CH_2OAc	H	213–215	h

[a] Letter codes, under columns for "Solvent", "Units", or as italic superscripts, have the following designations: a, acetone-d_6; b, $\mu(\lambda_{max})$; c, $\nu(cm^{-1})$; d, D_2O; e, $CDCl_3$; f, this carbon bears

entropies, which are the rate-determining parameter, are consistent with an ordered and polar transition state structure. In benzene solutions the kinetics at high aniline concentrations deviate from the third-order equation owing to association of aniline in this solvent.

Oae and co-workers[490] reported second-order rate constants for the reactions of arylmethyl chloride with a series of amines and first-order rate constants for the formolysis reactions of the same chlorides. The reactivity sequence for the reactions with amines resembles those found for the methanoloysis[74] and for the reaction with aniline,[61] whereas in the formolysis the furan derivative reacts markedly faster. This facile S_N1 type C–Cl dissociation can be related to the formation of abnormal ring substitution products, as observed in the abnormal displacement reaction of 2-chloromethylfuran with cyanide ion.[409]

GENERAL FORMULA[a]



	Infrared		UV			
δ_{CH_2CONH}	Units		λ_{max}	ϵ	m/e	Reference
3.89	b	5.7, 5.8			318	469
3.85	c	2500–3600, 3270, 1780 1728, 1690, 1645, 1530				470
3.9	b	5.67, 5.73, 5.98, 6.22	238	12,800		469
			255	10,440		
3.8					392	469
4.72	c	3320, 1780, 1755, 1730 1680, 1510	238	8,600		470
			268	7,400		
3.76	c	3400, 3320, 1780, 1725, 1680, 1515	240	14,200		470
			268	13,400		
3.75	c	3400, 1777, 1720, 1685, 1598, 1500	232	8,600		470
			315	8,600		
	c	1794, 1763, 1742, 1666, 1523				471
	b	5.60, 5.8, 6.07				470, 472
3.9			235	10,570		473
			(255)	6,900		
231[i]	b	5.63, 5.79, 6.05, 6.57, 9.75	240	15,100		474
227[i]						474
232[i]	b	5.72, 5.81, 6.04, 6.52, 9.57				474
227[i]						474

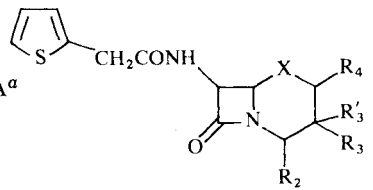
no hydrogens; g, 6H, 7H-*cis*-isomer; h, DMSO-d_6; i, in hertz, probably run on a 60 Mc spectrometer; j, 6H, 7H trans isomer.

The secondary α-deuterium isotope effects in the halogen exchange of benzyl and thenyl chlorides were studied by Östman,[491] who found small effects according to the reactivity sequence: 2-thienyl > phenyl > 3-thienyl. Molecular orbital calculations with a pd^2-hybridized thiophene model agree with the foregoing experimental rate ratios.

The alkaline hydrolysis of the esters of arylacetic acids has been investigated,[352] but unfortunately no rate constants are available from *Chemical Abstracts*.

The polarographic reduction of 3-heteroaryl acrylates (ArCH=CHCOOH) to 3-heteroanyl propionates ($ArCH_2CH_2COOMe$) has been studied.[492] The half-wave potential was found to be positive in the order pyrrole < benzene < furan < thiophene, and σ_n values representing the electron-attracting capacity of the aromatic rings, were calculated to be 0.6, 1.5, 2.27, and 2.55 for the foregoing rings, respectively.

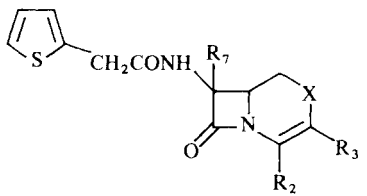
TABLE 32. MELTING POINTS AND SPECTRAL DATA FOR CEPHALOSPORINS OF GENERAL FORMULA[a]



X	R_2	R_3	R'_3	R_4	Melting Point (°C)	NMR Solvent	NMR $\delta(CH_2COOH)$	Infrared	Reference
C[c]	CO_2Me	H	H		176–178	a	3.90	3230, 1775, 1738, 1655	475
S	COOH	CH_2		H	178	b	3.76		461
S	COOH	Me	Cl	H	80 dec.	a	3.88		476
S	$COOCH_2C_6H_4$-*p*-OMe	CH_2		H	114	a			461
S	$COOCH_2C_6H_4$-*p*-NO_2	CH_2		H	139–141	b	3.82		461
S	$COOCH_2C_6H_4$-*p*-NO_2	Me	Cl	H	70 dec.	b	3.85		476

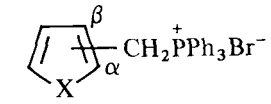
[a]Letter designations: a, $CDCl_3$; b, DMSO-d_6; c, thiophene ring fused to this carbon at 2 position and to R_4 at 3 position.

TABLE 33. MELTING POINTS AND SPECTRAL DATA FOR CEPHALOSPORINS OF GENERAL FORMULA[a]

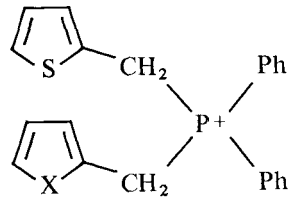


X	R_2	R_3	R_7	Melting Point (°C)	NMR Solvent	NMR $\delta_{(CH_2CONH)}$	Infrared	UV λ_{max}	UV ϵ	Reference
O	COOH	CH_2OAc	H	182 dec.			3300–2500, 1780, 1750, 1720, 1680, 1535, 1620	272	8,650	477
O	COOH	CH_2OAc	OMe	150–155 dec.				270	9,340	478
S	COOH	H	H	206–210	a	3.85				479
S	$COOCHPh_2$	H	H		b	3.65	1760, 1710, 1670	307		479

[a] Letter designations: a, $CDCl_3$; b, acetone-d_6.



X = CH=CH 214
α-O 215
β-O 216
α-S 217
β-S 218



X = O 219
CH = CH 220

The alkaline hydrolysis of heteroarylmethyltriphenyl phosphonium bromides **215** to **218** to give triphenylphosphine oxide and the respective methyl-substituted heterocyclic compounds is generally considered to proceed according to the mechanism depicted in Scheme 23.[215] These reactions follow a third-order kinetics according to the rate law: rate $= k_{obs}[R_4P^+]\,[OH^-]^2$. The hydrolysis rates decrease in the order 2-furylmethyl > 2-thenyl > benzyl > 3-thenyl > 3-furylmethyl, the rate decrease being accompanied by an increase in the activation energy. These data were interpreted in terms of the electron-withdrawing nature of the heteroaryl groups and the relative stabilities of carbanions **221** eliminated in the rate-determining step.[216] The 3-heteroaryl carbanions were found to be less stable than the benzyl carbanion, whereas the alkaline hydrolysis of the salts **219** and **220**[217] showed the 2-furylmethyl to be more stable than 2-thenyl carbanion, both being more stable than benzyl. The inductive electron-withdrawing effect of the heteroatoms in 2-heteroarylmethyl carbanions (together with possible 3-d orbital participation in the 2-thenyl compound) evidently prevails over the greater possibilities of mesomeric delocalization in the benzyl case.

In the polarographic reduction of (heteroarylmethyl)triphenylphosphonium bromides **214** to **218** the ease of reduction correlates best with the order of stability of the formed carbanions.[493]

Kinetic studies on the alkaline hydrolysis of heteroarylmethyl phosphonate esters **222** to **224** show that this reaction follows a second-order rate law.[227] The observed reactivity sequence is again: 2-furylmethyl > 2-thenyl > benzyl.

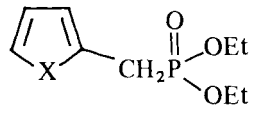
$$R_4P^+ + OH^- \rightleftharpoons R_4P\cdot OH$$

$$R_4P\cdot OH + OH^- \rightleftharpoons R_4P\cdot O^- + H_2O$$

$$R_4P\cdot O^- \xrightarrow[k_3]{\text{Slow}} R_3PO + R^- \qquad \textbf{221}$$

$$R^- + H_2O \longrightarrow RH + OH^-$$

Scheme 23



X = O	222
S	223
CH=CH	224

The kinetic data on side-chain reactivity of arylmethyl derivatives are summarized in Table 34, where reactivities relative to the 2-thiophene derivative as unity are reported. Table 34 shows that 2-furylmethyl derivatives react in all cases faster than 2-thenyl compounds, whereas benzyls and 3-substituted derivatives are slower. First-order rates for the methanolysis of 2-choromethyl selenophene are higher than those for the thiophene analogue, whereas third-order rates for the reaction with aniline are slightly lower.

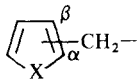
The reactivity order observed in Table 34 reflects the electron-withdrawing inductive effect of the heteroatoms in five-membered rings.[494]

A quantitative estimation of the effects of the heteroatoms and of other substituents on side-chain reactivity is generally achieved by using linear free energy relationships such as the Hammett equation;[495,496] however, different approaches can be used.

An approach implies the calculation of Hammett sigma replacement values for the heteroatoms, regarded as substituents, assuming rho values for five-membered heterocycles to be equal to those in benzenoid compounds.[495,497] However, these sets of values are of nongeneral validity;[496] even the set derived from the pK_a of carboxylic[498] is different from that derived from the alkaline hydrolysis of carboxylic esters.[499] The reasons for the difference between these sets of values has not yet been clarified, neither has the extent of importance of hydrogen bonding in these compounds.[495]

An alternative approach for the study of substituent effects in benzene and in five-membered heterocycles applies the Hammett equation to five-membered rings considering the 4- and 5-positions are meta- and paralike, respectively, and interprets the rho values for heterocyclic and benzene systems as a measure of the intensity of transmission of substituent effects through the rings.[495] The latter procedure has recently been criticized and direct comparison of the effects of substituents in a heterocyclic ring with those of the substituents in a benzene ring, acting on an identical reaction site, recommended.[500]

In the author's opinion, although the foregoing approaches can provide useful information for understanding the behavior of the heterocycles in a given reaction, great caution should be adopted in attempting generalizations involving rigorous quantitative comparisons. Caution is suggested both by the discrepancies in the sigma values for the heteroatoms in heterocyclic rings[496] and by statistical analysis of single parameter[501-506] and of multiparameter[501,506-509] equations in the benzene series. In particular, the limits of multiparameter equations in statistically disentangling substituent "effects" have been pointed out.[507,509,510] Recently, in

TABLE 34. SIDE-CHAIN RELATIVE REACTIVITIES OF ARYLMETHYL DERIVATIVES 

Reaction	X = α—O	α—Se	α—S	CH=CH	β—S	β—O
Methanolysis of chloromethyl derivatives[a] (k_1, 25°, MeOH)	9.6	5.4	1			
Formolysis of chloromethyl derivatives[b,c] (k_1, 20°, 20% dioxane)	460		1	<0.03		
Arylmethyl chlorides + cyclohexyl amine[b] (k_2, 80°, DMF)	1.5		1	0.56		
Arylmethyl chlorides + anisidine[b] (k_2, 80°, DMF)	3.2		1	0.75		
Arylmethyl chlorides + aniline[b] (k_2, 80°, DMF)	1.4		1	0.53		
Arylmethyl chlorides + piperidine[b] (k_2, 80°, DMF)	17		1	0.33		
Arylmethyl chlorides + morfoline[b] (k_2, 80°, DMF)	16		1	0.56		
Arylmethyl chlorides + pyridine[b] (k_2, 80°, DMF)	1.3		1	0.42		
Alkaline hydrolysis of arylmethyl phosphonate esters (k_2, 50°, aqueous dioxan)[d]	1.8		1	0.30		
Isotopic halogen exchange reaction of $ArCD_2Cl$[e] (k_2, 40° DMF)			1	0.34	0.28	
Arylmethyl chlorides + aniline[f] (k_3, 30°, MeCN)	1.4	0.83	1	0.28		
Arylmethyl chlorides + aniline[f] (k_3, 30°, benzene)	2.2		1	0.053		
Alkaline hydrolysis of $ArCH_2\overset{+}{P}Ph_3\ Br^-$[g] ($k_3$, 30°, 50% aqueous EtOH, 0.1 *M* KCl)	2.1		1	0.036	0.016	0.011

[a] Ref. 74.
[b] Ref. 490.
[c] Rates for benzyl chloride are much lower and were measured at 80°C.
[d] Ref. 227.
[e] Ref. 491.
[f] Refs. 61 and 488.
[g] Ref. 216

contrast with ^{13}C NMR studies reporting no significant superiority of a dual-substituent treatment,[511] a defense of the validity of the dual-substituent parameter (dsp) equation has appeared in the literature.[512]

It is worth mentioning in this context a review by Sjöström and Wold[509] who suggest to regard linear free energy relationships (LFERs) as empirical models of local validity (i.e., locally valid linearizations of complicated relationships) rather than "fundamental laws of chemistry" (multiparameter equations of general validity in which each parameter describes "fundamental" effects). As an alternative and a check to the ordinary use of LFERs the same research group applied principal component analysis, one of the new multivariate statistical methods called pattern recognition,[506,513-515] in many fields of physical organic chemistry, such as the study of solvent effects,[516-518] of acidity functions,[519] of ^{13}C NMR shifts,[510,520-524] and of substituent effects.[509,525,526] In the latter field this methodology provides interesting information on the redundancy of substituent parameter scales and allows the classification of substituents into four groups: electron withdrawing, electron donating, alkyls, and halogens.[526]

Multivariate statistics has also been applied to LFERs in the thiophene series providing new insights into the use of the Hammett equation for substituted thiophenes.[527] Principal component analysis pointed out that alpha-substituted thiophenes require the same sigma substituent constants as those derived for para-substituted benzenic compounds, due to a strict proportionality of the substituent effects in the heterocyclic and homocyclic systems. Accordingly, the use of a unique reaction constant for both systems does not appear to be warranted. Partial least squares analysis indicated that two independent effects are linearly transferred from benzenes to thiophenes.[527]

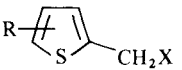
IX. TABLES OF COMPOUNDS

In these tables some of the reference numbers are accompanied with small letters, the significance being that the paper concerned deals with one or several of the following topics:

a.	Practical application
c.	Cotton effect, circular dichroism
d.	Dipole moment
e.	Medicament, pesticid
f.	Fluorescence, phosphorescence
g.	Vapor-phase chromatography
h.	HMO and other theoretical evaluations
i.	Infrared spectrometry
k.	Kinetic data
l.	Living material
m.	Mass spectrometry
n.	Nuclear quadrupole resonance

o. Microwave spectrometry
p. Polarography
q. Raman spectrometry
r. Nuclear-magnetic-resonance spectrometry
s. Electron-spin resonance spectrometry
u. Ultraviolet spectrometry
v. Other physical determinations
w. Thin-layer chromatography
x. X-ray diffraction
z. Optical properties

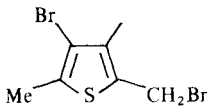
Tables 35 to 50 report melting points of thenyl derivatives while Tables 51 and 52 give reference to thienylacetamido cephalosporins for which no physical properties are available.

TABLE 35. 2-HALOMETHYLTHIOPHENES[a] 

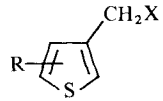
X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
Cl	H	H	H		78–82/18	9
					82/21	8
					38–40/0.5	61r
					65–67/15	11i,m,r
Cl	Me	H	H		80–83/12–13	13
Cl	COOMe	H	H		80–81/1	67i
Cl	NO_2	H	H	49–50		16
Cl	Br	H	H		106–108/12	14,15
					72–75/3	528
Cl	I	H	H			14r
Cl	Br	Br	H	31–32		528
Cl	CH_2Cl	H	COOMe	70–76		137
Cl	Cl	H	Cl		125–128/30	17
					80–114/1–2	529
Cl	Br	H	CH_2Cl	39–40		528
Cl	Br	H	Br	22–24		528
Cl	NO_2	H	NO_2	64		530
Cl	H	NO_2	H		99–102/1.3	7r
					105–107/2	16
Cl	H	CH_2Cl	Br	47–48		528
Cl	H	H	Me		83–84/14	18
Cl	H	H	Et		105/13.7	19
Cl	H	H	cyclo-C_6H_{11}			531
Cl	H	H	*t*-Bu		67–71/1	17
Cl	H	H	chloro-*t*-Bu		105–109/1.5	532
Cl	H	H	$CH(Me)_2(2C_4H_2S\text{-}5CH_2Cl)$		182–185/2	533
Cl	H	H	$CH{=}CHCH_2Cl$		103–106/5	534

TABLE 35. (*Continued*)

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
Cl	H	H	C_6H_4-*p*-Cl	81.5–83.5		535
Cl	H	H	C_6H_4-*p*-Br	96–97 dec.		28
Cl	H	H	CH_2Cl		105–107/2	127
Cl	H	H	C≡CSMe		113–118/0.4	20r
Cl	H	H	Cl		95–96/15	120
					83–85/8	536
					67–68/1	22
					92–94/15	60
					96–98/17	22
Cl	H	H	Br		72–73/3	60r
					82–83/1	2
					77–80/3	528
Cl	H	H	COMe		120–123/2	534
Cl	H	H	COOMe		93/0.2	534
Cl	H	H	NO_2		112–114/4	16
					105–107/2	530
					120–121/0.7	143i
					98–100/0.5	7r
Cl	CH_2Cl	Me	COOMe	98.5–99.5		23r
Cl	Br	CH_2Cl	Br	88–89		528
Cl	Br	Br	CH_2Cl	68–69		528
CH_2Cl	H	H	H		108/20	297, 537
$(CH_2)_2Cl$	H	H	H		101/14	297, 378
$(CH_2)_4Cl$	H	H	H		85–86/0.05	50
$(CH_2)_4Cl$	H	H	$COCH_2COOEt$	45.5–46.5	176–177/0.25	50
$(CH_2)_6Cl$	H	H	H		94–96/0.07	50
$(CH_2)_6Cl$	H	H	$COCH_2COOEt$		140–150/4 × 10^{-5}	50
$(CH_2)_8Cl$	H	H	H		126.5–131/0.7	50
$(CH_2)_8Cl$	H	H	$COCH_2COOEt$	30.6–31.3		50

$(CH_2)_{10}Cl$	H	H	H		116–124/0.04	50
$(CH_2)_{10}Cl$	H	H	$COCH_2COOEt$	38.2–38.7		50
Br	H	H	H	–10	55/1.5	24
Br	Br	H	H		60–125/1	17
Br	NO_2	H	H	60–62		29
Br	CH_2Br	H	H	49–50		27 r
Br	Br	H	Br		104–108/1	17
Br	H	COOH	H	170–173		65 r
Br	H	H	Me		90/13	538, 539
Br	H	H	COOEt		140–142/4	30
Br	H	H	Br		71/1.2	24
Br	Br	Br	Br	86		540
Br		Br	Me	116–118		66 u
				114–116[b]		66
				113–115[c]		66
CH_2Br	H	H	H		87–88/13–15	11
					100–102/15	541
I	H	Cl	Cl	48		48
$(CH_2)_4I$	H	H	$COCH_2COOEt$	–8		50
$(CH_2)_6I$	H	H	$COCH_2COOEt$		150/0.0025	50
$(CH_2)_8I$	H	H	$COCH_2COOEt$	29.5–30.7		50, 490
$(CH_2)_{10}I$	H	H	$COCH_2COOEt$	41.5–42.5		50

[a] For the meaning of letters, please see the text in Section IX.
[b] (R)–(+) form.
[c] (S)–(–) form.

TABLE 36. 3-HALOMETHYLTHIOPHENES 

X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
Cl	H	H	H		74–75/14	31
Cl	Me	H	H		58–59/3.8	32
Cl	COOH	H	H	163–165		67r
Cl	Me	H	Me		92/1	33r
					110–115/13	542
					108/15	543
					96–115/13	544
Cl	*t*-Bu	H	*t*-Bu		137/13	377, 381
Cl	CH_2Cl	H	COOMe	70–76		137
Cl	Cl	H	Cl		100–105/11	40
					108/14	377
					125–128/30	17
Cl	SMe	H	SMe	100–101		545
Cl	SEt	H	Et		120–122.5/3	546
Cl	SPh	H	Et		156/50	68i,r
Cl	SO_2CH_2Ph	H	Et	54–55.5		546
Cl	H	Br	H		108–110/13	14
Cl	H	I	H			14r
Cl	H	CH_2Cl	H	51–53	98/2.2	23r,u
Cl	H	OMe	Ph		138/0.1	34
Cl	H	H	CHO		85–90/0.03	69r
Cl	H	H	COMe			547
Cl	H	H		47–48	117–120/1	548
Cl	Me	CH_2Cl	Me	67–68	135–145/13	544
Cl	Et	CH_2Cl	Et	53–54	138–148/9	544
Cl	*t*-Bu	CH_2Cl	*t*-Bu	86–86.5		70, 544
Cl	Br	CH_2Cl	Br	94.5–95.5		528
Cl	Cl	CH_2OH	Cl	79–80		71r,u
Cl	Cl	CH_2Cl	Cl	41–42	137–145/2	35
Cl	Cl	CH_2OSO_2Me	Cl	58–59		71r,u
Cl	SMe	CH_2Cl	SMe	78–78.5		545
Cl	SEt	CH_2Cl	Et		160–180/3	546
Cl	SEt	CH_2Cl	SEt		157–169/1	545
Cl	SO_2Me	CH_2Cl	SO_2Me	214–215		545
Cl	SO_2Et	CH_2Cl	SO_2Et	114–115		545
CH_2Cl	H	H	H		92–93/7	549
					96.5/16	297
CH_2Cl	Cl	H	Cl		105/2	377, 380
$(CH_2)_2Cl$	H	H	H		111/18	297, 378
$(CH_2)_2Cl$	Cl	H	Cl		128/2	377, 380
$(CH_2)_2Cl$	*t*-Bu	H	*t*-Bu		143/1.5	381
					146/15	377

TABLE 36. (*Continued*)

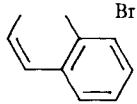
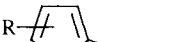
X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$(CH_2)_3Cl$	H	H	H		126.5/18	297, 379
$(CH_2)_3Cl$	Me	H	Me		147/18	288
$(CH_2)_4Cl$	H	H	H		139.5/17	297, 379
Br	H	H	H	−9	50/1.5	24
					75–78/1	37
					80–90/11	40
Br	Cl	H	H		100–106/10	40
					88/1	39
Br	Br	H	H		78/2	24
					113/7	39
					120–125/11	40
Br	NO_2	H	H	62		41
				63–65		29
Br	Ph	H	Br	78–79		28r
Br	Cl	H	Cl		104.5–106/4	39
Br	H	CH_2Br	H	83		70r
Br	H	Br	H		80–90/0.2	40r
					110–136/10	40
Br	H	H	COOH	172–175		69r,u
Br	H	H	COOMe	65–67		69r,u
Br	H	H	COOEt		128–130/3	30
Br	COOMe	CH_2Br	COOMe	124.5–126		42r,u
Br	Br	CH_2Br	Br	113–115		43r,u
Br	Br	Br	Br	63–67		550
Br	Br					551i,m,r
CH_2Br	H	H	H	91.5–92		552
I	H	H		53–57		548
CH_2I	Cl	CH_2I	Cl	93.5–94.5		23

TABLE 37. 2-HYDROXYMETHYLTHIOPHENES AND DERIVATIVES R- 

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
OH	H	H	H		91/8	112
					86/10	553
					98–99/15	12
					95.7–96.1/12	18
					94.5–96/12	554
OH	Me	H	H		70–74/1.5	51
					103–104/13	13
OH	CH_2OH	H	H		133.5–134./0.25	27i,r,u
OH	COOH	H	H	108		555i
OH	COOMe	H	H	61–62		67i,r
OH	Br	H	H		147–148/20	14i,r
OH	I	H	H	49–49.5		14i,r
OH	NO_2	H	H	71–72		16
OH	H	COOH	H	135–136		65r
				132		555i
OH	H	H	COOH	121		555i
OH	H	Cl	Cl	46	138–139/13	48
OH	H	NO_2	H	54–55		16
OH	H	H	Me		105–106/12	18, 556
OH	H	H	C_6H_4-*p*-Cl	125–130		535
OH	H	H	CH_2NHMe		123–124/2.3	557
OH	H	H	CH_2CH_2OMe			558
OH	H	H	$CH=CH_2$			559i,r,u
OH	H	H	$CH_2C\equiv CH$			559, 560
OH	H	H	$C\equiv C(2C_4H_3S)$	82		145
OH	H	H	$C\equiv CSMe$	34–36	135–140/0.2	20i,r
OH	H	H	COOH	121		30
OH	H	H	Cl	125–130		535
OH	H	H	I		88–89/0.7	118r,u
OH	H	H	OMe		84/0.7	111
OH	H	H	OPh			172

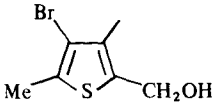
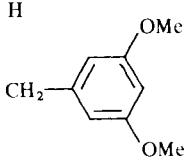
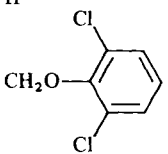
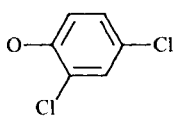
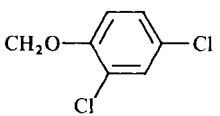
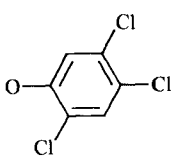
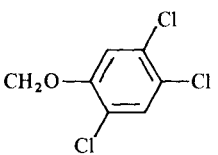
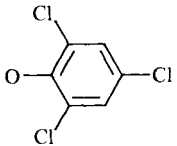
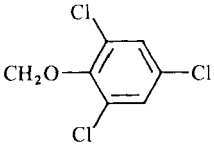
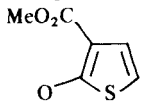
OH	H	H	NO_2		117–137/0.15	561
					95–117/0.15	143 i
					115–118/2	41
					148–150/3	16
OH		Br	Me	90–92[a]		66
				128–130[b]		66
				123–126[c]		66
OH	COOH	Cl	Me	177–179		342
OH	Cl	COOH	Me	177–179		342
OH	Br	Br	Br	127–128		540
CH_2OH	H	H	H	108	87–89/0.3	562 i
				52–53[d]	99–100/7	563
CH_2OH	H	H	H		108/13	11 i,m,r
					112/12	297
				56–57[d]	112–114/19	541
CH_2OH	Me	H	Me		130/17	543
CH_2OH	H	Me	H	68–69[d]	87–89/2	563
CH_2OH	H	H	*t*-Bu	73–74[d]	115–116/3	563
CH_2OH	H	H	CH_2NEt_2		162–165/15	564
CH_2OH	H	H	Cl	57–58[d]	98.5–100/1–2	563
$(CH_2)_2OH$	H	H	H		123.5/17	53 r, 297
$(CH_2)_2OH$	$(CH_2)_3OH$	H	H		148–152/0.02	565 r
$(CH_2)_2OH$	Me	H	Me		149/16	543
$(CH_2)_2OH$	H	$(CH_2)_3OH$	H		153–157/0.025	565 r
$(CH_2)_2OH$	H	H	Me			566
$(CH_2)_3OH$	H	H	H			53
$(CH_2)_3OH$	H	H			165/0.01	359 i,r
OMe	H	H	H		66.7–68.4/16	119
OMe	CH_2OMe	H	H		51–52/0.1	27 i, r
OMe	COOMe	H	H		66/1	67 i, r
OMe	H	COOH	H	73–74		65 r
OMe	H	Cl	Cl		113/12	48

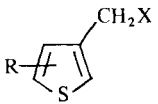
TABLE 37. (*Continued*)

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
OMe	H	H	CH_2OMe	55.5		567
OMe	H	H	Cl		147–148/1.5	18
OEt	H	Cl	Cl		124/12	48
OEt	H	H	Me		86/15	539
OEt	H	H	CH_2OEt	53		567
OEt	H	H	Cl		81–82/6	120
OPr	H	Cl	Cl		176/12	48
OBu	H	Cl	Cl		147/12	48
OPh	COOH	H	H	163–165		67
OPh	H	COOH	H	124		65 r
OPh	H	H	CH_2OPh	80–82		568
OC_6H_4-*p*-Cl	H	Cl	Cl	62		48
OC_6H_4-*p*-NO_2	H	Cl	Cl	151		48
OC_6H_4-*o*-COOH	H	H	H		Yellow oil	67 i, r
OC_6H_4-*o*-CO_2Et	H	H	H		80–90/1	67 i, r
OC_6H_4-*o*-Cl	H	H		46–48		568
	H	H		72–74		568
	H	H		124–126		568

	H	H		50–51		568
OCH_2-2-Thienyl	H	H	H		172–173/9	11 i, m, r
	CO_2Me	H	H		111–112	67 i, m, r
OAc	H	H	H		97.3–97.4/12	18
OAc	NO_2	H	H	58.5–60.5		29
OAc	H	NO_2	H	27–29	129–131/3.5	16 r
					120–122/1.4	7 r
OAc	H	Cl	Cl		137/13	48
OAc	H	H	COOEt		146–147/4	30
OAc	H	H	$C{\equiv}C(2C_4H_3S)$	47		145 i, r, u
OAc	H	H	Cl		130–132/24	120
OAc	H	H	Br		92–96/3	41
OAc	H	H	I		95/0.3	569
OAc	H	H	NO_2	35		561
				36–37	132/0.3	561
				38–39		41
				34–36		7 r
CH_2OAc	H	H	H		115–117/16	564
OCOEt	H	H	H		108–110/18	120
O–C_5H_{11}-*n*	H	H	H		104–105/13	120
OCOPh	H	H	H	58–59	134–135/0.9	120
$OCOC_6H_4$-*o*-OH	H	H	H	60.5–62		67 i, r
OCONHMe	H	Br	Br			570 e
OCONHMe	H	H	$CH_2OCONHMe$	89–91		571
OCONHEt	H	H	$CH_2OCONHEt$	98–100		571
$OCONHCH_2COOH$	H	H	H	85–87		572
$OCONHCH_2COOEt$	H	H	H		170/0.1	572
$OCO(2C_4H_3S)$	H	H	H	31–32	121–123/0.05	121

[a] Racemic form.
[b] (R)–(+) form.
[c] (S)–(–) form.
[d] Phenylurethane.

TABLE 38. 3-HYDROXYMETHYLTHIOPHENES AND DERIVATIVES



X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
OH	H	H	H		88–90/10	122
					106–115/20	41
OH	Me	H	H		77–79/0.4	32
OH	Me	H	Me		112–113/10	544
					118–121/15	123
OH	NO_2	H	H	90–92		29
				88–91		41
OH	Br	H	H		142–145/18	14 i, r
OH	SEt	H	Et		134/4	546
OH	H	CH_2OH	H	65–66		23 r, u
				64–65		70
OH	H	Br	H	53–54		41
OH	H	I	H	81.5–83		14 i, r
OH	H	OC_6H_4-*o*-NHMe	H			573
OH	H	OMe	Ph		139–141/0.1	34
OH	H	H	COMe			547
OH	H	H	COOH	114		65 r
				124		30
OH	Me	CH_2OH	Me	76–77		574
OH	*t*-Bu	CH_2OH	*t*-Bu	167–169		71
OH	Cl	CH_2OH	Cl	105–106		23 i, r, u
				107–107.5		71 i
				103–104		137
				134–135		138 r
OH	Cl	CH_2Cl	Cl	79–80		71 i, r, u
OH	SMe	CH_2OH	SMe	73		575

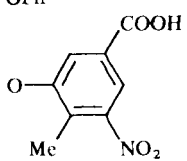
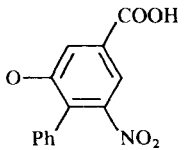
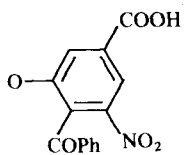
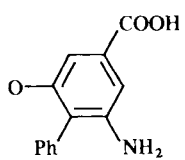
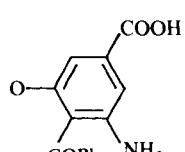
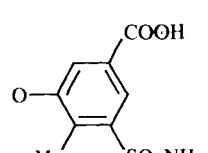
OH	SEt	CH_2OH	SEt	56.5–57.0		575
CH_2OH	H	H	H		67/0.5	51
					120/18	297
CH_2OH	Me	H	H		86.5–87.5/2	32
CH_2OH	Cl	H	Cl		120/2	377, 380
$(CH_2)_2OH$	H	H	H		133/10	378
					133/16	297
$(CH_2)_2OH$	*t*-Bu	H	*t*-Bu		148/15	377, 381
$(CH_2)_2OH$	Cl	H	Cl		137/2	377, 380
$(CH_2)_2OH$	H	$(CH_2)_3OH$	H	69–70	156–160/0.025	565 i, r
$(CH_2)_3OH$	H	H	H		142–143/18	297, 379
$(CH_2)_3OH$	Me	H	Me		153/18	288
$(CH_2)_4OH$	H	H	H		151/17	297
OMe	H	H	H		65–67/17	60 r, 576
					26/0.2	124
OMe	CHO	H	H		122–124/0.5	124
OMe	COOH	H	H	126–127		125 i, r
OMe	COOMe	H	H		66/1	67
OMe	$C(Ph)_2OH$	H	H	102–104		124
OMe	SMe	H	H		65–68/0.03	124
OMe	H	H	CHO		83–88/0.1	69 r
OMe	H	H	COOH	90–92		69 m, r
OMe	Me	CH_2OMe	Me		155–161/20	574
OEt	SMe	CH_2OEt	SMe		166/3	545
OEt	SEt	H	Et		115–116/5	546
OPh	COOH	H	H	148–151		67
OPh	H	H	COOH	134–136		65r
	H	H	H	152–154		577

TABLE 38. (*Continued*)

X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
	H	H	H	184–186		577
	H	H	H	201–203		577
	H	H	H	139–140		577
	H	H	H	227–229		577
	H	H	H	223–224		577

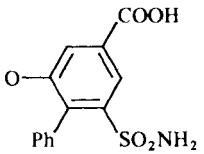
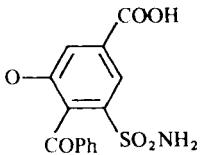
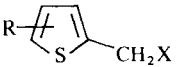
	H	H	H	222–223		577
	H	H	H	177–178		577
OC_6H_4-*m*-CH_2COOH	COOH	H	H	187–189		67
OC_6H_4-*p*-CH_2COOH	COOH	H	H	229–232		67
OC_6H_4-*m*-CH(Me)COOH	COOH	H	H	192–194		67
OAc	H	H	H		105.5/16	41
OAc	NO_2	H	H	88–91		41
OAc	Me	H	Me		125–128/16	544
OAc	H	H	COMe			547
OAc	H	H	COOEt		150–152/5	30
OAc	H	H	NO_2	65–65.5		41
OAc	Cl	CH_2OAc	Cl	96.5–97.5		137
OAc	SMe	CH_2OAc	SMe	85.5–86.5		575
OAc	SEt	CH_2OAc	SEt	37.5–38.5		575
OAc	SO_2Et	CH_2OAc	SO_2Et	148.5		575
OSO_2Me	Cl	CH_2Cl	Cl	58–59		71 i, r, u
OSO_2Me	Cl	CH_2OSO_2Me	Cl	85–86		71 i, r, u

TABLE 39. 2-THIOMETHYLTHIOPHENES 

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
SH	H	H	H		86/5	578
$SC(NH_2)$=NH.HCl	H	H	H	194–196		579
$SC(NH_2)$=NH.HCl	H	H	$CH_2SC(NH_2)=\overset{+}{N}H_2Cl^-$	220 dec.		127
SH	H	COOH	H	106–107		65 r
SH	H	H	CH_2SH		120–121/2	127 e
SH	H	Cl	Cl		136–138/14.5	580
CH_2SH	H	H	H		110/15	399
$(CH_2)_2SH$	H	H	H		117/14	399
SMe	H	H	H		101–103/15	581
					94.5/15	578
SMe	H	H	Cl			582
SEt	H	H	H		93–94/9	129
					66–69/3	583
SEt	CH_2SEt	H	H		142–144/3	98 r, u
SEt	CH_2SEt	H	COOMe		182–184/0.9	98 r, u
SEt	H	COOH	H	99–101		65 r
SEt	H	Cl	Cl		157/15	580
SEt	H	H	$CH=NC_6H_4$-*p*-Me	66.5–67.5		584
SEt	H	H	$CH=N(2\text{-}C_{10}H_7)$	86–86.5		584
SEt	H	H	$CH_2NHC_6H_4$-*p*-OH	63–64		584
SEt	H	H	Br		97–98/3	129
SPr	H	Cl	Cl		168/15	580
SBu	H	H	H		126–128/13	585
S-*n*-C_6H_{13}	H	H	H		106–109/2	583
SBu	H	H	Me		125.5–126/4	585
SBu	H	H	$CH_2NH(2\text{-}C_{10}H_7)$	2–4		584
SBu	H	H	$CH=NC_6H_4$-*p*-Me	35–37		584

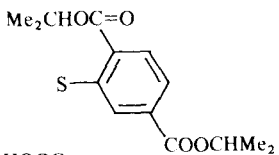
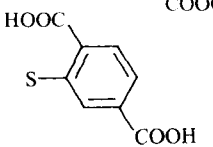
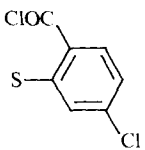
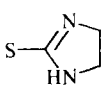
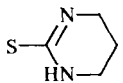
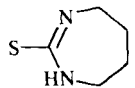
SBu	H	H	$CH{=}NC_6H_4$-*p*-Cl	51.5–52.5		584
SBu	H	H	$CH{=}N(2\text{-}C_{10}H_7)$	79–80		584
SBu	H	Cl	Cl		179/15	580
S-*i*-Bu	H	H	H		89–91/3.5	583
S-*i*-Bu	H	H	$CH_2NHC_6H_4$-*p*-OH	69–70		584
S-*t*-Bu	H	H	H		102–103.5/6	586
S-*iso*-Amyl	H	H	H		90–91/4	129
SPh	H	H	H		152–153/7	128
SPh	COOH	H	H	135–136		67
SC_6H_4-*m*-CH_2COOH	COOH	H	H	146–148		67
SC_6H_4-*p*-Me	H	H	H		164–165/7	128
SC_6H_4-*p*-Me	H	Cl	Cl	69		580
SC_6H_4-*p*-(*t*-Bu)	H	H	H		187–188/7	128
	H	H	H	57–58[a]		587
	H	H	H	280–282[a]		587
	H	H	H	80–81[a]		587
	H	H	H	173–175[b] dec.		588e

TABLE 39. *(Continued)*

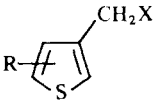
X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
	H	H	H	160–162[b] dec.		588 e
	H	H	H	158–159[b]		588 e
SCH_2Ph	H	H	H		120–121/1.5	583
$SCH_2(2C_4H_3S)$	H	H	H		129–131/1.5	583
SCH_2COOH	H	H	H		206/15	135 i, r
					201–202/16	398
					204/17	397
SCH_2COOH	H	Cl	Cl	95	196.5/16	578, 580
SCH_2COOMe	H	H	H		99–100/0.4	398
SCH_2COOEt	H	H	H		168.5–169/18	397
					160/15.5	578
SCH_2COCl	H	H	H		150/16	397
SCH_2CONH_2	H	H	H	105		397
SCH(Me)COOH	H	H	H	62	194/14	578
SCH(Me)COOEt	H	H	H		155/14	578
$S(CH_2)_2COOH$	H	H	H		204/16	578
$S(CH_2)_2COOEt$	H	H	H		126/1	583
$S(CH_2)_2CN$	H	H	H		127–130/2.5	583
$S(CH_2)_2NH_2$	H	H	CH_2NMe_2			589
$S(CH_2)_2NHC(=CHNO_2)NHMe$	H	H	CH_2NMe_2			589 e
$S(CH_2)_3OH$	H	H	H		178.5/12	397
SCN	NO_2	H	H	109–110		60 r, 64
SCN	Br	H	H		Oil	528

SCN	Br	Br	H		Oil	528
SCN	Br	H	Br	68–69		528
SCN	H	Cl	Cl	70		580
SCN	H	Br	CH_2SCN	94–95		528
SCN	H	H	CH_2SCN	69–72		130
SCN	H	H	Cl		121–123/1.4	120
SCN	H	H	NO_2	44–45		530
SCN	H	H	Br		Oil	528
SCN	Br	Br	Br	122–123		528
SCN	Br	CH_2SCN	Br	131–132		528
SCN	Br	Br	CH_2SCN	135.5–136.5		528
SCOMe	H	H	H		58–60/2	590
SCOEt	H	H	H		79–83/2	590
SCOPh	H	H	H		155/2.5	590
SCOPh	H	H	CH_2SCOPh	89–90		127
$SCSNH_2$	H	Cl	Cl	130		580
$SCSNEt_2$	H	H	H		150–152/0.33	591
$SCSN(C_4H_9)_2$	H	H	H		151–152/0.01	591
$SCSN(Me)CH_2Ph$	H	H	H	57–59		591
$SCSN(Et)CH_2Ph$	H	H	H		197–198/0.05	591
SCSN(Et)Ph	H	H	H	53.5–54.5		591
SCSN(Me)Ph	H	H	H	97–98		591
$SCSN(Me)CH_2C_4H_3S$	H	H	H	67–67.5		591
$SCSN(Et)CH_2C_4H_3S$	H	H	H	51–52.5		591
$SCSN(C_6H_4Me)CH_2C_4H_3S$	H	H	H	80–81		591
$SCSN(C_6H_4OH)CH_2C_4H_3S$	H	H	H	103–104		591
$SCSN(C_6H_4OMe)CH_2C_4H_3S$	H	H	H	86–87		591
SCSOEt	H	H	H		120–127/0.4	120
SCSOEt	H	H	Cl		145–147/1.4	120
SOEt	H	H	H		174–178/12	129
SOEt	H	Cl	Cl	92		580
SOPr	H	Cl	Cl	106		580
SOBu	H	Cl	Cl	82		580

TABLE 39. (*Continued*)

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
SOPh	H	Cl	Cl	137		580
SOC_6H_4-*p*-(*t*-Bu)	H	H	H	51		128
SO_2Me	H	H	Cl	79–80		592
SO_2Et	H	H	H	55–56		129
SO_2Et	H	H	Br	62–63		129
SO_2Et	H	H	OAc	111–112		129
SO_2Ph	H	H	H	138		128
SO_2Ph	H	COOH	H	197–199		65 r
$SO_2C_6H_4$-*p*-Me	H	H	H	101		128
				132–133		136 r
$SO_2C_6H_4$-*p*-Me	H	Cl	Cl	175–176		580
$SO_2C_6H_4$-*p*-(*t*-Bu)	H	H	H	87		128

[a] Not specified if 2- or 3-thiophene derivative.
[b] Hydrochloride.

TABLE 40. 3-THIOMETHYLTHIOPHENES 

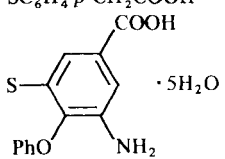
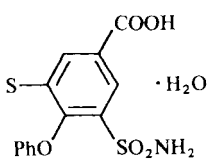
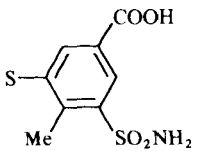
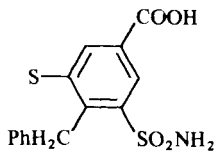
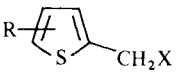
X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
SH	H	H	H		102/16	126
$SC(NH_2)$=NH HBr	H	H	H	145–145.5		126
SH	Me	H	Me		112/15	400
$SC(NH_2)$=NH HCl	Me	H	Me	188		400
SH	H	H	COOH	128–130		65 r
$SC(NH_2)$=NH HBr	H	H	COOEt	197–198		30
CH_2SH	H	H	H		105/13	399
CH_2SH	Me	H	Me		130/18	401
					119.5/16	399
$(CH_2)_2SH$	H	H	H		113.5/14	399
SEt	H	H	COOH	80		65 r
SPh	COOH	H	H	142–143		67
SC_6H_4-*o*-COOH	H	H	H	185	220/0.8	593
SC_6H_4-*o*-COOEt	H	H	H		195/3.2	593
SC_6H_4-*o*-CH_2COOH	COOH	H	H	171–173		67
SC_6H_4-*p*-CH_2COOH	COOH	H	H	187–189		67
	H	H	H	153		594 e
	H	H	H	226–227		594e

TABLE 40. *(Continued)*

X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
	H	H	H	215–217		577e
	H	H	H	198–199		577e
SCH_2COOH	H	H	H	44–45		126, 398
SCH_2COOH	Me	H	Me	170		135i,r
				73	205/16	400
SCH_2COOMe	H	H	H		128–129/1.2	398
SCH_2COOEt	H	H	H		163/15	126
SCH_2COOEt	Me	H	Me		168/17	400
SCH_2CONH_2	H	H	H	90		126
SCH_2CONH_2	Me	H	Me	99		400
$S(CH_2)_2COOH$	H	H	H	76	208.5/14	126
$S(CH_2)_2COOEt$	H	H	H		177.5/14	126
$S(CH_2)_2CONH_2$	H	H	H	95		126
$S(CH_2)_3COOH$	H	H	H	38–38.5	175/0.7	126
$S(CH_2)_3COOEt$	H	H	H		191/16	126
$S(CH_2)_3CONH_2$	H	H	H	111		126
$S(CH_2)_3OH$	H	H	H		182/14	126
$CH_2S(CH_2)_2COOH$	H	H	H	43	214/13	399
$CH_2S(CH_2)_2CONH_2$	H	H	H	89.5		399

$S(CH_2)_2COOH$	Me	H	Me	58	218/18	400
$S(CH_2)_2COOEt$	Me	H	Me		188/17	400
$S(CH_2)_2CONH_2$	Me	H	Me	89		400
$S(CH_2)_3COOH$	Me	H	Me	35	198.5/2.4	400
$S(CH_2)_3COOEt$	Me	H	Me		203/10	400
$S(CH_2)_3CONH_2$	Me	H	Me	94		400
$S(CH_2)_3OH$	Me	H	Me		149/14.5	400
CH_2SCH_2COOH	Me	H	Me		221.5/18	401
CH_2SCH_2COOEt	Me	H	Me		189/19	401
$CH_2SCH_2CONH_2$	Me	H	Me	75		401
$(CH_2)_2SCH_2COOH$	H	H	H		213.5/14	399
$(CH_2)_2SCH_2CONH_2$	H	H	H	56		399
$CH_2S(CH_2)_2COOH$	Me	H	Me		196/2	399
$CH_2S(CH_2)_2CONH_2$	Me	H	Me	50		399
$CH_2S(CH_2)_3OH$	Me	H	Me		201.5–202/18	401
$CH_2S(CH_2)_3COOH$	H	H	H		200/14	399
SCN	NO_2	H	H	76		60 r
SO-*p*-tolyl	COOMe	H	H	129.5–131.5		595
SO_2Ph	H	H	COOH	188–190		65 r
SO_2-*p*-tolyl	COOMe	H	H	93–96		595
$SP(O)(OMe)SCH_2CHMe_2$	H	Cl	Cl			596
$SP(O)(OEt)SCH_2CHMe_2$	H	Cl	Cl			597

TABLE 41. 2-AMINOMETHYL DERIVATIVES 

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
NH_2	H	H	H		77/16	553
					55–65/5	598
					58/5	186
				193–194[a]	73–75/11	599
				188[a]		600
				188–189[a]		601
					75/16	185
NH_2	Me	H	H	224–226[a]	78/4.2	557, 601
NH_2	Ph	H	H	237–238[a]		28
NH_2	H	Cl	Cl		126/13	48
NH_2	H	H	Me	196–197[a]	67–68/3	557
				197–198[a]		601
NH_2	H	H	*t*-Bu	229–230[a]	120–122/5	185, 602
NH_2	H	H	CH_2COOH	228–230 dec.		20
NH_2	H	H	$CH_2N(COMe)C_6H_{13}$		170–172/2	603
NH_2	H	H	$C(2C_4H_3S\text{-}5CH_2NH_2)Me_2$		165–168/2	533
NH_2	H	H	Cl	280–282[a]		601
				119.5–120[b]	71/2	557
NH_2	H	H	SO_2Me	56		604
NH_2	H	H	SO_2Me	213–214[a]		604
NH_2	H	H	SO_2Et	196–197[a]		604
NH_2	H	H	SO_2-*n*-C_5H_{11}	206–207[a]		604
$\overset{+}{N}H_2CH_2SO_3^-$	H	H	H	135–136 dec.		214
$\overset{+}{N}H_2CH_2SO_3^-$	Me	H	H	140–141 dec.		214
$\overset{+}{N}H_2CH_2SO_3^-$	H	H	Me	138–140 dec.		214
$\overset{+}{N}H_2CH_2SO_3^-$	H	H	Cl	141–142		214
CH_2NH_2	H	H	H		65/2	238

				200–202[a]		599
				202–204[a]	72–74/3	278
					200–201/760	605 i
					66–67/3.75	606
CH_2NH_2	H	H	Me		75–76/3.5	606
CH_2NH_2	H	H	Ph	226[a]		607
CH_2NH_2	H	H	C_6H_4-*p*-OMe	283[a]		607
CH_2NH_2	H	H	OMe		78–80/0.6	562 u
$(CH_2)_2NH_2$	H	H	H	194–195[a]	110–112/19	599
NHMe	H	H	H		81–83/13	47 i, m, r
				189–190[a]	75–80/14	599
					41–42/1.2	608
				190–192[a]		609
NHMe	H	H	Me		87/12	610
NHMe	H	H	CH_2OH	100–101[b]	123–124/2.3	557
NHMe	H	H	$C(2C_4H_2S\text{-}5CH_2NHMe)Me_2$		210–213/3	533
NHEt	H	H	H	137–138[a]	79–80/10	609, 611
NHEt	H	H	Me		108/18	611
NH-*n*-Bu	H	H	H	188–190[a]	98–100/6	189
NH-*n*-Bu	H	H	Cl	195[a]	129–132/8	189
					129–132/8.4	612
NH-*i*-Bu	H	H	H		112–113/17	611
NH-*i*-Bu	H	H			179–180/8	603
NH-*i*-Amyl	H	H	H		132–133/21	611
NH-*i*-Amyl	H	H	Me		147–147.5/23	611
NHC_6H_{11}	H	H	H	207–209[a]	96–97/0.6	189
NHC_6H_{11}	H	H	Cl	218[a]	113–117/0.6	189
NHC_8H_{17}	H	H	H	188–190[a]	150–155/5	613
NH-*n*-$C_{10}H_{21}$	H	H			230–233/2	603
NH-Cetyl	H	H	H		195–210/1	614
NH-Cyclohexyl	H	H	Cl		124–127/1.6	612

TABLE 41. *(Continued)*

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
NHPh	H	H	H	37–38	155–158/6	61r
					132–134/4	615
					184–185/13–15	11i,m
					150–155/4	616
NHPh	H	Cl	Cl	212[a]		48
NHC_6H_4-*o*-Me	H	H	H		148–149/5	617
					134–136/4	615
NHC_6H_4-*o*-OH	H	H	H	83–83.5		617
NHC_6H_4-*o*-OMe	H	H	H		163–164/7	617
NHC_6H_4-*o*-COOH	H	H	H	160–161		617
NHC_6H_4-*o*-COOMe	H	H	H		191–193/2	617
NHC_6H_4-*m*-NO_2	H	H	H	75–76		617
NHC_6H_4-*m*-NH_2	H	H	H	80–80.5		617
NHC_6H_4-*p*-Me	H	H	H		121–122/0.1	617
NHC_6H_4-*p*-Me	H	Cl	Cl	217[a]		48
NHC_6H_4-*p*-Me	H	H	SEt	28–29	177–179/0.3	584
NHC_6H_4-*p*-Me	H	H	SC_6H_4-*p*-OMe	53–54		584
NHC_6H_4-*p*-Me	H	H	SO_2Et	112–113		584
NHC_6H_4-*p*-OH	H	H	H	104–105		585, 617
NHC_6H_4-*p*-OH	H	H	Me	131–132		585, 617
NHC_6H_4-*p*-OH	H	H	SEt	89–90		584, 585
NHC_6H_4-*p*-OH	H	H	CH_2S-*i*-Bu	69–70		585
NHC_6H_4-*p*-OH	H	H	SCH_2Et	63–64		585
NHC_6H_4-*p*-OH	H	H	SC_6H_4OMe	83–84		584, 585
NHC_6H_4-*p*-OMe	H	H	H	64–65	160–162/3	615, 617
NHC_6H_4-*p*-OMe	H	H	Me	50–51		617
NHC_6H_4-*p*-COOH	H	H	H	170–172		617
NHC_6H_4-*p*-COOH	Cl	H	Cl			618e
NHC_6H_4-*p*-COOMe	H	H	H	90–91		617

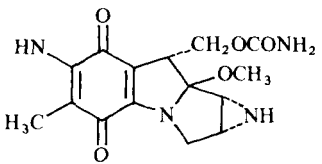
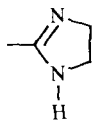
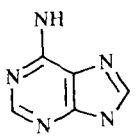
NHC_6H_4-*p*-COOEt	H	H	H	107–108		617
NHC_6H_4-*p*-NHCOMe	H	H	H	161–162		617
NHC_6H_4-*p*-NHPh	H	H	H	63–63.5		617
NHC_6H_4-*p*-$NHCH_2$-2-thienyl	H	H	H	118–119		617
NHC_6H_4-*p*-Cl	H	H	H		154–155/4	615
NHC_6H_4-*p*-Cl	H	H	SEt	15–16		584
NHC_6H_4-*p*-Cl	H	H	SC_6H_4-*p*-OMe	61–62		584
$NHCH_2Ph$	H	H	H	248–250[a] dec.	145–147/2	619
					120–122/0.2	620
					155–160/5	621
NH(2-naphtyl)	H	H	H		195–210/1.5	621
					195–197/3	615
NH(2-naphtyl)	H	H	SEt	29–30		584
NH(2-naphtyl)	H	H	SC_6H_4-*p*-Me	85–86		584
$NH(2C_{10}H_7)$	H	H	SEt	29–30		585
$NH(2C_{10}H_7)$	H	H	CH_2SBu	2–4		585
$NH(2C_{10}H_7)$	H	H	SC_6H_4-*p*-OMe	85–86		585
	H	H	H	92–94		622 r
	H	H	H	120–122[c]		588 e
	H	H	H	250 dec.		623

TABLE 41. (*Continued*)

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CH_2NHMe	H	H	H	154–155[a]	90–91/13	599
CH_2NHMe	H	H	OMe		78–80/1	562
CH_2NHEt	H	H	H	167–168[a]	103–105/22	613
CH_2NHBu	H	H	H	260–261[a]	129–132/18	613
CH_2NH-cyclo-C_6H_{11}	H	H	H	233–234[a]	139–142/5	613
$NHCH_2Ph$	H	Cl	Cl	269[a]		48
$NHCH_2(2C_4H_3S)$	H	H	H	247[a]	183–188/17	613
					124–125/1.5	611
					169/13	47i, m, r
$NHCH_2(2C_4H_3O)$	H	H	H		115–116/1.7	611
NH(2-pyridyl)	H	H	Cl		163–168/1.9	189
				87–90	163–168/1.9	612
$NHCH_2SO_3H$	H	H	H	135–137		624
$NHCH_2SO_3H$	H	H	Me	138–140 dec.		624
$NHCH_2SO_3H$	H	H	Cl	142–143		624
$NHCH_2SO_3H$	Me	H	H	140–141		624
CH_2NHCHO	H	H	H		135–145/0.4	562
CH_2NHCHO	H	H	OMe		152–155/0.4	562i
$CH_2NHCOMe$	H	H	H	45.5–46.5		238
				50–51		606
$CH_2NHCOMe$	H	H	Me		117–118/0.12	606
$CH_2NHCOMe$	H	H	OMe	37	151–154/0.5	562
$CH_2NHCOPh$	H	H	H	61		238
$CH_2NHCOPh$	H	H	OMe	68–69		562
$(CH_2)_2NHMe$	H	H	H	127–128[a]	112–114/19	599
				129–130[a]	86–89/3	613
$(CH_2)_2NHEt$	H	H	H	138–139[a]	97–98/5	613
$(CH_2)_2NHBu$	H	H	H	225–227[a]	109–113/2	613

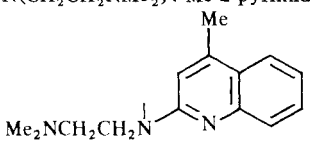
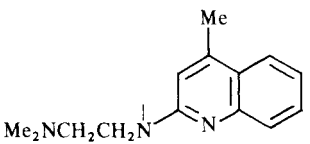
$(CH_2)_2NHC_6H_{13}$	H	H	H	248–250[a]	142–144/3	613
$(CH_2)_2NH(CH_2)_2NH_2$	H	H	H	241–242[a]	143–145/6	613
$NH(CH_2)_2OH$	H	H	H		111–112/1.3	536
$NH(CH_2)_2OH$	H	H	Cl		132–134/13	536
$(CH_2)_2NH$ thienyl	H	H	H	84		625
NMe_2	H	H	H		71/14	47 i, m, r
					58–60/8	124 r
					67/11	626
				151–152[d]		627
				154–156[d]	83/30	628
				172[e]		25
NMe_2	Me	H	H	179.5–180.5[d]	61/2.5	608, 629
					91–92/20	223 r
				167–169[f] dec.		13
NMe_2	$C(OH)Ph_2$	H	Me	194[d]		124 i
					117–118[g]	124 i, r
NMe_2	H	H	Me		108–110[g]	124 i, r
					83–84/15	630
NMe_2	H	H	CH_2NMe_2		96–97/3	567
NMe_2	H	H	CH(OH)Ph	140–142		631
NMe_2	H	H	$C(OH)Ph_2$	79–83		631
NMe_2	H	H	CHO		95–104/2.5	124 i, r
NMe_2	H	H	Cl	193.5–194.5[d]	75–78/5	629
					42–44/0.5	608
NMe_2	H	H	$SiMe_3$		65–67/0.9	124 i, r
NMeEt	H	H	H	154[h]		627
				134–135[d]		627
NMe-*n*-Pr	H	H	H	124–126[d]		627
NMe-*n*-Bu	H	H	H	123–123.5[d]		627
NMe-*n*-C_5H_{11}	H	H	H	128–129[d]		627
NMe-*n*-C_6H_{13}	H	H	H	118[d]		627
NMe-*n*-C_7H_{15}	H	H	H	77.5[d]		627
NMe-*n*-C_9H_{19}	H	H	H	132–134[d]		627
NMe-*n*-$C_{14}H_{29}$	H	H	H	56–57[d]		627

TABLE 41. *(Continued)*

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
NMe-*n*-$C_{16}H_{33}$	H	H	H	73–73.5[d]		627
NMe-*n*-$C_{18}H_{37}$	H	H	H	80–81[d]		627
NMePh	H	H	H	161–162[f]	179–180/13–15	11 i, m, r
N(CH_2Ph)Me	H	H	H	165[d]	148–152/12	25, 225 i, r
N(2-thenyl)Me	H	H	H	151–152[d]		47 i, r
				187–189[f]		47 i, r
N(Me)CH(Me)Ph	H	H	H		170–173/13	225 i, m, r
N(Me)CH_2CH_2Ph	H	H	H		177–179/13	225 i, m, r
N(Me)$CH_2C_6H_4$-*o*-Me	H	H	H		175–177/13	225 i, m, r
N(Me)$CH_2C_6H_4$-*p*-Me	H	H	H		176–177/13	225 i, m, r
N(Me)CH(2-thenyl)Me	H	H	H		162–165/13	47 i, m, r
N(Me)$CH_2CH_2C_4H_3S$	H	H	H	142–143[a]	185–189/16	613
$(CH_2)_2$N(Me)$(CH_2)_3C_4H_3S$	H	H	H	108–110[i]	185–186/3	613
N(Me)$CH_2CH_2NMe_2$	H	H	H	230–231[a]	83–92/4	536
N(Me)$(CH_2)_3$N(Me)2C_4H_3S	H	H	H	219[j]		632
N(Me)$(CH_2)_4$N(Me)2C_4H_3S	H	H	H	223[j]		632
N(Me)$(CH_2)_5$N(Me)2C_4H_3S	H	H	H	111–114[j]		632
N(Me)$(CH_2)_6$N(Me)2C_4H_3S	H	H	H	218–220[j]		632
N(Me)$(CH_2)_9$N(Me)2C_4H_3S	H	H	H	226[j]		632
N(Me)$(CH_2)_{10}$N(Me)2C_4H_3S	H	H	H	220[j]		632
N(Me)C(S)SCH_2COMe	H	H	H	52–53		591
N(Me)C(S)SCH_2CONH_2	H	H	H	167–169[i]		591
N(Me)C(S)SCH_2COOH	H	H	H	118–119		591
N(Me)C(S)SCH_2COOMe	H	H	H	57.5–58.5		591
N(Me)C(S)SCH_2COOBu	H	H	H	57–58		591
N(Me)C(S)SCH_2CONH_2	H	H	H	129–130		591
N(Me)C(S)$SCH_2CONHNH_2$	H	H	H	121–122		591
N(Me)C(S)$SCH_2CH_2NEt_2$	H	H	H		167–170/0.02	591
N(Me)C(S)SCH_2CH_2OCONHPh	H	H	H	84–85		591

$N(Me)C(S)SCH_2CH_2OCOC_6H_4$-*p*-$NO_2$	H	H	H	89–90		591
CH_2NMe_2	H	H	H	249–251[d]	99/27	628
$CH_2N(Me)Ph$	H	H	H		187/13–15	11
$CH_2N(Me)CH_2 2C_4H_3S$	H	H	H		177–179/13	47 i, m, r
$CH_2N(Me)CH_2CH_2 2C_4H_3S$	H	H	H	128–130[a]	194–196/15	613
$(CH_2)_2NMe_2$	H	H	H	185–186[d]	86/15	628
				186–186.5[d]	104–106/14	241
$(CH_2)_2NMe_2$	H	H	cyclo-C_3H_5	88.5–90[d]	102–106/0.8	241
$(CH_2)_2NMe_2$	H	H	Ph	226.5–227[d]	152/0.7	241
$(CH_2)_2NMe_2$	H	H	OMe	212–213[d]		562
$N(CH_2CH_2NMe_2)C_6H_4$-*o*-Cl	H	H	H	184–185[a]	175–176/3.5	536
$N(CH_2CH_2NMe_2)C_6H_4$-*m*-Cl	H	H	H	163–165[a]	190–191/3.5	536
$N(CH_2CH_2NMe_2)C_6H_4$-*p*-Cl	H	H	H	186–187[a]	184–186/1.5	536
$N(CH_2CH_2NMe_2)C_6H_4$-*p*-OMe	H	H	H	147–148[a]	175–180/1.5	536
$N(CH_2CH_2NMe_2)Ph$	H	H	Cl	163–164[a]	171/2	536
$N(CH_2CH_2NMe_2)C_6H_4$-*o*-Cl	H	H	Cl	143–144[a]	184–186/2	536
$N(CH_2CH_2NMe_2)C_6H_4$-*m*-Cl	H	H	Cl	166–168[a]	195–197/2	536
$N(CH_2CH_2NMe_2)C_6H_4$-*p*-Cl	H	H	Cl	186–188[a]	197–200/2	536
$N(CH_2CH_2NMe_2)C_6H_4$-*p*-OMe	H	H	Cl	108–110[a]	178/1.5	536
$N(CH_2CH_2NMe_2)$2-pyridyl	H	H	H	162–165[a]	123–135/0.1	17
$N(CH_2CH_2NMe_2)$2-pyridyl	H	H	H		166–168/2	633
$N(CH_2CH_2NMe_2)$2-pyridyl	Br	H	H	184–185[a]		17
$N(CH_2CH_2NMe_2)$2-pyridyl	Br	H	Br	208–209[a]	150–160/0.001	17
$N(CH_2CH_2NMe_2)$2-pyridyl	H	H	*t*-Bu	145–146[a]	185–190/3.5	17
$N(CH_2CH_2NMe_2)$2-pyridyl	H	H	COOH	198–200[k]		17
$N(CH_2CH_2NMe_2)$2-pyridyl	H	H	Cl	106–108[a]	155–156/1	17
					155–156/1	22
				115–116[l]	190–194/5	189
				110–111[a]	171–173/1.8	536
$N(CH_2CH_2NMe_2)$2-pyridyl	H	H	Br		173–175/1	22
				124–126[a]	173–175/1	17
$N(CH_2CH_2NMe_2)$-5-Br-2-pyridyl	H	H	H	140–141[a]	175–185/0.6	17
$N(CH_2CH_2NMe_2)$-5-Br-2-pyridyl	H	H	*t*-Bu	175–176[a]		17

TABLE 41. *(Continued)*

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$N(CH_2CH_2NMe_2)$-5-Br-2-pyridyl	H	H	Cl	136–137[a]		17
$N(CH_2CH_2NMe_2)$-5-Br-2-pyridyl	H	H	Br	163–166[a]	175–190/0.0001	17
$N(CH_2CH_2NMe_2)$2-thiazolyl	H	H	H	157–158[a]		634
$N(CH_2CH_2NMe_2)$2-thiazolyl	H	H	Br	166–167[a]		634
$N(CH_2CH_2NMe_2)$4-Me-2-pyrimidyl	H	H	H	140–143[a]	147–148/1.2	536
	H	H	H		159–172/0.5	635
	H	H	Cl		161–164/0.07	635
$(CH_2)_3NMe_2$	H	H	H	208–210[d]	47/0.1	628
NEt_2	H	H	H	161[h]		627
				149–150[a]	79–81/7	189
				156[d]	40/1.5	632
					98–100/18	636
NEt_2	H	CH_2NEt_2	H	191–192[m]		603
NEt_2	H	H	Me	125–126[d]	94–95/8.5	636
NEt_2	H	H	Et	91–93[n]	109/8–9	636
NEt_2	H	H	CH_2NEt_2		130–132/3	567
					101–102/2	603
NEt_2	H	H			125–132/2	603

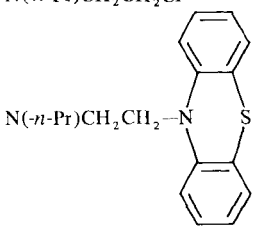
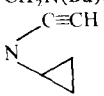
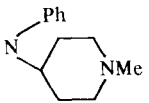
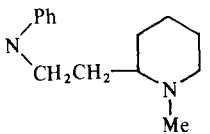
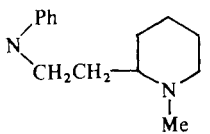
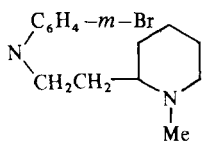
NEt_2	H	H	$CH_2 2C_4H_3S$		136–137/5	533
NEt_2	H	H	$CH(2C_4H_2S\text{-}5CH_2NEt_2)Me$		179–181/0.55	533
NEt_2	H	H	$C(OH)Me_2$	77–79		567
NEt_2	H	H	$C(Me)(Et)2C_4H_3S$	77–79[o]	151–152/3	636
NEt_2	H	H	Cl	122[a]	105–108/10	189, 612
NEt-*n*-Pr	H	H	H	149–151[h]		627
NEt-*n*-Bu	H	H	H	142–143[h]		627
NEt-*n*-C_5H_{11}	H	H	H	99–101[h]		627
NEt-*n*-$C_{14}H_{29}$	H	H	H	11–12[h]		627
NEt-*n*-$C_{16}H_{33}$	H	H	H	26[h]		627
NEt-*n*-$C_{18}H_{37}$	H	H	H	34–35[h]		627
NEtPh	H	H	H	82.7	128/1	11 m, 637
$N(Et)CH_2Ph$	H	H	H		80–81/0.08	225 i, m, r
$CH_2N(Et)(CH_2)_2C_4H_3S$	H	H	H	119–120[a]	181–183/7	613
$CH_2N(Et)(CH_2)_2C_6H_{11}$	H	H	H	133–134[a]	171–172/6	613
$(CH_2)_2N(Et)(CH_2)_2Ph$	H	H	H	118–120[i]	187–188/6	613
$(CH_2)_2N(Et)(CH_2)_3C_4H_3S$	H	H	H	90–92[i]	204–206/6	613
$N(Et)(CH_2)_{10}N(Et)2C_4H_3S$	H	H	H	176–180[j]		632
$N(n\text{-}Pr)CH_2CH_2OH$	H	H	Cl		169–172/14	638
$N(n\text{-}Pr)CH_2CH_2Cl$	H	H	Cl	118[a]	164–167/14	638
	H	H	Cl	147–148[a]		638
$CH_2N(i\text{-}Pr)(CH_2)_4C_4H_3S$	H	H	H	97–98[a]	198–202/4	613
$CH_2N(Bu)(CH_2)_2C_4H_3S$	H	H	H	126–128[a]	196–198/8	613
	H	H	H	132–134[a]	98–100/4	639

TABLE 41. *(Continued)*

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$(CH_2)_2N(Bu)(CH_2)_3C_4H_3S$	H	H	H	64–65[i]	197–200/2	613
$CH_2N(C_6H_{11})(CH_2)_2Ph$	H	H	H	119–121[a]	232–234/8	613
$N(Ph)CH_2COOEt$	H	H	H		155–165/0.3	616
$N(Ph)CH_2CH_2NMe_2$	H	H	H		183–185/7	633
$N(Ph)CH_2CH_2NC_5H_{10}$	H	H	H		215–218/5	633
$N(Ph)CH_2CH(Me)NMe_2$	H	H	H		164–171/3	633
$N(Ph)(CH_2)_3NMe_2$	H	H	H		158–161/3	633
	H	H	H			640
	H	H	H	116–118[a]		641
	H	H	Br		190/0.01	641
	H	H	Br	122–124[p]		641

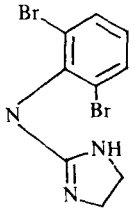
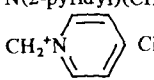
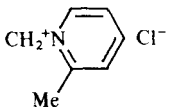
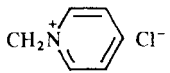
	*H*	*H*	*H*			642 e
$N(CH_2Ph)_2$	H	H	H	79–80		620
$N(CH_2CH_2OH)CH_2Ph$	H	H	H		166–167/1	536
				146–147[a]	135–145/0.07	619
$N(CH_2CH_2Cl)CH_2Ph$	H	H	H	167–168[a]		536
$N(CH_2CH_2Br)CH_2Ph$	H	H	H	164.5–165.5[a]		620
$N(CH_2CH_2I)CH_2Ph$	H	H	H	162–163[c]		620
$N(CH_2C_6H_4\text{-}o\text{-}Cl)(CH_2CH(OH)C_6H_4\text{-}p\text{-}Cl)$	H	H	H	178[a]		643 r
$N(CH_2C_6H_4\text{-}o\text{-}Cl)(CH_2CH(OH)C_6H_4\text{-}p\text{-}Me)$	H	H	H	68		643 r
$N(CH_2C_6H_4\text{-}o\text{-}Cl)(CH_2CH(OH)C_6H_4\text{-}p\text{-}OMe)$	H	H	H			643 r
$N(CH_2CH_2OH)$2-*thenyl*	H	H	H		151–152/1	536
$N(CH_2CH_2Cl)$2-thenyl	H	H	H	147–148[a]		536
$N(CH_2C_4H_3S)C_8H_{17}$	H	H	H	84–86[a]	214–218/7	613
$N(CH_2CH_2OH)$5-Cl-2-thenyl	H	H	Cl		204–206/2	536
$N(CH_2CH_2Cl)$5-Cl-2-thenyl	H	H	Cl	179–180[a]		536
$N(2\text{-pyridyl})(CH_2)_2NC_5H_{10}$	H	H	H		189–194/1	633
$N(2\text{-pyridyl})CH_2CH(Me)NMe_2$	H	H	H		162–169/1.5	633
$N(2\text{-pyridyl})(CH_2)_3NMe_2$	H	H	H		171–174/4	633
	H	H	H	111–112		628

TABLE 41. (*Continued*)

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
	H	H	H	168–169		628
	Me	H	H	183–184		628
$N(CH_2CH_2OH)_2$	H	H	H		156–158/1	644
				152–153[q]		645
$N(CH_2CH_2OH)_2$	H	H	Me	147–148[q]		645
$N(CH_2CH_2Cl)_2$	H	H	H	102–104		644
$N(CH_2CH_2Cl)_2$	H	H	Me	107–109[q]		645
$CH_2N(CH_2CH_2Cl)_2$	H	H	H	193–194[q]		549
$N(CH_2CH_2Br)_2$	H	H	H	150–152[i]		646
$N(CH_2CH_2Br)_2$	H	H	Me	140–143[i]		646
	H	H	H		91–92/13	224 i, m, r
	H	H	H		102–104/7	564
	H	Cl	Cl	235[q]		48
	H	H		30–31		567

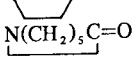
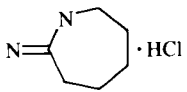
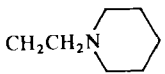
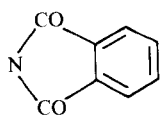
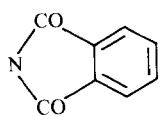
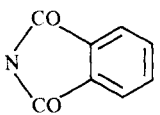
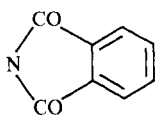
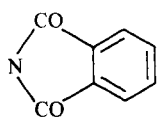
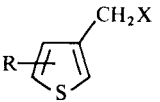
	H	H	COPh			647
	H	H	Cl	71–73.5		120
	H	H	H			648
	H	H	H	189–190[a]	135–138/7	613
	H	H	H	220–221[a]	140–143/20	613
	H	H	$C(OH)Me_2$	102–103		567
	H	H	$C{\equiv}CC(OH)Me_2$		198–199/1	567
	H	H	H	125–127		649
	H	H	Me	123–124		649

TABLE 41. *(Continued)*

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
	H	H	SO_2Me	185–185.5		604
	H	H	SO_2Et	115–116		604
	H	H	SO_2-*n*-C_5H_{11}	101–101.5		604

[a] Hydrochloride.
[b] Phenylthiourea.
[c] Hydroiodide.
[d] Methiodide.
[e] Methyl bromide.
[f] Methyl chloride.
[g] Temperature of steam distillation.
[h] Ethyl iodide.
[i] Hydrobromide.
[j] Bismethyl bromide.
[k] Dipicrate.
[l] Citrate.
[m] Bishydrochloride.
[n] Picrate.
[o] Oxalate.
[p] With sintering at 105°C.
[q] Picrolonate

TABLE 42. 3-AMINOMETHYLTHIOPHENES 

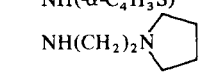
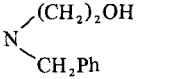
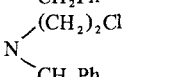
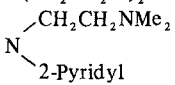
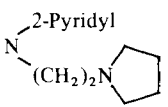
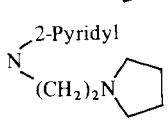
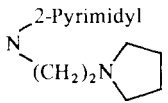
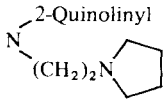
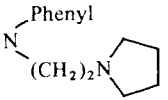
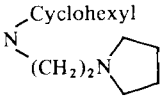
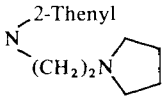
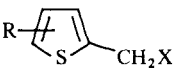
X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
NH_2	1-Pyrryl	H	H		160/4	226 i
NH_2	SEt	H	Et	177–179[a]	110–120/8	650
NH_2	Me	CH_2NHMe	Me		127/8	574
NH_2	Ph	H	H	235–236[a]		28 m
NHCHO	1-Pyrryl	H	H	70		226 i, r
NHCOMe	1-Pyrryl	H	H	105		226 i, r
NHCOEt	1-Pyrryl	H	H	85		226 i, r
NHCOPh	1-Pyrryl	H	H	100		226 i, r
$NHCOC_7H_7$	1-Pyrryl	H	H	140		226 i, r
$NHCO(\alpha\text{-}C_4H_3S)$	1-Pyrryl	H	H	118		226 i, r
NHEt	Cl	CH_2NHEt	Cl	80–81	106–116/0.5	23 i, r, u
$NH(\alpha\text{-}C_4H_3S)$	H	H	H	240–241[a]	171–181/12	651
	H	H	H		92–102/0.4	651
CH_2NH_2	H	H	H	215–216[a]	65–68/3	652
					60–62/2–3	238
CH_2NHAc	H	H	H	70.5		238
$CH_2NHCOPh$	H	H	H	109		238
$CH_2N{=}CHPh$	H	H	H	33–35	170–192/7	652
CH_2NHMe	H	H	H	148–149[a]	87–91/7	652
NMe_2	H	H	H		74–75/20	223
					28–32/0.12	124 i, r
NMe_2	CHO	H	H		62–63/0.03	124 r
NMe_2	COPh	H	H		122–124/0.5	124 r
NMe_2	Cl	H	H		31–32/0.6	124 r
NMe_2	Br	H	H		59–60/1.3	124 r

TABLE 42. (*Continued*)

X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
NMe_2	Me	H	Me		79–81/18	630
NMe_2	Me	CH_2NMe_2	Me	29.5–30.5	110/8	574
NEt_2	H	H	COMe			547
$\overset{+}{N}Me_3Cl^-$	SCH_2Ph	H	Et	159.5–161		546
	H	H	H	146–147[a]	135–145/0.07	619
	H	H	H	177–178[a] dec.		619
$N(CH_2CH_2OH)_2$	H	H	H	82–83.5[a]		653 r
$N(CH_2CH_2OH)_2$	Br	H	H	70.5–71.5		653 r
$N(CH_2CH_2OH)_2$	Cl	H	H	143.5–144.5[a]		653 r
$N(CH_2CH_2Cl)_2$	H	H	H	109–110.5[a]		653 r
$N(CH_2CH_2Cl)_2$	Br	H	H	130.5–131.5[a]		653 r
$N(CH_2CH_2Cl)_2$	Cl	H	H	164–165.5[a]		653 r
$N(CH_2CH_2Cl)_2$	SEt	H	Et	92.5–94[a]		546
	Cl	H	Cl	168–170[a]	174–180/1	17
	H	H	H	111–113[b]	155–165/0.5	651
	H	H	Cl	117–118[b]	168–172/0.1	651

	H	H	Cl	125–126[b]	180–181/0.2	651
	H	H	H	246–247[a]	155–160/0.2	651
	H	H	H	126–130[b]	198–199/1.3	651
	H	H	H	95–97[b]	153–154/0.2	651
	H	H	H	97–100[b]	167–170/0.25	651
$CH_2N(CH_2CH_2Cl)_2$	H	H	H	200–201[a]		549

[a] Hydrochloride.
[b] Citrate.

TABLE 43. 2-PHOSPHOMETHYLTHIOPHENES R- 

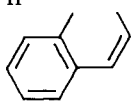
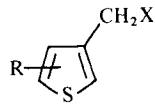
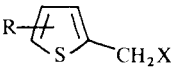
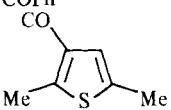
X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$\overset{+}{P}Ph_3Cl^-$	H	H	H	311		215
$\overset{+}{P}Ph_3Br^-$	H	H	H	>300 dec.		216
				320 dec.		26
$\overset{+}{P}Ph_3Cl^-$	I	H	H			14
$\overset{+}{P}Ph_32Cl^-$	H	H	$CH_2\overset{+}{P}Ph_3$	220 dec		251
$\overset{+}{P}(CH_2Ph)Ph_2Br^-$	H	H		258–260		217 r
$\overset{+}{P}(CH_2\text{-}2C_4H_3O)Ph_2Br^-$	H	H	H	222–224		217 r
$\overset{+}{P}Ph_3Br^-$	H			298–300		249
$PO(OH)_2$	H	H	H	108–109		220
$PO(OEt)_2$	H	H	H		120–124/0.06	654
					138–140/2.2	227 r
					133–138/5	218
					119–124/0.5	40
					84–89/0.03	228 r
$PO(OEt)_2$	Br	H	H		116–118/0.003	40
$PO(OBu)_2$	H	H	H		147–150/3	220

TABLE 44. 3-PHOSPHOMETHYLTHIOPHENES



X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$\overset{+}{P}Ph_3Br^-$	H	H	H	313–315		216 r
$\overset{+}{P}Ph_3Cl^-$	H	Br	H			14
$\overset{+}{P}Ph_3Cl^-$	H	I	H	248		14
$\overset{+}{P}Ph_3Cl^-$	Me	Me	Me			655
$PO(OEt)_2$	H	H	H		123–133/0.7	227 r
					99–100/0.1	219
					128–132/1	40
$P(OEt)_2$	COOMe	H	H		134–138/0.06	219
$P(OEt)_2$	Cl	H	H		109–110/0.004	40
$PO(OEt)_2$	Br	H	H		130–134/0.01	40
$PO(OEt)_2$	Cl	H	Cl		120/0.1	40
$P(OEt)_2$	Br	H	Br		131–135/0.08	219
$P(OEt)_2$	H	Br	H		115–122/0.005	40

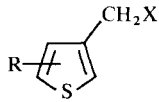
TABLE 45. 2-THENYL ALDEHYDES AND KETONES 

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CHO	H	H	H	131–132[a]	69–74/8	263, 268
				78–80.5[b]		656
					85/0.01	262 i, u
CHO	H	H	Cl	147–147.5[a]	55–60/5	263
CH_2CHO	H	H	H		140/6	274 i, m, r
					60/0.7	657 i, r
CH_2CHO	H	H	CH_2CH_2CHO		107–110/0.008	565 i, r, 657 i
COMe	H	H	H		114–115/23	8
					66/1.3	264
				179–180[a]	75–77/5.5	270
				116–117[c]		270
COEt	H	H	H		58/0.2	264
CO-*n*-Pr	H	H	H		83/0.9	264
CO-*i*-Pr	H	H	H		90/2.2	264
CO-*n*-Bu	H	H	H		74/0.3	264
CO-*i*-Bu	H	H	H		80/0.4	264
CO-*s*-Bu	H	H	H		76/0.3	264
CO-*n*-C_5H_{11}	H	H	H		84/0.2	264
COPh	H	H	H		Oil	266 i, r
	H	H	Cl		160–162/0.2	267 i, r, u
CH_2COMe	H	H	H		150/6	274 i, m, r
				156[a]	121/15	658, 659
				145[c]	118/13	658
					108–113/11	276
CH_2COMe	H	H	Me		170/10	274 i, m, r

CH_2COMe	H	H	COMe	74–74.5	170/5	274 i, m, r
CH_2COMe	H	H	CO_2Me		180/1	274 i, m, r
CH_2COMe	H	H	CH_2CO_2Me		155/2	274 i, m, r
CH_2COEt	H	H	H		160/20	274 i, m, r
				137[a]		658
				138[c]	125–127/11	658
CH_2CO-*i*-Pr	H	H	H		170/20	274 i, m, r
CH_2COPh	H	H	H	57–57.5	170/5	274 i, m, r
				143[a]		658
				168–169[c]		658
				42	205–215/15	658
$(CH_2)_2COMe$	H	H	H		160/8	274 i, m, r
				226[a]		658
				259[c]	130–155/13	658
$(CH_2)_2COMe$	H	H	CO_2Me		160/1	274 i, m, r
$(CH_2)_2COEt$	H	H	H	228.5[a]		658
				259[c]	140–155/13	658
$(CH_2)_3COMe$	H	H	H	134[a]		658
				84–85[c]	140–141/10	658
$(CH_2)_4COMe$	H	H	H	128.5–129[a]	151–152/11	658
$(CH_2)_5COMe$	H	H	H	93[c]	161–162/12	658
				131.5[a]		658
$(CH_2)_8COMe$	H	H	H	103–103.5[a]	205/15.5	658

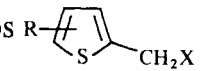
[a] Semicarbazone.
[b] Oxime.
[c] 2,4-Dinitrophenylhydrazone.

TABLE 46. 3-THENYL ALDEHYDES AND KETONES



X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CHO	H	H	H	145–146[a]		269
CH_2CHO	H	H	H		150/10	274 i, m, r
					65/0.5	657
COMe	H	H	H	111.5–112[b]		271, 652 i, m, r
				73–73.5[c]	83/5	271 i, m, r, 652
COMe	COOH	H	H	127–129		275 i, r
COMe	H	COOH	H	153–154		275 i, r
COMe	Me	CH_2COMe	Me	182–183		574
COPh	COOH	H	H	199–201		275
COPh	H	COOH	H	212–214		275 r
CH_2COMe	H	H	H		150/10	274 i, m, r
CH_2COEt	H	H	H		170/10	274 i, m, r
CH_2CO-*i*-Pr	H	H	H		170/10	274 i, m, r
CH_2COPh	H	H	H	49.5–50	180/3	274 i, m, r

[a] Semicarbazone.
[b] 2,4-Dinitrophenylhydrazone.
[c] Oxime.

TABLE 47. 2-THIOPHENEACETIC ACIDS 

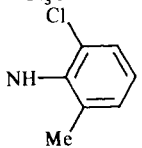
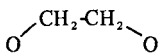
X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
COOH	H	H	H	61–62.5		32, 660
				66		8
				76		279
				62–63		21, 292
				63–64		278, 280
				75–76		320
				64		282
COOH		H	H	167–169 dec.		661
COOH		H	H			662
COOH	Me	H	Ph	130		663
COOH	COOH	H	Me	217–219		342 i, r, u
COOH	H	COOH	H	210		65 r
COOH	H	COOH	Me	224–226		275 i, r
				219		55
COOH	H	Me	Et	56		663
COOH	H	Cl	Cl	106		664
COOH			COOH	323 dec.		127
COOH	H	H	Et	~10	168/14	19
COOH	H	H	CH_2COOH	189–190		665
COOH	H	H	CH_2N-Phtal.	180–182		20 r
COOH	H	H	CH_2NH_2	228–230 dec.		20 i, r
COOH	H	H	CH_2NHCO_2-*t*-Bu	116–117		20 i, r

TABLE 47. *(Continued)*

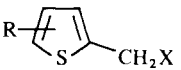
X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$(CH_2)_2COOH$	H	H	H	51.5–52.5[b]	Oil	292
					172–174/20	50
$(CH_2)_3COOH$	H	H	H	39–41	163–164/9	50
$(CH_2)_3COOH$	H	H	$(CH_2)_4COOH$	140.5–142.5		50
$(CH_2)_3COOH$	H	H	$(CH_2)_5COOH$	80.5–84		50
$(CH_2)_4COOH$	H	H	H	41–41.5	205/20	50, 541
$(CH_2)_4COOH$	H	H	$(CH_2)_5COOH$	60–68		50
$(CH_2)_5COOH$	H	H	H	28–30	148–152	50
				30	195.5/10	658
$(CH_2)_6COOH$	H	H	H	14.2–15.6	147–150/0.03	50
				15	219/17	541
$(CH_2)_7COOH$	H	H	H	32–33		299
				35–36	217/10	50, 658
				37–38		668
$(CH_2)_8COOH$	H	H	H	27–28		299
				33–34		50
				25.5	222/10	658
$(CH_2)_8COOH$	Me	H	H	40–42		384
$(CH_2)_8COOH$	H	Me	H	54.5–55.5		384
$(CH_2)_8COOH$	H	H	$(CH_2)_3$-Cyclohexyl	47.5		671
$(CH_2)_8COOH$	H	H	$(CH_2)_6$-Cyclohexyl	44.5–45		672
$(CH_2)_8COOH$	H	H	$(CH_2)_{10}$-Cyclohexyl	57		672
$(CH_2)_8COOH$	H	H	$(CH_2)_{12}$-Cyclohexyl	62		672
$(CH_2)_9COOH$	H	H	H	43	230/10	658
				47–48.5		50
$(CH_2)_9COOH$	Me	H	H	47.5–49.5		384
$(CH_2)_9COOH$	H	Me	H	52–54		384
				48–51		299
$(CH_2)_{10}COOH$	H	H	H	41–42.5		299
				39–40.5		50

COOH	H	H	Ph	143	663
				142–144	666
COOH	H	H	C(Me)=NOH	172–173[a] dec.	21
COOH	H	H	$CH(OH)CH_2C_6H_5$	107.5	300 i, r
COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-F	126–127	300 i, r
COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-Cl	129–131	300 i, r
COOH	H	H	$CH(OH)CH_2C_6H_4$-*m*-Cl	108	300 i, r
COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-Br	128–129	300 i, r
COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-OMe	96.5	300 i, r
COOH	H	H	$CH(OH)CH_2C_6H_4$-*p*-iso-Bu	123	300 i, r
COOH	H	H	$CH{=}CHC_6H_5$	144–145	300 i, r
COOH	H	H	$CH{=}CHC_6H_4$-*p*-F	173–175	300 i, r
COOH	H	H	$CH{=}CHC_6H_4$-*p*-Cl	181–183	300 i, r
COOH	H	H	$CH{=}CHC_6H_4$-*m*-Cl	164	300 i, r
COOH	H	H	$CH{=}CHC_6H_4$-*p*-Br	184	300 i, r
COOH	H	H	$CH{=}CHC_6H_4$-*p*-OMe	178	300 i, r
COOH	H	H	$CH{=}CHC_6H_4$-*p*-iso-Bu	163	300 i, r
COOH	H	H	Cyclohexyl		531
COOH	H	H	COMe	130–131	21, 340
COOH	H	H	COOH	206–207 dec.	667
COOH	H	H	Cl	66–67	340
				65–66	12, 120
				64.5–65.5	21
				61–63	267
COOH	H	H	Br	63–64	12
CH_2COOH	H	H	H	44–45	292
				49–49.5	668
				47.5–48	658
CH_2COOH	OH	OH	H	194–197	669
CH_2COOH	H	H	Me	42	670
CH_2COOH	H	H	Ph	148	607
CH_2COOH	H	H	C_6H_4-*p*-OMe	178	607
CH_2COOH	H	H	C_6H_4-*p*-Cl	150–151	535

TABLE 47. (*Continued*)

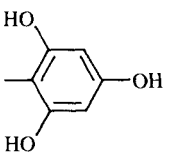
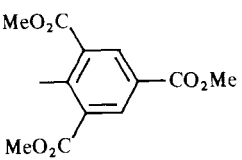
X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$(CH_2)_{10}COOH$	H	H	Me	69–71		383
$(CH_2)_{10}COOH$	H	H	$(CH_2)_3$-Cyclohexyl		238–241/1.5	671
$(CH_2)_{10}COOH$	H	H	$(CH_2)_6$-Cyclohexyl	52		672
				64		673
$(CH_2)_{10}COOH$	H	H	$(CH_2)_{10}$-Cyclohexyl	71.5–72		673
$(CH_2)_{10}COOH$	H	H	$(CH_2)_{12}$-Cyclohexyl	75.5		673
$(CH_2)_{11}COOH$	H	H	H	57.5–59		50
$(CH_2)_{11}COOH$	H	H	$(CH_2)_3$-Cyclohexyl	55–56		673
$(CH_2)_{11}COOH$	H	H	$(CH_2)_{13}$-Cyclohexyl	71		673
$(CH_2)_{12}COOH$	H	H	H	51.5–53		299
$(CH_2)_{13}COOH$	H	H	$(CH_2)_{13}$-Cyclohexyl	74.5–75		673
$(CH_2)_{14}COOH$	H	H	$(CH_2)_{10}$-Cyclohexyl	71–72		672
$(CH_2)_{15}COOH$	H	H	$(CH_2)_3$-Cyclohexyl	70		673
$(CH_2)_{16}COOH$	H	H	H	67.0–68.5		299
$(CH_2)_{16}COOH$	H	H	$(CH_2)_6$-Cyclohexyl	68–69		672
$(CH_2)_{16}COOH$	H	H	$(CH_2)_{10}$-Cyclohexyl	75–75.5		672
$(CH_2)_{16}COOH$	H	H	$(CH_2)_{12}$-Cyclohexyl	77.5		672

[a] Syn and anti isomers.
[b] *p*-Bromophenacyl ester.

TABLE 48. 2-THIOPHENEACETIC ACID DERIVATIVES 

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CN	H	H	H		111–113/15	12
					115–120/22	9, 320
					110–113/13	321
					90–94/10	674
					87–90/3	278
CN	CH_2CN	H	H	71	125–135/0.01	70
CN	OMe	H	H		112–114/2.2	343 i
CN	Br	H	Me		148–150/15	675
CN	H	Cl	Cl	45		664
CN	H	H	CH_2CN	39–40		665
CN	H	H	$CH(OH)CH_2C_6H_5$		Oil	300
CN	H	H	$CH(OH)CH_2C_6H_4$-*p*-F	69–70		300
CN	H	H	$CH(OH)CH_2C_6H_4$-*p*-Cl	77–78		300
CN	H	H	$CH(OH)CH_2C_6H_4$-*m*-Cl		Oil	300
CN	H	H	$CH(OH)CH_2C_6H_4$-*p*-Br	93–93.5		300
CN	H	H	$CH(OH)CH_2C_6H_4$-*p*-OMe	93		300
CN	H	H	$CH(OH)CH_2C_6H_4$-*p*-iso-Bu	78		300
CH	H	H	$CH(OH)CH_2C_6H_4$-*p*-NO_2	115.5		300 i, r
CN	H	H	$CH{=}CHC_6H_5$	110–111		300 i, r
CH	H	H	$CH{=}CHC_6H_4$-*p*-F	101		300 i, r
CN	H	H	$CH{=}CHC_6H_4$-*p*-Cl	123		300 i, r
CN	H	H	$CH{=}CHC_6H_4$-*m*-Cl	83		300 i, r
CN	H	H	$CH{=}CHC_6H_4$-*p*-Br	143		300 i, r
CN	H	H	$CH{=}CHC_6H_4$-*p*-OMe	145		300 i, r
CN	N	H	$CH{=}CHC_6H_4$-*p*-iso-Bu	95		300 i, r
CN	H	H	$CH{=}CHC_6H_4$-*p*-NO_2	123		300 i, r
CN	H	H	$COCH_2C_6H_5$	68		300 i, r

TABLE 48. (*Continued*)

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CN	H	H	$COCH_2C_6H_4$-*p*-F	92–93		300 i, r
CN	H	H	$COCH_2C_6H_4$-*p*-Cl	134		300 i, r
CN	H	H	$COCH_2C_6H_4$-*m*-Cl	104–105		300 i, r
CN	H	H	$COCH_2C_6H_4$-*p*-Br	137–138		300 i, r
CN	H	H	$COCH_2C_6H_4$-*p*-OMe	84		300 i, r
CN	H	H	$COCH_2C_6H_4$-*p*-iso-Bu	99–101		300 i, r
CN	H	H	$COCH_2C_6H_4$-*p*-NO_2	119		300 i, r
CN	H	H	Et		132/17	19
CN	H	H	Cyclo-C_6H_{11}			531
CN	H	H	Cl		79–80/0.5	12
					124–131/13	21
					130/15	143
					117–119/17	120
					104/3	674
CN	H	H	Br	32–33	114–116/0.8	12
CN	H	H	I	58–58.5		60 r
CN	H	H		232–234		343 i, r
CN	H	H		113–116		343 i, r
CN	H	H	OMe		110–113/2	343

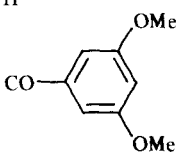
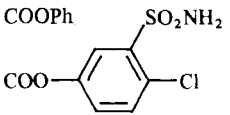
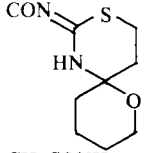
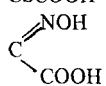
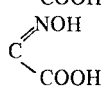
CH_2CN	H	H	H		129/17	541
					156–158/35	676
CH_2CN	Me	H	H		66/0.08–0.1	677, 678
CH_2CN	H	H	C_6H_4-*p*-Cl	74–75		535
COOMe	H	H	H		119–122/25	282
					115–118/23	320
					100–104/14	21, 280
					85/5	293
COOMe	$\overset{+}{N}H_3Cl^-$	H	H	176.5–180 dec.		661
COOMe	H	Cl	Cl		124–128/16	664
COOMe	H	H	*t*-Bu		75–76/0.15	21
COOMe	H	H	C_6H_4-*p*-Cl	78–80		535
COOMe	H	H	C(Me)=NOH	57–59[a]		21
				72–73[a]		21
				126–127[a]		21
COOMe	H	H	COMe	44–46	114–124/0.15	21
COOMe	H	H	Br		75–84/0.06	21
COOMe	H	H	Cl		67–72/0.5	120
					77–78/0.4	21
CH_2COOMe	H	H	H		50/0.005	668
CH_2COOMe	H	H	Ph	75		607
CH_2COOMe	H	H	C_6H_4-*p*-OMe	94		607
$(CH_2)_2COOMe$	H	H	H		67–70/15	359 i, r
$(CH_2)_2COOMe$	H	H		42–43	220/0.01	359 i, r
$(CH_2)_3COOMe$	H	H	H		141.5–143/14	50
$(CH_2)_3COOMe$	H	H	$(CH_2)_4COOMe$		182–185/2	50
$(CH_2)_3COOMe$	H	H	$(CH_2)_5COOMe$		194–195.5/1	50
$(CH_2)_3COOMe$	H	H	$CO(CH_2)_3COOMe$	67.5–69		50
$(CH_2)_3COOMe$	H	H	$CO(CH_2)_4COOEt$		224–225/0.5	50

TABLE 48. (*Continued*)

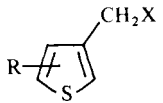
X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$(CH_2)_4COOMe$	H	H	H		113–114/1	50
$(CH_2)_4COOMe$	H	H	$CO(CH_2)_4COOEt$	33–34.5	233–237/1	50
COOEt	H	H	H		124–129/26	320
					120/22	8
					100–106/6	322
					119–121/23	9
COOEt	COOEt	H	H		120–130/0.5	70 r
COOEt	H	H	Me		Oil	345 i, r, u
COOEt	OH	CN	MeCHEt		155/0.1	679
COOEt	H	H	C_6H_4-*p*-Cl	66–68		535
CH_2COOEt	H	H	H		122–122.5/5	658
$(CH_2)_5COOEt$	H	H	H		182/16	658
$(CH_2)_7COOEt$	H	H	H		114/0.3	668
$(CH_2)_9COOEt$	H	H	H		219–223/13	658
COO-*n*-Bu	H	H	H		80–82/0.3	21
COO-*n*-Bu	H	H	C_6H_4-*p*-Cl	34–35		535
COOPh	H	H	C_6H_4-*p*-Cl	101–103		535
	H	H	H	133–134		680–682
$COOCH_2Ph$	H	H	C_6H_4-*p*-Cl	71–72		535
COCl	H	H	H		105–106/22	8
					73/5	293
COCl	H	H	Et		125/16	19
COCl	H	H	COCl			667
CH_2COCl	H	H	H		116/16	658
					121/15	541
$(CH_2)_2COCl$	H	H	H		114–116/6	50

$(CH_2)_3COCl$	H	H	H		102–105/1	50
$(CH_2)_4COCl$	H	H	H		147/7.5	541
					118–119/3.5	50
$(CH_2)_5COCl$	H	H	H		120–125/0.5	50
					164/10	658
$(CH_2)_6COCl$	H	H	H		169/7.5	541
					157–160/3	50
$(CH_2)_7COCl$	H	H	H		142–146/1	50
					165/3.2	658
$(CH_2)_8COCl$	H	H	H		190/5.5	658
					163–165/2	50
$(CH_2)_9COCl$	H	H	H		200/6	658
					154–155/0.2	50
$(CH_2)_{10}COCl$	H	H	H		175–180/0.7	50
$CONH_2$	H	H	H	147–148		32, 278
				148		8, 292
				146.5		282, 683
				146–147		21
$CONH_2$	Me	H	H	142		291
$CONH_2$	Me	Me	H	152		291
$CONH_2$	Me	H	Et	98–99		684
$CONH_2$	H	Me	Me	165–166		291
$CONH_2$	H	H	Me	143–144		291
$CONH_2$	H	H	Et	148		291
				143		19
$CONH_2$	H	H	*t*-Bu	134–136		21
$CONH_2$	H	H	C_6H_4-*p*-Cl	209–210		535
$CONH_2$	H	H	$CH{=}CHC_6H_4$-*p*-NO_2	196–197		300 i, r
$CONH_2$	H	H	COMe	149–150		21
$CONH_2$	H	H	$CONH_2$	*207–208 dec.*		667
$CONH_2$	H	H	Cl	121–122		21, 120
$CONH_2$	H	H	Br	125.5–126.5		21
CONHPh	H	H	H	116–117		338 i
$CONHC_6H_4$-*o*-Me	H	H	H	150–152		338 i

TABLE 48. (*Continued*)

X	R_3	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$CONHNH_2$	H	H	H	96–98		685
				100		686
$CONHNH_2$	H	H	C_6H_4-*p*-Cl	166–168		535
$CONHNH_2$	H	H	Cl	104–105		686
$CONH(CH_2)_2NEt_2$	H	H	H	101–103		535
$CONH(CH_2)_2OH$	H	H	H	66–67		687
	H	H	H	115–116		688
CH_2CONH_2	H	H	H	102		658
				99–100		292
$CH_2CONHNH_2$	H	H	Ph	151		607
$CH_2CONHNH_2$	H	H	C_6H_4-*p*-OMe	165		607
$(CH_2)_2CONH_2$	H	H	H	83–84		292
$(CH_2)_5CONH_2$	H	H	H	102		658
$(CH_2)_6CONH_2$	H	H	H	95		541
$(CH_2)_7CONH_2$	H	H	H	94.5		658
$(CH_2)_8CONH_2$	H	H	H	83		541
				91		658
$(CH_2)_9CONH_2$	H	H	H	97–97.5		658
CSCOOH	OMe	H	H	212–214 dec.		343
CSCOOH	H	H	OMe	191–193		343
	H	H	OMe	143–145 dec.		343
	OMe	H	H	121–123 dec.		343

[a] Syn and anti forms.

TABLE 49. 3-THIOPHENEACETIC ACIDS 

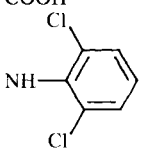
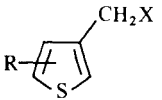
X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
COOH	H	H	H	79.5		296, 297
				79–80		37
COOH	Me	H	H	68.3–69.3		32
COOH	COOH	H	H	189–191		275 i
COOH	Me	H	Me	69–70		123
				68.5	145/3	543
				87		542
COOH	Me	H	Ph	117.5–119.5		535
COOH	Cl	H	Cl	103	160/2	377, 380
COOH	Br	H	Br	117–118		346 i, r
COOH	SPh	H	Et	73–75		68 i
COOH	$S(2C_4H_3S)$	H	Et	75–78		68 r
COOH	H	COOH	H	210–213		275
COOH	H		H			662
COOH	H	H	COOH	208–210		65 r
COOH	H	H	COMe			547
COOH	Me	Me	Me	104–106		342
COOH	Me	COOH	*t*-Bu			70 r
COOH	*t*-Bu	COOH	*t*-Bu	250		70 i, r
COOH	Cl	CH_2CONH_2	Cl	231–232		70 i
CH_2COOH	H	H	H	61–62		652
				59.5	165/14	297, 378

TABLE 49. (*Continued*)

X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CH_2COOH	COMe	H	H	114–116		689 r
CH_2COOH	Me	H	Me	58.5	185/18	543
				59–60		123
CH_2COOH	*t*-Bu	H	*t*-Bu	145	175/1.5	377, 381
CH_2COOH	Cl	H	Cl	65	170/2	377
CH_2COOH	Br	H	Br	89		689
$(CH_2)_2COOH$	H	H	H		175/18	297, 537
$(CH_2)_2COOH$	Me	H	Me	58	188/18	288
				58–59		123
$(CH_2)_2COOH$	*t*-Bu	H	*t*-Bu	110		377, 381
$(CH_2)_2COOH$	Cl	H	Cl	42.5–45		690
				42	166/2	377, 380
$(CH_2)_2COOH$	H	H	Cl	92–93		390
$(CH_2)_3COOH$	H	H	H	63.5	180/18	297, 378
$(CH_2)_3COOH$	Me	H	Me	39	192/17	288
$(CH_2)_3COOH$	*t*-Bu	H	*t*-Bu	87	190/1.5	377, 381
$(CH_2)_3COOH$	Cl	H	Cl	47	190/2	377, 380
				44–44.5		690
$(CH_2)_4COOH$	H	H	H		190/17	297, 379
$(CH_2)_4COOH$	Me	H	Me		210/16	288
$(CH_2)_4COOH$	Me	$(CH_2)_5COOH$	Me	93–93.7		50
$(CH_2)_5COOH$	H	H	H	45		297
$(CH_2)_5COOH$	Me	H	Me	46		288

TABLE 50. 3-THIOPHENEACETIC ACID DERIVATIVES



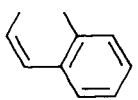
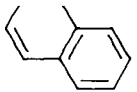
X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CN	H	H	H		110–111/11	12
					114–116/12	35
					116/16	296, 297
					120–121/23	8
					70–75/1–2	238
					124–125/16	652
CN	COOH	H	H	135–136		275 i, r, u
CN	Me	H	Me		130/16	543
					180–185/15	691
CN	Cl	H	Cl		135/2	377, 380
CN	SEt	H	Et		130–131/4	546
CN	SPh	H	Et		168/50	68 i, r
CN	$S(2C_4H_3S)$	H	Et		170/80	68 r
CN	SO_2Et	H	Et	67.5–68		546
CN	H	COOH	H	171–172.5		275
CN	H	CH_2CN	H	102		70 i, r
CN	H	OMe	Ph		146/0.1	34
CN	H			102		551 i, m, r
CN	H	H	COMe			547
CN	H	H	COOMe		110/0.2	65 r
CN	Me	CH_2CN	Me	125–125.5		574
CN	*t*-Bu	CH_2CN	*t*-Bu	196		70 i, r
CN	Cl	CH_2CN	Cl	144–146		692

TABLE 50. *(Continued)*

X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
CN	Br			172–173		551 i, m, r
CN	$SiMe_3$	CH_2CN	$SiMe_3$	141–143		692
CH_2CN	H	H	H		136–138/14	693, 694
$(CH_2)_2CN$	Cl	H	Cl		146/2	377, 380
$(CH_2)_4CN$	H	H	H		172/17	297, 379
COOMe	H	H	H			332
COOMe	Me	CH_2COOMe	*t*-Bu			70 i, m, r
COOMe	*t*-Bu	CH_2COOMe	*t*-Bu	97		70 i, r
$(CH_2)_3COOMe$	Me	$(CH_2)_4COOMe$	Me		177–179/0.25	50
$(CH_2)_3COOMe$	CH_2Cl	$(CH_2)_4COOMe$	CH_2Cl	64		50
$(CH_2)_4COOMe$	Me	H	Me		120–121/1	50
$(CH_2)_4COOMe$	Me	$CO(CH_2)_4COOEt$	Me		209–214/1	50
$(CH_2)_4COOMe$	Me	$(CH_2)_5COOMe$	Me		200–205/1	50
COOEt	H	H	H		87/0.15	266
COOEt	COOH	H	H	144–145.5		275 i, r
COOEt	H	COOH	H	159.5–161		275 r
COOEt	H	CH_2COOEt	H		120–130/0.5	70 i, r
COOEt	H	OMe	Ph		158–160/0.2	34
$(CH_2)_2COOEt$	H	H	H		153/18	297
COCl	H	H	H		103/16	296
CH_2COCl	H	H	H		90–100/3	652
$(CH_2)_2COCl$	Cl	H	Cl		125–127/2	690
$(CH_2)_3COCl$	Cl	H	Cl		146–148/2	690
$CONH_2$	H	H	H	154–155		291
				112		297
				152		296

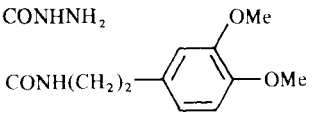
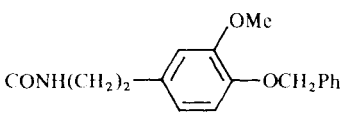
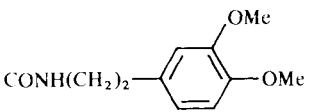
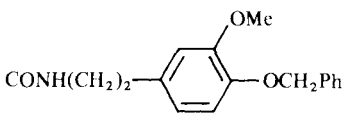
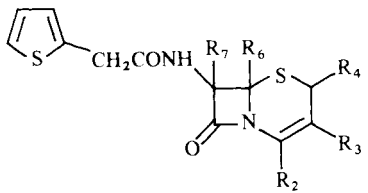
$CONH_2$	Me	H	Me	153–154	123
				147–148	695
$CONH_2$	Et	H	Et	116–117	291
$CONH_2$	Cl	H	Cl	133	377
				134	380
$CONH_2$	H	COOH	H	193–194	275
$CONH_2$	*t*-Bu	CH_2CONH_2	*t*-Bu	240	70 i, r
$CONH_2$	Cl	CH_2CONH_2	Cl	260–261	70 i
CONHMe	H	H	H	75	652
CONHMe	H	COOH	H	162–164	275
$CONHNH_2$	H	H	H	83–84	696
	H	H	H	94–95	697 i, r
	H	H	H	82–83	697 i, r
	Br	H	Br	124	346 i, r
	Br	H	Br	115–116	346 i, r
CH_2CONH_2	H	H	H	116.5	297, 378
CH_2CONH_2	Me	H	Me	140	543
CH_2CONH_2	*t*-Bu	H	*t*-Bu	162	377
CH_2CONH_2	Cl	H	Cl	98	377, 380
$(CH_2)_2CONH_2$	H	H	H	76	297, 537

TABLE 50. *(Continued)*

X	R_2	R_4	R_5	Melting Point (°C)	Boiling Point (°C)	Reference
$(CH_2)_2CONH_2$	Me	H	Me	103		288
$(CH_2)_2CONH_2$	*t*-Bu	H	*t*-Bu	164		377
$(CH_2)_2CONH_2$	Cl	H	Cl	103		377
$(CH_2)_3CONH_2$	H	H	H	112		297, 378
$(CH_2)_3CONH_2$	Me	H	Me	103		288
$(CH_2)_3CONH_2$	*t*-Bu	H	*t*-Bu	118		377
$(CH_2)_3CONH_2$	Cl	H	Cl	77		377
$(CH_2)_4CONH_2$	H	H	H	89.5		297, 379
$(CH_2)_4CONH_2$	Me	H	Me	68.5		288
$(CH_2)_5CONH_2$	H	H	H	108		297
$(CH_2)_5CONH_2$	Me	H	Me	69		288

TABLE 51. CEPHALOSPORINS OF GENERAL FORMULA



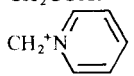
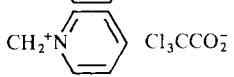
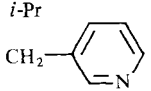
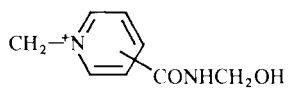
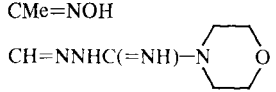
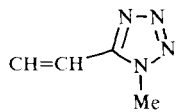
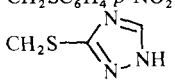
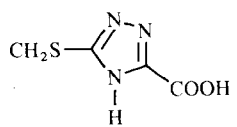
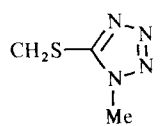
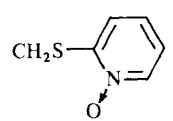
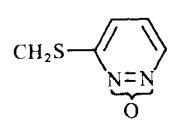
R_2	R_3	R_4	R_6	R_7	Reference
COOH Cephalothin	CH_2COAc	H	H	H	698–708
COONa	CH_2COAc	H	H	H	709–714
COO^- Cephaloridine		H	H	H	715, 716
COOH		H	H	H	717
COOH	Et	H	H	H	718–720
COOH	*i*-Pr	H	H	H	718, 719
COOH		H	H	H	721, 722
COO^-		H	H	H	723
COOH	CH_2(5Me-1,3,4-Thiadiazol-2-yl)thio	H	H	H	724
COOH	$CH{=}NNH_2$	H	H	H	725
COOH	$CMe{=}NOH$	H	H	H	726
COOH		H	H	H	727

TABLE 51. (*Continued*)

R_2	R_3	R_4	R_6	R_7	Reference
COOH		H	H	H	418, 728
COOH	CH_2OH	H	H	H	729
COOH	$(CH_2)_2OAc$	H	H	H	730
COOH	CH_2SR	H	H	H	731, 732
COOH	OMe	H	H	H	733
COOH	$CH_2SC_6H_4$-*p*-NO_2	H	H	H	734
COOH		H	H	H	735, 736
COOH		H	H	H	737
COOH		H	H	H	738
COOH		H	H	H	739
COOH		H	H	H	739

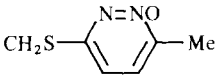
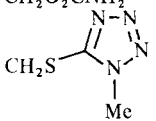
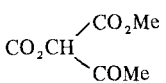
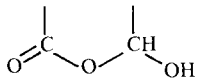
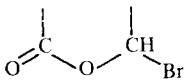
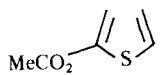
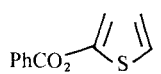
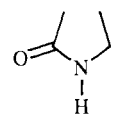
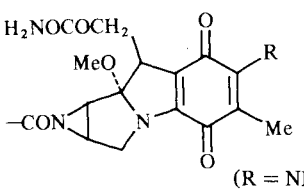
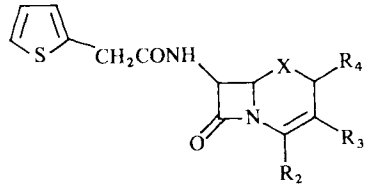
COOH		H	H	H	740, 741
COOH	Cl	H	H	H	742
COOH	Halogen	H	H	H	743
COOH	H	Me	H	H	744
COOH	Me	H	OMe	H	745
COOH	H	Me_2[a]	H	H	746
COOH	Me	H	O Alkyl	H	747
COOH	Me	H	S Alkyl	H	747
COOH	Me	H	H	OMe	748, 749
COOH	CH_2OMe	H	H	OMe	750
COOH	$CH_2O_2CNH_2$	H	H	OMe	751–758
COONa		Me	H	H	759
COONa	1,2-Dihydro-2-oxo-4-pyrimidinyl	H	H	H	760
COOR	OMe	H	H	H	761
$CO_2CH_2C_6H_4$-*p*-OMe	C_6H_4-*p*-COOMe	H	H	H	762
$CO_2CH_2C_6H_4$-*p*-NO_2	OH	H	H	H	763
$CO_2CH_2C_6H_4$-*p*-NO_2	O_3S Alkyl (or aryl)	H	H	H	763, 764
$CO_2CH_2CCl_3$	CH_2OAc	H	H	H	765, 766
$CO_2CH_2C_6H_4$-*p*-NO_2	Pyrrolidin	H	H	H	767
CO_2CHPh_2	CHO	H	H	H	768
CO_2CHPh_2	$CH_2O_2CNH_2$	H	H	OMe	769–774
CO_2CHPh_2	Morpholine (or piperidine)	H	H	H	767
	CH_2OAc	H	H	H	775

TABLE 51. *(Continued)*

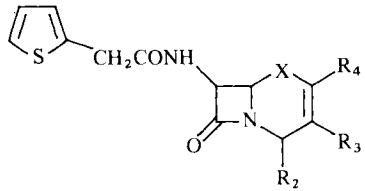
R_2	R_3	R_4	R_6	R_7	References
CON(Pr-iso)NHPr-iso	CH_2OAc	H	H	H	418
COOMe	CH_2I	H	H	OMe	738
CO_2CH_2OMe	$CH_2O_2CHN_2$	H	H	OMe	776, 777
		H	H	H	727, 768, 778, 779
		H	H	H	780
		H	H	H	781
		H	H	H	781
		H	H	H	781, 782
 (R = NH_2, OMe)	CH_2OAc	H	H	H	783

[a] The 4-carbon bears two methyls and no hydrogen.

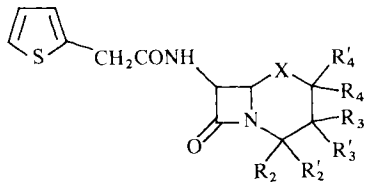
TABLE 52. CEPHALOSPHORINS



X	R_2	R_3	R_4	Reference
CH_2	COOH	H	H	784–786
O	COOH	H	H	787
O	COOH	Me	H	788, 789
SO	COOH	Me	H	790
SO	COOH	H	Me	744



S	COO-*t*-Bu	CH_2I	H	738



X	R_2	R'_2	R_3	R'_3	R_4	R'_4	Reference
S	H	COOH	Me	Cl	H	H	791
S	H	$COCH_2C_6H_4$-*p*-NO_2	Me	Halogen	H	H	792

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