THIOPHENE AND ITS DERIVATIVES

Part Five

Edited by

Salo Gronowitz

University of Lund
Lund, Sweden

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THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

ARNOLD WEISSBERGER, *Founding Editor*

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The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction created as many problems as it solved, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry*, and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

EDWARD C. TAYLOR

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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 was 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 up to the end of the 1980s. 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 systematically treat functionalized simple thiophenes, such as alkylthiophenes, halothiophenes, aminothiophenes, and thiophenecarboxylic acids. The latter chapters, as is customary in the Taylor–Weissberger 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: 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 five-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: 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, an extensive treatment of physical properties of thiophenes is given. The second chapter deals with the important nucleophilic substitutions of thiophenes, and in the third chapter the many important results in the expanding field of biologically active thiophenes, obtained between 1983 and 1988, are summarized.

Finally, in Part 5, vinyl thiophenes and thienyl acetylenes are treated. A second chapter covers thienyllithium and other organometallic derivatives of thiophene, and in the last chapter, bithienyls are covered.

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. Part 5 was completed during my stay as Fogarty Scholar-in-Residence at the NIH.

SALO GRONOWITZ

Lund, Sweden
December 1991

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THIOPHENE AND ITS DERIVATIVES

Part Five

This is a part of the forty-fourth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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CHAPTER I

Vinylthiophenes and Thienylacetylenes

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I. INTRODUCTION

Much research has been carried out on thiophenes in conjugation with double and triple bonds. This is partly due to their existence in nature and the pharmacologic activities of certain derivatives.

The largest section of this Chapter covers the preparation of vinylthiophenes. A systematic description of the preparation of vinylthiophenes according to the types of the three other substituents at the double bond in vinylthiophene would be very repetitious and confusing. We have therefore preferred to describe the preparation according to the reactions used to create vinylthiophenes.

Sections II.1–II.6 treat the various condensations of thiophenecarbonyl derivatives with active methylene derivatives, creating the double bond according to the aldol condensation, the Claisen–Schmidt condensation, the Erlenmeyer azlactone synthesis, the Knoevenagel and Perkin reactions, the Stobbe reaction, and many other methods. In Sections II.7 and II.8, the condensation of thiophenes with an active methyl or methylene group with aldehydes is treated. Section II.9 covers the use of the important Wittig reaction for the preparation of vinylthiophene. Section II.10 treats the dehydration of 1-(thienyl)carbinols obtained in various ways; and Section II.11, the dehydration of 2-(thienyl)alkanols. In Section II.12, the dehydrohalogenation of 1-(thienyl)alkylhalides is covered; and in Section II.13, the direct preparation of vinylthiophenes from thiophenecarbonyl derivatives. Section II.14 treats methods of preparing vinylthiophenes by the reaction of thiophenes, halothiophenes, and thienylmetal derivatives with alkenes. This method has become of great importance during recent years. Finally, in Sections II.15–II.19 more special methods for the synthesis of vinylthiophenes, such as ring-closure reactions, isomerizations, and rearrangements, as well as ring opening of thiophene-fused ring systms and dehydrogenation of alkylthiophenes, are discussed.

The various vinylthiophenes that have been prepared are systematically collected in the tables, together with physical properties and yields.

Section III of this chapter covers the reactions of vinylthiophenes in a systematic manner.

Sections IV and V, on pharmaceutically active vinylthiophenes and naturally occuring vinylthiophenes and the physical properties of vinylthiophenes, are very short, since most of these subjects are fully treated in other chapters of this series.

Section VI covers the little work that has been carried out on thiophenes with cumulative double bonds.

The synthesis of thienylacetylenes, in Section VII, is organized in the same way as for vinylthiophenes. In Sections VII.1 and VII.2, the preparations from thiophenecarbonyl derivatives and vinylthiophenes, respectively, are reported. Sections VII.3 and VII.4 treat the more modern and important methods from iodothiophenes and cuprous acetylides and the palladium-catalyzed couplings of halothiophenes.

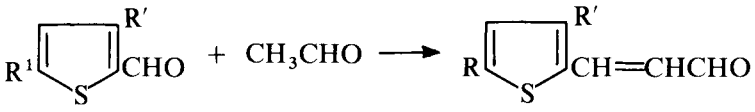
More unusual methods, such as the preparation through ring-closure reactions, and from precursors, containing a triple bond, are covered in Sections VII.5 and VII.6. The reactions of thienylacetylenes are discussed in Section VIII. For the same reasons as in the section on vinylthiophenes, only a brief description of physical properties and naturally occuring thienylacetylenes is given in Sections IX and X.

II. PREPARATION OF VINYLTHIOPHENES

1. Condensation of Thiophene Aldehydes with Aldehydes and Ketones

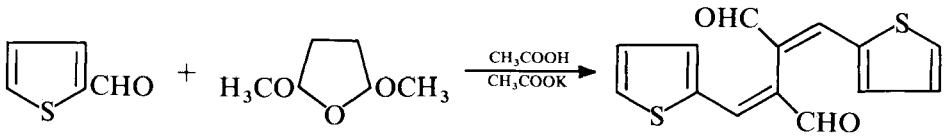
A. Aldol Condensations

2-Thiophene aldehydes behave like benzaldehyde in aldol-type condensations. In the mixed aldol condensation with acetaldehyde, β-(thienyl)acroleins (Scheme 1) were obtained in about a 30–50% yield, using 10% sodium hydroxide in aqueous ethanol.[1–5] Alternatively, piperidine acetate in 70% ethanol[6] or 25% potassium hydroxide in methanol (with 5-nitro-2-thiophenealdehyde[7–10] and 5-cyano-2-thiophenealdehyde[11,12]) has been used in the preparation of β-(2-thienyl)acroleins. 3-Thiophene aldehyde has also been condensed with acetaldehyde to give β-(3-thienyl)acrolein.[13,14]



Scheme 1

Examples of other aldehydes that have been condensed with thiophene aldehydes are chloroacetaldehyde,[15] propionaldehyde,[16,17] and butyraldehyde.[16] 2-Thiophene aldehyde has also been condensed with butanedial, produced in situ by hydrolysis of 2,5-dimethoxytetrahydrofuran **1**, to give (2-thienyl)-2,3-diformylbutadiene **2** in a 24% yield[18] (Scheme 2). Mixed aldol condensations between thiophene aldehydes and aliphatic ketones, such as



1 **2**

Scheme 2

acetone, have been carried out using sodium hydroxide[2,19–24] or with nitro-substituted thiophene aldehydes, ammonium acetate in glacial acetic acid.[25]

Derivatives of 2,5-thiophene dialdehyde such as 2-(diethoxymethyl)-5-formylthiophene have been condensed with aliphatic aldehydes using 3% potassium hydroxide.[26] 3,4-Diformylthiophene, as well as its 3,4-CDO derivatives, have been condensed with acetone and various deuterated acetones in connection with an analysis of the IR spectra of cyclohepta[*c*]thiophen-6-ones.[27] Tetramethyl-2-thiazulen-6-one was prepared through base-catalyzed condensation of 2,5-dimethylthiophene-3,4-dialdehyde and diethyl ketone.[28] In the Cu(II)-promoted aldol condensation between 2-thiophene aldehyde and 2-butanone, the methylene group was regiospecifically attacked,[29] in contrast to condensation under acidic conditions.[30] α-Acetylenic methyl ketones have also been condensed with thiophene aldehydes.[31]

Especially cyclic ketones, such as cyclopentanone,[32–35] cyclohexanones,[32–34,36,37] cycloheptanone,[32,34,35,38] cyclooctanone,[38] and benzo-fused cyclohexanones,[39,40] have been extensively used in aldol condensations. With symmetric cycloalkanones, both mono and bi adducts were prepared.

B. Claisen–Schmidt Condensations

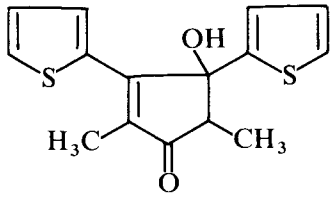
Numerous examples of the Claisen–Schmidt condensation between thiophene aldehydes and aryl methyl ketones have been reported. They were carried out in connection with studies of the chemical and physical properties of thiophene analogues of chalcones. Among the aryl methyl ketones used are acetophenone,[41,43] substituted acetophenones,[15,25,34,35,36,40,41,44–59] acetylnaphthalenes,[34,47,60] various acetylthiophenes,[22,25,34,35,40,43,45,57,61–63] acetylpyrroles,[41,43,57,64] acetylfurans,[25,43,57] acetylselenophenes,[43] acetylpyridines,[43,45,57] acetylbenzofurans,[41] acetylindoles,[67] acetylcarbazoles,[68] acetylferrocene,[66] and various methyl ketones.[41,69,70] Other, more unusual, ketones, used in condensations with thiophene aldehydes for the synthesis of potentially pharmacologically active compounds, include 4-acetylpyrine.[71]

Aqueous and ethanolic sodium or potassium hydroxide were used as the condensation agent in most cases. In a few cases with nitro-substituted thiophene aldehydes, ammonium acetate in acetic acid,[25] or sulfuric acid in acetic acid[46] was used. Another example of an acidic Claisen–Schmidt reaction is the condensation of 2,5-diformylthiophene with 4-hydroxyacetophenone, using methanolic hydrogen chloride, which is claimed to give better yields.[43] In the condensation of 2-thiophene aldehyde with dehydroacetic acid, piperidine in chloroform was used,[54] and in the condensation with 2-acetylbenzimidazol, the agent was piperidine in methanol.[67] 1-Acetylindoxyl reacted with 2-thiophene aldehyde and 5-nitro-2-thiophene aldehyde, using a few drops of piperidine as catalyst, to give, after hydrolysis, 2-(thenylidene)indoxyls.[72]

C. Various Other Condensations

The base-catalyzed reaction of 2-thenil **3** with diethyl ketone gave **4**, which on treatment with concentrated sulfuric acid in acetic acid was dehydrated and dimerized to give **5**, (R = 2-thienyl). In contrast, base-catalyzed condensation of 2-furil with diethyl ketone gave directly **5** (R = 2-furyl).[73]

3



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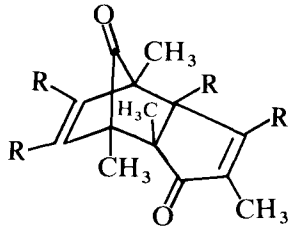
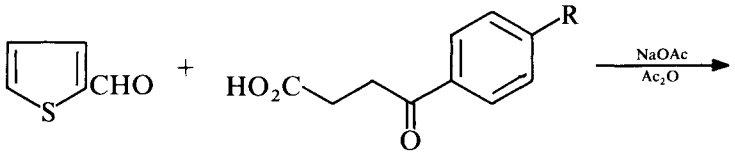


5

The reaction of 5-nitro-2-thiophene aldehyde with ethyl pyruvate in the presence of concentrated sulfuric acid has been used for the preparation of ethyl 5-nitro-2-thenylidene pyruvate.[65] 2-Thiophene aldehyde reacts with 3-aroylpropionic acids **6** or their sodium salts in the presence of acetic anhydride to give cis–trans isomeric enol lactones **7**[74,75] (Scheme 3).



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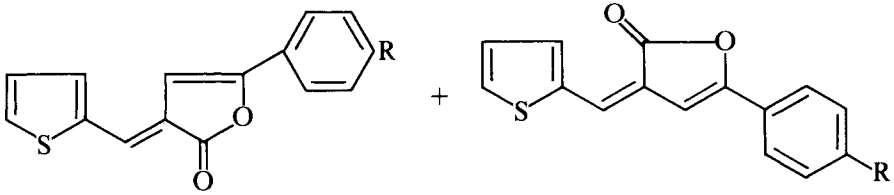
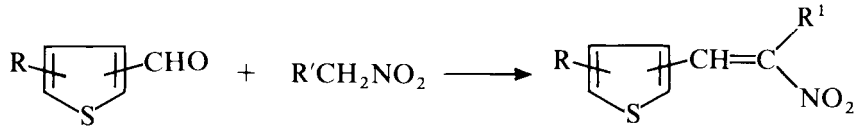


7

Scheme 3

2. Condensation of Thiophene Aldehydes with Nitro Derivatives

Various conditions have been used for the condensation of thiophene aldehydes with nitroalkanes, especially nitromethane, but also nitroethane and phenylnitromethane, which leads to 1-(thienyl)-2-nitroalkenes **8** (Scheme 4). These



R′ = H, CH_3, C_6H_5 **8**

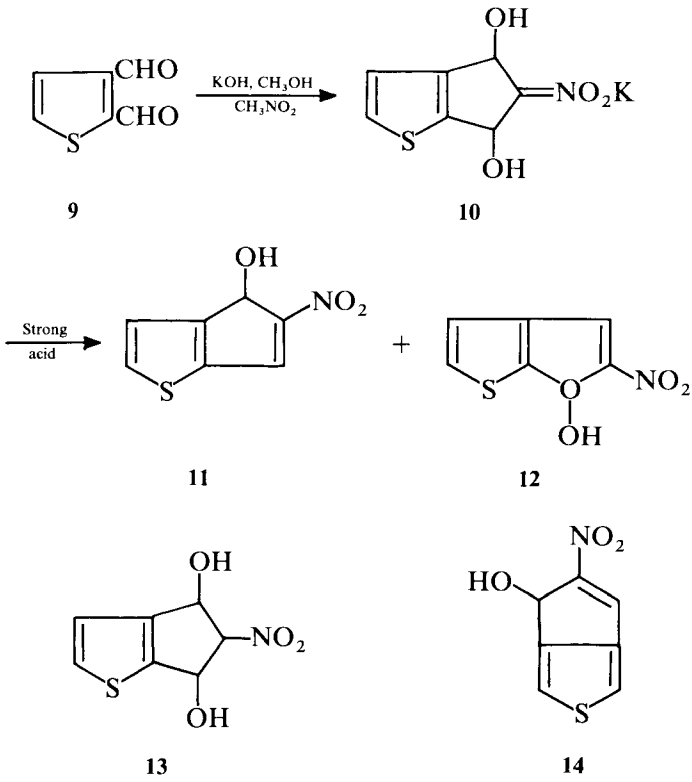
Scheme 4

compounds are important intermediates for the synthesis of other thiophene derivatives and are also of interest for their antibacterial properties.[11,76–81]

The most frequently used method in the reaction with nitromethane is an adaption of the *Organic Synthesis* preparation of β-nitrostyrene.[82] In this preparation, an approximately 50% aqueous solution of sodium hydroxide is added to a methanolic solution of benzaldehyde and nitromethane with cooling. Elimination is achieved by adding the reaction product to hydrochloric acid. The application of these conditions to thiophene aldehydes gave yields varying between 14 and 83%.[80,83–86] In some cases, potassium hydroxide in methanol was used.[11,59,87] The use of magnesium aluminium ethoxide gave lower yields.[83]

Another modification, reported by Russian workers, uses methylamine hydrochloride and sodium carbonate as catalysts in ethanol. Normally yields of about 50% are obtained.[88,89] A third method uses primary amines, such as butylamine or amylamine, reaction times of 3–4 days, and temperatures varying between 25 and 60°C.[84,90–92] Yields of 50–80% were obtained. In a fourth method, developed by Robertson,[93,94] a Schiff base with propyl-, butyl-, or benzylamine is first prepared and then reacted with glacial acetic acid.[93–96] The yields are in most cases better than those obtained with the other methods (> 80%), and this method seems especially useful with nitroethane and phenylnitromethane.

In the condensation of 2-formyl-3-thiophene ethylene acetal and 3-formyl-2-thiophene ethylene acetal with nitromethane, partial hydrolysis of the acetal occurred to give mixtures that could be completely hydrolyzed to 2-(β-nitrovinyl)-3-thiophene aldehyde and 3-(β-nitrovinyl)-2-thiophene aldehyde. Alternatively, the mixture could be transformed to 2-(β-2-nitrovinyl)-3-thiophene ethylene acetal and 3-(β-nitrovinyl)-2-thiophene aldehyde ethylene acetal by acid-catalyzed reaction with ethylene glycol.[87] The reaction of 2,3-diformylthiophene **9** with potassium hydroxide in methanol and nitromethane gave a quantitative yield of potassium 5,6-dihydro-4,6-dihydroxy-4,4-cyclopenta[*b*]thiophene-5-nitrate **10**, which with strong acid gave a 65 : 35 mixture of **11** and **12**, while weak-acid treatment of **10** yielded **13**.[97] In a recent publication, which does not quote Ref. 97, it is claimed that only **11** is obtained in a 53% yield after recrystallization from ethanol.[98] They also obtained **14** in a 12% yield from 3,4-diformylthiophene[98] (Scheme 5).

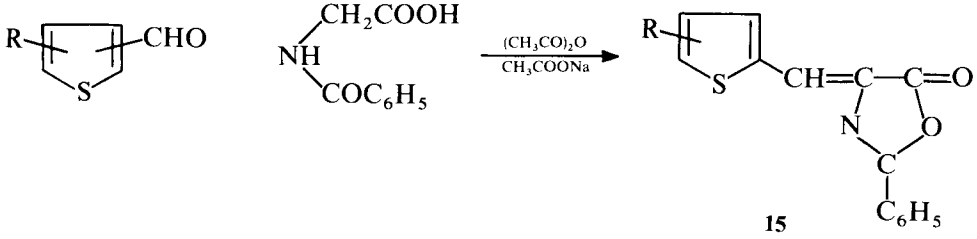


Scheme 5

3. Condensation of Thiophene Aldehydes with Cyclic Active Methylene Derivatives

A. The Erlenmeyer Azlactone Synthesis

The Erlenmeyer azlactone synthesis (Scheme 6), using fused sodium acetate and acetic anhydride, and hippuric acid, has been applied to many thiophene aldehydes[44,74,86,99–103] for the syntheses of 4-(thenal)-5-oxazolines **15**.



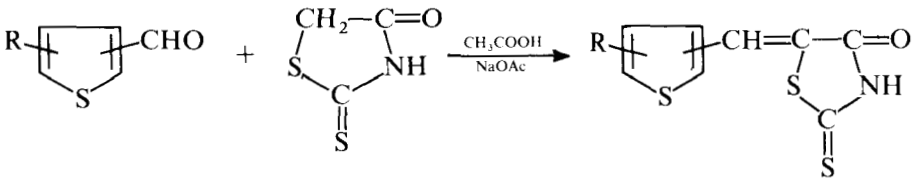
15

Scheme 6

In a few cases, acetylglycine was used.[104,105] 2-Thiophene aldehyde has also been condensed with a number of aroylated glycines.[105] In most cases no mention of stereoisomerism is made, except for the condensation of 4,5-dichloro-2-thiophene aldehyde with hippuric acid.[44] However, no proof for the structure was given and the minor isomer could be due to the presence of an isomeric dichloro-2-thiophene aldehyde.

B. Condensations with Rhodanine

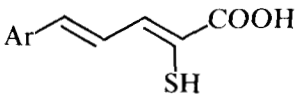
Numerous thiophene aldehydes have also been condensed with rhodanine in glacial acetic acid–sodium acetate to give thenal rhodanines **16** in almost quantitative yields.[49,99,101,106,107] They were mainly prepared as intermediates for the synthesis of α-amino acids,[99] β-thienyl-α-mercaptoacrylic acids[106] and α-keto acids (Scheme 7).



16

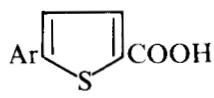
Scheme 7

Besides thiophene aldehydes, thienyl acroleins, such as 2-thienyl acrolein, 2-chloro-3-thiophene acrolein, and 2,5-dichloro-3-thiophene acrolein, were also condensed with rhodanine, which were hydrolyzed to **16a** and then oxidatively ring-closed to **16b**. Similarly, condensation of the aldehyde **16c** with rhodanine gave **16d**, which after hydrolysis and ring-closure led to **16e**.[108]

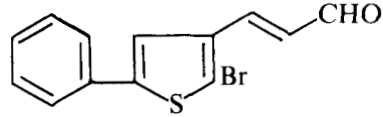


16a

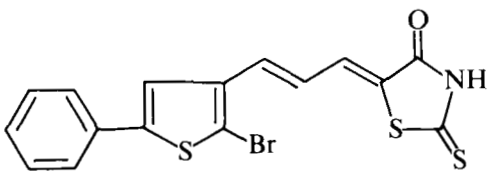
Ar = 2-Th, 2-Cl-3-Th, 2,5-di-Cl-3-Th



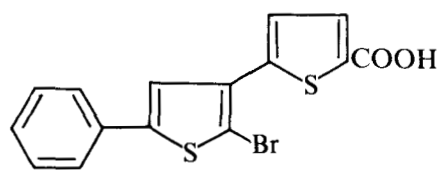
16b



16c



16d

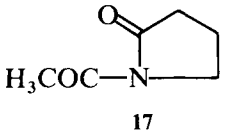


16e

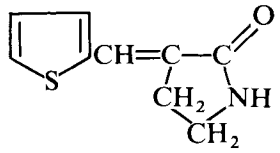
Some rhodanine derivatives of 2-acetylthiophenes have also been prepared through the reaction of the ketones in concentrated ammonia and alcohol. The yields averaged about 30%. The mildew-preventing activity of these and some other rhodanine derivatives has been studied.[109] Some N-methylated, phenylated, and allylated rhodanines have also been condensed with 2-thiophene aldehyde.[110]

C. Various Other Condensations

Thiophene aldehydes have also been condensed with other cyclic active methylene derivatives. The condensation of 2-thiophene aldehyde with **17**, using sodium hydride in THF as base, gave **18** in a 45% yield after acid hydrolysis.[111]

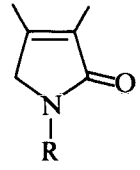


17



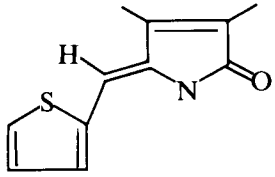
18

Condensation of 2-thiophene aldehyde with **19** (R = H), using 4 N sodium hydroxide in methanol, gave the *Z*-isomer **20** (R = H), which could be photochemically isomerized to the *E*-isomer **21** (R = H). Condensation of **19** ($R = CH_3$) gave mixtures of the *Z*- and *E*-isomers.[112] Condensation of 2-thiophene aldehyde with **22**, using trifluoroacetic acid, yielded **23**.[113] The



R = H, CH_3

19



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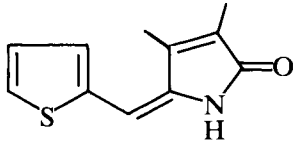

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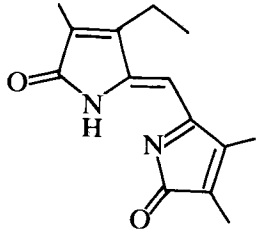

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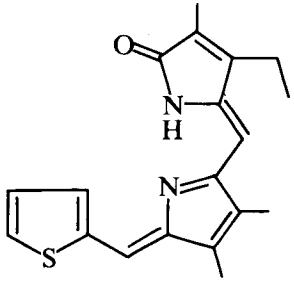

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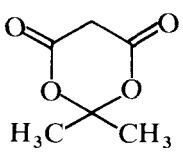

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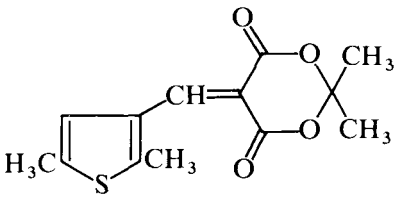

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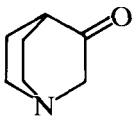

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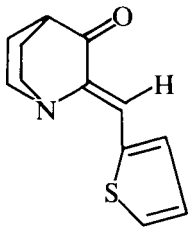

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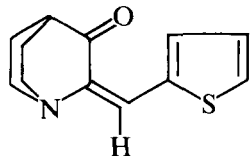
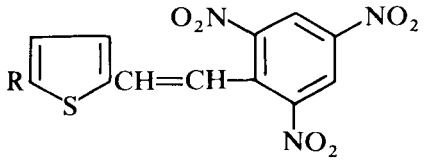


28

reaction of 2,5-dimethyl-3-thiophene aldehyde with **24**, using piperidine and acetic acid in benzene, yielded **25**, which on pyrolysis gave 2-methyl-benzo[*b*]thiophen-6-ol.[114] Condensation in alkaline medium of **26** with 2-thiophene aldehyde gave the *cis*-isomer **27**, which on treatment with hydrogen chloride isomerized to the *trans*-isomer **28**.[115] Barbituric acid has been condensed with 2-thiophene aldehyde[116] and 2,5-diformylthiophene.[117]

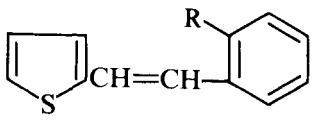
4. Condensation of Thiophene Aldehydes with Acidic Methyl Groups Bound to Rings

Methyl groups bound to electron-withdrawing rings have been condensed with various thiophene aldehydes. Thus, 2-thiophene aldehyde, 5-chloro-, and 5-methyl-2-thiophene aldehyde, with 2,4,6-trinitrotoluene, using piperidine in xylene and a Dean–Stark trap, gave 68% of **29**.[49,118] 2,5-Dimethyl-3-thiophene aldehyde has also been condensed with 2,4,6-trinitrotoluene.[118] 1-(2-Thienyl)-2-(*o*-carboxyphenyl)ethylene **30** (R = COOH) and 1-(2-thienyl)-2-(*o*-cyanophenyl)ethene **30** (R = CN) have been obtained by condensation of 2-thiophene



R = H, CH_3, Cl

29

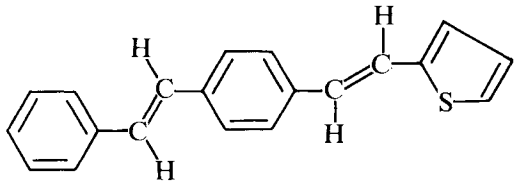


R = CN, COOH

30

aldehyde with ethyl *o*-methylbenzoate and *o*-methylbenzonitrile.[119] If the anil of 2-thiophene aldehyde is used, condensation with various methyl-substituted aromatic carbocycles can be achieved, if the reaction is carried out in *N,N*-dimethylformamide in the presence of potassium hydroxide or potassium *t*-butoxide. Compounds **31–35** were prepared in this way.[120,121] 3-Cyano-4-methylpyridine was condensed with 2- and 3-thiophene aldehyde, using *t*-butoxide in *t*-butanol–benzene or sodium methoxide in methanol to give the *trans*-amides, compounds **42** and **43**, respectively.[122]

In connection with investigations of the properties of surfactant complexes, a number of compounds of types **36** and **37** were obtained (R = C_2H_5, C_6H_{13},



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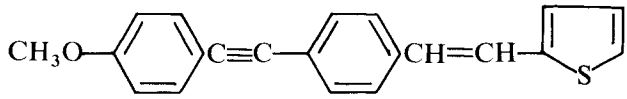

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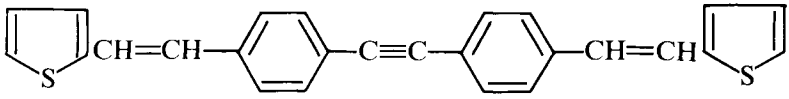

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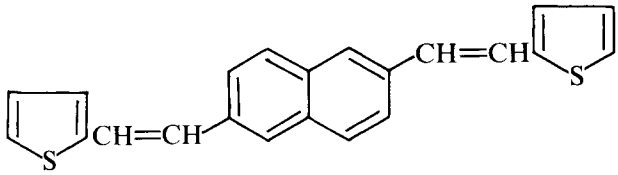

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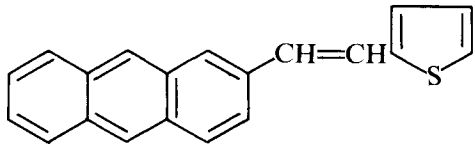

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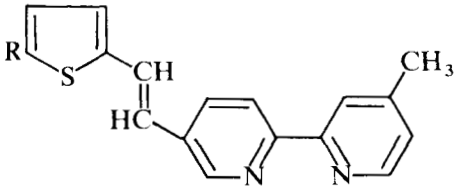
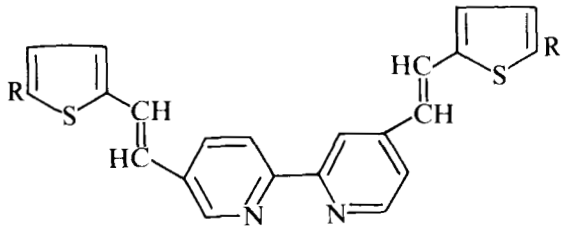
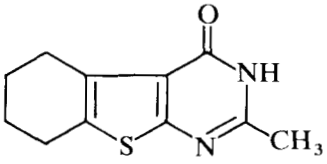
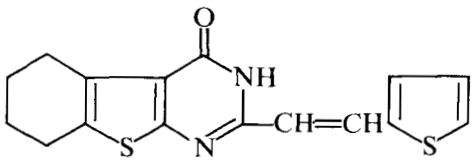




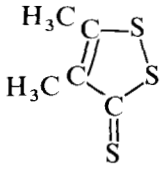
$R = C_2H_5, C_6H_{13}, C_{10}H_{21}, C_{12}H_{25}, C_{14}H_{29}$

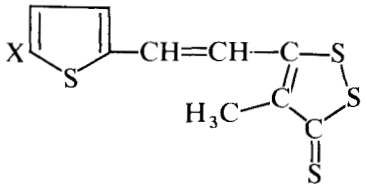
36 **37**





38 **39**





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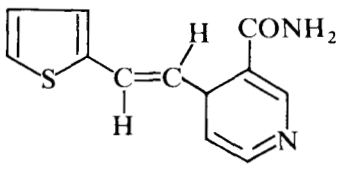
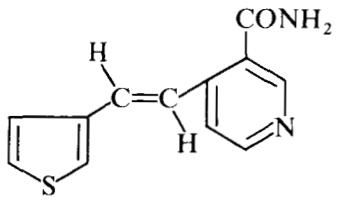
$X = H, Br$

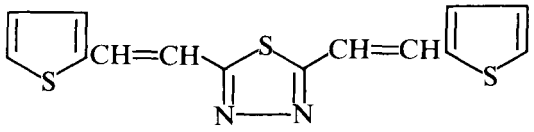
41





42 **43**

$C_{10}H_{21}$, $C_{12}H_{25}$, $C_{14}H_{29}$) through the reaction of 5-substituted 2-thiophene aldehydes with 4,4′-dimethyl-2,2′-bipyridyl in refluxing butyric anhydride. Compounds **36** and **37** could easily be separated, and their relative proportions depend on the proportions of the reagents.[123] The condensation of 2-thiophene aldehyde with **38** gave **39**.[124] The 1,2-dithiol-3-thione **40** was condensed with 2-thiophene aldehyde and 5-bromo-2-thiophene aldehyde, using piperidine as a catalyst, to give **41**, in connection with the synthesis of compounds with schistosomocidal activity. 2-Thiophene aldehyde was condensed with 2,5-dimethyl-1,3,4-thiadiazole to give **44** in connection with work on



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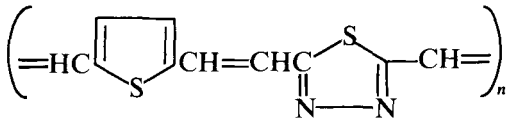
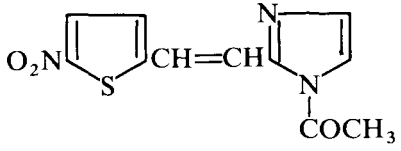


45

polyheteroarylene alkenylenes.[125] Benzoic anhydride was used as a condensating agent. When 2,5-thiophene dialdehyde was used in this reaction, polymeric **45** was obtained.

5-Nitro-2-thiophene aldehyde was condensed with 2-methylimidazole and 2-methylbenzimidazole in acetic anhydride acetic acid to give the N-acylated derivative **46** as an intermediate, which was subsequently deacetylated by hydrolysis with 6 M hydrochloric acid.[126] The same condensation method was also applied to 2-methylpyridine and 2-methylquinazoline to give directly **47** and **48**.[126] In a similar way, 5-nitro-2-thiophene aldehyde was condensed with 2-methyl-5-acetylamino-1,3,4-thiadiazole to give **50**.[127]



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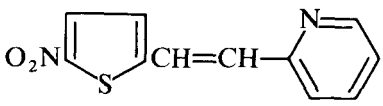

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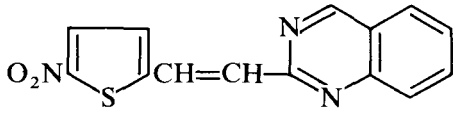

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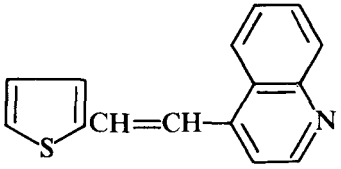

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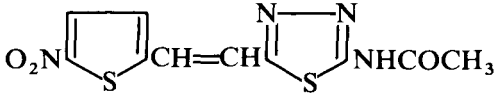

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