THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

ARNOLD WEISSBERGER, *Founding Editor*

THIOPHENE AND ITS DERIVATIVES

Part Five

Edited by

Salo Gronowitz

University of Lund
Lund, Sweden

AN INTERSCIENCE® PUBLICATION

JOHN WILEY AND SONS

NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

In recognition of the importance of preserving what has been written, it is a policy of John Wiley & Sons, Inc., to have books of enduring value published in the United States printed on acid-free paper, and we exert our best efforts to that end.

Copyright © 1992 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction of translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

(Revised for vol. 5)

Thiophene and its derivatives.

(The Chemistry of heterocyclic compounds, 0069-3154; v. 44)
"An Interscience publication."
Includes bibliographies and indexes.
1. Thiophene. I. Gronowitz, Salo. II. Series.
QD403.T55 1985 547'.594 84-15356
ISBN 0-471-38120-9 (v. 1)
ISBN 0-471-52944-3 (v. 5)

Contributors

Torbjörn Frejd, *Division of Organic Chemistry 2, Chemical Center, University of Lund, Lund, Sweden*

Salo Gronowitz, *Division of Organic Chemistry 1, Chemical Center, University of Lund, Lund, Sweden*

Rolf Håkansson, *University College of Kalmar, Kalmar, Sweden*

Anna-Britta Hörnfeldt, *Division of Organic Chemistry 1, Chemical Center, University of Lund, Lund, Sweden*

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

Department of Chemistry
Princeton University
Princeton, New Jersey

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

Contents

I. Vinylthiophenes and Thienylacetylenes 1
SALO GRONOWITZ and ANNA-BRITTA HÖRNFELDT

II. Organometallic Derivatives of Thiophenes 257
TORBJÖRN FREJD

III. Syntheses, Reactions, and Physical Properties of Bithienyls and Polythienyls and Closely Related Compounds 755
ROLF HÅKANSSON

Index 907

THIOPHENE AND ITS DERIVATIVES

Part Five

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

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

CHAPTER I

Vinylthiophenes and Thienylacetylenes

Salo Gronowitz and Anna-Britta Hörnfeldt

Division of Organic Chemistry 1
Chemical Center
University of Lund
Lund, Sweden

I. Introduction 3
II. Preparation of Vinylthiophenes 4
1. Condensation of Thiophene Aldehydes with Aldehydes and Ketones 4
A. Aldol Condensations 4
B. Claisen–Schmidt Condensations 5
C. Various Other Condensations 6
2. Condensation of Thiophene Aldehydes with Nitro Derivatives 6
3. Condensation of Thiophene Aldehydes with Cyclic Active Methylene Derivatives 8
A. Erlenmeyer Azlactone Synthesis 8
B. Condensations with Rhodanine 9
C. Various Other Condensations 10
4. Condensation of Thiophene Aldehydes with Acidic Methyl Groups Bound to Rings 11
5. Condensation of Thiophene Aldehydes with Active Methylene Derivatives, Malonic Esters, Malonitriles, and Related Compounds; Preparation of 3-(Thienyl)acrylic Acids 17
A. Knoevenagel Reaction 17
B. Perkin Reaction 18
C. Mixed Claisen Condensation 18
D. Condensation with Arylacetic Acids 18
E. Condensation with Ethyl Azidoacetates 19
F. Other Condensation Reactions 19
6. Stobbe Condensation 26
7. Condensation of Thiopheneacetic Acids and Thenyl Cyanides with Aromatic Aldehydes 31
A. Thiopheneacetic Acids 31
B. Thenyl Cyanides 32
8. Condensation of Activated Methylthiophenes with Aldehydes 33
9. Wittig Reaction 34
A. From Thenyl Triphenylphosphonium Halides and Aldehydes 34
B. The Phosphonate Method (Wadworth–Emmons–Horner Reaction) 42
C. From Thiophene Aldehydes and Triphenylalkylphosphonium Salts 43
D. From Thiophene Aldehydes and Phosphonates 49

The Chemistry of Heterocyclic Compounds, Volume 44: Thiophene and Its Derivatives, Part Five, Edited by Salo Gronowitz.
ISBN 0-471-52944-3 © 1992 John Wiley & Sons, Inc.

10. Dehydration of 1-(Thienyl)carbinols 52
A. Introduction 52
B. Dehydration of Secondary Alcohols Obtained by Reduction of Thiophene Ketones 52
C. Dehydration of Alcohols Obtained from Thienyl Metal Derivatives and Carbonyl Compounds 56
D. Dehydration of Alcohols Obtained from Thiophenecarbonyl Derivatives and Organometallic Reagents 62
E. Dehydration of Alcohols Obtained from Thiophenecarbonyl Compounds through the Reformatsky Reaction 65
11. Dehydration of 2-(2-Thienyl)alkanols 66
12. Dehydrohalogenation of 1-(Thienyl)alkyl Halides 67
13. From Thiophenecarbonyl Compounds by Various Other Methods 68
14. From Thiophenes, Halothiophenes, and Thienyl Metal Derivatives and Alkenes 74
A. From Thiophenes and Alkenes 74
B. Transition-Metal-Catalyzed Couplings 76
15. Vinylthiophenes via Ring-Closure Reactions 80
16. Vinylthiophenes via Isomerizations and Rearrangements 83
17. Vinylthiophenes via Ring Opening of Thiophene-Fused Ring Systems 84
18. Vinylthiophenes from Alkylthiophenes 85
19. Various Other Methods 86
III. Reactions of Vinylthiophene Derivatives 91
1. Reactions with Conservation of the Double Bond 91
2. Electrophilic Substitution on Vinylthiophenes 95
3. Ring-Closure Reactions of Vinylthiophenes with Conservation of the Double Bond 97
4. Reactions with Addition to the Double Bond 112
A. Catalytic Hydrogenation 112
B. Hydride Reductions 113
C. Various Other Reductions 114
D. Electrophilic Additions 115
E. Addition of Sulfur-Containing Groups 116
F. Addition of Nitrogen Nucleophiles 117
G. Michael Additions of Carbanions to Vinylthiophenes 120
5. Dimerization Reactions of Vinylthiophenes 122
6. Cycloadditions of Vinylthiophenes 122
7. Polymerization of Vinylthiophenes 131
IV. Vinylthiophenes of Potential Pharmaceutical Interest 131
V. Physical Properties of Vinylthiophenes 132
VI. Thiophenes with Cumulative Double Bonds 133
1. Two Cumulative Bonds (Allenes) 133
2. Three Cumulative Bonds 133
3. Four Cumulative Bonds 134
VII. Preparation of Thienylacetylenes 135
1. From Thiophenecarbonyl Derivatives 135
2. From Vinylthiophenes 137
3. From Iodothiophenes and Cuprous Acetylides 138
4. Palladium-Catalyzed Synthesis from Halothiophenes and Acetylides 139
5. Ring-Closure Reactions to Thienylacetylenes 140
6. Thienylacetylenes from Precursors Containing Triple Bonds 140
VIII. Reactions of Thienylacetylenes 144
IX. Physical Properties of Thienylacetylenes 148
X. Naturally Occurring Thienylacetylenes 148
XI. Tables of Compounds 148
References 230

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.

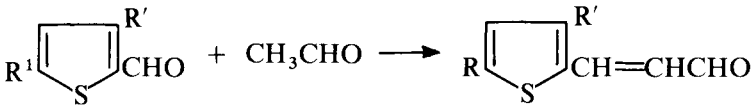
More unusual methods, such as the preparation through ring-closure reactions, and from precursors, containing a triple bond, are covered in Sections VII.5 and VII.6. The reactions of thienylacetylenes are discussed in Section VIII. For the same reasons as in the section on vinylthiophenes, only a brief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

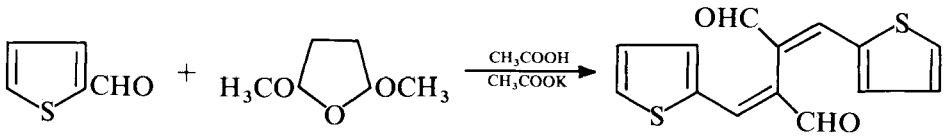
A. Aldol Condensations

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

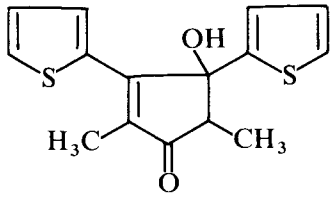
Numerous examples of the Claisen–Schmidt condensation between thiophene aldehydes and aryl methyl ketones have been reported. They were carried out in connection with studies of the chemical and physical properties of thiophene analogues of chalcones. Among the aryl methyl ketones used are acetophenone,[41,43] 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]

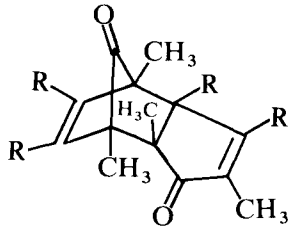
C. Various Other Condensations

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

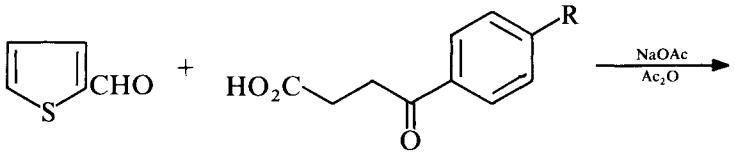


4

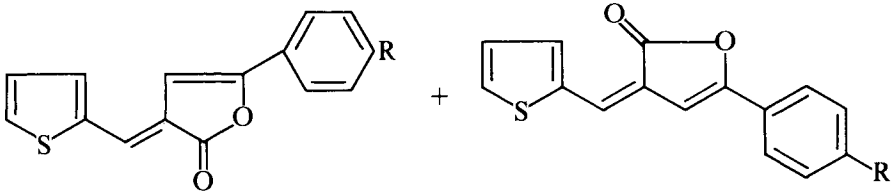


5

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).



6

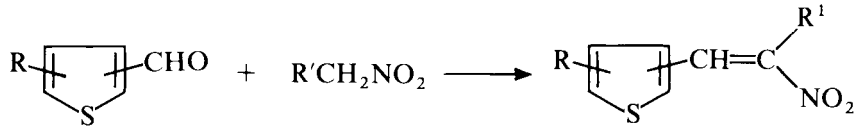


7

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**

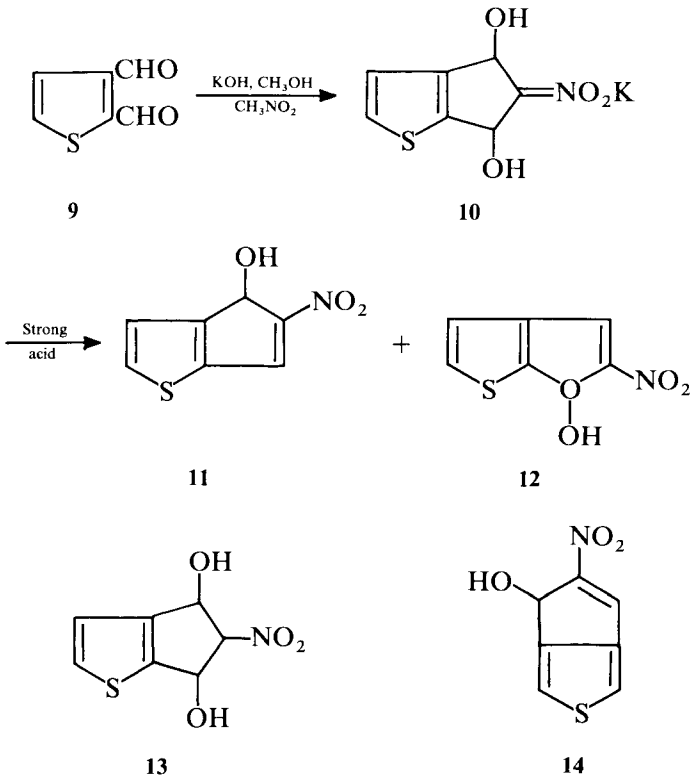
Scheme 4

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).

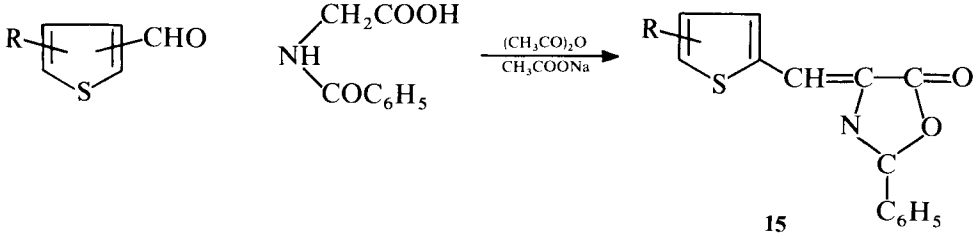


Scheme 5

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**.



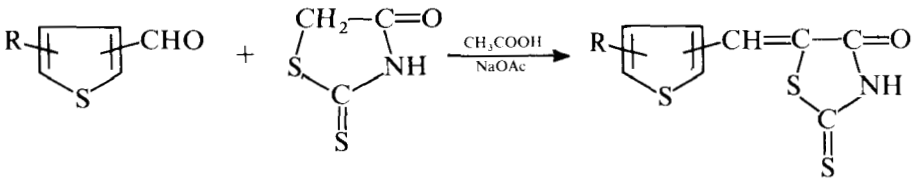
15

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

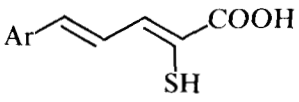
Numerous thiophene aldehydes have also been condensed with rhodanine in glacial acetic acid–sodium acetate to give thenal rhodanines **16** in almost quantitative yields.[49,99,101,106,107] They were mainly prepared as intermediates for the synthesis of α-amino acids,[99] β-thienyl-α-mercaptoacrylic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



16

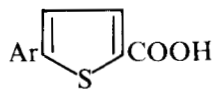
Scheme 7

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]

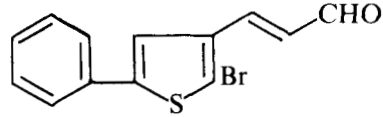


16a

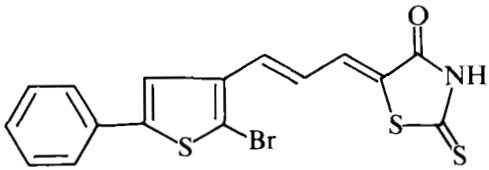
Ar = 2-Th, 2-Cl-3-Th, 2,5-di-Cl-3-Th



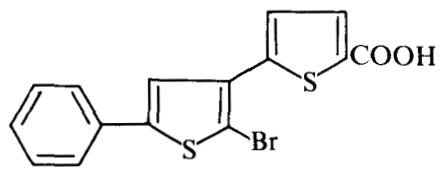
16b



16c



16d

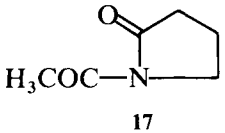


16e

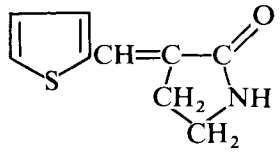
Some rhodanine derivatives of 2-acetylthiophenes have also been prepared through the reaction of the ketones in concentrated ammonia and alcohol. The yields averaged about 30%. The mildew-preventing activity of these and some other rhodanine derivatives has been studied.[109] Some N-methylated, phenylated,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

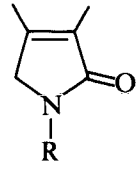


17



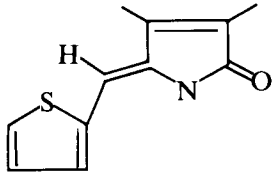
18

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

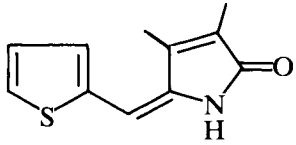


R = H, CH_3

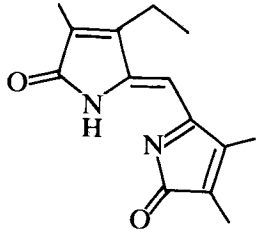
19



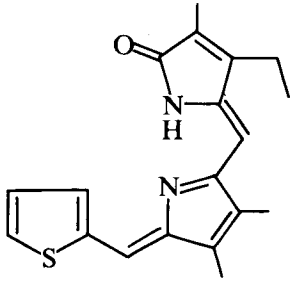
20



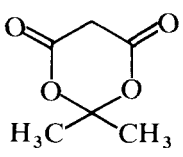
21



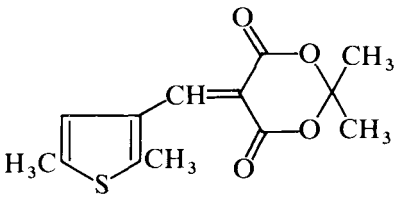
22



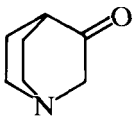
23



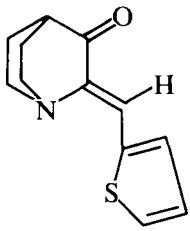
24



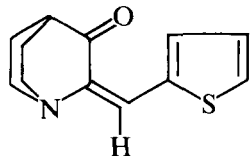
25



26



27

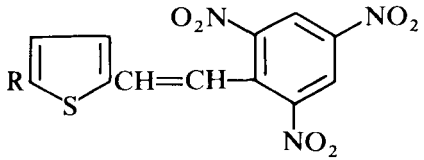


28

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]

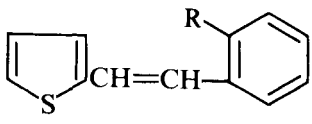
4. Condensation of Thiophene Aldehydes with Acidic Methyl Groups Bound to Rings

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

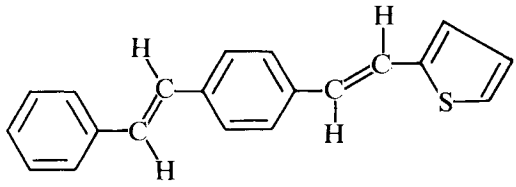


R = CN, COOH

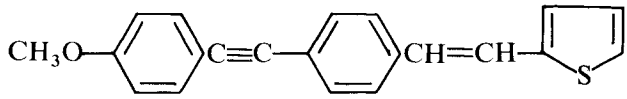
30

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]

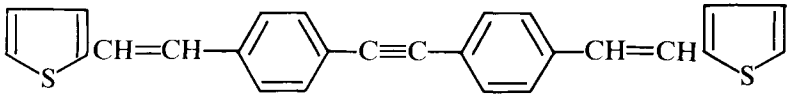
In connection with investigations of the properties of surfactant complexes, a number of compounds of types **36** and **37** were obtained (R = C_2H_5, C_6H_{13},



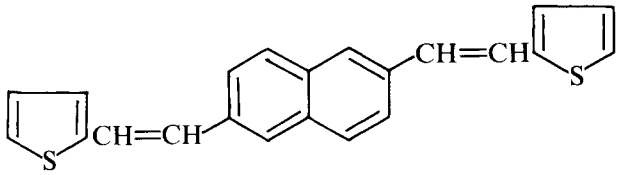
31



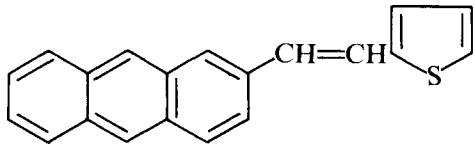
32



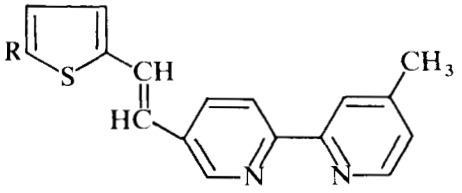
33

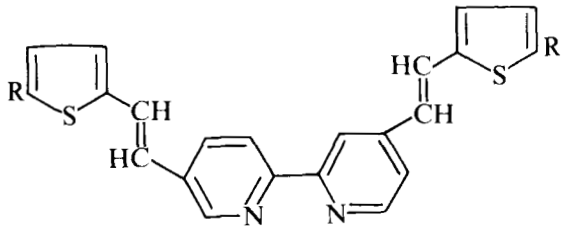


34



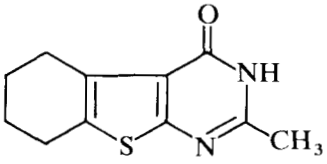
35

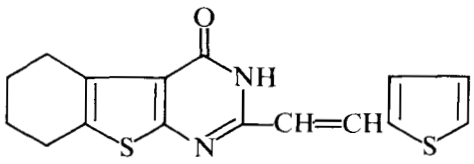




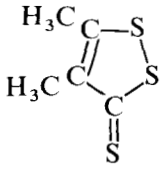
$R = C_2H_5, C_6H_{13}, C_{10}H_{21}, C_{12}H_{25}, C_{14}H_{29}$

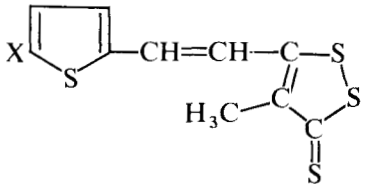
36 **37**





38 **39**

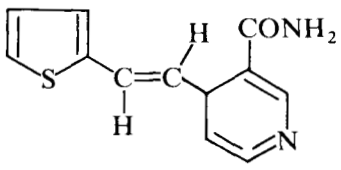


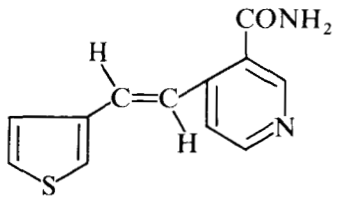


40

$X = H, Br$

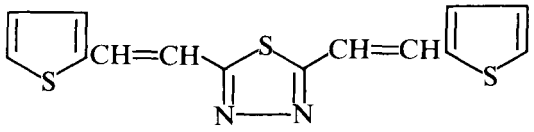
41



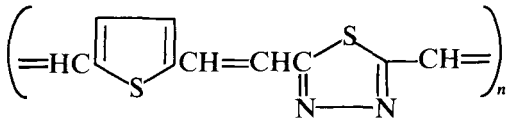


42 **43**

$C_{10}H_{21}$, $C_{12}H_{25}$, $C_{14}H_{29}$) 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



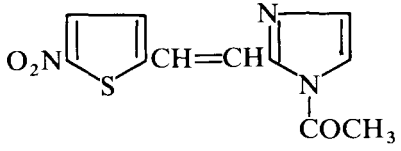
44



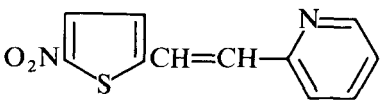
45

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.

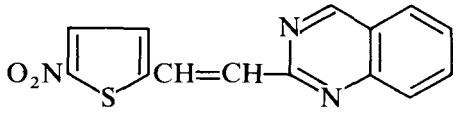
5-Nitro-2-thiophene aldehyde was condensed with 2-methylimidazole and 2-methylbenzimidazole in acetic anhydride acetic acid to give the N-acylated derivative **46** as an intermediate, which was subsequently deacetylated by hydrolysis with 6 M hydrochloric acid.[126] The same condensation method was 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]



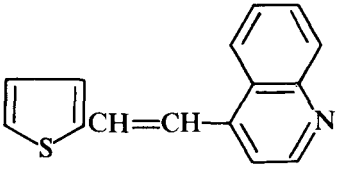
46



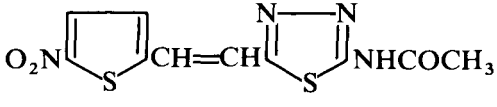
47



48

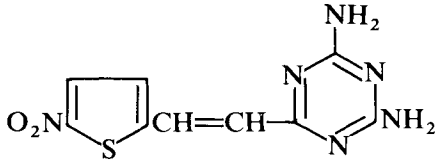


49

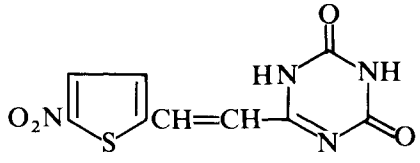


50

5-Nitro-2-thiophene aldehyde was condensed with 2,4-diamino-6-methyl-*s*-triazine and 2,4-dichloro-6-methyl-*s*-triazine, using concentrated sulfuric acid and 5% hydrochloric acid in ethanol as a condensating agent, to give **51** and **52**, respectively.[128] All of these condensation products of 5-nitro-2-thiophene aldehyde were prepared in order to evaluate their pharmacologic properties.



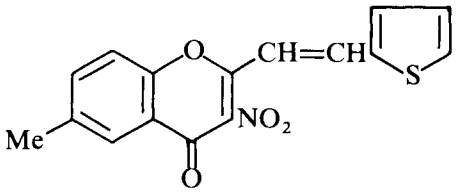
51



52

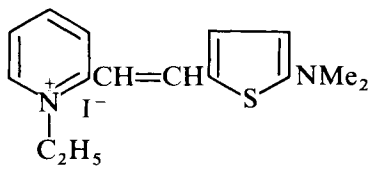
In another modification, 2-thiophene aldehyde was condensed with 4-methylquinoline by heating, with its hydrochloride to 160–170°C, to give **49**.[129]

In connection with the synthesis of some pyrrolo[3,2-*b*][1]benzopyrans, the styrylchromanone **53** was prepared by the condensation of 2-thiophene aldehyde with 2,6-dimethyl-3-nitrochromone, using piperidine in methanol as a condensating agent.[130]

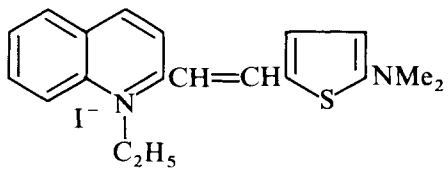


53

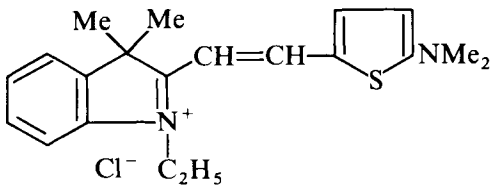
In connection with work on mono- and dimethine dyes from 5-dimethylamino-2-thiophene aldehyde, compounds **54–56**[131] and **57–59** were obtained,[132] using various condensating agents, such as acetic anhydride.



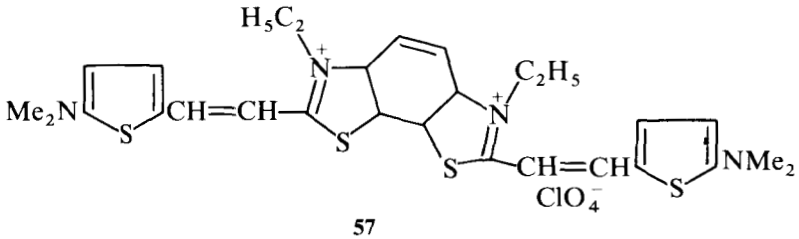
54



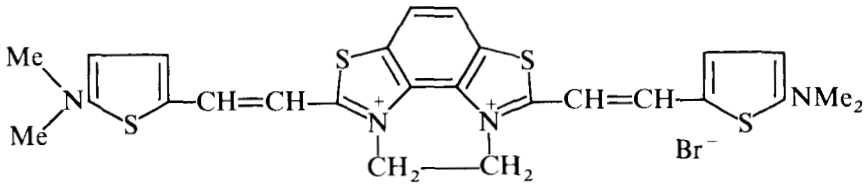
55



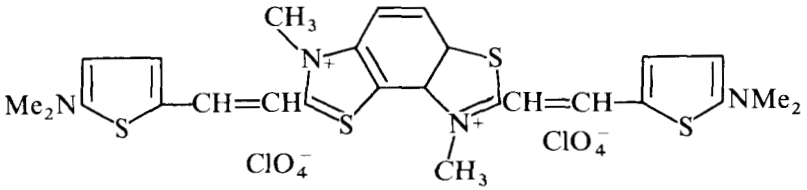
56



57

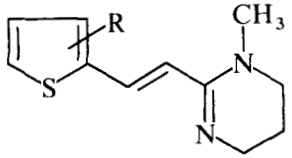


58



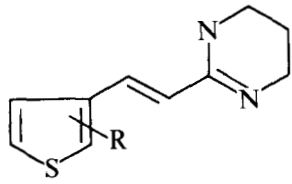
59

Condensation of 2-thiophene aldehyde with 2-benzylpyridine using acetic anhydride gave 1-phenyl-1-(2-pyridyl)-2-(2-thienyl)ethene.[133] Extensive work on this type of condensation has been carried out in connection with the synthesis of the anthelmintic agent pyrantel **60a** and other cyclic amidines, imidazolines, and thiazolines. Some of the *trans*-isomers of **60** were converted to the *cis*-isomers by the use of sunlight. The reaction was carried out in refluxing toluene, using a Dean–Stark trap.[134–138] The compounds were isolated as



a R = H
b R = 3-CH_3
c R = 4-CH_3
d R = 3-C_2H_5
e R = 3-Br
f R = 5-CH_3

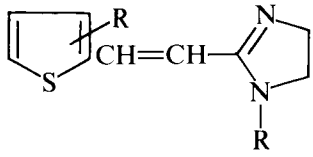
60



a R = H
b R = CH_3

61

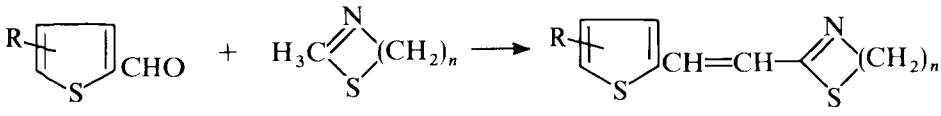
various salts. In another modification, ethyl acetate was used as a solvent and hydrogen chloride as a catalyst. In this way **60a–f** were prepared, although the 3-methyl isomers were not isomerically pure, due to difficulties in obtaining pure 3-methyl-2-thiophene aldehyde. Compounds **61a–b** were prepared in the same way.[135,139] Fluoride catalysis in the condensation of 2-thiophene aldehydes and 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine has also been studied.[140]



a R = H
b R = 3-CH_3

62

The condensation of 2-thiophene aldehydes and other aromatic aldehydes with 2-methyl-2-thiazoline **63** ($n = 2$) and with 5,6-dihydro-2-methyl-4*H*-1,3-thiazines **63** ($n = 3$) in refluxing xylene, using a Dean–Stark moisture trap, was used for the preparation of 2-(thienylvinyl)thiazolines **64** ($n = 2$) and 2-(thienylvinyl)dihydrothiazines **64** ($n = 3$) (Scheme 8).[141,142]



$n = 2, 3$ $n = 2, 3$
63 **64**

Scheme 8

5. Condensation of Thiophene Aldehydes with Active Methylene Derivatives, Malonic Esters, Malonitriles, and Related Compounds; Preparation of 3-(Thienyl)acrylic Acids

A. Knoevenagel Reaction

The Doebner modification of the Knoevenagel condensation, using malonic acid, pyridine, and piperidine, has been successfully applied to 2-thiophene aldehydes[13,22,83,86,116,143–159] and 3-thiophene aldehydes.[36,160–162] From the 3-(thienyl)acrylic acids thus obtained esters were prepared, giving yields of about 80%.

Alternatively, Knoevenagel condensation was carried out with esters of malonic acid, using piperidine and benzoic acid as a catalyst and benzene as a solvent, as in the preparation of diethyl 2-thenalmalonates.[152,154,155,163–167]

B. Perkin Reaction

The Perkin reaction, using acetic anhydride and sodium acetate, is claimed not to work well with 2-thiophene aldehyde.[83,146,147] Although a 63% yield has been obtained with 2,3-dichloro-5-thiophene aldehyde.[154] The Perkin reaction also appears to work well with 5-nitro-2-thiophene aldehyde,[7] and has also been carried out between 2-thiophene aldehyde and propionic acid.[168]

C. Mixed Claisen Condensation

A third way of preparing 3-(thienyl)acrylates is the mixed Claisen condensation of thiophene aldehydes with methyl or ethyl acetate, utilizing sodium ethoxide in xylene.[83,156] By carrying out the reaction at -10 to -15°C, yields of up to 50% could be achieved. The Claisen synthesis is not as useful as the Doebner modification and sometimes fails, as with 5-chloro-2-thiophene aldehyde, which gives 5-chloro-2-thiophenecarboxylic acid as the main product.[83] The compounds obtained in the Claisen condensation and in the Doebner modification are the *trans*-isomers, as shown by ^{1}H NMR.[156,157,167,169] However, if the thenaldicarboxylic acids are first prepared by the Knoevenagel reaction of 5-substituted 2-thiophene aldehydes (triethylamine and malonic acid in glacial acetic acid)[154,171] and then decarboxylated in acetic anhydride at 140°C, a mixture of *cis*- and *trans*-acrylic acids is obtained, containing about 5% of the *cis*-isomers, which could be separated by chromatography or fractional crystallization. All the *cis*-isomers were photochemically converted to the *trans*-isomers.[171]

Esters of the 3-(thienyl)acrylic acids were usually prepared by esterification, using small amounts of concentrated sulfuric acid,[161] or, for the methylester, methanol and hydrochloric acid as catalysts,[157,170] or via the acid chlorides.[145] Alternatively, the esters were obtained directly as mentioned above through the Claisen condensation or by carrying out the Doebner modification with ethyl or methyl hydrogen malonate.[161,162] The Doebner reaction has also been carried out with methyl malonic acid.[169] Half-amides of malonic acid, such as malono-*p*-iodoanilic acid[1023] and malono-*o*-anisidic acid, have also been condensed with 2-thiophene aldehyde, according to Knoevenagel. β-(Thienyl)acrylic acids were obtained as by-products in the syntheses of β-amino acids of the thiophene series, in which thiophene aldehydes were reacted with malonic acid and ammonium acetate in ethanol (Rodionov reaction).[172,173] Reducing the reaction times with 5-methyl- and 5-ethyl-2-thiophene aldehyde gave good yields of the acid ammonium salts of (5-methyl-2-thienyl)methylene malonic acid and (5-ethyl-2-thienyl)methylene malonic acid.[172]

D. Condensation with Arylacetic Acids

Thiophene aldehydes have been condensed in a Perkin-type reaction with arylacetic acids, using triethylamine and acetic anhydride.[152,169,174–181] A

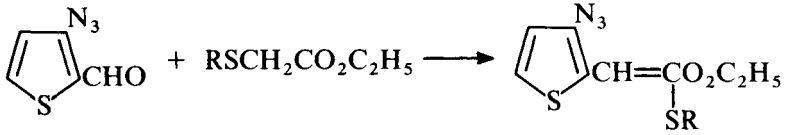
mixture of *E*- and *Z*-isomers is usually obtained, which has been separated by fractional crystallization. The structure was often established by ^{1}H NMR after decarboxylation.

E. Condensation with Ethyl Azidoacetates

Condensation of thiophene aldehydes with ethyl azidoacetate, using sodium ethoxide in ethanol, has been used for the preparation of 3-(thienyl)-2-azidoacrylic esters.[166,182–186] These compounds have been used in the synthesis of thienopyrroles. The reaction with 2,5- and 3,4-diformylthiophene gave a mixture of the mono and di condensation products, while 2,3- and 2,4-diformylthiophene gave the two mono condensation products and the di condensation product.[170,184] In order to obtain more well-defined products, one of the aldehyde groups was protected as the acetal before the condensation.[185,187]

F. Other Condensation Reactions

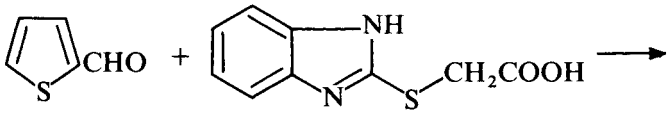
Condensation of 3-azido-2-thiophene aldehyde **65** with ethyl phenylthioacetate and with ethyl ethylthioacetate, using sodium ethoxide in ethanol, gave **66** in high yields.[188,189] 3-Azido-2-thiophene aldehyde has also been condensed with ethyl(phenylsulfinyl)acetate and ethyl(phenylsulfonyl)acetate, using piperidinium acetate in ethanol, to give the corresponding 3-(3-azido-2-thienyl)acrylic esters.[188]



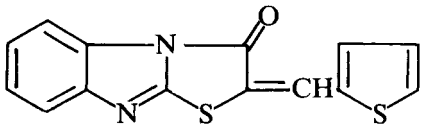
65 **66**

R = CH_3, C_6H_5

The condensation of 2-thiophene aldehyde with (*o*-nitrophenylthio)acetic acid was carried out, using ammonium acetate and piperidine in acetic acid.[190]



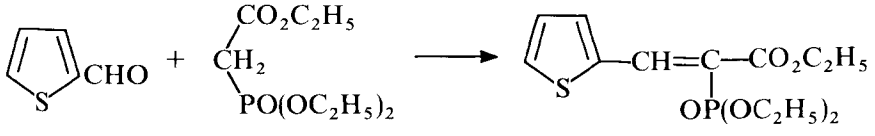
67



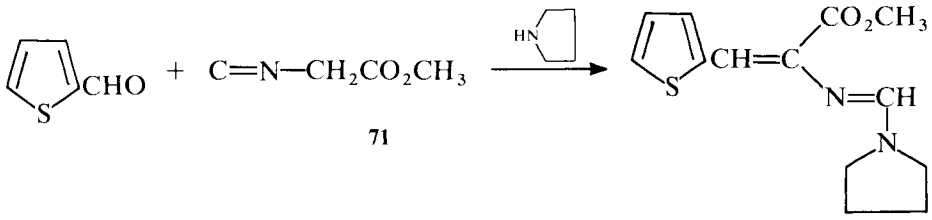
68

The condensation of 2-thiophene aldehyde with (2-benzimidazolylthio)acetic acid **67** in the presence of acetic anhydride potassium acetate gave directly **68**.[191]

In the presence of titanium tetrachloride and an organic base in THF, triethyl phosphonoacetic acid **69** undergoes condensation with many aldehydes, including 2-thiophene aldehyde, to give **70**.[192] This methodology has been employed in the condensation of 2-thiophene aldehyde with ethyl acetoacetate and ethyl nitroacetate to give ethyl 2-acetyl- and ethyl 2-nitro-3-(2-thienyl)acrylate.[193] The reaction of methyl isocyanoacetate **71** with 2-thiophene aldehyde in the presence of secondary amines gave methyl α-[(amino)methylene]acrylates **72**, with the *E*-isomer as the predominant product.



69 **70**



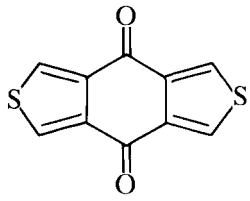
71 **72**

The reaction is assumed to proceed by a Michael-type addition of the amine to the methyl α-isocyanoacrylate, followed by a synchronous elimination–insertion of the amine into the isocyano group.[194] If 2-thiophene aldehyde and methyl isocyanoacetate were reacted with sodium hydride as a base, the α-formylaminoacrylates were obtained, which were readily converted to methyl α-isocyanoacrylates, using phosphoryl chloride in the presence of triethylamine.[194]

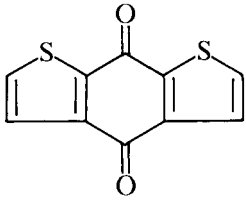
The condensation of 2-thiophene aldehyde and ethyl cyanoacetate to produce 2-cyano-3-(thienyl)acrylic esters has been carried out in the absence of solvent, using piperidine as a catalyst.[155,195] In other cases, sodium ethoxide in ethanol,[196,197] piperidine in ethanol,[198,199] or glacial acetic acid[200] was used. Phenyl 2-thienyl ketone has also been reacted with ethyl cyanoacetate, using ammonium acetate and acetic acid in toluene as a condensating agent.[201,202] β-(Thienyl)acrolein was condensed with ethyl cyanoacetate to give ethyl 2-cyano-5-(2-thienyl)-2,4-pentadiene-1-carboxylate in a 90% yield.[15]

2-Acyl-3-(thienyl)acrylic acids and esters have been prepared through condensation of thiophene aldehyde with 1,3-keto esters, using piperidine in ethanol[155,188,203] as a catalyst. High yields were obtained below room temperature in the presence of titanium tetrachloride.[193]

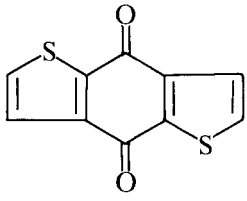
3-(Thienyl)acrylonitriles are easily prepared through the condensation of thiophene aldehydes and ketones with malonitriles, using a few drops of pyridine or triethylamine[152,164,204–209] or sodium ethoxide[196,197] in ethanol as a solvent. For alkyl 2-thienyl ketones, the reaction was carried out with ammonium acetate in glacial acetic acid–toluene, and water was separated off with a Dean–Stark trap.[208,210,211] Condensation of *p*-tolyl-2-iodo-5-thienyl ketone with malonitrile gave the desired condensation product in a 20–30% yield.[212,213] The yield decreased with branching of the chain. In order to obtain a good yield of **77–80** from the ketones **73–76**, the titanium tetrachloride-mediated condensation with malonitrile in pyridine chloroform had to be used.[214,215] Compounds **77–80** are of interest in connection with studies on conducting charge-transfer salts.



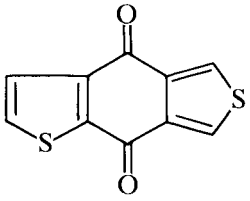
73



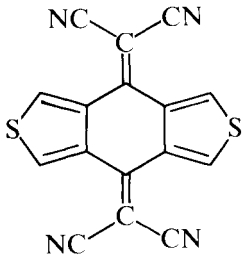
74



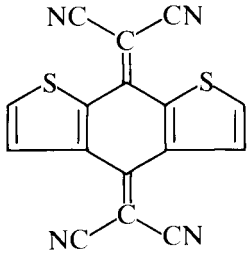
75



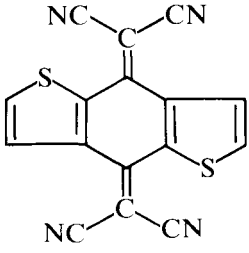
76



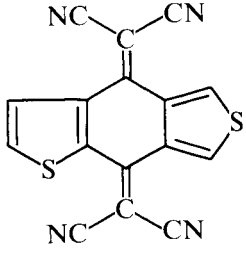
77



78



79



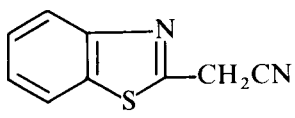
80

The reaction of thiophene aldehydes with cyanoacetic acid in pyridine-toluene, using a Dean–Stark trap, leads to condensation and decarboxylation to give 3-(2-thienyl)- and 3-(3-thienyl)acrylonitrile.[162,216,217] A mixture of 54% of *trans*-3-(3-thienyl)acrylonitrile and 46% of the *cis*-isomer was obtained in

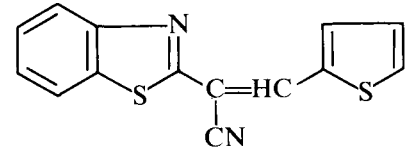
pure form.[162] On the other hand, the *cis–trans*-isomers of 3-(4-bromo-2-thienyl)acrylonitrile were obtained in pure form by chromatography.[162] If the reaction between 2-thiophene aldehyde and cyanoacetic acid is carried out in the absence of pyridine, no decarboxylation occurs, and *E*-2-cyano-3-(2-thienyl)acrylic acid is obtained.[169]

2-Carbamido-3-(thienyl)acrylonitriles could be prepared by using cyanoacetamide in the condensation with 2-thiophene aldehyde or 2-acetylthiophene, with ammonium acetate and acetic acid in ethanol.[210] Condensation of 2-thiophene aldehyde has been carried out with many arylacetonitriles and heterocyclic acetonitriles, using ethoxide, hydroxide, or piperidine in ethanol to give numerous 2-aryl-3-(thienyl)acetonitriles.[36,39,101,155,218–231] With 5-nitro-2-thiophene aldehyde, pyridine must be used as a catalyst.[223]

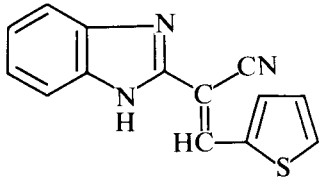
Compound **81** is another heterocyclic substituted acetonitrile that was used in this reaction to give **82** as the condensation product. Condensation of 2-cyanomethyl benzimidazole with 2-thiophene aldehyde, using hydrogen chloride in ethanol, gave **83**, while ethanol and pyridine gave the zwitterionic product **84**. Structures **83** and **84** could be converted into each other by treatment with base and acid, respectively.[232]



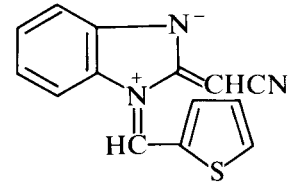
81



82



83

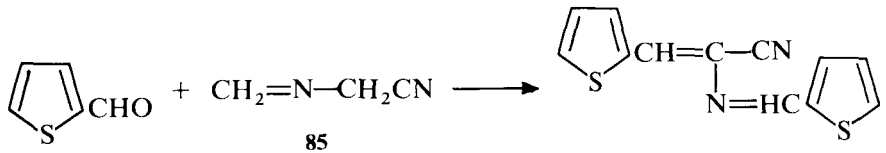


84

According to ^{1}H NMR analysis, the isolated compounds appear to be the *Z*-isomers.[233] The reaction rates of the sodium methoxide-catalyzed condensation of 2-thiophene aldehydes with a large number of heteroaromatic acetonitriles were measured in methanol. The reaction rate was found to be third-order overall and first-order with respect to each reactant. The reaction rates of 2-thiophene aldehyde with acetonitriles are lower than those of benzaldehyde, indicating that the thienyl group behaves as an electron-donating substituent. The reactivity order with respect to acetonitriles was 3-pyridylacetonitrile > 2-thiopheneacetonitrile > phenylacetonitrile > 3-thiopheneacetonitrile.[225]

Condensation of 2-thiophene aldehyde with benzoyl acetonitrile, using triethylamine in acetic acid, gave 2-benzoyl-3-(2-thienyl)-acrylonitrile.[234] The

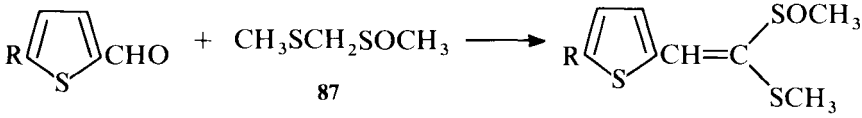
condensation of methylene aminoacetonitrile **85** with 2-thiophene aldehyde in the presence of sodium ethoxide or Triton B, gave **86**.[235]



85 **86**

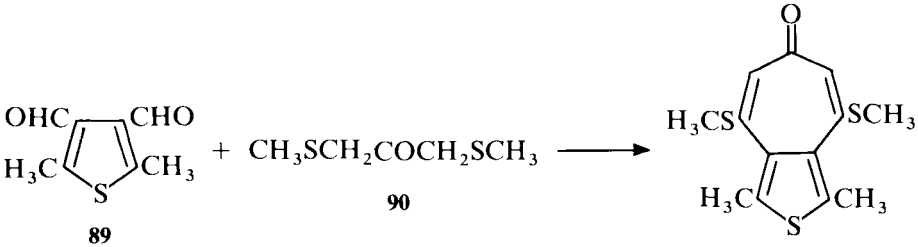
The reaction of 2-thiophene aldehyde with sulfonylamidoacetonitrile in the presence of ammonium acetate and an amine, yielded 3-(2-thienyl)-2-sulfonylamidoacrylonitrile.[42]

4,5-Dichloro-2-thiophene aldehyde has been condensed with 1,3-diketones, such as acetyl acetone and benzoyl acetone, to give (among other products) 2,2'-diacyl-2-(4,5-dichloro-2-thienyl)ethenes.[155] Many different compounds with methyl or methylene groups, activated by various sulfur functions, have been condensed with thiophene aldehydes. Thus, methyl methylthiomethyl sulfoxide **87** yields the synthetically useful condensation product **88** on reaction with thiophene aldehydes, using Triton B in methanol.[152,188,236,237]



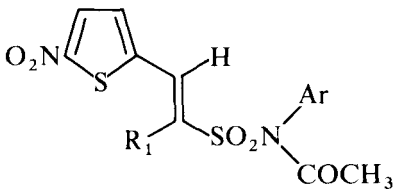
87 **88**

The reaction of thiophene aldehydes with sulfonylacetic acid in glacial acetic acid and benzylamine yielded the α,β-unsaturated sulfones.[238] 2-Thiophene aldehyde gave 1-(2-thienyl)-2-trichloromethylsulfonylethene with trichloromethylalkylsulfones in the presence of a base.[239] The reaction of dimethylsulfone with butyllithium followed by the aldehyde was used for the preparation of 2-(3-azido-2-thienyl)vinyl methyl sulfone.[188] The reaction of 2,5-dimethyl-3,4-diformylthiophene **89** with 1,3-bis-methylthioacetone **90** in methanol, using triethylamine as a base, gave the thienotropones **91** in an 84% yield.[240]



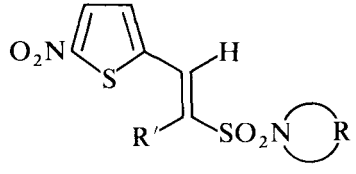
89 **90** **91**

5-Nitro-2-thiophene aldehyde was also condensed with various ethyl arylaminosulfonyl acetates to give **92** and **93**.[241]



$R_1 = H, CH_3$

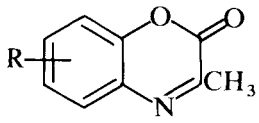
92

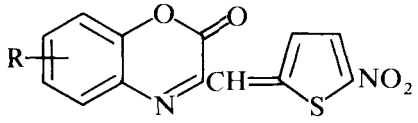


$R' = H, CO_2C_2H_5$

93

The titanium tetrachloride-promoted condensation of 2-thiophene aldehyde with tetraalkyl methylene diphosphonates has been used for the preparation of tetraalkyl 2-thenylidene methanediphosphonates.[192] Condensation of 3-methyl-2*H*-1,4-benzoxazin-2-ones **94** with 5-nitro-2-thiophene aldehyde has been carried out by heating in acetic acid–acetic anhydride to give **95**, which were of interest for testing of their biological activity.[65]

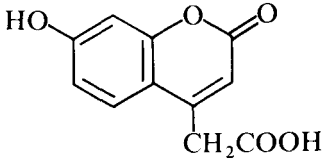




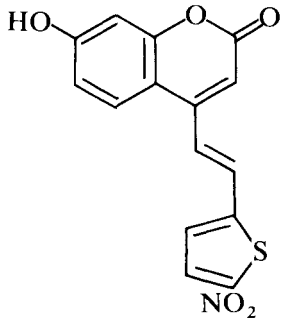
R = H, 6-Cl, 8-Cl, 6-CH_3, 6,8-$(CH_3)_2$, 6-NO_2

94 **95**

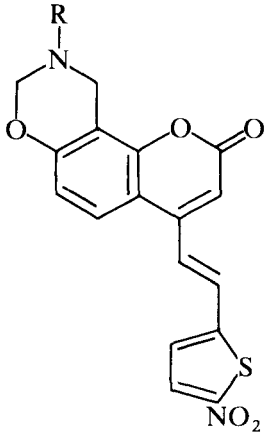
Condensation of **96** with 5-nitro-2-thiophene aldehyde gave **97**, which was further modified to give biologically active **98**.[242] 2-Thiophene aldehyde and



96

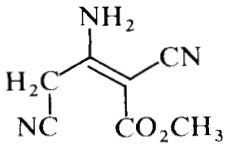


97

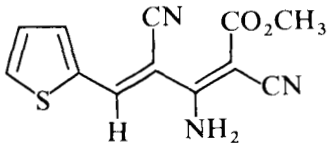


98

5-nitro-2-thiophene aldehyde have also been condensed with barbituric acid.[243] The condensation of 2-thiophene aldehyde with **99**, using piperidine and acetic acid in benzene, with water separation, gave **100** in a 50% yield.[244]

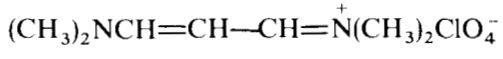


99

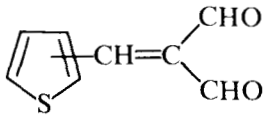


100

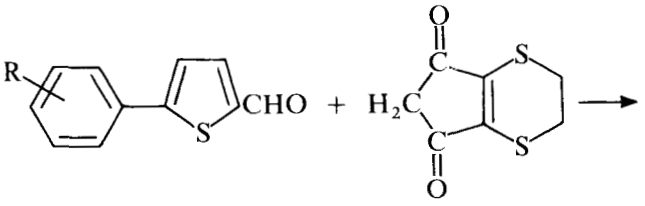
The condensation of 2- and 3-thiophene aldehyde with **101**, a malonaldehyde equivalent, gave **102** in a 86% and a 75% yield, respectively, using acetic anhydride and zinc chloride for the condensation.[245] In connection with an IR spectroscopical investigation and study of the Hammett equation, thiophene aldehydes of type **103** were condensed with **104** to give **105**.[246] 2-Thiophene aldehyde has also been condensed with some anhydrides of homophthalic acids **106** to give **107**.[247]



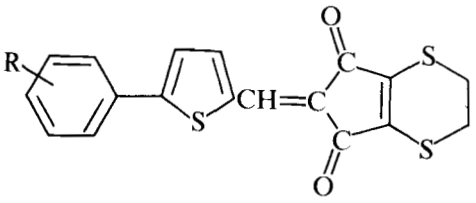
101



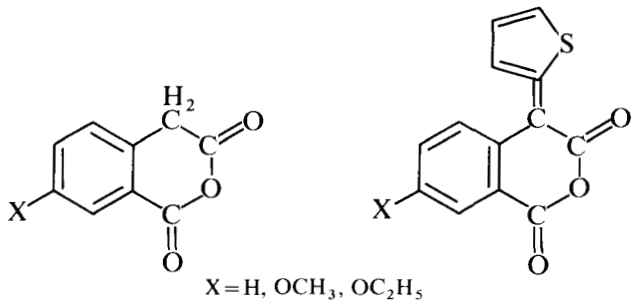
102



103 **104**



105

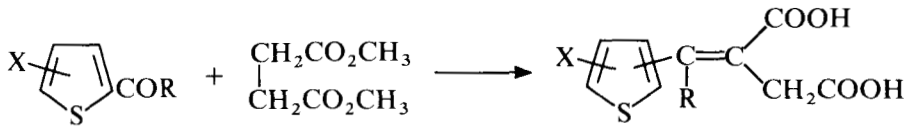


X = H, OCH_3, OC_2H_5

106 **107**

6. Stobbe Condensation

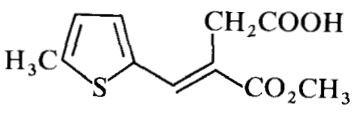
The Stobbe condensation between thiophene aldehydes or thienyl ketones with succinates can also be used for the synthesis of 3-(thienyl)acrylic acids and derivatives of type **108** according to the generalized Scheme 9.[248–253] These products have been used for the preparation of benzo[*b*]thiophene derivatives. This cyclization was also utilized as a proof of the stereochemistry of the acid **108**.



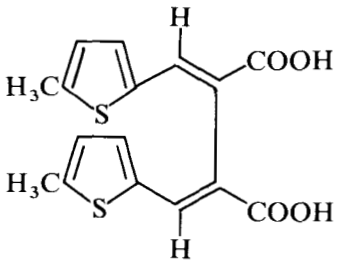
108

Scheme 9

The condensation of 5-methyl-2-thiophene aldehyde with dimethyl succinate in the presence of potassium *t*-butoxide or sodium hydride gave predominantly **109** (75%), together with about 14% of the α,β-disubstituted acid **110**, which was converted to the anhydride.[248] Similarly, the condensation of methyl 2-thienyl

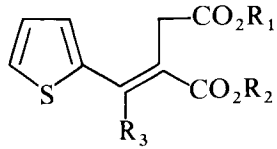


109



110

and phenyl 2-thienyl ketone with dimethyl succinate gave the (*E*)-half-esters **111**, which were converted to the diacids, the anhydrides, and the isomeric half-esters and ring-closed to benzo[*b*]thiophenes.[250]

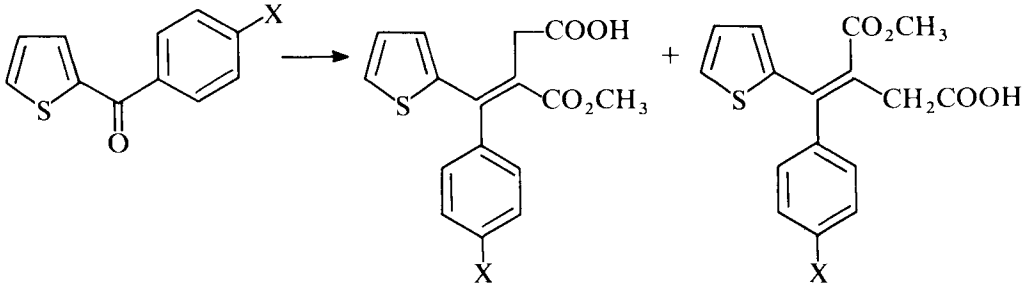


$R_1=H$	$R_2=CH_3$	$R_3=CH_3$
$R_1=H$	$R_2=H$	$R_3=CH_3$
$R_1=CH_3$	$R_2=H$	$R_3=CH_3$
$R_1=H$	$R_2=CH_3$	$R_3=C_6H_5$
$R_1=H$	$R_2=H$	$R_3=C_6H_5$
$R_1=CH_3$	$R_2=H$	$R_3=C_6H_5$

111

Other thienyl ketones, which have been used in the condensation with dimethyl succinate, include *p*-chlorophenyl-2-thienylketone,[249] *p*-anisyl-2-thienyl ketone,[252] *p*-tolyl-2-thienyl ketone,[213] and *p*-tolyl-2-iodo-5-thienyl ketone.[212]

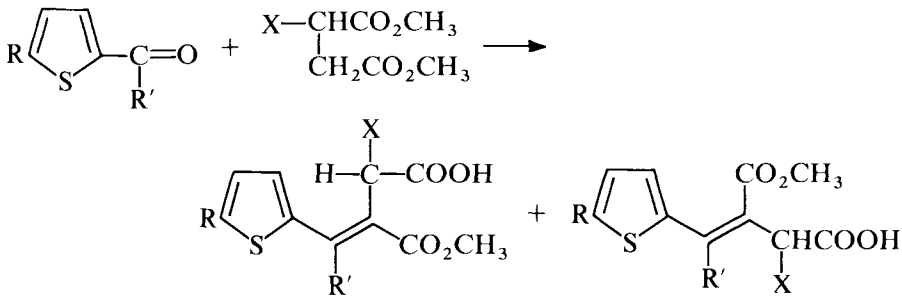
The *p*-chloro and *p*-methoxy derivatives gave mixtures of stereoisomers **112** and **113**, which could be ring-closed to benzo[*b*]thiophene and naphthalene derivatives, respectively,[249,252] while from the *p*-methyl derivative, as well as from *p*-tolyl-2-iodo-5-thienyl ketone, only the *trans*-isomer **112** could be isolated.[212,213]



X = Cl, OCH_3, CH_3

112 **113**

Thiophene aldehydes and ketones have also been condensed with dimethyl methylsuccinate[251] and dimethyl phenylsuccinate.[253] With dimethyl methylsuccinate predominantly the (*E*)-half-esters **114** were obtained, which were ring-closed to benzo[*b*]thiophenes and hydrolyzed to the diacids, which were transformed to the anhydrides. On methanolysis, the anhydrides gave the isomeric half-esters. On the other hand, dimethyl phenylsuccinate gave the (*E*)- and (*Z*)-half-esters **114** and **115** in about equal amounts; the (*E*)-isomers could be obtained in pure form by crystallization[253] (Scheme 10).

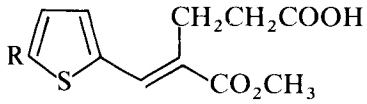


114 **115**

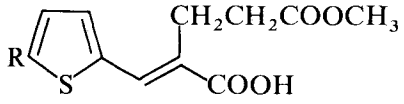
R = H	R′ = H	X = CH_3
R = CH_3	R′ = H	X = CH_3
R = H	R′ = CH_3	X = CH_3
R = H	R′ = C_6H_5	X = CH_3
R = H	R′ = H	X = C_6H_5
R = CH_3	R′ = H	X = C_6H_5
R = H	R′ = C_6H_5	X = C_6H_5

Scheme 10

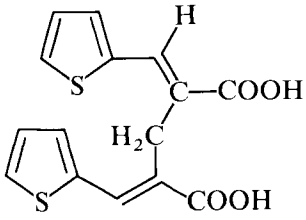
The condensation of 2-thiophene aldehyde and 5-methyl-2-thiophene aldehyde with dimethyl glutarate in the presence of sodium hydride gave predominantly the (*E*)-half-esters **116** and **117**.[254] Compound **118** was obtained as a by-product. By reaction with acetic anhydride, both **117** and **118** converted to the anhydrides **119** and **120**.[254]



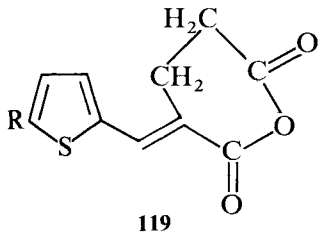
116



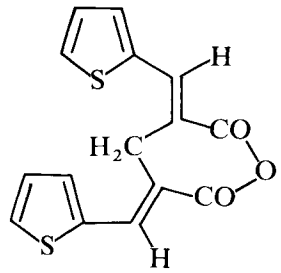
117



118

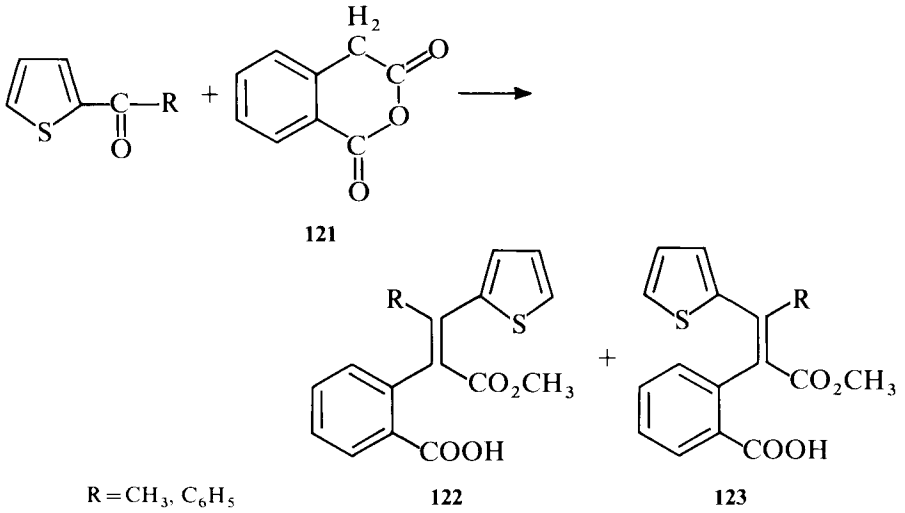


119



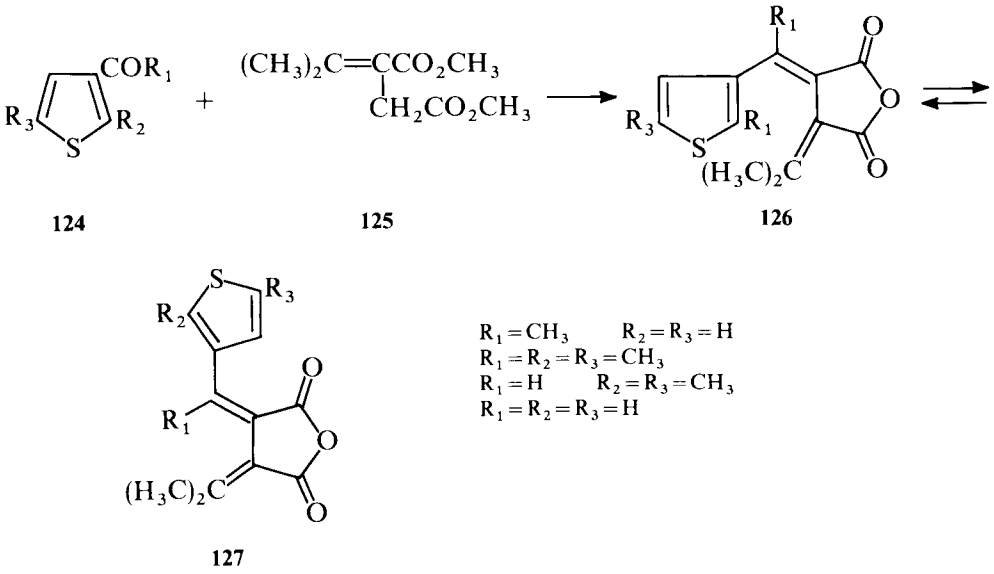
120

The condensation of methyl 2-thienyl ketone and phenyl 2-thienyl ketone with dimethyl homophthalate **121** gave predominantly the (*Z*)-isomer **122**, but the (*E*)-isomer **123** were also isolated in an about 10% yield[255] (Scheme 11).



Scheme 11

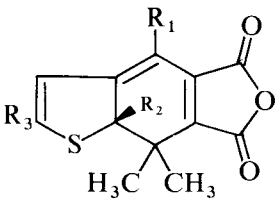
The Stobbe condensation has recently been used in the preparation of important photochromic heterocyclic fulgides.[256] The condensation of 3-acetylthiophene **124** (R_1 = Me, $R_2 = R_3$ = H) and **125** with sodium hydride in toluene, followed by hydrolysis of the half-ester with potassium hydroxide and treatment of the dried potassium salt of the diacid with acetyl chloride, gave the (*E*)-fulgide **126** (R_1 = Me, $R_2 = R_3$ = H). This was also the case when 3-thiophene aldehyde was used in this reaction, and a 54% yield of **126**



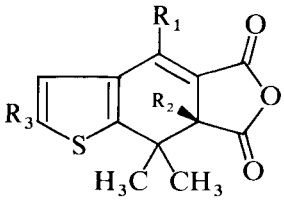
Scheme 12

($R_1 = R_2 = R_3 = H$) was obtained. On the other hand, under the same reaction conditions, 3-acetyl-2,5-dimethylthiophene and 3-formyl-2,5-dimethylthiophene gave the (*Z*)-fulgides **127** ($R_1 = R_2 = R_3 = Me$) and **127** ($R_1 = H$, $R_2 = R_3 = Me$) in a high yield. The (*E*)- and (*Z*)-fulgides can be photochemically isomerized into each other (Scheme 12).

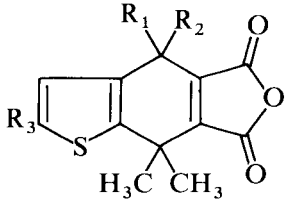
On heating **126** ($R_1 = CH_3$, $R_2 = R_3 = H$) is cyclized to **128**, and with further hydrogen shift sometimes isomerized to **129**. Also **126** ($R_1 = R_2 = R_3 = CH_3$) ring-closed to **128**. Compounds of type **128** were isomerized to **130** on treatment with catalytic amounts of trichloroacetic acid. Interestingly, **128** ($R_1 = R_2 = R_3 = H$) could not be isomerized to **129** or **130**.



128

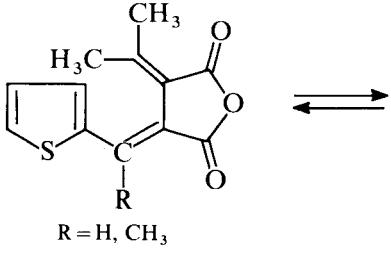


129



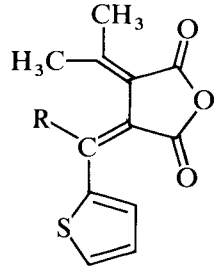
130

2-Thiophene aldehyde and 2-acetylthiophene were also reacted with **125** to give the (*E*)-fulgides **131**, which could be isomerized photochemically to the (*Z*)-fulgide. Compound **131** ($R = CH_3$) was photocyclized to **133**, while **131** ($R = H$) underwent thermal ring closure and acid-catalyzed 1,3-H shift to give **134**.[256]

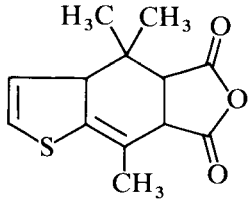


$R = H, CH_3$

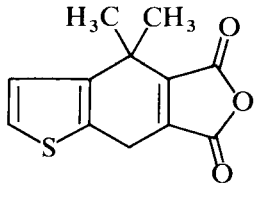
131



132



133

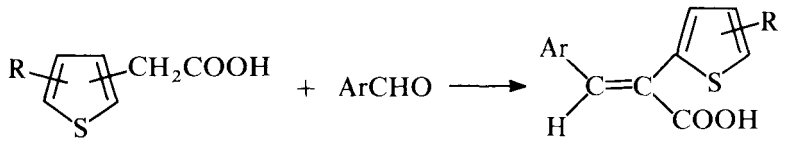


134

7. Condensation of Thiopheneacetic Acids and Thenyl Cyanides with Aromatic Aldehydes

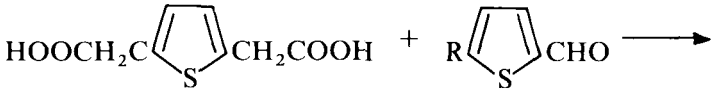
A. Thiopheneacetic Acids

Thiopheneacetic acids have been condensed with aromatic aldehydes in a modified Perkin reaction, using acetic anhydride and triethylamine, to give 2-(thienyl)acrylic acids.[179,257–260] This reaction leads predominantly to the isomer in which the aryl groups are cis-oriented, in contrast to the corresponding condensation of thenyl cyanide, which gives the *trans*-isomer (Scheme 13).[216]



Scheme 13

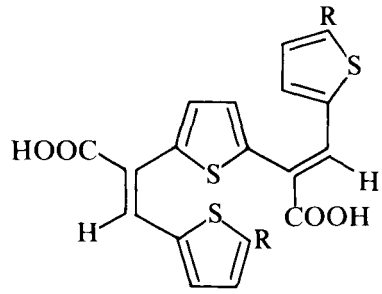
Acetic anhydride and $ZnCl_2$ has also been used in this condensation. The condensation of 2- and 3-thienylacetic acid with *o*-fluorobenzaldehyde gave directly 3-(2-thienyl)- and 3-(3-thienyl)coumarin.[262] The condensation of thio-2,5-diacetic acid **135** and 2-thiophene aldehydes **136** therefore leads to **137**, while the condensation with 2,5-dicyanomethylthiophene **138** with these aldehydes, using a few drops of sodium methoxide in methanol, gave **139** as the main product.[261] Thiophene-2,5-diacetic acid has also been condensed with the dialdehyde **140** to give the cyclic product **141** in a 21% yield.[263]



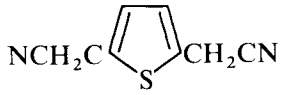
135

R = H, CH_3OCH_2

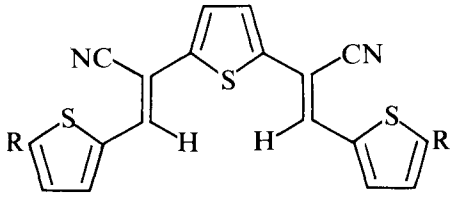
136



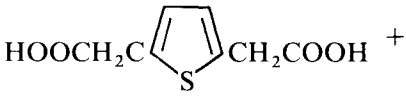
137



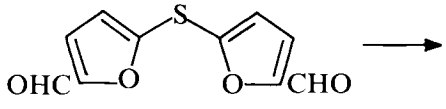
138



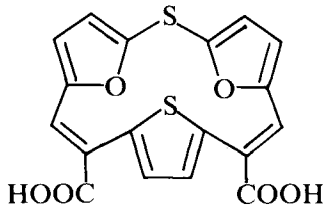
139



135



140

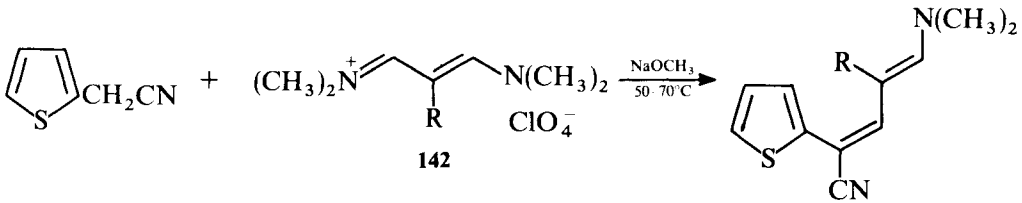


141

2-Thiopheneacetic acid was condensed with phthalic anhydride to 2-thenylidene phthalide, using sodium acetate and 1-methylpyrrolidone at 205°C.[264]

B. Thenyl Cyanides

A large number of 2-(thenyl)acrylonitriles have been prepared from various thenyl cyanides and aromatic aldehydes by using a few drops of 50% aqueous potassium hydroxide as a solvent[118,220,231,265–270] or sodium ethoxide or *t*-butoxide in the corresponding alcohol.[101,258,271,272] 2-Thenyl cyanide has also been successfully condensed with acetaldehyde to give 2-(1-cyanoallyl)-thiophene in a 87 : 13 *E*–*Z* mixture in an 84% yield.[273] The reaction of 2-thenyl cyanide with **142** gave **143**, which on heating to 160–220°C ring-closed to the corresponding benzo[*b*]thiophene derivatives.[274]

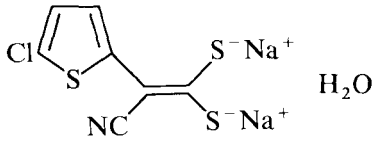


142

R = H, CH_3, OCH_3, $CH_2C_6H_5$, C_6H_5

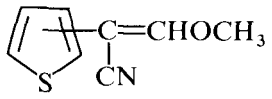
143

The condensation of 5-chloro-2-thenyl cyanide with carbon disulfide in the presence of sodium hydride led to the hydrated salt **144**.

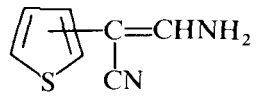


144

The condensation of 2- and 3-thenyl cyanide, with ethyl formate in the presence of sodium ethoxide, gave **145** on methylation with methyl iodide in DMF, which on reaction with ammonia gave **146**.[275]



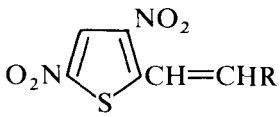
145



146

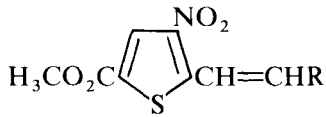
8. Condensation of Activated Methylthiophenes with Aldehydes

Doubly activated 2-methylthiophenes, such as 2,4-dinitro-5-methylthiophene or 2-carbomethoxy-4-nitro-5-methylthiophene, are easily condensed with various aromatic and heterocyclic aldehydes, using anhydrous xylene as a solvent and a few drops of piperidine as a catalyst, with water separation, to give compounds **147** and **148**, which most probably have trans configuration.[276] The yields in the



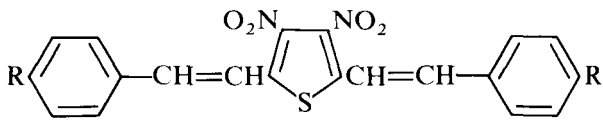
R = 3-Th
R = 2-Th
R = 2-Fu
R = —CH=CHPh
R = C_6H_5

147



R = 3-Th
R = 2-Th
R = 5-Cl-2-Th
R = —CH=CHPh

148

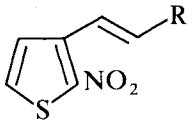


R = H
R = OCH_3
R = Cl

149

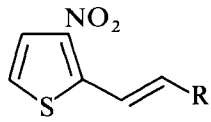
condensation with cinnamaldehyde were very low. Dinitrodistyrylthiophenes **149** were prepared in an 80–85% yield from 2,5-dimethyl-3,4-dinitrothiophene and the appropriate aldehyde, normally using no solvent and pyrrolidine as a catalyst.[277]

The methyl group in the *o*-methylnitrothiophenes shows varying reactivity toward aldehydes under base catalysis. 3-Methyl-2-nitrothiophene, in contrast to *o*-methylnitrotoluene, reacts to give vinyl derivatives. Heating under reflux with 40% formalin in methanol, containing catalytic amounts of pyrrolidine and acetic acid, gave a 73% yield of 2-nitro-3-vinylthiophene, while a similar reaction with benzaldehyde and *p*-anisaldehyde, using ethanol as a solvent and pyrrolidine as a catalyst, gave the corresponding *trans*-olefins **150**.[278,279] The isomeric 2-methyl-3-nitrothiophene reacted even faster with benzaldehydes and in a better yield than 3-methyl-2-nitrothiophenes to give **151**.[279]



R = H
R = C_6H_5
R = *p*-$CH_3OC_6H_4$—
R = *p*-ClC_6H_4—
R = 2-Th

150



151

On the other hand, applying these reaction conditions to 2-thiophene aldehyde gave only low yields of the desired product, and much tar. *However*, by reacting the methyl nitrothiophenes with 2 mol of 2-thiophene aldehyde at 100°C without solvent and with piperidine as a catalyst, good yields of **150** (R = 2-thienyl) and **151** (R = 2-thienyl) were obtained.[280] In the condensation with formaldehyde, 2-methyl-3-nitrothiophene reacted differently and gave *trans*-1,2-bis-(3-nitro-2-thienyl)cyclobutane as the main product,[280] together with 3-nitro-2-vinylthiophene. The structure of the main product was proved by X-ray crystallography.[281] 3-Methyl-4-nitrothiophene could not be condensed with formaldehyde or 2-thiophene aldehyde.[280]

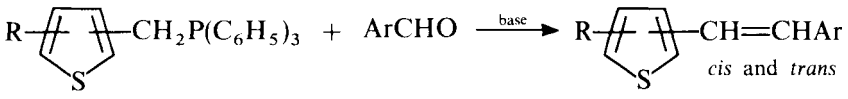
9. Wittig Reaction

A. From Thenyl Triphenylphosphonium Halides and Aldehydes

The Wittig reaction has been extensively used for the preparation of thienylvinyl derivatives, especially 1-thienyl-2-arylethenes (thiophene analogs of stilbene).[282–291]

The starting triphenylphosphonium halides were easily obtained by the reaction of thenyl halides with triphenyl phosphine. The thenyl halides were

prepared by chloromethylation of thiophenes or side-chain bromination of methylthiophenes. Compounds **152** were then reacted with various aromatic aldehydes to give **153** (see also Scheme 14).



152 **153**

Various bases and solvents have been used in this reaction, for instance, potassium *t*-butoxide,[282] sodium methoxide,[285] and sodium or lithium ethoxide[288,292,293] in the corresponding alcohols. In particular, sodium methoxide in *N*,*N*-dimethylformamide[284,286,287,290] has been used extensively. Butyllithium in hexane[294] has also been used.

In another modification, 3-bromomethyl-2-nitrothiophene was reacted with aromatic aldehydes in the presence of triphenylphosphine in methylene chloride; the reaction was catalyzed by ethylene oxide and conducted at 0°C.[289]

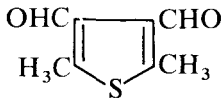
It is well known that the cis : trans ratio of the olefins obtained in the Wittig reaction depends on the reaction conditions. Normally, selectivity is very low, as in the reaction between triphenyl thenylidene phosphorane and 2-thiophene aldehyde. Unexpectedly high amounts of *cis*-isomers were, however obtained with ortho-halo-substituted thiophene aldehydes.[286] This is not a steric effect, since less *cis*-isomer was obtained using *ortho*-iodothiophene aldehydes.[295]

The cis : trans ratio of the stilbenes formed in the Wittig reaction of benzyltri(heteroaryl)phosphonium salts with benzaldehyde in ethanolic ethoxide decreased markedly in the series 2-furyl > 2-thienyl > phenyl > 1-methylpyroll-2-yl.[296]

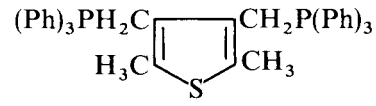
The reaction of (3-bromo-2-thenyl)triphenylphosphonium chloride and (2-bromo-3-thenyl)triphenylphosphonium bromide with furfural gave lower selectivity than did the corresponding reactions with 2-thiophene aldehyde. This was especially noticeable in the reaction of **161** with 3-bromo-2-furan aldehyde, which gave a cis : trans ratio of 34 : 66, while 3-bromo-2-thiophene aldehyde gave a cis : trans ratio of 70 : 30.[287]

The *trans*-isomers are easy to obtain in pure form by recrystallization because of their greater insolubility. It is also possible to transform the *cis*-isomer to the *trans*-isomer by catalysis with iodine.[295] It is more difficult to obtain the *cis*-isomer in pure form, but this has been achieved by fractional distillation, followed by recrystallization.[295]

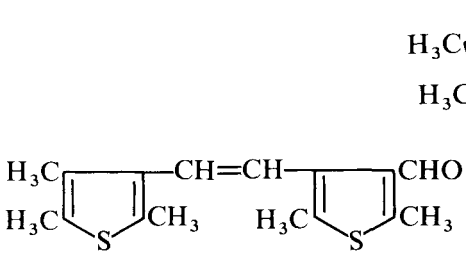
The 1,2-(dithenyl)ethenes and related compounds have been extensively used for the preparation of dithieno analogs of phenanthrene by photochemical ring closure.[282,297] From the six isomeric *cis*-1,2-di(*ortho*-bromothienyl)ethenes, all isomeric dithieno analogs of phenanthrene were obtained by halogen–metal exchange and coupling with cupric chloride.[195] The reaction of **154** with **155** gave cis–trans mixtures of **156** as the main product, in addition to minor



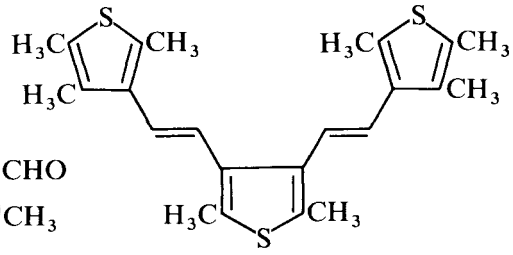
154



155



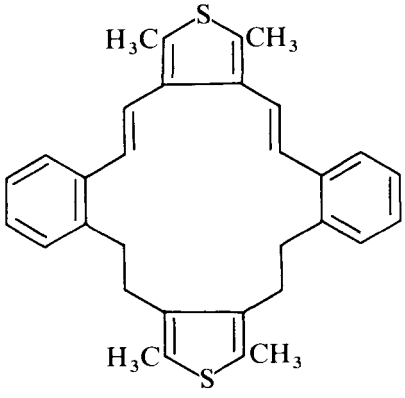
156



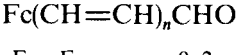
157

amounts of **157**. The two methyl groups at C-4 of the terminal thiophene nuclei of **157** arose from the hydrolysis of unchanged ylid.

From the reaction of **155** with *o*-phthalaldehyde, **158** could be isolated.[298] 2-Thenyl triphenylphosphonium halide has been reacted with **159** to give **160**.[299]

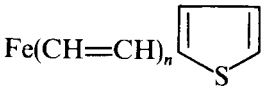


158



Fe = Ferrocene = 0, 2

159

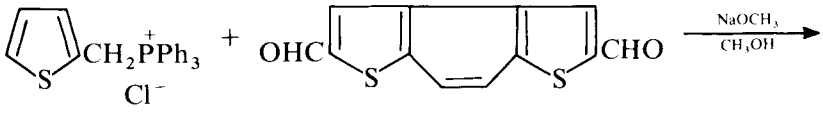


$n = 1$–3

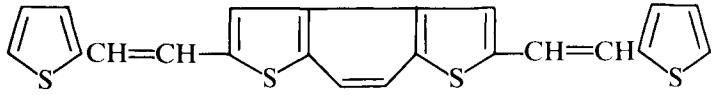
160

The Wittig reaction has also been carried out with specifically tritium-labeled thiophene aldehydes and phosphoranes, in order to prepare labeled dithieno analogs of phenanthrene for a study of the rates of electrophilic detritiation.[294] Coupling of **161** with **162** gave **163**, which on photolysis ring-closed to a heterohelicence.[285] Similar condensations for the same purpose have also been carried out with **161** and 2,5-diformylthieno[2,3-*b*]thiophene.[300]

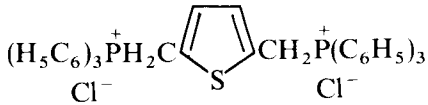
The bifunctional phosphonium salt **164** was reacted with the dialdehyde **165** and gave **166** in an 18% yield.[263] However, attempts to couple **164** with 2,2′-bis-5-formylthienyl ketone failed.[297]



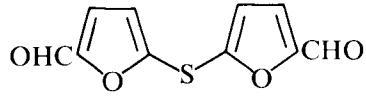
161 162



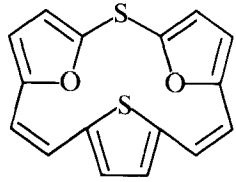
163



164

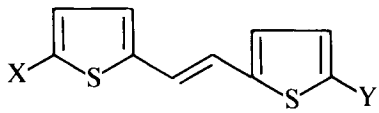


165



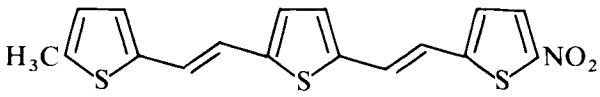
166

In connection with work on spectroscopic properties and electrical conductivity, unsymmetric compounds of type **167**, as well as more complex systems, such as **168** and **169**, were prepared by the Wittig reaction, followed by isomerization with iodine.[301]

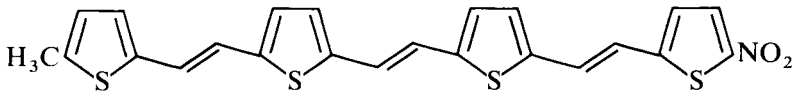


$X=CH_3$,	$Y=NO_2$
$X=Br$,	$Y=NO_2$
$X=Br$,	$Y=CH_3$
$X=Br$,	$Y=Cl$
$X=Br$,	$Y=OCH_3$
$X=OCH_3$,	$Y=CH_3$
$X=Br$,	$Y=CHO$

167



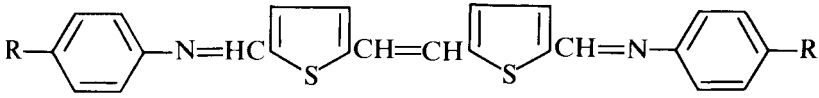
168



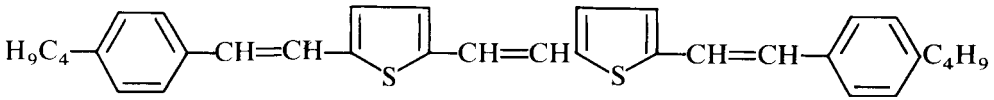
169

Even more complex bicyclic aromatic compounds have been obtained by carrying out a sixfold Wittig reaction between aromatic bisphosphonium salts, such as **164** and 1,3,5-benzenetricarbaldehehyde, although the yields were very low.[302]

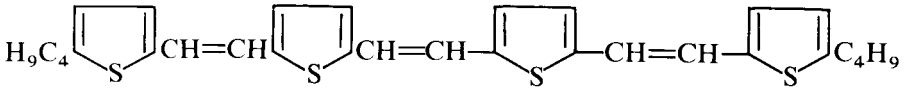
In connection with work on liquid crystals, *trans,trans*-5,5′-bis(5-butyl-2-thienylvinyl)-2,2′-bithienyl was prepared from 5-butyl-2-triphenylphosphoniumethylthiophene chloride and 2,2′-bithienyl-5,5′-dicarbaldehyde.[303] In this connection **170–172** have been prepared from **173** and appropriate aniline derivatives (**170**) or Wittig reactions (**171** and **172**).[304]



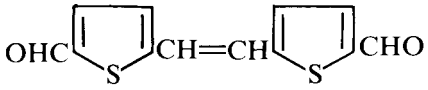
170



171

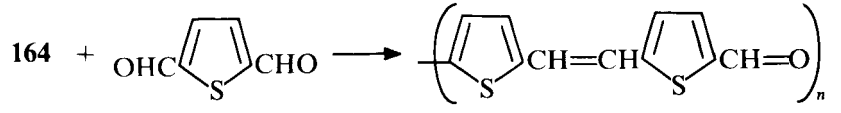


172

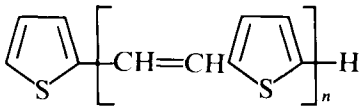


173

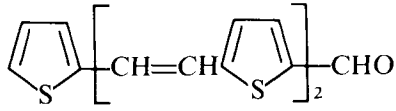
The reaction between bifunctional phosphonium salts with bifunctional aldehydes can, of course, be used for the synthesis of polymers **174**. Oligomers of **175** (n = 2–6) have been obtained by stepwise Wittig reactions. Thus **175** (n = 2) was prepared from 2 mol of 2- thiophene aldehyde and **164**. Vilsmeyer formylation of **175** (n = 2) gave **176**, which on reaction with **161** gave **175** (n = 3). The aldehyde **176** was also prepared through Wittig reaction between **177** and **178**.



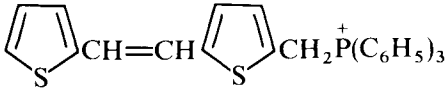
n = 2–6 **174**



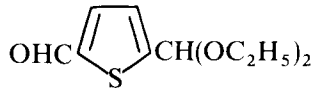
175



176

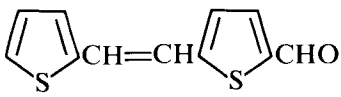


177

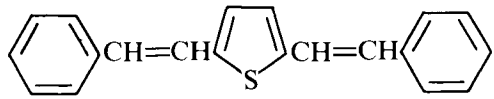


178

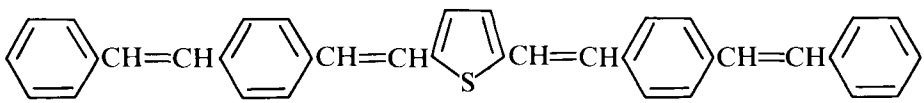
Using 2 mol of the aldehyde **179** with **164** gave a quantitative yield of **175** ($n = 4$). Aldehyde **179** could also be prepared by Vilsmeyer formylation, as well as through a Wittig reaction between **178** and **161**. Finally, **175** ($n = 6$) was prepared by the Wittig reaction of 2 mol of **176** with **164**.[293] The compounds **175** were obtained as *cis–trans*-isomeric mixtures and were converted to the all-*trans*-isomers by refluxing with catalytic amounts or iodine in xylene.[293] The bisphosphonium reagent **164** was also reacted with terephthalaldehyde, isophthalaldehyde, and phthalaldehyde to give polymers.[305] In this investigation, model compounds for the polymers, such as **180** and the analogous compound, derived from piperonal, as well as **181**, were prepared by Wittig reactions.[305]



179

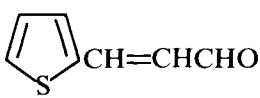


180

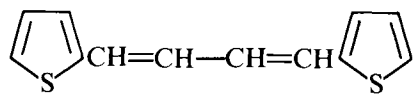


181

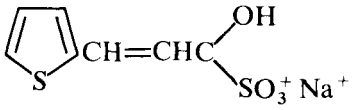
The Wittig reaction between **182** and **161** gave **183** in a statistical mixture of *cis–trans*-isomers in a 53% yield, which was isomerized to the all-*trans*-isomer with iodine. A much better yield (85%) of **183** and only *trans*-isomers was obtained by reacting **161** with **184** in anhydrous DMF with potassium *t*-butoxide.[306] This was considered to be the best method. Other variations of the Wittig reaction were also studied in order to prepare **183**. The phosphonate



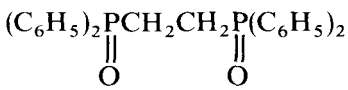
182



183



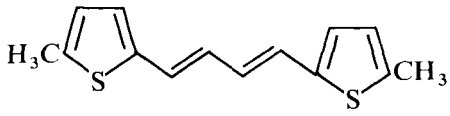
184



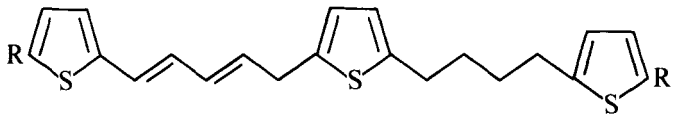
185

method (Wadworth–Emmons–Horner reaction) (see Section B) gave 69% of pure *trans–trans*-isomer. Reaction of 2-thiophene aldehyde with **185** gave the trans–trans form in a 73% yield, while trimeric glyoxal hydrate and **161** gave **183** in a low yield as a cis-trans mixture.[306,307]

Other butadienes prepared by the Wittig reaction include **186**, **187**, and **188**. The latter compound was prepared by the Wittig reaction of 2 mol of **182** with **189**.

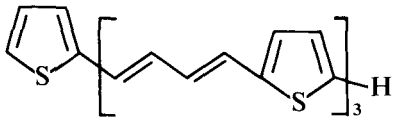


186

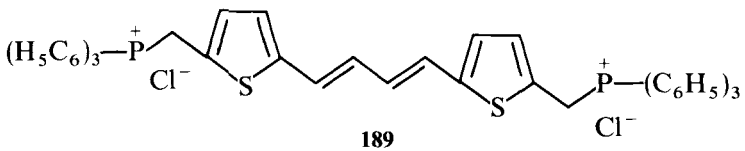


R = H, CH_3

187

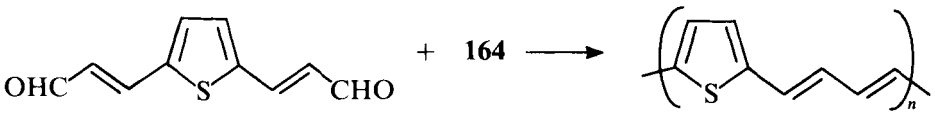


188



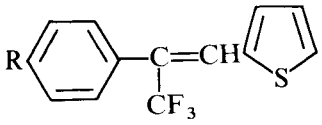
189

Poly-(2,5-thienylene)-1,3-butadienylene **191** was obtained from **190**.

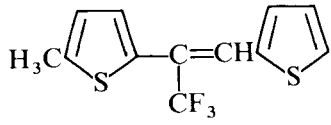


190 191

Compounds **192** and **193** were prepared by the Wittig reaction between phenyl trifluoromethyl ketone and **161** and 2-methyl-5-trifluoroacetylthiophene and **161**, respectively.

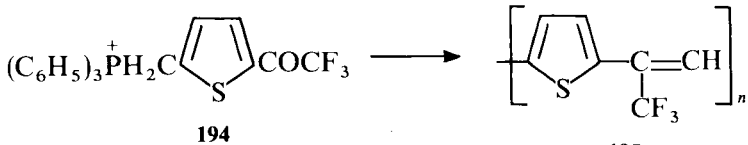


192



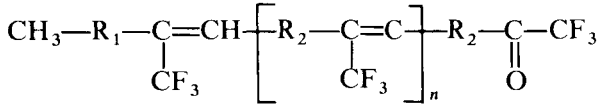
193

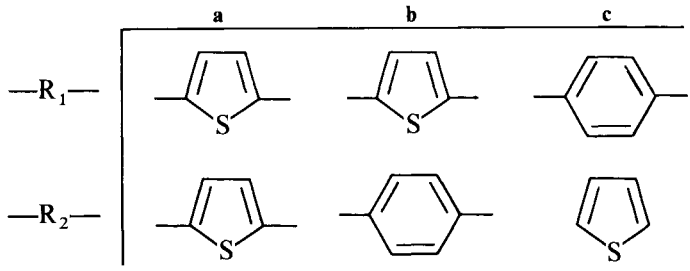
Polymers **195** were prepared by self-condensation of **194**, using phase-transfer conditions (dibenzo-18-crown-6, KF in $CHCl_3$). By polycondensation, using the ylid from **194** and *p*-trifluoroacetyltoluene, 5-methyl-2-acetylthiophene, and *p*-trifluoroacetyl benzyltriphenylphosphorane in suitable proportions, polymers with structures **196** were obtained and studied by mass-spectral techniques.[308]



194

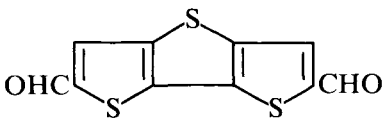
195



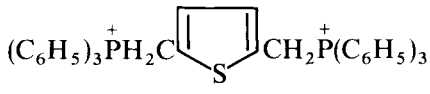


196

Other polymers were prepared from the dialdehyde **197** and the ylid from **198**.[309]

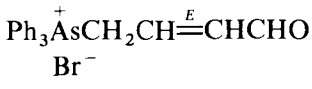


197

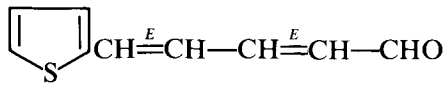


198

2-Thiophene aldehyde reacts stereoselectively with **199** in ether-THF, containing traces of water and with potassium carbonate as a base, to give **200** in a 79% yield.[310]



199

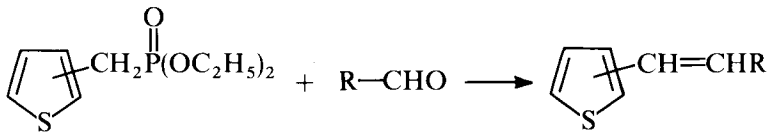


200

The Wittig reaction has also been essential for the synthesis of many naturally occurring thiophenes (see Part 1, Chapter 3 of this series), and a first application of the Wittig reaction for the synthesis of 1,2-di-(2-thienyl)ethene was given in that connection.[311]

B. The Phosphonate Method (Wadworth–Emmons–Horner Reaction)

The phosphonate method is a useful alternative to the classical Wittig reaction, if the *trans*-isomer is desired. The necessary diethyl thenyl phosphonates are prepared by the Arbusov reaction, that is, heating the thenyl halides with triethylphosphite to 100–160°C for a few hours (Scheme 14).



Scheme 14

The condensation of the thenyl phosphonates with aldehydes and ketones was in most cases carried out using a 50% excess of sodium ethylate or methylate in DMF at 25–40°C,[264,283,287,290,312–318] sodium hydride in 1,1-dimethoxyethane,[291,319–321] or sodium hydride in DMSO.[322,323] The carbonyl compounds utilized were benzaldehyde and various substituted benzaldehydes,[264,290,315,318,320,322,323] 1-naphthaldehyde,[324] polycyclic aromatic aldehydes,[315] thiophene aldehydes,[283,312,313,315,317,319] furanaldehydes,[287] pyrrolyl aldehydes,[291,326] benzo[*b*]thiophene aldehydes and dibenzothiophene aldehydes,[325] 2-acetylthiophene,[319] and acetylnaphthalene.[321]

In most reactions of thenyl phosphonates with aromatic aldehydes, a few percent ($\leq 10\%$) of the *cis*-isomers were formed, in addition to the *trans*-isomers, but there are some exceptions. Thus, in the reaction of diethyl 2-chloro-3-thenylphosphonate with 4-bromo-3-thiophene aldehyde, 33% of the *cis*-isomer was formed, and in the reaction of 2,5-dichloro-3-thenylphosphonate with the same aldehyde, equal amounts of *cis*- and *trans*-isomers were obtained.[313] In the reaction of diethyl 2-thenylphosphonate with 2 pyrrolyl

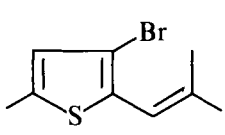
aldehyde, the *E*–*Z*-isomers were formed in the ratio of 2.3 : 1.[291] The bromo-substituted 1,2-dithienyl ethenes are useful starting materials for other 1,2-dithienyl ethenes, and ring-closed products and have, for instance, been converted to carboxy-[286,313] and azido-substituted 1,2-di(thienyl)ethenes.[317] The coupling between substituted thenyl phosphonates and substituted thiophene aldehydes was also used in connection with the synthesis of potential antidepressant agents.[314,316]

C. From Thiophene Aldehydes and Triphenylalkylphosphonium Salts

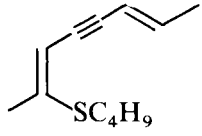
Alternatively, thienyl ethenes can be prepared by interchanging the aldehyde and phosphonium or phosphonate component, which, of course, leads to the same products. The yields are in many cases similar, and which combination is used is determined by the availability of the starting material.

The classic Wittig procedure has been followed in the reaction of the ylide from benzyl triphenylphosphonium chloride with various 2-thiophene aldehydes in the preparation of *trans*-2-styrylthiophenes.[95,292,327,328]

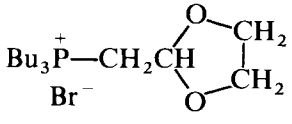
3-Bromo-2-methyl-5-thiophene aldehyde has been condensed with isopropylidenephosphorane to give **201**, which on halogen–metal exchange at room temperature ring-opened to give **202**.[329] 2- and 3-thiophene aldehyde and 2- and 3-thienylacrolein reacted with **203** to give **204** and **205**, respectively, in a 70–80% yield.[330]



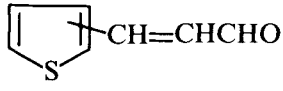
201



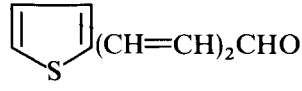
202



203

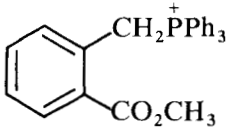


204

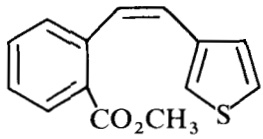


205

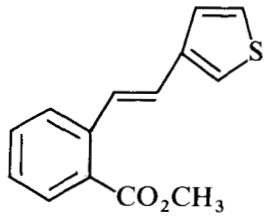
The reaction of the ylide from **206** with 3-thiophene aldehyde gave the *cis*-isomer **207** and the *trans*-isomer **208** in a ratio of 7 : 3. This was also the case with 3-selenophene aldehyde, while 3-furan aldehyde gave a 1 : 1 ratio.[331] 2-Iodo-5-(1-propenyl)thiophene was prepared from 2-formyl-5-iodothiophene and the ylide from ethyl triphenylphosphonium bromide.[332] The ylide from methyl triphenylphosphonium bromide, generated by treatment with sodium hydride in DMSO, was reacted with 5-bromo-5′-formylbithienyl in the preparation of **209**, an intermediate in the synthesis of a compound occurring in *Tagetes erecta*.[333] The same ylide, generated with butyllithium in THF, was



206

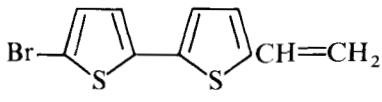


207

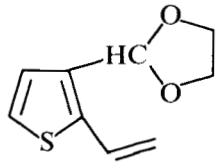


208

reacted with 2,3-diformylthiophene, in which the 3-formyl group was protected as ethylene acetal, to give **210**, which was used as an intermediate for the synthesis of thienopyridines.[334]

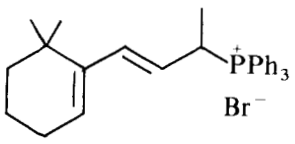


209

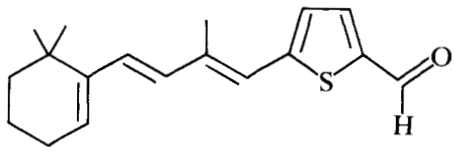


210

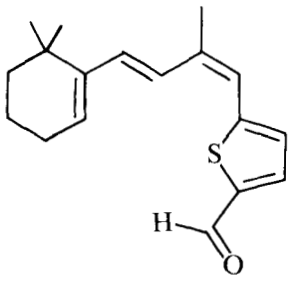
The reaction of the ylide from **211** and 1 mol of 2,5-thiophene dialdehyde gave a mixture of the retinal analogs **212** and **213** in about equal amounts.[335] In connection with synthetic approaches to complex antitumor agents, a cis–trans mixture of **214** was prepared from the pyrrol-2-yl-methylphosphonium iodide and 2-thiophene aldehyde, and the mixture was photochemically ring-closed to a thieno indole.[336]



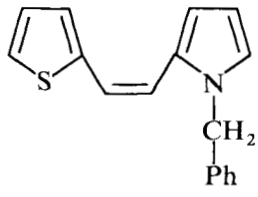
211



212

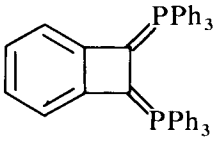


213

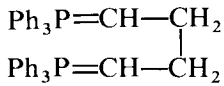


214

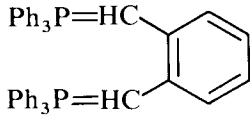
The Wittig reaction between 2,3-diformylthiophene and the ylides **215–219** has been used for the synthesis of the polycyclic systems **220–224**.[337,1025,1026] From 2,5-dimethyl-3,4-thiophene dialdehyde and **218** the *c*-annelated system **225** was also obtained.[337]



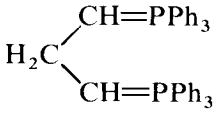
215



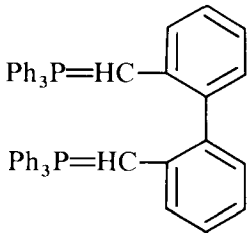
216



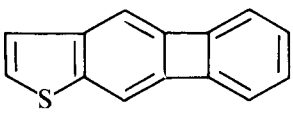
217



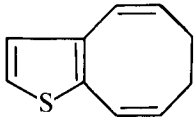
218



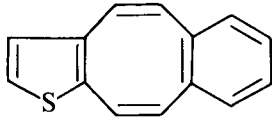
219



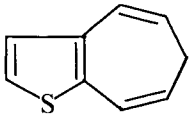
220



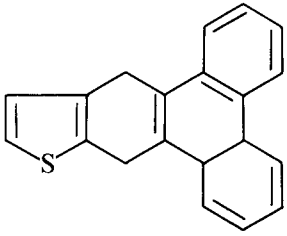
221



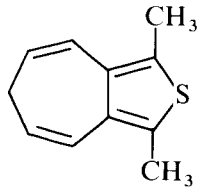
222



223

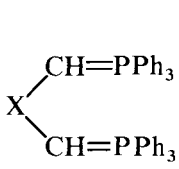


224



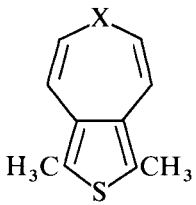
225

The yields in these reactions were mostly lower than 10%. In other cyclizations, the ylides **226** were used in the reaction with 2,5-dimethyl-3,4-diformylthiophene and 2,3-diformylthiophene to give **227** and benzo[*b*]thiophene, respectively. The latter was formed by elimination of sulfur from the intermediate instable thiepin.[338] Similarly, from **226** (X = O), the oxepin **227** (X = O) was obtained.[339] The reaction of **226** (X = S) with **228** gave a 3.5% yield of **229**.[340]



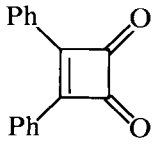
X = O, S

226

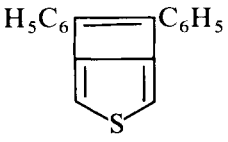


X = O, S

227

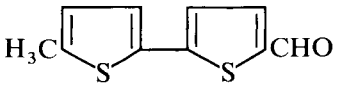


228

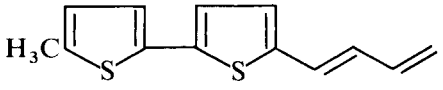


229

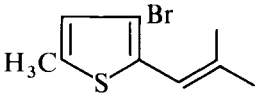
The reaction of **230** with allyl triphenylphosphonium bromide gave **231**.[341,342] 3-Bromo-5-methyl-2-thiophene aldehyde was reacted with the ylide from isopropyl-triphenylphosphonium bromide to give the **232**, which on treatment with butyllithium ring-opened to **233**.[329]



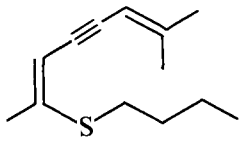
230



231

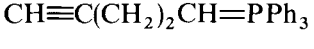


232

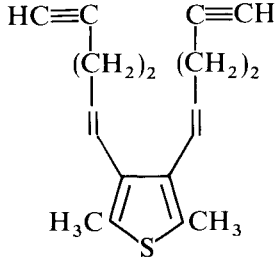


233

In connection with work on bridged thia[17]annulenes, two equivalents (2 eq) of the ylide **234** were reacted with 2,5-dimethyl-3,4-diformylthiophene to give **235**.[243]

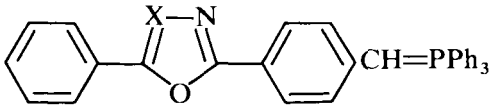


234



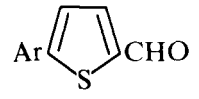
235

Compounds with scintillation properties include 1,4-bis(2-vinylthienyl)benzene, which has been prepared from 2 eq of 2-thiophene aldehyde and *p*-xylene bis(triphenyl)phosphonium chloride.[344] Other compounds with scintillation properties **238** were prepared through the Wittig reaction between **236** and **237**.[345]



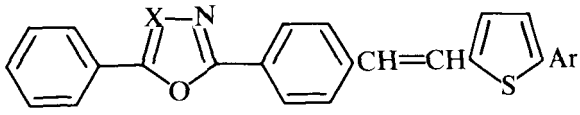
X = CH, N

236



Ar = C_6H_5, 4-ClC_6H_4
4-BrC_6H_4, 4-$O_2NC_6H_4$

237

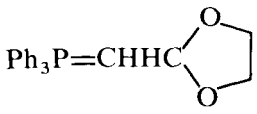


238

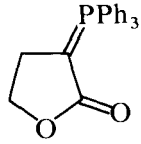
X = CH, N

In connection with work on liquid crystals, *trans,trans*-5,5′-bis(4-butylphenyl)-2,2′-bithienyl was prepared from 4-butylbenzyltriphenylphosphonium bromide and 2,2′-bithienyl-5,5′-dicarbaldehyde.[303]

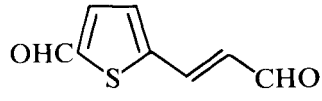
Special ylides, such as **239**[346,347] and **240**,[348] have been used for the preparation of unsaturated aldehydes, including **241** and **242**. 5-Nitro-2-thiophene aldehyde was reacted with **243** to give 1-aryl-3-(5-nitro-2-thienyl)propenones.[349] 2-Thiophene aldehyde was reacted with **244** to give **245** in a 70–80% yield.[350]



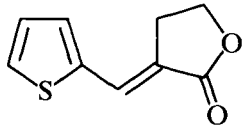
239



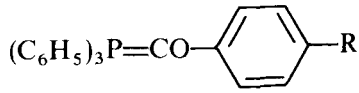
240



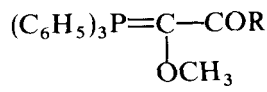
241



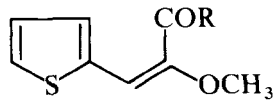
242



243

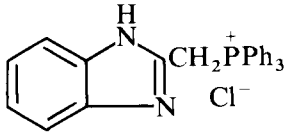


244

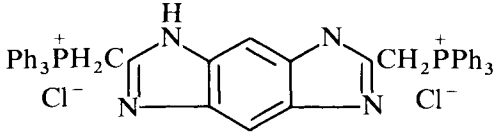


245

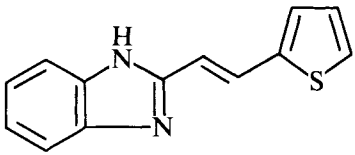
As mentioned above, the Wittig reaction has been used for the preparation of polymers. Ylides derived from **246** and **247** were reacted with 2-thiophene aldehyde to give **248** and **249**, respectively.[351]



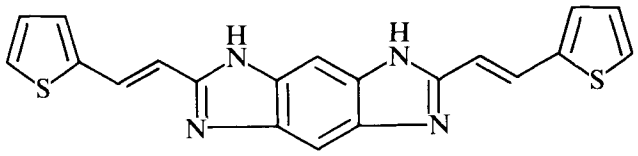
246



247

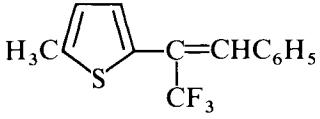


248

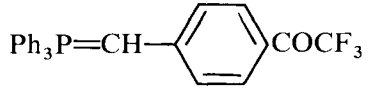


249

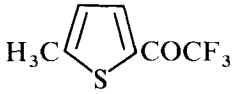
Another example is the preparation of **250** from benzyltriphenylphosphonium chloride and 2-methyl-5-trifluoroacetylthiophene, in connection with polymerizaton of compounds, such as **253**, derived from **251** and **252**.[308]



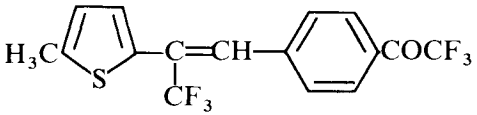
250



251

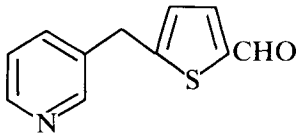


252

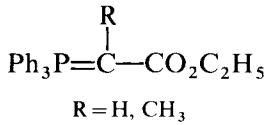


253

In connection with the synthesis of selective inhibitors of thromboxane synthetase, **256** was prepared through the Wittig reaction of **254** with **255**.[352]

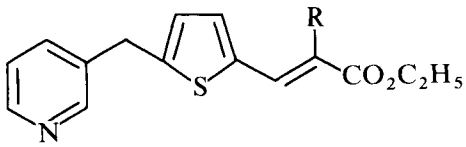


254



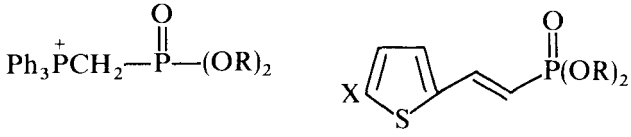
R = H, CH_3

255



256

The reaction of the Wittig reagent from **257** with 2-thiophene aldehyde and 5-nitro-2-thiophene aldehyde gave **258** in a high yield.[353]



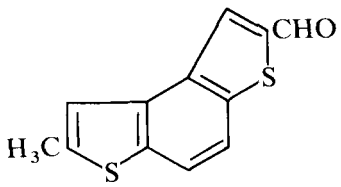
R = Ph, C_2H_5
X = H, NO_2

257 **258**

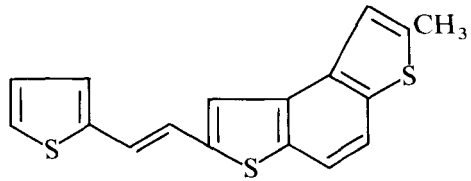
D. From Thiophene Aldehydes and Phosphonates

The phosphonate method, using various ylides and thiophene carbonyl derivatives, has been employed with diethyl benzylphosphonate and 2-thiophene aldehyde,[354,355] 4-methyl-2-thiophene aldehyde,[356] 5-methyl-2-thiophene aldehyde,[322] 3-thiophene aldehyde, and 3-acetylthiophene[320] and 5-styryl-2-thiophene aldehyde,[355] with diethyl *m*- and *p*-methylbenzylphosphonate and 2-thiophene aldehyde[322] and 2,4- and 3,4-dichlorobenzylphosphonates and 2-thiophene aldehyde,[357] 3-thiophene aldehyde.[320] The same method has been used with diethyl methylsulfonylmethyl phosphonate and 2-thiophene aldehyde[358] and with diethyl (2-carboethoxy-3-furylmethyl)phosphonate and 3-thiophene aldehyde.[287]

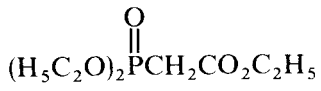
Diethyl 1-naphthylmethylphosphonate has been condensed with 4-methyl-2-thiophene aldehyde.[359] The phosphonate method was also used in connection with the synthesis of heterohelicenes. Thus, reacting **259** with 2-thenylphosphonate gave **260**.[360] Ethyl esters of 2-(thienyl)acrylic acids and 2-(thienyl)-diacrylic acids have been obtained from **261** and various aldehydes, such as 2- and 3-thiophene aldehydes, the four isomeric dialdehydes, and the acetylthiophenes.[361–365]



259

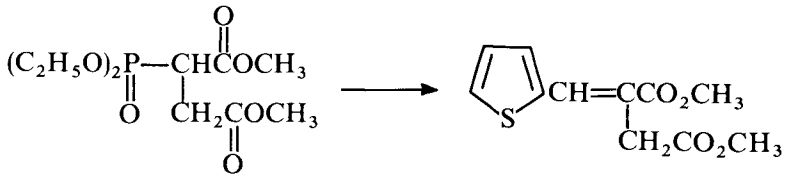


260



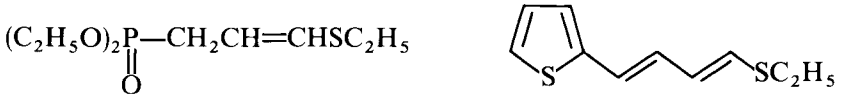
261

The reaction of 2-thiophene aldehyde with **262** gave a product **263**, similar to that from the Stobbe condensation.[366]



262 **263**

The phosphonate **264** gave an 80% yield of **265**[367] with 2-thiophene aldehyde.

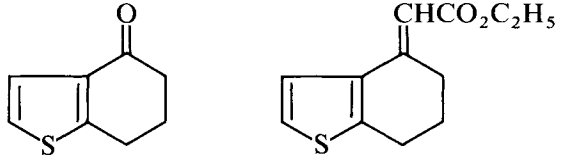


264 **265**

The reaction of 2-thiophene aldehyde with **266** gave **267**.[368] Polyenyl-substituted thiophenes have been prepared by the Wittig reactions, using various combinations of unsaturated aldehydes and phosphorus ylides.[369]

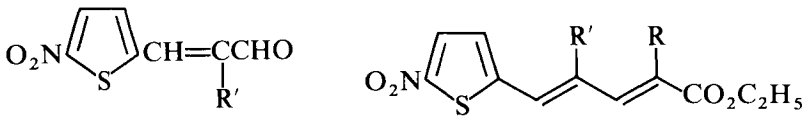
266 **267**

The ketone **268** has been reacted with triethyl phosphonoacetate to give **269**.[370]



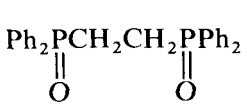
268 **269**

From aldehydes **270** and the appropriate phosphonate, compounds **271** were obtained.[16]

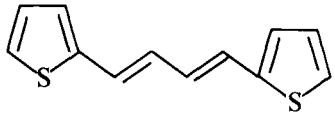


270 **271**

In a special modification of the phosphonate method, 2 mol of 2-thiophene aldehyde were reacted with **272** to give **273**.[306]

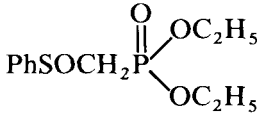


272

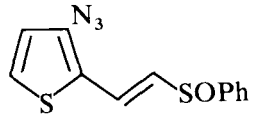


273

The reaction of **274** with butyllithium at $-78°C$, followed by 3-azido-2-thiophene aldehyde, gave **275** in a 65% yield.[188]

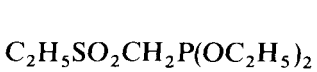


274

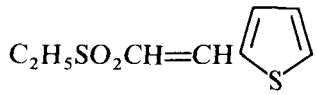


275

A patent describes the use of **276** in the preparation of **277** through the reaction with sodium hydride and 2-thiophene aldehyde.[371]



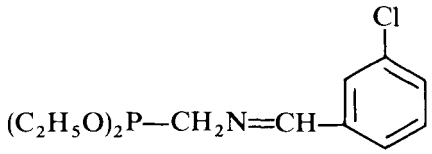
276



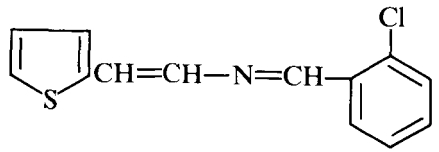
277

The bisulfite adducts of 2-thiophene aldehyde can be used in, both the Wittig reaction and the phosphonate modification, giving a higher yield of olefins than the aldehyde.[372,373]

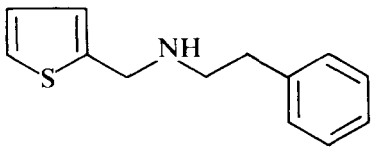
The reaction of the phosphonate **278** with 2-thiophene aldehyde in the presence of sodium hydride does not give the expected **279**, since reduction of



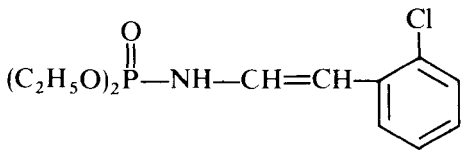
278



279

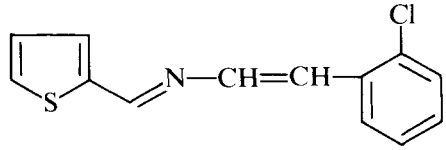


280



281

the product yielded **280**. The reason for this is that in the presence of base, **278** first rearranges to **281**, which with 2-thiophene aldehyde gives **282**.[374]

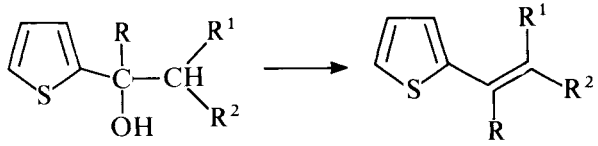


282

10. Dehydration of 1-(Thienyl)carbinols

A. Introduction

An often used conventional route to thienylvinyl derivatives **284** is the dehydration of 1-(thienyl)alkanols **283**. Secondary alcohols have often been prepared from thienyl ketones (obtained by Friedel–Crafts acylation of thiophenes) through reduction with $LiAlH_4$ or $NaBH_4$.



283 **284**

Alternatively, the alcohols **283** can be obtained through the reaction of Grignard reagents with thiophene aldehydes, thiophene ketones, through the reaction of thienyllithium, or thiophene magnesium derivatives with aldehydes, ketones, or esters. In many cases, the intermediate alcohols were not isolated and dehydration carried out directly with various acidic agents.

The usual problems connected with the dehydration step in the form of carbonium ion rearrangement, and lack of regio- and stereospecificity are also observed in the thiophene series. Alternatively, thermal dehydration under neutral or alkaline conditions has been carried out. For a short review on dehydration, see Ref. 375. Instead of dehydration, dehydrohalogenation has been applied to α-halogenated derivatives, obtained by side-chain bromination or in direct electrophilic substitutions.

B. Dehydration of Secondary Alcohols Obtained by Reduction of Thiophene Ketones

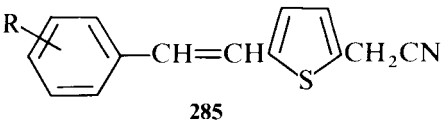
The easily polymerizable 2-vinylthiophene has been obtained by reduction of 2-acetylthiophene with $LiAlH_4$, followed by dehydration of the intermediate

carbinol, by heating at 180–190°C (100 mmHg in the presence of 1.5% by weight of $KHSO_4$ and a small amount of hydroquinone).[376] For earlier work on the reduction of 2-acetothienone and dehydration of the resulting carbinol, see Refs 378 and 379.

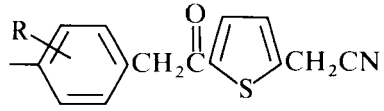
3-Vinylthiophene was prepared in a 54% yield by heating the carbinol to reflux in the presence of 1.2% of hydroquinone,[380] in analogy with the preparation of 2-vinylthiophene, according to Nazzaro and Bullock.[379] 2,5-Dichloro-3-vinylthiophene was prepared from the corresponding carbinol, obtained by aluminium isopropoxide reduction of the ketone.[381] Other examples describe the reduction of 5-alkyl-substituted 2-acetylthiophenes with $NaBH_4$ in ethanol, followed by dehydration with P_2O_5 in refluxing benzene[382] or by decomposition of the carbinol by vacuum distillation.[383]

3-Methyl-2-vinylthiophene was prepared by treating the carbinol with fused potassium hydroxide.[384] Reduction of 2-iodo-5-propionylthiophene with sodium borohydride and dehydration, using *p*-toluenesulfonic acid in benzene and azeotropic water removal, gave 2-iodo-5-(prop-1-enyl)thiophene.[322] 2-Propenylthiophene has been prepared by the Tschugaeff method by preparing the xanthogenate from 1-(2-thienyl)propanol, obtained by $LiAlH_4$ reduction of 2-propionylthiophene and decomposition at 150–200°C.[385] 1,3-Dichloro-4*H*-cyclopenta[*c*]thiophene was prepared by dehydration of the corresponding alcohol.[386]

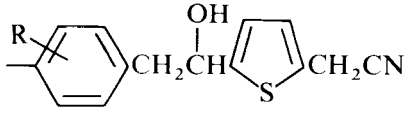
In connection with syntheses of compounds that inhibit platelet aggregation, compounds **285** were prepared by reduction with $NaBH_4$ of the ketones **286**, prepared by Friedel–Crafts acylation of 2-thenylcyanide, and reduction with $NaBH_4$ to **287**, followed by dehydration with 20–40% sulfuric acid.[152] It was not possible to transform **285** to the corresponding acids through acid or alkaline hydrolysis. However, **287** could be hydrolyzed to the acids with potassium hydroxide and dehydrated to **288** with 50% sulfuric or phosphoric acid.[152] Furthermore, some ketones, which are functionalized in the side chain, have been reduced and dehydrated. Thus **289** was prepared by treatment of the carbinol with pyridine and methanesulfonyl chloride in DMF[387] and **290**, by dehydration with acetic anhydride in acetic acid.[388] Some pyridinium derivatives were similarly prepared.[388]



285

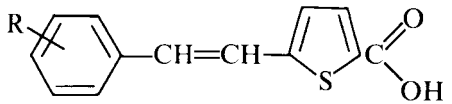


286

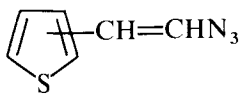


R = H, *p*-F, *p*-Cl, *m*-Cl, *p*-Br
p-OCH_3, *p*-isoC$_4$H$_9$, *p*-NO_2

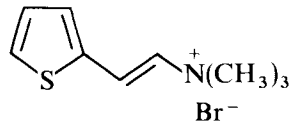
287



288

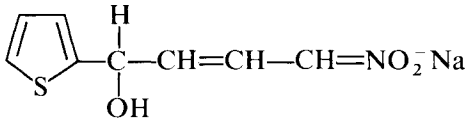


289

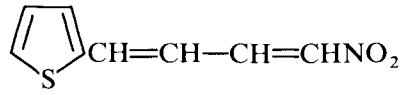


290

Compound **291**, obtained by reduction of the corresponding ketone with $NaBH_4$, gave **292** on treatment with hydrochloric acid.[389]

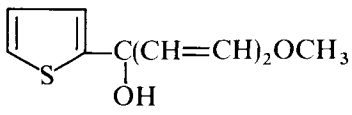


291

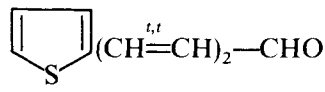


292

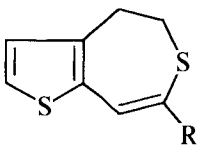
Treatment of **293** with acid gave **294**.[390] Similarly, **295–298** were obtained by reduction of the corresponding ketone with $NaBH_4$, followed by dehydration with polyphosphoric acid.[391,392] If the dehydration is carried out with *p*-toluenesulfonic acid in benzene, the product is **299**.[393]



293

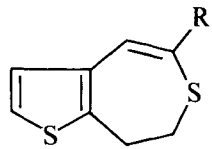


294



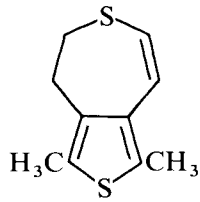
R = H, CH_3

295

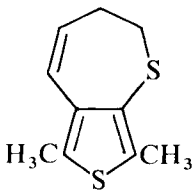


R = H, CH_3

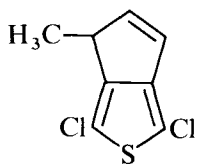
296



297



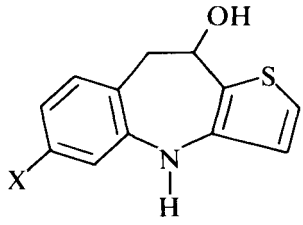
298



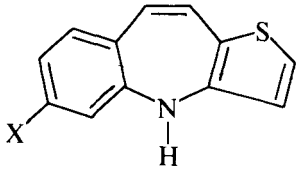
299

Acid treatment of **300**, obtained by $NaBH_4$ reduction of the corresponding ketone under different conditions, led only to complex mixtures of products. However, it was found that the hydroxyl group could be cleanly eliminated to give **301** under neutral conditions, by refluxing with Al_2O_3 CBT 1.[394]

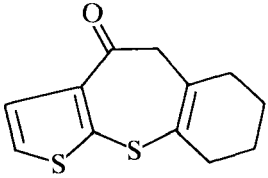
The ketone **302** was transformed to the enamine **303**, using the titanium tetrachloride method.[1027]



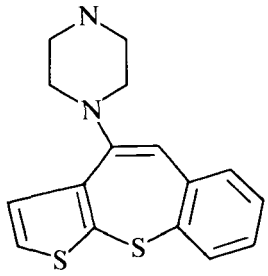
300



301

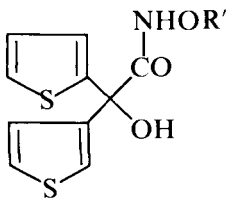


302

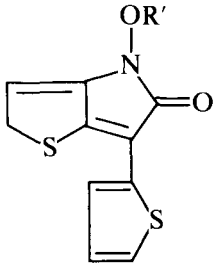


303

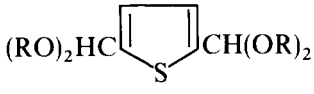
Dehydration of **304** with dicyclohexylcarbodiimide at room temperature gave the interesting product **305**.[395] The reaction of **306** with vinyl ether and anhydrous zinc chloride in glacial acetic acid yields **307**, which on hydrolysis with hydrochloric acid gave **308**.[1028] Metalation of **309**, followed by reaction with DMF and acid hydrolysis, gave **310**.[396] From the kinetics of the thermolysis of 1-thienylethyl acetates to vinylthiophenes, σ^+ constants for the 2- and 3-thienyl groups were obtained.[397]



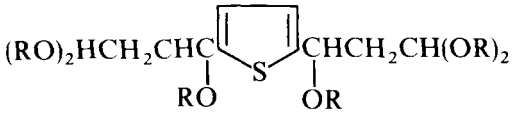
304



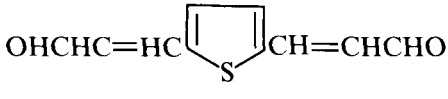
305



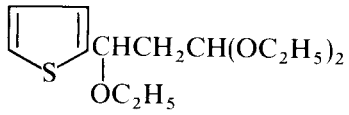
306



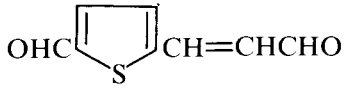
307



308



309

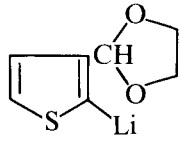


310

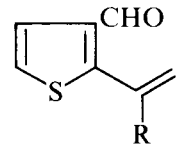
C. *Dehydration of Alcohols Obtained from Thienyl Metal Derivatives and Carbonyl Compounds*

3-Vinylthiophene was first obtained from 3-thiophene magnesium bromide and acetaldehyde. Dehydration was achieved with $KHSO_4$.[398,399] 3-Vinylthiophene was recently prepared again from 1-(3-thienyl)ethanol, obtained from 3-thienyllithium and acetaldehyde, by thermal dehydration through an alumina column at 250°C and 50 mmHg, although the yield was poor.[400] 5-Bromo-2-vinylthiophene was prepared by dehydration of the carbinol obtained from the mono-Grignard reagent of 2,5-dibromothiophene and acetaldehyde. Dehydration was achieved in this case by steam distillation in 2% sulfuric acid.[381] 5-Chloro-2-vinylthiophene was prepared by dehydration of the corresponding carbinol, synthesized from 5-chloro-2-thienyllithium or from the Grignard reagent of 2-bromo-5-chlorothiophene and acetaldehyde, or by Meerwein–Ponndorf–Verley reduction of 5-chloro-2-acetylthiophene.[381] Dehydration was achieved in the vapor phase over alumina at 300°C.[381] 3,4,5-Trichlorovinylthiophene was prepared via 3,4,5-trichlorothienyllithium, obtained through halogen–metal exchange from tetrachlorothiophene.[381] The above-mentioned lithium and Grignard reagents were also reacted with propionaldehyde and acetone to give isopropenyl thiophenes[280,381,401] and propenylthiophenes. In the earlier work, dehydration was usually achieved in the vapor phase over alumina at 300°C. Refluxing with anhydrous oxalic acid was used recently.[280]

In connection with the development of a new synthesis of thienopyridines, the lithium derivative **311** was reacted with acetone and acetophenone, giving **312** after hydrolysis and dehydration.[334]



311

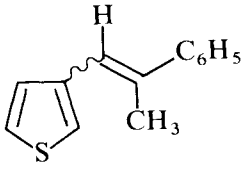


R = CH_3, C_6H_5

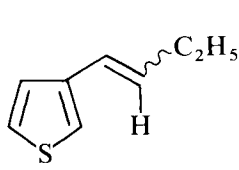
312

From 2-thiophene magnesium bromide and phenylacetaldehyde, 1-phenyl-2-(2-thienyl)ethene was obtained after dehydration with $KHSO_4$.[402] 3-Thienyllithium was reacted with 2-phenylpropenal and phenylacetone, and the carbinols dehydrated by refluxing in concentrated hydrochloric acid to give **313**

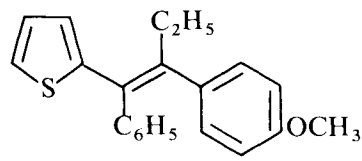
and **314**, respectively.[320] The 2-isomers were prepared in a similar manner.[322] Such compounds were needed for photochemial ring closure to phenanthrene analogs. In connection with work on stilbestrol analogs, **315** was prepared through reaction of 2-thienyllithium with 4-(*p*-anisyl)hexan-3-one. Dehydration was carried out with oxalic acid in aqueous ethanol.[403]



313



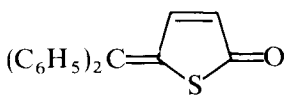
314



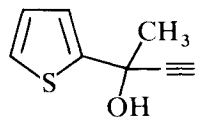
315

2-Thiophene magnesium halides have been reacted with ethyl *p*-methoxyphenyl acetate and 2-(phenylacetyl)thiophene for the preparation of triaryl-substituted ethenes, in connection with interest in estrogen antagonists. Dehydration was achieved by treating with anhydrous formic acid or by distillation *in vacuo* with a few drops of 20% sulfuric acid.[404]

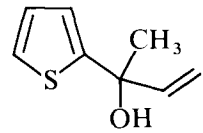
The product from the reaction of 5-methoxy-2-thienyllithium with benzophenone was demethylated on acid treatment, yielding **316**. 5-Methoxy-2-thienylllithium has also been added to various steroidal ketones, and under mild conditions, dehydration could be achieved without demethylation.[405] The reaction of 2-thiophene magnesium bromide with methyl vinyl ketone, or the reduction of **317** with sodium in liquid ammonia, gave **318**, which was dehydrated to the easily polymerized 2-(2-thienyl)butadiene **319**, characterized as the Diels–Alder adduct **320**.[406]



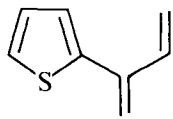
316



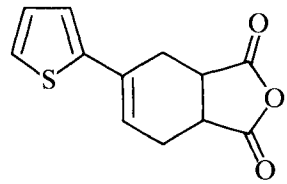
317



318

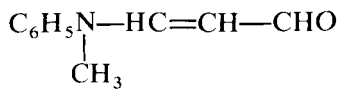


319

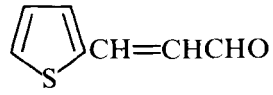


320

The reaction of 2-thiophene magnesium halide with **321** gave **322** in a 60% yield.[407]

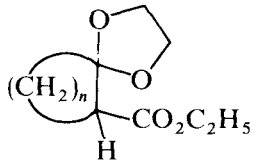


321



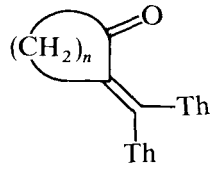
322

The reaction of 2-thiophene magnesium bromide or 3-thienyllithium with **323** gave mixtures of **324** and **325**, where $n = 3$, and only **325** where $n = 4$, on dehydration with hydrochloric acid of the intermediate carbinol.[408]

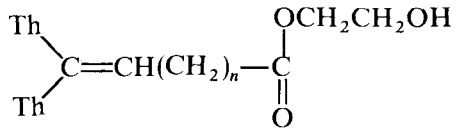


$n = 3, 4$

323

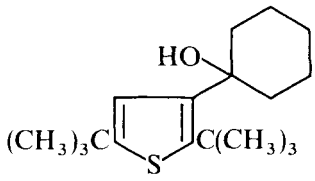


324

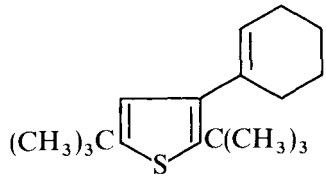


325

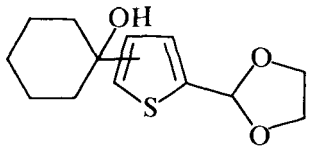
Various substituted thienyllithium or magnesium derivatives[409] have been reacted with cyclohexanone to give cyclohexenylthiophenes in connection with interest in phenylthiophenes, which were obtained on aromatization of the cyclohexenyl derivatives with chloranil.[157,409–412] The intermediate carbinol seldom was isolated, since acidic workup led directly to the cyclohexenyl derivatives. One exception was the sterically crowded carbinol **326**. In this case, refluxing with *p*-toluenesulfonic acid in benzene with water separation was



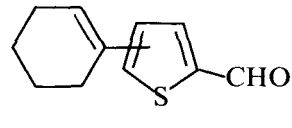
326



327



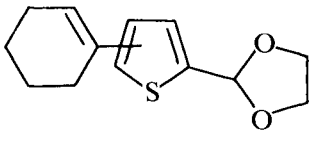
328



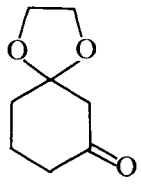
329

necessary to achieve dehydration to **327**.[412] The same was true for the 2-*t*-butyl derivative.[412] 3-(1-Cyclohexenyl)thiophene has been used as starting material for physiologically active compounds.[413] If **328**, prepared from 4- and 5-bromothiophene aldehyde ethylene acetal through halogen–metal exchange and reaction with cyclohexanone, was treated with $POCl_3$ and pyridine in refluxing benzene, both dehydration and acetal hydrolysis occurred to give **329** in somewhat impure and unstable form.

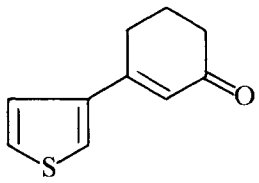
However, it was found that treatment of **328** with $POCl_3$ and pyridine at room temperature gave only dehydration to **330**, which on treatment with 90% acetic acid gave pure **329**.[157] The reaction of 3-thienyllithium with **331** gave **332** after dehydration with hydrochloric acid, which was aromatized with sulfur to 3-(3-hydroxyphenyl)thiophene.[414]



330

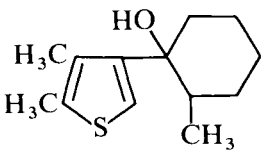


331

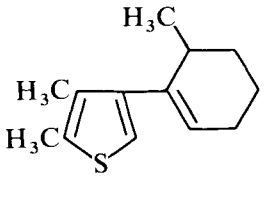


332

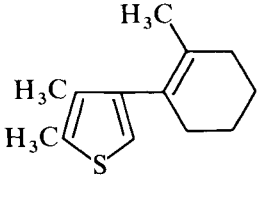
Another reason for the synthesis of cyclohexenylthiophenes was in connection with work on optically active (atropisomeric) thiophenes. Thus the reaction of 2,3-dimethyl-4-thienyllithium and 2-methylcyclohexanone gave **333**, which on dehydration with 5 M hydrochloric acid at room temperature gave a mixture of **334** and **335** in the ratio 8 : 2.[415] Similarly, the carbinol derived from the reaction of 2,5-dimethyl-3-thienyllithium led to a mixture of **336** and **337** in a 3 : 1 ratio. However, by using *p*-toluenesulfonic acid in toluene for the dehydration, the desired compounds **335**[416] and **337**[415] could be obtained exclusively. From 2,5-dimethyl-4-bromo-3-thienyllithium and 2-methyl-2-cyclohexanone, **339** and **340** were prepared.[415] In order to increase the steric hindrance, 4-bromo-2,5-dimethyl-3-thienyllithium was reacted with 2,6-dimethylcyclohexanone and 2,2,6-trimethylcyclohexanone to give **341** and **342** after dehydration of the intermediate carbinols with *p*-toluenesulfonic acid in toluene. Halogen–metal exchange of **342** with butyllithium followed by reaction with carbon dioxide gave **343**, which indeed could be resolved into optical antipodes.[416]



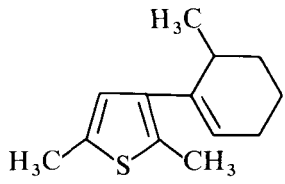
333



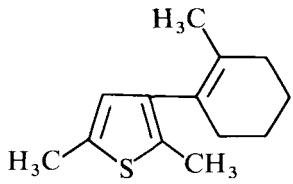
334



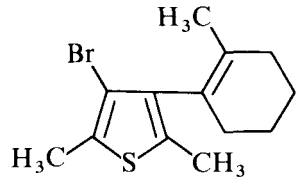
335



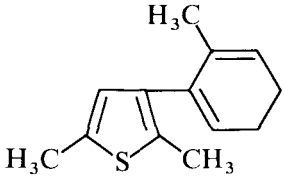
336



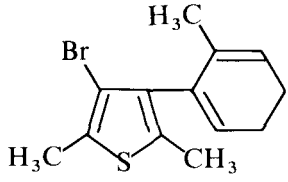
337



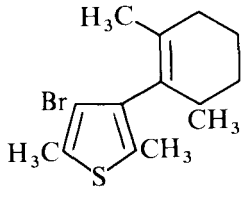
338



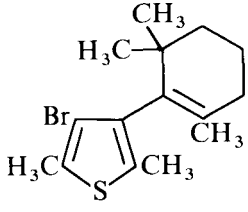
339



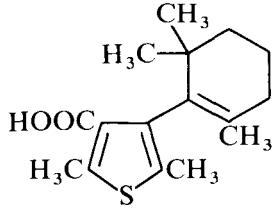
340



341

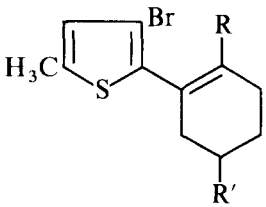


342



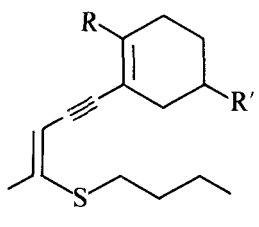
343

Metalation of 4-bromo-2-methylthiophene with LDA, followed by 2-methylcyclohexanone and (−)-menthone, gave **344**, which on halogen–metal exchange with butyllithium at room temperature ring-opened to give **345**.[329] Both 2- and 3-thienyllithium have been reacted with various cyclic ketones, and the mass spectra of the cycloalkenylthiophenes, obtained after dehydration, were studied.[417] The reaction of 2,5-dimethyl-3-thienyllithium, 4-bromo-2,5-dimethyl-3-thienyllithium, and 3-thienyllithium with (−)-methone gave, respectively, **346** and **347** after dehydration of the intermediate carbinols. It is important to use only 0.1 eq of *p*-toluenesulfonic acid in the dehydration. If one



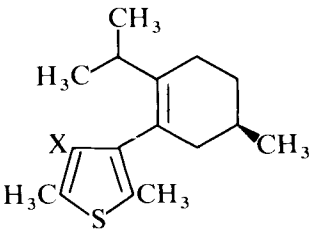
R = CH_3, R′ = H
R = $CH(CH_3)_2$, R′ = CH_3

344



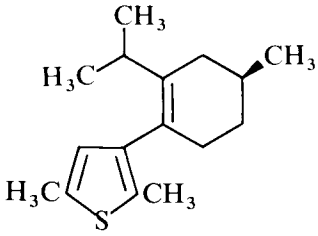
345

equivalent was used, as is normally the case, ring closure to the free 4-position occurred to give **348**.[418] 3-Thiophene magnesium bromide has also been reacted with cycloheptanone and cyclooctanone, in addition to methyl-substituted cyclohexanones and fused cycloalkanones. Dehydration to the thienylcycloalkene was achieved with 10% sulfuric acid.[409]

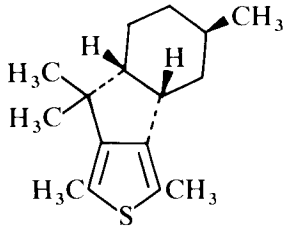


X = H, Br

346

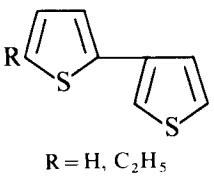


347



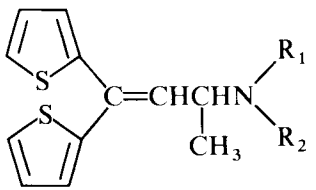
348

2-Thiophene magnesium bromide and 5-ethyl-2-thiophene magnesium bromide were reacted with 3-ketotetrahydrothiophene to give **349** after acidic decomposition, steam distillation and aromatization with chloranil.[419] The Grignard reaction of optically active steroid derivatives with 2- and 3-thiophene magnesium bromide has been used for the preparation of thienyl γ-lactones.[420] In connection with work on thiophene derivatives with analgesic and other pharmacologic activity, geminal dithienyl derivatives, such as **350**,[421–426] analogous 3-thienyl isomers,[427–429] **351** and **352**,[430] and related compounds **353**,[431] as well as tinofedrin **354**,[432–434] have been prepared through the reaction of 2- or 3-thienyllithium or thiophene magnesium bromide with

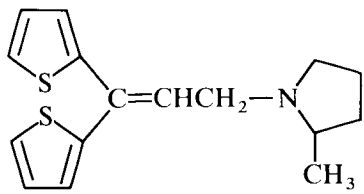


R = H, C_2H_5

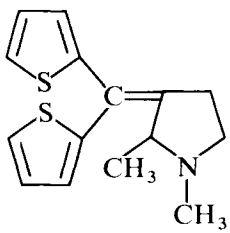
349



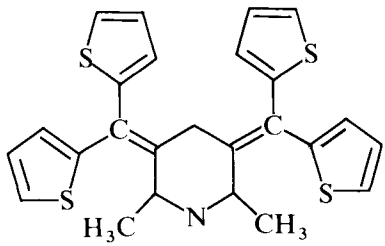
350



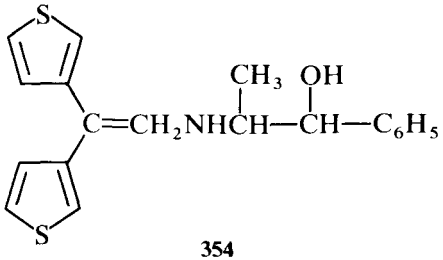
351



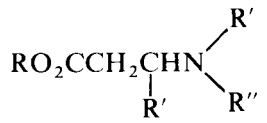
352



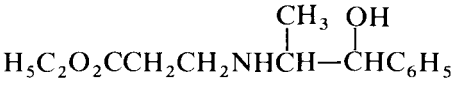
353



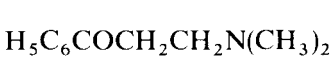
354



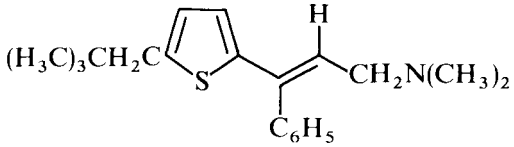
355



356



357



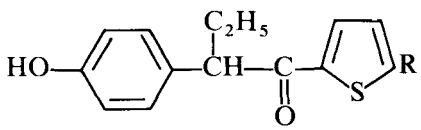
358

appropriate esters, such as **355** or **356**. The piperidino derivative of **350** has been resolved into antipodes.[435] Reaction of 5-neopentyl-2-thienyllithium with **357** gave **358** after dehydration with HCl–HOAc, with antihistaminic properties.[436]

D. Dehydration of Alcohols Obtained from Thiophenecarbonyl Derivatives and Organometallic Reagents

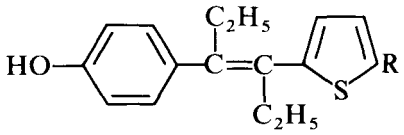
2-Thiophene aldehydes and 2-acetylthiophenes have been reacted with aryl- and alkyl-Grignard reagents.[311,437–443]

The reaction of **359** with excess ethylmagnesium bromide, followed by dehydration by refluxing with 6% aqueous oxalic acid, gave some thiophene analogs of diethylstilbestrol **360**.[444] The reaction of ethyl 2-thienylglyoxylate with cyclopentylmagnesium bromide gave **361** after dehydration.[445]

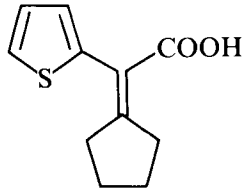


R = H, Br

359

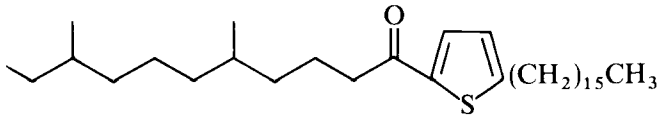


360

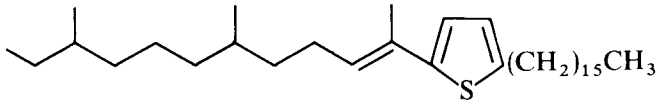


361

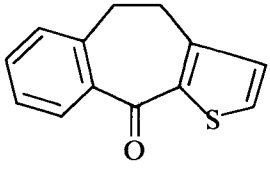
In connection with the preparation of long-chain branched alkanes through Raney-nickel desulfurization, ketone **362** was reacted with methylmagnesium iodide and dehydrated with dilute hydrochloric acid to yield **363**.[446] Various Grignard reagents with amino groups have been added to the ketone **364**, to give **365** after dehydration.[264,447–449] Various derivatives have also been prepared from **366** and various Grignard reagents, containing amino groups.[450]



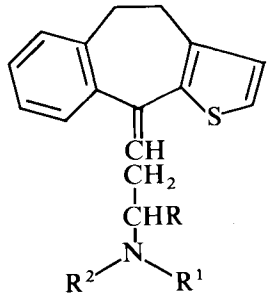
362



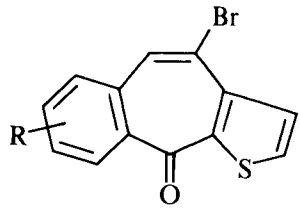
363



364

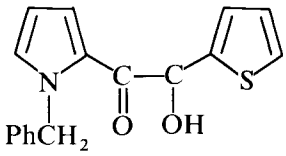


365

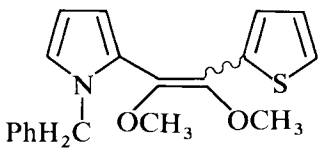


366

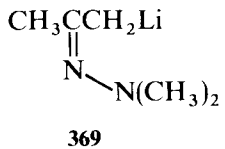
Reaction of **367** with methyl *p*-toluene sulfonate and potassium *t*-butoxide in DMSO gave **368**.[451] The reaction of **369** with 2,2′- and 3,3′-dithienyl ketone gave **370** after dehydration and hydrolysis of the hydrazone. Similarly, from **371**, **372** was obtained.[452]



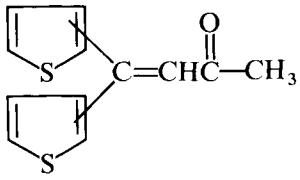
367



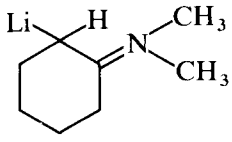
368



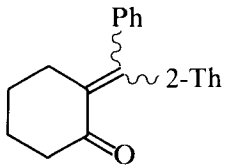
369



370



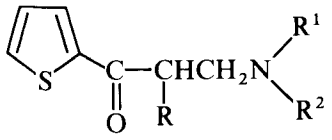
371



372

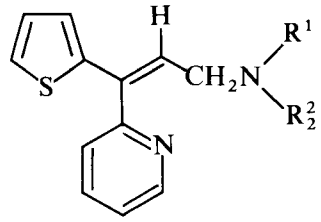
Buu-Hoi and coworkers in particular, but also some other groups, synthesized a large number of thienylethylene derivatives, especially thiophene analogs of stilbene, in connection with studies of thiophene derivatives of potential biological interest. They reacted thiophene aldehydes, and especially various thienyl aryl ketones, with benzylmagnesium halides. Dehydration was usually achieved by refluxing the crude carbinol for 5 min with 98% formic acid.[118,267,404,441,453–460] The yields in the reactions with benzyl Grignard reagents were variable, due to the formation of bibenzyls.[441] In the earlier papers no structural assignments of the isomeric triaryl ethenes were made, and although in some cases sharp melting points are given, the isomeric purity is not obvious. In later work, *cis–trans*-isomers were separated by chromatography on alumina.[441]

In connection with the synthesis of thiophene derivatives with potential antispasmodic, analgesic, or local anesthetic properties, 2-acetyl and 2-propionylthiophene were converted to Mannich bases, **373**, which were then reacted with benzylmagnesium halides, arylmagnesium halides, 2-picolyllithium, or aryllithium derivatives, to give compounds such as **374** and **375**. Dehydration was carried out with 85% aqueous sulfuric acid. *Cis–trans*-isomers were in some cases separated by fractional crystallization or base-exchange chromatography and structural assignments were made by spectroscopic means.[461–467] For the synthesis of similar structures, using thienyllithium or thiophene magnesium halides see also Section C.

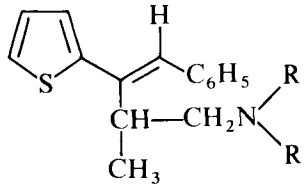


R = H, CH_3

373



374

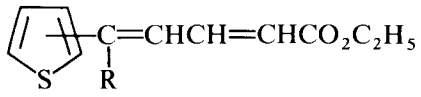


375

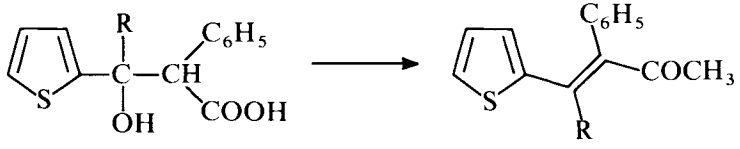
E. Dehydration of Alcohols Obtained from Thiophenecarbonyl Compounds through the Reformatsky Reaction

The Reformatsky reaction of thiophene aldehydes or ketones with α-bromo esters and zinc has been extensively studied.[468–471] The resulting hydroxy compounds partly dehydrate on vacuum distillation. However, complete dehydration to β-thienylacrylates was almost quantitatively achieved through refluxing for a few hours with 6% aqueous oxalic acid.[468] The isomeric purity and structure of the tri- and tetra-substituted ethenes was not determined.

The Reformatsky reaction between thienylcarbonyl derivatives and ethyl γ-bromocrotonate gave mixtures of isomeric hydroxy derivatives, which, however, on dehydration gave **376**.[470] Various modifications of the Reformatsky reaction with thenylcarbonyl derivatives have been investigated. Reaction of 2-acetylthiophene with ethyl chloroacetate, using a magnesium copper alloy, gave ethyl β-methyl-β-(2-thienyl)acrylate in a 40% yield. Using magnesium and mercuric chloride allowed the condensation with ethyl α-bromoisovalerate and ethyl bromomalonate with 2-acetylthiophene, and after dehydration ethyl α-isopropyl-β-methyl-β-(2-thienyl)acrylate and ethyl α-carbethoxy-β-methyl-β-(2-thienyl)acrylate were obtained in 43% and 30% yields, respectively.[469] The Reformatsky reaction between 2-acetylthiophene and ethyl dibromo- or dichloro acetate, using zinc and cupric chloride, gave the same products as with the monohaloester, but in a lower yield, since reduction of one halogen occurred.[469] The Reformatsky reaction has also been carried out with phenyl 2-thienyl ketone and dithienyl ketone,[472,473] and dehydration was performed



376

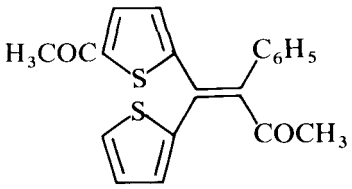


377 378

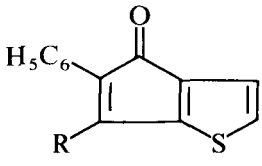
with oxalic acid. Reaction of **377** with acetic anhydride acetic acid in the presence of zinc chloride led unexpectedly to methyl ketone **378**.

Mixtures of stereoisomers were obtained, which were separated. The reaction probably proceeds via the mixed anhydride.[474]

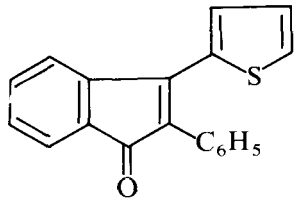
The reaction of **377** (R = 2-thienyl) gave acetylation in one of the thiophene rings, leading to **379** under these conditions as the main product and **378** (R = 2-thienyl) as the minor one. It was not proved which thiophene ring was acetylated, although acetylation of **378** (R = 2-thienyl) gave **379**.[474] Under other reaction conditions, **379** could be transformed to various products. Treatment with concentrated sulfuric acid for a few minutes led to **380**. If dehydration was carried out in acetic anhydride in the presence of $AlCl_3$, **377** (R = Ph) gave **380** (R = Ph) as well as **381**.[475]



379



380

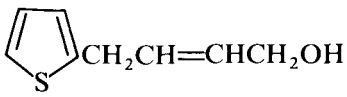


381

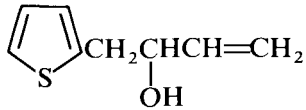
11. Dehydration of 2-(2-Thienyl)alkanols

The reaction of 2-thienylsodium[476] or 2-thienylmagnesium iodide[477,478] with ethylene oxide gave 2-(2-thienyl)ethanol, which was dehydrated to 2-vinylthiophene, either with aqueous hydrochloric acid[476,477] or by distilling from copper and powdered potassium hydroxide.[478] The reaction of 2-thienylsodium and 2-thienylmagnesium bromide with various epoxides, such as propylene oxide, styrene oxide, and epichlorohydrin, have been compared. The Grignard route gives higher yields of the thienylethanols. Dehydration was achieved by distillation from an equal weight of potassium hydrogen sulfate.[402]

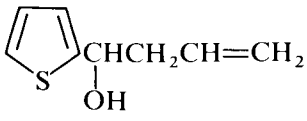
The reaction of 2-thienylmagnesium bromide with butadiene monoxide gave **382**, while the corresponding reaction with 2-thienylsodium led to **383**. A third carbinol **384** was obtained through the reaction of 2-thiophene aldehyde with allylmagnesium bromide. Dehydration of these three butenols with anhydrous potassium hydrogen sulfate gave the very easily polymerized 1-(2-thienyl)-1,3-butadiene **385**, which could not be purified, but was characterized as the Diels–Alder adduct with maleic anhydride **386**.[406]



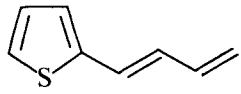
382



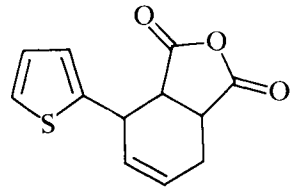
383



384



385

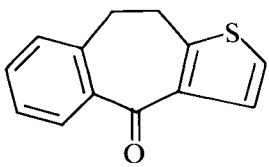


386

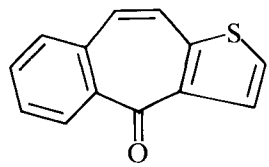
12. Dehydrohalogenation of 1-(Thienyl)alkyl Halides

Chloroethylation of thiophene with paraldehyde and hydrochloric acid gives 1-(2-thienyl)ethyl chloride, which is dehydrochlorinated without isolation to 2-vinylthiophene, via quaternization with pyridine.[479-481] A detailed procedure has been publised in *Organic Synthesis*, which gives a 50–55% yield based on thiophene.[482] 5-Chloro-2-vinylthiophene and 5-bromo-2-vinylthiophene have been obtained in 47 and 35% yields, respectively, by essentially the same procedure.[483] 2-Vinylthiophene has also been obtained by catalytic dehydrogenation of 2-ethylthiophene over a copper–iron catalyst at high temperature.[484]

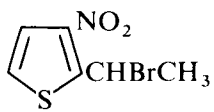
Side-chain bromination of **387**, followed by dehydrobromination, has been used for the preparation of **388**.[264] Bromination of 2-ethyl-3-nitrothiophene gave **389**, which was transformed to the carbinol via the formate ester. Dehydration to **390** was achieved with *p*-toluenesulfonic acid in benzene with azeotropic removal of water.[280]



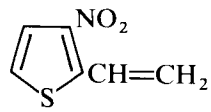
387



388

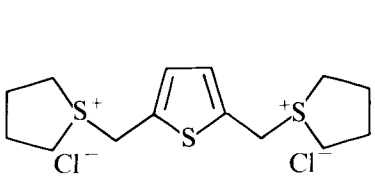


389

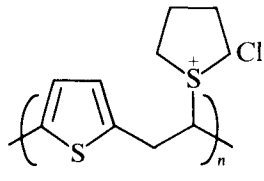


390

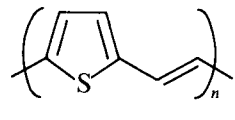
Reaction of 2,5-dichloromethylthiophene with tetrahydrothiophene gave **391**, which on treatment with sodium hydroxide polymerized to **392**, which in turn on heating gave the highly conducting substance poly-(2,5-thienylene)vinylene **393**.[485]



391



392

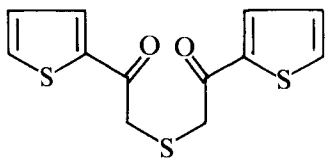


393

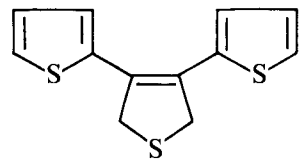
13. From Thiophenecarbonyl Compounds by Various Other Methods

The treatment of 2-acetylthiophene with PCl_5, followed by dehydrochlorination, is a poor method for synthesizing 2-thienylacetylene. It was shown that the major products are the *E*- and *Z*-isomers of 1,2-dichloro-1-(2-thienyl)ethene.[486] The Corey method, which is the reaction of thiophene aldehydes with carbon tetrabromide and triphenylphosphine, gives 1,1-dibromo-2-(2-thienyl)ethenes in quantitative yields; these compounds have been used as intermediates for the synthesis of thienylacetylenes.[487–490] Reduction of 2-thiophene aldehyde with a low-valent titanium reagent prepared from $TiCl_4$ and zinc gave *E*-1,2-di(2-thienyl)ethene in a 71% yield. The reaction was also successfully applied to 5-formyl-2,2′-bithienyl and 5-formyl-2,2′ : 5′-2″-terthienyl.[488,491]

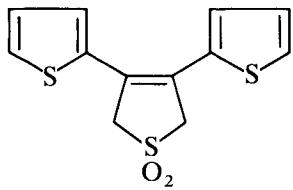
From **394**, **395** was similarly prepared, and through oxidation with *m*-CPBA **395** was converted to **396** in an 87% yield. Heating of **396** to 170°C at 0.3 mmHg gave **397** in a 91% yield.[492]



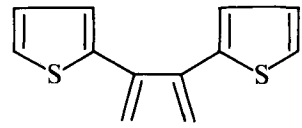
394



395

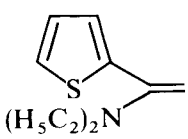


396

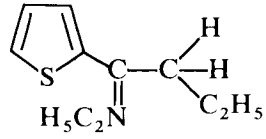


397

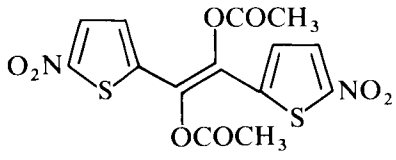
The reaction of 2-acetylthiophene with diethylamine in the presence of $TiCl_4$ led to a mixture containing 80% of **398** and 20% of **399** in a 58% yield.[493] Only 5-nitro-2-thenaldehyde and the corresponding furan derivative gave self-condensation products as **400** on reaction with pyridine in acetic anhydride.[494]



398



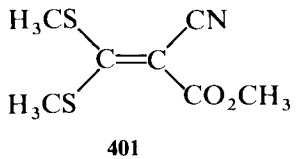
399



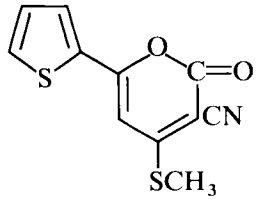
400

In contrast to simple benzaldehydes, the reaction of 2-thiophene aldehyde with dichloroketene gives direct decarboxylation of the intermediate β-lactone, yielding 1,1-dichloro-2-(2-thienyl)ethylene in a low yield.[495] The reaction of *Z*-2-(trimethylsiloxy)vinyllithium, prepared through halogen–metal exchange between *Z*-2-(trimethylsilyloxy)vinyl bromide and *t*-butyllithium at $-70°C$, with 2-thiophene aldehyde, gave (*E*)-3-(2-thienyl)propenal in a quantitative yield, and appeared to be the best method for *vinylogation* of carbonyl compounds.[496] The reaction of 2-thiophene aldehyde with ethoxyacetylene in the presence of 1 eq of BF_3 etherate gave ethyl 2-(2-thienyl)acrylate in a 53% yield.[497,498]

The reaction of **401** with 2-acetylthiophene and potassium hydroxide in DMF led to **402** in an 88% yield.[499]

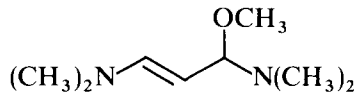


401

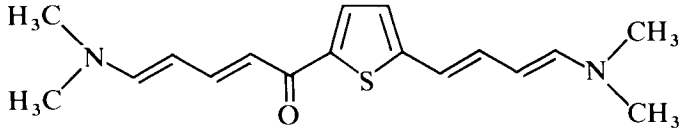


402

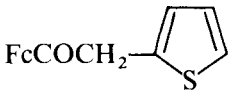
The condensation of 2-acetyl-5-methylthiophene with **403** occurs at both methyl groups, yielding **404** in a 64% yield.[500] The reaction of the ferrocenyl derivative **405** with the Vilsmeyer reagent gave **406** as a cis–trans mixture as the main product, besides smaller amounts of the nonformylated α-chlorovinylferrocene.[501] β-Chloro-β-(2-thienyl)acrolein has similarly been prepared in a low yield by treating 2-acetylthiophene with the Vilsmeyer reagent.[502]



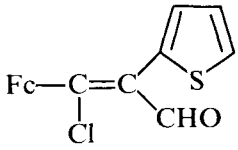
403



404

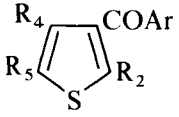


405



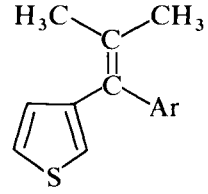
406

Photochemical reactions of the ketones **407** with isobutylene in benzene gave **408** in a low yield.



$R_2=CH_3$, $R_4=R_5=H$
$R_4=CH_3$, $R_2=R_5=H$
$R_2=R_5=CH_3$, $R_4=H$
$R_2=R_4=R_5=H$

407

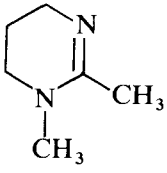


$Ar=C_6H_5$
$Ar=C_6H_5$
$Ar=C_6H_5$
$Ar=o\text{-}CH_3C_6H_4$

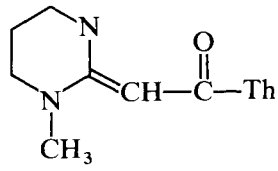
408

Authentic **408** was also prepared in a very low yield through the reaction of **407** with isopropylmagnesium bromide.[503]

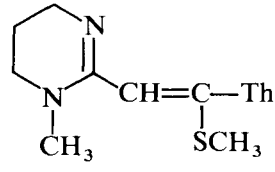
Reaction of thiophene aldehydes with **409** and sulfur (Willgerodt–Kindler) gave **410**, which on methylation with methyl iodide yielded **411**.[504]



409

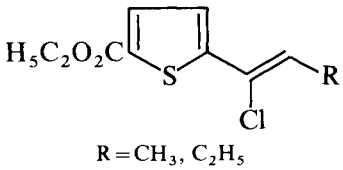


410



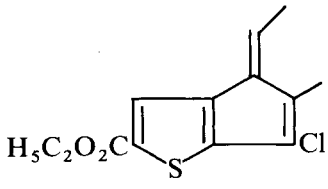
411

When ethyl 2-thiophenecarboxylate was treated with propionyl chloride or butyryl chloride in the presence of $FeCl_3$, **412** was obtained in a 62% (R = CH_3) and 51% (R = C_2H_5) yield, in addition to **413** in 18% (R = CH_3) and **414** in a 21% (R = C_2H_5) yield. The reaction of ethyl 5-butyryl-2-thiophenecarboxylate



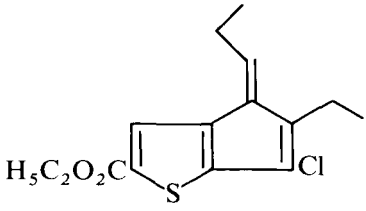
$R=CH_3$, C_2H_5

412

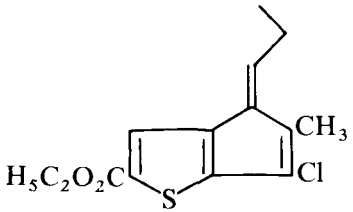


413

with propionyl chloride and $FeCl_3$ gave only **412** (R = C_2H_5), while ethyl 4-butyryl-2-thiophenecarboxylate gave **415**.[505]



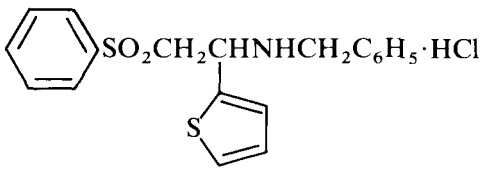
414



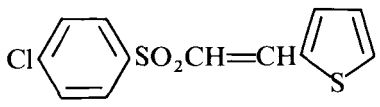
415

The reaction of 2-acetylthiophene with diethyl phosphite and 3–10 mol% of sodium amide, followed by heating of the intermediate hydroxyphosphonate at 140°C, gave a 56% yield of 2-vinylthiophene.[506]

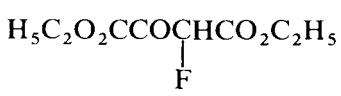
Reaction of 2-thiophene aldehyde and benzylamine with *p*-chlorobenzenesulfonylacetic acid in refluxing glacial acetic acid led to **416** in a 23% yield. Heating of **416** with a small amount of methanol resulted in an 8% yield of **417**.[507] The condensation of 2-thiophene aldehyde in dibutyl ether with **418** gave **419** in a 60% yield.[508]



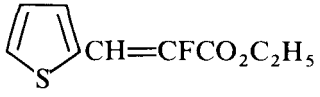
416



417

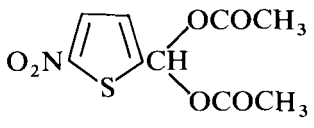


418

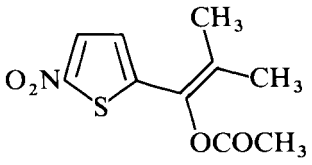


419

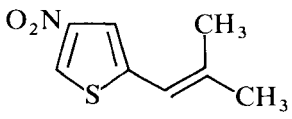
The reaction of the diacetate from 5-nitro-2-thiophene aldehyde **420** with lithium 2-nitropropan-2-ide in DMSO gave **421** in a 70–80% yield.[509] The reaction of 4-nitro-2-thenylidene acetate proceeded differently and produced only small amounts of **422** and **423**.[510]



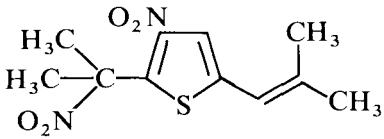
420



421



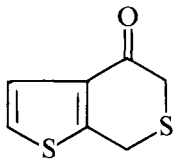
422



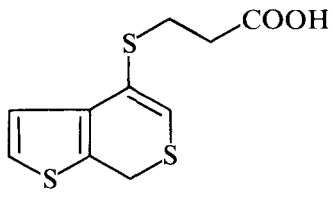
423

Vinylthiophenes were also present in low yields in the complex reaction mixtures formed in the reaction of 4-nitro-thienyl-methyl and -ethyl chlorides and acetates with lithium 2-nitropropan-2-ide.[511]

The reaction of **424** with β-mercaptopropionic acid in benzene with *p*-toluenesulfonic acid and water separation yielded 65% of **425**.[512]

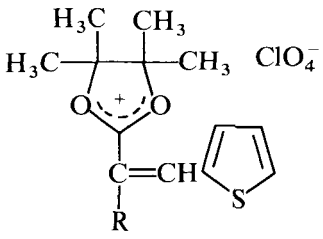


424



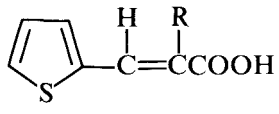
425

The reaction of 2-thiophene aldehyde diethyl acetal with 2-alkyl-4,4,5,5-tetramethyldioxolanium perchlorate in acetic acid–acetic anhydride led to **426**, which on brief hydrolysis with 5% sodium hydroxide gave the acrylic acids **427**.[513]



R = H, CH_3

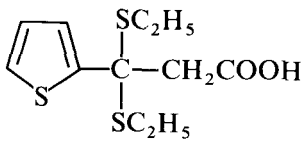
426



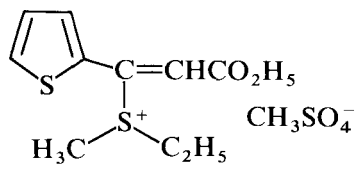
R = H, CH_3

427

The reaction of **428** with dimethylsulfate gave **429**.[514]



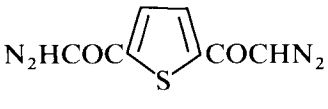
428



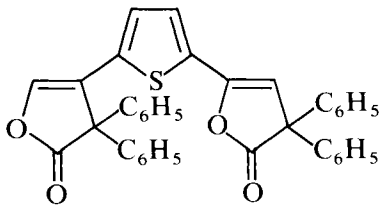
429

A number of thienylvinyl derivatives have been prepared via carbenoid intermediates. Thus, oxidation of the hydrazone from 2,2′-dithienyl ketone produced the corresponding diaryldiazomethane derivatives, which reacted with dichlorocarbene derived from chloroform, methyl, or ethyl trichloroacetate, to give 1,1-dichloro-2,2-di(2-thienyl)ethene and 1,1-dichloro-2-phenyl-(2-thienyl)ethene in a 23% and a 49% yield.[517–519]

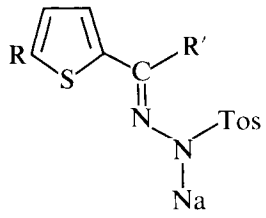
The 2,5-bisdiazoacetylthiophene **430**, prepared from 2,5-thiophenedicarboxylic acid dichloride, yielded 18% of **431** with diphenyl ketene.[515] The pyrolytic reactions of the sodium salts of tosylhydrazones derived from 2-thiophene aldehydes and ketones **432** at 300°C, lead to *cis–trans*-isomeric ethylenes **433** and **434** as the main products via the diazo compound and carbenes.[516] From 3-thiophene aldehyde tosylhydrazone, 7% of *cis*-1,2-di(3-thienyl)ethene and 17% of the *trans*-isomer was obtained.[516]



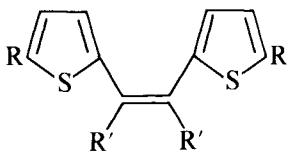
430

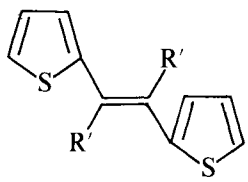


431



432

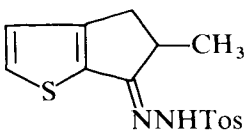




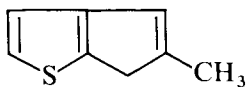
	Yield	
R = R′ = H	8%	20%
R = H, R = CH_3	–	19%
R = CH_3, R′ = H	7%	14%

433 **434**

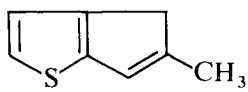
Treatment of the tosylhydrazone **435** with 2.5 eq of butyllithium gave a mixture of **436** and **437** in a 41% yield.[520]



435

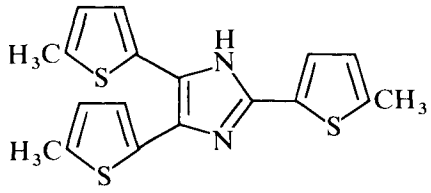


436



437

Pyrolysis of the azines derived from 2-thiophene aldehyde and 5-methyl-2-thiophene aldehyde gave 1,2-di(2-thienyl)ethene and the corresponding 5-methyl derivative in about 30% yield. In the latter case the imidazole **438** was also reportedly formed.[321,522]



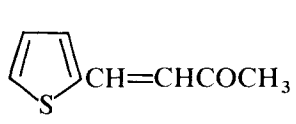
438

14. From Thiophenes, Halothiophenes, and Thienyl Metal Derivatives and Alkenes

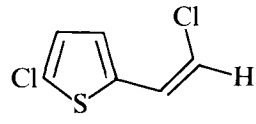
A. From Thiophenes and Alkenes

Treatment of thiophene with 2-bromo-1-(5-nitro-2-furyl)ethene in 1,2-dichloroethane in the presence of anhydrous $AlCl_3$ gave 2-(2-thienyl)-1-(5-nitro-2-furyl)ethene in a good yield.[523]

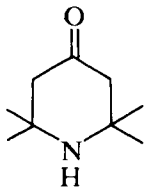
Electrophilic condensation of thiophene with 2-acetylvinyl chloride with $SnCl_4$ as a catalyst led to **439**.[524] The reaction of chloroacetaldehyde diethylacetal with 2-chlorothiophene in the presence of 72% sulfuric acid gives the *cis*-isomer **440** in a 16% yield.[525] Thiophene 3-methyl- and 3-bromothiophene have been condensed at 60–100°C, using 85% sulfuric acid with **441** to produce **442**. With 2-chloro and 2-methylthiophene mono-substituted products were obtained. Thiophene was also condensed with 1,2,5-trimethylpiperid-4-one to give **443**.[526] The pyrromethene **444** has been prepared form 2-thiophene aldehyde and 3-ethyl-2,4-dimethylpyrrol through reaction with $POCl_3$ and neutralization of the precipitate with $Ca(OH)_2$.[527]



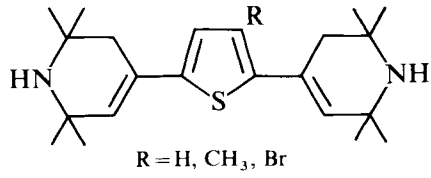
439



440

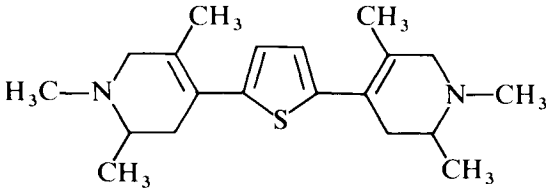


441

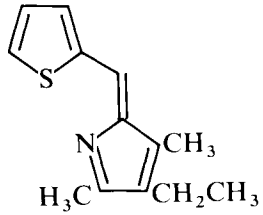


R = H, CH_3, Br

442



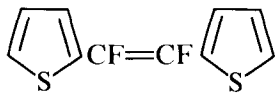
443



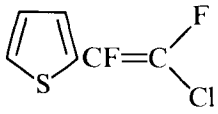
444

The reaction of 2-thiophene magnesium bromide with 1-(methylanilino)-propene-3-al gave 1-(2-thienyl)propen-3-al.[528]

Dixon found in 1955 that aromatic lithium compounds reacted with fluoro-olefins at -60 to $-80°C$ with the elimination of lithium fluoride. Thus 2-thienyllithium gave a 30% yield of **445** with tetrafluoroethylene, and a 55% yield of **446** was obtained with trifluorochloroethylene.[529,530]

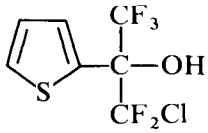


445

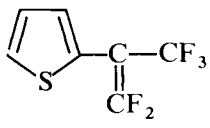


446

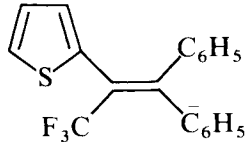
The latter compound can also be prepared from thienylmagnesium, calcium, and strontium derivatives.[531] The reaction with trifluorochloroethylene has also been applied to 5-bromo-2-thienyllithium, 5-trimethylsilyl-2-thienyllithium, and 2,5-dilithiothiophene.[532] Reaction of 2-thienyllithium with pentafluorochloroacetone gave **447**, which was converted to **448** with zinc and zinc chloride. On reaction with 2 eq of phenyllithium, **448** gave **449**.[533] The reaction of 2-thienyllithium with 1,1-dichloro-2,2-difluoroethene gave **450** in an 81% yield.[534] Compound **451** has also been prepared from 2,5-dilithiothiophene.[535]



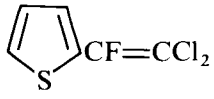
447



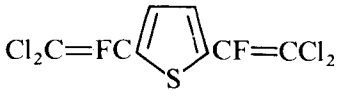
448



449



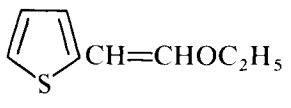
450



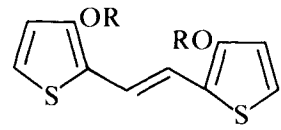
451

B. Transition-Metal-Catalyzed Couplings

The direct coupling of thiophenes with olefins catalyzed by transition-metal complexes has revolutionized the synthesis of vinylthiophenes during the last 10–15 years. In 1972, Corriu showed that nickel compounds, such as nickel(II) acetyl acetonate or $(PPh_3)_2NiCl_2$, catalyzed the coupling between aromatic Grignard reagents and olefinic halides. From 2-thienylmagnesium bromide and *trans*-styrylbromide, *trans*-2-styrylthiophene was obtained.[536] 3-Methoxy- and 3-ethoxy-2-thienylmagnesium bromide were coupled under nickel catalysis with 1,2-dichloroethene to give **453**, which was polymerized to poly(3-alkoxy)(-2,5-thienylenevinylenes).[537] β-Bromovinyl ethyl ether and *vic*-bromotrimethylsilyl-oxyalkenes could also be coupled with 2-thienylmagnesium bromide, using $[Ni(dppp)Cl_2]$ as a catalyst to produce **452** in a 53% yield[538] and **454**[539] in a 27% yield as the hydrolyzed **455**. 2-Thienylmagnesium bromide has been coupled with 1,2-dichloroethene to *trans* 1,2-dithienylethene, using the same catalyst.[540]

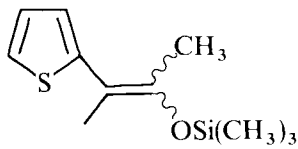


452

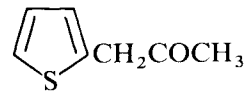


$R = CH_3, C_2H_5$

453

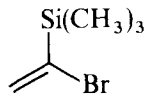


454

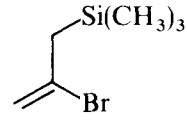


455

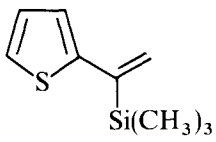
2-Thienylmagnesium has been coupled in the presence of catalytic amounts of $PdCl_2(dppb)$ with **456** and **457** to give **458** and **459** in a 81 and 78% yields, respectively. Alternatively, **459** was also prepared from 2-bromothiophene and the zinc derivative **460**.



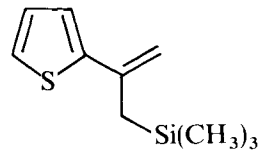
456



457



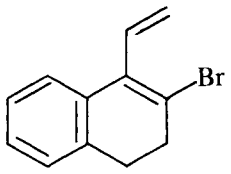
458



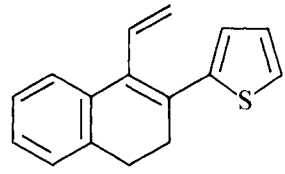
459

460

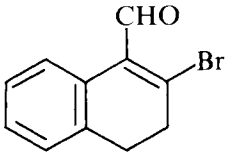
3-Thienyl isomers were prepared from 3-bromothiophene and 1-trimethylsilylvinylmagnesium bromide or zinc chloride. The zinc derivatives gave no by-products in the form of bithienyl or double-bond isomers.[541] Instead of Grignard reagents, organozinc derivatives can also be used. Thus, the Pd-catalyzed coupling between 2-thienylzinc and vinyl bromide has been employed for the preparation of 2-vinylthiophene in a 66% yield.[542] 2-Thienylzinc bromide (from the lithium derivative) was coupled with **461** to give **462**. The reaction could also be carried out in the opposite sense by reacting 2-iodothiophene with the zinc derivative derived from **461**. Compound **463** and its acetal were also coupled with 2-thienylzinc bromide to give the corresponding vinylthiophenes.[543] Fluorinated vinylzinc dervatives, such as **464**, have been coupled with 2-iodothiophene under Pd(0) catalysis to give **465**.[545,546]



461



462

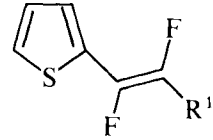


463

R^1—CF=CF ~ ZnCl

R^1 = F, *s*-C_4H_9

464



465

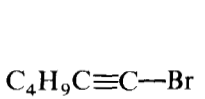
5-Methyl-2-thienylmercury chloride has been cross-coupled with vinyl bromide using $ClRh(PPh_3)_3$ as a catalyst, which led to 5-methyl-2-vinylthiophene.[547] In the presence of catalytic amounts of $Rh_4(CO)_{12}$, thiophene adds to diphenylacetylene to produce 1-(2-thienyl)-1,2-diphenylethene in a 48% yield.[548]

In 1973 Asano and coworkers demonstrated that the reaction of thiophene with stoichiometric amounts or palladium(II) and styrene gave a mixture of 13% *trans*-2-styrylthiophene and 36% *trans,trans*-2,5-distyrylthiophene.[549] 2-Thienylpalladium chloride has also been prepared from the chloromercury derivative and Li_2PdCl_4 and reacted with olefins.[550] Palladium-assisted alkenylation of thiophenes was later also carried out with acrylonitrile and methyl acrylate, giving mixtures of mono- and divinylated products.[551] 2-Thiophene aldehyde was also alkenylated in the 5-position with methyl acrylate.[1016] The alkenylation could, however, be rendered catalytic by using a $Pd(OAc)_2$–$Cu(OAc)_2$ catalyst system.[551]

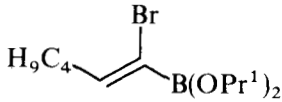
The Heck reaction, i.e., Pd(0)-catalyzed vinylic substitution reactions with aromatic halides, has been applied to 2-bromothiophene and 4-vinylpyridine, using triethylamine as a base to give (*E*)-2-(4′-pyridylvinyl)thiophene in a

57% yield.[552] In this way, 2-iodothiophene was coupled to styrene.[553] Using 2- and 3-iodothiophene and vinyltrimethylsilane, high yields of the *E*-trimethyl(thienylvinyl)silanes were produced. The presence of silver nitrate enhanced the rate of reaction and completely suppressed desilylation.[554] Studies of Pd(0)-catalyzed reactions between 2- and 3-bromothiophene and allylic alcohols have revealed that the corresponding 3-(thienyl)aldehydes together with olefinic products are formed via the enols.[555] Thiophene-containing prostaglandin endoperoxide analogs were prepared by the addition of thienylpalladium species to bicyclic olefins and subsequent treatment with alkenyl or alkynyl organometallic.[556,557]

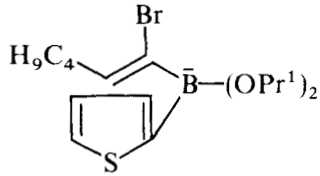
A stereo/regiospecific synthesis of trisubstituted alkenes, such as 1-(2-thienyl)-1-phenyl-2-alkylethenes, is the reaction of **466** with dibromoborane–dimethyl sulfide complex, followed by treatment with potassium triisopropoxide to give **467**, which is reacted with 2-thienyllithium to give **468**, which yields **469** after reaction with base. Palladium(0)-catalyzed coupling with iodobenzene led to **470**. If **467** was first reacted with phenyllithium and then with 2-iodothiophene, **471** was obtained. Yields are claimed to be greater than 95% and the isomeric purity, higher than 97%.[558]



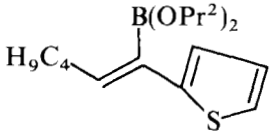
466



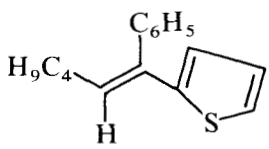
467



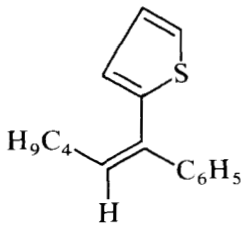
468



469

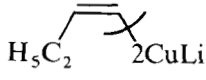


470

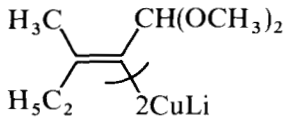


471

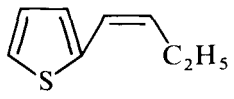
Reaction of the cuprates **472** and **473** with 2-iodothiophene in the presence of $ZnBr_2$ and a Pd(0) catalyst gave **474** and **475**, with almost exclusively *cis* stereochemistry.[559]



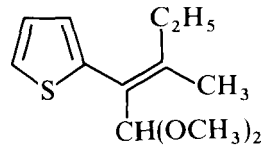
472



473

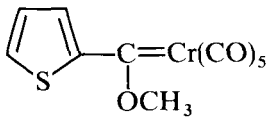


474

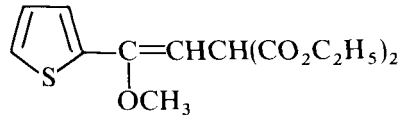


475

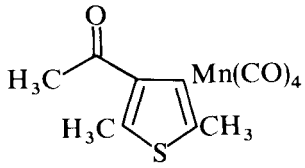
The 2-thienylmethoxychromium carbene complex **476** reacted with ethyl propiolate in the presence of alcohol to give **477** in a 1 : 2 mixture of stereoisomers in an 81% yield.[560] The manganese derivative **478** reacts with methyl acrylate in the presence of Pd(II) to give 34% of **479** and 56% of **480**. Compound **481** gave compounds of type **480** only.[561]



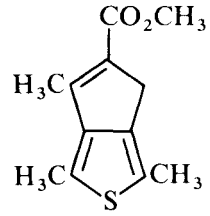
476



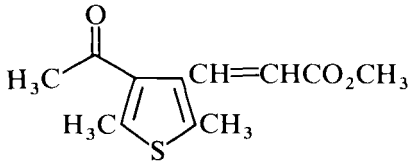
477



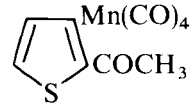
478



479

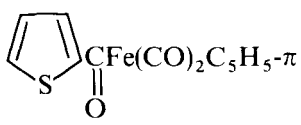


480

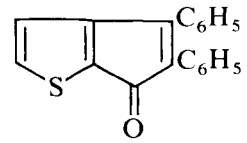


481

The reaction of **482** with diphenylacetylene gave **483** in a 52% yield.[562] The mechanism of these interesting reactions of thienyl transition metal derivatives was discussed.



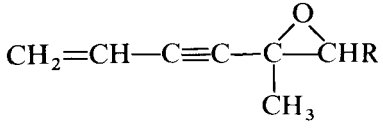
482



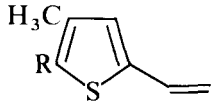
483

15. Vinylthiophenes via Ring-Closure Reactions

A patent describes the formation of 3-vinylthiophene and 2-methyl-3-vinylthiophene through a reaction of 3-methylpentane and 3-ethyl-1-pentene with sulfur dioxide over a Ca–Ni phosphate catalyst at 550°C and atmospheric pressure.[563] Reaction of vinylacetylenic epoxides, **484**, with hydrogen sulfide and $B(OH)_3$ at 50°C gave 2-vinylthiophenes **485**.[564] The same reaction with 2-methyl-4-(1-hydroxycyclohexyl)-1,2-epoxy-3-butyne led to 4-methyl-2-(1-cyclohexenyl)thiophene after dehydration with 5% H_2SO_4. 4-Methyl-2-(1-cyclopentenyl)thiophene was obtained similarly.[565]



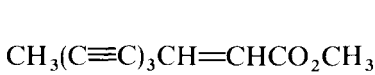
484



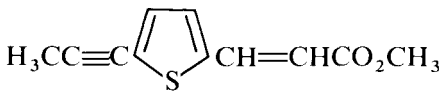
R = H, CH_3

485

The reaction of **486** with hydrogen sulfide was used for the preparation of **487**[143,566] in connection with investigations of the biosynthesis of naturally occurring thiophenes. Reaction of **488** with sodium sulfide gave **489**.[567]

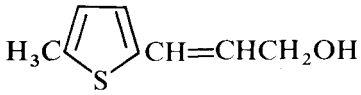


486



487

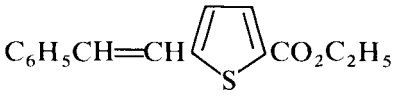
488



489

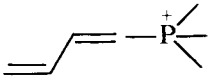
Reaction of **490** with ethyl thioglycolate gave **491**.[568]

490

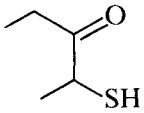


491

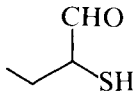
The reaction of **492** with **493** and **494**, using pyridine as a solvent, produced 2-methyl-3-ethyl- and 2-ethyl-4-vinylthiophene, respectively.[569] On reaction of γ,γ-dimethylallenyllithium with sulfur dichloride in THF at -70°C, a low yield of **495** was obtained.[570]



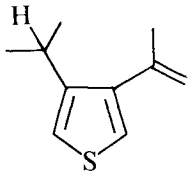
492



493

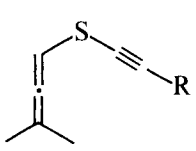


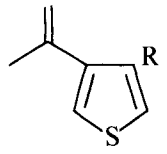
494



495

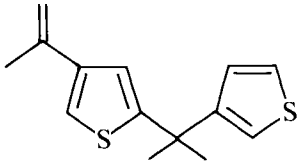
All four allenyl ethynyl sulfides **496** undergo cyclization to thiophene derivatives **497** on heating in isopropanol. In general, the reaction was accompanied by the formation of polymers. In the reaction of **496** (R = H), **498–500** were also obtained as by-products, in addition to **497** (R = H).[571]



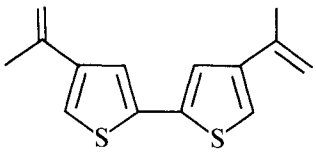


R = H, CH_3, C_2H_5, C_6H_5

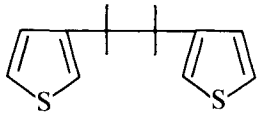
496 497



498

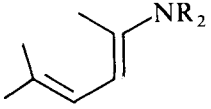


499

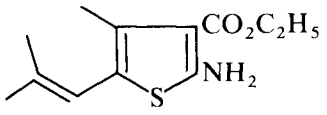


500

Reaction of **501** with ethyl cyanoacetate and sulfur gave **502** in good yield.[572]

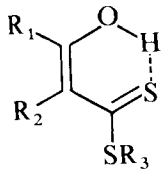


501

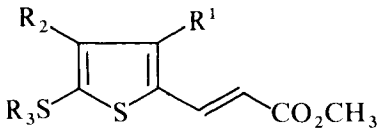


502

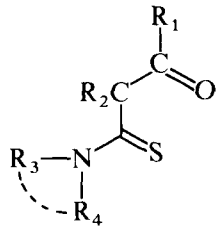
The reaction of **503** with methyl 4-bromocrotonate in the presence of potassium carbonate in acetone yielded **504**. From the thioamides **505** under the same conditions, **506** was obtained.[573]



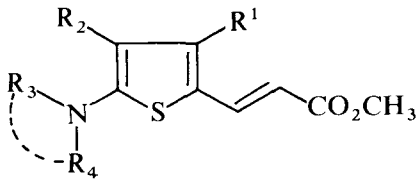
503



504

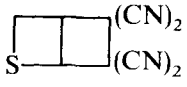


505

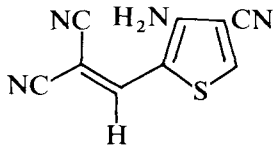


506

2*H*-Thiete reacts with tetracyanoethylene in methylene chloride to give **507**, which on refluxing in benzene yields **508** (96%). The structure was proved by X-ray diffraction, and a reaction path was suggested.[574]

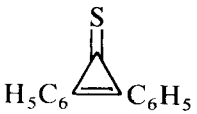


507

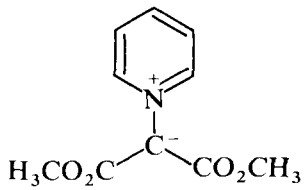


508

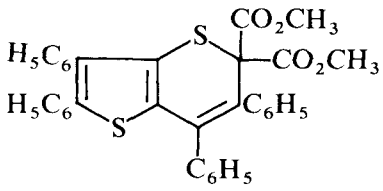
Among the products formed in the reaction of **509** with **510** was **511**.[713]



509

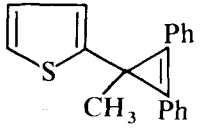


510

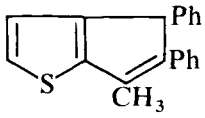


511

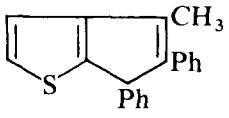
Direct irradiation of **512** in benzene gave **513** in a 94% yield, while the 3-isomer corresponding to **512** gave **514** in a 90% yield. Thermal reactions of **512** led to **515**, in addition to **513**, while the corresponding 3-isomer, in addition to **514**, gave **516**.[575]



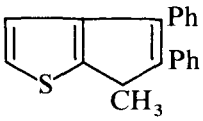
512



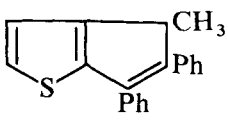
513



514



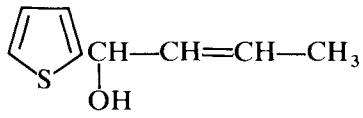
515



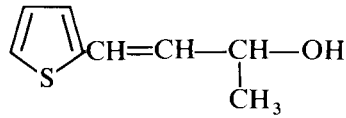
516

16. Vinylthiophenes via Isomerizations and Rearrangements

Treatment of **517** with 0.1 M hydrogen chloride in 60% aqueous acetone gave **518**, which was also prepared by the addition of methylmagnesium bromide to β-2-thienylacryl aldehyde.[576] The kinetics of these anionotropic reagents was studied and the effect of the 2-thienyl group compared with that of the phenyl and 2-furyl groups.[577]

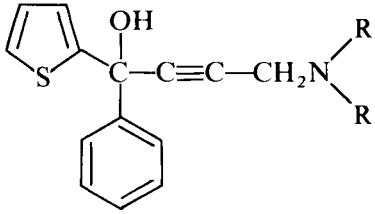


517



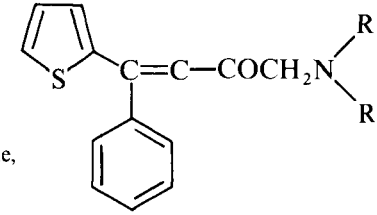
518

The Meyer–Schuster rearrangement of **519**, brought about by refluxing in aqueous formic acid, gave **520** in a 45–79% yield.[578]



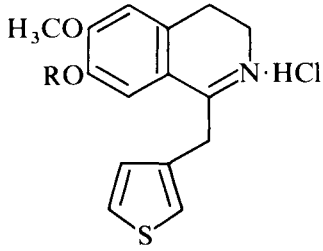
519

R = diethylamine, morphline, piperidine, pyrrolidine

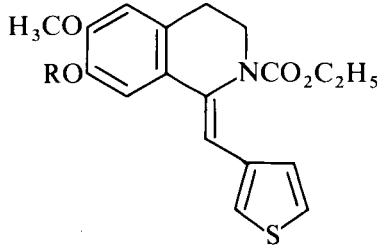


520

The reaction of **521** with ethyl chloroformate led to isomerization of the double bond to give **522**, as well as to carbethoxylation.[579]

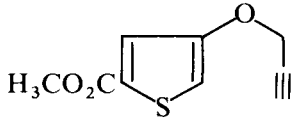


521

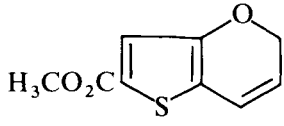


522

Refluxing **523** in xylene led to a 72% yield of **524**.[580]

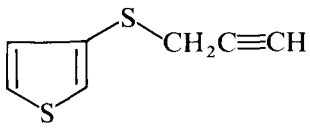


523

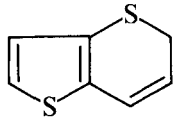


524

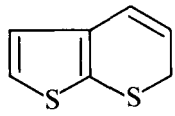
Heating **525** in HMPA at 170–180°C gave **526**, while the 2-isomer corresponding to **525** gave **527**.[581]



525

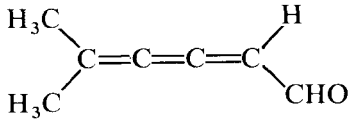


526

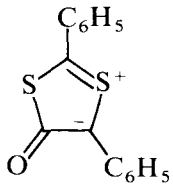


527

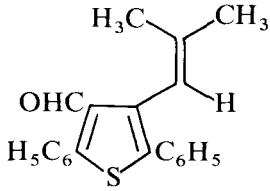
The cumulene **528** reacted with **529** to give the thiophene derivative **530** in 36% yield, among other products.[582]



528



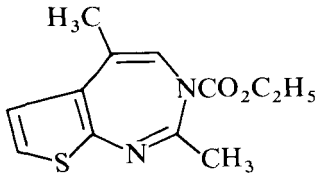
529



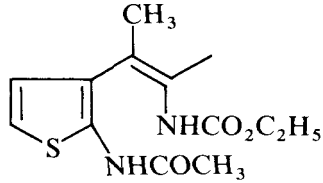
530

17. Vinylthiophenes via Ring Opening of Thiophene-Fused Ring Systems

Treatment of **531** with methanolic hydrogen chloride gave **532**.[583]

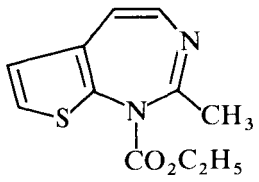


531

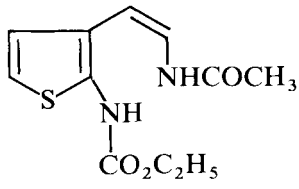


532

On acid treatment of **533**, on the other hand, **534** was obtained.[584]

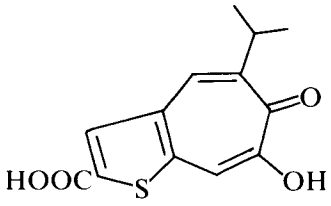


533

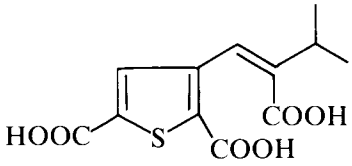


534

Treatment of **535** with 35% hydrogen peroxide in sodium hydroxide gave **536**, which was transformed to the trimethyl ester with diazomethane.[585]

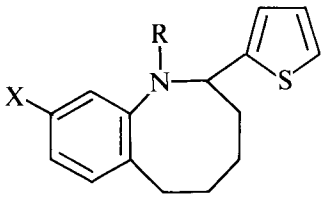


535

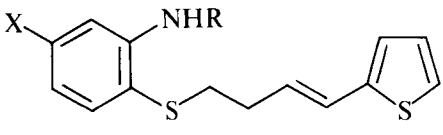


536

Acid hydrolysis or heating of **537** gave **538**.[586]

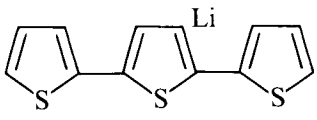


537

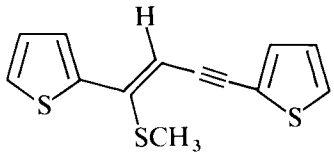


538

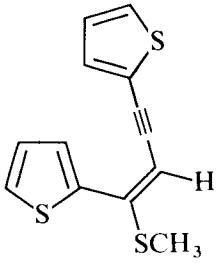
Ring opening of **539** followed by methylation with methyl iodide gave a mixture of the *cis*- and *trans*-isomers **540** and **541**, which occur naturally in *Berkheya* and *Cullumia* species.[587]



539



540



541

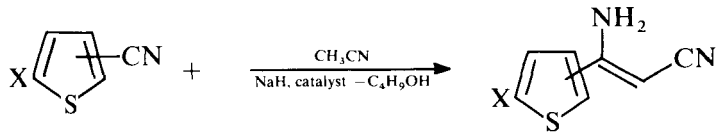
18. Vinylthiophenes from Alkylthiophenes

Patents describe the use of various catalysts for the preparation of vinylthiophene through dehydrogenation at higher temperatures.[588–590] Vapor-phase cracking of 1,1-bis(2-thienyl)ethane gave 2-vinylthiophene.[591] Liquid-phase

oxidation of 3-methyl-2-ethylthiophene with catalysts consisting of dimeric carboxylate complexes of cobalt(II) with pyridine, quinoline, or quinaldine yielded 3-ethyl-2-vinylthiophene, among other products.[592]

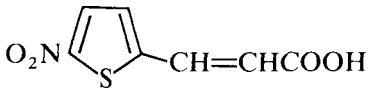
19. Various Other Methods

The condensation of acetonitrile anion with 2- and 3-thiophenenitrile and 5-chloro- and 5-fluoro-2-thiophenenitrile, using sodium hydride in ether, containing a catalytic amount of *t*-butanol, gave *β*-amino-*β*-thienyl-acrylonitriles **542**.[593] This technique avoids the displacement of fluorine or chlorine by nucleophilic bases, which are often used.

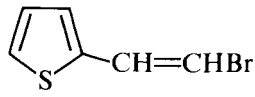


542

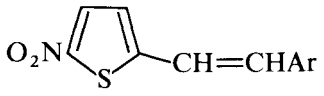
The reaction of **543** with NBS in aqueous sodium carbonate gave **544** as a mixture of *Z*- and *E*-isomers in the proportions 1 : 1.75, from which the *E*-isomer was obtained pure on chromatography on silica. Electrophilic substitution of *Z*-**544** with aromatic and heteroaromatic compounds in the presence of $AlCl_3$ gave *Z*-**545**.[594] With phenols, mixtures of isomers were obtained. The structure of **545** was investigated by means of ^1H NMR, UV spectra, and dipole moments. The compound *Z*-**545** has also been reacted with various nucleophiles to give **546**. It reacted with phenoxide (X = $^-OC_6H_4$-4-CH_3), thiophenoxide (X = $^-SC_6H_4$-4-CH_3), and azide ion to give a mixture of *Z*- and *E*-isomers, with *p*-toluenesulfinate, dimethylamine, and morpholine to give the *E*-isomer, and with trimethyl amine and pyridine to give the *Z*-isomer.[595]



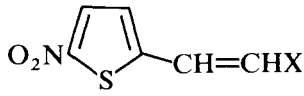
543



544



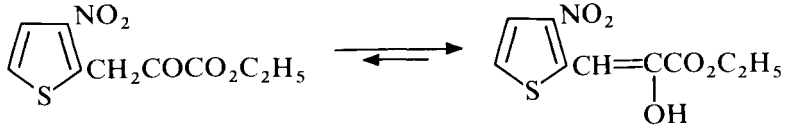
545



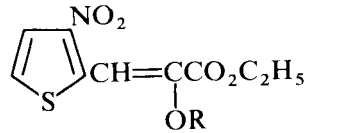
546

2-Thienylacetaldehyde diethyl acetal reacted with butyllithium and water to give 2-thienyl-*β*-vinyl ether in a 78% yield. Reaction of the lithiated product with trimethylsilyl chloride instead of water gave 5-trimethylsilyl-2-thienyl-*β*-vinyl ether.[596] Vinyl ethers have also been prepared by *O*-alkylation of the

tautomeric system **547**, which yielded **548**. With pyrrolidine, **547** gave **549**.[597] From **550** the enolsulfonate **551** has been prepared by reaction with the arylsulfonyl chloride, using ethoxide in ethanol.[598]

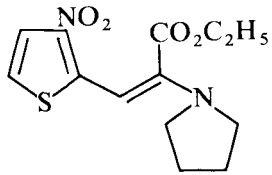


547



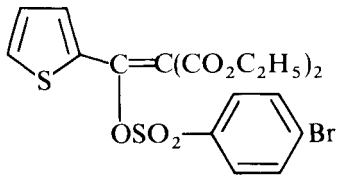
$R = C_6H_5CH_2, CH_3, CH_2C_6H_4\text{-}NO_2\text{-}p$

548



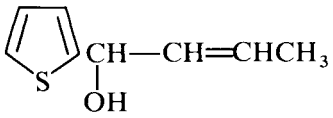
549

550

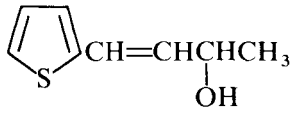


551

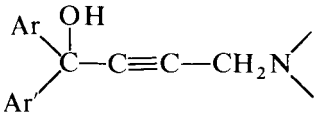
Acid-catalyzed rearrangement of **552** leads to **553**.[576] In a similar type of reaction, called the *Meyer–Schuster rearrangement*, the acetylenic derivatives **554** are transformed to the ethylenic ketones **555**.[578]



552

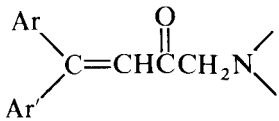


553



554

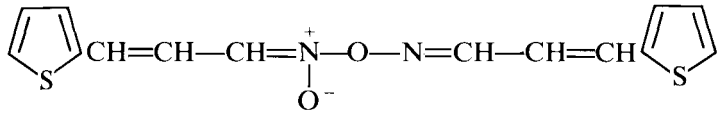
$Ar = C_6H_5$, $Ar' = 2\text{-Th}$



555

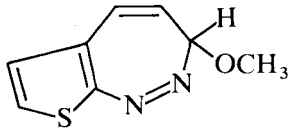
β-2-Thienylacrolein has been condensed with phenylacetic acid and acetic anhydride to give 1-phenyl-4-(2-thienyl)butadiene, with β-benzalpropionic acid to give 1-phenyl-6-(2-thienyl)-1,3,5-hexatriene, and with β-cinnamylpropionic acid to give 1-phenyl-8-(2-thienyl)-1,3,5,7-octatetraene.[6]

The aldoxime anhydride-N-oxide **556** was prepared from 2-thienylacrolein oxime through reaction with anhydrous lead tetraacetate in ether.[599]

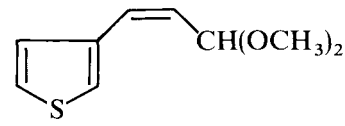


556

Reaction of **557** with sodium methoxide led to **558**.[600]

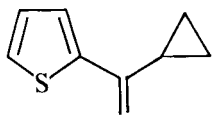


557

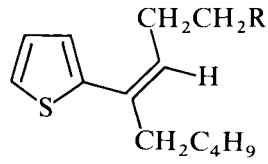


558

The vinylcyclopropane **559** reacted differently with butyllithium than the analogous benzene derivative, which ring-closed to a naphthalene derivative. Instead, a mixture of (**560**, R = H) and (**561**, R = H) was obtained in a 54% yield in a 1 : 4 ratio after hydrolysis. Reaction with trimethylsilyl chloride produced (**560**, R = $Si(CH_3)_3$) and (**561**, R = $Si(CH_3)_3$), which established the position of the lithium and shows that metalation of the thiophene ring had not occurred.[601]

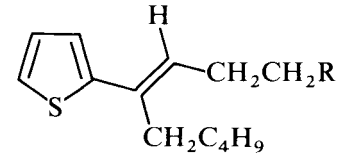


559



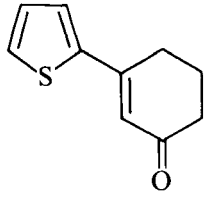
R = H, $(CH_3)_3Si$

560

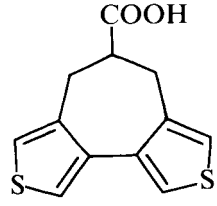


561

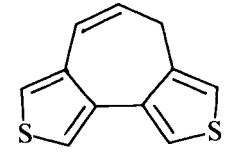
Photochemical reaction of **559** with $Fe(CO)_5$ or $Fe_2(CO)_9$ yielded **562**.[602] Treatment of **563** with $Pb(OAc)_4$ gave **564**.[61] Reaction of **565** with sodium sulfide led to **566**.[567]



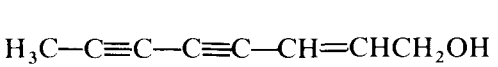
562



563



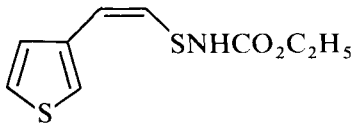
564



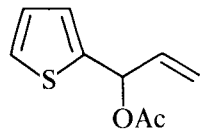
565

566

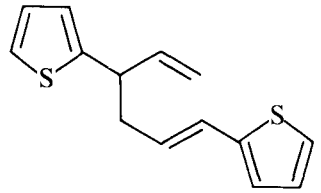
The reaction of thiophene with ethyl azidoformate gave **567**, together with other products.[603] Palladium-catalyzed homo-coupling of the allylic acetate **568** *in situ* with electrochemically generated allyl tin reagent gave **569** in a 55% yield.[604]



567

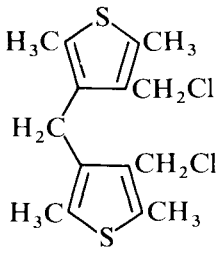


568

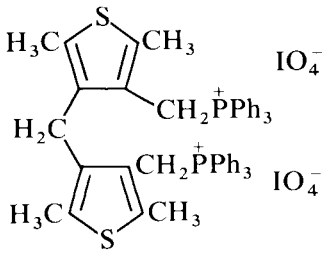


569

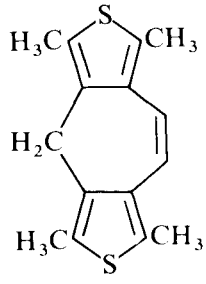
The reaction of **570** with triphenyl phosphine and sodium periodate led to **571**, which on treatment with lithium ethoxide in ethanol yielded **572**.[605]



570



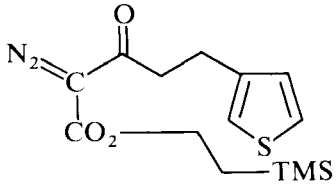
571



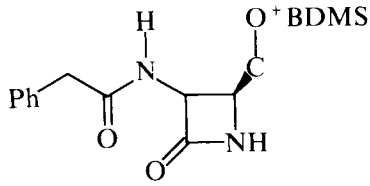
572

Reaction of 2-chloromethylthiophene or di-2-thenylsulfide with sulfur at 180–185°C gave 1,2-di-(2-thienyl)ethylene in 10 and 19% yields, respectively.[606]

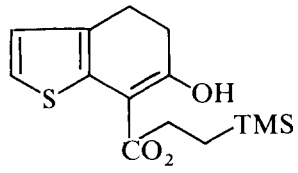
The reaction of **573** with **574** under rhodium catalysis did not give the expected insertion of the diazoketoester in the NH bond. Instead, as a result of carbene insertion in the thiophene ring, **575** was obtained in a 53% yield.[607]



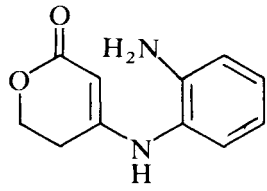
573



574

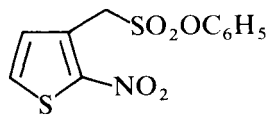


575

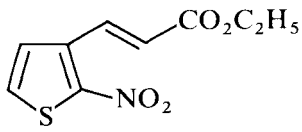


576

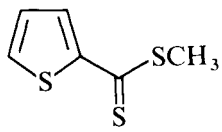
The reaction of **577** with ethyl bromoacetate in the presence of a base gave **578** in an 80% yield.[608] The reaction of **579** with malonitrile in the presence of sodium hydride in THF, followed by methylation with dimethyl sulfate, led to **580**.[609]



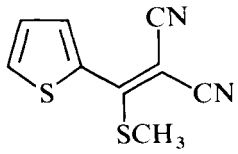
577



578

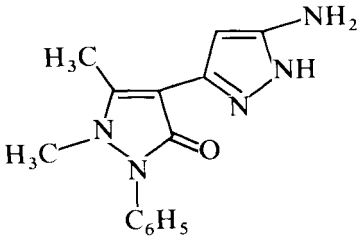


579

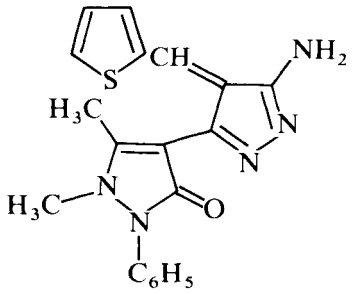


580

The reaction of **581** with 2-thiophene aldehyde gave **582**.[208]

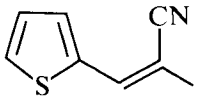


581

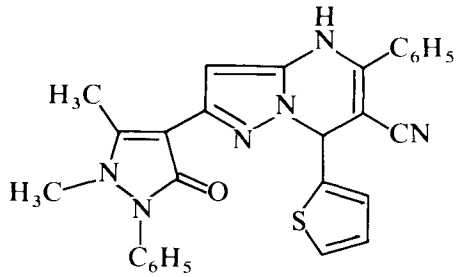


582

The same product was also obtained when **581** was reacted with 2-thenalmalonitrile and ethyl β-cyanothienylacrylate, while **583** gave **584**.[208] Thienylacetylene derivatives have been catalytically reduced to thienyl ethene derivatives, using Lindlar's catalyst or other Pd catalysts.[343,610–612]



583



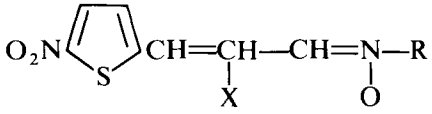
584

III. REACTIONS OF VINYLTHIOPHENE DERIVATIVES

1. Reactions with Conservation of the Double Bond

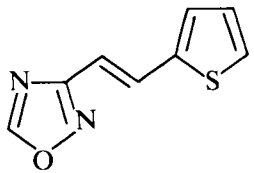
Methyl affinities have been determined for styrene derivatives, including 2-vinylthiophene.[613] Many esters and amide derivatives have been prepared from 2-(thienyl)acrylic acids in connection with the synthesis of compounds of potential medicinal interest.[126,145,150,154,614–622] The protonation of β-2-furyl- and β-2-thienylacryl amides and cinnamides has been compared.[617] The reaction kinetics of cinnamoyl, β-2-furylacryloyl, and β-2-thienylacryloyl chlorides with anilines in benzene has been studied. The results show that the reaction mechanism is the same as that for the benzoylation reaction.[623]

The reaction of β-(5-nitro-2-thienyl)acrolein and β-(5-nitro-2-thienyl)-α-bromoacrolein with hydroxylamines has been used in the synthesis of N-substituted nitrones **585**.[624] A mixture of *cis*- and *trans*-3-(2-thienyl)acrylonitrile gave the *trans*-amide oxime with hydroxylamine. The less reactive *cis*-nitrile was recovered, and on heating under reflux with an excess of methanolic hydroxylamine solution *cis*-3-(2-thienyl)acrylamide oxime was obtained, which on treatment with triethyl orthoformate and boron trifluoride led to **586**. 2,4-Dinitrophenylhydrazones have been prepared from thiophene analogs of di- and trimethoxychalcones,[58] as well as semicarbazones,[20] thiosemicarbazones of β-2-thienylacrolein,[20,626] oximes,[627] and anils.[628]



X = H. R = CH_2CH_2OH
X = H. R = cyclohexyl
X = H. R = C_6H_5
X = Br. R = CH_2CH_2OH
X = Br. R = CH_3

585



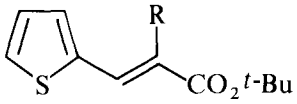
586

The configuration of the oximes of thenylideneacetone has been studied.[629] The reaction of (2-thienyl)methylene malonitrile with hydrogen sulfide in benzene, containing catalytic amounts of triethylamine, gave 2-cyano-3-(2-thienyl)-thioacrylamide.[630] Aminolysis of 2-methyl-4-(2-thienylmethylene)-5-(4*H*)-oxazolone with sodium salts of amino acids yielded N-acetyl-3-(2-thienyl)alanyl amino acids.[631]

The kinetics of the reaction of *cis*-2-(*β*-bromvinyl)-5-nitrothiophene with piperidine, which yields 2-(*β*-piperidinovinyl)-5-nitrothiophene, has been studied.[632]

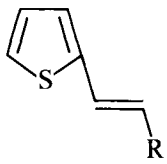
Condensation products have been obtained from thienylacryl aldehydes and ketones.[17,633,634] Mannich condensation products from (thienyl)-3-butene-2-ones[19,629,635–637] and α-cyclopentylidene-2-thienyl acetonitrile have been prepared.[272]

Decarboxylation of thenalmalonic acids was achieved by heating in acetic anhydride.[171] Compounds, such as **587** have been transformed to **588** by heating in the presence of catalytic amounts of *p*-toluenesulfonic acid.[199,203] Copper and quinoline have been used for the decarboxylation of *β*-(thienyl)-acrylic acids.[15,638–640]



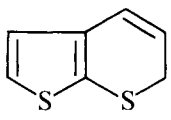
R = COR_1, CN

587

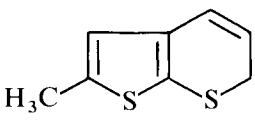


588

Many thiophene analogs of chalcones have been reduced to the corresponding alcohols with sodium borohydride.[641,642] Many other carbonyl compounds, containing the vinylthiophene unit, have been reduced to the alcohol stage[5,152,578,643] or to a methylene group[286,312,644,645] without reduction of the double bond. In the latter case, $LiAlH_4$ or $LiAlH_4/AlCl_3$ was used. Thenalacetone reacts with aryl Grignard reagents via 1,2-additon, while 1-(2-thienyl)-2-(2-thenoyl)ethene gave predominantly 1,4-addition.[646] MnO_2 has been used for the oxidation of 3-(2-thienyl)allyl alcohols to the corresponding aldehydes.[567] The double bond in 2-vinylthiophenes does not interfere in the metalation[331,645,647–649] or halogen–metal exchange reaction of the thiophene ring,[286,312,313,650,651] nor in cyclopalladation reactions.[556] Grignard reagents have been obtained from bromovinylthiophenes.[292] The reaction of **589** with

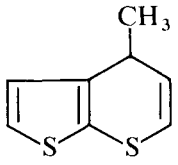


589

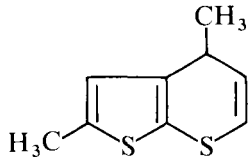


590

sodium amide in liquid ammonia or butyllithium, followed by methyl iodide, gave **590–592** in varying proportions, depending on reaction time.[649] Reduction of nitro groups to amino groups in nitrovinylthiophenes has been achieved with stannous chloride[363] and Mohr's salt.[652]

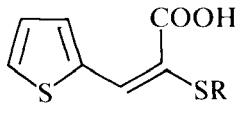


591

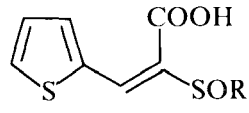


592

Oxidation of compounds **593** and **594** has been achieved with hydrogen peroxide in acetic acid. The corresponding sulfone was also prepared.[653–655]

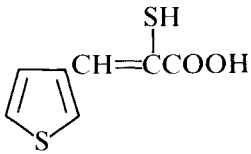


593

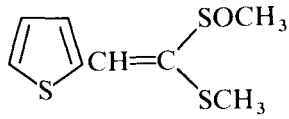


594

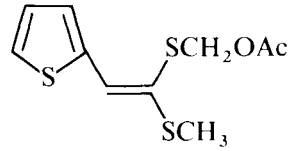
Oxidation of **595**, obtained through alkaline hydrolysis of the condensation product of 3-thiophene aldehyde with rhodanine, iodine in ethanol, or benzoyl peroxide, gave the corresponding disulfide.[106,656] Reaction of **596** with acetic anhydride at 100°C gave **597**, which on reaction with ethanol and acid or secondary amine gave methyl thienyl dithioacetates and thienyl thioacetamides, respectively.[237]



595

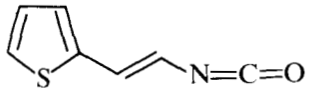


596

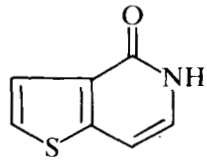


597

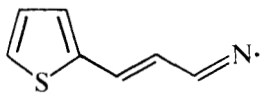
The Hofmann reaction of 2-thienyl acrylamide has been studied.[657] The Curtius reaction of 2-thienylacrylic acid azide has been extensively used for the synthesis of thienopyridines, since the intermediate isocyanate **598** is very unstable and can decompose explosively on attempted distillation. On heating in diphenyl ether, the isocyanates ring-close to form **599**.[144,658–660] 2-Thienyl-acryl aldehyde was reacted with *O*-methylhydroxylamine to yield the *O*-methyl oxime, which on flash-vacuum thermolysis at 650°C and 0.01–0.001 torr gave the thienopyridine **601** via **600**.[661,662]



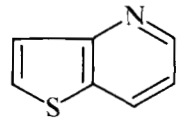
598



599



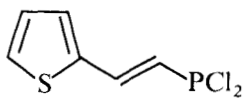
600



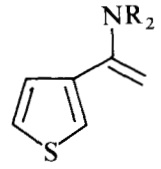
601

As mentioned previously, many cyclohexenylthiophenes have been transformed to phenylthiophenes through aromatization with chloranil,[411,412] DDQ,[157] or sulfur.[409]

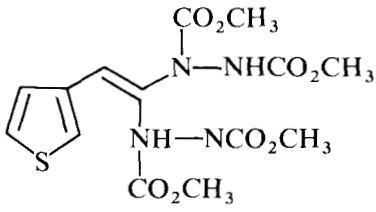
Starting from **602**, prepared by the reaction of 2-vinylthiophene with PCl_5 in PCl_3, numerous compounds modified at the phosphorous atom have been prepared.[663] The reaction of **603** with 2 mol of dimethyl azodicarboxylate in benzene led to **604** and **605**, especially in the presence of water.[493]



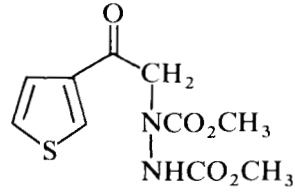
602



603



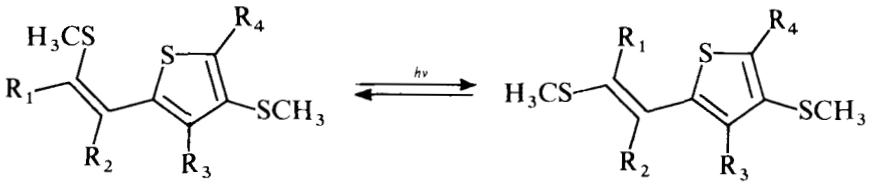
604



605

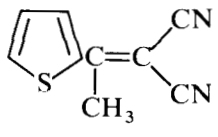
The effect of total concentration on the unsensitized photochemical cis–trans isomerization of 1,2-di-(2-thienyl)ethylene in benzene solution has been studied. As expected, thermal equilibration produces only the *trans*-isomer. At low concentration ($< 10^{-2}$ M) the *cis*-isomer predominated in the photostationary state. The results are consistent with the collisional quenching of the first excited singlet state of the *trans*-isomer and of a twisted triplet configuration, by ground-state *trans*-ethylene molecules.[664]

The acid- and base-catalyzed isomerization of *cis*-3-(2-thienyl)-2-arylacrylonitriles,[665] as well as the selenium-catalyzed reaction,[666] have been studied. The photochemical isomerization of **606** to **607** has also been investigated.[667]

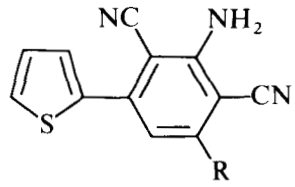


606 **607**

It is claimed that the reaction of **608** with cinnamonitriles leads to **609**.[209] The reaction of **610** with morpholine or piperidine at room temperature led to deep-rooted rearrangement, which yielded **611**. A reaction via ring opening of the thiophene ring by attack of the amine at the thiophenic 5-carbon was suggested.[195]

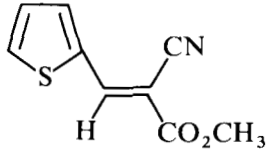


608

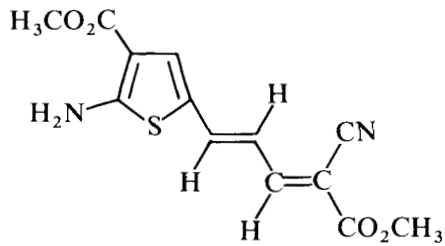


R = Ar, 2-Th

609



610



611

2. Electrophilic Substitution on Vinylthiophenes

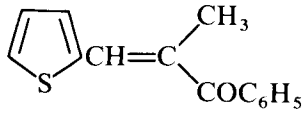
The reaction of vinylthiophenes with electrophilic reagents leads to substitution on the double bond, or in the thiophene ring, or to addition across the double bond, depending on the substituent already present in the thiophene ring or at the double bond.

Thus bromination of triarylethenes with Br_2 or NBS, in which one of the rings is a thiophene ring, occurs mainly at the double bond. Dibromination then

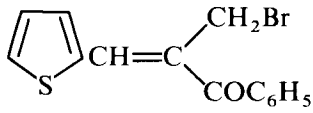
occurs in the thiophene ring.[455–459,668,669] β-3-Thienylacrylic acid, on the other hand, gave β-(2-bromo-3-thienyl)acrylic acid with 1 eq of bromine, and with excess bromine both substitution and addition occurred, yielding β-(2,5-dibromo-3-thienyl)-α,β-dibromopropionic acid. In hot carbon tetrachloride, only addition occurred and β-3-thienyl-α,β-dibromopropionic acid was obtained in a high yield.[670] β-2-Thienylacrylic acid adds bromine in hot carbon tetrachloride to produce β-(2-thienyl)-α,β-dibromopropionic acid.[671] Especially when the reactive 5-position of the thiophene ring is blocked, as in ethyl 3-(5-nitro-2-thienyl)acrylate, bromination can be achieved at the double bond to give ethyl 2-bromo-3-(5-nitro-2-thienyl)acrylate.[145] β-(5-Nitro-2-thienyl)-acrolein has also been brominated to β-(5-nitro-2-thienyl)-α-bromoacrolein.[7] The 5-cyano derivative reacted similarly.[12]

2-Styrylthiophene reacts with 1 eq of NBS to give 5-bromo-2-styrylthiophene. With 2 eq, the double bond was also attacked, and after treatment with a base, *trans*-2-phenyl-3-(5-bromo-2-thienyl)ethylene oxide was obtained.[640] 2-Bromo-3-(2-thienyl)acrylophenones have been prepared by the action of tetrabromo-*o*-benzoquinones on the corresponding acrylophenones.[672]

Allylic methyl groups have also been brominated; thus **612** gave, with NBS and α,α′-azobisisobutyronitrile in CCl_4, **613**.[168]



612



613

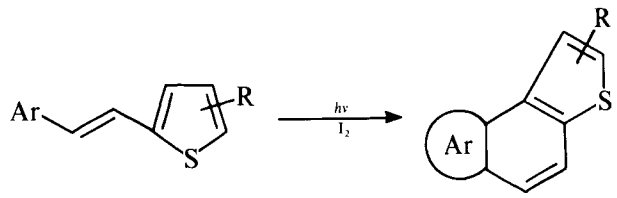
2-Styrylthiophenes are Vilsmeyer formylated and Friedel–Crafts acetylated in the 5-position of the thiophene ring.[335,455]

Many studies of the nitration of vinylthiophene derivatives have been carried out. Nitration of *trans*-2-styrylthiophene in CCl_4, nitroethane and acetic anhydride gave, somewhat surprisingly, the 3-nitro-2-styrylthiophene as the main product and the 5-nitro-isomer in smaller amounts.[95] Nitration of β-3-thienylacrylic acid has been claimed to give only the 2-nitro derivative.[161] However, a later detailed study showed that under various conditions the 2- and 5-isomers were formed in approximately equal proportions. Nitrations of the methyl ester with nitric acid in acetic anhydride gave the 2- and 5-isomers in a 2 : 1 ratio.[162] 2-Fluoro-3-(2-thienyl)acrylic acid is most probably nitrated in the 5-position of the thiophene ring.[508] Churkin and coworkers have studied the nitration of 4-(2-thienyl)-3-buten-2-one and related compounds. They found that nitration with potassium nitrate in concentrated sulfuric acid gave a mixture of the 5- and 4-nitro derivatives in the ratio 2.6 : 1.[673,674] The nitration of 4-(5-alkyl)-2-thienyl-3-buten-2-ones with nitric acid in acetic anhydride gave a mixture of 3- and α-nitro-isomers,[675,676] whereas nitration with nitric acid,

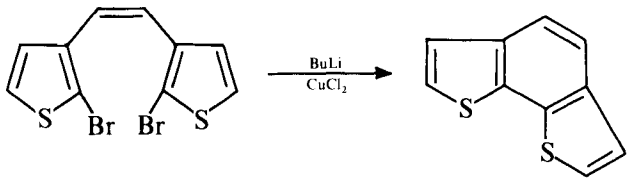
copper, and aluminum nitrates in carbon tetrachloride, dichloroethane, and acetonitrile led to the production of only the α-nitroketone.[676] Furthermore, nitration in trifluoroacetic acid and in the presence of aluminum chloride proceeds with the formation of a single α-nitroketone.[677] The nitration of 2-thioazulene-6-ones has been studied.[678] The nitration of 1-(2-thienyl)-2-nitro-1-propene with fuming nitric acid is claimed to give the 5-isomer.[80] The reaction of β-(2-thienyl)acrylic acids with aryldiazonium salts under Meerwein's conditions gave styrylthiophenes.[146,147]

3. Ring-Closure Reactions of Vinylthiophenes with Conservation of the Double Bond

One of the most important uses of 1-aryl-2-thienylethenes is their photochemical ring closure in the presence of small amounts of iodine and their oxidation to tricyclic heterocyclic systems with the phenanthrene annelation pattern (Scheme 15), as first described by Carruthers and Stewart in 1965.[441,679] The aryl group has been almost any kind of benzenoid compound or aromatic five-membered heterocyclic compound. Thus, Wynberg et al. synthesized a number of dithiophene analogs of phenanthrene[319] and used this approach for the synthesis of a number of heterohelicenes.[285,300,360] The yields in the photochemical coupling are usually very high. A drawback is, of course, that when the ortho positions in the two rings are not equivalent, mixtures of products might be obtained. In the case of 2,3-di(3-thienyl)ethene, no coupling was observed. All six isomers of dithiophene analogs could, however, be prepared from the *cis*-1,2-di(*o*-bromothienyl)ethenes through halogen–metal exchange, followed by coupling with $CuCl_2$, as illustrated in Scheme 16.[680]

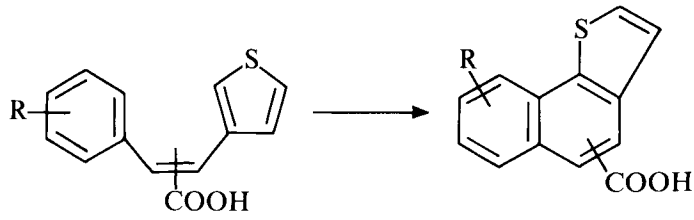


Scheme 15



Scheme 16

The photochemical coupling was also essential in the synthesis of naphthothiophenes and benzodithiophenes with antimalarial activity and DNA intercalating properties. In order to have a handle for introducing a side chain, the coupling was carried out with carboxylic acids (Scheme 17).[179,258,260,681]



Scheme 17

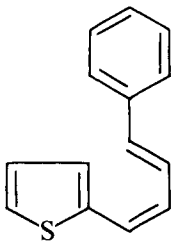
The photocyclization strategy was recently used in connection with the synthesis of antitumor agent CC-1065 and analogs. In this connection, thieno[3,2-*e*]indoles were prepared.[336,451] During recent years the most extensive use of the photochemical coupling of 1,2-aryl-thienyl ethenes has been made by Castle and coworkers in connection with a study of coal-derived polycyclic aromatic hydrocarbons and their carcinogenic activity. They prepared phenanthro[*b*]thiophenes,[324] phenaleno[1,9-*bc*]thiophene,[356] pyreno[*b*]thiophenes,[321] benzo[4,5]phenaleno[1,9-*bc*]thiophene and benzo[4,5]phenaleno-[9,1-*bc*]thiophene,[359] dinaphthothiophenes,[323] all six monomethyl derivatives of naphtho[2,1-*b*]thiophene,[322] naphtho[1,2-*b*]thiophene and all eight monomethyl derivatives,[320] 8-substituted naphtho[2,1-*b*]thiophenes,[259] angular polycyclic thiophenes containing two thiophene rings,[325] benzannelated analogs of phenanthro[1,2-*b*]thiophene and [2,1-*b*]thiophene,[682] and the congested helicene phenanthro[3′,4′ : 3,4]phenanthro-[2,1-*b*]thiophene.[271] Detailed NMR studies have been carried out on the latter ring system. Other examples are given in Ref. 553.

The photocyclization of heterocyclic analogs of stilbene can also be carried out under a nitrogen atmosphere if catalytic amounts of Pd on carbon are used as the oxidant.[683] The photoconversion of some iodophenyl(thienyl)ethenes and iodothienyl(phenyl)ethenes to naphthothiophenes and benzodithiophenes, respectively, has also been carried out. The results suggest that the intermediate in these cyclizations is also a dihydro derivative that undergoes dehydrogenation, and not an aryl radical that effects an intramolecular substitution.[684]

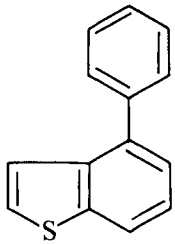
The photocyclization of **614** gave **615**, while **616** gave **617**. Similarly, 1,4-di-(2′-thienyl)-1,3-butadiene and the analogous 3-isomer gave 4-(2-thienyl)-benzo[*b*]thiophene and 7-(3-thienyl)benzo[*b*]thiophene.[685]

The photochemical reaction of **618** with **619** gave predominantly **620**. With **621**, **622** was obtained.[686,687]

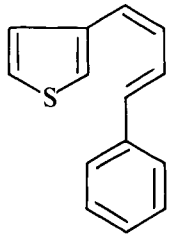
The reaction of 3-(2-thienyl)acrylic acids **623** with thionyl chloride in pyridine leads to chlorinated thieno[3,2-*b*]thiophenecarboxylic acid **624** in low



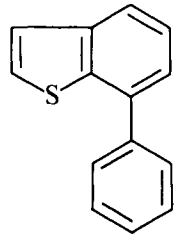
614



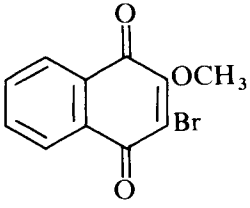
615



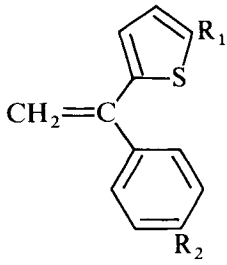
616



617

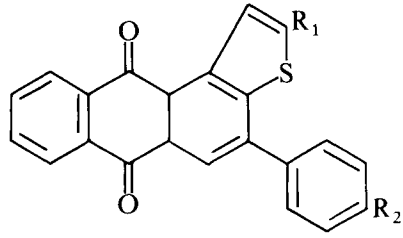


618

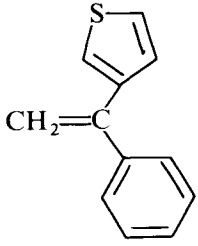


$R_1 = R_2 = H$
$R_1 = C_2H_5$, $R_2 = H$
$R_1 = H$, $R_2 = CH_3$
$R_1 = H$, $R_2 = Cl$

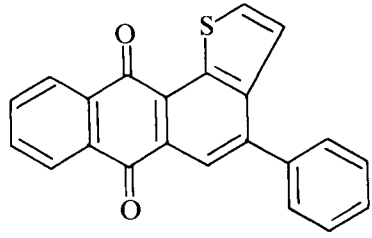
619



620

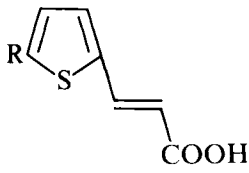


621



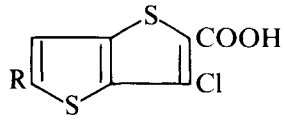
622

yields.[159,362] With 3-[3-thienyl]acrylic acid, however, a 63% yield of 3-chlorothienol[2,3-*b*]thiophenecarboxylic acid was obtained.[362,1029]



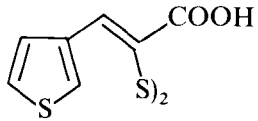
$R = Cl, Br, CH_3$

623

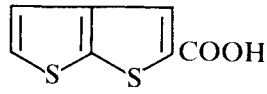


624

Another way of reaching the thieno[2,3-*b*]thiophene system is the reaction of **625** with iodine in dioxane, which gives **626**. This ring closure does not work with the 2-isomer.[688] The reaction of 3-[2-thienyl]- and 3-[3-thienyl]acrylic acid with selenium oxychloride in chlorobenzene-pyridine gave tetrachloroselenolo[3,2-*b*]thiophene and tetrachloroselenolo[2,3-*b*]thiophene, respectively.[689]

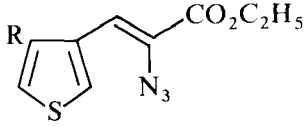


625

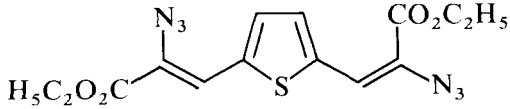


626

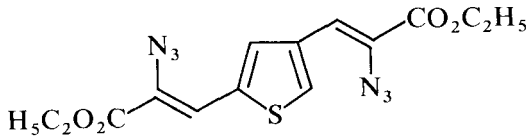
3-(Thienyl)-2-azidoacrylic acids have been of great use for the synthesis of various condensed systems. Heating **627**, **628**, **629**, and **630** in xylene gave **631**,[185] **632**, **633**, and **634** respectively.[184]



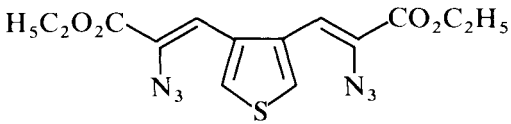
627



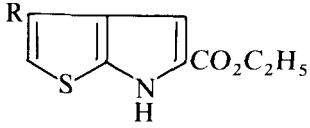
628



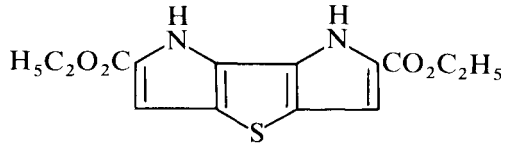
629



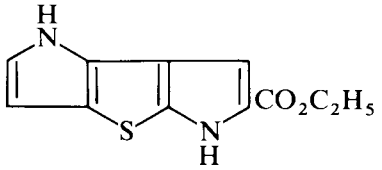
630



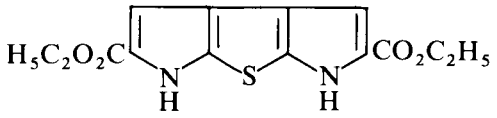
631



632

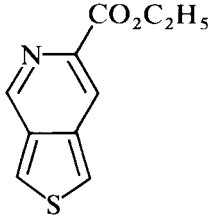


633

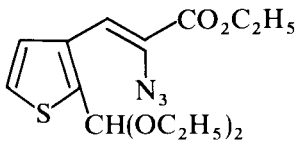


634

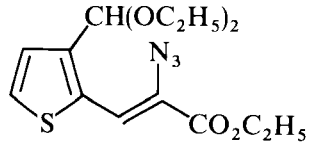
From **630**, approximately equal amounts of **635** were obtained as a second product.[184] Various other thieno[2,3-*b*]pyrroles and thieno[3,2-*b*]pyrroles have been prepared from 5-substituted 3-(3-thienyl)-2-azidoacrylates and 5-substituted 3-(3-thienyl)-2-azidoacrylates.[186] On the other hand, reaction of **636** and **637**, gave only thieno[2,3-*c*]- and thieno[3,2-*c*]pyridine derivatives **638** and **639**.[690]



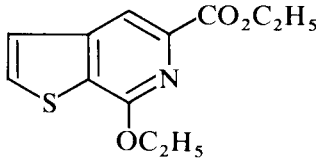
635



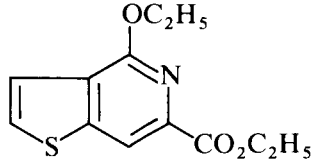
636



637

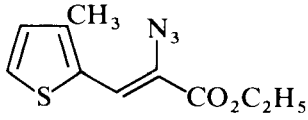


638

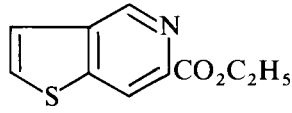


639

A similar synthesis of *c*-fused pyridines is the thermal decomposition of 2-azidoacrylates, bearing an *ortho*-methyl group. Thus, the reaction of **640** gave **641**.[691]



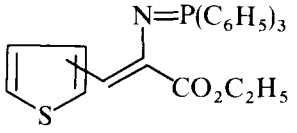
640



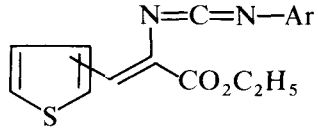
641

Another recent synthesis of thieno[*c*]pyridines is the reaction of 3-(2-thienyl)- and 3-(3-thienyl)-2-azidoacrylate with triphenylphosphine in methylene chloride

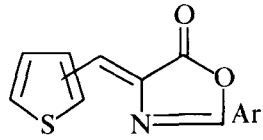
to give **642**, which on reaction with arylisocyanates yields **643**. With aroyl chlorides, **644** was obtained.[692] On heating **643** at 150°C, **645** and **646** were obtained in good yields.[693]



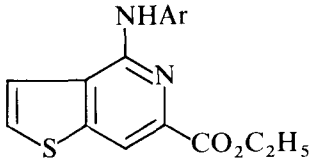
642



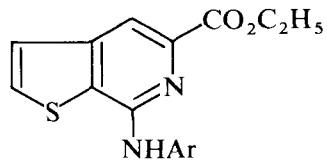
643



644

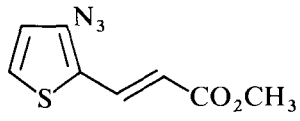


645

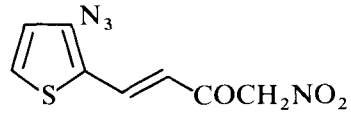


646

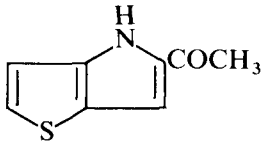
3-Azido-2-Vinylthiophenes **647** and **648** gave, on heating, thieno[3,2-*b*]-pyrroles **649** and **650**.[694] Reese and coworkers have extensively studied the chemistry of 3-azido-2-vinylthiophenes. Thus the decomposition of **651** gave the stable ylid **652**.



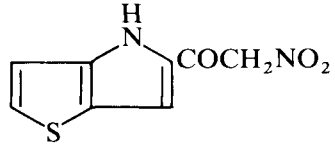
647



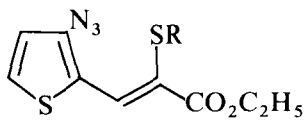
648



649

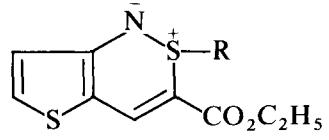


650



$R = C_6H_5, CH_3$

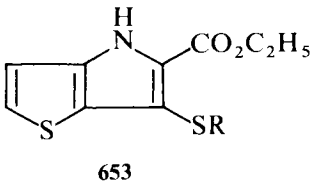
651



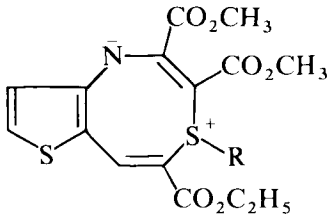
652

On photolysis, **652** gave **653**, suggesting that the MeS and PhS groups undergo very rapid [1,5]-sigmatropic shifts.[189,695,696] The ylid **652** (R = Ph) also reacted with dimethyl acetylenedicarboxylate to give **654**.[697] Thermal decomposi-

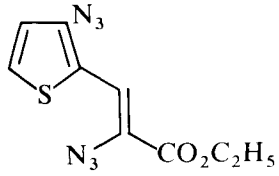
tion of **655** in refluxing xylene gave a 26% yield of **656** and 27% of **657**. The latter compound was formed via extrusion of acetylene, as indicated in **658**,[166,698] and the former, via intramolecular coupling of nitrenes.



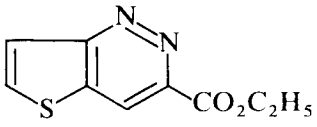
653



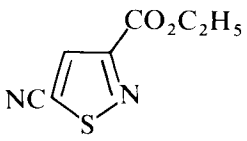
654



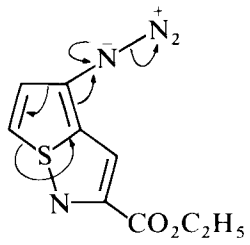
655



656

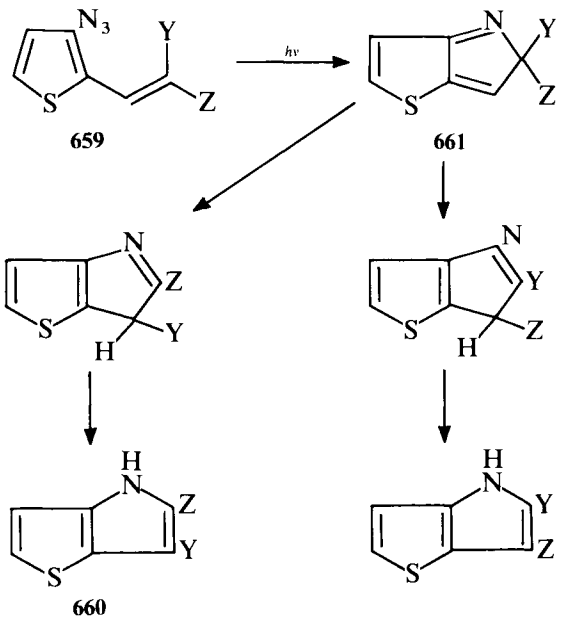


657



658

On irradiation in acetonitrile, the 3-azido-2-vinylthiophenes **659** gave the thieno[3,2-*b*]pyrroles **660** as the sole or major products, formed by migration of



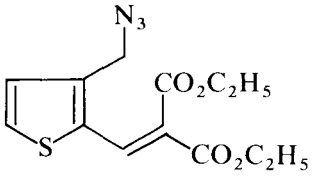
659 **661** **660**

$Y=COCr_3$	$Z=CO_2C_2H_5$
$Y=H$	$Z=COCH_3$
$Y=SC_6H_3$	$Z=CO_2C_2H_5$
$Y=SCH_3$	$Z=CO_2C_2H_5$
$Y=SO_2C_6H_5$	$Z=CO_2C_2H_5$
$Y=SOC_6H_5$	$Z=CO_2C_2H_5$
$Y=SOCH_3$	$Z=SCH_3$
$Y=SCH_3$	$Z=H$
$Y=SOC_6H_5$	$Z=H$
$Y=H$	$Z=SO_2CH_3$

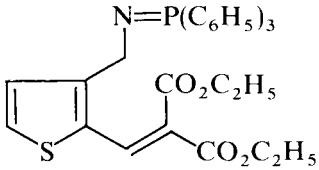
Scheme 18

group Y (Scheme 18) in preference to or in competition with group Z. In the nonaromatic fused 2*H*-pyrrole intermediate **661**, sulfur groups migrating particularly rapidly.[188,698,699]

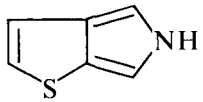
The reaction of **662** with triphenylphosphine produced the 5*H*-thieno-[2,3-*c*]pyrrole **664** via **663**.[700]



662



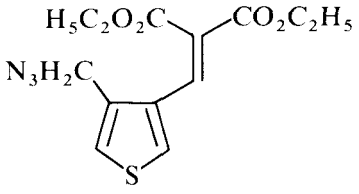
663



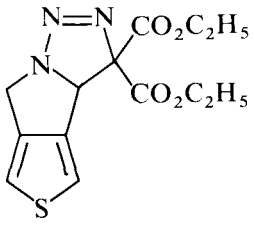
664

Similarly, **665** was synthesized from **666** by intramolecular 1,3-dipolar cycloaddition, followed by acid-catalyzed 1,3-dipolar cycloreversion of the dihydrotriazole intermediate **667**. The very unstable **665** was trapped as the N-phenylmaleimide adduct.[167] Thermal decomposition of azidodithienyl-1,2-ethenes **668** gave 4*H*-thieno[3,2-*b*]pyrroles **669**. The analog compounds **670** were reduced to the amino compounds **671** under these conditions.[701]

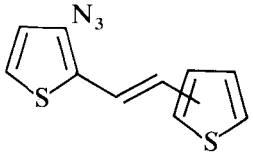
665



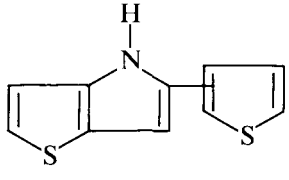
666



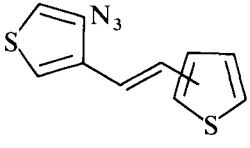
667



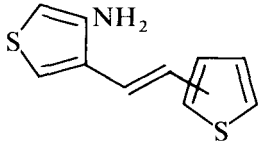
668



669

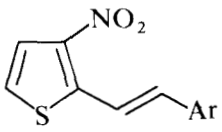


670

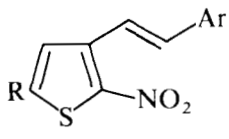


671

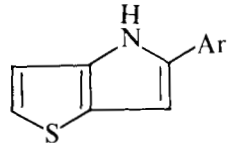
Another route to thienopyrrole systems is the reductive ring-closure reaction of **672** and **673** with triethyl phosphite to **674** and **675**, respectively.[277,279,289,702] Compound **677** was obtained from **676**.[130]



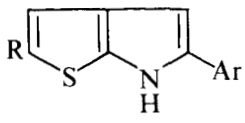
672



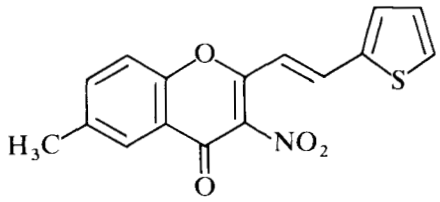
673



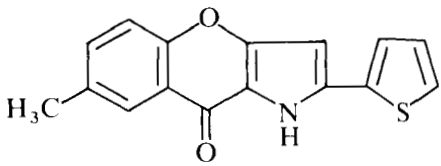
674



675

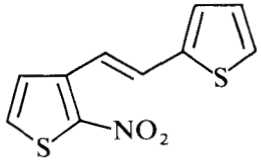


676

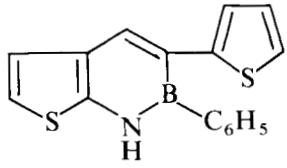


677

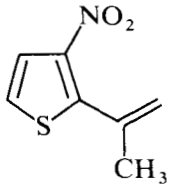
o-Nitrovinylthiophenes, such as **678**, could be hydrogenated to the unstable amino derivative, using large amounts of Pd on charcoal, which without isolation was reacted with dichlorophenylborane to give **679**.[162] Alternatively, $SnCl_2$ has been used as with **680**. The resulting amine–tin tetrachloride double salt was then directly converted to **681** with dichlorophenylborane.[703]



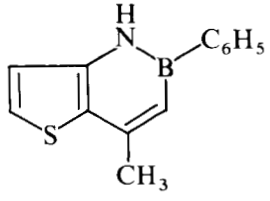
678



679

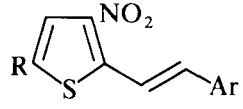


680



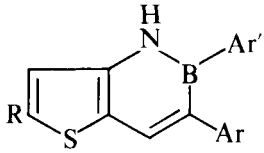
681

With the same technique, **682** could be reduced to the amino derivatives, which, as described previously, were ring-closed to heteroaromatic boron compounds **683**.[703] Tin and hydrochloric acid have also been used for the reduction of *o*-nitrovinylthiophenes.[704] Some amino vinylthiophenes, used for the preparation of heteroaromatic boron compounds, have been obtained directly from *o*-aminovinyl derivatives, prepared from *o*-aminocarbonyl derivatives by introduction of the double bond.[703,704]



$R = CO_2CH_3$, $R = H$
Ar = 2-Th

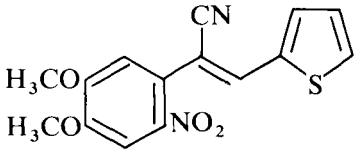
682



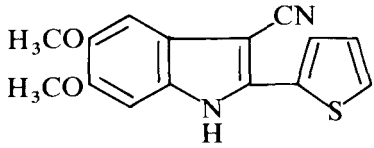
$Ar' = C_6H_5$, C_6F_5

683

Reductive cyclization of **684** with iron and acetic acid gave the 2-(2-thienyl)-substituted indole **685**.[222,705]

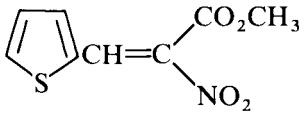


684

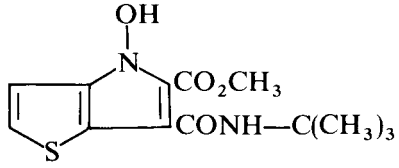


685

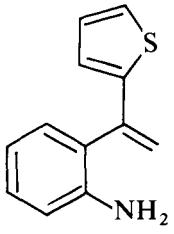
The nitrovinyl derivative **686** underwent a cycloaddition reaction with *t*-butylisonitrile to give **687**.[706] Diazotization of **688** yielded **689** in a low yield.[707,708]



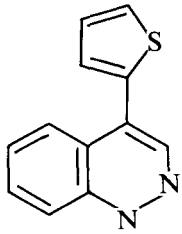
686



687

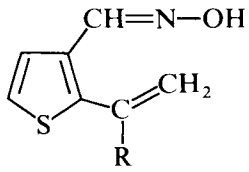


688



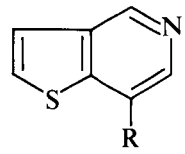
689

Thienopyridines **691** have been obtained by heating the oximes **690** in decaline at 200°C.[334]



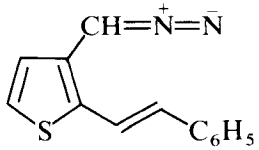
R = H, CH_3, C_6H_5

690

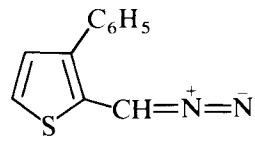


691

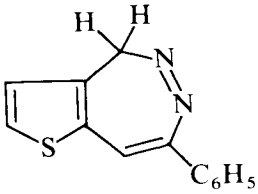
The cyclization of **692** and **693**, derived from the sodium salt of the tosylhydrazones by heating in 1,2-dimethoxyethane, gave **694** and **695**, respectively, while **696** did not cyclize, but gave carbene-derived products.[292]



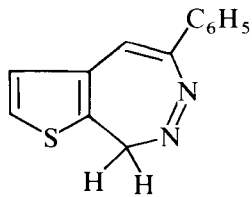
692



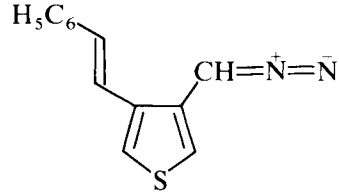
693



694

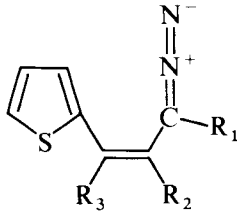


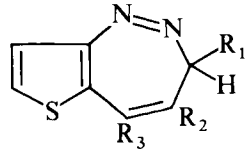
695

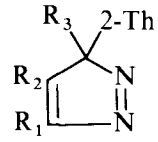


696

The decomposition of the diazo compounds **697**, obtained from the sodium salt of the tosylhydrazones, led, through cyclization, to **698** or **699**, as shown in the scheme. Compound **699b** underwent thermal ring expansion to give **698b**.



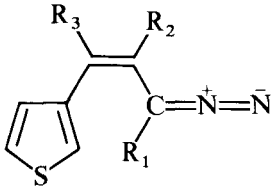


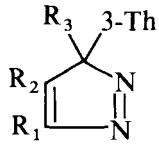


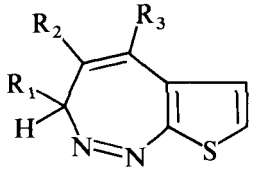
a	$R_1, R_2 = (CH_2)_3$,	R_3 = 2-Th	85%	0%
b	$R_1 = CH_3$, R_2 = H,	R_3 = 2-Th	19%	49%
c	$R_1, R_2 = (CH_2)_4$,	R_3 = Ph	10%	85%

697 **698** **699**

The 3-isomer **700** reacted similarly to give **701** and **702**.[408] Only 3-alkoxy-2-vinylthiophene **703**, among the three isomeric *o*-alkoxyvinylthiophenes, reacted with $HCl–HClO_4$ to give the pyrylium salt **704**.[57,196] On zinc dust reduction, **705** yielded **706**.[190] Treatment of **707** with pyridine hydrochloride gave **708**.[118]

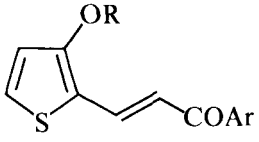






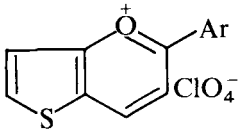
a	$R_1, R_2 = (CH_2)_3$,	R_3 = 3-Th	0%
b	$R_1 = CH_3$, R_2 = H,	R_3 = 3-Th	43%

700 **701** 90% 8% **702**

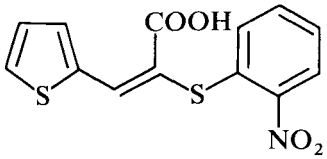


R = CH_3, $C(CH_3)_3$

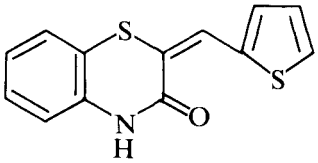
703



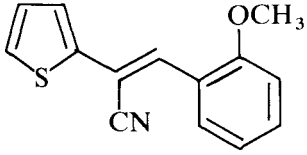
704



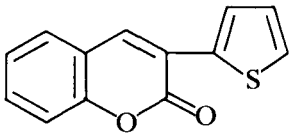
705



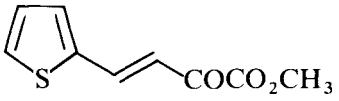
706



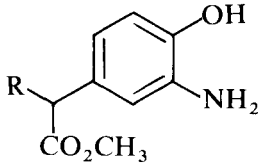
707



708

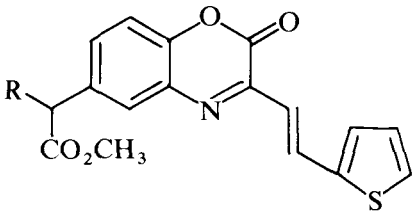


709



R = H, CH_3

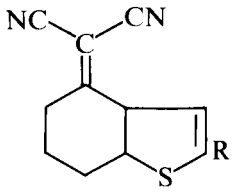
710



711

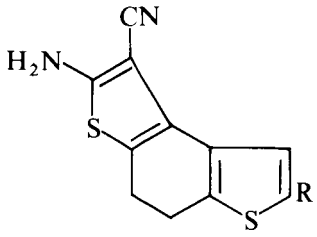
The condensation of **709** with **710** yielded **711**, of interest as potential blood platelet aggregation inhibitors.[709]

The Gewald reaction of **712** with sulfur yielded **713**.[710]



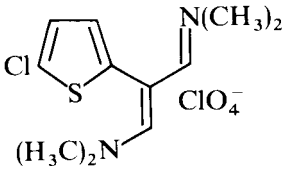
R = H, Br

712

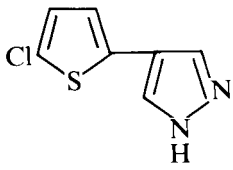


713

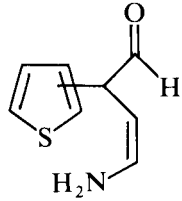
Vinamidinium salts **714**, on reaction with hydrazine hydrate in refluxing methanol, gave the pyrazole **715**. Alternatively, in order to obtain both parent compounds, thienyl malonaldehydronitriles were hydrogenated to **716**, which, on reaction with hydrazine hydrate yielded the desired **717**.[711]



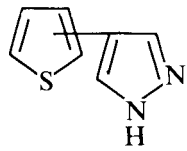
714



715

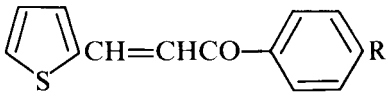


716



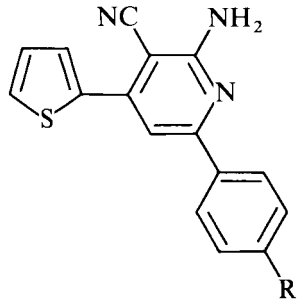
717

The reaction of **718** with malonitrile in the presence of ammonium acetate gave **719**.[712] With ethyl cyanoacetates, the corresponding pyridines were obtained.[67,712] A reaction path via Michael addition is suggested.



R = H, OCH_3, Cl

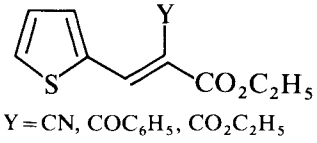
718



719

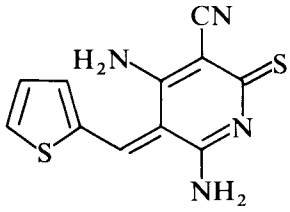
The reaction of compounds **720** (Y = CN) with cyanothioacetamide yielded **721**. Similar structures were suggested as products in the reaction of **720** (Y = COPh,

$CO_2C_2H_5$).[714] The reaction of **722** with 3-(2-thienyl)-2-cyanoacrylonitrile gave **723**.[715] A similar reaction with **724** led to **725**.[234]

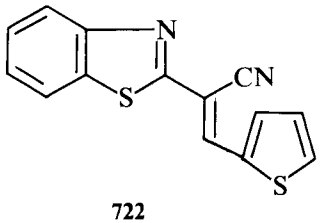


Y = CN, COC_6H_5, $CO_2C_2H_5$

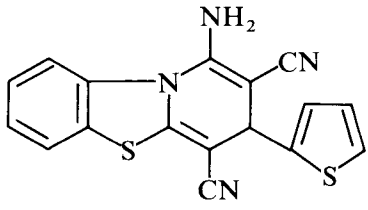
720



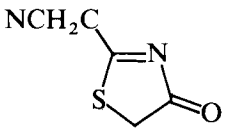
721



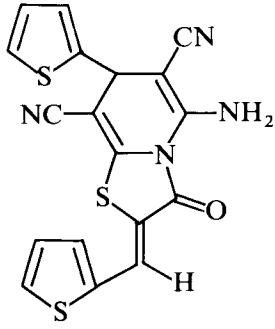
722



723

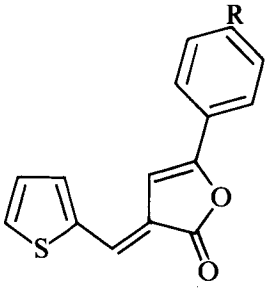


724

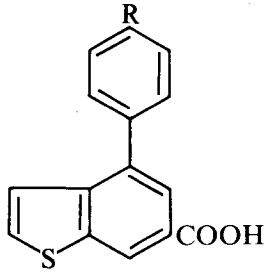


725

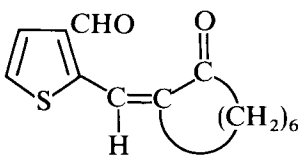
Refluxing in acetic acid–hydrochloric acid isomerized **726** to **727**.[75] Compound **728** was condensed with alkali to form **730**, while **729** gave only a very low yield.



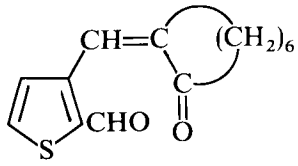
726



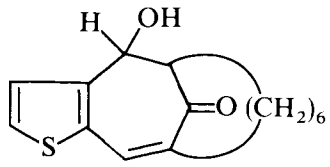
727



728

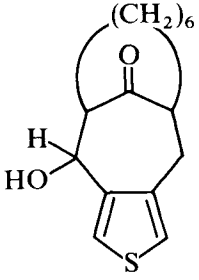


729

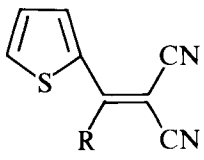


730

In addition, **731** could be obtained in good yield from the corresponding 3,4-isomer.[38] Treatment of **732** with polyphosphoric acid resulted in **733**.[210]

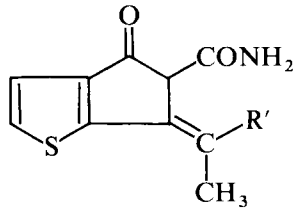


731



$R = C_2H_5$, i-C_3H_7

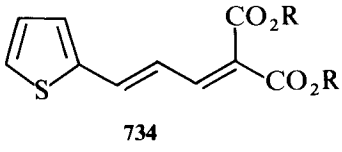
732



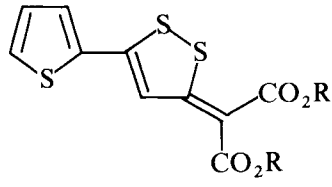
$R' = H$, CH_3

733

Compound **734** reacted with sulfur to give **735**.[3]

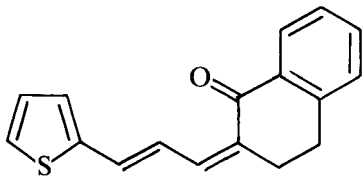


734

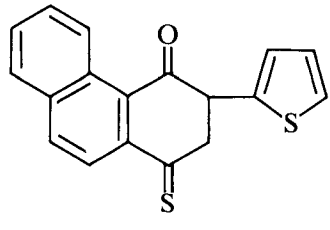


735

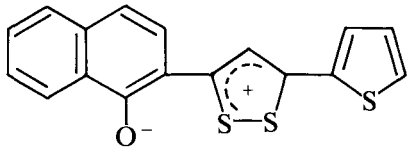
From **736** and sulfur, 8% of **737** and 6% of **738** were obtained.[4]



736



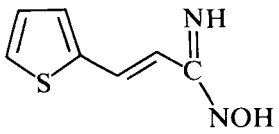
737



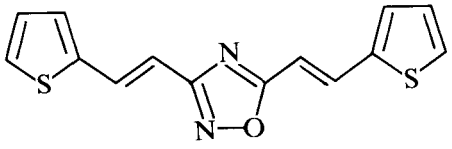
738

The reaction of thiophene analogs of chalcones with ethyl acetoacetate gave substituted cyclohexenones,[50] while the reaction with ethyl cyanoacetate gave substituted 2,3,4,5-tetrahydro-8-oxaquinolines.[716]

Starting from **739**, compound **740** was prepared for testing of anthelmintic activity.[717]



739



740

4. Reactions with Addition to the Double Bond

A. Catalytic Hydrogenation

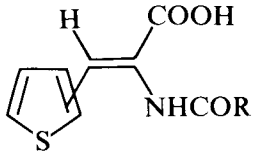
The thiophene sulfur poisons most hydrogenation catalysts, such as palladium on charcoal. In a few cases, successful hydrogenations have been achieved with thiophenevinyl derivatives, mostly using large amounts of palladium. However, thienylacrylic acids are efficiently reduced.[157,217,440,628,643,718] 3-(2-Thienyl)acrylic acid could also be reduced to the propionic acid with a 10% lead–sodium alloy[718] or 2% sodium–amalgam.[36] 2-Nitro-2-vinylthiophene was hydrogenated to 3-ethyl-2-nitrothiophene, using Pd/C as a catalyst, while the isomeric 3-nitro-2-vinylthiophene gave a mixture of 2-ethyl-3-nitro- and 2-ethyl-3-aminothiophene. In 2-nitro-3-[2-(2-thienyl)ethenyl]thiophene, only the nitro group was reduced.[162]

The rate of hydrogenation of 1-(2-thienyl)-2-nitroethene over Pd/C was found to be much slower than that of the corresponding benzene or furan derivative. The main reaction product was the oxime of 2-thienylacetaldehyde.[719]

A breakthrough in the hydrogenation of vinylthiophenes was the discovery that the Wilkinson rhodium catalyst, tris(triphenylphosphine)chlororhodium(I), was not especially poisoned by the thiophene sulfur, so that homogeneous hydrogenation could be carried out.[283] With the help of this catalyst, numerous substituted 1,2-dithienylethanes have been reduced to the corresponding

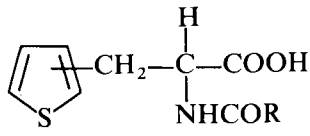
1,2-dithienylethanes without dehalogenation.[286,287,290,312–314,316,720–722] Azido groups are not reduced.[317]

Homogeneous catalytic hydrogenation of **741**, using optically active Rh–DIOP complexes, was used for the asymmetric synthesis of **742**, but with rather low *e,e* values.[723]



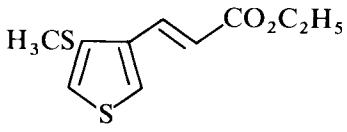
R = CH_3, C_6H_5

741

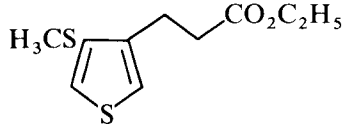


742

Diimine, generated by the sodium metaperiodate oxidation of hydrazine, was used for the hydrogenation of **743** to **744** without oxidation of the sulfide function.[724]

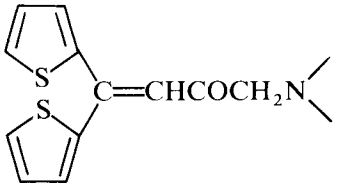


743

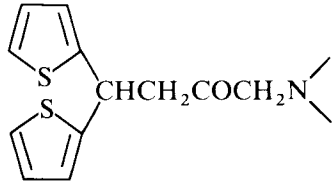


744

Vinylthiophenes have been utilized in connection with the synthesis of aliphatic compounds through Raney nickel desulfurization (see Part 1, Chapter VI of this series). The double bond is completely hydrogenated during this process.[102,103,219,382,725–727] However, Raney nickel catalyst has in a few cases been used under alkaline conditions to reduce the double bond, as in the transformation of **745** to **746** without desulfurization.[578]



745

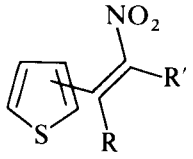


746

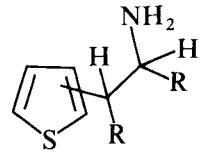
Raney nickel could also be used for the reduction of 2-(thienyl)malonaldehydronitrile to 2-(thienyl)-3-aminopropenal.[728]

B. Hydride Reductions

Numerous papers describe the reduction of compounds **747** to the saturated amines **748**, using $LiAlH_4$.[85,88–92,729–731]

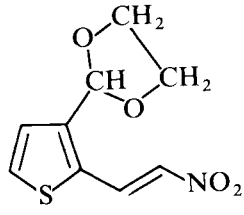


747

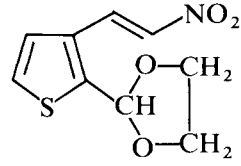


748

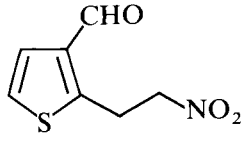
Reverse addition of $LiAlH_4$ to nitro olefins led to selective reduction of the double bond. The Nef reaction then led to ketones.[732] Reduction of **749** and **750** with sodium borohydride in ethanol gave **751** and **752**, respectively.[87]



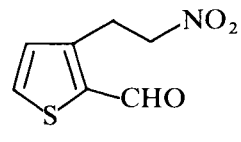
749



750

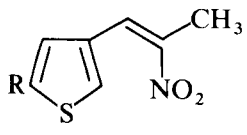


751

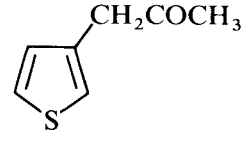


752

Reduction of **753** with iron and hydrochloric acid yielded **754**.[96]



753



754

2-(β-Nitrovinyl)thiophene was reduced to the amine by 1-benzyl-1,4-dihydronicotinamide.[1030] Triethylsilane and TFA have been used to transform compounds analogous to chalcones to the saturated ketone.[61]

C. Various Other Reductions

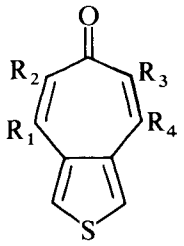
Alkali metal reduction of some thienylethene derivatives at − 80°C yielded the corresponding radical anions, whose ESR (electron-spin resonance) spectra

have been interpreted by the use of deuterated derivatives.[733] A series of [2,4]cyclophanetetraenes, containing thiophene rings, has been shown to undergo reversible two-electron reduction at a mercury electrode in DMF solution.[734]

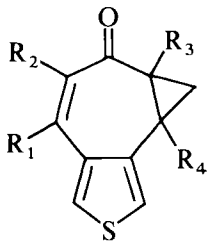
D. Electrophilic Additions

The addition of bromine in CCl_4 or thiocyanogen in benzene to 2-vinylthiophene, 2-chloro-, and 2-bromo-5-vinylthiophene gives the dibromo- and dithiocyano addition products.[479,735] Bromine has also been added to the double bond of several chalcone analogs for use in further synthesis.[44,55,56,66,672,736–739] Thiophene analogs of chalcone give epoxides on reaction with alkaline hydrogen peroxide.[59,740,741]

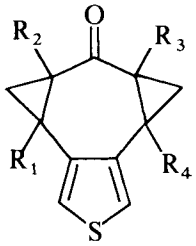
Dichlorocarbene has been added to the double bond of some 2-vinylthiophenes.[742] Extensive investigations of the addition of dimethyloxosulfonium methylide to thienotropones, such as **755**, to give the cyclopropanated derivatives **756** and **757** have been carried out; [*b*]-fused systems were also studied.[743–747]



755

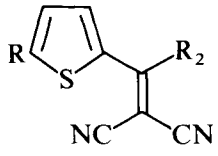


756

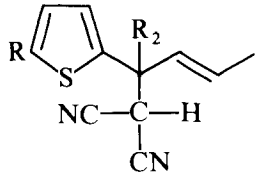


757

The hydroboration of 2-vinylthiophene with various hydroborating reagents has been studied. With bulky reagents, such as dicyclohexylborane and disiamylborane, only 2-(2-thienyl)ethanol was found after oxidation, while borane methylsulfide gave 7% of 1-(2-thienyl)ethanol and 39% of the 2-isomer. With disiamylborane, 2-propenylthiophene gave 96% 1-(2-thienyl)-1-propanol and 4% of 1-(2-thienyl)-2-propanol.[748] Irradiation of 1,1-dicyano-2-(2-thienyl)ethenes **758** and allyl tributylstannane in the presence of phenanthrene in aqueous acetonitrile afforded **759** regioselectively.[749]

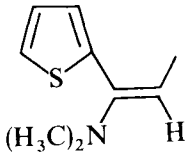


758

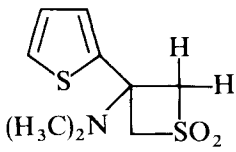


759

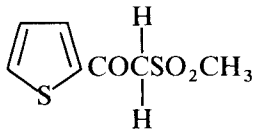
The reaction of **760** with sulfene, derived from methyl sulfonyl chloride and triethylamine, gave **761** and small amounts of **762**.[750]



760



761

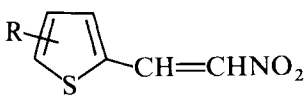


762

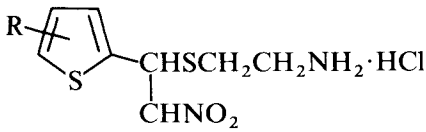
The kinetics and mechanism of the permanganate oxidation of (*E*)-3-(thienyl)-2-propenates have been studied. The reaction is first-order in permanganate and first-order in substrate. Support was obtained for a rate-determining step leading to the formation of a metallocyclooxetane or a cyclic manganate(V) diester.[169]

E. Addition of Sulfur-Containing Groups

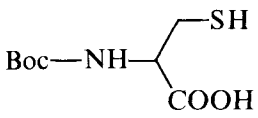
Nitrovinyl derivatives **763** reacted with 2-aminoethanethiol in the presence of pyrrolidine to give **764**.[751] The thiol **765** reacted similarly with the nitrovinylthiophenes to give **766**, which were used as intermediates in the synthesis of 1,4-thiazinepine-5-one derivatives.[752] The action of thiophenol on the bisamide **767**, with irradiation by UV light, resulted in the formation of **768**. The bis(urethane) reacted similarly.[753]



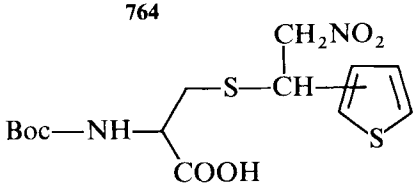
763



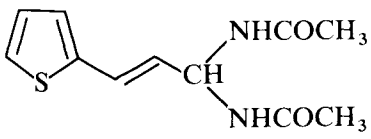
764



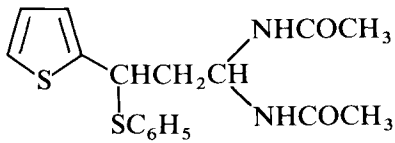
765



766

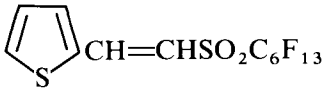


767



768

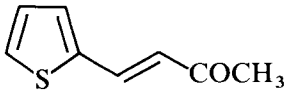
In connection with the synthesis of fungicides, a large number of substituted thiophenols, benzyl thiols and aliphatic thiols were added to thiophene and furan analog of chalcone.[754] The reaction of **769** with thiophenol and methylthioglycolate in the presence of Triton B gave **770**.[755] Reaction of **771** with *p*-toluenesulfinic acid gave **772**.[756]



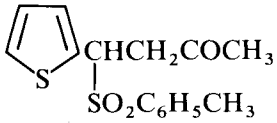
769

R = C_6H_5, $CH_2CO_2CH_3$

770



771

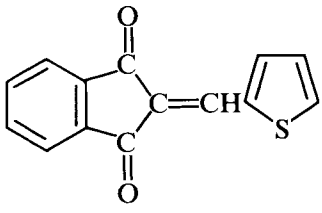


772

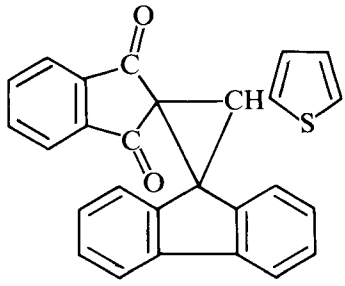
F. Addition of Nitrogen Nucleophiles

The reaction of thiophene analogs of chalcone with hydrazine has been used for the preparation of thienyl-substituted pyrazolines.[43,66,736,757–760] The reaction of diazomethane with 2-vinylthiophene gave 3-(2-thienyl)-Δ^1-pyrazoline, which underwent prototropic isomerization to 3-(2-thienyl)-Δ^2-pyrazoline, which on heating was converted to 2-cyclopropylthiophene.[761] 3-Cyclopropylthiophene was prepared from 3-(3-thienyl)acrolein and hydrazine.[13]

The reaction of **773** with 9-diazofluorene gave **774**, with a cyclopropane structure.[762]

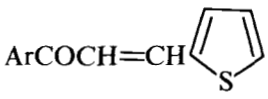


773

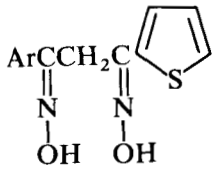


774

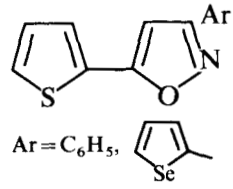
The reaction of **775** with hydroxylamine led to **776**, which on treatment with acetic acid yielded **777**.[763] Similarly, 2-bromo-3-(2-thienyl)acrylophenones react with hydroxylamine to give thienylisoxazoles.[672]



775



776

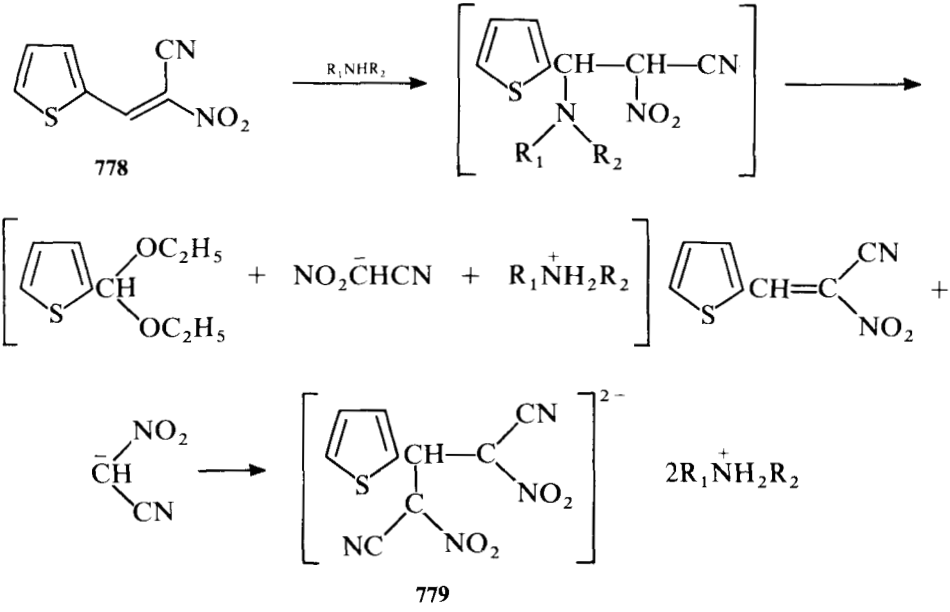


777

The condensation reactions of some alkenylthiophenes with phenol and hexachlorocyclopentadiene have been studied.[764] It has been shown that in the reaction of 1-methylsulfinyl-1-methylthio-2-(thienyl)ethenes with methanol and hydrogen chloride, methyl α-methylthio-thienylacetates are formed as byproducts, in addition to methyl arylacetates. When the aryl group is strongly electron-donating, such as 5-methoxy-2-thienyl, 5-phenyl-2-thienyl or 5-(*p*-methoxyphenyl)-2-thienyl, the α-methylthioarylacetate becomes the main product.[736]

The reaction of **778** with secondary amines in ethanol led to **779** through a complicated path, as indicated in Scheme 19.[765]

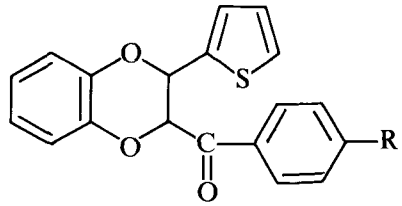
778



779

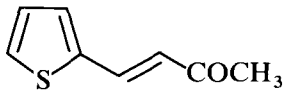
Scheme 19

3-(2-Thienyl)acrylophenones are claimed to react with tetrachloro-*o*-benzoquinone to give **780**. The reaction of **781** with trimethylsilyl chloride, Mg, and HMPT yielded 70% of **782** and 15% of **783**. 3-(2-Thienyl)acrylonitrile gave **784** with the same reagent.[766]

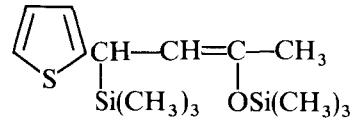


R=Cl, OCH_3

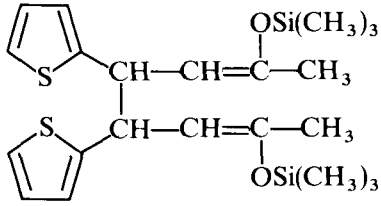
780



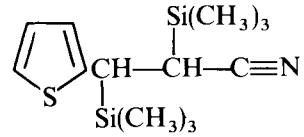
781



782



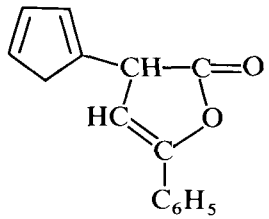
783



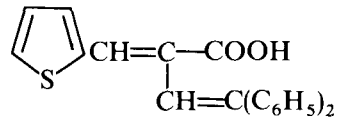
784

As mentioned previously, thenal rhodanines have been transformed to thiopyruvic acids through alkaline hydrolysis, and the acids have then been used for the synthesis of α-amino acids.[99,104]

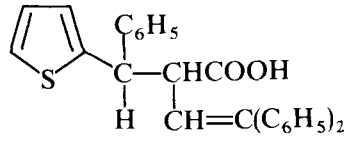
When **785** was reacted with excess benzene and anhydrous $AlCl_3$, intermolecular ring closure to benzo[*b*]thiophenes did not occur. Instead, **787** was obtained, presumably via **786**.[74]



785



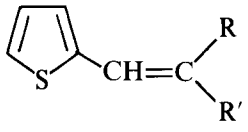
786



787

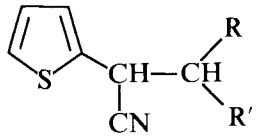
G. Michael Additions of Carbanions to Vinylthiophenes

The addition of sodium or potassium cyanide to **788** gave **789**.[165,199,201] Similarly, **790** yielded **791**.[211]

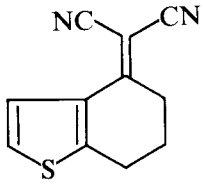


$R = R' = CO_2C_2H_5$
$R = CN, \quad R' = CO_2C_2H_5$
$R = CN, \quad R' = CO_2C(CH_3)_3$

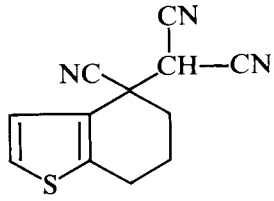
788



789

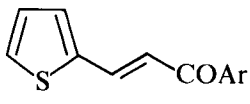


790



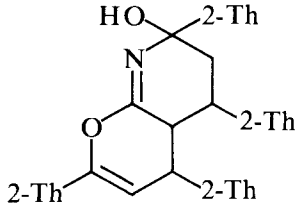
791

The reaction of the chalcones **792** with ethyl cyanoacetate in the presence of piperidine in ethanol gave a 2 : 1 adduct **793**.[716]



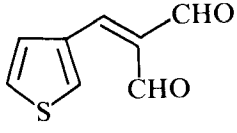
Ar = 2-Th, 2-Fu

792

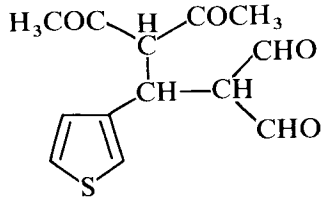


793

3-Thenylidenemalonaldehyde **794** reacted with β-dicarbonyl compounds, such as acetylacetone, with catalysis by (2,4-pentanedionato)copper(I) and



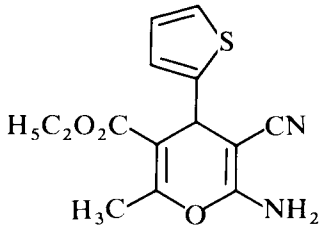
794



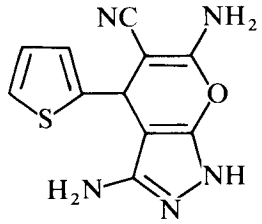
795

bis(2,4-pentadionato)copper(II) together with boron trifluoride etherate, to give the Michael addition product **795**.[767]

The reaction of 3-(2-thienyl)acrylonitrile with ethyl acetoacetate led through ring closure to **796**, after Michael addition.[768] Similarly **797** was prepared by the reaction of 2-thenylidenemalonitrile with 3-amino-2-pyrazoline-5-one.[107]

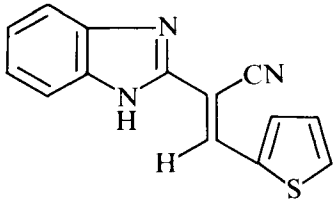


796

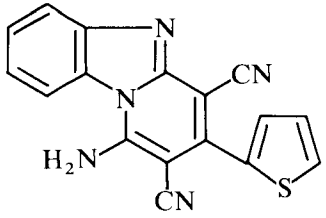


797

The reaction of **798** with malonitrile in ethanolic piperidine gave **799** after Michael addition, ring closure, and oxidation.[232]

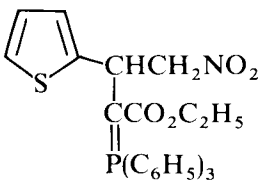


798

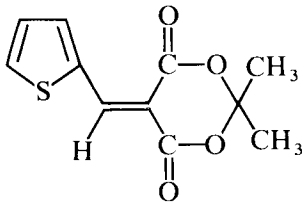


799

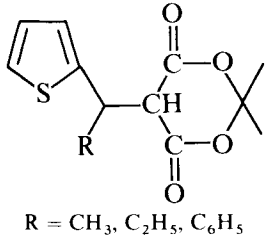
The reaction of (carbethoxymethylene)triphenylphosphorane with 1-(2-thienyl)-2-nitroethene gave **800**.[769] Addition products of 1-(2-thienyl)-2-nitroethene with dimethyl malonate have also been obtained.[770] Conjugate addition of Grignard reagents to thiophene analogs of chalcones has been observed with α-naphthylmagnesium bromide.[771] Addition of phenyl and thienylmagnesium bromide also gave minor amounts of the 1,2-addition product.[772] Only 1,4-addition of 2-thiophenemagnesium bromide to diethyl 2-thenalmalonate was observed.[163] Conjugate addition also occurred on reaction of **801** with some Grignard reagents to give **802**.[773]



800



801



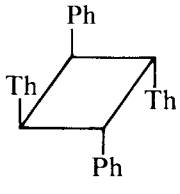
R = CH_3, C_2H_5, C_6H_5

802

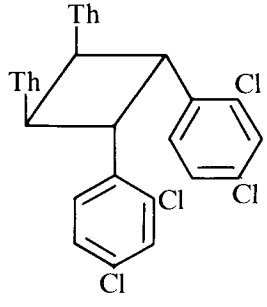
1,4-Addition to chalcone analogs has also been achieved with methyllithium–Cu(I).[24]

5. Dimerization Reactions of Vinylthiophenes

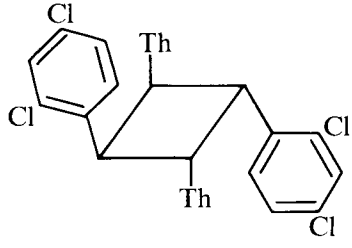
Photolysis of 1-(2-thienyl)-2-benzoylethene gave a low yield of *trans–trans–trans*-1,2-dibenzoyl-3,4-di-2-thienylcyclobutane, while 1-(2-thienyl)-2-(2-thenoyl)-ethene gave a mixture of *trans–trans–trans*-1,2-di-2-thienyl-3,4-di-2-thenoylcyclobutane and *trans–cis–trans*-1,3-di-2-thienyl-2,4-di-2-thenoylcyclobutane.[774] The solution and solid-state photodimerization of *trans*-1-phenyl-2-(2-thienyl)-ethene, *trans*-1-(2,4-dichlorophenyl)-2-(2-thienyl)ethene, and *trans*-1-(3,4-dichlorophenyl)-(2-thienyl)ethene have been studied. The solid-state behavior is crystal-lattice-controlled and the first- and last-mentioned ethenes were light-stable. In solution, however, *trans*-1-phenyl-2-(2-thienyl)ethene, in contrast to earlier reports, underwent photodimerization, and one of the photoproducts was **803**. 1-(2,4-Dichlorophenyl)-2-(2-thienyl)ethene gave only the topochemically expected mirror-symmetric dimer **804**. In solution both **804** and **805** were obtained, while the 3,4-dichloro isomer gave all four possible cyclobutane isomers from the union of *trans*-monomers.[357] The solid-state photooligomerization of **806** has been studied.[775]



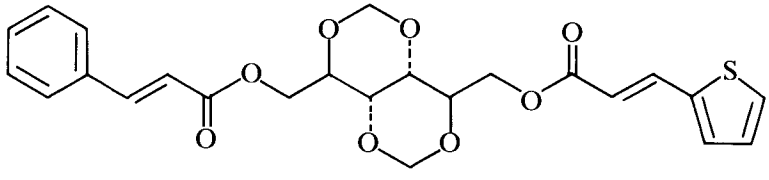
803



804



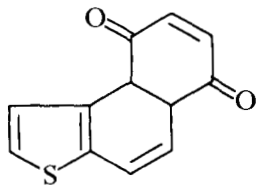
805



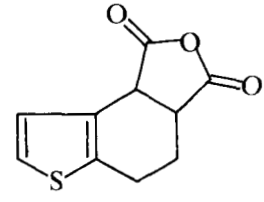
806

6. Cycloadditions of Vinylthiophenes

Vinylthiophenes can react as both dienophiles and dienes in the Diels–Alder reaction. 2-Vinylthiophene behaves as a moderately active diene with benzoquinone and maleic anhydride to form **807** and **808**, respectively.[477,776]

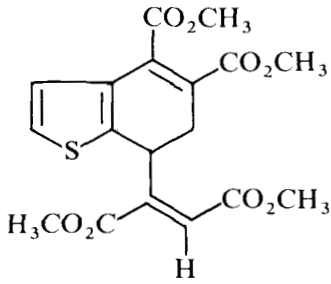


807

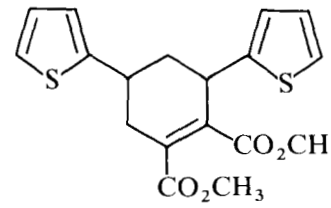


808

In a later, careful investigation, other dienophiles, such as dimethyl acetylenedicarboxylate, methyl propiolate, and methyl acrylate, were used. Products included simple benzo[*b*]thiophenecarboxylates, but the acetylenic dienophiles also yielded 1,2-adducts, such as **809** and the corresponding *cis*-isomer. Compound **810** was also formed in the reaction with dimethyl acetylenedicarboxylate, along with much polymer material.[377]

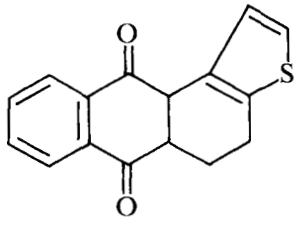


809

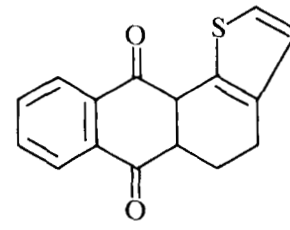


810

Naphthoquinone was reacted with 2- and 3-vinylthiophene to give **811** and **812**, respectively.[380]

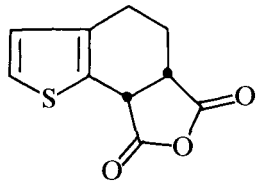


811

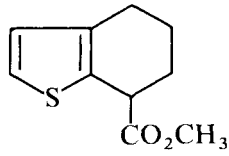


812

Cycloaddition reactions between 3-vinylthiophene and maleic anhydride, methylacrylate, dimethyl acetylenedicarboxylate, and methyl propiolate have been investigated. The reaction with maleic anhydride was straightforward and gave **813** in high yield. The reaction with methyl acrylate was slow, even at 160°C, and **814** was obtained in 31% yield.

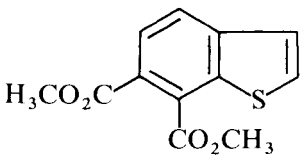


813

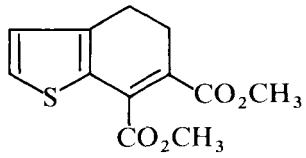


814

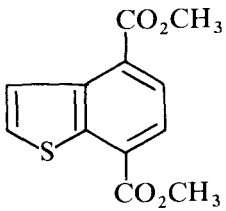
Dimethyl acetylenedicarboxylate reacted slowly with 3-vinylthiophene and gave two major products, the primary dihydro product **816** and its aromatization product **815**. With methyl propiolate six different adducts, **817–822**, were isolated.



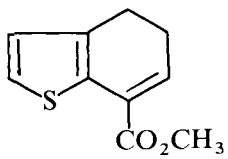
815



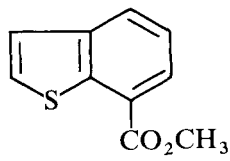
816



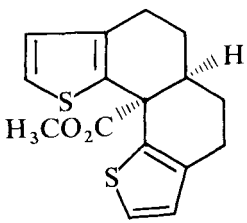
817



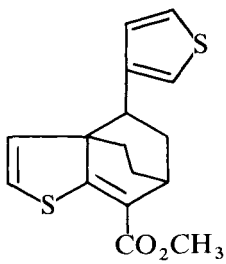
818



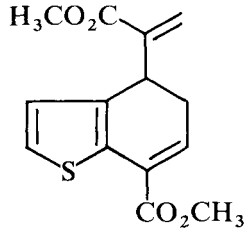
819



820



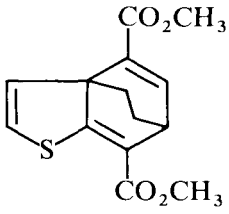
821



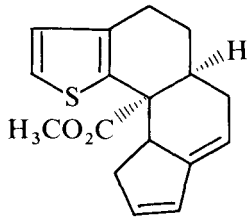
822

Compound **817** is most probably formed via addition of a second molecule of propiolate to **818**, yielding **823** as an intermediate, which loses ethene to give **817**. Addition of a second mole of 3-vinylthiophene to **818** gives **820** via isomerization of **824** or, alternatively, gives **821**. Compounds of type **820** and **821** were not observed in the reaction of 2-vinylthiophene.[400] The reaction of

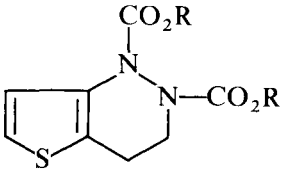
2-vinylthiophene with azodicarboxylates gave a mixture of compounds **825** and **826**, which could not be separated. Treatment of this mixture (R = t-C_4H_9) with TFA and oxygen gave **827**. Compound **828**, on the other hand, gave both the Diels–Alder adduct and the ene product **829**.[777] Various thienylcycloalkenes react with maleic anhydride at 100°C without a solvent to give the expected adducts. In some cases bis adducts were observed.[409]



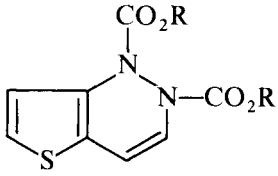
823



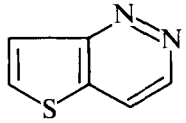
824



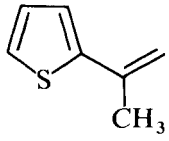
825



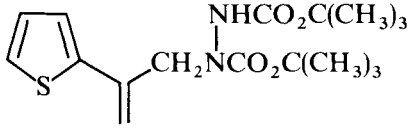
826



827

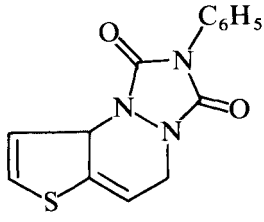


828

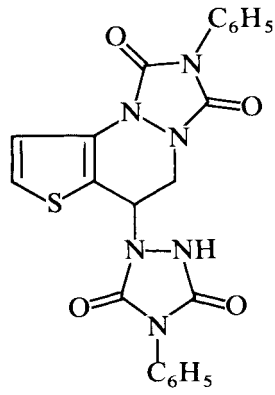


829

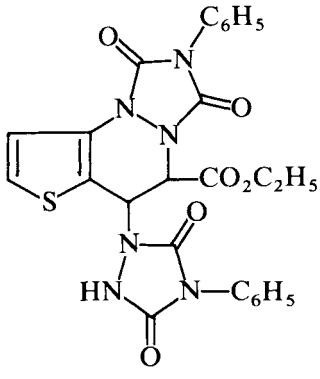
The reaction of 2-vinylthiophene with 4-phenyl-1,2-triazolo-3,5-dione (PTAD) in dioxane at room temperature gave the 1 : 1 adduct **830**, while in ether the 1 : 2 adduct **831** was obtained. From 3-bromo-2-vinylthiophene **832** was obtained in a 46% yield after treatment with potassium carbonate. Addition of PTAD to ethyl 3-(2-thienyl)acrylate gave two 2 : 1 adducts, **833** and **834**, in 46 and 8% yields, respectively. These are presumably formed from the initial Diels–Alder adduct by ene reactions with a second mole of PTAD.[166] Diethyl azodicarboxylate did not react with ethyl 3-(2-thienyl)acrylate even on heating at 156°C. However, using a Lewis acid (boron trifluoride–ether) as a solvent, **834**, which is not a Diels–Alder adduct, was obtained in a 15% yield.[166] Compound **830** was first obtained from 2-vinylthiophene and PTAD in methylene chloride at -20°C.[778]



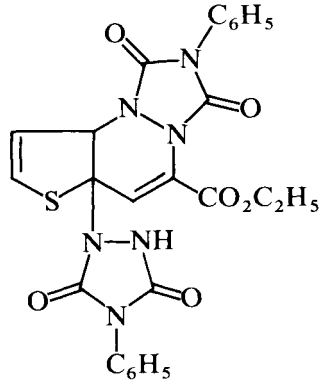
830



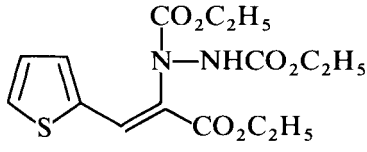
831



832

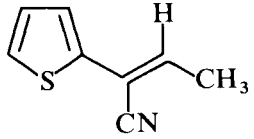


833

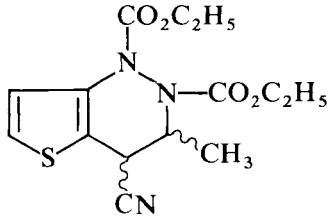


834

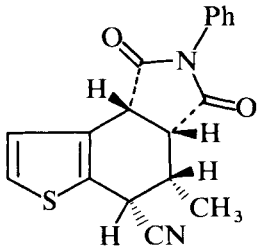
The cyanovinyl derivative **835** gave the normal adduct **836** in refluxing acetonitrile with diethyl azodicarboxylate. N-Phenylmaleimide reacted more slowly with **835**, and two isomers, **837** and **838**, were isolated in 30 and 14% yields, respectively. From the reaction of **835** with methyl propiolate, four products, **839**, **840**, and two diastereomers of **841**, were isolated in low yields, and much polymer formation occurred. After a reaction time of 11 days, **835** gave three compounds with dimethyl acetylenedicarboxylate, **842**, a mixture of diastereomers of **843** and **844**, isolated in 8, 25, and 14% yields, respectively, after chromatography on silica gel.[273]



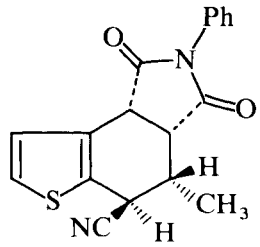
835



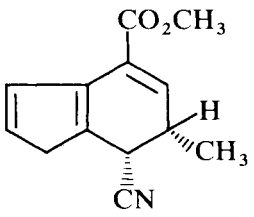
836



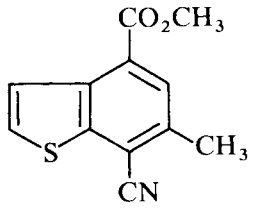
837



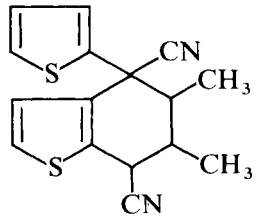
838



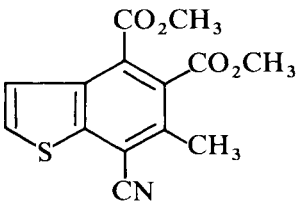
839



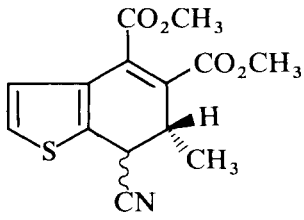
840



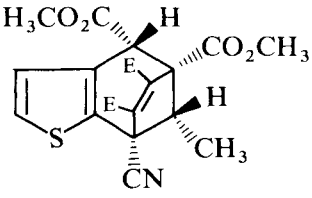
841



842

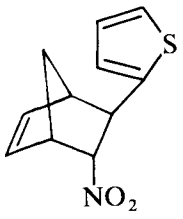


843

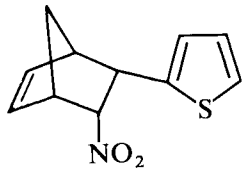


844

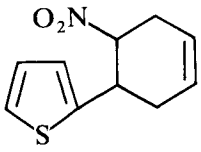
In the reaction of *trans*-1-(2-thienyl)-2-nitroethene with cyclopentadiene, the *endo*-**845** and *exo*-**846** nitro compounds were obtained.[779] The nitrovinylthiophene has also been reacted with butadiene and dimethylbutadiene in a Carius tube at 140°C to give **847** and **848**.



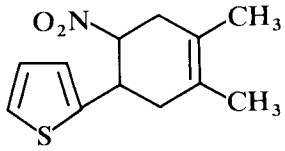
845



846

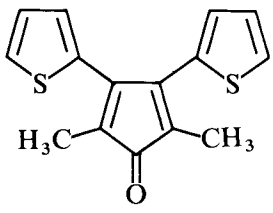


847

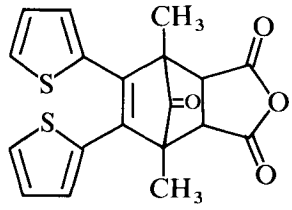


848

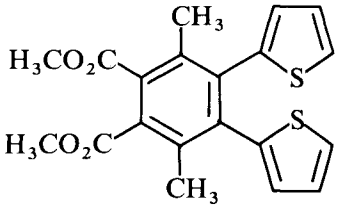
Compound **849** reacts with maleic anhydride, dimethyl acetylenedicarboxylate, and cyclohexadiene to give **850**, **851**, and **852**, respectively.[73]



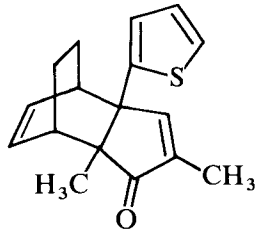
849



850

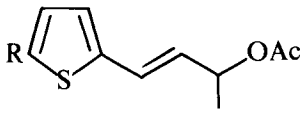


851



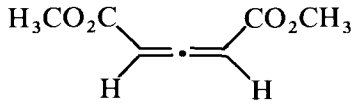
852

In contrast to their furan analogs, the thiophenes **853** did not undergo cycloaddition reaction with the allene **854**. However, intramolecular cyclization of **855**



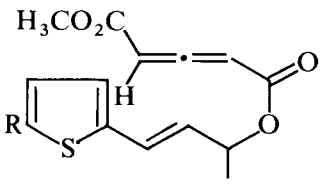
R = H, CH_3

853

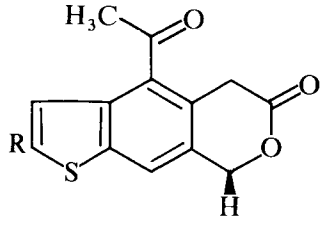


854

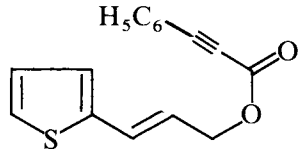
to **856** was achieved in low yields after reflux in toluene.[5] Intramolecular Diels–Alder reactions have also been achieved with **857**.[14]



855

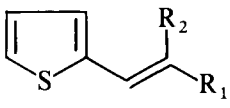


856

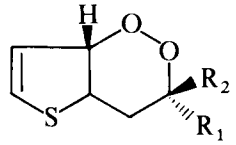


857

Sensitized (tetraphenylporphine) photooxygenation by singlet oxygen has been carried out with **858**, stereospecifically yielding the corresponding stable 1,4-endoperoxide **859**. From **860** the endoperoxide **861**, together with the allylic peroxide **862**, was formed, except with **860** (R_1 = H, R_2 = C_6H_5), which gave **861** in only a 15% yield.[780] The reaction of 2-(2-thienyl)acrolein with butylvinyl ether at 200°C led to **863**.[781]

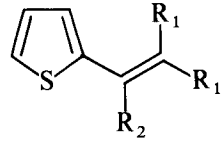


858

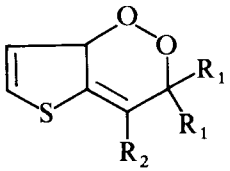


$R_1 = R_2 = CH_3$
$R_1 = R_2 = H$
$R_1 = CH_3$, $R_2 = H$
$R_1 = C_6H_5$, $R_2 = H$

859

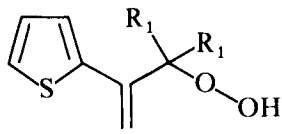


860

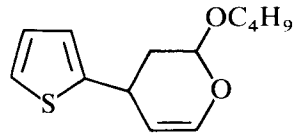


$R_1 = H$, $R_2 = CH_3$
$R_1 = R_2 = CH_3$
$R_1 = H$, $R_2 = C_6H_5$

861

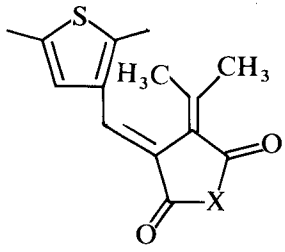


862



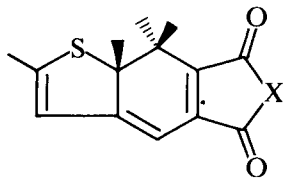
863

Photocyclization, and in some cases electrochemical cyclization, of **864** yielded **865**. It was suggested that the electrochemical cyclization proceeds via a radical anion, which could be observed in certain cases.[782]



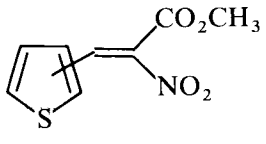
X = O
X = NC_6H_5
X = p-$NO_2C_6H_4$—N—
X = NCH_2COOH
X = $NCH_2C_6H_5$

864

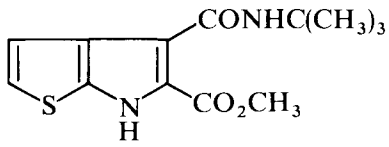


865

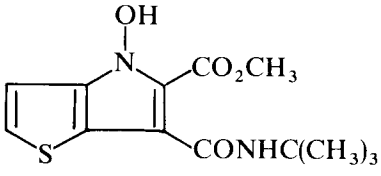
[1,4]-Cycloaddition of isocyanides to various aryl nitroalkenes has been studied. From the 3-thienyl isomer of **866**, **867** was obtained on reaction with *t*-butylisonitrile. The intermediate 1-hydroxy derivative was probably reduced by the excess *t*-butylisonitrile. On the other hand, the 2-thienyl isomer of **866** yielded **868**.[783]



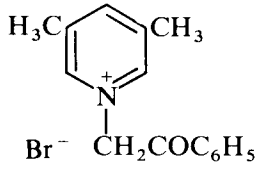
866



867

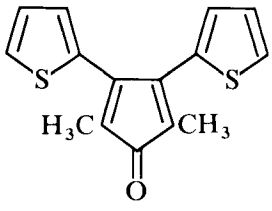


868

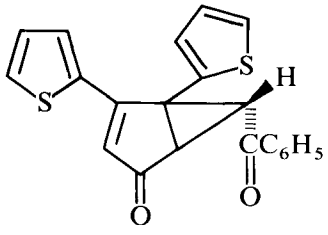


869

The reaction of **869** with **870** in the presence of potassium carbonate gave **871**.[784]



870



871

7. Polymerization of Vinylthiophenes

2-Vinylthiophene, and its 5-chloro derivative, and chlorinated 3-vinylthiophene, have been polymerized alone and with styrene, methyl methacrylate, vinyl acetate, and maleic anhydride, using benzoyl peroxide as an initiator. Isopropenylthiophenes did not polymerize alone, but did copolymerize.[381] The properties of the polymers were studied.[785] Vinylthiophene polymerization processes have been patented.[786] The polymerization kinetics of 2-vinylthiophene have been studied.[787,788] With benzene as a diluent, the overall rate of polymerization was proportional to the 2.5 power of the monomer concentration, suggesting that the thermal initiation is a termolecular process.[787] In another study 2- and 3-vinylthiophenes were polymerized with several catalysts of the Ziegler type. All the polymers obtained were shown to be amorphous by their X-ray diffractions.[789]

Sodium adducts of 2-vinylthiophene were used as initiators in its polymerization, as well as of other vinyl compounds.[790] Molecular-orbital consideration of the ionic polymerizability of vinylthiophenes have been published.[791] Thiophene analogs of chalcones have been studied in copolymerization reactions with a wide variety of monomers.[22] The photochemical sulfochlorination of polyvinylthiophene has been investigated.[792] The 300-MHz ^{1}H NMR spectrum of 2-polyvinylthiophene[793] and the ^{13}C NMR spectra of 2- and 3-polyvinylthiophene have been studied.[794]

Tough, flexible films of poly-(2,5-thienylene)vinylene, which exhibit conductivity of 60 S/cm on iodine doping, were prepared through a soluble precursor polymer.[795]

IV. VINYLTHIOPHENES OF POTENTIAL PHARMACEUTICAL INTEREST

Much of the interest in vinylthiophenes during the years has been caused by attempts to prepare pharmacologically active compounds. The more important results have been treated in Press' chapters of pharmacologically active compounds in general. Only few references are given here.

Buu-Hoi and coworkers, as mentioned previously, prepared thiophene analogs of stilbene and triphenylethene as possible oestrogens.[796–800] Different types of vinylthiophene have been evaluated for their antibacterial activity[801–811] and nematodicidal and general antiparasitic activity.[812–819]

During many years there was a high level of activity in the study of the analgesic activity of dithienylbutenylamines and related compounds.[820–823] Other pharmaceutical properties were studied with certain types of vinylthiophenes,[833–836] as well as pesticidal properties.[837–840]

Naturally occurring vinylthiophene derivatives have been discussed in Part 1, Chapter III, of this series, which treats naturally occurring thiophenes in

general. In this chapter, therefore, only references to papers containing thiophene vinyl compounds will be given.[611,612,841-852]

V. PHYSICAL PROPERTIES OF VINYLTHIOPHENES

The physical properties of vinylthiophenes are discussed and tabulated in Part 4, Chapter I of this series in the context of a general treatment of the physical properties of thiophenes. In this section, therefore, only references to some characteristic physical properties will be given. Different types of theoretical calculations have been carried out on vinylthiophene-containing molecules.[853-856] The acid constants of 3-(thienyl)acrylic acids have been measured.[180,857,858]

Dipole moments have been measured for styrylthiophenes[859] and chalcogen analogs.[860-864] *Polarographic data* have been obtained.[865-868]

The ^{1}H and ^{13}C NMR spectra of 3-(thienyl)acrylates;[156,869] 1,2-aryl(thienyl)-ethenes;[594,870-874] α-nitro-β-thienylethenes;[864,875,876] β-thienyl-α,β-unsaturated esters, ketones, and nitriles;[641,877-881] cyclopentathiophenes;[882] and other compounds related to vinylthiophenes[883-886] have been analyzed.

The *IR spectra* of vinylthiophenes have been studied for various purposes.[27,887-893] *Cis–trans*-isomers were identified,[327,884,894] and the C=O stretching bands in various thiophene analogs of chalcones were studied,[895-899] as well as keto-enol tautomerism.[900] Raman spectra were also analyzed.[901]

The *UV spectra* of *cis-* and *trans*-styrylthiophenes[327,892,894,895] and thiophenepolyenes[369,902-904] have been studied. The He(I) and He(II) photoelectron spectra of styrylthiophene and α-cyanostyrylthiophene have been reported.[895] Most extensive studies have been carried out on the UV spectra of thiophene analogs of chalcones and related compounds.[32,641,642,864,905-915] Ultraviolet spectroscopy has also been used for the determination of the basicities of thiophene analogs of chalcones,[897,898,916-920] as well as their interaction with $FeCl_3$.[921-923] The UV spectra of thiophene-annelated tropylium cations and tropones have been measured.[924] The fluorescence spectrum and scintillation properties of 1,4-bis-(2-vinylthienyl)benzene[344] and thienylvinylthienyl benzene derivatives of 2,5-diaryloxadiazoles[345] have been studied.

The triplet-state photophysical behavior of *trans*-1-(2-anthryl)-2-(2-thienyl)-ethene and some analogs compounds has been studied by laser flash photolysis and pulse radiolysis. Triplet-related transformation and decay processes with associated lifetimes of 100–120 ns were observed at the initial stage, following the laser excitation, and tentatively attributed to intramolecular relaxation in the initially formed triplet conformers in the form of rotation of the aryl group quasi-single bonds.[925] Charge-transfer complexes between 1,2-diheteroarylethenes with iodine and TCNQ have been studied. The conductivities were relatively low and fell in the range of those for semiconductors.[326]

The mass spectra of various compounds containing vinylthiophene units have been studied.[417,639,926-929]

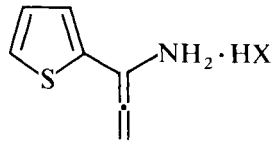
A number of vinylenes, containing 2,5-dithienyl-5-5'-diyl or 1,2-dithienylethene units, have been studied in relation to their liquid-crystalline properties by DTA analysis, and visually by their textures in microscopy with polarized light.[303,304] Bisdimethine dyes, containing thiophenevinyl grouping, have been studied.[132]

VI. THIOPHENES WITH CUMULATIVE DOUBLE BONDS

1. Two Cumulative Bonds (Allenes)

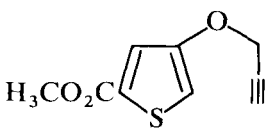
The nickel-catalyzed reaction of 2-thiophene magnesium bromide with **872** gave **873** in an 88.7% yield.[930]

872

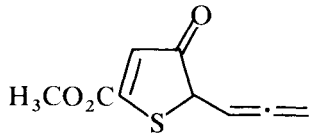


873

In the Claisen rearrangement of **874**, **875** is assumed to be an intermediate.[580]



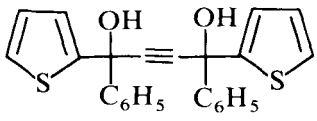
874



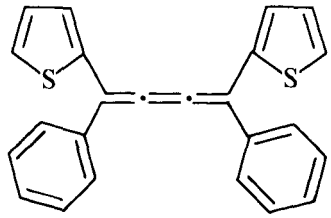
875

2. Three Cumulative Bonds

The reaction of acetylene dimagnesium bromide with phenyl 2-thienyl ketone led to **876**, which on reaction with hydroiodic acid in acetone gave the cumulene **877**. Its UV spectrum was studied.[931] The reaction of **878** with a base gave the

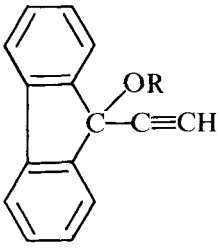


876

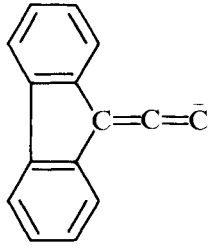


877

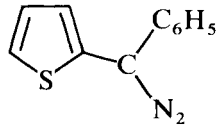
vinylidene carbene **879** as an intermediate, which was captured by the diazo compound **880** present, giving, via **881** and loss of nitrogen, the cumulene **882**.[932]



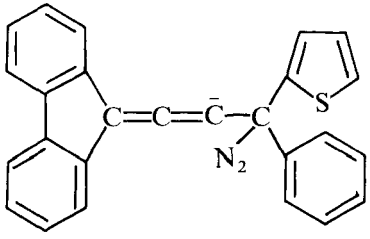
878



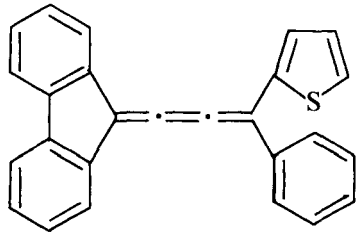
879



880



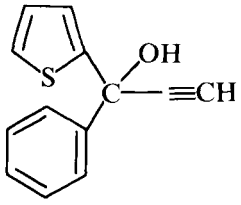
881



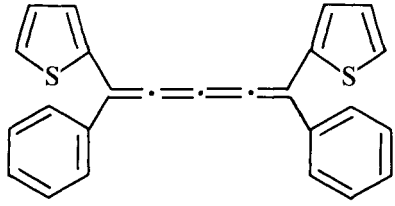
882

3. Four Cumulative Bonds

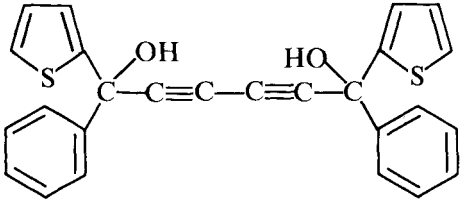
The reaction of the dimagnesium salt of diacetylene with phenyl 2-thienyl ketone led to **885**, which upon the same treatment as described for **884**, gave **886**



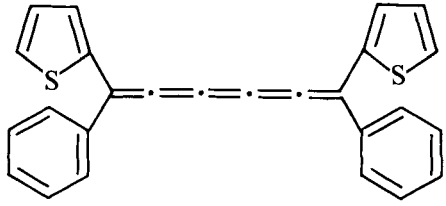
883



884



885



886

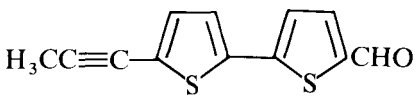
in a low yield.[934] A detailed review of the synthesis of hexapentaenes has been published.[935]

VII. PREPARATION OF THIENYLACETYLENES

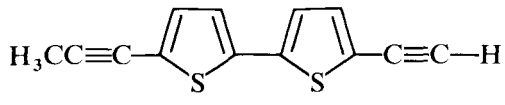
1. From Thiophenecarbonyl Derivatives

A classical method for the preparation of 2-thienylacetylene was the reaction of 2-acetylthiophenes with PCl_5 followed by dehydrochlorination. It has been claimed that 2-thienylacetylene, 3-methyl-2-thienylacetylene, 4-methyl-2-thienylacetylene, 5-chloro-2-thienylacetylene, and 2,5-dichloro-3-thienylacetylene have been prepared in a 60–80% yield when the dehydrochlorination of the intermediate chlorinated compounds is carried out with sodium amide in liquid ammonia.[936–938] Similarly, 5-methyl-,[939] 5-phenyl-,[937] and 5-(2-thienyl)-[311,611] acetylene have been prepared, albeit in rather low yields. However, a recent reinvestigation of this reaction with 2-acetylthiophene indicated that only small amounts of 2-thienylacetylene are formed, and that the major products are the *E*- and *Z*-isomers of 1,2-dichloro-1-(2-thienyl)ethene, with minor amounts of 1,1-dichloro-1-(2-thienyl)ethane, 1-chloro-1-(2-thienyl)ethene, 2-(chloroacetyl)-thiophene, and 2-(dichloroacetyl)thiophene. These authors claim that the best method for converting 2-acetylthiophene to 2-thienylacetylene is through the reaction of 2-(bromoacetyl)thiophene with triethyl phosphite, followed by treatment with sodium amide,[486] which was previously used for the synthesis of the 5-phenyl-substituted derivative.[940] A low yield was also observed in the reaction of 2-acetyl-5-methylthiophene with PCl_5, followed by dehydrochlorination, which gave the desired acetylene in an only 16% yield in the dehydrochlorination step.[939] The chlorination–dechlorination procedure also gives low yields in other cases.[611] However, by applying the classical method of preparing the sodium salt of 2-thienylacetylene, followed by reaction with methyl iodide, 2-(1-propynyl)thiophene was obtained in a 30% yield, based on 2-acetylthiophene.[941]

A very convenient methodology for the preparation of acetylenes from aldehydes, introduced by Corey, is the reaction of aldehydes with zinc, CBr_4, and triphenylphosphine, which with thiophene aldehydes yields the 1,1-dibromo-2-(thienyl)ethenes. On treatment with butyllithium or methyllithium at $-78°C$, these dibromo compounds give the lithium salts of thienyl acetylenes in excellent yields.[333,342,487,488,942–946] Excess butyllithium and high concentrations must be avoided, since this leads to polymerization and alkylation of the free α-position of the thiophene ring.[490] The reaction has been carried out on 5-phenyl- and 5-(2-thienyl)-substituted 2-thiophene aldehydes.[945] The method tolerates acetylenic functions very well, as illustrated in the synthesis of **888** from **887**.[944]



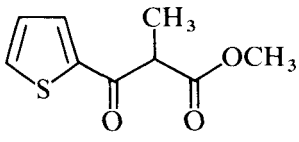
887



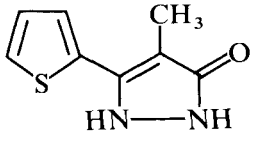
888

After dimerization, acetylenes have also been extensively used for the synthesis of terthienyls. Diaryl ketones, such as 2,2′-dithienyl ketones, have been reacted with hydrazine to form the hydrazone, which was oxidized to the diazo compound. On reaction with dichlorocarbene, the diazo compound yielded 1,1-di-(2-thienyl)-2,2-dichloroethene, which on treatment with methyllithium or sodium in refluxing ether gave 1,2-di-(2-thienyl)acetylene in a 27% yield.[519]

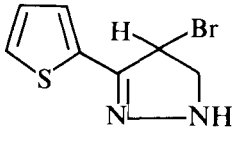
The reaction of **889**, obtained by carbethoxylation of ethyl 2-thienyl ketone, with hydrazine, led to **890**, which was brominated to **891**.



889

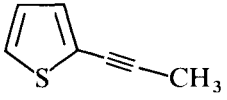


890

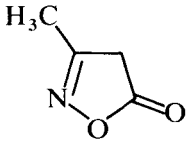


891

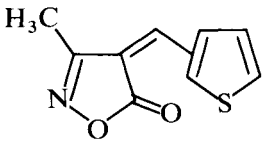
Treatment of **891** with sodium hyroxide and $K_3Fe(CN)_6$ in water gave **892** in a 66% yield. Reaction of 2- and 3-thiophene aldehyde with **893** gave **894**, which on flash photolysis yielded 2- and 3-thienylacetylene.[948]



892

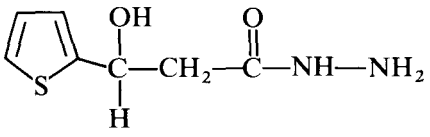


893

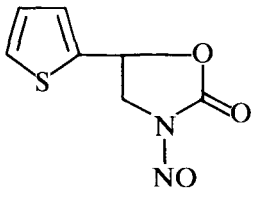


894

Compound **895** was converted to **896**, which on treatment with sodium methoxide in methanol, gave 2-thienylacetylene in a 79% yield.[949]

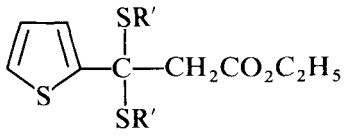


895

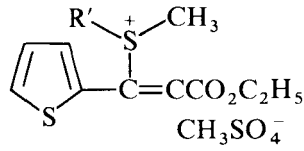


896

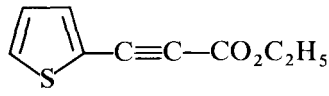
The reaction of **897** with dimethyl sulfate gave **898**, which on treatment with aqueous alkali at 0°C gave **899**.[514]



897



898

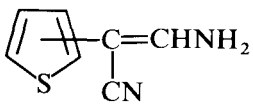


899

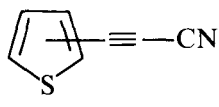
2. From Vinylthiophenes

Addition of bromine to various vinylthiophenes, such as 3-vinylthiophene,[399] 2-propenylthiophene,[385] 3-ethyl-3-(1-thienyl)acrylates,[2,595] and 1,2-diarylethenes, such as 1-phenyl-2-(2-thienyl)ethene and 1,2-di-(2-thienyl)ethene,[311] followed by treatment of the vicinal dibromo derivatives with a strong base, gave thienylacetylene derivatives. The reaction of 2-thienyllithium with 1,1-dichloro-2,2-difluoroethene gave, 1,1-dichloro-2-fluoro-2-(2-thienyl)ethene, which with excess butyllithium gave 2-thienylacetylene.[534] Similarly, 2,5-diethynylthiophene has been prepared.[535]

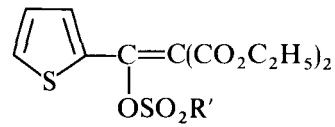
The reaction of **900** with butylnitrite in benzene yielded **901**.[275] 2-Thienylpropiolic acid was obtained in a 51% yield on treatment of **902** with alkali.[598]



900

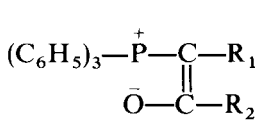


901

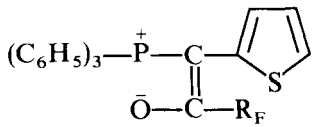


902

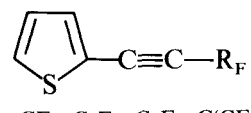
Pyrolysis of **903** is useful method for the synthesis of acetylenes, especially if R_2 is an electron-withdrawing group, such as a perfluorinated alkyl group. Thus, from **904**, **905** was obtained.[950]



903



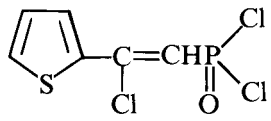
904



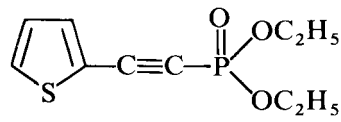
$R_F = CF_3, C_2F_5, C_3F_7, C(CF_2)_3$

905

Reaction of **906** with triethylamine, followed by esterification with ethanol–pyridine, gave **907**.[951]

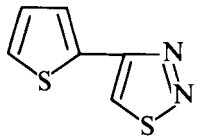


906

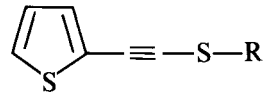


907

The reaction of **908** with a strong base, such as an organolithium compound, sodamide, methylsulfinyl carbanion, or potassium *t*-butoxide, resulted in the cleavage of the thiadiazole ring system with evolution of nitrogen and formation of alkali metal alkynethiolates, which on reaction with alkyl halides or aryl halides, give **909**.[952, 953]



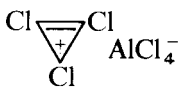
908



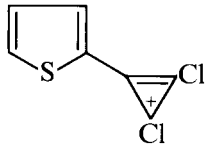
$R = CH_3, C_2H_5, CO_2C_2H_5$

909

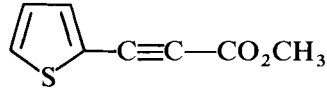
The addition of thiophene to the trichlorocyclopropenium cation **910** led to **911**, which on reaction with methyl alcohol gave **912** in a 95% yield.[954]



910



911



912

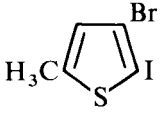
3. From Iodothiophenes and Cuprous Acetylides

Numerous thiophene acetylene derivatives have been prepared from iodothiophenes and copper acetylides, especially in connection with the synthesis of naturally occurring derivatives.[332, 343, 390, 842, 955–965] Generally, the cuprous acetylide was reacted with the iodothiophene in refluxing pyridine for 2–6 h. The cuprous acetylides were prepared by quickly adding a large excess of cuprous chloride or cuprous iodide, freshly dissolved in 12 M aqueous ammonia, to the acetylene in ethanol. All cuprous acetylides are explosive when dry and vary in ease of detonation. In general, the acetylides were freshly prepared or stored under water, and then dried before use. No marked deterioration in yields was observed when slightly damp cuprous acetylides were used.[965]

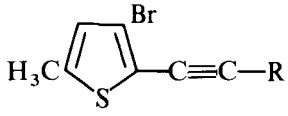
Acetylenic thiophenes have been prepared by a copper- or cobalt-catalyzed coupling of an arylmagnesium iodide and a bromoacetylene, or from an aryl iodide and a magnesium acetylide; the second method gave better results.[966]

4. Palladium-Catalyzed Synthesis from Halothiophenes and Acetylides

During the last few years, there has been a great development in the use of Pd(0)-catalyzed reactions to form carbon–carbon bonds, and this has also been utilized for the preparation of thienylacetylene derivatives. In the coupling, acetylenic zinc derivatives,[329] magnesium derivatives, especially trimethylsilylacetylene magnesium,[967, 968] and tin derivatives[969] have been reacted with bromo- and (preferentially) iodothiophenes. From **913** and the appropriate acetylene zinc derivative, prepared from the lithium acetylide and $ZnCl_2$, **914** was obtained.



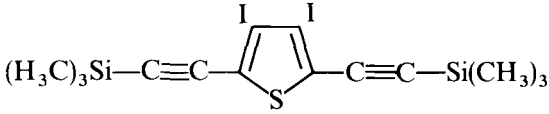
913



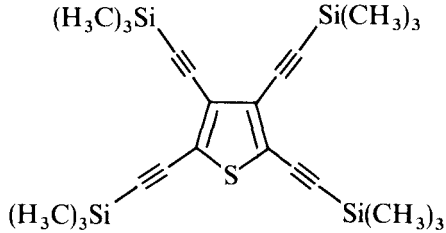
$R = CH_3, C_6H_5, C(CH_3)_3, Si(CH_3)_3$

914

In other modifications of the Pd(0)-catalyzed coupling reaction, the acetylene is reacted with cuprous iodide in benzene under phase-transfer conditions, using benzyl trimethylammonium chloride and sodium hydroxide[333, 342, 944, 965] or isopropylamine and cuprous iodide.[970] Tetraiodothiophene, under the latter conditions, gave with 2 mol of trimethylsilylacetylene, **915** in an 84% yield. The product could be coupled with 2 mol of the same reagent to give **916** in a 45% yield.

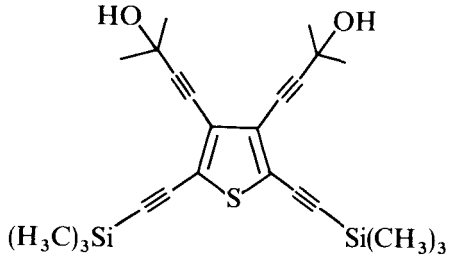


915



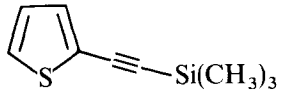
916

With 2-methyl-3-butyn-2-ol, **917** was obtained in an 86% yield. Treatment of **916** and **917** with potassium hydroxide in methanol gave desilylated, very

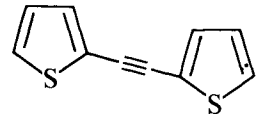


917

explosive acetylenes in high yields.[970] In a third modification of this coupling, acetylenes, in which the acidic hydrogen is silylated, have been used. Thus, 2-iodothiophene was reacted with **918** to give **919** in a 68% yield.[967]



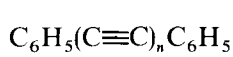
918



919

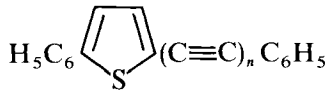
5. Ring-Closure Reactions to Thienylacetylenes

The reaction of triacetylenes with hydrogen sulfide under weakly alkaline conditions yields thienylacetylenes. From **920**, compounds **921** were obtained.[143]



$n = 3, 4$

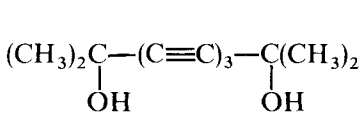
920



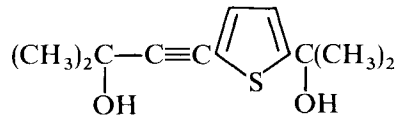
$n = 1, 2$

921

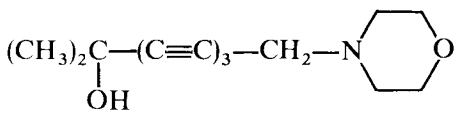
Compound **922** gave **923**, while the unsymmetric **924** is claimed to give only **925**.[971]



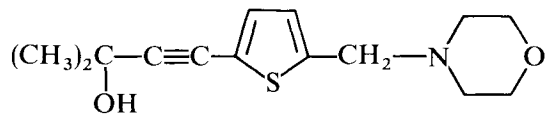
922



923



924



925

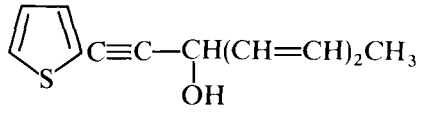
6. Thienylacetylenes from Precursors Containing Triple Bonds

The lithium and magnesium salts of thienylacetylene have been alkylated to give alkyl thienylacetylenes.[940–942] Their reactions with carbon dioxide gave thienylpropiolic acids.[534, 535, 949]

The lithium and magnesium derivatives have also been reacted with various aldehydes to give acetylenic carbinols.[311, 846] Thus the reaction of 2-thienylacetylene magnesium bromide with **926** gave **927**.[846]

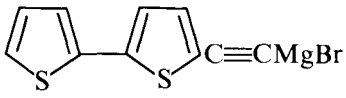
$OHC(CH{\equiv}CH)_2CH_3$

926

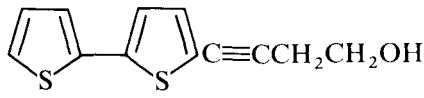


927

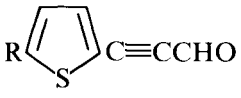
The reaction of **928** with ethylene oxide gave **929**,[611,842] and with *N*,*N*-dimethyl formamide **930** (R = Th) was obtained.[311] Similarly, **930** (R = CH_3) was prepared.[939] These aldehydes were transformed by the Wittig reaction to naturally occurring thiophenes, such as **931**,[939] **932**,[972] and **933**.[612]



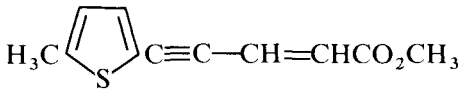
928



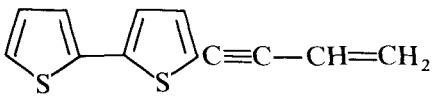
929



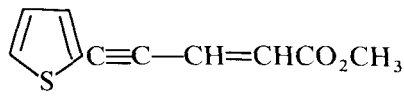
930



931



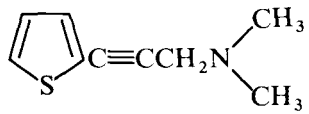
932



933

Sodium acetylides did not react directly with carbon dioxide to give propiolic acids. However, they did react with ethyl chloroformate to give ethyl thienylpropiolates, which were hydrolyzed to the acids with 1.5 N sodium hydroxide at room temperature.[938]

Palladium(0)-catalyzed coupling of 2-thienylacetylene with methyl *trans*-β-iodoacrylate in the presence of cuprous iodide and triethylamine gave the *trans* form of **933**.[977] 2-Ethyl-2,2′-bithienyl was coupled under phase-transfer conditions with vinyl bromide to give **932**.[967] The Mannich reaction of 2-thienylacetylene with parformaldehyde and dimethylamine gave **934** in a 91% yield.[973]



934

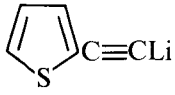
Mercury derivatives have been prepared from thienylacetylenes for characterization, but also for studies of bactericidal and antifungal properties.[961,974,975]

Lithium acetylides have also been reacted with trimethylsilyl chloride to yield the protected derivatives.[534,535] 1-Chloro-2-(2-thienyl)acetylene and 1-iodo-2-(2-thienyl)acetylene were obtained from 2-thienylacetylene and hypochlorite

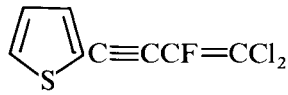
and from 2-thienylacetylene magnesium iodide and iodine, respectively.[976] 1-Bromo-2-(2-thienyl)acetylene was prepared from the acetylene and bromine in 10 M sodium hydroxide.[968]

The trimethylsilyl group of 1-(thienyl)-2-trimethylsilylacetylenes is conveniently removed with 0.1–1 M aqueous potassium hydroxide in methanol.[967,968,970]

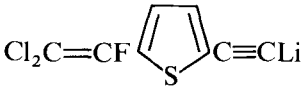
The reaction of **935** with 1,1-dichloro-2,2-difluoroethene gave **936**.[534] Similarly, **937** gave **938**.[535]



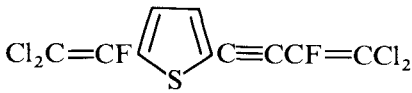
935



936

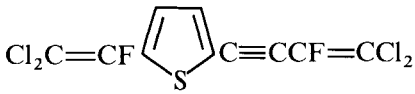


937

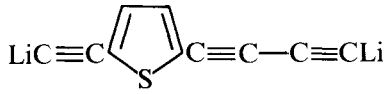


938

Further reactions of **936** with butyllithium gave the salt of the diyne. The reaction can thus be used for the extension of terminal acetylene bonds.[534] Reaction of **939** with excess butyllithium produced **940**, which could be protonated, silylated, and carboxylated.[535]

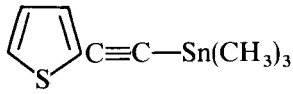


939

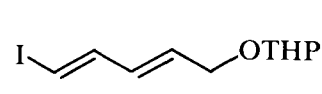


940

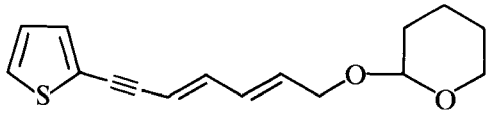
Reaction of 2-thienylacetylene with (dimethylamino)trimethylstannane gave **941**, which on Pd(0)-catalyzed coupling with **942** yielded **943**, which was deprotected to a naturally occurring insecticide.[969]



941

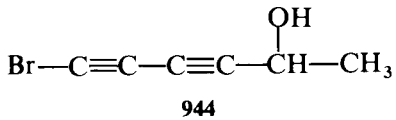


942

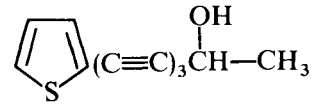


943

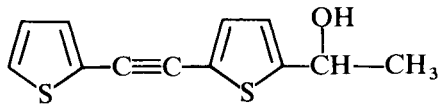
Treatment of 2-thienylacetylene with cuprous chloride hydroxylamine hydrochloride and ethylamine in methanol (Cadot–Chodkiewitz) and **944** gave **945**, which on reaction with hydrogen sulfide was ring-closed to **946**.[311]



944



945

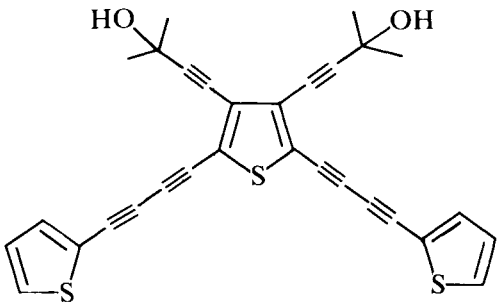


946

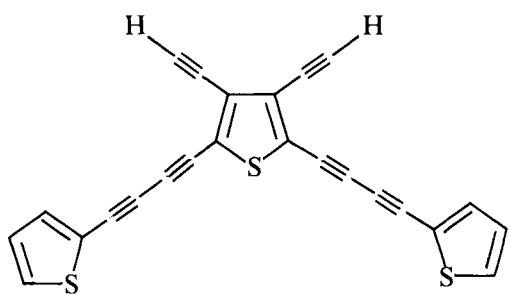
This method was also used in the reaction of 1-bromo-2-(2-thienyl)acetylene with 2-thienylacetylene, 3-thienylacetylene, and 2-ethinyl-2,2′-bithienyl to give 1,4-di(2-thienyl)diacetylene,[968] 1-(2-thienyl)-4-(3-thienyl)-diacetylene,[946] and 1-(2-thienyl)-4-(2,2′-bithienyl-5)-diacetylene.[488]

An often used method for the synthesis of 1,4-di(thienyl)diacetylene is the reaction of thienylacetylenes with potassium ferricyanide[980] or cupric chloride[978] with oxygen in the presence of Cu (Glaser coupling).[487,488,490,535,943,970,978–980,981] Most of the 1,4-di(thienyl)acetylenes were used as intermediates for the preparation of terthiophenes, which were prepared through their reaction with hydrogen sulfide under weakly alkaline conditions.[487,488,490,943,946,968,981]

The Glaser coupling can also be used for unsymmetric coupling, as is shown by the synthesis of **947** from desilylated **917** and 2-thienylacetylene. Reaction of **947** with potassium hydroxide in toluene at 100°C gave **948** in a 62% yield.[970]



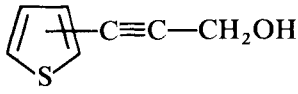
947



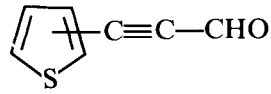
948

The reaction of 2-thienylacetylene with Pd(0), cuprous iodide, triethylamine, and chloroacetone in benzene gives 1,4-di-(2-thienyl)butadiene in an 87% yield.[968] Another procedure for the preparation of 1,4-di(thienyl)diacetylene, using an organoborane-mediated approach, introduced by H. C. Brown, is useful for unsymmetrically substituted diacetylenes. The lithium salts of each acetylenic reagent were introduced successively onto a boron compound to form a complex, which is coupled to the diacetylene by iodine oxidation. This was used for the synthesis of 1-(2-thienyl)-4-(2,2-bithienyl-5)-diacetylene.[488]

Propargylic alcohols, such as **949**, are oxidized with MnO_2 or NiO_2 to **950**.[390,949,960,961,964] Treatment of **950** with 4 M sodium hydroxide leads to decarbonylation, yielding the thienylacetylene.[960,961] Thienylpropiolic acids can be decarboxylated under cupric ion catalysis.[960,961] The tosylate of **949** can be reduced with LiAlH to the methyl derivative.[964] Aldehydes, such as **950**, have been reduced with $LiAlH_4$ or sodium borohydride to **949**.[982]



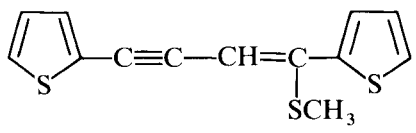
949



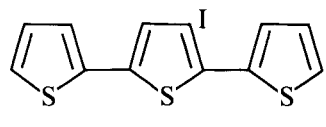
950

VIII. REACTIONS OF THIENYLACETYLENES

A large excess of Lindlar catalyst had to be used for the transformation of thienylacetylene to *cis*-thienylethene derivatives.[343,610–612] Complete hydrogenation of 1,4-di(thienyl)diacetylenes to 1,4-dithienylbutanes over a Pd catalyst has been achieved.[980] With Raney nickel (Ni W-7), complete hydrogenation and desulfurization has been obtained. Thus, from 1,4-di-(5-butyl-2-thienyl)-diacetylene, *n*-eicosane was prepared.[490] The addition of methyl thiolate to 1,4-di-(2-thienyl)diacetylene gave a *cis–trans* mixture (1 : 2) of **951** in a 60% yield, and it was oxidized to the sulfone.[979] Compound **951** was also prepared from **952**, obtained by palladium-catalyzed coupling of 2,3,5-triiodothiophene and 2-thiopheneboronic acid, through halogen–metal exchange with phenyl lithium, which leads to ring opening, followed by reaction with methyl iodide.[587]



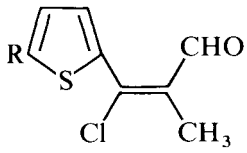
951



952

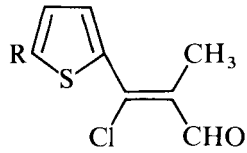
4-Chlorothiophenol and 2,4,5-trichlorothiophenol were reacted with 2-thienylacetylene to give *trans*-1-(4′-chlorophenylthio)-2-(2-thienyl)ethene (80%) via radical addition and *cis*-2-(2-thienyl)-1-(2,4,5-trichlorophenylthio)ethene (50%) via nucleophilic addition. The ethenes were oxidized with 30% hydrogen peroxide to the corresponding sulfones.[984] The triple bond of thienylacetylenes is more prone to undergo addition reactions than is that of the corresponding phenyl analog. Thus, chloromethylation of 2-propylthiophene in hydrochloric acid with aqueous formaldehyde also led to hydration, giving 5-chloromethyl-2-propionylthiophene. Boiling of 2-propynylthiophene with a lead–nitrate solution also gave hydration to 2-propionylthiophene.[385] Attempted Vilsmeyer formylation of 2-propynylthiophene did not lead to formylation of the free

5-position, but instead 38% of **953** (R = H) and 7% of **954** (R = H) were obtained.[965]



R = H, C_6H_5

953

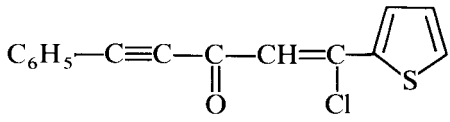


R = H, C_6H_5

954

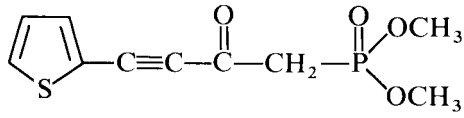
No junipal was obtained as previously claimed in the literature. Similarly, 5-phenyl-2-propynylthiophene gave a mixture of **953** (R = C_6H_5) and **954** (R = C_6H_5) in a total yield of 45% and in a 9 : 1 ratio.[965]

Another example of the high reactivity of the triple bond in thienylacetylene is illustrated in the reaction of 2-thienylpropiolic acid chloride with phenyl(trimethylsilyl)acetylene in the presence of Lewis acids, which gives **955** in a 54% yield, while arylpropiolic acids give the expected unsymmetric 1,4-pentadiyne-3-ones.[954] 1-Alkylthio-2-(thienyl)acetylenes are easily hydrolyzed to thienylacetic acids with dilute sulfuric acid.[952, 953]



955

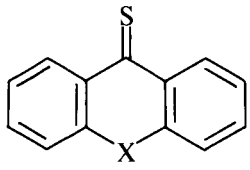
The reaction of ethyl 2-thienylpropiolate with dimethyl lithiomethane phosphonate gives a normal Claisen condensation to yield **956**, which was used in connection with synthesis of prostaglandin analogs.[986]



956

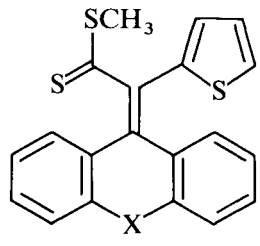
The reaction between h^5-cyclopentadienyldicarbonyl cobalt and phenyl 2-thienylacetylene gave a 78% yield of h^5-cyclopentadienyl, h^4-diphenyldi-2-thienylcyclobutadiene)cobalt. The structure was proven by X-ray crystallography.[987]

The photochemical reaction of **957** with 1-methylthio-2-(2-thienyl) acetylene gave mainly **958** and small amounts of **959** and **960** (X = S).[988] Phenyl-2-thienylacetylene, which, in contrast to other diarylacetylenes, did not react detectably with naphthalene on irradiation, formed no tetracyclic adduct with 1-methoxynaphthalene, but gave a compound that had structure **961** in



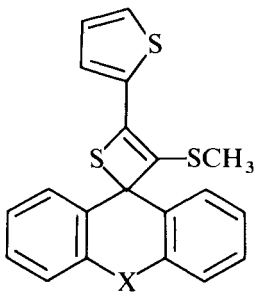
X = O, S

957



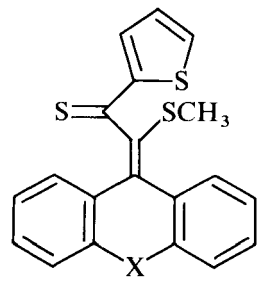
X = O, S

958



X = O, S

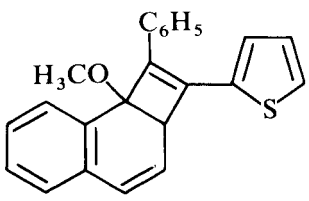
959



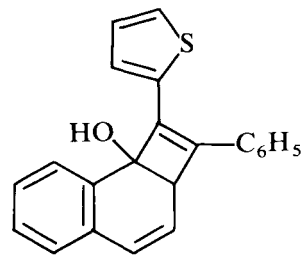
X = O, S

960

only a 0.6% yield, which on chromatography on silicic acid was demethylated, giving **962**.[989] 1,4-Di-(2-thienyl)diacetylene is cleaved by OsO–HIO to give 2-thienylpropargyl aldehyde.[612]



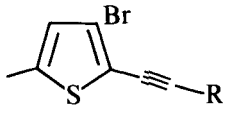
961



962

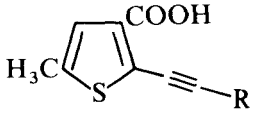
As mentioned before, electrophilic aromatic substitution on the thiophene ring of thienylacetylenes has not been very successful. However, functionalization can be achieved through metalation of the 5-position with butyllithium, followed by reaction with electrophiles, as in the synthesis of junipal by metalation of 2-propynylthiophene, followed by reaction with *N*,*N*-dimethylformamide,[941,990] or in the synthesis of 1-methylthio-2-(5-hydroxymethyl-2-thienyl)acetylene by metalation of 1-methylthio-2-(2-thienyl)acetylene, followed by reaction with formaldehyde.[952]

Halogen–metal exchange of **963** at 0°C, followed by reaction with carbon dioxide, was used in the synthesis of **964**. Halogen–metal exchange at room temperature gave ring opening to thiovinylacetylenes, which were trapped with methyl iodide, to give **965**.[329] The rate constants for base-catalyzed hydrogen exchange have been measured for **966** in sodium methoxide methanol.[991]

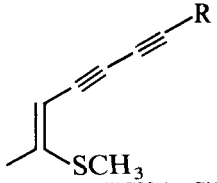


R = CH_3, C_6H_5

963

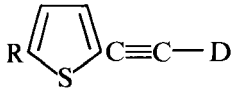


964



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

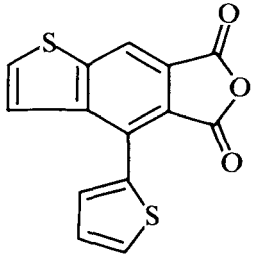
965



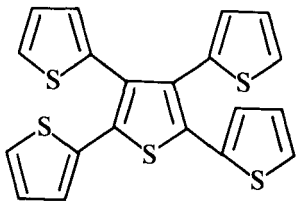
R = H, Br

966

Competitive metalation of equimolar amounts of 2-thienyl-acetylene and phenylacetylene with insufficient amounts of *n*-butyllithium showed that the ratio of lithium 2-thienylacetylide to lithium phenylacetylide was 2.4 : 1, indicating that 2-thienylacetylene is more acidic than phenylacetylene.[976] Second-order rate constants k for reactions of thiolates with 1-halogeno-2-(2-thienyl)acetylenes were measured in methanol–water, and the mechanism was discussed.[976] The general reaction of arylpropiolic acids with *N*,*N*-dicyclohexylcarbodiimide has been applied to 2-thienylpropiolic acid and gave **967** in a 91% yield. The mechanism was discussed.[992] The reaction of di-(2-thienyl)acetylene with sulfur in benzene at 205–215°C in an autoclave gave a 57% yield of **968**.



967



968

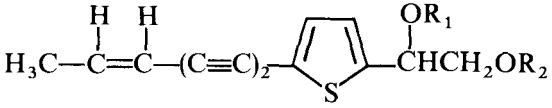
IX. PHYSICAL PROPERTIES OF THIENYLACETYLENES

Physical properties are discussed in Part 4, Chapter I of this series. Infrared absorption spectra have been reported,[994] as well as polarographic studies of the mercury derivative of 2-thienylacetylene.[995]

X. NATURALLY OCCURRING THIENYLACETYLENES

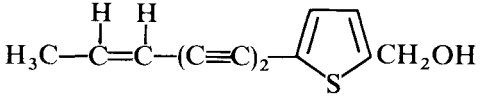
Naturally occurring thienylacetylene derivatives are discussed in Part 1, Chapter III of this series. Only references treating this subject are included here.[612, 841, 843, 845, 849–852, 996–1011]

During recent years, there has been very little activity in this field. A short paper described the isolation of four compounds, **969** and **970**, from *Leuzea carthamoides*.[1012]



$R_1 = R_2 = Ac$
$R_1 = H, \quad R_2 = Ac$
$R_1 = R_2 = H$

969



970

The role of oxygen in photosensitation by polyacetylenes from species of the plant family Asteraceae has been studied.[1013]

XI. TABLES OF COMPOUNDS

The tables give various types of vinylthiophenes and thienylacetylenes characterized by the different substituents on the double and triple bonds. The compounds are given with increasing CH numbers. We have tried to include all compounds that have been described in the literature after 1952. However, it is clear 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.

Abbreviations Used in the Tables

Certain frequently recurring ring systems or other groups have been abbreviated in the tables in the following way:

anthr	anthracenyl
cyclop	cyclopentyl
Fe	ferrocenyl
Fu	furyl
imid	imidazolyl
imi	dihydroimidazolyl
mal	maleic acid
male	maleate
napht	naphthyl
oxaz	oxazolyl
py	pyrrolyl
pyr	pyridinyl
pyrim	pyrimidyl
pyrimi	tetrahydropyrimidyl
quin	quinolyl
Se	selenienyl
tart	tartaric acid
Th	thienyl
thiad	thiadiazolyl
thiaz	dihydrothiazinyl
thiazo	thiazolidine
triaz	1,3,5-triazinyl

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.

Vinylthiophenes

a	from thiophene aldehydes and aryl acetonitriles
b	from thienyllithium derivatives and fluoroethenes
c	from thenalmalonic acids through decarboxylation
d	through Claisen condensation
e	through esterification of 3-(thienyl)acrylic acids
f	through Perkin-type condensation
g	through mixed aldol condensation

h	through hydrolysis of esters
i	through Doebner reactions
j	through Reformatsky reactions
k	from thenylphosphonium derivatives or phosphonates and aldehydes
l	from arylphosphonium derivatives or phosphonates and thiophene aldehydes
m	from thienylmetal derivatives and ketones followed by dehydration
n	from thiophenecarbonyl derivatives and metalorganic reagents or hydride
o	through various methods
p	from acidic methylthiophenes and aldehydes
q	from acidic methyl derivatives and thiophene aldehydes
r	through Pd-catalyzed coupling reactions
s	from vinylthiophenes by modification of substituents through Claisen–Schmidt condensation
u	from cyanothiophenes and thiophenecarbonyl derivatives and malonitrile and related compounds
v	from thiophene aldehydes and esters
w	from thenyl cyanides and aldehydes
x	from thiopheneacetic acids and aldehydes
y	through Stobbe condensation
ö	from thiophene aldehydes or ketones and cyclic active methylene derivatives

Thienylacetylenes

z	from halothiophenes and copper acetylides
ab	from Grignard reagents and bromoacetylenes
ac	through modification of thienylacetylenes
ad	from vinylthiophenes
ae	from acetylthiophenes
af	through ring opening of thienylthiadiazoles
ag	from phosphonium derivatives
ah	through oxidative coupling reactions of thienylacetylenes

TABLES

Table 1 Vinylthiophenes
Table 2 1-(Thienyl)-1-alkyl- or arylethenes
Table 3 *E*-1,2-Di(thienyl)ethenes
Table 4 *Z*-1-(Thienyl)-2-arylethenes
Table 5 *E*-1-(Thienyl)-2-arylethenes

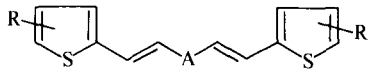
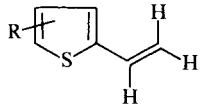
Table 6 *E*-1-(Thienyl)-2-hetarylethenes
Table 7 1-(Thienyl)-2-alkylethenes
Table 8 1-(Thienyl)-1,2-dialkyl- or arylethenes
Table 9 1-(Thienyl)-2,2-dialkyl- or arylethenes
Table 10 1-(Thienyl)-1,2,2-trialkyl- or arylethenes
Table 11 *β*-(Nitrovinyl)thiophenes from nitroalkanes and aldehydes
Table 12 1-(Thienyl)ethenes containing at least one group that is not alkyl or aryl
Table 13 3-(Thienyl)acryl aldehydes and alkylketones
Table 14 3-(Thienyl)acryl aryl ketones
Table 15 3-(Thienyl)acryl heterocyclic ketones excluding thiophene ketones
Table 16 3-(Thienyl)acryl thienyl ketones
Table 17 1-(Thienyl)-1-cyano-2,3-dialkyl or aryl ethenes
Table 18 3-(Thienyl)-2-arylacrylonitriles
Table 19 3-(Thienyl)-2-heterocyclic acrylonitriles
Table 20 3-(Thienyl)acrylonitriles
Table 21 2-(Thienyl)acrylic acids
Table 22 3-(Thienyl)acrylic acids
Table 23 Esters of 3-(thienyl)acrylic acids
Table 24 3-Substituted-3-(thienyl)acrylic acids and esters
Table 25 2-Alkyl- and 2-aryl-substituted 3-(thienyl)acrylic acids and esters
Table 26 Various 2-substituted 3-(thienyl)acrylic acids and esters
Table 27 2-Acyl- and 2-cyanoacrylic acids and esters
Table 28 2,3-Disubstituted 3-(thienyl)acrylic acids and esters
Table 29 Syntheses of thenalmalonic acid and esters through Knoevenagel condensations
Table 30 Thenalrhodanines from thiophene aldehydes and cyclic active methylene derivatives
Table 31 Thenal azlactones from thiophene aldehydes and cyclic active methylene derivatives
Table 32 2-(Thenal)succinic anhydrides from Stobbe condensations
Table 33 Symmetric 2,5-divinylthiophenes
Table 34 1-(Thienyl)1,3-butadienes
Table 35 1-(2-Thienyl)polyenes
Table 36 Compounds of type 

Table 37 Thienylacetylenes
Table 38 2,5-Thienyl Diacetylenes
Table 39 1,4-Di(thienyl)diacetylenes

TABLE 1. Vinylthiophenes



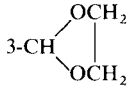
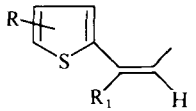
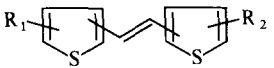
CH	Th Group	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mm Hg)	Ref.
C_6H_3	3,4,5-tri-Cl-2-Th	m	70	83–84/1	381
C_6H_4	2,5-di-Cl-3-Th	m	64	55–56/1	381
C_6H_5	5-Br-2-Th	m	34, 35	64–65/5, 85, 87/16	381, 479
	5-Cl-2-Th	m	72, 47	56–57/7, 73–78/20	381, 479
C_6H_6	2-Th	m	80, 49	64–65/49, 65–67/50	377, 983
	2-Th	m	50–55	65–67/50	479, 482
	2-Th	l	40	60–41	369
	2-Th	r	66		542
	2-Th	o		65.5–66.5/48	478
	3-Th	m	54	55–59/20	380
	3-Th	m	55–60	46–48/15	398–400
	3-Th	o	35		569
C_7H_8	5-CH_3-2-Th	m	64	30–36/2–3	383
	3-CH_3-2-Th	n		71–72/10	384
	4-CH_3-2-Th	o		67–70/10	564
C_8H_{10}	4,5-di-CH_3-2-Th	o		68–70/8	564
C_9H_{10}		l	77	135–137/2	334
C_9H_{12}	4-C_2H_5-5-CH_3-2-Th	o	31		569
$C_{10}H_7$	5-(5-Br-2-Th)-2-Th	l	80		333

TABLE 2. 1-(Thienyl)-1-alkyl- or Arylethenes



CH	Th Group	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_7H_5	3,4,5-tri-Cl-2-Th	CH_3	m	63	93–94/2	381
C_7H_6	2,5-di-Cl-3-Th	CH_3	m	83	77–78/1	381
C_7H_7	5-Br-2-Th	CH_3	m	53	84–85/3	381
	3-Br-2-Th	CH_3	m	75	96–98/16	280
	5-Cl-2-Th	CH_3	m	84	78–79/10	381
C_7H_8	2-Th	CH_3	n	45	68/18	439
	2-Th	CH_3	m	59, 24	66–67/20, 60/15	381, 401
	3-Th	CH_3	o			571
C_8H_8	3-CHO-2-Th	CH_3	m	66	125–128/1	334
C_8H_{10}	5-CH_3-2-Th	CH_3	n	42		440
	4-CH_3-3-Th	CH_3	o	70		571
C_9H_{12}	4-C_2H_5-3-Th	CH_3	o	23		571
$C_{10}H_{16}$	2-Th	$-CH_2Si(CH_3)_3$	r	66		541
$C_{10}H_{16}$	2-Th	$CH_2Si(CH_3)_3$	r	78		541
$C_{12}H_{10}$	2-Th	C_6H_5	n		106/2	438
$C_{13}H_9$	2-Th	3-F_3C-C_6H_4	n		90–105/0.1–0.2	438
$C_{13}H_{10}$	3-CHO-2-Th	C_6H_5	m	72	167–170/1	334
$C_{13}H_{12}$	4-C_6H_5-3-Th	CH_3	o	100		571
	2-Th	3-CH_3-C_6H_4	n		102–105/0.04	438
	2-Th	4-CH_3-C_6H_4	n		85–86/0.035	438
$C_{16}H_{12}$	2-Th	1-napht	n		142–145/0.025	438

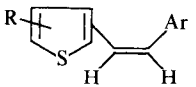
TABLE 3. *E*-1,2-Di(thienyl)ethenes



CH	Th Group	Th′ Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{10}H_5$	2,5-di-Cl-3-Th	4-Br-3-Th	k		94	313
$C_{10}H_6$	4-Br-3-Th	2-Cl-3-Th	k		121	313
	5-Cl-2-Br-3-Th	2-Th	k	68	58–61	314
	5-Cl-2-Br-3-Th	3-Th	k	80	73–78	316
	5-Br-2-Th	5-Cl-2-Th	k	29	104–105	301
	4-Br-3-Th	4-I-3-Th	k		127–128	295
	5-Br-2-Th	5-O_2N-2-Th	k	59	177–178	301
	3-Br-2-Th	3-Br-2-Th	k		154	313
	2-Br-3-Th	4-Br-3-Th	k		139–140	295
	2-Br-3-Th	3-Br-2-Th	k		148–149	295
	2-Br-3-Th	2-Br-3-Th	k		149–150	295
	4-Br-3-Th	4-Br-3-Th	k		126	295
	3-Br-2-Th	4-Br-3-Th	k		139–140	295
	3-I-2-Th	3-I-2-Th	k		178.5–180	295
	3-I-2-Th	4-I-3-Th	k		163–164	295
	2,4-di-NO_2-2-Th	2-Th	p	70	235–237	276
	2,4-di-NO_2-2-Th	3-Th	p	48.5	204–205	276
$C_{10}H_7$	2-Th	4-Br-3-Th	k	96	52–53	312
	3-Th	3-Br-2-Th	k		41	317
	3-Th	4-Br-3-Th	k	94	62	312
	2-Br-3-Th	3-Th	k		62	313
	3-Br-2-Th	2-Th	k		53	313
	2-Th	3-I-2-Th	k		65	317
	3-Th	3-I-2-Th	k		60	317

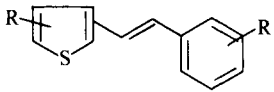
	5-O_2N-2-Th	2-Th	s	59	102–103	864
	3-O_2N-2-Th	2-Th	p	43	68.1–68.8	1014
	2-O_2N-3-Th	2-Th	p	60	101–103	1014
	3-N_3-2-Th	2-Th	s	50	65	317
	2-Th	3-N_3-2-Th	k	52	65	317
	3-N_3-2-Th	3-Th	s	50	74	317
	3-Th	3-N_3-2-Th	k	45	74	317
	2-Th	4-N_3-3-Th	k	55	58	317
	4-N_3-3-Th	2-Th	s	45	58	317
	3-Th	4-N_3-3-Th	k	50	77	317
	4-N_3-3-Th	3-Th	s	50	77	317
$C_{10}H_8$	2-Th	2-Th	k		133–135	282
	2-Th	2-Th	o	71	133	491
	2-Th	2-Th	r	30	133–134	540
	2-Th	2-Th	k	68, 97	133–134	319, 283
	2-Th	3-Th	k	40	137–137.5	319
	3-Th	3-Th	k	40	166.5–167	319
$C_{11}H_7$	5-Br-2-Th	5-CHO-2-Th	k	35	129–131	301
$C_{11}H_8$	5-Cl-2-Br-3-Th	4-CH_3-2-Th	k	64	45–47	314
	5-Cl-2-Br-3-Th	5-CH_3-2-Th	k	72	65–66	314
$C_{11}H_9$	5-Br-2-Th	5-CH_3O-2-Th	k	73	77–78.5	301
	5-Br-2-Th	5-CH_3-2-Th	k	44	114–115	301
	5-CH_3-2-Th	5-O_2N-2-Th	k	20	133–134	301
$C_{11}H_{10}$	2-Th	3-CH_3-2-Th	k	40	60–60.5	319
	2-Th	4-CH_3-2-Th	k	41	101–105.5	319
	2-Th	5-CH_3-2-Th	k	60	61.5–62.5	319
$C_{12}H_8$	5-CH_3OOC-3-O_2N-2-Th	5-Cl-2-Th	p	91	177–178	276
$C_{12}H_9$	5-CH_3OOC-3-O_2N-2-Th	3-Th	p	74	139–140	276
	5-CH_3OOC-3-O_2N-2-Th	2-Th	p	59	139–140	276
$C_{12}H_{12}$	5-CH_3-2-Th	5-CH_3O-2-Th	k	67	69–70.5	301
	5-CH_3-2-Th	5-CH_3-2-Th	k	62	123–124	301

TABLE 4. *Z*-l-(Thienyl)-2-arylethenes



CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{10}H_6$	3-Br-2-Th	3-Br-2-Th	k		60–61	286
	2-Br-3-Th	2-Br-3-Th	k		55–56	286
	4-Br-3-Th	3-Br-2-Th	k		62–63	295
	4-Br-3-Th	2-Br-3-Th	k		41–42	295
	4-Br-3-Th	4-Br-3-Th	k		35–37	295
	3-Br-2-Th	2-Br-3-Th	k		(85% pure)	295
	4-Br-3-Th	2-Cl-3-Th	k		130–133/0.005	286
	3-I-2-Th	4-I-3-Th	k		60–61	295
$C_{10}H_9$	2-Th	2-py	k		57–60	291
$C_{11}H_7$	4-HOOC-3-Th	2-Cl-3-Th	s	95	152	286
$C_{11}H_8$	2-HOOC-3-Th	3-Th	s	64	149–150	286
	3-HOOC-2-Th	2-Th	s	63	108–109	286
$C_{14}H_{12}$	3-Th	2-$CH_3OOCC_6H_4$	s	58	156–158/0.3	331
$C_{15}H_{20}$	2-Th	1-H_3C-2-pyrim tart	q		160–161	135
$C_{16}H_{22}$	3-H_3C-2-Th	1-H_3C-2-pyrim tart	q		141–143	135
$C_{16}H_{14}$	2-Th	Fc	k		68–70	299
	2-Th	Fc	l		68–70	299

TABLE 5. *E*-1-(Thienyl)-2-arylethenes



CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{12}H_6$	5-Cl-2-Th	2,4,6-tri-O_2N-C_6H_2	q		150	118
$C_{12}H_7$	2-Th	2,4,6-tri-O_2N-C_6H_2	q	68	140	49, 118
$C_{12}H_8$	2-O_2N-3-Th	4-Cl-C_6H_4	p	35	103–104	279
	2-O_2N-3-Th	4-Cl-C_6H_4	k	70	105–106	289
	3-O_2N-2-Th	4-Cl-C_6H_4	p	51	111–112	279
	5-O_2N-2-Th	4-Cl-3-HO-C_6H_3	s	50	221–222	864
	5-O_2N-2-Th	3-Cl-2-HO-C_6H_3	s	3.6	126–130	864
	5-O_2N-2-Th	2-Cl-4-HO-C_6H_3	s	43	208–210	864
	5-O_2N-2-Th	3-Cl-6-HO-C_6H_3	s	12	185–187	864
	2-Th	3,4-di-Cl-C_6H_3	l	45	96–97	357
	2-Th	2,4-di-Cl-C_6H_3	l	45	61–62.5	357
	5-O_2N-2-Th	4-O_2N-C_6H_4	l		238	327
	5-O_2N-2-Th	3-O_2N-C_6H_4	l		211	327
	5-O_2N-2-Th	2-O_2N-C_6H_4	l		188–189	327
	4-O_2N-2-Th	4-O_2N-C_6H_4	l		199	327
	4-O_2N-2-Th	3-O_2N-C_6H_4	l		196–197	327
	4-O_2N-2-Th	2-O_2N-C_6H_4	l		182	327
$C_{12}H_9$	4-Br-3-Th	C_6H_5	l	67	52–53	292
	2-Br-3-Th	C_6H_5	l	58	78–80	292
	5-O_2N-2-Th	C_6H_5	l	50	137–138, 138	327, 95
	3-O_2N-2-Th	C_6H_5	l	25	88	327, 95
	4-O_2N-2-Th	C_6H_5	l		90	327
	2-O_2N-3-Th	C_6H_5	k	75	110–111	289

TABLE 5. (*Continued*)

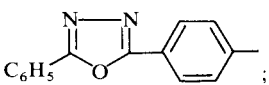
CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{12}H_9$	2-O_2N-3-Th	C_6H_5	p	32	108–109	279
	3-O_2N-2-Th	C_6H_5	p	50	86–87	279
	2-Th	2-O_2N-C_6H_4	l		76	327
	2-Th	3-O_2N-C_6H_4	l		122–123	327
	2-Th	4-O_2N-C_6H_4	l		174	327, 328
	5-O_2N-2-Th	4-HO-C_6H_4	s	40	240–243	864
	5-O_2N-2-Th	2-HO-C_6H_4	s	4	143–145	864
$C_{12}H_{10}$	2-Th	C_6H_5	k	78	110–111	323
	2-Th	C_6H_5	l	77	112–113	354, 355
	2-Th	C_6H_5	l	75	112	95
	2-Th	C_6H_5	l		112	327
	2-Th	C_6H_5	n		111	118
	2-Th	C_6H_5	m		109–110	402
	2-Th	C_6H_5	o		109–110	402
	2-Th	C_6H_5	r	13	144–145?	549
	3-Th	C_6H_5	l	73	123–124	320
	3-Th	C_6H_5	k	78	123–124	320
$C_{12}H_{11}$	2-O_2N-3-Th	4-$CH_3OC_6H_4$	k	70	128–129	289
$C_{13}H_8$	2,5-di-Cl-3-Th	2-HOOC-C_6H_4	k	71	203–204	290
$C_{13}H_9$	2-Th	4-Br-2-HOOC-C_6H_3	k	72	174–175	264
	2-Th	4-Cl-2-HOOC-C_6H_3	k	88	152–153	264
	2-Th	5-Cl-2-HOOC-C_6H_3	k	85	198–200	264
	2-O_2N-3-Th	3,4-OCH_2O-C_6H_3	k	80	130–132	289
	5-H_3C-2-Th	2,4,6-tri-O_2N-C_6H_2	q		164–165	118

$C_{12}H_{10}$	5-OHC-2-Th	C_6H_5	s	87	83–85	355
	2-Th	2-HOOC-C_6H_4	k	85	136–137	264
	5-O_2N-2-Th	3-Cl-4-H_3C-6-HO-C_6H_2	k	14	192–193	864
$C_{13}H_{11}$	5-O_2N-2-Th	4-CH_3O-C_6H_4	s	52	174–175	864
	2-O_2N-3-Th	4-CH_3O-C_6H_4	p	34	128–129	279
	3-O_2N-2-Th	4-CH_3O-C_6H_4	p	50	105–106	279
$C_{13}H_{12}$	5-H_3C-2-Th	C_6H_5	l	15	85	322
	5-H_3C-2-Th	C_6H_5	n		85	118
	4-H_3C-2-Th	C_6H_5	l	87	67	356
	3-H_3C-2-Th	C_6H_5	l	43	52–53	292
	2-Th	2-H_3C-C_6H_4	n		120/0.5	441
	2-Th	2-H_3C-C_6H_4	k	75	120/0.5	322
	2-Th	3-H_3C-C_6H_4	n		80	441
	2-Th	3-H_3C-C_6H_4	l	83	80	322
	2-Th	3-H_3C-C_6H_4	k	83	80	322
	2-Th	4-H_3C-C_6H_4	n		110	441
	2-Th	4-H_3C-C_6H_4	l	78	116	322
	2-Th	4-H_3C-C_6H_4	k	58	115–116	322
	3-Th	2-H_3C-C_6H_4	k	73	96–97	320
	3-Th	2-H_3C-C_6H_4	k	80	96–97	320
	3-Th	3-H_3C-C_6H_4	k	70	75–76	320
	3-Th	4-H_3C-C_6H_4	k	78	123–124	320
	3-Th	4-H_3C-C_6H_4	k	85	123–124	320
$C_{14}H_{10}$	5-$NCCH_2$-2-Th	4-Br-C_6H_4	n	68	143	152
	5-$NCCH_2$-2-Th	4-Cl-C_6H_4	n	66	123	152
	5-$NCCH_2$-2-Th	3-Cl-C_6H_4	n	68	83	152
	5-H_3COOC-3-O_2N-2-Th	4-Cl-C_6H_4	p	89	147–148	279
	5-$NCCH_2$-2-Th	4-F-C_6H_4	n	66	101	152
	5-$NCCH_2$-2-Th	4-O_2N-C_6H_4	n	53	123	152

TABLE 5. *(Continued)*

CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{14}H_{11}$	5-$HOOCCH_2$-2-Th	4-Br-C_6H_4	n	41	184	152
	5-$HOOCCH_2$-2-Th	4-Cl-C_6H_4	n	49	181–183	152
	5-$HOOCCH_2$-2-Th	3-Cl-C_6H_4	n	51	164	152
	5-$HOOCCH_2$-2-Th	4-F-C_6H_4	n	40	173–175	152
	5-H_3COOC-3-O_2N-2-Th	C_6H_5	p	86	106–107	279
	2,5-di-H_3C-2-Th	2,4,6-tri-O_2N-C_6H_2	q		175	118
	5-$NCCH_2$-2-Th	C_6H_5	n	51	110–111	152
$C_{14}H_{12}$	5-$HOOCCH_2$-2-Th	C_6H_5	n	31	144–145	152
	2-Th	4-H_3CO-2-$HOOC$-C_6H_3	k	82	170–171	264
$C_{14}H_{13}$	2-O_2N-3-Th	3,4-di-H_3CO-C_6H_3	k	75	172–173	289
$C_{14}H_{14}$	2,5-di-H_3C-3-Th	C_6H_5	n		195–205/13	118
	5-H_5C_2-2-Th	C_6H_5	n		190–195/13	118
	5-H_3C-2-Th	4-H_3C-C_6H_4	n		94	118
$C_{15}H_{13}$	$NCCH_2$-2-Th	4-H_3CO-C_6H_4	n	67	145	152
	5-H_3COOC-3-O_2N-2-Th	4-H_3CO-C_6H_4	p	88	139–140	279
$C_{15}H_{14}$	5-$HOOCCH_2$-2-Th	4-H_3CO-C_6H_4	n	48	178	152
$C_{15}H_{16}$	2,5-di-H_3C-3-Th	4-H_3CO-C_6H_4	n		101	118
$C_{16}H_{12}$	2-Th	1-napht	k	85	100.5–101	324
	3-Th	1-napht	k	76	98.5–99	324
$C_{16}H_{14}$	2-Th	Fc	l	41	151–152	299
	2-Th	Fc	k		151–152	299
$C_{17}H_{14}$	4-H_3C-2-Th	1-napht	l	68	74–75	359
$C_{18}H_{19}$	$NCCH_2$-2-Th	4-$H_3CCH(CH_3)$-CH_2-C_6H_4	n	71	95	152

$C_{18}H_{20}$	HOOCCH$_2$-2-Th	4-H$_3$CCH(CH$_3$)-CH$_2$-C$_6$H$_4$	n	47	163	152
$C_{20}H_{14}$	2-Th	2-anthr	q	70	280–281	120
$C_{20}H_{16}$	2-Th	4-C$_6$H$_5$CH=CH-C$_6$H$_4$	q	20	258–259	120
$C_{21}H_{16}$	2-Th	4-(4-H$_3$COC$_6$H$_4$)-CH=CH-C$_6$H$_4$	q	35	211–212	120
$C_{26}H_{17}$	5-(4-Br-C$_6$H$_4$)-2-Th	A	l	64	250–251	345
	5-(4-Cl-C$_6$H$_4$)-2-Th	A	l	62	229–230	345
	5-(4-O$_2$N-C$_6$H$_4$)-2-Th	A	l	58	266–267	345
$C_{26}H_{18}$	5-C$_6$H$_5$-2-Th	A	l	51	233–234	345
$C_{27}H_{18}$	5-(4-Br-C$_6$H$_4$)-2-Th	B	l	37.5	213–214	345
	5-(4-Cl-C$_6$H$_4$)-2-Th	B	l	73	217–218	345
	5-(4-O$_2$N-C$_6$H$_4$)-2-Th	B	l	62	234–235	345
$C_{27}H_{19}$	5-C$_6$H$_5$-2-Th	B	l	45	214–215	345
$C_{27}H_{20}$	5-(4-H$_3$CO-C$_6$H$_4$)-2-Th	A	l	48	199–201	345
$C_{28}H_{21}$	5-(4-H$_3$C-C$_6$H$_4$)-2-Th	B	l	52	198–199	345
	5-(4-H$_3$CO-C$_6$H$_5$)-2-Th	B	l	55	211–212	345
$C_{30}H_{20}$	5-(5-C$_6$H$_5$-2-oxaz)-2-Th	B	l	46	202–203	345

A =  ;

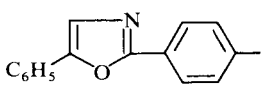
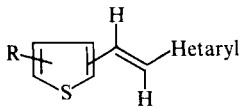
B = 

TABLE 6. *E*-1-(Thienyl)-2-hetarylethenes



CH	Th Group	Hetaryl Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
C_9H_6	5-O_2N-2-Th	4,6-di-HO-triaz	q	56	255–260	128
C_9H_8	5-O_2N-2-Th	4,6-di-H_2N-tiaz	q	82	250	128
C_9H_9	2-Th	2-thiazo	q		119–120	141
$C_{10}H_6$	3-Br-2-Th	3-Br-2-fur	k		104	287
	2-Br-3-Th	3-Br-2-fur	k	99	103–104	287
	2,4-di-O_2N-2-Th	2-fur	p	43.5	186–187	276
$C_{10}H_7$	2-Br-3-Th	2-fur	k		43–44	287
	2-Th	3-Br-2-fur	k	84	63–64	287
$C_{10}H_8$	2-Th	2-fur	k	65	78–79	319
	5-O_2N-2-Th	5-H_3CCONH-2-thiad	q		328–330	127
$C_{10}H_9$	2-Th	2-py	k	50	141–144	291
$C_{10}H_{11}$	2-Th	Thiazi	q		61–62	141
$C_{10}H_{12}$	3-H_3C-2-Th	2-thiazo HCl	q		224–225	141
	3-Th	Thiazi HPF_6	q		149–150	141
$C_{11}H_8$	5-O_2N-2-Th	2-pyr	q	40	183–185	126
$C_{11}H_9$	5-O_2N-2-Th	2-(1-CH_3CO)-imid	q	21	185–191	126
	2-Th	4-pyr	r	57		552
$C_{11}H_{11}$	2-Th	1-CH_3-2-py	k	75	65–66	291, 326

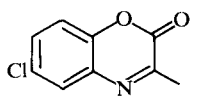
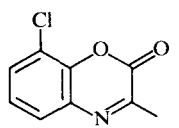
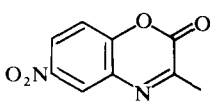
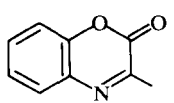
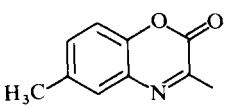
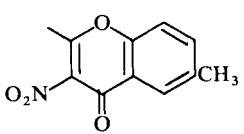
$C_{11}H_{14}$	5-H_3C-2-Th	Thiazi HPF_6	q		144–146	141
	4-H_3C-2-Th	Thiazi HCl	q		197–198	141
	3-H_3C-2-Th	Thiazi HCl	q		252–254	141
$C_{11}H_{15}$	3-H_3C-2-Th	1-CH_3-2-imid HCl	q		243–244	135
	3-H_3C-2-Th	pyrim HCl	q		236–237	135
$C_{12}H_{10}$	3-Th	3-NH_2CO-4-pyr	q	62	207–209	122
	2-Th	3-NH_2CO-4-pyr	q	86	201–202	122
$C_{12}H_{17}$	5-H_3C-2-Th	1-H_3C-2-pyrim HPF_6	q		151–152	135
	4-H_3C-2-Th	1-H_3C-2-pyrim HCl	q		225–226	135
$C_{13}H_{10}$	2-Th	2-benzimidazolyl	l	44	242–243	351
$C_{13}H_{12}$	3-Th	2-H_5C_2OOC-3-Fu	l	78	78–79	287
$C_{13}H_{14}$	2-Th	2-imid mal	q		162–163	135
$C_{14}H_7$	5-O_2N-2-Th		q	25	230	65
	5-O_2N-2-Th		q	75	205	65
	5-O_2N-2-Th		q	55	245	65
$C_{14}H_8$	2-Th		q	80	250	65

TABLE 6. (*Continued*)

CH	Th Group	Hetaryl Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{14}H_9$	5-O_2N-2-Th	2-quinazolyl	q	41	212–213	126
$C_{14}H_{10}$	2-Th	3-benzo-Th	k	84	89–90	325
	2-Th	3-benzo-Th	l	80	89–90	325
	2-Th	2-benzo-Th	k	86	176–177	325
	2-Th	2-benzo-Th	l	83	176–177	325
	3-Th	3-benzo-Th	k	81	85–86	325
	3-Th	3-benzo-Th	l	81	85–86	325
	3-Th	2-benzo-Th	k	83	208	325
	3-Th	3-benzo-Th	l	81	208	325
$C_{14}H_{15}$	2-Th	2-thiaz mal	q		169–171	141
$C_{14}H_{16}$	2-Th	2-pyrim mal	q		153–155	135
$C_{15}H_{10}$	5-O_2N-2-Th		q	35	195	65
$C_{15}H_{11}$	2-Th	4-quin	q	25	86	129
$C_{15}H_{18}$	3-Th	1-H_3C-2-pyrim mal	q		193–194	135
$C_{15}H_{19}$	3-Br-2-Th	1-H_3C-2-pyrim tart			110–113	135
	5-$(CH_3)_2N$-2-Th	1-C_2H_5-pyr I^-	q	41	272	131
$C_{15}H_{26}$	2-Th	1-H_3C-2-pyrim tart	q		147–148	135
$C_{16}H_{11}$	2-Th		q	70	224	130

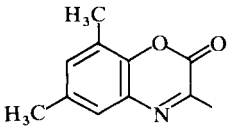
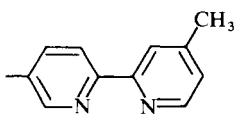
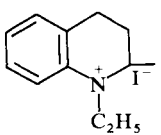
$C_{16}H_{12}$	5-O_2N-2-Th		q	79	180	65
$C_{16}H_{13}$	2-Th	1-$C_6H_5SO_2$-2-py	k	53	61–62.5	291
$C_{16}H_{22}$	3-H_3C-2-Th	1-H_3C-2-pyrim tart	q		169–171	135
$C_{17}H_{15}$	2-Th	1-$C_6H_5CH_2$-2-py	l	85	mixt E,Z	336
$C_{17}H_{20}$	2-Th	1-H_3C-2-imid TosOH	q		162–164	135
$C_{17}H_{22}$	3-H_5C_2-2-Th	1-H_3C-2-pyrim mal	q		167–171	135
$C_{18}H_{12}$	2-Th	1-dibenzo Th	l	82	101–102	325
	2-Th	4-dibenzo Th	l	71	139–140	325
	2-Th	4-dibenzo Th	k	79	139–140	325
	2-Th	2-dibenzo Th	k	88	193–194	325
	3-Th	1-dibenzo Th	l	85	109–110	325
	3-Th	4-dibenzo Th	l	62	119–120	325
	3-Th	4-dibenzo Th	k	76	119–120	325
	3-Th	2-dibenzo Th	k	68	181–182	325
$C_{19}H_{18}$	5-H_5C_2-2-Th		q		128.5–130	123
$C_{19}H_{21}$	5-$(H_3C)_2N$-2-Th		q	46	249	131

TABLE 6. (*Continued*)

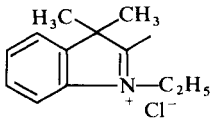
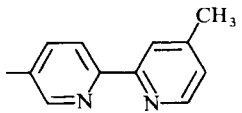
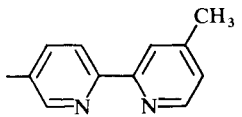
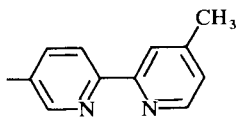
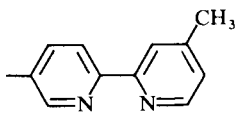
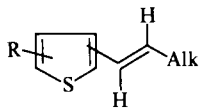
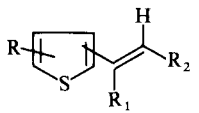
CH	Th Group	Hetaryl Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{19}H_{23}$	5-$(CH_3)_2$N-2-Th		q	78	239	131
$C_{23}H_{26}$	$H_{13}C_6$-2-Th		q		58–62	123
$C_{27}H_{34}$	$H_{21}C_{10}$-2-Th		q		55.5–56	123
$C_{29}H_{38}$	$H_{25}C_{12}$-2-Th		q		52.6–53.5	123
$C_{31}H_{42}$	$H_{29}C_{14}$-2-Th		q		41–42	123

TABLE 7. 1-(Thienyl)-2-alkylethenes



CH	Th Group	Alkyl Group	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_7H_7	5-Cl-2-Th	CH_3	n	47	82–88/7	381
	5-I-2-Th	CH_3	l		88–89/0.2	332
	5-I-2-Th	CH_3	n		88–89/0.2	332
	5-O_2N-2-Th	CH_2OH	s		78–80	7
C_7H_8	2-Th	CH_3	o	70	63–64/14	402
C_8H_{10}	2-Th	—$CHCH(OH)CH_3$	o		80–81/0.5	576
$C_{15}H_{13}$	2-Th	—$CHCH(OCOC_6H_4$-4-$NO_2)$-CH_3	o		66	576
$C_{25}H_4$	$5H_3C(CH_2)_{15}$-2-Th	$CH_2CO_2CH_3$	n			382

TABLE 8. 1-(Thienyl)-1,2-dialkyl- or Arylethenes[a]



CH	Th Group	R_1	R_2	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{10}H_{12}$	2-Th	$-(CH_2)_4$		m	91.5	89–91/0.1	410
	2-Th	$-(CH_2)_4$		m	83	117–120/5	411
	4-H_3C-2-Th	$-(CH_2)_3-$		o			565
$C_{11}H_{12}$	5-OHC-2-Th	$-(CH_2)_4-$		m	45	57–59	157
	5-OHC-3-Th	$-(CH_2)_4-$		m	34	38–39	157
$C_{11}H_{14}$	5-H_3C-3-Th	$-(CH_2)_4-$		m	62	53–55	412
	4-H_3C-2-Th	$-(CH_2)_4-$		m	62	128–132/13	412
	4-H_3C-2-Th	$-(CH_2)_4-$		o		105–106/3	565
	2-Th	$-(CH_2)_5-$		m	68	106/0.05	409
	2-Th	$-(CH_2CH(CH_3)(CH_2)_2-$		m	92	90/0.5	409
	2-Th	$-CH_2CH_2CH(CH_3)CH_2-$		m	99	104/0.4	409
$C_{12}H_{16}$	2,5-di-H_3C-2-Th	$-(CH_2)_4-$		m	85	134–136/8	412
	2-Th	$-(CH_2)_6-$		m	59	127/3	409
$C_{13}H_{15}$	4-Br-2,5-di-H_3C-3-Th	$-C(CH_3)=CH(CH_2)_2-$		m		130–131/2	415
$C_{13}H_{16}$	2,5-di-H_3C-3-Th	$-C(CH_3)=CH(CH_2)_2-$		m		117–119/2.5	415
$C_{13}H_{18}$	5-Cl-2-Th	$-C(CH_3)_2NHC(CH_3)_2CH_2-$		m	37	127/0.6	526

$C_{13}H_{19}$	2-Th	—$C(CH_3)_2NHC(CH_3)_2CH_2$—		m	64	141–142/12	526
$C_{14}H_{11}$	5-H_3C-2-Th	CF_3	C_6H_5	l	84	155–160	308
$C_{14}H_{16}$	2-Th	2-pyr	—$CH_2N(CH_3)_2$	n		116–122/0.05	461
$C_{14}H_{20}$	2-$C(CH_3)_3$-3-Th	—$(CH_2)_4$—		m	89	41–42	412
$C_{14}H_{21}$	5-H_3C-2-Th	—$C(CH_3)_2NHC(CH_3)_2CH_2$—		m	52	56.5–57	526
$C_{16}H_{12}$	2-Th	2-Th	C_6H_5	m		75	404
	2-Th	2-Th	C_6H_5	n		225–230/13	454
$C_{16}H_{18}$	2-Th	2-Th	—$(CH_2)_3COOCH_2CH_2OH$	m	51		408
$C_{16}H_{20}$	2-Th	—$CH(CH_3)CH_2N$-$(CH_3)_2$	—2-pyr	n			464
$C_{17}H_{20}$	2-Th	2-Th	—$(CH_2)_4COO(CH_2)_2OH$	m	83		408
	3-Th	3-Th	$(CH_2)_4COO(CH_2)_2OH$	m	75		408
$C_{17}H_{21}$	2-Th	$CH(CH_3)CH_2N(CH_3)_2$	C_6H_5	n			464
$C_{18}H_{13}$	5-Br-2-Th	C_6H_5	C_6H_5	n	86	192–194/0.5	455
	2-Th	4-ClC_6H_4	C_6H_5	n	89	78	455
	5-Cl-2-Th	C_6H_5	C_6H_5	n		73	459
$C_{18}H_{14}$	2-Th	C_6H_5	C_6H_5	n		72	404
$C_{18}H_{16}$	2-Th	2-Th	4-C_2H_5O-C_6H_4	m		65	404
	2,5-di-H_3C-2-Th	2-Th	C_6H_5	n		85	454
$C_{18}H_{18}$	3-Th	3-Th	—$(CH_2)_3COO(CH_2)_2OH$	m	36	98	408
$C_{18}H_{28}$	2,5-di-$(CH_3)_3C$-3-Th	—$(CH_2)_4$—		m	85	69–71	412
$C_{19}H_{15}$	2-Th	4-$CH_3OC_6H_4$	4-Cl-C_6H_4	n	94	112	455
	2-Th	4-$CH_3C_6H_4$	4-Cl-C_6H_4	n	86	76	455
	5-Cl-2-Th	C_6H_5	C_6H_5	*n*		245–250/17	459

TABLE 8. (*Continued*)

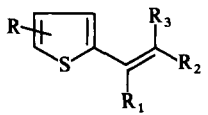
CH	Th Group	R_1	R_2	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mm Hg)	Ref.
$C_{19}H_{16}$	2-Th	4-$CH_3OC_6H_4$	C_6H_5	n		240–242/13	459
	2-Th	4-$CH_3OC_6H_4$	C_6H_5	n		73.5	404
	2-Th	3-$CH_3OC_6H_4$	C_6H_5	n			456
	2-Th	2-$CH_3OC_6H_4$	C_6H_5	n		70–71	457
	2-Th	4-$CH_3C_6H_4$	C_6H_5	n	88	61	455
	2-Th	4-CH_3S-C_6H_4	C_6H_5	n		118	267
$C_{20}H_{18}$	2-Th	C_6H_5	4-$C_2H_5OC_6H_4$	n		87	404
	2-Th	4-H_5C_2-S-C_6H_4	C_6H_5	n		60	267
$C_{21}H_{20}$	2-Th	4-$CH_3OC_6H_4$	4-H_5C_2O-C_6H_4	n		105	404
$C_{22}H_{16}$	2-Th	2-napht	C_6H_5	n		95	455
$C_{24}H_{17}$	5-(4-Cl-C_6H_4)-2-Th	C_6H_5	C_6H_5	n		127	458
	5-Cl-2-Th	4-C_6H_5-C_6H_4	C_6H_5	n	90	115	459
$C_{24}H_{18}$	5-C_6H_5-2-Th	C_6H_5	C_6H_5	n		90	669
	2-Th	4-C_6H_5-C_6H_4	C_6H_5	n		113	454
$C_{25}H_{20}$	5-H_3C-2-Th	4-C_6H_5-C_6H_4	C_6H_5	n		90	454
	5-(4-H_3C-C_6H_4)-2-Th	C_6H_5	C_6H_5	n		115	458

[a] Isomeric structure and isomeric purity of 1-(thienyl)-1,2-diarylethenes were not ascertained.

TABLE 9. 1-(Thienyl)-2,2-dialkyl- or Arylethenes

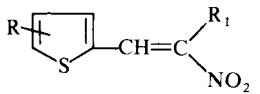
CH	Th Group	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_9	4-O_2N-2-Th	CH_3	CH_3	o	4–4.5	70–75	510
C_8H_{10}	2-Th	CH_3	CH_3	n	83	75/12	437
$C_{11}H_{10}$	2-Th	2-Th	CH_3	k	40	42–42.5	319
$C_{11}H_{14}$	5-$(CH_3)_2C(NO)_2$-4-O_2N-2-Th	CH_3	CH_3	o	12–14	96–97	510
$C_{13}H_{12}$	3-Th	CH_3	C_6H_5	m	65	60	320
	3-Th	CH_3	C_6H_5	k	65	60	320
	3-Th	CH_3	C_6H_5	m	70	66	320
$C_{17}H_{13}$	2-Th	2-pyr	C_6H_5	t	70	77	133
$C_{17}H_{14}$	2-Th	CH_3	1-napht	k	82		321
$C_{18}H_{14}$	2-Th	C_6H_5	C_6H_5	k	68	59	288

TABLE 10. 1-(Thienyl)-1,2,2-trialkyl- or Arylethenes



CH	Thienyl Group	R_1	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{11}H_{14}$	2-Th		$-(CH_2)_4-$	CH_3	m	73	101/3	409
$C_{13}H_{17}$	4-Br-2,5-di-H_3C-2-Th		$-(CH_2)_4-$	CH_3	m	55	101–113/0.2	415
$C_{13}H_{18}$	4,5-di-H_3C-3-Th		$-(CH_2)_2-$	CH_3	m	36	118–120/1.2	416
$C_{14}H_{19}$	4-Br-2,5-di-H_3C-3-Th		$-CH(CH_3)(CH_2)_3-$	CH_3	m	30	135–137/1	416
$C_{14}H_{20}$	3-Th		$-CH_2CH(CH_3)CH_2CH_2-$	$CH(CH_3)_2$	m	63	104–106/1	416
$C_{15}H_{16}$	3-Th	2-H_3C-C_6H_4	CH_3	CH_3	n	9		503
	4-H_3C-3-Th	C_6H_5	CH_3	CH_3	n	17		503
	2-H_3C-3-Th	C_6H_5	CH_3	CH_3	n	12		503
$C_{15}H_{21}$	4-Br-2,5-di-H_3C-2-Th		$-C(CH_3)_2$-$(CH_2)_3-$	CH_3	m	44	100–125/0.3	416
$C_{16}H_{17}$	5-Br-2-Th	C_2H_5	4-HO-C_6H_4	C_2H_5	n			444
$C_{16}H_{18}$	2-Th	C_2H_5	4-HO-C_6H_4	C_2H_5	n			444
	2-Th	C_2H_5	C_6H_5	C_2H_5	n		154/10	404
	2,5-di-H_3C-2-Th	C_6H_5	CH_3	CH_3	n	12		503
$C_{16}H_{23}$	4-Br-2,5-di-H_3C-2-Th		$-CH_2CH(CH_3)CH_2CH_2$	$CH(CH_3)_2$	m	69	118–120/0.5	418
$C_{16}H_{24}$	2,5-di-H_3C-2-Th		$-CH_2CH(CH_3)CH_2CH_2-$	$CH(CH_3)_2$	m	80	108–112/0.5	418
$C_{17}H_{20}$	2-Th	C_2H_5	4-$CH_3OC_6H_4$	C_2H_5	m	21	75–78	403
$C_{19}H_{13}$	2-Th	CF_3	C_6H_5	C_6H_5	o	15	77–80	533

TABLE 11. β-(Nitrovinyl)thiophenes from Nitroalkanes and Aldehydes



CH	Th Group	R_1	Yield (%)	m.p.(°C) b.p. (°C/mmHg)	Ref.
C_6H_2	3,4,5-tri-Cl-2-Th	H	94	46–50	59
C_6H_4	4-Br-2-Th	H	45	104–105	85
	5-Br-2-Th	H	65, 69	91–92	83, 85
	4-Br-3-Th	H	55	100–101	85
	5-Cl-2-Th	H	40, 72	84–85	83, 85
	5-O_2N-2-Th	H		102–104	11
C_6H_5	2-Th	H	83, 78	80–81, 79–80	80, 83–85
	3-Th	H	78, 25	96–97	85, 730
C_7H_4	5-NC-2-Th	H	77, 63	181–182	11, 77
C_7H_5	5-OHC-2-Th	H	85	172–173	86
	2-OHC-3-Th	H		123–124	87
	3-OHC-2-Th	H	40	135–136.5	87
	3,5-di-Cl-2-Th	CH_3	79	72–73	92
	3,4-di-Cl-2-Th	CH_3	52	91–92	92
	4,5-di-Cl-2-Th	CH_3	84	103–104	92
C_7H_6	4-Cl-2-Th	CH_3	87	60–61	92
	3-Cl-2-Th	CH_3	57	74	92
	5-Cl-2-Th	CH_3	75	102–103	92

TABLE 11. (*Continued*)

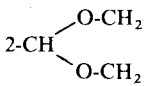
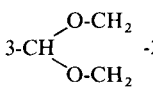
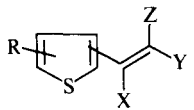
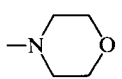
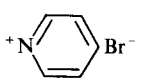
CH	Th Group	R_1	Yield (%)	m.p.(°C) b.p. (°C/mmHg)	Ref.
C_7H_7	2-Th	CH_3	32, 50, 44, 70, 73	68–69	76, 80, 83, 84, 91, 92
	3-Th	CH_3	79, 72	71–72, 72.5–73	96, 730
	5-CH_3O-2-Th	H	54	129–130	90
	3-H_3C-2-Th	H	14	66–67	83
	5-H_3C-2-Th	H	48	79–81	84
C_8H_9	5-H_3C-2-Th	CH_3	46, 90	117	84, 96
	5-H_3C-3-Th	CH_3	90	57–59	96
	2-Th	C_2H_5	52	120–122/2.3, 32	91
	2-S-CH_3-5-OCH_3-3-Th	H	52	111–112	89
	5-S-CH_3-2-OCH_3-3-Th	H	79	88–89	89
	5-C_2H_5-S-2-Th	H	55	62.5–64.5	88
	5-C_2H_5-2-Th	H	32	56–57	83
	3-C_2H_5S-2-Th	H	52	63–64	88
C_9H_9	 -3-Th	H		134–135	87
	 -2-Th	H		112–113	87
C_9H_{11}	5-H_7C_3-2-Th	H	26	36.5	83
$C_{10}H_{11}$	5-H_5C_2-3-Th	CH_3			96
$C_{10}H_{13}$	5-H_5C_2-2-C_2H_5S-3-Th	H	47	45–47	88
$C_{12}H_9$	2-Th	C_6H_5	81	126.5–127	93, 94, 95

TABLE 12. 1-(Thienyl)ethenes Containing at Least One Group that Is Not Alkyl or Aryl



CH	Th group	X	Y	Z	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_6H_2	5-Br-2-Th	F	Cl	F	b	60	128/27	532
C_6H_3	2-Th	F	Cl	Cl	b	81	105–106/9	534
	2-Th	F	Cl	F	b	55	90/14	530
	2-Th	F	F	F	o	78	33/10	546
C_6H_4	5-O_2N-2-Th	H	Br	H	j		79–80	864
	2-Th	H	Br	Br	l	96	57–58	487
	3-Th	H	Br	Br	l	93	25	487
	2-Th	H	H	Cl	o	16	108–111/12	525
	5-O_2N-2-Th	H	H	N_3	j	71	82–87[a]	595
C_6H_5	2-Th	H	N_3	H	n	75		387
	3-Th	H	N_3	H	n	70		387
C_7H_3	2-Th	CF_3	F	F	n	44	128–130/760	533
C_7H_6	5-H_3C-2-Th	H	Br	Br	l	100	64–65	487
	3-H_3C-2-Th	H	Br	Br	l	97	37–38.5	487
C_7H_7	3-N_3-2-Th	H	SOC_6H_5	H	l	65		188
C_7H_8	2-Th	H	SO_2CH_3	H	l	85	77	358
C_8H_{10}	2-Th	H	OC_2H_5	H	o	78	116–117/25	596
	2-Th	H	$SO_2C_2H_5$	H	l		46.5–48.5	371
	5-O_2N-2-Th	H	$N(CH_3)_2$	H	j	80	124–127	595

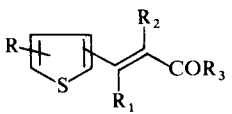
TABLE 12. (*Continued*)

CH	Th group	X	Y	Z	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_9H_{11}	5-$(H_3C)_3$Si-2-Th	F	Cl	F	b	85	123/20	532
C_9H_{13}	5-O_2N-2-Th	H	H	$\overset{+}{N}(CH_3)_3Br^-$	j	80	160–165	595
C_9H_{14}	2-Th	H	$\overset{+}{N}(CH_3)_3Br^-$	H	n	23	190–192	388
	3-Th	$Si(CH_3)_3$	H	H	r	60, 72		541
	2-Th	$Si(CH_3)_3$	H	H	r	81		541
	3-Th	H	$Si(CH_3)_3$	H	r	73		554
	2-Th	H	$Si(CH_3)_3$	H	r	74		554
$C_{10}H_6$	2-Th	F	2-Th	F	b	30	98	530
$C_{10}H_{11}$	5-HOOC-2-Th	Cl	CH_3	H	o	62	169–170	505
	5-O_2N-2-Th	—$OCOCH_3$	CH_3	CH_3	o	70–80		509
$C_{10}H_{12}$	2-Th	F	C_4H_9-*s*	F	r	50	48–49/0.1	546
	5-O_2N-2-Th	H		H	j	80	165–168	595
$C_{10}H_{14}$	5-O_2N-2-Th	H	—$PO(OC_2H_5)_2$	H	l			353
$C_{10}H_{15}$	2-Th	H	—$PO(OC_2H_5)_2$	H	l			353
$C_{11}H_9$	5-O_2N-2-Th	H	H		j	75	215–220	595
$C_{11}H_{10}$	5-O_2N-2-Th	H	—$OCOCH_3$	—$OCOCH_3$	s		170–171	7

$C_{11}H_{13}$	5-H_5C_2OOC-2-Th	Cl	C_2H_5	H	o	51	139–140	505
$C_{11}H_{18}$	5-$(CH_3)_3$Si-2-Th	H	OC_2H_5	H	o	87	72–74/0.025	596
$C_{12}H_8$	5-C_6H_5-2-Th	H	Br	Br	l		88	489
$C_{12}H_{10}$	2-Th	H	4-$ClC_6H_4SO_2$—	H	o	83	177–178	507
$C_{12}H_{12}$	2-Th	H	2-CH_3-l-pyr$^+Br^-$	H	n		188–189	388
	2-Th	H	3-H_3C-l-pyr$^+Br^-$	H	n		205–206	388
	2-Th	H	4-H_3C-l-pyr$^+Br^-$	H	n		239–240	388
	2-Th	H	1-pyr$^+PF_6^-$	CH_3	n		178–180	388
$C_{12}H_{16}$	2-Th	SCH_3	1-H_3C-2-pyrim	H	o		127–130	504
$C_{13}H_{11}$	5-O_2N-2-Th	H	4-CH_3-C_6H_4S	H	s	85	—[a]	595
	5-O_2N-2-Th	H	4-H_3C-C_6H_4O	H	s	100	75–80[a]	505
	5-O_2N-2-Th	H	H	4-$CH_3C_6H_4SO_2$	s	85	138–140	595
$C_{13}H_{18}$	3-H_3C-2-Th	SCH_3	1-CH_3-2-pyrim	H	o			
$C_{16}H_{20}$	5-$(CH_3)_2C_6H_5$Si-2-Th	H	—OC_2H_5	H	o	62	156/0.45	596
$C_{17}H_{13}$	2-Th	CHO	Fc	Cl	o	66	110–115	501
$C_{18}H_{14}$	5-O_2N-2-Th	H	—$PO(OC_6H_5)_2$	H	l	84	124–125	353
$C_{18}H_{15}$	2-Th	H	—$PO(OC_6H_5)_2$	H	l	77	118–119	353

[a] Mixture of *Z*- and *E*-isomers.

TABLE 13. 3-(Thienyl)acryl Aldehydes and Alkylketones



CH	Th Group	R_1	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_7H_4	5-O_2N-2-Th	Br	H	H	s		181–188	7
C_7H_5	2-Th	H	Cl	H	g	42	131–139/6	15
	5-Cl-2-Th	H	H	H	g	42	35–36	9, 15
	2-Th	Cl	H	H	o	11	55–57	502
	5-O_2N-2-Th	H	H	H	g	87	126, 129–130	7, 8, 16
C_7H_6	2-Th	H	H	H	g	54	105–108/0.4	2
	2-Th	H	H	H	g	36	108–112/5	6
	2-Th	H	H	H	g	30	95/1	3, 4
	2-Th	H	H	H	n	100		496
	3-Th	H	H	H	g	30		13
C_8H_5	5-NC-2-Th	H	H	H	g	43	128–130	11, 12
C_8H_6	2-Th	H	CHO	H	o	75	56–58.5	245
	2-Th	H	CHO	H	o	86	96–97	245
C_8H_7	5-Cl-2-Th	H	H	CH_3	g			19
	5-O_2N-2-Th	H	CH_3	H	g	60	133–134	16

C_8H_8	3-H_3C-2-Th	H	H	H	g	39	133–136/3	15
	2-Th	H	H	CH_3	g	64	34–35	2
	2-Th	H	H	CH_3	g	69	151–153/14	22
	2-Th	H	H	CH_3	g	72	94.5/0.7	20
	2-Th	H	CH_3	H	g	54	27–30	17
C_9H_9	5-H_3C-4-NO_2-2-Th	H	H	CH_3	g	95	149–150	25
C_9H_{10}	2-Th	H	CH_3	CH_3	g	77		29
$C_{10}H_8$	4,5-di-Cl-2-Th	H	$COCH_3$	CH_3	o	25	89–90	155
$C_{10}H_9$	5-O_2N-2-Th	H	H	$CO_2C_2H_5$	g	47	118–120	65
$C_{10}H_{10}$	2-Th	H	—$(CH_2)_3$—		g	35	79	32
$C_{10}H_{11}$	5-H_5C_2-4-O_2N-2-Th	H	H	CH_3	g	65	72–73	25
	5-O_2N-2-Th	H	C_3H_7	H	g	42	107	16
$C_{11}H_{12}$	2-Th	H	—$(CH_2)_4$—		g	53	81	32
$C_{11}H_{14}$	2-Th	H	H	$C(CH_3)_3$	g	89	112	862
$C_{12}H_{10}$	2-Th	2-Th	H	CH_3	n	57		408
	3-Th	3-Th	H	CH_3	n	68		408
$C_{12}H_{14}$	2-Th	H	—$(CH_2)_3CHCH_3$—		g	60	155	34
$C_{12}H_{16}$	2-Th	H	—$(CH_2)_4CH_3$	H	g		190–194/35	227
$C_{14}H_{12}$	2-Th	2-Th	—$(CH_2)_3$—		n	33	90–91	408
	3-Th	3-Th	—$(CH_2)_3$—		n	22	78–80	408
$C_{14}H_{16}$	2-OHC-3-Th	H	—$(CH_2)_6$—		l		84	26, 38
	3-OHC-2-Th	H	—$(CH_2)_6$—		g		84	26
	3-OHC-2-Th	H	—$(CH_2)_6$—		g		75	26

TABLE 13. (*Continued*)

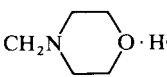
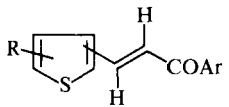
CH	Th Group	R_1	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{15}H_{10}$	4,5-di-Cl-2-Th	H	COC_6H_5	CH_3	o	46.5	144–165	155
$C_{15}H_{12}$	2-Th	H	$(CH_2)_2$-$C_6H_4^{-2}$		g		89.5–90	39
$C_{15}H_{14}$	2-Th	CH_3	C_6H_5	CH_3	o	34.5	101–102	474
	2-Th	CH_3	C_6H_5	CH_3	o	12.5	134–135	474
$C_{16}H_{14}$	5-H_3C-2-Th		—$(CH_2)_2$-$C_6H_4^{-2}$		g		104	40
$C_{16}H_{16}$	2-Th	C_2H_5	C_6H_5	CH_3	o	27	66–67	474
	2-Th	C_2H_5	C_6H_5	CH_3	o	7		474
$C_{17}H_{16}$	2-Th	C_6H_5	—$(CH_2)_4$—		o	84	119–120	408
	5-H_5C_2-2-Th	H	—$(CH_2)_2$-$C_6H_4^{-2}$		g		59	39
$C_{18}H_{20}$	2-Th	C_6H_5	H	—$CH_2N(CH_2)_4 \cdot HCl$	o	45	184–185	578
	2-Th	C_6H_5	H		o	73	186–187	578
$C_{18}H_{22}$	2-Th	C_6H_5	H	—$CH_2N(C_2H_5)_2$ mal	o	52	131–132	578
$C_{19}H_{20}$	2-Th	C_6H_5	H	—$CH_2N(CH_2)_5 \cdot HCl$	o	61	172–173	578
$C_{20}H_{16}$	2-Th	C_6H_5	C_6H_5	CH_3	o	21	112–113	408
	5-H_3C-CO-2-Th	2-Th	C_6H_5	CH_3	o	21	164–165	408

TABLE 14. 3-(Thienyl)acryl Aryl Ketones



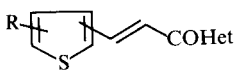
CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p.(°C) b.p. (°C/mmHg)	Ref.
$C_{13}H_7$	4,5-di-Cl-2-Th	4-Cl-C_6H_4	t	82	180	44
$C_{13}H_8$	4-Br-2-Th	2-HO-5-O_2N-C_6H_3	t	65	195	45
	4,5-di-Cl-2-Th	2-HO-C_6H_4	t	26	154	44
	5-O_2N-2-Th	4-O_2N-C_6H_4	t	41	259	46
$C_{13}H_9$	4-Br-2-Th	2-HOC_6H_4	t	11	108	45
	3-Br-2-Th	2-HOC_6H_4	t	10	124	45
	2-Th	4-O_2N-C_6H_4	t	90, 96	173–174	47, 56
	2-Th	3-O_2N-C_6H_4	t	70	113–114	47, 56
	5-O_2N-2-Th	C_6H_5	t	48	181	46
	2-Th	2-HO-5-O_2N-C_6H_3	t	71	190–191	48
	2-Th	4-HO-3-O_2N-C_6H_3	t	70	128–130	48
$C_{13}H_{10}$	2-Th	C_6H_5	t	96	59	49
	2-Th	C_6H_5	t	55, 82	59–60, 59	50, 151
	3-Th	C_6H_5	t	69	77	36
	2-Th	2-HOC_6H_4	t		99–100	758

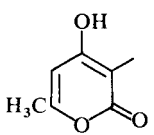
TABLE 14. (*Continued*)

CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p.(°C) b.p. (°C/mmHg)	Ref.
$C_{14}H_{10}$	4,5-di-Cl-2-Th	4-CH_3-C_6H_4	t	69	130	44
	4,5-di-Cl-2-Th	4-CH_3O-C_6H_4	t	79	152	44
	5-H_3C-2-Th	3,4-di-Cl-C_6H_3	t		121	40
$C_{14}H_{11}$	2-Th	3-Br-4-CH_3O-2-HO-C_6H_2	t	85	178	55
	2-Th	3-Cl-4-CH_3O-C_6H_3	t		157	47
	5-H_3C-2-Th	3-O_2N-C_6H_4	t		132	40
	5-H_3C-4-O_2N-2-Th	C_6H_5	t	73	179–180	25
	5-O_2N-2-Th	4-CH_3O-C_6H_4	t	40	212	46
$C_{14}H_{12}$	2-Th	4-CH_3-C_6H_4	t	75, 86	79	34, 50
	2-Th	4-CH_3-C_6H_4	t	98	77–78	56
	2-Th	4-CH_3O-C_6H_4	t	88	103.5–104.5	56
	2-Th	4-CH_3O-C_6H_4	t	98	104–106	49
	2-Th	4-CH_3O-C_6H_4	t	75	106–107	50
	3-CH_3O-2-Th	C_6H_5	t		94	57
$C_{15}H_{10}$	5-O_2N-2-Th	4-O_2N-C_6H_4	t	40	233	46
$C_{15}H_{11}$	5-O_2N-2-Th	C_6H_5	t	20	172	46
$C_{15}H_{13}$	5-H_3C-2-Th	3-Cl-4-H_3CO-C_6H_3	t		141	47
	5-H_5C_2-4-O_2N-2-Th	C_6H_5	t	77	139–140	25
	5-O_2N-2-Th	2,4-di-CH_3O-C_6H_3	t	15	162	46
$C_{15}H_{14}$	2-Th	3,4-di-CH_3O-C_6H_3	t	73	86.5	58
$C_{16}H_{10}$	2-Th	2-HO-$C_6H_4Cr(CO)_3$	t		146	70

$C_{16}H_{14}$	4,5-di-Cl-2-Th	4-H_7C_3O-C_6H_4	t	71	100	44
$C_{16}H_{16}$	2-Th	2,4,5-tri-CH_3O-C_6H_2	t	84	104	58
$C_{17}H_{11}$	5-O_2N-2-Th	1-napht	t	43	156–158	60
	5-O_2N-2-Th	2-napht	t	39	198–199	60
$C_{17}H_{12}$	2-Th	1-napht	t	43, 45	68	34, 35
	2-Th	1-napht	t	83	61–63	60
	2-Th	2-napht	t	55, 57	98–99	34, 35
	2-Th	2-napht	t	67	96–97	60
$C_{17}H_{14}$	2-Th	Fc	t	75	149	69
$C_{17}H_{16}$	2-Th	2,4-di-CH_3O-C_6H_3	t	80	71	58
$C_{17}H_{18}$	3-$(CH_3)_3CO$-2-TH	C_6H_5	t	65	90	57
	2-$(CH_3)_3CO$-3-Th	C_6H_5	t	65	120	57
	4-$(CH_3)_3CO$-3-TH	C_6H_5	t	55	68	57
$C_{18}H_{18}$	2-Th	—CH═CH-2,4,6-tri-CH_3O-C_6H_2	t	85	160	58
$C_{19}H_{11}$	3,4,5-tri-Cl-2-Th	C_6H_5	t	88	106	59
$C_{19}H_{14}$	2-Th	4-C_6H_5-C_6H_4	t	51, 97	310, 155–156	34, 56
	2-Th	4-C_6H_5-S-C_6H_4	t		95	47
$C_{19}H_{16}$	2,5-di-H_3C-3-Th	2-napht	t		109	47
$C_{19}H_{20}$	5-H_3C-2-Th	4-cyclop C_6H_4	t		92	40
$C_{20}H_{15}$	5-H_3C-4-O_2N-2-Th	4-C_6H_5-C_6H_4	t	12	241–242	25
$C_{21}H_{19}$	5-C_6H_5-2-Th	4-$(CH_3)_2N$-C_6H_4	t	74	184–187	41
$C_{22}H_{16}$	2-Th	4-(4-$CH_3OC_6H_4$)-C_6H_4	t		207	47

TABLE 15. 3-(Thienyl)acryl Heterocyclic Ketones Excluding Thiophene Ketones



CH	Th Group	Het Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{11}H_8$	2-Th	2-Se	t	73	101	64
$C_{12}H_8$	5-Br-2-Th	2-pyr	t	80	145	45
	4-Br-2-Th	2-pyr	t	70	136	45
$C_{12}H_9$	5-H_3C-4-O_2N-2-Th	2-Fu	t	76	158–159	25
$C_{13}H_{10}$	2-Th		t		157	54
$C_{13}H_{11}$	5-H_5C_2-4-O_2N-2-Th	2-Fu	t	18	142–143	25
$C_{14}H_{10}$	2-Th	2-benzimid	t	71	222	67
$C_{15}H_{10}$	5-O_2N-2-Th	—$N(COCH_3)C_6H_4$-2-	t	38	217–219	72

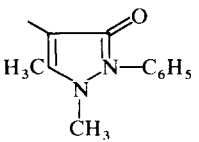
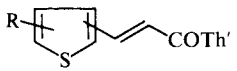
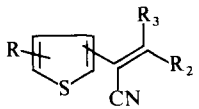
$C_{15}H_{11}$	2-Th	—N(COCH$_3$)C$_6$H$_4$-2-	t	74	130–131	72
$C_{15}H_{16}$	3-(H$_3$C)$_3$CO-2-Th	2-Fu	t	50	110	57
$C_{15}H_{17}$	3-(H$_3$C)$_3$CO-2-Th	2-py	t	30	107	57
$C_{16}H_{17}$	3-(H$_3$C)$_3$CO-2-Th	4-pyr	t	25	98	57
	3-(H$_3$C)$_3$CO-2-Th	3-pyr	t	40	79	57
	3-(H$_3$C)$_3$CO-2-Th	2-pyr	t	65	93	57
$C_{17}H_{13}$	5-C$_6$H$_5$-2-Th	2-pyr	t	32	240–242	41
$C_{18}H_{16}$	2-Th		t	93	238	71
$C_{21}H_{14}$	5-C$_6$H$_5$-2-Th	benzoFu	t	54	209–212	41
$C_{25}H_{16}$	5-C$_6$H$_5$-2-Th	2-dibenzoFu	t	62	174–176	41

TABLE 16. 3-(Thienyl)acryl Thienyl Ketones



CH	Th Group	Th' Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{11}H_6$	5-Cl-2-Th	5-Br-2-Th	t		132	47
	5-Br-2-Th	5-Br-2-Th	t	40	244	45
	4-Br-2-Th	3-Br-2-Th	t	50	96–96.5	61
	3-Br-2-Th	5-Br-2-Th	t	33	135	45
$C_{11}H_7$	2-Th	5-Br-2-Th	t	20	113, 115	47, 45
	5-Br-2-Th	2-Th	t	60	100	45
	5-Cl-2-Th	2-Th	t		104	47
	2-Th	5-Cl-2-Th	t		100	47
$C_{11}H_8$	2-Th	2-Th	t	90	100–101	34, 35
	2-Th	2-Th	t	71	99.2–99.8	22
$C_{12}H_8$	5-H_3C-2-Th	5-Cl-2-Th	t		115	40
$C_{12}H_9$	5-CH_3-4-O_2N-2-Th	2-Th	t	55	171–172	25
$C_{12}H_{10}$	5-H_3C-2-Th	2-Th	t		100	47
$C_{13}H_{11}$	2,5-di-H_3C-3-Th	5-Br-2-Th	t		120	47
	5-H_5C_2-4-O_2N-2-Th	2-Th	t	34	132–133	25
$C_{13}H_{12}$	2-Th	5-H_5C_2-2-Th	t		85	47
$C_{15}H_9$	5-O_2N-2-Th	5-(2-Th)-2-Th	t	30	237–238	25
$C_{15}H_{16}$	3-$(H_3C)_3CO$-2-Th	2-Th	t	50	90	57
$C_{16}H_{11}$	5-H_3C-4-O_2N-2-Th	5-(2-Th)-2-Th	t	14	235–235.5	25
$C_{17}H_6$	3,4,5-tri-Cl-2-Th	2,4,5-tri-Cl-2-Th	t	86	145–146	59
$C_{17}H_{11}$	5-C_6H_5-2-Th	5-Br-2-Th	t	62	154–157	41
$C_{35}H_{24}$	3,5-di-C_6H_5-2-Th	2,5-di-C_6H_5-2-Th	t		182	229

TABLE 17. 1-(Thienyl)-1-cyano-2,3-dialkyl or Aryl Ethenes



CH	Th Group	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
C_7H_6	2-Th	NH_2	H	o	94	124	275
	3-Th	NH_2	H	o	95	110	275
	3-Th	OCH_3	H	w	82[a]	60	275
	2-Th	OCH_3	H	w	86[b]		275
$C_{11}H_7$	2-Th	2-Fu	H	w		79, 80	118, 981
	3-Th	2-Fu	H	w		54.5	981
$C_{11}H_{12}$	2-Th	$-(CH_2)_4-$		w	42	46–48	272
$C_{13}H_7$	2-Th	3,4-di-Cl-C_6H_3	H	w	89	119, 110–111	258, 269
	2-Th	2,4-di-Cl-C_6H_3	H	w		150	269
	2-Th	2,4-di-Cl-C_6H_3	H	w	96	145–146	258
$C_{13}H_8$	2-Th	4-Br-C_6H_4	H	w	75	90–91	258
	2-Th	4-Cl-C_6H_4	H	w		90	118
	2-Th	4-F-C_6H_4	H	w		77	269
	2-Th	4-HO-C_6H_4	H	o		176	118
	2-Th	3,4-di-HO-C_6H_3	H	o		179–181	118
	2-Th	C_6H_5	H	w	60	74–75	258
	2-Th	C_6H_5	H	w	92	80	682
	2-Th	C_6H_5	H	w		75	265
	2-Th	C_6H_5	H	w	77	75.5–76.5	101
	3-Th	C_6H_5	H	w	94	75	682
	3-Th	C_6H_5	H	w		69	981

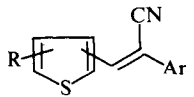
TABLE 17. (*Continued*)

CH	Th Group	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{14}H_8$	2-Th	4-F_3C-C_6H_4	H	w	42	110–111	258
$C_{14}H_9$	3-Th	3,4-OCH_2O-C_6H_3	H	w		124	981
	2-Th	3,4-OCH_2O-C_6H_3	H	w		106	118
$C_{14}H_{11}$	2-Th	2-CH_3O-C_6H_4	H	w		81	118
	2-Th	4-CH_3O-C_6H_4	H	w		74, 75	118, 266
	3-Th	4-CH_3O-C_6H_4	H	w		64	981
	3-Th	2-H_3C-C_6H_4	H	w	98	100	682
	2-Th	2-H_3C-C_6H_4	H	w	99	84	682
	2-Th	4-CH_3S-C_6H_4	H	w		89	267
$C_{15}H_9$	2-Th	3-benzo-Th	H	w		105	220, 231
$C_{15}H_{12}$	2,5-di-H_3C-2-Th	4-Cl-C_6H_4	H	w		106	269
	2,5-di-H_3C-2-Th	4-F-C_6H_4	H	w		85	269
$C_{15}H_{13}$	3-Th	3,4-di-CH_3O-C_6H_3	H	w		102	981
	2-Th	3,4-di-CH_3O-C_6H_3	H	w		86	118
	2-Th	3-H_3C-4-CH_3S-C_6H_3	H	w		98	267

$C_{15}H_{14}$	2-Th	4-$(H_3C)_2$-N-C_6H_4	H	w		160	118
$C_{17}H_{11}$	3-Th	1-napht	H	w		143	981
	2-Th	1-napht	H	w	75	110, 112–113	266, 269, 271
	2-Th	2-napht	H	w		115	269
$C_{18}H_{12}$	2-Th	2-CH_3O-5-Br-1-napht	H	w		130	268
$C_{18}H_{13}$	2-Th	2-H_3CS-1-napht	H	w		142	270
$C_{19}H_{13}$	2-Th	5-acenapht	H	w		143	269
$C_{19}H_{15}$	2,5-di-H_3C-3-Th	2-napht	H	w		102	269
	2,5-di-H_3C-3-Th	1-napht	H	w		100	269
$C_{21}H_{13}$	2-Th	9-anthr	H	w		203	1015
$C_{22}H_{15}$	2-Th	10-H_3C-9-anthr	H	w		196	1015
$C_{23}H_{17}$	2,5-di-H_3C-2-Th	9-anthr	H	w		210	1015
$C_{25}H_{17}$	2,5-di-H_3C-2-Th	3-pyren	H	w		182	269

[a] *E* 85%; *Z* 15%.
[b] *Z* or *E*.

TABLE 18. 3-(Thienyl)-2-arylacrylonitriles



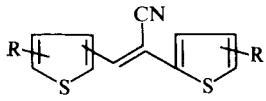
CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{13}H_6$	4,5-di-Cl-2-Th	4-O_2N-C_6H_4	a	59	217	155
$C_{13}H_7$	2-Th	3,4-di-Cl-C_6H_3	a		162	228
	5-Cl-2-Th	C_6H_5	a		177	269
	5-Cl-2-Th	4-I-C_6H_4	a		167	269
	5-Br-2-Th	4-Br-C_6H_4	a		183	223
	5-Br-2-Th	4-Cl-C_6H_4	a		178, 179	223, 233
	5-Cl-2-Th	4-Br-C_6H_4	a		171	269
	5-Br-2-Th	4-O_2N-C_6H_4	a		230, 225	223, 233
$C_{13}H_8$	2-Th	4-Cl-C_6H_4	a		124, 128	269, 225
	2-Th	4-Cl-C_6H_4	a		146	223, 233
	2-Th	4-Br-C_6H_4	a		118, 118	225, 269
	2-Th	4-F-C_6H_4	a		94, 94	225, 269
	2-Th	4-I-C_6H_4	a		112	269
	2-Th	4-O_2N-C_6H_4	a		199	233
$C_{13}H_9$	2-Th	C_6H_5	a	82	89.5–90.5	101
	2-Th	C_6H_5	a		92	233
	3-Th	C_6H_5	a	53.8	68	36
$C_{13}H_{10}$	5-H_3C-2-Th	4-O_2N-C_6H_4	a		225	233
$C_{13}H_{11}$	5-Br-2-Th	C_6H_5	a		150	233
$C_{14}H_9$	5-OHC-2-Th	C_6H_5	a		180	117

$C_{14}H_{10}$	5-Br-2-Th	4-H_3C-C_6H_4	a		150, 151	223, 233
	5-Br-2-Th	4-H_3CO-C_6H_4	a		151, 149	223, 233
	5-H_3C-2-Th	4-Cl-C_6H_4	a		141	233
$C_{14}H_{11}$	2-Th	4-H_3CO-C_6H_4	a		78	233
	2-Th	4-H_3C-C_6H_4	a		119	233
	5-H_3C-2-Th	C_6H_5	a		88	233
$C_{15}H_{12}$	5-H_5C_2-2-Th	4-Br-C_6H_4	a		118, 120	39, 269
	2,5-di-H_3C-2-Th	4-Br-C_6H_4	a		157	269
	5-H_5C_2-2-Th	4-Cl-C_6H_4	a		121	269
	2,5-di-H_3C-2-Th	4-Cl-C_6H_4	a		147	269
	5-H_5C_2-2-Th	4-F-C_6H_4	a		90	269
	2,5-di-H_3C-2-Th	4-F-C_6H_4	a		98	269
	5-H_5C_2-2-Th	4-I-C_6H_4	a		128	269
	2,5-di-H_3C-2-Th	4-I-C_6H_4	a		146	269
	5-H_5C_2-2-Th	4-O_2N-C_6H_4	a		173	269
	5-H_3C-2-Th	4-CH_3O-C_6H_4	a		88	233
	2-Th	2-O_2N-4,5-di-CH_3O-C_6H_2	a		187–188	705, 222, 985
$C_{15}H_{13}$	2-Th	3,4-di-CH_3O-C_6H_3	a	91	122–123.5	218
	5-H_3C-2-Th	4-H_3C-C_6H_4	a		100	233
	5-H_5C_2-2-Th	C_6H_5	a		105	39
$C_{16}H_{13}$	2-Th	3,4-di-$(CH_2)_3$-C_6H_3	a		111.5	220
$C_{16}H_{15}$	5-H_5C_2-2-Th	4-H_3C-C_6H_4	a		87	269
$C_{17}H_{10}$	5-Br-2-Th	2-napht	a		194	223
	2-Th	4-F-1-napht	a		162	221
$C_{17}H_{11}$	2-Th	2-napht	a		127	269
$C_{17}H_{16}$	5-$CH_3CH(CH_3)CH_2$-2-Th	4-Br-C_6H_4	a		88	269
	5-$CH_3CH(CH_3)CH_2$-2-Th	4-Cl-C_6H_4	a		96	269
	5-$CH_3CH(CH_3)CH_2$-2-Th	4-F-C_6H_4	a		86	269
	5-$(CH_3)_2CHCH_2$-2-Th	4-I-C_6H_4	a		89	269
	5-$(CH_3)_2CHCH_2$-2-Th	4-O_2N-C_6H_4	a		159	269

TABLE 18. (*Continued*)

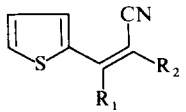
CH	Th Group	Aryl Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{17}H_{17}$	5-$(CH_3)_2CHCH_2$-2-Th	4-HO-C_6H_4	a		128	269
	5-$(H_3C)_2CHCH_2$-2-Th	C_6H_5	a		53	269
$C_{18}H_{19}$	5-$(CH_3)_2CHCH_2$-2-Th	4-H_3CO-C_6H_4	a		63	269
$C_{19}H_{12}$	5-(3-Cl-C_6H_4)-2-Th	C_6H_5	a		161	229
$C_{19}H_{15}$	2,5-di-H_3C-3-Th	2-napht	a		131	269
	5-H_5C_2-2-Th	2-napht	a		102	39
$C_{20}H_{14}$	5-$C_6H_5CH_2$-2-Th	4-Br-C_6H_4	a		132	269
	5-$C_6H_5CH_2$-2-Th	4-Cl-C_6H_4	a		105	269
	5-$C_6H_5CH_2$-2-Th	4-F-C_6H_4	a		102	269
	5-$C_6H_5CH_2$-2-Th	4-I-C_6H_4	a			269
	5-$C_6H_5CH_2$-2-Th	4-O_2N-C_6H_4	a		152	269
$C_{20}H_{15}$	5-$C_6H_5CH_2$-2-Th	C_6H_5	a		95	269
	5-(3-H_3C-C_6H_4)-2-Th	C_6H_5	a		139	229
$C_{21}H_{17}$	5-$C_6H_5CH_2$-2-Th	4-CH_3-C_6H_4	a		106	269
	5-$C_6H_5CH_2$-2-Th	4-CH_3-C_6H_4	a		110	269
$C_{21}H_{19}$	2,5-di-H_5C_2-3-Th	2-napht	a		80	226
	5-$(CH_3)_2CHCH_2$-2-Th	2-napht	a		110	269
$C_{21}H_{25}$	2,5-di-$(H_3C)_3C$-3-Th	C_6H_5	a		136	227
$C_{24}H_{17}$	5-$C_6H_5CH_2$-2-Th	2-napht	a		131	269
$C_{25}H_{17}$	3,5-di-C_6H_5-2-Th	C_6H_5	a		178	229

TABLE 19. 3-(Thienyl)-2-heterocyclic Acrylonitriles



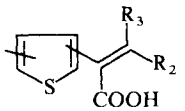
CH	3-Th Group	Het Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{11}H_6$	5-Br-2-Th	2-Th	a		120	223
$C_{11}H_7$	2-Th	2-Th	a	89	129.5–130.5	101
	2-Th	2-Th	a		131	265
	3-Th	3-Th	a		75	981, 230
	2-Th	3-Th	a		99	981, 230
$C_{12}H_8$	2-Th	3-Pyr	a		152	225
$C_{15}H_8$	5-Cl-2-Th	3-benzo Th	a		185	231
	5-Br-2-Th	3-benzo Th	a		183	231
$C_{15}H_9$	2-Th	2-benzo Th	a	82	137	715
	3-Th	3-benzo Th	a		120	220
	2-Th	3-benzo Th	a		124	231
$C_{16}H_{11}$	5-H_3C-2-Th	3-benzo Th	a		134	231
$C_{17}H_{13}$	2,5-di-H_3C-2-Th	3-benzo Th	a		185	231
$C_{18}H_{13}$	5-$C_6H_5CH_2$-2-Th	2-Th	a		119	269

TABLE 20. 3-(Thienyl)acrylonitriles



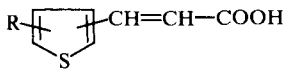
CH	Th Group	R_1	R_2	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_7H_4	2-Br-4-Th	H	H *cis*	u	16	58.0–59.3	162
	2-Br-4-Th	H	H *trans*	u	28	76.6–77.8	162
C_7H_5	3-Th	H	H	u	75, 52 *trans*		162
	2-Th	H	H	u	45 *cis*	b.p. 154/30 mmHg	217
C_7H_6	5-Cl-2-Th	NH_2	H	u	33	99.5–100	593
	5-F-2-Th	NH_2	H	u	66	86–87	593
	2-Th	NH_2	H	u	24	50–54	593, 205
	3-Th	NH_2	H		17	67–69.5	593
C_8H_3	5-O_2N-2-Th	H	CN	u	93	149	206
C_8H_4	2-Th	H	CN	u	86, 50	95–96, 96–97	210, 207
C_8H_6	2-Th	H	$CONH_2$	u	93	166	210
C_9H_6	2-Th	CH_3	CN	u	77	85	210
C_9H_8	2-Th	CH_3	$CONH_2$	u	86	150–151	593
$C_{10}H_8$	2-Th	C_2H_5	CN	u	44	31	593
$C_{11}H_{10}$	2-Th	$CH(CH_3)_2$	CN	u	25	56	593
$C_{12}H_8$	2-Th	H	2-Th-CH=N—	u		145	235
$C_{12}H_{12}$	2-Th	$C(CH_3)_3$	CN	u	14	103–104	593
$C_{14}H_8$	5-C_6H_5S-2-Th	H	CN	u	92	65	197
	5-$C_6H_5SO_2$-2-Th	H	CN	u	86.5	165–167	197
$C_{14}H_9$	2-Th	H	COC_6H_5	u	75	100–101	234
$C_{15}H_9$	5-I-2-Th	4-H_3C-C_6H_4	CN	u	30	102–104	212
$C_{15}H_{10}$	2-Th	4-H_3C-C_6H_4	CN	u	24	103–105	213

TABLE 21. 2-(Thienyl)acrylic Acids



CH	Th Group	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{11}H_{12}$	2-Th	—$(CH_2)_4$—		n		144–146	445
$C_{13}H_7$	5-Cl-2-Th	2,4-di-Cl-C_6H_3	H	x	51	113–114	257
$C_{13}H_8$	5-Cl-2-Th	4-Br-C_6H_4	H	x	55	218–220	257
	3-Th	2,4-di-Cl-C_6H_3	H	x	71	185–186	179
	2-Th	2,4-di-Cl-C_6H_3	H	x	50	128–130	258
$C_{13}H_9$	3-Th	4-Br-C_6H_4	H	x	64	219–220	179
	2-Th	4-Br-C_9H_4	H	x	55	200–202	258
$C_{13}H_{10}$	3-Th	C_6H_5	H	x	79	181–182	179
	2-Th	C_6H_5	H	x	40	168–170	258
	2-Th	C_6H_5	H	x	20	116–117	258
$C_{14}H_8$	5-Cl-2-Th	4-F_3C-C_6H_4	H	x	45	156–157	257
$C_{14}H_9$	2-Th	4-F_3C-C_6H_4	H	x	86	142–143	258
	3-Th	4-F_3C-C_6H_4	H	x	78	123–126	179
$C_{14}H_{10}$	5-H_3C-2-Th	2,4-di-Cl-C_6H_4	H	x	64	131–134	257
$C_{14}H_{11}$	5-H_3C-2-Th	4-Br-C_6H_4	H	x	34	102–104	257
$C_{15}H_{11}$	5-H_3C-2-Th	4-F_3C-C_6H_4	H	x	28	172–174	257
$C_{15}H_{13}$	2,5-di-H_3C-2-Th	2-O_2N-C_6H_4	H	x	62	196	652
	2,5-di-H_3C-2-Th	2-H_2N-C_6H_4-HCl	H	o	66	215–217	652

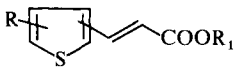
TABLE 22. 3-(Thienyl)acrylic Acids



CH	Th Group	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
C_7H_4	2,5-di-Br-3-Th	i	80	220–221	160
	4,5-di-Cl-2-Th	c	63	235–236	154
C_7H_5	5-Br-3-Th	i	96	189–192	162
	5-Br-3-Th	h		185	362
	4-Br-3-Th	h		228	362
	5-Cl-2-Th	i	85, 70	201–203	83
				204–207	159
	E-5-Br-2-Th	i	72	212–214	159, 171
				209–210	144, 169
				213–215	
				210–212	
	Z-5-Br-3-Th	c		153–155	171
	2-Br-3-Th	i	70	224–227	160
	5-Cl-3-Th	i	86	184.5–184.8	162
	Z-5-O_2N-2-Th	c		195 197	171
	E-5-NO_2-2-Th	i	83	251–252	153–171
				255–256	169, 7
	3-O_2N-2-Th	i		214–215	153
	2-O_2N-3-Th	i	79	220–222	161
C_7H_5D	2-Th	i		145–145.7	169

C_7H_6	3-Th	i	85, 78	151–152	
				153–153.5	36, 161
	2-Th	o	75	144–145	513
	3-Th	h			
	2-Th	h		141	362
	2-Th	o	75	144–145	362
	3-Th	h		141	362
	2-Th	h		208	362
	Z-2-Th	c		136–137	171
	E-2-Th	i	80, 85	143–145	83, 149
				143–144	498
				146–147	151, 171
	E-2-Th				
C_8H_6	4-OHC-2-Th	h		208	362
	3-OHC-2-Th	h		204	362
	5-OHC-2-Th	h		194	362
	5-OHC-2-Th	i	60	166–167	169, 86
$C_{10}H_8$	5-(HOOCCH=CH)-3-Th	i		> 300	164
	4-(HOOCCH=CH)-3-Th	h		290	362
	5-(HOOCCH=CH)-2-Th	h		300	362
	4-(HOOCCH=CH)-2-Th	h		290	362
C_9H_{10}	5-H_3C-2-Th	i	82, 65	165–166	83
				164–167	159, 169
	3-H_3C-2-Th	i	80	172–173	83
				170–171.5	169
	5-H_3C-2-Th	i	85	102–103	83
$C_{10}H_{12}$	5-C_3H_7-2-Th	i	83	109–110	83
$C_{13}H_{10}$	5-H_5C_6-2-Th	i	91	183–189	157
	4-H_5C_6-2-Th	i	83	190–192	157
$C_{13}H_{14}$	4-(1-cyclohexene)-2-Th	i	71	158–160	157

TABLE 23. Esters of 3-(Thienyl)acrylic Acids



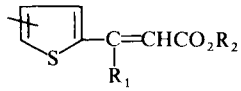
CH	Th Group	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_6	4,5-di-Cl-2-Th	CH_3	e	48	89	154
C_8H_7	3-Br-2-Th	CH_3	d		76	156
	5-Br-3-Th	CH_3	e	76	48	162
	5-Br-3-Th	CH_3	c	56	49.4–50.0	162
	4-Br-2-Th	CH_3	d		75	156
	5-Cl-3-Th	CH_3	e	69	57.2–58.2	162
	4-Cl-2-Th	CH_3	d		80	156
	5-Cl-2-Th	CH_3	d		53	156
	5-I-2-Th	CH_3	d		88	156
	3-I-2-Th	CH_3	d		78	156
	4-I-2-Th	CH_3	d		44	156
	5-O_2N-2-Th	CH_3	e		156–157	145
C_8H_8	3-Th	CH_3	e	74	48.4–49.0	162
	3-OHC-2-Th	CH_3	d		112	156
C_8H_9	3-H_2N-2-Th	CH_3	l	75	101.7–105.6	363
C_9H_8	4,5-di-Br-2-Th	C_2H_5	c	62	71.3–73.2	162
	4,5-di-Cl-2-Th	C_2H_5	e	25	85.5	154
	5-OHC-2-Th	CH_3	r	34	68–69	1016
	4-OHC-2-Th	CH_3	d		96	156

C_9H_9	5-Br-3-Th	C_2H_5	l	72	144/1	362
	4-Br-2-Th	C_2H_5	l	87	130/1	362
	4-Br-3-Th	C_2H_5	l	77	128/0.7	362
	5-Br-2-Th	C_2H_5	j	53–55	141–144/3	468
	3-O_2N-2-Th	C_2H_5	l	40	45	362
	5-O_2N-2-Th	C_2H_5	e		96–98	7
	2-O_2N-3-Th	C_2H_5	e		73–74	161
C_9H_{10}	4-H_3C-2-Th	CH_3	d		123–124/3	156
	5-H_3C-2-Th	CH_3	d		55	156
	3-H_3C-2-Th	CH_3	d		113–113.5/2	156
	2-Th	C_2H_5	d	49	110–116/3.5	83
	2-Th	C_2H_5	j		115–116/1	471
	2-Th	C_2H_5	l	88	95/0.2	362
	2-Th	C_2H_5	o	52	80–86/1	498
	3-Th	C_2H_5	l	80	105/0.3	362
C_9H_{10}	3-Th	C_2H_5	e		148/14	161
	3-Th	C_2H_5	c	86	148/14	161
	3-Th	C_2H_5	j		114–115/1	471
	3-CH_3O-2-Th	CH_3	d		52	156
	4-CH_3O-2-Th	CH_3	d		73	156
	5-H_3CO-2-Th	CH_3	d		56	156
$C_{10}H_{10}$	4,5-di-Cl-2-Th	CH_3	c	23	48	154
	3-H_3CCO-2-Th	CH_3	d		82	156
	4-H_3CCO-2-Th	CH_3	d		86	156
	5-H_3CCO-2-Th	CH_3	d		147	156
	3-OHC-2-Th	C_2H_5	l	81	133	362
	5-OHC-2-Th	C_2H_5	l	76	170/1	362
	4-OHC-2-Th	C_2H_5	l	75	175/0.2	362
$C_{10}H_{11}$	5-O_2N-2-Th	$CH(CH_3)_2$	e		79–80	145
	5-O_2N-2-Th	C_3H_7	e		73–74	145

TABLE 23. (*Continued*)

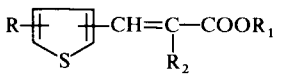
CH	Th Group	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{10}H_{12}$	5-H_3C-2-Th	C_2H_5	d	55	116–122/5	83
	3-H_3C-2-Th	C_2H_5	d	58	121–126/3	83
	3-H_3C-2-Th	C_2H_5	j	40–45	122–126/4	468
$C_{11}H_{13}$	5-O_2N-2-Th	C_4H_9	e		63–64	145
$C_{11}H_{14}$	2-Th	C_4H_5	e		182–184/18	149
	5-H_5C_2-2-Th	C_2H_5	d	57	122–128/18	83
$C_{12}H_{15}$	5-O_2N-2-Th	C_5H_{11}	e		54.5–55	145
$C_{12}H_{16}$	5-H_7C_3-2-Th	C_2H_5	d	63	135–140/2	83
$C_{13}H_9$	5-O_2N-2-Th	C_6H_5	e		137–138	145
$C_{14}H_{11}$	5-O_2N-2-Th	$C_6H_5CH_2$	e		81–83	145
$C_{14}H_{12}$	5-C_6H_5-2-Th	CH_3	e	65	137–138	157
	4-C_6H_5-2-Th	CH_3	e	63	85–87	157
$C_{14}H_{16}$	4-($H_5C_2O_2C$-CH=CH)-3-Th	C_2H_5	l	65	73	362
	3-($H_5C_2O_2C$-CH=CH)-3-Th	C_2H_5	l	46	70	362
	4-($H_5C_2O_2C$-CH=CH)-2-Th	C_2H_5	l	70	116	362
$C_{14}H_{20}$	5-$(C_2H_5O)_2CH$-2-Th	C_2H_5	l	76	170/1	362
	3-$(C_2H_5O)_2CH$-2-Th	C_2H_5	l	78	150/0.5	362
	5-$(C_2H_5O)_2CH$-2-Th	C_2H_5	l	77	185/11	362
$C_{21}H_{20}$	5-O_2N-2-Th	4-$C(CH_3)_2CH_2C(CH_3)_3$	e		137–138	145

TABLE 24. 3-Substituted 3-(Thienyl)acrylic Acids and Esters



CH	Th Group	R_1	R_2	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_8	2-Th	CH_3	H	h		112–112.5	469
	2-Th	CH_3	H	j		112–112.5	468
$C_{10}H_{12}$	2-Th	CH_3	C_2H_5	j		104–106/1	471
	2-Th	CH_3	C_2H_5	j	40	118–120/4	469
	3-Th	CH_3	C_2H_5	j	62	116–119/4	468
						99–100/1	471
$C_{11}H_{14}$	2-Th	C_2H_5	C_2H_5	j		116–117/1	471
$C_{12}H_{16}$	2-Th	C_3H_7	C_2H_5	j		117–119/1	471
$C_{13}H_{12}$	2-Th	2-Th	C_2H_5	j		140–145/0.2	473
$C_{15}H_{14}$	2-Th	C_6H_5	C_2H_5	j		135–140/0.2	473

TABLE 25. 2-Alkyl- and 2-Aryl-Substituted 3-(Thienyl)acrylic Acids and Esters



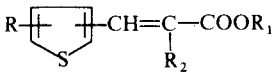
CH	Th Group	R_2	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_8	2-Th	CH_3	H	f		145.2–145.7	169
	3-Th	CH_3	H	f	52.5	131–133	169
C_9H_{10}	2-Th	CH_3	CH_3	f	58	92/67	168
$C_{10}H_{12}$	2-Th	CH_3	C_2H_5	j		112–113/2	468
						109–110/0.5	471
	3-Th	CH_3	C_2H_5	j		112–113/1	471
$C_{11}H_6$	5-Cl-2-Th	5-Cl-2-Th	H	f	56	208–210	260
$C_{11}H_7$	2-Th	5-Cl-2-Th	H	f	54	194–195	260
$C_{11}H_8$	*Z*-2-Th	2-Th	H	f	41	240–241	260, 1017
	E-2-Th	2-Th	H	f	9.9	174–175.5	260, 1017
$C_{11}H_{12}$	2-Th	$CH_2CO_2CH_3$	CH_3	g		143–146/0.9	1018
$C_{11}H_{14}$	3-H_3C-2-Th	CH_3	C_2H_5	j		108–110/1	468
$C_{12}H_{10}$	*Z*-2-Th	2-Th	CH_3	f		75–78.5	260
	E-2-Th	2-Th	CH_3	f		Oil	260
	5-H_3C-2-Th	2-Th	H	f	21	232–234	1017
	2-Th	5-H_3C-2-Th	H	f	15.6	208–210	1017

$C_{13}H_8$	3-Th	2,4-di-Cl-C_6H_3	H	f	32	195–197	179
	5-O_2N-2-Th	4-O_2N-C_6H_4	H	f		245.5–245.8	175
$C_{13}H_9$	2-Th	4-Br-C_6H_4	H	f	85	238–240	179
	3-Th	4-Br-C_6H_4	H	f	31	217–218	179
	E-2-Th	4-Cl-C_6H_4	H	f		220–221	177
	Z-2-Th	4-Cl-C_6H_4	H	f		158–159	177
	2-Th	2-I-C_6H_4	H	f			179
	E-2-Th	4-O_2N-C_6H_4	H	f	95	233–234	174, 177
						231–233	
	Z-2-Th	4-O_2N-C_6H_4	H	f		183–184	177
$C_{13}H_{10}$	3-Th	C_6H_5	H	f	63	177–179	179
	E-2-Th	C_6H_5	H	f	98	185–186	638
						190–192	640
						187–187.5	169
						186–188	179
						187–189	177
	Z-2-Th	C_6H_5	H	f	0.8	135–136	169
						127–128	177
$C_{13}H_{12}$	5-CH_3-2-Th	5-CH_3-2-Th	H	f	35	214–215	1017
	2-Th	5-CH_3-2-Th	CH_3	f		94–95	1017
	5-CH_3-2-Th	2-Th	CH_3	f		73–74.5	1017
$C_{13}H_{18}$	3-CH_3-2-Th	$CH(CH_3)_2$	C_2H_5	j	55	118–120/1.5	468
$C_{14}H_8$	5-Br-2-Th	4-CF_3-C_6H_4	H	f	42	196–197	179

TABLE 25. (*Continued*)

CH	Th Group	R_2	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{14}H_9$	2-Th	4-CF_3-C_6H_4	H	f	51	248–249	179
	3-Th	4-CF_3-C_6H_4	H	f	75	237–240	179
$C_{14}H_{12}$	*E*-2-Th	4-CH_3-C_6H_4	H	f		208–209	179
	Z-2-Th	4-CH_3-C_6H_4	H	f		153–154	179
	E-2-Th	C_6H_5	CH_3	f	90	78–80	179
$C_{14}H_{14}$	5-CH_3-2-Th	5-CH_3-2-Th	CH_3	f		74–76	1017
$C_{14}H_{22}$	*E*-2-Th	4-CH_3O-C_6H_4	H	f	88	200–202	179
						199	638
	Z-2-Th	4-CH_3O-C_6H_4	H	f	22	128–130	638
$C_{21}H_{16}$	*E*-5-C_6H_5CH=*cis*-CH-2-Th	C_6H_5	H	f	37	196–198	638
$C_{22}H_{18}$	*E*-5-(4-$CH_3OC_6H_4$)CH=*cis*-CH-2-Th	C_6H_5	H	f	37	221–223	638
	E-5-C_6H_5-CH=*cis*-CH-2-Th	4-CH_3O-C_6H_4	H	f	38	202–203	638
$C_{23}H_{20}$	*E*-5-(4-$CH_3OC_6H_4$)CH=*cis*-CH-2-Th	4-CH_3O-C_6H_4	H	f	40	242–245	638

TABLE 26. Various 2-Substituted 3-(Thienyl)acrylic Acids and Esters

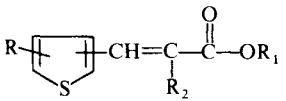


CH	Th Group	R_1	R_2	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_8	2-Th	H	CH_3	o	97	112	513
C_9H_7	2-Th	CH_3	—N=C	v	95	77–78	194
C_9H_8	5-Br-2-Th	C_2H_5	N_3	v	25	Oil	186
	5-Br-3-Th	C_2H_5	N_3	v	18	Oil	186
	3-N_3-2-Th	C_2H_5	N_3	v	63	67–68	166
C_9H_9	2-Th	CH_3	NHCHO	v	39	135–137	194
	2-Th	C_2H_5	NO_2	v	88	154/1.5, 79–81	193
	2-Th	C_2H_5	N_3	v	55	42	186
					48	42.5	182
	3-Th	C_2H_5	N_3	v	50	33	186
					65	32	182
$C_{10}H_9$	2-OHC-3-Th	C_2H_5	N_3	v	81	128–129	187
	5-OHC-3-Th	C_2H_5	N_3	v	1.3	84	184
	4-OHC-2-Th	C_2H_5	N_3	v	6.6	60	184
	5-OHC-2-Th	C_2H_5	N_3	v		138	184
	3-OHC-2-Th	C_2H_5	N_3	v	75	136	187
	4-OHC-3-Th	C_2H_5	N_3	v	13	121	184

TABLE 26. (*Continued*)

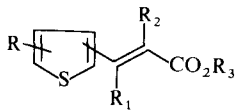
CH	Th Group	R_1	R_2	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{10}H_{11}$	3-H_3C-2-Th	C_2H_5	N_3	v			183–185
	3-N_3-2-Th	C_2H_5	SCH_3	v	80		182, 189
	3-NO_2-Th	C_2H_5	OCH_3	o	24	74.5–75.5	597
$C_{13}H_9$	2-Th	H	—S-C_6H_4-NO_2-2	v	38	232–235	190
$C_{13}H_{17}$	2-Th	CH_3	N═CHN$(CH_2)_4 \cdot$ HCl	v	53	170–172	194
$C_{13}H_{19}$	2-Th	C_2H_5	—$OP(OC_2H_5)_2$	v	94	163–164/0.3	192
$C_{14}H_{14}$	5-($C_2H_5OCC(N_3)$═CH)-2-Th	C_2H_5	N_3	v	41	134	184
	4-($C_2H_5O_2CC(N_3)$═CH)-2-Th	C_2H_5	N_3	v	28	110	184
	4-($C_2H_5O_2CC(N_3)$═CH)-3-Th	C_2H_5	N_3	v	15	140	184
	3-($C_2H_5O_2CC(N_3)$═CH)-2-Th	C_2H_5	N_3	v	14	130	187
$C_{15}H_{13}$	3-N_3-2-Th	C_2H_5	SC_6H_5	v	85	106–108	189
	3-N_3-2-Th	C_2H_5	SOC_6H_5	v	48	125–126	189
	3-N_3-2-Th	C_2H_5	$SO_2C_6H_5$	v	80	128–130	189

TABLE 27. 2-Acyl- and 2-Cyanoacrylic Acids and Esters



CH	Th Groups	R_2	R_1	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
C_8H_5	2-Th	CN	H	v	76	232–234.5	169
C_9H_7	2-Th	CN	CH_3	v	96	111–112	195
$C_{10}H_7$	4,5-di-Cl-2-Th	CN	C_2H_5	v	80	171	155
$C_{10}H_9$	2-Th	CN	C_2H_5	v	93	93–94	1019
$C_{11}H_{11}$	3-N_3-2-Th	$COCH_3$	C_2H_5	v	85	63–64	188
$C_{11}H_{12}$	2-Th	$COCH_3$	C_2H_5	v	92	78–79	193
$C_{12}H_{13}$	2-Th	CN	$C(CH_3)_3$	v	98	119	199, 109
$C_{13}H_{16}$	2-Th	$COCH_3$	$C(CH_3)_3$	v	68	84–85	203
$C_{14}H_{17}$	3-$(CH_3)_3CO$-2-Th	CN	C_2H_5	v			1020
$C_{15}H_{11}$	5-C_6H_5S-2-Th	CN	CH_3	v	88	89–90	197
	5-$C_6H_5SO_2$-2-Th	CN	CH_3	v	88	173–174	197
$C_{16}H_{12}$	4,5-di-Cl-2-Th	COC_6H_5	C_2H_5	v	48	131	155

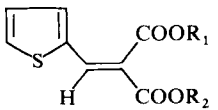
TABLE 28. 2,3-Disubstituted 3-(Thienyl)acrylic Acids and Esters



CH	Th Group	R_1	R_2	R_3	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{10}H_{10}$	5-H_3C-2-Th	H	CH_2COOH	H	y	87	200	248
	2-Th	CH_3	CH_2COOH	H	y		155	250
	2-Th	CH_3	$CH_2CO_2CH_3$	H	y		85	250
	2-Th	H	$CH(CH_3)COOH$	H	y		168	251
	2-Th	H	CH_2CH_2COOH	H	y	85	204–205	254
	5-H_3C-2-Th	H	CH_2CH_2COOH	H	y	80	226	254
$C_{11}H_{12}$	2-Th	H	$CH(CH_3)CO_2CH_3$	H	y		142	251
	5-H_3C-2-Th	H	$CH(CH_3)COOH$	H	y		185	251
	2-Th	CH_3	$CH(CH_3)COOH$	H	y		105	251
	2-Th	H	CH_2CH_2COOH	H	y	62	106–107	254
	5-H_3C-2-Th	H	CH_2COOH	CH_3	y	71	106	248
	5-H_3C-2-Th	H	$CH_2CO_2CH_3$	H	y		135	248
	2-Th	CH_3	CH_2COOH	CH_3	y	82		250
	2-Th	H	$CH(CH_3)COOH$	CH_3	y		134	251
$C_{11}H_{14}$	2-Th	CH_3	CH_3	C_2H_5	j		110–112/3	471
	2-Th	CH_3	CH_3	C_2H_5	j		104–105/2	468
	2-Th	CH_3	$CH(CH_3)_2$	C_2H_5	j		53–53.5	469
	3-Th	CH_3	CH_3	C_2H_5	j		103–105/1.5	471
$C_{12}H_{14}$	5-H_3C-2-Th	H	$CH(CH_3)COOH$	CH_3	y		101	251
	2-Th	CH_3	$CH(CH_3)COOH$	CH_3	y		40	251
	5-H_3C-2-Th	H	$CH(CH_3)CO_2CH_3$	H	y		171	251
	2-Th	CH_3	$CH(CH_3)CO_2CH_3$	H	y		84	251
	5-H_3C-2-Th	H	CH_2CH_2COOH	H	y	58	110	254

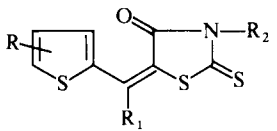
$C_{12}H_{16}$	2-Th	C_2H_5	CH_3	C_2H_5	j		111–112/1	471
$C_{13}H_{16}$	2-Th	CH_3	$CO_2C_2H_5$	C_2H_5	j	10–12	155/1.5	468
$C_{13}H_{18}$	2-Th	CH_3	$CH(CH_3)_2$	C_2H_5	j	16–20	156–160/1.5	468
	2-Th	CH_3	$CH(CH_3)_2$	C_2H_5	j	43	115–118/3	469
	2-Th	C_3H_7	CH_3	C_2H_5	j		114–115/1	471
$C_{15}H_{11}$	2-Th	4-Cl-C_6H_4	CH_2COOH	H	y		168–169	249
	2-Th	4-Cl-C_6H_4	CH_2COOH	H	y		135–137	249
$C_{15}H_{12}$	2-Th	C_6H_5	CH_2COOH	H	y		148	250
	2-Th	H	$CH(C_6H_5)COOH$	H	y		185	1021
$C_{16}H_{13}$	2-Th	4-Cl-C_6H_4	CH_2COOH	CH_3	y		115–117	249
	5-I-2-Th	4-H_3C-C_6H_4	CH_2COOH	CH_3	y	20	90	212
	2-Th	C_6H_5	CN	C_2H_5	u	53	77–78	201
$C_{16}H_{14}$	2-Th	C_6H_5	$CH_2CO_2CH_3$	H	y		124	250
	2-Th	4-H_3C-C_6H_4	CH_2COOH	H	y	77	154–156	213
	2-Th	C_6H_5	$CH(CH_3)COOH$	H	y		189	251
	2-Th	H	$CH(C_6H_5)COOH$	CH_3	y	55	194	1021
	2-Th	H	$CH(C_6H_5)COOH$	CH_3	y	45		1021
	2-Th	C_6H_5	CH_2COOH	CH_3	y		118	250
	5-H_3C-2-Th	H	$CH(C_6H_5)COOH$	H	y		188	1021
	2-Th	H	$CH(C_6H_5)COOH$	H	y		120	1021
	2-Th	CH_3	2-HOOC-C_6H_4	H	y	10	115	255
	2-Th	CH_3	2-HOOC-C_6H_4	H	y	72	145	255
	2-Th	4-CH_3O-C_6H_4	CH_2COOH	H	y		115–116	252
$C_{17}H_{16}$	2-Th	C_6H_5	$CH(CH_3)COOH$	CH_3	y		122	251
	2-Th	C_6H_5	$CH(CH_3)CO_2CH_3$	H	y		104	251
	5-H_3C-2-Th	H	$CH(C_6H_5)COOH$	CH_3	y	47	189	1021
	2-Th	4-H_3CO-C_6H_4	CH_2COOH	H	y		180–182	252
$C_{21}H_{16}$	2-Th	C_6H_5	2-HOOC-C_6H_4	CH_3	y	77	168	155
	2-Th	C_6H_5	2-HOOC-C_6H_4	CH_3	y	13	130	255
	2-Th	C_6H_5	$CH(C_6H_5)COOH$	H	y		209	1021
$C_{22}H_{18}$	2-Th	C_6H_5	$CH(C_6H_5)CO_2CH_3$	H	y		69	1021
	2-Th	C_6H_5	$CH(C_6H_5)COOH$	CH_3	y	77	210	1021

TABLE 29. Syntheses of Thenalmalonic Acid and Esters through Knoevenagel Condensations



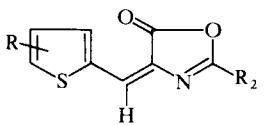
CH	Th Group	R_1	R_2	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_4	4,5-di-Cl-2-Th	H	H	65	218	154
C_8H_5	5-Br-2-Th	H	H	65	196–198	171
	5-O_2N-2-Th	H	H	72	230–232	171
C_8H_6	2-Th	H	H	63	221–222	171
C_9H_{11}	5-H_3C-2-Th	H	NH_4		182	172
$C_{10}H_8$	4,5-di-Cl-2-Th	CH_3	CH_3	34	102	155
$C_{10}H_{10}$	5-H_5C_2-2-Th	H	H		136–137	172
$C_{12}H_{13}$	3-N_3-2-Th	C_2H_5	C_2H_5	96	39–41	166
$C_{12}H_{14}$	2-Th	C_2H_5	C_2H_5	86, 84	153/0.7, 150–152/1	163, 165
$C_{12}H_{16}$	3-H_3C-2-Th	C_2H_5	C_2H_5			1022
$C_{14}H_{10}$	2-Th	H	NHC_6H_4-I-*p*		224	1023
$C_{17}H_{24}$	5-$(CH_3)_2$CH-2-Th	C_2H_5	C_2H_5	74	203–204/3	86
$C_{20}H_{19}$	5-[(4-$O_2NC_6H_5$)CH=CH]-2-Th	C_2H_5	C_2H_5	80	135	152
$C_{20}H_{24}$	5-[$(C_2H_5O_2C)_2$C=CH]-2-Th	C_2H_5	C_2H_5		68–69	164

TABLE 30. Thenalrhodanines from Thiophene Aldehydes and Cyclic Active Methylene Derivatives



CH	Th Group	R_1	R_2	Yield (%)	m.p. (°C)	Ref.
C_8H_4	5-Br-2-Th	H	H	92	245.5–246.5	99
	5-Cl-2-Th	H	H	92	237–237.5	99
					229–230	109
C_8H_5	2-Th	H	H	95	231–232	99
					227–232	109
	3-Th	H	H	93	213–214	106
C_9H_6	5-Br-2-Th	CH_3	H	30	214–215	109
C_9H_7	2-Th	H	CH_3	81	170–175	110
	3-H_3C-2-Th	H	H	94	226–227.5	99
	5-H_3C-2-Th	H	H	94	221.5–222.5	99
	2-Th	CH_3	H	30	218–221.5	109
$C_{10}H_9$	3,4-di-H_3C-2-Th	H	H	85	263–264	101
	5-H_5C_2-2-Th	H	H	94	166–167	99
$C_{11}H_9$	2-Th	H	$CH_2CH{=}CH_2$	86	148–149	110
$C_{11}H_{11}$	5-H_7C_3-2-Th	H	H	90	134–135.5	99
	3,4,5-tri-H_3C-2-Th	H	H	68	275–276	101
$C_{12}H_{15}$	5-$(CH_3)_3C$-2-Th	CH_3	H	30	192–193	109
$C_{14}H_9$	2-Th	H	C_6H_5	67	198–200	110

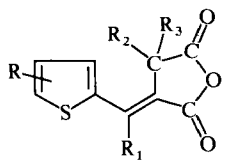
TABLE 31. Thenal Azlactones from Thiophene Aldehydes and Cyclic Active Methylene Derivatives

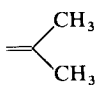
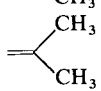


CH	Th Group	R_2	Yield (%)	m.p. (°C)	Ref.
C_9H_6	2-NO_2-3-Th	CH_3	56	196–198	104
	3-NO_2-2-Th	CH_3	65	185–186	104
C_9H_7	2-Th	CH_3	40	134	105
$C_{14}H_7$	2-Th	3,5-Cl-O_2N-C_6H_3	35	251	105
$C_{14}H_8$	5-Br-2-Th	C_6H_5	64	186–187	99
	2-Th	4-Cl-C_6H_4	42	182	105
	2-Th	2-Cl-C_6H_4	35	153	105
	5-Cl-2-Th	C_6H_5	61	182.5–183.5	99
	2-Th	4-O_2N-C_6H_4	66	217	105
	2-Th	3-O_2N-C_6H_4	60	175	105
	2-Th	2-O_2N-C_6H_4	14	172	105
$C_{14}H_9$	2-Th	C_6H_5	68, 72	174–175	99, 102, 103

$C_{15}H_7$	4,5-di-Cl-2-Th	C_6H_5	59	228–229	44
$C_{15}H_9$	2-Th	3,4-OCH_2O-C_6H_3	54	238	105
$C_{15}H_{11}$	5-H_3C-2-Th	C_6H_5	58	152–153	99
	3-H_3C-2-Th	C_6H_5	60	151–152	99
	2-Th	4-CH_3O-C_6H_4	43	200	105
$C_{16}H_{11}$	2-Th	$C_6H_5CH{=}CH$	40	154	105
$C_{16}H_{12}$	5-CH_3CONH-2-Th	C_6H_5	66	273–276	103
$C_{16}H_{13}$	5-H_5C_2-2-Th	C_6H_5	60, 73	107.5–109, 110.2–110.8	99, 102, 103
	3,4-di-H_3C-2-Th	C_6H_5	54	195–196	101
	4,5-di-H_3C-2-Th	C_6H_5	75	205–206	101
	2,5-di-H_3C-3-Th	C_6H_5	79	142.5–143.5	101
$C_{17}H_{15}$	5-H_7C_3-2-Th	C_6H_5	60	97–98.5	99
	3,4,5-tri-H_3C-2-Th	C_6H_5	61	193.5–194.5	101
	2,4,5-tri-H_3C-2-Th	C_6H_5	18	101–102.5	101
$C_{18}H_{17}$	5-$(CH_3)_2CHCH_2$-2-Th	C_6H_5	68	135.5–136	102, 103
$C_{20}H_{19}$	5-$C_2H_5O_2C(CH_2)_3$-2-Th	C_6H_5	57	86–87	103

TABLE 32. 2-(Thenal)succinic Anhydrides from Stobbe Condensations



CH	Th Group	R_1	R_2	R_3	Yield (%)	m.p. (°C)	Ref.
$C_{10}H_8$	2-Th	CH_3	H	H		132	250
	2-Th	H	CH_3	H		123	251
$C_{11}H_{10}$	5-H_3C-2-Th	H	CH_3	H		72	251
	2-Th	CH_3	CH_3	H		62	251
$C_{12}H_{10}$	3-Th	H			54	121	256
	2-Th	H			72	83–84	256

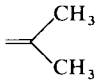
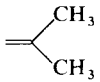
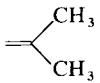
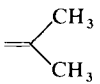
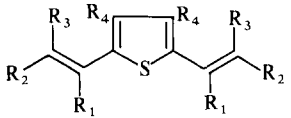
$C_{13}H_{12}$	2-Th	CH_3					86	256
	3-Th	CH_3				10	93	256
$C_{14}H_{14}$	2,5-di-H_3C-3-Th	H					116	256
$C_{15}H_{10}$	2-Th	C_6H_5	H		H		135	250
	2-Th	H	C_6H_5		H		152	253
$C_{15}H_{16}$	2,5-di-H_3C-2-Th	H				90	155–156	256
$C_{16}H_{12}$	2-Th	C_6H_5	CH_3		H		137	251
	5-H_3C-2-Th	H	C_6H_5		H		167	253
$C_{21}H_{14}$	2-Th	C_6H_5	C_6H_5		H		156	253

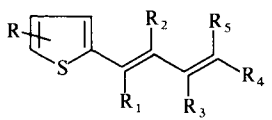
TABLE 33. Symmetric 2,5-Divinylthiophenes



CH	R_1	R_2	R_3	R_4	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_2	F	Cl	Cl	H	o	64	85–86	535
	F	F	Cl	H	o	76	140/30	532
	H	H	H	H	l	30	45/17	369
$C_{12}H_4$	H	CN	CN	H	u		265–266	164
$C_{12}H_{12}$	H	H	—CH=CH_2	H	l	1	128/0.2	369
$C_{14}H_{16}$	H	$CO_2C_2H_5$	H	H	l	7	91	362
$C_{16}H_{12}$	H	2-Th	H	H	k	30	151	315
$C_{18}H_{12}$	H	2-ThCO	H	H	t	85	209.5	43
	H	2-Sel-CO	H	H	t	50	200	43
	H	2-Fur-CO	H	H	t	80	195.5	43
$C_{18}H_{14}$	H	2-Py-CO	H	H	t	53	261	43
$C_{18}H_{16}$	H	5-H_3C-2-Th	H	H	k	64	151–153	301
$C_{18}H_{18}$	H	1-H_3C-2-Py	H	H	k	66	115	326
$C_{20}H_{12}$	H	4-Cl-C_6H_4—	H	NO_2	p		288–289	277
$C_{20}H_{14}$	H	4-Cl-C_6H_4	H	H	k	22	203	315
	H	2-Pyr-CO	H	H	t	78	192	43
	H	3-Pyr-CO	H	H	t	24	186	43
	H	C_6H_5	H	NO_2	p		248–249	277
	H	4-O_2N-C_6H_4	H	H	k	35	275	315

$C_{20}H_{16}$	H	C_6H_5	H	H	l	66	196–198	355
	H	C_6H_5	H	H	r	36	192.5–194	549
	H	C_6H_5	H	H	k	30	197	315
$C_{20}H_{30}$		—$CH_2CH(CH_3)N(CH_3)CH_2$—	CH_3	H	o	32	73–75	526
$C_{22}H_{14}$	H	4-Br-C_6H_4-CO	H	H	t	65	198	43
	H	4-Cl-C_6H_4-CO	H	H	t	59	202	43
	H	4-O_2N-C_6H_4-CO	H	H	t	49	187.5	43
$C_{22}H_{16}$	H	C_6H_5-CO	H	H	t	80	185	43
	H	4-HO-C_6H_4-CO	H	H	t	60	232.2	43
	H	2-benzimid	H	H	l	61	335	351
$C_{22}H_{18}$	H	4-CH_3O-C_6H_4—	H	NO_2	p		252–253	277
$C_{22}H_{20}$	H	4-CH_3O-C_6H_4—	H	H	k	30	243	315
$C_{22}H_{34}$		—$CH_2C(CH_3)_2NHC(CH_3)_2$—	H	H	o	67	124–125	526
$C_{22}H_{36}$		—$CH_2C(CH_3)_2NHC(CH_3)_2$—	H	CH_3, H	o	81	93–94	526
$C_{24}H_{14}$	H	—N=$C(C_6H_5)OCO$—		H	o	82	288–289	86
$C_{24}H_{20}$	H	4-H_3C-C_6H_4CO	H	H	t	85	200	43
	H	4-H_3CO-C_6H_4CO	H	H	t	69	204	43
$C_{26}H_{24}$	H	2,4-di-CH_3O-C_6H_3CO	H	H	t	39	172	43
$C_{26}H_{26}$	H	4-$(CH_3)_2N$-C_6H_4CO	H	H	t	51	191	43
$C_{28}H_{20}$	H	2-napht	H	H	k	35	247	315
$C_{32}H_{24}$	C_6H_5	C_6H_5	H	H	o	71	142	455
	H	4-C_6H_5-C_6H_4	H	H	k	40	314	315
$C_{36}H_{24}$	H	9-anthr	H	H	k	30	283	315

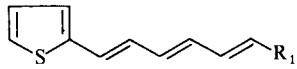
TABLE 34. 1-(Thienyl)1,3-butadienes



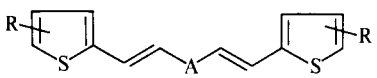
CH	Th Group	R_1	R_2	R_3	R_4	R_5	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_7	2-Th	H	H	H	H	NO_2	o	60	98	389
C_8H_8	2-Th	H	H	H	H	H	k	38	84/12	369
	2-Th	H	H	H	H	H	l	16	82/11	369
$C_{10}H_{12}$	2-Th	H	H	H	H	SC_2H_5	l	80	121–126/0.4	367
$C_{11}H_{11}$	5-O_2N-2-Th	H	H	H	H	$CO_2C_2H_5$	l	88	110–113	16
$C_{11}H_{12}$	2-Th	H	H	H	H	$CO_2C_2H_5$	l		148–149/1	470
	3-Th	H	H	H	H	$CO_2C_2H_5$	l		149–151/1	470
$C_{12}H_{10}$	2-Th	H	H	H	H	2-Th	l	73	168–169	306
	3-Th	H	H	H	H	3-Th	k	67	204	1024
	2-Th	H	H	H	H	3-Th	k	73	182	1024
$C_{12}H_{13}$	5-O_2N-2-Th	H	CH_3	H	H	$CO_2C_2H_5$	l	86	147–148	16
	5-O_2N-2-Th	H	H	H	CH_3	$CO_2C_2H_5$	l	85	122–123	16

$C_{12}H_{14}$	2-Th	CH_3	H	H	H	$CO_2C_2H_5$	j	26	147–148.5/1	470
$C_{13}H_{15}$	5-O_2N-2-Th	H	CH_3	H	CH_3	$CO_2C_2H_5$	l	80	97.5–98	16
	5-O_2N-2-Th	H	C_2H_5	H	H	$CO_2C_2H_5$	l	78	120–122	16
$C_{13}H_{16}$	2-Th	C_2H_5	H	H	H	$CO_2C_2H_5$	j	25	149–150/1	470
	3-H_3C-2-Th	CH_3	H	H	H	$CO_2C_2H_5$	j	20	164–165/1	470
$C_{14}H_{10}$	3,5-di-O_2N-2-Th	H	H	H	H	C_6H_5	p	1.2	241–242	276
$C_{14}H_{11}$	2-O_2N-3-Th	H	H	H	H	C_6H_5	k	65	151–153	289
$C_{14}H_{12}$	2-Th	H	H	H	H	C_6H_5	i	29	141.5–142	6
	2-Th	H	H	H	H	C_6H_5	k	79	151	1024
	2-Th	H	H	H	H	C_6H_5	l	38	151–152	368
	3-Th	H	H	H	H	C_6H_5	k	71	164	1024
$C_{14}H_{17}$	5-O_2N-2-Th	H	C_2H_5	H	CH_3	$CO_2C_2H_5$	l	83	78	16
$C_{14}H_{18}$	2-Th	C_3H_7	H	H	H	$CO_2C_2H_5$	j	32	162–164/1	470
$C_{15}H_{11}$	2-Th	CN	H	H	H	C_6H_5	w		107	266
	3-Th	CN	H	H	H	C_6H_5	w		115	981
$C_{15}H_{14}$	2-Th	H	H	H	H	4-CH_3O-C_6H_4	k	43	160	1024
$C_{16}H_{13}$	5-CH_3O_2C-3-O_2N-2-Th	H	H	H	H	C_6H_5	p	9	156–157	276
$C_{18}H_{16}$	2-Th	H	H	H	H	Fc	k	63	176–178	299

TABLE 35. 1-(2-Thienyl)polyenes



CH	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{10}H_{10}$	H	l	34	78–79	369
	H	l	10	66/0.2	369
	H	l	20	90/2	369
$C_{16}H_{14}$	C_6H_5	f	30	174–175	6
$C_{18}H_{16}$	$C_6H_5CH{=}CH_2$	f	19	206–207	6
$C_{20}H_{18}$	Fc	k	36	194–196	299

TABLE 36. Compounds of Type 

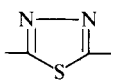
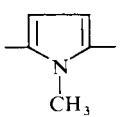
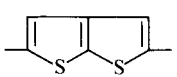
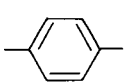
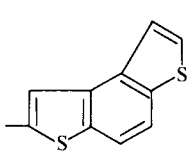
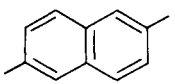
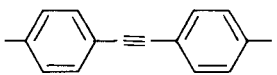
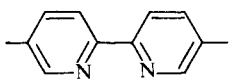
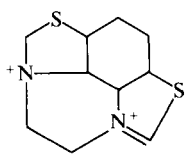
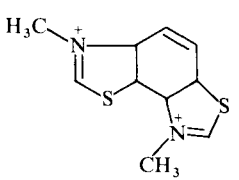
CH	Th Group	A	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{14}H_{10}$	2-Th		q	47	204–205	125
$C_{17}H_{15}$	2-Th		k	60	175	326
$C_{18}H_{12}$	2-Th		k	95	325–327	300
$C_{18}H_{14}$	2-Th		l	61	275	344
$C_{22}H_{14}$	2-Th		k	86	230	285

TABLE 36. (*Continued*)

CH	Th Group	A	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{22}H_{16}$	2-Th		q	51	299–300	120
$C_{26}H_{18}$	2-Th		q	67	316–317	120
$C_{26}H_{24}$	5-H_5C_2-2-Th		q		176–177	123
$C_{26}H_{26}$	5-$(CH_3)_2$N-2-Th		q	12	> 300	132
$C_{26}H_{28}$	5-$(CH_3)_2$N-2-Th		q	24	> 300	132

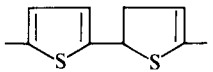
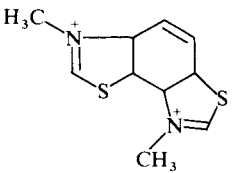
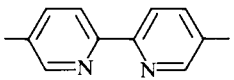
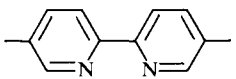
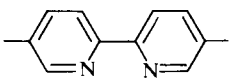
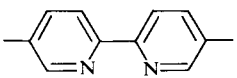
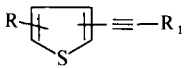
$C_{28}H_{30}$	5-H_9C_4-2-Th		k	53	165	303
$C_{28}H_{32}$	5-$(CH_3)_2N$-2-Th		q	29	> 300	132
$C_{34}H_{40}$	5-$H_{13}C_6$-2-Th		q		90–95	123
$C_{42}H_{56}$	5-$H_{21}C_{10}$-2-Th		q		102–103.5	123
$C_{46}H_{64}$	5-$H_{25}C_{12}$-2-Th		q		98	123
$C_{50}H_{72}$	5-$H_{29}C_{14}$-2-Th		q		97–100	123

TABLE 37. Thienylacetylenes



CH	Th Group	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_6H_2	2,5-di-Cl-2-Th	H	ae	45, 91	95/10	936, 938
C_6H_3	5-Cl-2-Th	H	ae	24	82/5	936
	5-I-2-Th	H	ac			961
C_6H_4	2-Th	H	ad		31–33/3.5	2
	2-Th	H	o	79	54–60/20	949
	2-Th	H	ad	68	46/15	487
	2-Th	H	ae	66, 80	31–33/3	936
	2-Th	H	ae	76		486
	2-Th	H	ac	85	53–54/25	968
	2-Th	H	r	84		969
	3-Th	H	ae		65–67/60	399
	3-Th	H	ad	56	48–50/15	487
C_7H_2	2,5-di-Cl-2-Th	COOH	ac	79	139–141	938
C_7H_3	5-Br-2-Th	COOH	ad	35–40	125–126	2
	5-Cl-2-Th	COOH	ad	40–45	118–120	2
	5-Cl-2-Th	COOH	ac	45	118–120	938
	5-I-2-Th	CHO	z		66	961
	2-Th	CF_3	ag	55	136/760	950
	5-I-2-Th	$CH(OC_2H_5)_2$	z		82–83	959
	2-Th	CN	ad	27		275
	3-Th	CN	ad	49	39.5	275
C_7H_4	2-Th	COOH	ac	72	130–133	949, 534
	2-Th	COOH	ad	30	130–131	2
	2-Th	COOH	ad	51.5	133–135	598
	2-Th	COOH	ac	85	130–133	938

C_7H_5	5-I-2-Th	CH_2OH	z		58	961
	5-I-2-Th	CH_2OH	z	52	82–83	957
C_7H_6	2-Th	CH_2OH	z	67	88–89	955
	2-Th	CH_2OH	r	90	82/0.03	967
	2-Th	CH_3	ac	30	65–66/7	941
	2-Th	CH_3	ad	72	100–122/15	385
	2-Th	CH_3	r	93	81/15	965
	5-H_3C-2-Th	H	ad	68	103–105/50	487
	5-H_3C-2-Th	H	ae	16	29–31/0.3	939
	3-H_3C-2-Th	H	ae	53	53/7	936
	3-H_3C-2-Th	H	ad	48	110/50	487
	4-H_3C-2-Th	H	ae	62	62/7	936
	2-Th	SCH_3	af	86	72–74/0.2	952
C_8H_3	2-Th	C_2F_5	ag	94	154/760	950
C_8H_6	5-CH_2-2-Th	CHO	ac	47	42	939
	5-OHC-2-Th	CH_3	z	61	78–79	955, 959
	2-Th	$CH{=}CH_2$	ac	93		967
	5-H_3C-2-Th	COOH	ac	60	115–118	938
	2-Th	CO_2CH_3	o	95	54–55	954
C_8H_7	3-Br-5-H_3C-2-Th	CH_3	r	68	120–122/8	329
C_8H_8	2-Th	SC_2H_5	af	81	72–74/0.1	953
C_9H_3	2-Th	C_3F_7	ag	92	186–187/760	950
	2-Th	$(CF_2)_3Cl$	ag	72	207–208/760	950
C_9H_6	2,5-di-Cl-3-Th	$CO_2C_2H_5$	ac	80	92–95/1	938
C_9H_7	5-Cl-2-Th	$CO_2C_2H_5$	ac	45	56–58/1	938
C_9H_8	2-Th	—CH=CH—CH_2OH	z	58		390
	2-Th	$CO_2C_2H_5$	ac	91	95–98/1	938
	2-Th	—S-$CO_2C_2H_5$	af	80	114–115/0.5	953
C_9H_{12}	2-Th	$Si(CH_3)_3$	r	98	104/15	968
	2-Th	$Sn(CH_3)_3$	ac	92	94–96/6	969

TABLE 37. (*Continued*)

CH	Th Group	R_1	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
$C_{10}H_6$	5-(2-Th)-2-Th	H	ac	65		967
	5-(2-Th)-2-Th	H	r	65		967
	2-Th	2-Th	ad		95	311
$C_{10}H_8$	2-Th	$CH{=}CHCO_2CH_3$	ac	85	70	977
$C_{10}H_{10}$	3-H_3C-2-Th	$CO_2C_2H_5$	ac	70	65–67/1	938
	5-($H_3CCH{=}CH$)-2-Th	CH_3	z		60/0.01	332
$C_{10}H_{13}$	3-Br-5-H_3C-2-Th	$Si(CH_3)_3$	r	57	135–139/10	329
$C_{11}H_3$	2-Th	$-C_3F_7OCF(CF_3)_2$	ag	69	228–229/790	950
$C_{11}H_4$	2-Th	$CH(OC_2H_5)_2$	z		103–105/0.6	959
$C_{11}H_6$	5-(2-Th)-2-Th	CHO	ac		66	311
	5-OHC-2-Th	2-Th	z	24	79	982
$C_{11}H_8$	5-C_6H_5-2-Th	H	r	60	67–68	967
$C_{11}H_{13}$	3-Br-5-H_3C-2-Th	$C(CH_3)_3$	r	72	119–121/8	329
$C_{11}H_{14}$	2-Th	$CH(OC_2H_5)_2$	r	100	103–106/6	967
$C_{12}H_8$	2-Th	CH=CH-2-Fu	z	60	60–62	955
	5-(5-OHC-2-Th)-2-Th	CH_3	r	83	145	944
	2-Th	C_6H_5	ad	94	60	311
	2-Th	C_6H_5	r	85	51–52	967
	2-Th	C_5H_5	z	75	50.0–50.5	958
	2-Th	C_6H_5	ab	44	48.5–49.5	966
	5-C_6H_5-2-Th	H	ac	60	67–68	967
	5-(2-Th)-2-Th	$CH{=}CH_2$	ab	35		966
	5-(2-Th)-2-Th	$CH{=}CH_2$	ab	10		966
	5-(2-Th)-2-Th	$CH{=}CH_2$	z	48	80–85/0.005	955
$C_{12}H_{10}$	5-(2-Th)-2-Th	CH_2CH_2OH	z	51	66–67	955
	5-(2-Th)-2-Th	CH_2CH_2OH	r	87	71–72	967

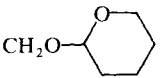
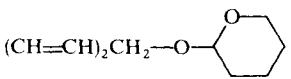
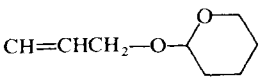
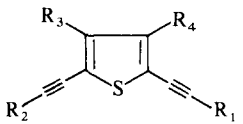
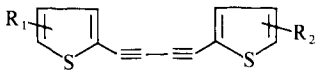
	5-(2-Th)-2-Th	CH_2CH_2OH	ac		66–67	611
	5-(2-Th)-2-Th	$CH(OH)CH_3$	ac		59	311
	5-(5′-$HOCH_2$-2-Th)-2-Th	CH_3	r	95	87–88	342
	2-Th	$(CH{=}CH)_2CH{=}CH_2$	ac	46		846
	5-(5′-$CH_2{=}CH$-2-Th)-2-Th	CH_3	r	85		342, 333
$C_{12}H_{14}$	2-Th		z		143–145/1.3	959
$C_{12}H_{16}$	5-H_3C-2-Th	$CH(OC_2H_5)_2$	z	85	98–99/0.4	955, 959
$C_{13}H_9$	3-Br-5-H_3C-2-Th	C_6H_5	r	70	140–144/0.2	329
$C_{13}H_{10}$	5-C_6H_5-2-Th	CH_3	ac	60, 72	43–44	940, 942
	5-C_6H_5-2-Th	CH_3	z	51	43–44	955, 959
	5-C_6H_5-2-Th	CH_3	r	80	44–45	965
	5-(5-CH_3-2-Th)-2-Th	$CH{=}CH_2$	z	53	61	955
$C_{13}H_{12}$	5-(5-OHC-2-Th)-2-Th	CH_2CH_2OH	r	97		342
$C_{14}H_{10}$	5-C_6H_5-2-Th	$CH{=}CH_2$	ac	89		967
	5-$CH{=}CH$-2-Th	C_6H_5	ac		105/0.01	311
	5-(2-Th)-2-Th	C_6H_5	r	77	91	967
$C_{15}H_{12}$	5-(2-$C_2H_5O_2C$-2-Th)-2-Th	$CH{=}CH_2$	z	43	110	955
	5-C_2H_5OCO-2-Th	2-Fu	z	55	150–152/1	955
$C_{16}H_{10}$	5-(2-Th)-2-Th	C_6H_5	ab	51	89–90	966
	5-(2-Th)-2-Th	C_6H_5	ab	6		966
$C_{16}H_{12}$	2-Th	Fc	z	80	106–107	958
$C_{16}H_{18}$	2-Th		ac	93		977
$C_{17}H_{20}$	5-ACH_2-OCH_2-2-Th		z	54	150/0.3	963

TABLE 38. 2,5-Thienyl Diacetylenes



CH	R_1	R_2	R_3	R_4	Method of Preparation	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	Ref.
C_8H_4	H	H	H	H	ac	92	40/0.1	970
$C_{10}H_4$	COOH	COOH	H	H	ac	72		535
$C_{10}H_6$	$CH(OCH_3)_2$	$CH(OCH_3)_2$	H	H	z	72		982
	$CH(OCH_3)_2$	CH_3	H	H	z	68	70	962
$C_{10}H_8$	CH_2OH	CH_2OH	H	H	z	58	131–131.5	956
$C_{12}H_4$	H	H	C≡CH	C≡CH	ac	91		970
$C_{13}H_8$	2-Th	CH_2OH	H	H	z		90.5	964
	2-Th	CH_2OH	H	H	r	87	93.5–95	967
$C_{14}H_8$	$Si(CH_3)_3$	$Si(CH_3)_3$	I	I	r	84	148–150	970
$C_{14}H_{20}$	$Si(CH_3)_3$	$Si(CH_3)_3$	H	H	r	98	80–81	970
$C_{15}H_{10}$	3-AcO-2-Th	CH_3	H	H	z	46	96	962
$C_{16}H_{12}$	C≡C-$Si(CH_3)_3$	$(CH_3)_3Si$	H	H	ac	59	182/2	535
$C_{18}H_{26}$	H	H	—C≡C—OH	—C≡C—OH	ac	89		970
$C_{22}H_{16}$	4-CH_3-C_6H_4	4-CH_3-C_6H_4	H	H	z	17		343
$C_{24}H_{32}$	$Si(CH_3)_3$	$Si(CH_3)_3$	—C≡C—OH	—C≡C—OH	r	86	153–155	970
$C_{24}H_{36}$	$Si(CH_3)_3$	$Si(CH_3)_3$	C≡$Si(CH_3)_3$	C≡$Si(CH_3)_3$	r			970

TABLE 39. 4-Di(thienyl)diacetylenes



CH	Th Group 1	Th Group 2	Method of Preparation	Yield (%)	m.p. (°C)	Ref.
$C_{12}H_2$	2,5-di-Cl-3-Th	2,5-di-Cl-3-Th	ah	55, 85, 78	69–70	980
$C_{12}H_6$	2-Th	2-Fu	ah	58	53–55	968
	2-Th	2-Th	ah	53, 95, 65	88–89	980
	2-Th	2-Th	ah	60		979
	2-Th	2-Th	ah	87	92.5–93	968
	2-Th	2-Th	ah	87	92–95	487
	2-Th	3-Th	ah	91	96–97	946
	3-Th	3-Th	ah	73	111.5–112.5	487
$C_{14}H_{10}$	5-H_3C-2-Th	5-H_3C-2-Th	ah	94	89–91	487
	3-H_3C-2-Th	3-H_3C-2-Th	ah	74	88–89	487
	3-H_3C-2-Th	3-H_3C-2-Th	ah	55, 85	62–63	980
$C_{16}H_8$	5-(2-Th)-2-Th	2-Th	ah	95	120–121	488
$C_{20}H_{10}$	5-(2-Th)-2-Th	5-(2-Th)-2-Th	ah	73	167	488
$C_{20}H_{24}$	5-C_4H_9-2-Th	5-C_4H_9-2-Th	ah		47–48	715
$C_{22}H_{22}$	5-$(CH_3)_3SiC{\equiv}C$-2-Th	5-$(CH_3)_3SiC{\equiv}C$-2-Th	ah	78	82.5–83.5	535

REFERENCES

1. K. E. Schulte, J. Reisch, W. Herrmann, and G. Bohn, *Arch. Pharm.*, **296**, 456 (1963).
2. H. Keskin R. E. Miller, and F. F. Nord, *J. Org. Chem.*, **16**, 199 (1951).
3. H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1171 (1963).
4. Y. Poirier and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 865 (1967).
5. C. P. Dell, E. H. Smith, and D. Warburton, *J. Chem. Soc. Perkin Trans. I*, 747 (1985).
6. R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 1380 (1951).
7. G. Carrara, R. Ettorre, F. Fava, G. Rolland, E. Testa, and A. Vecchi, *J. Am. Chem. Soc.*, **76**, 4391 (1954).
8. G. Carrara, R. Ettorre, Br. Patent 744,961.
9. G. Carrara, Br. Patent 744,187.
10. G. Carrara, U.S. Patent 2,779,686.
11. A. Vecchi and G. Melone, *J. Org. Chem.*, **22**, 1636 (1957).
12. G. Malone and A. Vecchi, U.S. Patent 2,993,834.
13. R. M. Kellogg and J. Buter, *J. Org. Chem.*, **36**, 2236 (1971).
14. L. H. Klemm and K. W. Gopinath, *J. Het. Chem.*, **2**, 225 (1965).
15. R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 1720 (1951).
16. H. Saikachi, Y. Taniguchi, and H. Ogawa, *Yakugaku Zasshi*, **82**, 1262 (1962).
17. G. Jones and M. J. Robinson, *J. Chem. Soc. Perkin Trans. I*, 505 (1977).
18. A. M. Elgendy, A. Mallouli, and Y. Lepage, *Synthesis*, 898 (1980).
19. S. B. Britten and W. L. Nobles, *J. Miss. Acad. Sci.*, **6**, 36 (1954).
20. G. Combes, M. Hebbelynck, and J. Ledrut, *Bull. Soc. Chim. Fr.*, 315 (1953).
21. V. I. Esafov, I. F. Utrobina, N. I. Kiskina, and Y. B. Tubanov, *Khim. Getserotsik. Soedin*, **3**, 295 (1972).
22. C. S. Marvel, J. M. Quinn, and J. S. Showell, *J. Org. Chem.*, **18**, 1730 (1953).
23. D. A. Kulikova, Y. D. Churkin, and L. V. Panfilova, *Khim. Farm. Zh.*, **14**, 36 (1980).
24. N. Geum, F. Ghozland, J. P. Gorrichon, and P. Maroni, *Bull. Soc. Pharm. Bordeaux*, **120**, 39 (1981).
25. Y. D. Churkin and L. V. Panfilova, *Khim. Geterotsikl. Soedin*, **8**, 1048 (1980).
26. P. Pastour and F. Papillon, Fr. Patent 1,600,050.
27. Y. Cozien, J. Lauransan, P. Saumagne, R. Guilard, and M. Elborai, *Bull. Soc. Chim. Fr., Part 1*, 327 (1980).
28. M. Winn and F. G. Bordwell, *J. Org. Chem.*, **32**, 1610 (1967).
29. M. Iwata and S. Emoto, *Bull. Chem. Soc. Jpn.*, **49**, 1369 (1976).
30. B. Unterhalt and H. J. Reinhold, *Arch. Pharm. Ber. Deut. Pharm. Ges.*, **305**, 463 (1972).
31. A. S. Nakhmanovich, V. J. Knutov, and L. G. Klochkova, *Khim. Alselilena. Tr. Vses. Conf. 3rd.*, 103 (1968).
32. S. V. Tsukerman, L. A. Kutulya, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **34**, 3597 (1964).
33. R. Pallaud, *Chim. Anal.*, **38**, 155 (1956).
34. R. Pallaud and F. Delaveau, *Bull. Soc. Chim. Fr.*, 1220 (1955).
35. R. Pallaud and F. Delaveau, *Compt. Rend.*, **237**, 1254 (1953).
36. M. Lj. Mihailoic and M. Tot, *J. Org. Chem.*, **22**, 652 (1957).
37. W. B. Scanlon, Ger. Patent 2,245,518.
38. R. Guilard, P. Fourmari, and M. Fontesse, *Bull. Soc. Chim. Fr.*, 4349 (1972).

39. P. Cagniant and Mme. P. Cagniant, *Bull. Soc. Chim. Fr.*, 713 (1952).
40. Ng. Ph. Buu-Hoi, Ng. Dat Xuong, and Th. Cong Trieu, *Bull. Soc. Chim. Fr.*, 584 (1961).
41. A. E. Lipkin and S. I. Borisov, *Chem. Het. Comp. USSR*, 691 (1968).
42. P. E. Cross and R. P. Dickinson, Br. Patent 1,342,520.
43. S. V. Tsukerman, L. N. Thiem, V. M. Nikitchenko, and V. F. Lavrushin, *Chem. Het. Comp. USSR*, 793 (1967).
44. E. Profft and H. E. Petzold, *J. Prakt. Chem.*, **16**, 26 (1962).
45. P. Fournari, R. Guilard, and M. Person, *Bull. Soc. Chim. Fr.*, 4115 (1967).
46. S. V. Tsukerman, V. M. Nikitchenko, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **32**, 2324 (1962).
47. Ng. Ph. Buu-Hoi, Ng. Dat Xuong, and M. Sy, *Bull, Soc. Chim. Fr.*, 1646 (1956).
48. T. Szell, A. Brand, and S. Ratanathanwongs, *J. Chem. Eng. Data*, **26**, 230 (1981).
49. W. S. Emerson and T. M. Patrick, Jr., *J. Org. Chem.*, **14**, 790 (1949).
50. G. A. Hanson, *Bull. Soc. Chim. Belges*, **67**, 712 (1958).
51. G. Henrio, G. Ple, and J. Morel, *Compt. Rend. Acad. Sci. Ser. C*, **278**, 125 (1974).
52. Y. A. Sharanin and L. G. Sharanina, *Chem. Het. Comp. USSR*, 1259 (1974).
53. A. Corvaisier, *Bull. Soc. Chim. Fr.*, 528 (1962).
54. R. H. Wilsey, C. H. Jarboe, Jr., and H. G. Ellert, *J. Am. Chem. Soc.*, **77**, 5102 (1955).
55. B. S. Holla and S. Y. Ambekar, *J. Indian Chem. Soc.*, **50**, 673 (1973).
56. J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **48**, 2215 (1970).
57. J.-M. Meunier and P. Fournari, *Bull. Soc. Chim. Fr.*, 3343 (1971).
58. V. F. Lavrushin, S. V. Tsukerman, and V. M. Nikitchenko, *Zh. Obshch. Khim.*, **31**, 2845 (1961).
59. A. N. Adopyan, S. G. Konkova, and A. A. Safaryan, *Zh. Org. Khim.*, **15**, 1045 (1979).
60. Yu. D. Churkin and V. I. Savin, *Chem. Het. Comp. USSR*, 273 (1968).
61. P. Pedaja and S. Gronowitz, *Chem. Scripta*, **20**, 53 (1982).
62. M. M. Elkerdawy and A. A. Elemam, *J. Chem. Soc. Pakistan*, **9**, 285 (1987).
63. S. Z. Taits, O. A. Kalinovskii, V. S. Bogdanov, and Y. L. Gol'dfarb, *Khim. Geterotsikl. Soedin*, 1467 (1970).
64. S. V. Tsukerman, V. D. Orlov, V. P. Izvekov, and V. F. Lavrushin, *Khim. Geterotsikl. Soedin*, 34 (1966).
65. D. R. Shridhar, B. Lal, N. K. Vaidya, K. K. Bhopale, and H. N. Tripathi, *Indian J. Chem. Sect. B*, **18**, 251 (1979).
66. A. M. Elkhawaga, K. M. Hassan, and A. A. Khalaf, *Z. Naturforsch. Sect. B*, **36**, 119 (1981).
67. H. H. Zoorob and E. S, Ismail, *Z. Naturforsch. Sect. B*, **31**, 1680 (1976).
68. V. M. Nikitechenko, S. Ibraqim, and V. F. Lavrushin, *Ukr. Khim. Zh.*, **39**, 368 (1973).
69. J. Boichard, J. P. Monin, and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 851 (1963).
70. J. Tirouflet and J. Besancon, *Bull. Soc. Chim. Fr.*, 2110 (1966).
71. I. A. Elsakka, A. Kandil, and M. H. Elmoghayar, *Arch. Pharm.*, **316**, 76 (1983).
72. J. Stetinova and J. Kovac, *Collect. Czech. Chem. Commun.*, **40**, 1750 (1975).
73. Y. Yamashita and M. Masumura, *Heterocycles*, **14**, 29 (1980).
74. R. Filler and H. A. Leipold, *J. Org. Chem.*, **27**, 4440 (1962).
75. N. R. Guirguis, B. M. Awad, and H. A. Saad, *Liebigs Ann. Chem.*, 1003 (1986).
76. M. Koremura, H. Oku, T. Shono, and T. Nakanishi, *Takmine Kenkyusho Nempo*, **13**, 216 (1961).
77. S. P. A. Lepetit, Br. Patent 825,241.
78. E. Bisagni, L. Montagnier, C. Viel, and J. C. Dore, Fr. Patent 2,115,089.

79. L. Montagnier, E. Bisagni, J. D. Bourzat, J. Gruest, J. P. Marquet, J. J. Pepin, and C. Rivalle, *Chim. Ther.*, **6**, 186 (1971).
80. M. Pianka, *J. Eci. Food Agr.*, **14**, 48 (1963).
81. O. Schales and H. A. Graefe, *J. Am. Chem. Soc.*, **74**, 4486 (1952).
82. D. E. Worrall, *Org. Synth. Coll.*, **1**, 413 (1941).
83. W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949).
84. M. L. Dressler and M. M. Joullié, *J. Heterocycl.*, 1257 (1970).
85. S. Gronowitz and E. Sandberg, *Arkiv Kemi*, **32**, 217 (1970).
86. V. I. Rogovik and Y. L. Gol'dfarb, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2178 (1963).
87. J. Skramstad, *Acta Chem. Scand.*, **26**, 556 (1972).
88. Y. L. Gol'dfarb, M. B. Ibragimova, and O. A. Kalinovskii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1098 (1962).
89. Y. L. Gol'dfarb, M. A. Kalik, V. K. Zavyalova, E. F. Lavretskaya, and S. A. Sukhanova, *Chem. Het. Comp. USSR*, 962 (1984).
90. W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **77**, 3529 (1955).
91. R. T. Gilsdorf and F. F. Nord, *J. Org. Chem.*, **15**, 807 (1950).
92. S. Conde, R. Madronero, M. P. Fernandez-Tomé, and J. Delrio, *J. Med. Chem.*, **21**, 978 (1978).
93. D. N. Robertson, *J. Org. Chem.*, **25**, 47 (1960).
94. D. N. Robertson, U.S. Patent 2,899,429.
95. A. Arcoria, E. Maccarone, and G. A. Tomaselli, *J. Heterocycl. Chem.*, **10**, 191 (1973).
96. L. V. Dulenko, G. N. Dorofeenko, S. N. Baranov, I. G. Katts, and V. L. Dulenko, *Chem. Het. Comp. USSR*, 294 (1971).
97. J. Skramstad, *Acta Chem. Scand.*, **25**, 1287 (1971).
98. M. E. Borai and M. Fahmy, *Heterocycles*, **26**, 385 (1987).
99. B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 81 (1950).
100. B. F. Crowe and F. F. Nord, *Nature*, **163**, 876 (1949).
101. B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 1177 (1950).
102. B. P. Fabrichnyi, E. A. Krasnovskaya, and Y. L. Gol'dfarb, *Dokl. Akad. Nauk SSSR*, **143**, 1370 (1968).
103. B. P. Fabrichnyi, E. A. Krasnyanskaya, I. F. Shalavina, and Y. L. Gol'dfarb, *Zh. Obshch. Khim.*, **33**, 2697 (1963).
104. H. R. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, *J. Am. Chem. Soc.*, **79**, 2556 (1957).
105. O. P. Singhal and P. I. Ittyeran, *J. Indian Chem. Soc.*, **42**, 579 (1965).
106. E. E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32 (1956).
107. G. E. H. Elgemeie, B. Y. Riad, G. A. Nawwar, and S. Elgamal, *Arch. Pharm.*, **320**, 223 (1987).
108. J. Tirouflet and A. Corvaisier, *Compt. Rend. Acad. Sci., Ser. C*, **250**, 1276 (1960).
109. C. Brown, Ch. K. Bradsher, S. M. Bond, and R. J. Grantham, *Ind. Eng. Chem.*, **46**, 1508 (1954).
110. F. C. Brown, Ch. K. Bradsher, S. M. Bond, and M. Potter, *J. Am. Chem. Soc.*, **73**, 2357 (1951).
111. R. S. McDowell, *Spectrochim. Acta, Part A*, **30A**, 1271 (1974).
112. J. A. de Groot, H. Jansen, R. Fokkens, and J. Lugtenburg, *Rec. Trav. Chim.—J. Roy. Neth. Chem.*, **102**, 114 (1983).
113. D. Eichinger and H. Falk, *Monatsh. Chem.*, **118**, 91 (1987).
114. G. J. Baxter, R. F. C. Brown, and G. L. McMullen, *Aust. J. Chem.*, **27**, 2605 (1974).
115. O. I. Gorbyleva, T. Y. Filipenko, E. E. Mikhlina, K. F. Turchin, Y. N. Sheinker, and L. N. Yakhontov, *Chem. Het. Comp. USSR*, 948 (1982).
116. H. G. Morren, G. Dony, and S. Levis, *J. Pharm. Belg.*, **7**, 65 (1952).

117. M. Vaysse and P. Pastour, *Compt. Rend.*, **259**, 2865 (1964).
118. Ng. Ph. Buu-Hoi, Ng. Hoan, and D. Lavit, *J. Chem. Soc.*, 2130 (1950).
119. K. Soda, K. Noda, M. Aida, and A. Hayashi, Jpn. Patent 73 28.909.
120. A. E. Siegrist, P. Liechti, H. R. Meyer, and K. Weber, *Helv. Chim. Acta*, **52**, 2521 (1969).
121. A. E. Siegrist, P. Liechti, H. R. Meyer, and K. Weber, S. Afr. Patent 68 04.421.
122. F. J. Villani, E. A. Wefer, T. A. Mann, J. Mayer, L. Peer, and A. S. Levy, *J. Heterocycl. Chem.*, **9**, 1203 (1972).
123. O. Johansen, C. Kowala, A. W. H. Mau, and W. H. F. Sasse, *Aust. J. Chem.*, **32**, 1453 (1979).
124. R. Pech and R. Bohm, *Pharmazie*, **42**, 131 (1987).
125. G. Kossmehl, I. Dornacher, and G. Manecke, *Makromol. Chem.*, **175**, 1359 (1974).
126. D. W. Henry, V. H. Brown, M. Cory, J. G. Johansson, and E. Bueding, *J. Med. Chem.*, **16**, 1287 (1973).
127. C. F. Boehringer & Soehne, GmbH, Fr. Patent 1,377,687.
128. J. K. Chakrabarti and A. Todd, *Eur. J. Med. Chem.—Chim. Ther.*, **9**, 146 (1974).
129. C. T. Bahner, H. Kinder, and L. Gulman, *J. Med. Chem.*, **8**, 397 (1965).
130. C. Paparao, K. V. Rao, and V. Sundaramurthy, *Synthesis*, 234 (1981).
131. F. A. Mikhailenko, L. I. Shevchuk, and I. T. Rozhdestvenskaya, *Khim. Geterotsikl. Soedin*, 316 (1975).
132. F. A. Mikhailenko, L. I. Shevchuk, and A. A. Shulezhko, *Zh. Org. Khim.*, **8**, 2014 (1972).
133. Ng. Ph. Buu-Hoi, R. Huls, and Ng. D. Xuong, *J. Org. Chem.*, **20**, 1407 (1955).
134. Pfizer Corp., Fr. Patent 1,501,756.
135. J. W. McFarland, L. H. Conover, H. Howers, W. C. Austin, R. L. Cornwell, and J. Danilewicz, *J. Med. Chem.*, **12**, 1066 (1969).
136. R. V. Kasubick and J. W. McFarland, S. Afr. Patent 68 00.516.
137. W. C. Austin, L. H. Conover, and J. W. McFarland, Br. Patent 1,120,587.
138. J. W. McFarland, S. Afr. Patent 68 01.182.
139. L. H. Conover, J. W. McFarland, and W. C. Austin, S. Afr. Patent 67 06.178.
140. P. M. Lelean and J. A. Morris, *Chem. Commun.*, 239 (1968).
141. J. W. McFarland, H. L. Howes Jr., L. H. Conover, J. E. Lynch, W. C. Austin, and D. H. Morgan, *J. Med. Chem.*, **13**, 113 (1970).
142. Pfizer Corp., Neth. Patent 6,610,204.
143. K. E. Schulte, J. Reisch, and L. Hoerner, *Berichte*, **95**, 1943 (1962).
144. F. Eloy and A. Deryckere, *Bull. Soc. Chim. Belges*, **79**, 301 (1970).
145. R. Kimura, T. Yabuuchi, and M. Hisaki, *Chem. Pharm. Bull. (Tokyo)*, **10**, 1232 (1962).
146. W. Freund, *J. Chem. Soc.*, 2889 (1953).
147. W. Freund, *J. Chem. Soc.*, 3073 (1952).
148. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 226 (1974).
149. D. P. M. Bocher and A. Raffali, Fr. Patent 1,386,166.
150. B. Maziere, M. Maziere, J. C. Bavay, and Ng. Dat-Xuong, *Chim. Ther.*, **4**, 265 (1969).
151. Centre National de la Recherche Scientifique, Fr. Patent 1,458,540.
152. A. S. Yoshimura, S. Takahashi, A. Kawamata, K. Kikugawa, H. Suehiro, and A. Aoki, *Chem. Pharm. Bull. (Tokyo)*, **26**, 685 (1978).
153. C. Sone and Y. Matsuki, *Nippon Kagaku Zasshi*, **83**, 496 (1962).
154. E. Profft and H. Mitternacht, *J. Prakt. Chem.*, **16**, 13 (1962).
155. E. Profft and D. Gerber, *J. Prakt. Chem.*, **16**, 8 (1962).
156. H. Satonaka, *Bull. Chem. Soc. Jpn.*, **57**, 473 (1984).

157. A. L. Johnson, *J. Org. Chem.*, **41**, 1320 (1976).
158. L. M. Kutsyna, R. P. Sidorova, L. V. Voevoda, I. K. Ishchenko, and N. P. Demchenko, *Izv. Akad. Nauk SSSR, Ser. Fiz.*, **26**, 1304 (1962).
159. W. B. Wright, *J. Heterocycl. Chem.*, **9**, 879 (1972).
160. E. Campaigne, L. Fedor, and R. E. Johnson, *J. Heterocycl. Chem.*, **1**, 242 (1964).
161. W. J. Raich and C. S. Hamilton, *J. Am. Chem. Soc.*, **79**, 3800 (1957).
162. S. Gronowitz and I. Ander, *Chem. Scripta*, **15**, 145 (1980).
163. D. Muller, J. F. Muller, and D. Cagniant, *J. Chem. Res.*, 3673 (1977).
164. C. Sone, *Bull. Chem. Soc. Jpn.*, **37**, 1197 (1964).
165. K. Petterson, *Arkiv Kemi*, **7**, 39 (1954).
166. C. J. Moody, C. W. Rees, and S. C. Tsoi, *J. Chem. Soc. Perkin Trans. I*, 915 (1984).
167. C.-K. Sha, C.-P. Tsou, and S.-L. Wang, *J. Chem. Soc., Chem. Commun.*, 320 (1988).
168. V. Zvak, J. Kovac, M. Dandarova, T. Gracza, and M. Kriz, *Coll. Czech. Chem. Commun.*, **49**, 1764 (1984).
169. F. Freeman and L. Y. Chang, *J. Am. Chem. Soc.*, **108**, 4504 (1986).
170. M. Farnier, S. Soth, and P. Fournari, *Can. J. Chem.*, **54**, 1066 (1986).
171. Y. Taniguchi and H. Kato, *Chem. Pharm. Bull. (Tokyo)*, **21**, 2070 (1973).
172. Y. L. Gol'dfarb, G. P. Fabrichnyi, and I. F. Shalavina, *Zh. Obshch. Khim.*, **28**, 213 (1958).
173. V. P. Mamaev and T. D. Rubina, *Zh. Obshch. Khim.*, **27**, 464 (1957).
174. H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **87**, 1364 (1967).
175. H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **88**, 1054 (1968).
176. A. G. Makhsumov, T. Y. Nasriddinov, and A. M. Sladkov, *Zh. Org. Khim.*, **7**, 1764 (1971).
177. S. Fisichella, G. Scarlata, and D. Sciotto, *Ann. Chim. Rome*, **63**, 55 (1973).
178. H. C. Caldwell and W. G. Groves, U.S. Patent 3,503,952.
179. B. P. Das, R. T. Cunningham, and D. W. Boykin, *J. Med. Chem.*, **16**, 1361 (1973).
180. E. Maccarone, A. Mamo, G. Perrini, and M. Torre, *J. Heterocycl. Chem.*, **18**, 395 (1981).
181. P. S. Bailey and H. H. Hwang, *J. Org. Chem.*, **50**, 1778 (1985).
182. H. Hemetsberger and D. Knittel, *Monatsh. Chem.*, **103**, 194 (1972).
183. M. Farnier, S. Soth, and P. Fournari, *Compt. Rend. Acad. Sci., Ser. C*, **277**, 2249 (1973).
184. M. Farnier, S. Soth, and P. Fournari, *Can. J. Chem.*, **54**, 1074 (1976).
185. S. Soth, M. Farnier, and P. Fournari, *Bull. Soc. Chim. Fr.*, **2**, 2511 (1975).
186. J. Eras, C. Galvez, and F. Garcia, *J. Heterocycl. Chem.*, **21**, 215 (1984).
187. M. Farnier, S. Soth, and P. Fournari, *J. Can. Chem.*, **54**, 1066 (1976).
188. R. S. Gairns, C. J. Moody, and C. W. Rees, *J. Chem. Soc. Perkin Trans. I*, 501 (1986).
189. C. J. Moody, C. W. Rees, S. C. Tsoi, and D. J. Williams, *J. Chem. Soc. Chem. Commun.*, 927 (1981).
190. V. Baliah and T. Rangarajan, *J. Chem. Soc.*, 4703 (1960).
191. M. Lacova and F. Volna, *Acta Fac. Rerum Natur. Univ. Comenianae, Chim.*, 1 (1972).
192. W. Lehnert, *Tetrahedron*, **30**, 301 (1974).
193. W. Lehnert, *Tetrahedron*, **28**, 663 (1972).
194. M. Suzuki, K. Nunami, T. Moriya, K. Matsumoto, and N. Yoneda, *J. Org. Chem.*, **43**, 4933 (1978).
195. H. Vasuda and H. Midorikawa, *J. Org. Chem.*, **36**, 2196 (1971).
196. G. Henrie, G. Ple, and J. Morel, *Compt. Rend. Acad. Sci., Ser. C*, **278**, 125 (1974).
197. R. Kada, V. Knoppova, J. Kovac, and M. Balag, *Coll. Czech. Chem. Commun.*, **45**, 2360 (1980).

198. J. W. Brooks and S. J. Lukasiewicz, U.S. Patent 2,480,832.
199. S. O. Lawesson, E. H. Larsen, and H. J. Jakobsen, *Arkiv Kemi*, **23**, 453 (1965).
200. B. Raecke, B. Blaser, W. Stein, H. Schirp, and H. Schutt, U.S. Patent 2,900,386.
201. E. J. Cragoe, Jr., Ch. M. Robb, and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950).
202. Wm. O. Ney, Jr., U.S. Patent 2,612,519.
203. S. O. Lawesson, E. H. Larsen, G. Sundstrom, and H. J. Jakobson, *Acta Chem. Scand.*, **17**, 2216 (1963).
204. A. H. Schlesinger and D. T. Mowry, U.S. Patent 2,683,659.
205. W. S. Emerson and T. M. Patrick, Jr., U.S. Patent 2,572,709.
206. T. M. Patrick, Jr., and W. S. Emerson, U.S. Patent 2,692,883.
207. H. G. Sturz and C. R. Noller, *J. Am. Chem. Soc.*, **71**, 2949 (1949).
208. A. G. A. Elagamey, F. M. A.-A. El-Taweal, and F. A. K. Amer, *J. Prakt. Chem.*, **329**, 469 (1987).
209. A. G. A. Elagamey, M. A. Sofan, Z. E. Kandeel, and M. H. Elnagdi, *Coll. Czech. Chem. Commun.*, **52**, 1561 (1987).
210. S. W. Schneller and D. R. Moore, *J. Org. Chem.*, **40**, 1840 (1975).
211. P. Stanetty, H. Fröhlich, and F. Sauter, *Arch. Pharm.*, **317**, 168 (1984).
212. H. H. Moussa and B. Haggag, *Indian J. Chem. Sect. B*, **19**, 156 (1980).
213. H. H. Moussa and S. Abdelmeguid, *J. Heterocycl. Chem.*, **18**, 1519 (1981).
214. V. G. K. Das, L. K. Mun, C. Wei, and T. C. W. Mak, *Organometallics*, **6**, 10 (1987).
215. K. Kobayashi and C. L. Gajurel, *J. Chem. Soc. Chem. Commun.*, 1779 (1986).
216. J. Benko, *Acta Chim. Acad. Sci. Hung.*, **34**, 217 (1962).
217. Chas. Pfizer & Co. Inc., Br. Patent 1,070,116.
218. E. R. Lavagnino and E. R. Shepard, *J. Org. Chem.*, **22**, 457 (1957).
219. Ng. Ph. Buu-Hoi and M. Sy, *J. Org. Chem.*, **23**, 97 (1958).
220. P. Cagniant and Mme P. Cagniant, *Compt. Rend.*, **232**, 238 (1951).
221. Ng. Ph. Buu-Hoi, V. Q. Yen, and N. D. Xuong, *J. Org. Chem.*, **23**, 189 (1958).
222. J. T. Suh, U.S. Patent 3,370,063.
223. Ng. Ph. Buu-Hoi and D. Lavit, *J. Chem. Soc.*, 1721 (1958).
224. N. Messina and E. V. Brown, *J. Am. Chem. Soc.*, **74**, 920 (1952).
225. G. Alberghina, M. E. Amato, A. Corsaro, S. Fisichella, and G. Scarlata, *J. Chem. Soc. Perkin Trans. II*, 353 (1985).
226. P. Cagniant and Mme P. Cagniant, *Bull. Soc. Chim. Fr.*, 713 (1953).
227. M. Sy, Ng. Ph. Buu-Hoi, and Ng. D. Xuong, *J. Chem. Soc.*, 21 (1955).
228. Ng. Ph. Buu-Hoi and Ng. D. Xuong, *Bull. Soc. Chim. Fr.*, 650 (1957).
229. P. Demerseman, Ng. Ph. Buu-Hoi, and R. Royer, *J. Chem. Soc.*, 4193 (1954).
230. M. M. P. Cagniant and Guy Merle, *Compt. Rend. Acad. Sci. Paris*, **264**, 112 (1967).
231. Ng. Ph. Buu-Hoi and Ng. Hoan, *J. Chem. Soc.*, 251 (1951).
232. M. A. Hammad, G. A. M. Nawwar, G. E. H. Elgemeie, and M. H. Elnagdi, *Heterocycles*, **23**, 2177 (1985).
233. F. P. Ballistreri, G. Musumarra, and G. Scarlata, *Chem. Scripta*, **18**, 214 (1981).
234. S. A. M. Osman, G. E. H. Elgemeie, G. A. M. Nawar, and M. H. Elnagdi, *Monatsh. Chem.*, **117**, 105 (1986).
235. J. R. Merchant, H. C. Kaushik, and D. D. Vaghani, *Indian J. Chem.*, **4**, 27 (1966).
236. S. Gronowitz and M. Herslöf, *Chem. Scripta*, **10**, 90 (1976).
237. K. Ogura, Y. Ito, and G. Tsuchihashi, *Synthesis*, 736 (1980).

238. V. Baliah and M. Seshapathirao, *J. Org. Chem.*, **24**, 867 (1959).
239. Inst. Org. Chem. Acad. Sci. Ukrainian S.S.R., Inst. Chem. Polymers and Monomers Acad. Sci. Ukrainian S.S.R., U.S.S.R. Patent 161,734.
240. G. Seitz and H. S. The, *Arch Pharm.*, **316**, (1983).
241. D. R. Shridhar, C. V. R. Sastry, K. B. Lal, A. K. Marwah, G. S. Reddi, K. K. Bhopale, H. N. Tripathi, R. S. Khokhar. K. Tripathi, and G. S. T. Sai, *Indian J. Chem. Sect. B*, **20**, 234 (1981).
242. D. R. Shridhar, C. V. R. Sastry, B. Lal, G. S. Reddi, K. K. Bhopale, R. S. Khokar, and K. Tripathi, *Indian J. Chem. Sect. B*, **19B**, 1065 (1980).
243. V. S. Egorova, V. N. Ivanova, and N. I. Putokhin, *Chem. Het. Comp.*, 654 (1967).
244. H. Junek, B. Thierrichter, and P. Wibmer, *Monatsh. Chem.*, **110**, 483 (1979).
245. Z. Arnold, D. Dvorak, and V. Kral, *Coll. Czech. Chem. Commun.*, **49**, 2613 (1984).
246. A. Perjessy, P. Hrnciar, and R. Sokolova, *Coll. Czech. Chem. Commun.*, **38**, 559 (1973).
247. J. Tirouflet and Y. Soufi, *Compt. Rend.*, **248**, 3568 (1959).
248. Mrs. S. M. Abdel-Wahhab, and N. R. El-Rayyes, *J. Prakt. Chem.*, **313**, 247 (1971).
249. H. H. Moussa, *Indian J. Chem. Sect. B*, **14**, 707 (1976).
250. N. R. Elrayyes, *J. Prakt. Chem.*, **315**, 300 (1973).
251. N. R. Elrayyes and N. A. Alsalman, *J. Prakt. Chem.*, **317**, 552 (1975).
252. H. H. Moussa and D. Zaki, *Indian J. Chem., Sect. B*, **15**, 555 (1977).
253. N. R. Elrayyes and N. A. Alsalman, *J. Heterocycl. Chem.*, **13**, 285 (1976).
254. C. W. Bird, C. K. Wong, and D. Y. Wong, *J. Prakt. Chem.*, **314**, 915 (1972).
255. N. R. Elrayyes and A. H. A. Ali, *J. Prakt. Chem.*, **317**, 1040 (1975).
256. A. P. Glaze, S. A. Harris, H. G. Heller, W. Johncock, S. N. Oliver, J. Strydom, and J. Whittall, *J. Chem. Soc. Perkin Trans. I*, 957 (1985).
257. B. P. Das, M. E. Nuss, and D. W. Boykin, *J. Med. Chem.*, **17**, 516 (1974).
258. B. P. Das, J. A. Campbell, F. B. Samples, R. A. Wallace, L. K. Whisenant, and R. W. Woodard, *J. Med. Chem.*, **15**, 370 (1972).
259. S. Kusuma, W. D. Wilson, and D. W. Boykin, *J. Heterocycl. Chem.*, **22**, 1229 (1985).
260. B. P. Das and D. W. Boykin, *J. Med. Chem.*, **16**, 413 (1973).
261. G. M. Badger, J. A. Elix, and G. E. Lewis, *Aust. J. Chem.*, **19**, 1243 (1966).
262. Y. Ming and D. W. Boykin, *Heterocycles*, **26**, 3229 (1987).
263. T. M. Cresp and M. V. Sargent, *J. Chem. Soc., Perkin Trans. I*, 1786 (1973).
264. G. Kimura, S. Kalchi, M. Koshi, and Y. Inaba, *Yuki Gosei Kagaku Kyokai Shi*, **22**, 461 (1964).
265. Mme. P. Cagniant, *Bull. Soc. Chim. Fr.*, 847 (1949).
266. P. Cagniant and Mme. P. Cagniant, *Compt. Rend.*, **229**, 1150 (1949).
267. Ng. Ph. Buu-Hoi and Ng. Hoan, *J. Org. Chem.*, **17**, 350 (1952).
268. Ng. Hoan, *Bull. Soc. Chim. Fr.*, 309 (1953).
269. Ng. Ph. Buu-Hoi, Ng. Hoan, and D. Lavit, *J. Chem. Soc.*, 4590 (1952).
270. Ng. Ph. Buu-Hoi, Ng. Hoan, and D. Lavit, *J. Chem. Soc.*, 485 (1953).
271. A. S. Zektzer, J. G. Stuart, G. E. Martin, and R. N. Castle, *J. Heterocycl. Chem.*, **23**, 1587 (1986).
272. M. Jackman, C. Bolen, F. C. Nachod, B. F. Tullar, and S. Archer, *J. Am. Chem. Soc.*, **71**, 2301 (1949).
273. B. Abarca, R. Ballesteros, and C. Soriano, *Tetrahedron*, **43**, 991 (1987).
274. R. M. Minyaev, V. I. Minkin, and V. N. Sheinker, *Zh. Org. Khim.*, **11**, 1968 (1975).
275. M. Cariou, *Bull. Soc. Chim. Fr.*, 651 (1979).
276. E. Campaigne, W. L. Fleming, and A. Dinner, *J. Heterocycl. Chem.*, **5**, 191 (1968).

277. P. Geetha, K. Rajagopalan, and S. Swaminathan, *Indian J. Chem., Sect. B*, **17**, 163 (1979).
278. K. Srinivasan, K. K. Balasubramanian, and S. Swaminathan, *Chem. Ind.*, **10**, 398 (1971).
279. K. Srinivasan, K. G. Srinivasan, K. K. Balasubramanian, and S. Swaminathan, *Synthesis*, 313 (1973).
280. S. Gronowitz and I. Ander, *Acta Chem. Scand.*, **B29**, 513 (1975).
281. I. Ander and B. Aurivillius, *Chem. Scripta*, **11**, 44 (1977).
282. C. E. Loader and C. J. Timmons, *J. Chem. Soc., C*, 1677 (1967).
283. A.-B. Hörnfeldt, J. S. Gronowitz, and S. Gronowitz, *Acta Chem. Scand.*, **22**, 2725 (1968).
284. S. Gronowitz and B. Yom-Tov, *Z. Chem.*, **10**, 389 (1970).
285. M. B. Groen, H. Schadenberg, and H. Wynberg, *J. Org. Chem.*, **36**, 2797 (1971).
286. B. Yom-Tov and S. Gronowitz, *Chem. Scripta*, **3**, 165 (1973).
287. U. Michael and S. Gronowitz, *Chem. Scripta*, **4**, 126 (1973).
288. F. A. Bottino, G. C. Pappalardo, G. Scarlata, D. Sciotto, and M. Torre, *Can. J. Chem.*, **56**, 2755 (1978).
289. G. Kumar, K. Rajagopalan, and S. Swaminathan, *Indian J. Chem., Sect. B*, **18**, 541 (1979).
290. E. Sarria and S. Vega, *An. Quim. C—Org. Bioquim.*, **81**, 284 (1985).
291. W. Hinz, R. Jones, and T. Anderson, *Synthesis*, 620 (1986).
292. D. P. Munro and J. T. Sharp, *J. Chem. Soc., Perkin Trans. I*, 1718 (1980).
293. G. Kossmehl. M. Härtel, and G. Manecke, *Makromol. Chem.*, **131**, 15 (1970).
294. W. J. Archer, R. Cook, and R. Taylor, *J. Chem. Perkin Trans. II*, 813 (1983).
295. S. Gronowitz and T. Dahlgren, *Chem. Scripta*, **12**, 57 (1977).
296. D. W. Allen and H. Ward, *Z. Naturforsch. B: Anorg. Chem., Org. Chem.*, **35B**, 754 (1980).
297. T. M. Cresp and M. V. Sargent, *J. Chem. Soc., Perkin Trans. I*, 2961 (1973).
298. W. Carruthers and M. G. Pellatt, *J. Chem. Soc. Perkin Trans. I*, 1136 (1973).
299. K. Schloegl and H. Egger, *Liebigs Ann.*, **676**, 76 (1964).
300. J. H. Dopper, D. Oudman, and H. Wynberg, *J. Am. Chem. Soc.*, **95**, 3692 (1973).
301. G. Manecke and M. Härtel, *Chem. Ber.*, **106**, 655 (1973).
302. H. E. Högberg and O. Wennerström, *Acta Chem. Scand., Ser. B*, **36**, 661 (1982).
303. G. Kossmehl and D. Budwill, *Z. Naturforsch. Sect. B*, **41**, 751 (1986).
304. G. Kossmehl and D. Budwill, *Z. Naturforsch. Sect. B*, **42**, 478 (1987).
305. G. Kossmehl, M. Härtel, and G. Manecke, *Makromol. Chem.*, **131**, 37 (1970).
306. G. Kossmehl, B. Bohn, and G. Manecke, *Makromol. Chem.*, **177**, 1857 (1976).
307. A. C. Barnes, J. F. Mo Ghie, and N. M. Waldron, *Chem. Ind.*, 1344 (1969).
308. G. Holzmann, G. Kossmehl, and R. Nuck, *Makromol. Chem-Macro. Chem. Phys.*, **183**, 1711 (1982).
309. G. Kossmehl, P. Beimling, and G. Manecke, *Makromol. Chem-Macro. Chem. Phys.*, **183**, 2771 (1982).
310. Y. Z. Huang, L. Shi, J. Yang, and J. Zhang, *Tetrahedron Lett.*, **28**, 2159 (1987).
311. F. Bohlmann and P. Herbst, *Chem. Ber.*, **95**, 2945 (1962).
312. B. Yom-Tov and S. Gronowitz, *J. Heterocycl. Chem.*, **15**, 285 (1978).
313. B. Yom-Tov and S. Gronowitz, *Chem. Scripta*, **3**, 37 (1973).
314. S. Gronowitz and L. Svensson, *Chem. Scripta*, **15**, 169 (1980).
315. L. Y. Malkes, R. A. Minakova, and L. V. Kozyreva, *Khim. Geterotsikl. Soedin*, 895 (1979).
316. B. Yom-Tov, S. Gronowitz, S. B. Ross, and N. E. Stjernström, *Acta Pharm. Suec.*, **11**, 149 (1974).

317. M. Farnier, M. Brost, B. Hanquet, and R. Guilard, *J. Heterocycl. Chem.*, **23**, 517 (1986).
318. Sandoz Ltd., Neth. Patent 6,408,529.
319. R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.*, **32**, 3093 (1967).
320. M. L. Tedjamulia, J. G. Stuart, Y. Tominaga, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **21** 1215 (1984).
321. R. Pratap, Y. Tominaga, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **18**, 973 (1981).
322. Y. Tominaga, M. L. Tedjamulia, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **20**, 487 (1983).
323. M. L. Tedjamulia, Y. Tominaga, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **20**, 1143 (1983).
324. M. Iwao, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **17**, 1259 (1980).
325. H. Kudo, M. L. Tedjamulia, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **21**, 185 (1984).
326. A. Berlin, S. Bradamante, R. Ferracioli, G. A. Pagani, and F. Sannicolo. *J. Chem. Soc., Perkin Trans. I*, 2631 (1987).
327. A. Arcoria, E. Maccarone, and G. T. Tomaselli, *Spectrochem. Acta, Part A*, **29A**, 1601 (1973).
328. A. Arcoria, S. Fisichella, G. Scarlata, and M. Torre, *Ann. Chim. Rome*, **62**, 723 (1973).
329. J. O. Karlsson, A. Svensson, and S. Gronowitz, *J. Org. Chem.*, **49**, 2018 (1984).
330. C. W. Spangler and R. K. McCoy, *Synth. Commun.*, **18**, 51 (1988).
331. A. Hallberg and P. Pedaja, *Tetrahedron*, **39**, 819 (1983).
332. R. F. Curtis and J. A. Taylor, *J. Chem. Soc. C*, 1813 (1969).
333. M. D'Auria, A. De Mico, F. D'Onofrio, and G. Piancatelli, *Gazz. Chim. Ital.*, **116**, 747 (1986).
334. S. Hibino, S. Kano, N. Mochizuki, and E. Sugino, *J. Org. Chem.*, **49**, 5006 (1984).
335. M. Muradinszweykowska, A. J. M. Peters, and J. Lugtenburg, *Rec. Trav. Chim.—J. Roy, Neth. Chem.*, **103**, 105 (1984).
336. V. H. Rawal, R. J. Jones, and M. P. Cava, *J. Org. Chem.*, **52**, 19 (1987).
337. D. N. Nicolaides and C. N. Coutrakis, *Synthesis*, 268 (1977).
338. D. N. Nicolaides, E. C. Tsakalidou, and C. T. Hatziantoniou, *J. Heterocycl. Chem.*, **19**, 1243 (1982).
339. K. Dimroth, G. Pohl, and H. Follmann, *Chem. Ber.*, **99**, 634 (1966).
340. P. J. Garratt and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **94**, 1022 (1972).
341. L. Skatteboel, *Acta Chem. Scand.*, **15**, 2047 (1961).
342. M. D'Auria, A. De Mico, F. D'Onofrio, and G. Piancatelli, *J. Org. Chem.*, **52**, 5243 (1987).
343. T. V. Brown, W. Carruthers, and M. G. Pellatt, *J. Chem. Soc., Perkin Trans. I*, 483 (1982).
344. A. Heller, *J. Chem. Phys.*, **40**, 2839 (1964).
345. L. S. Afanasiadi, L. D. Patsenker, S. A. Verezubova, A. P. Shkumat, and V. K. Polyakov, *Chem. Het. Comp. USSR*, 1028 (1986).
346. H. Saikachi, Y. Taniguchi, and H. Ogawa, *Yakugaku Zasshi*, **83**, 582 (1963).
347. T. M. Cresp, M. V. Sargent, and P. Vogel, *J. Chem. Soc., Perkin Trans. I*, 37 (1974).
348. D. C. Lankin, M. R. Scalise, J. C. Schmidt, and H. Zimmer, *J. Heterocycl. Chem.*, **11**, 631 (1974).
349. V. N. Listvan, *Khim. Geterotsikl. Soedin, USSR*, 1624 (1974).
350. E. Zbiral, *Tetrahedron Lett.*, 1483 (1965).
351. G. Manecke, L. Brandt, and G. Kossmehl, *Makromol. Chem.*, **178**, 1745 (1977).
352. T. Tanouchi, M. Kawamura, I. Ohyama, I. Kajiwara, Y. Iguchi, T. Okada, T. Miyamoto, K. Taniguchi, M. Hayashi, K. Iizuka, and M. Nakazawa, *J. Med. Chem.*, **24**, 1149 (1981).
353. E. Castagnino, S. Corsano, and B. Serena, *Gazz. Chim. Ital.*, **113**, 97 (1983).

354. E. J. Seus and C. V. Wilson, *J. Org. Chem.*, **26**, 5243 (1961).
355. E. J. Seus, *J. Heterocycl. Chem.*, **2**, 318 (1965).
356. Y. Tominaga, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **18**, 977 (1981).
357. B. S. Green and L. Heller, *J. Org. Chem.*, **39**, 196 (1974).
358. H. Fillion, M. H. Pera, J. L. Rappa, and C. Lu-Duc, *J. Heterocycl. Chem.*, **15**, 753 (1978).
359. Y. Tominaga, E. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **19**, 1125 (1982).
360. P. G. Lehman and H. Wynberg, *Aust. J. Chem.*, **27**, 315 (1974).
361. B. Capron, C. Paulmier, and P. Pastour, *Compt. Rend. Acad. Sci. Ser. C*, **277**, 167 (1973).
362. B. Capron, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr., Part 2*, 2575 (1975).
363. S. Gronowitz and I. Ander, *Chem. Scripta*, **15**, 135 (1980).
364. A. A. Macco, R. J. Debrouwer, P. M. M. Nossin, E. F. Godefroi, and H. M. Buck, *J. Org. Chem.*, **43**, 1591 (1978).
365. A. A. Macco, R. J. Debrouwer, and H. M. Buck, *J. Org. Chem.*, **42**, 3196 (1977).
366. B. Jezowska-Trezbiatowska, Z. Olejnik, and T. Lis, *J. Chem. Soc., Dalton Trans.*, 251 (1981).
367. G. Lavielle and G. Sturtz, *Bull. Soc. Chim. Fr.*, 1369 (1970).
368. H. J. Jahns and I. Mueller, *Z. Chem.*, **14**, 55 (1974).
369. J. W. van Reijendam, G. J. Heeres, and M. J. Janssen, *Tetrahedron*, **26**, 1291 (1970).
370. I. R. Trehan, G. L. Kad, S. Rani, and R. Bala, *Indian J. Chem., Sect. B*, **24**, 659 (1985).
371. J. L. Dever and I. C. Popoff, U.S. Patent 3,373,167.
372. G. Kossmehl and B. Bohn, *Angew. Chem.*, **85**, 230 (1973).
373. B. Bohn and G. Kossmehl, Ger. Patent 2,260,801.
374. A. Heymes and I. Chekroun, *Phosph. Sulf.*, **31**, 47 (1987).
375. R. Kattermann and P. P. Slonimski, *Compt. Rend.*, **250**, 220 (1960).
376. F. Clesse and H. Quiniou, *Bull. Soc. Chim. Fr.*, 1940 (1969).
377. B. Abarca, R. Ballesteros, E. Enriquez, and G. Jones, *Tetrahedron*, **41**, 2435 (1985).
378. D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946).
379. R. T. Nazzaro and J. L. Bullock, *J. Am. Chem. Soc.*, **68**, 2121 (1946).
380. Y. Tominaga, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **18**, 967 (1981).
381. G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.*, **70**, 2378 (1948).
382. S. Rao, U. T. Bhalerao, and B. D. Tilak, *Indian J. Chem.*, **26B**, 208 (1987).
383. T. V. Shchedrinskaya, P. A. Konstantinov, and M. N. Volkov, *Khim. Geterotsikl. Soedin*, 51 (1977).
384. M. N. Volkov and O. A. Kazakova, *Khim. Geterotsikl. Soedin*, 758 (1981).
385. M. Janda and F. Dvorak, *Coll. Czech. Chem. Commun.*, **27**, 372 (1962).
386. J. Skramstad, *Acta Chem. Scand.*, **23**, 703 (1969).
387. G. Kumar, K. Rajagopalan, S. Swaminathan, and K. K. Balasubramanian, *Indian J. Chem., Sect. B*, **20B**, 271 (1981).
388. J. W. McFarland and H. L. Howers Jr., *J. Med. Chem.*, **12**, 1079 (1969).
389. T. Severin, P. Adhikary, and I. Schnabel, *Chem. Ber.*, **102**, 1325 (1969).
390. F. Bohlmann and C. Huhn, *Chem. Ber.*, **110**, 1183 (1977).
391. P. Cagniant, *Compt. Rend. Acad. Sci. (Paris) Ser. C*, **271**, 375 (1970).
392. Mme P. Cagniant, G. Kirsch, and G. Champetier, *Compt. Rend. Acad. Sci. (Paris) Ser. C*, **272**, 92 (1971).
393. J. Skramstad, *Chem. Scripta*, **7**, 42 (1975).
394. J. Guillaume, L. Nedelec, M. Cariou, and A. Allais, *Heterocycles*, **15**, 1227 (1981).
395. D. Geffken and K. Strohauer, *Z. Naturforsch. Sect. B*, **41**, 89 (1986).

396. Y. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, *Khim. Geterotsikl. Soedin, USSR*, 220 (1965).
397. G. G. Smith and J. A. Kirby, *J. Heterocycl. Chem.*, 1101 (1971).
398. C. Troyanowsky, *Compt. Rend.*, **232**, 2236 (1951).
399. C. Troyanowsky, *Bull. Soc. Chim. Fr.*, 424 (1955).
400. B. Abarca, R. Ballesteros, E. Enriquez, and G. Jones, *Tetrahedron*, **43**, 269 (1987).
401. A.-B. Hörnfeldt, *Arkiv Kemi*, **22**, 211 (1964).
402. G. Van Zyl, J. F. Zack, Jr., E. S. Huyser, and P. L. Cook, *J. Am. Chem. Soc.*, **76**, 707 (1954).
403. R. L. Morgan, P. Tannhauser, R. J. Pratt, T. C. Myers, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 5658 (1955).
404. J. M. Robson, J. S. H. Davies, and W. Tebrich, *Br. J. Pharmacol.*, **5**, 376 (1950).
405. W. R. Biggerstaff, N. Sugisaka, and R. Albers, *J. Med. Chem.*, **12**, 1 (1969).
406. G. T. Gmitter and T. L. Benton, *J. Am. Chem. Soc.*, **72**, 4586 (1950).
407. C. Jutz, *Chem. Ber.*, **91**, 1867 (1958).
408. T. K. Miller and J. T. Sharp, *J. Chem. Soc., Perkin Trans. I*, 223 (1984).
409. J. Szmuszkovicz and E. J. Modest, *J. Am. Chem. Soc.*, **72**, 571 (1950).
410. L. F. Fieser and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **70**, 3352 (1948).
411. A. J. Kosak, R. J. F. Palchak, W. A. Steele, and Ch. M. Selwitz, *J. Am. Chem. Soc.*, **76**, 4450 (1950).
412. S. Gronowitz, J. Rehnö, K. Titlestad, M. Vadzis, B. Sjöberg, P. Bamberg, B. Ekström, and U. Forsgren, *Acta Pharm. Suec.*, **9**, 381 (1972).
413. D. Binder, C. R. Noe, and W. Bilek, *Arch. Pharm.*, **313**, 883 (1980).
414. L. J. Baldwin, S. Pakray, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **22**, 1667 (1985).
415. A. Svensson and R. Håkansson, *Chem. Scripta*, **18**, 202 (1981).
416. A. Svensson and R. Håkansson, *Chem. Scripta*, **20**, 78 (1982).
417. A. P. Rothwell, K. V. Wood, A. K. Gupta, and J. V. N. V. Prasad, *Org. Mass. Spectrom.*, **22**, 790 (1987).
418. A. Svensson and R. Håkansson, *Chem. Scripta*, **20**, 188 (1982).
419. H. Wynberg, A. Logothetis, and D. Ver Ploeg, *J. Am. Chem. Soc.*, **79**, 1972 (1957).
420. T. Komeno, H. Iwakura, and K. Takeda, *Heterocycles*, **10**, 207 (1978).
421. D. W. Adamson, W. M. Duffin, and A. F. Green, *Nature*, **167**, 153 (1951).
422. R. Kimura, T. Yabuuchi, and V. Tamura, *Chem. Pharm. Bull.*, **8**, 103 (1960).
423. D. W. Adamson, *J. Chem. Soc.*, 885 (1950).
424. N. Sugimoto, et al., Jpn. Patent 3922 (1956).
425. T. Kametani and Y. Akazawa, *J. Pharm. Soc. Jpn.*, **73**, 649 (1953).
426. D. W. Adamson and A. F. Green, *Nature*, **165**, 122 (1950).
427. Deutsche Gold- und Silber-Scheideanstalt vorm. Roessler, Br. Patent 1,328,545.
428. Innothera, Fr. Patent 1,462,206.
429. F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.*, **9**, 725 (1972).
430. S. Ohki, T. Azuma, and Y. Nagase, *Yakugaku Zasshi*, **89** 633 (1969).
431. N. Sugimoto, S. Saito, and N. Shigematsu, *J. Pharm. Soc. Jpn.*, **74**, 717 (1954).
432. V. A. Kleemann, J. Heese, and J. Engel, *Arzneim-Forsch-Drug Res.*, **31–2**, 1178 (1981).
433. J. Engel, K. Thiele, K. Posselt, and J. Heese, *Arzneim-Forsch-Drug Res.*, **30–2**, 1057 (1980).
434. J. Engel, A. V. Schlichtegroll, and W. S. Sheldrick, *Arzneim-Forsch-Drug Res.*, **32–1**, 475 (1982).
435. R. Kimura and T. Yabuuchi, *Chem. Pharm. Bull. (Tokyo)*, **7**, 171 (1959).

436. V. A. Smirnov and A. E. Lyskin, U.S.S.R. Patent 341,800.
437. J. Farkas and J. J. K. Novak, *Coll. Czech. Chem. Commun.*, **25**, 1815 (1960).
438. I. C. Beatty, U.S. Patent 2,526,319.
439. H. K. F. Hermans, A. G. Knaeps, and C. A. M. Van der Eycken, *Ind. Chim. Belg.*; **24**, 1467 (1959).
440. D. Mukherjee, L. C. Dunn, and K. N. Houk, *J. Am. Chem. Soc.*, **101**, 251 (1979).
441. W. Carruthers and H. N. M. Stewart, *J. Chem. Soc.*, 6221 (1965).
442. Ng. Ph. Buu-Hoi, Ng. Hoan, and Ng. H. Khoi, *Rec. Trav. Chim.*, **69**, 1053 (1950).
443. Y. L. Chen, C.-W. Chang, K. Hedberg, K. Guarino, W. M. Welch, L. Kiessling, J. A. Retsema, S. L. Haskell, M. Anderson, M. Manousos, and J. F. Barrett, *J. Antibiot.*, **60**, 803 (1987).
444. W. R. Biggerstaff and O. L. Stafford, *J. Am. Chem. Soc.*, **74**, 419 (1952).
445. K. Pelz and M. Protiva, *Coll. Czech. Chem. Commun.*, **32**, 2840 (1967).
446. M. Mc. C. Martin and J. G. Mac Connell, *Tetrahedron*, **26**, 307 (1970).
447. Sandoz Ltd., Neth. Patent 6,414,548.
448. Sandoz Ltd., Neth. Patent 6,414,606.
449. Farbwerke Hoechst A.-G., Br. Patent 1,127,064.
450. E. Waldvogel, G. Schwarb, J. M. Bastian, and J. P. Bourquin, *Helv. Chim. Acta*, **59**, 866 (1976).
451. R. J. Jones and M. P. Cava, *J. Chem. Soc., Chem. Commun.*, 826 (1986).
452. B. J. Cramer, W. Schroeder, W. J. Moran, C. H. Nield, M. Edwards, Ch. I. Jarowski, and B. Puetzer, *J. Am. Pharm. Assoc., Sci. Ed.*, **37**, 439 (1948).
453. Societe Anon. pour l'Industrie, Chimique, Fr. Patent 1,390,978.
454. Ng. Ph. Buu-Hoi and Ng. Hoan, *Rec. Trav. Chim.*, **68**, 5 (1949).
455. Ng. H. Nam, Ng. Ph. Buu-Hoi, and Ng. D. Xuong., *J. Chem. Soc.*, 1690 (1954).
456. Ng. Ph. Buu-Hoi, E. Lescot, Jr., and Ng. D. Xuong, *J. Org. Chem.*, **22**, 1057 (1957).
457. Ng. Ph. Buu-Hoi, E. Lescot, Jr., and Ng. D. Xuong, *J. Org. Chem.*, **23**, 1261 (1958).
458. Ng. Ph. Buu-Hoi and Ng. Hoan, *Rec. Trav. Chim.*, **69**, 1455 (1950).
459. Ng. Ph. Buu-Hoi, Ng. Hoan, and Ng. D. Xuong, *Rec. Trav. Chim.*, **69**, 1083 (1950).
460. Texaco Development Corp., Br. Patent 627,247.
461. D. W. Adamson and J. W. Billinghurst, *J. Chem. Soc.*, 1039 (1950).
462. D. W. Adamson, P. A. Barrett, J. W. Billinghurst, and T. S. G. Jones, *J. Chem. Soc.*, 2315 (1957).
463. F. C. Rogers and W. L. Nobles, *J. Pharm. Sci.*, **51**, 273 (1962).
464. A. F. Casy and J. L. Myers, *J. Chem. Soc.*, 4092 (1965).
465. P. A. Barrett, *J. Chem. Soc.*, 325 (1958).
466. A. F. Casy and A. P. Parulkar, *Can. J. Chem.*, **47**, 423 (1969).
467. N. Sugimoto, S. Saito, and S. Oshiro, *J. Pharm. Soc. Jpn.*, **73**, 1381 (1953).
468. R. E. Miller and F. F. Nord, *J. Org. Chem.*, **15**, 89 (1950).
469. R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951).
470. R. D. Schuetz and W. H. Houff, *J. Am. Chem. Soc.*, **77**, 1839 (1955).
471. R. D. Schuetz and W. H. Houff, *J. Am. Chem. Soc.*, **77**, 1836 (1955).
472. T. Kurihara, K. Kumamoto, and H. Takeda, *Tohoku Yakka Daigaku Kenkyu Nempo*, **14**, 51 (1967).
473. R. M. Acheson, K. E. MacPhee, P. G. Philpott, and J. A. Barltrop, *J. Chem. Soc.*, 698 (1956).
474. C. P. Ivanov and D. M. Mondeshka, *J. Prakt. Chem.*, **315**, 993 (1973).
475. C. P. Ivanov and D. M. Mondeshka, *Rev. Roum. Chim.*, **20**, 547 (1975).
476. J. W. Schick and H. D. Hartough, *J. Am. Chem. Soc.*, **70**, 1646 (1948).

477. J. F. Scully and E. V. Brown, *J. Am. Chem Soc.*, **75**, 6329 (1953).
478. I. V. Andreeva and M. M. Koton, *J. Gen. Chem. USSR*, **27**, 1079 (1957).
479. W. S. Emerson and T. M. Patrick, Jr., *J. Org. Chem.*, **13**, 729 (1948).
480. W. S. Emerson and T. M. Patrick, Jr., U.S. Patent 2,547,905.
481. W. S. Emerson and T. M. Patrick, Jr., U.S. Patent 2,556,419.
482. W. S. Emerson and T. M. Patrick, Jr., *Org. Synth.*, **38**, 86 (1958).
483. L. T. Hartmann, J. J. Lawton, and W. E. Carbone, *Blast. Furnace Steel Plant.*, **47**, 199 (1959).
484. A. A. Balandin, G. M. Marukyan, R. G. Seimovich, T. K. Lavrovskaya, and I. I. Levitskii, *Zh. Obshch. Khim.*, **30**, 381 (1960).
485. K. Y. Jen, M. Maxfield, L. W. Shacklette, and R. L. Elsenbaumer, *J. Chem. Soc., Chem. Commun.*, 3309 (1987).
486. J. Kagan, S. K. Arora, M. Bryzgis, S. N. Dhawan, K. Reid, S. P. Singh, and L. Tom, *J. Org. Chem.*, **48**, 703 (1983).
487. J. P. Beny, S. N. Dhawan, J. Kagan, and S. Sundlass, *J. Org. Chem.*, **47**, 2201 (1982).
488. J. Kagan and S. K. Arora, *J. Org. Chem.*, **48**, 4317 (1983).
489. J. Kagan, G. Chan, S. N. Dhawan, S. K. Arora, and I. Prakash, *J. Nat. Prod.*, **46**, 646 (1983).
490. D. M. Perrine and J. Kagan, *Heterocycles*, **24**, 365 (1986).
491. J. Nakayama, S. Murabayashi, and M. Hoshino, *Heterocycles*, **24**, 2639 (1986).
492. J. Nakayama, H. Machida, R. Saito, K. Akimoto, and M. Hoshino, *Chem. Lett.*, 1173 (1985).
493. L. N. Koikov, P. B. Terentev, V. N. Torocheshnikov, and N. S. Kulikov, *Zh. Org. Khim.*, **19**, 121 (1983).
494. A. Fujita, J. Matsumuto, S. Minami, and H. Takamatsu, *Chem. Pharm. Bull. (Tokyo)*, **13**, 1177 (1965).
495. H. O. Krabbenhoft, *J. Org. Chem.*, **43**, 1305 (1978).
496. L. Duhamel, G. Ple, and B. Contreras, *Org. Prep. Proc. Int.*, **18**, 219 (1986).
497. J. F. Arens, H. J. Tjakob, and H. Vieregge, U.S. Patent 3,030,359.
498. H. Vieregge, H. M. Schmidt, J. Renema. H. J. T. Bos, and J. F. Arens, *Rec. Trav. Chim. Pays-Bas*, **85**, 929 (1966).
499. Y. Tominaga, Y. Matsuda, and G. Kohayashi, *Heterocycles*, **4**, 1493 (1976).
500. Zh. A. Krasnaya, T. S. Stytsenko, E. P. Prokof'ev, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1362 (1980).
501. K. Schloegl and W. Steyrer, *Monatsh. Chem.*, **96**, 1520 (1965).
502. K. Bodendorf and R. Mayer, *Chem. Ber.*, **98**, 3554 (1965).
503. D. R. Arnold and C. P. Hadjiantonniou, *Can. J. Chem.*, **56**, 1970 (1978).
504. S. Rajappa, M. D. Nair, R. Sreenivasan, and B. G. Advani, *Tetrahedron*, **38**, 1673 (1982).
505. S. Pennanen, *Acta Chem. Scand.*, **26**, 2907 (1972).
506. U. Hasserodt and F. Korte, *Angew. Chem.*, **75**, 138 (1963).
507. W. L. Nobles and B. Blackburn Thompson, *J. Pharm. Sci.*, **54**, 576 (1965).
508. E. D. Bergmann, I. Shahak, E. Sal'i, and Z. Aizenshtat, *J. Chem. Soc., C.*, 1232 (1968).
509. D. J. Freeman, P. J. Newcombe, and R. K. Norris, *Aust. J. Chem.*, **29**, 327 (1976).
510. P. J. Newcombe and R. K. Norris, *Aust. J. Chem.*, **32**, 1709 (1979).
511. P. J. Newcombe and R. K. Norris, *Aust. J. Chem.*, **32**, 2647 (1979).
512. S. R. Ramadas and N. S. Chandrakumar, *Phosphor Sulfur Relat. Elem.*, **13**, 79 (1982).
513. G. N. Dorofeenko, L. V. Mezheritskaya, and Y. I. Ryabukhin, *Zh. Org. Khim.*, **9**, 390 (1973).
514. J. Gosselck, L. Beress, H. Schenk, and G. Schmidt, *Angew. Chem., Int. Ed.*, **4**, 1080 (1965).
515. W. Ried and H. Mengler, *Liebigs Ann. Chem.*, **678**, 113 (1964).

516. R. V. Hoffman, G. G. Orphanides, and H. Shechter, *J. Am. Chem. Soc.*, **100**, 7927 (1978).
517. H. L. Reimlinger, F. Billiau, and M. Peiren, *Chem. Ber.*, **97**, 3503 (1964).
518. Union Carbide European Research Associates S.A., Ger. Patent 1,170,411.
519. H. Reimlinger, *Chem. Ind. (London)*, 1306 (1969).
520. H. Volz and H. Kowarsch, *Tetrahedron Lett.*, 4375 (1976).
521. Ng. Ph. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, 955 (1967).
522. Ng. Ph. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, 2489 (1968).
523. J. Hrabovsky and J. Kovac, Czech. Patent 196,927.
524. A. N. Nesmeyanov, N. K. Kochetkov, and L. A. Matov, *Dokl. Akad. Nauk. SSSR.*, **92**, 85 (1953).
525. R. H. Sieber and P. Hornig, *Liebig Ann. Chem.*, **743**, 144 (1971).
526. L. A. Myshkina, F. M. Stoyanovich, and Ya. I. Gol'dfarb, *Bull. Acad Sci. USSR*, 357 (1982).
527. J. A. Vankoeveringe and J. Lugtenburg, *Rec. Trav. Chim.—J. Roy Neth. Chem.*, **96**, 55 (1977).
528. C. Jutz, Ger. Patent 1,114,798.
529. S. Dixon. U.S. Patent 2,874,166.
530. S. Dixon. *J. Org. Chem.*, **21**, 400 (1956).
531. V. A. Chernoplekova and K. A. Kocheshkov, *Zh. Org. Khim.*, **14**, 2392 (1978).
532. T. A. Starostina, L. F. Rybakova, and R. R. Shifrina, *Zh. Org. Khim.*, **16**, 1968 (1980).
533. W. J. Middleton, D. Metzger, and J. A. Snyder, *J. Med. Chem.*, **14**, 1193 (1971).
534. K. Okuhara, *J. Org. Chem.*, **41**, 1487 (1976).
535. K. Okuhara, *Bull. Chem. Soc. Jpn.*, **54**, 2045 (1981).
536. R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 144 (1972).
537. J. Kwan-Yue, H. Eckhardt, T. R. Jow, L. W. Shacklette, and R. L. Elsenbaumer, *J. Chem. Soc., Chem. Commun.*, 215 (1988).
538. Z. V. Todres, N. G. Furmanova, S. P. Avagyan, Y. T. Struchkov, and D. N. Kursanov, *Phosphor Sulfur Relat. Elem.*, **5**, 309 (1979).
539. K. Tamao, M. Zembayashi, and M. Kumada, *Chem. Lett.*, 1239 (1976).
540. J. P. Montheard and J. C. Dubois, *J. Heterocycl. Chem.*, **22**, 719 (1985).
541. A. Minato, K. Suzuki, K. Tamao, and M. Kumada, *Tetrahedron Lett.*, **25**, 83 (1984).
542. E. Negishi, F. T. Luo, R. Frisbee, and H. Matsushita, *Heterocycles*, **18**, 117 (1982).
543. T. L. Gilchrist and R. J. Summersell, *Tetrahedron Lett.*, **28**, 1469 (1987).
544. T. L. Gilchrist and F. J. Summersell. *J. Chem. Soc., Perkin Trans I.*, 2395 (1988).
545. F. Tellier, R. Sauvetre, J. F. Normant, Y. Dromzee, and Y. Jeannin, *J. Organometal Chem.*, **331**, 281 (1987).
546. J. P. Gillet, R. Sauvetre, and J. F. Normant, *Synthesis*, 538 (1986).
547. R. C. Larock, K. Narayanan, and S. S. Hershberger, *J. Org. Chem.*, **48**, 4377 (1983).
548. P. Hong, B. R. Cho, and H. Yamazaki, *Chem. Lett.*, 507 (1980).
549. R. Asano, I. Moritani, Y. Fujiwara, and S. Teranishi, *Bull. Chem. Soc. Jpn.*, **46**, 663 (1973).
550. A. Kasahara, T. Izumi, G. Saito, and T. Takeda, *Asahi Garasu Kogyo Gijutsu Shoreikai Kenkyu Hokoku*, **22**, 95 (1973).
551. Y. Fujiwara, D. Maruyama, M. Yoshidomi, and H. Taniguchi, *J. Org. Chem.*, **46**, 851 (1981).
552. W. C. Frank, Y. C. Kim, and R. F. Heck, *J. Org. Chem.*, **43**, 2947 (1978).
553. T. N. Sidorenko, G. A. Terenteva, O. S. Andrienko, Y. V. Savinykh, and V. S. Aksenov, *Khim. Geterot. Soedin, USSR*, 192 (1983).
554. K. Karabelas and A. Hallberg, *J. Org. Chem.*, **51**, 5286 (1986).
555. Y. Tamaru, Y. Yamada, and Z. Yoshida, *Tetrahedron*, **35**, 329 (1979).

556. R. C. Larock, D. R. Leach, and S. M. Bjorge, *Tetrahedron Lett.*, **23**, 715 (1982).
557. R. C. Larock, D. R. Leach, and S. M. Bjorge, *J. Org Chem.*, **51**, 5221 (1986).
558. M. Satoh, N. Miyaura, and A Suzuki, *Chem. Lett.*, 1329 (1986).
559. N. Jabri, A. Alexakis, and J. F. Normant, *Tetrahedron Lett.*, **22**, 3851 (1981).
560. A. Yamashita and T. A. Scahill, *Tetrahedron Lett.*, **23**, 3765 (1982).
561. L. H. P. Gommans, L. Main, and B. K. Nicholson, *J. Chem. Soc., Chem. Commun.*, 761 (1987).
562. N. K. DasGupta and F. W. Birss, *Tetrahedron*, **36**, 2711 (1980).
563. C. R. Adams. U.S. Patent 3,309,381.
564. F. Ya. Perveev and N. I. Kudryashova, *Dokl. Akad. Nauk SSSR*, **98**, 975 (1954).
565. F. Ya. Perveev and T. N. Kuren'gina, *J. Gen. Chem. USSR*, **25**, 1579 (1955).
566. K. E. Schulte, G. Ruecker, and W. Meinders, *Tetrahedron Lett.*, **6**, 659 (1965).
567. F. Bohlmann, P. Herbst, and I. Dohrmann, *Chem. Ber.*, **96**, 226 (1963).
568. V. I. Shvedov. I. A. Kharizomenova, and A. N. Griner, U.S.S.R. Patent 355,170.
569. J. M. Mcintosh and F. P. Seguin, *Can. J. Chem.*, **53**, 3526 (1975).
570. S. Braverman, Y. Duar, and D. Segev, *Tetrahedron Lett.*, **17**, 3181 (1976).
571. S. Braverman, Y. Duar, and M. Freund, *Isr. J. Chem.*, **26**, 108 (1985).
572. G. D. Madding and M. D. Thompson, *J. Heterocycl. Chem.*, **24**, 581 (1987).
573. A. Datta, H. Ila, and H. Junjappa, *Synthesis*, 556 (1988).
574. S. A. Marinuzzi-Brosemer, D. C. Dittmer, M. H. M. Chen, and J. Clardy, *J. Org. Chem.*, **50**, 799 (1985).
575. U. Chiacchio, A. Compagnini, R. Grimadi, G. Purrello, and A. Padwa, *J. Chem. Soc., Perkin Trans. I*, 915 (1983).
576. E. A. Braude, J. S. Fawcett, and D. D. E. Newman, *J. Chem. Soc.*, 4155 (1952).
577. E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 4158 (1952).
578. J. A. Gautier and C. Combet-Farnoux, *Bull. Soc. Chim. Fr.*, 2145 (1964).
579. S. Jeganathan and M. Srinivasan, *Indian J. Chem., Sect. B.*, **19**, 312 (1980).
580. M. R. Banks, J. M. Barker, and P. R. Huddleston, *J. Chem. Res. (S)*, 27 (1984).
581. L. Brandsma and H. J. T. Bos, *Rec. Trav. Chim.*, **88**, 732 (1969).
582. H. Gotthardt and R. Jung, *Chem. Ber.*, **118**, 3438 (1985).
583. N. F. Eweiss and A. A. Hosni, *J. Univ. Kuwait Sci.*, **8**, 195 (1981).
584. T. Tsuchiya, M. Enkaku, and H. Sawanishi, *Heterocycles*, **12**, 1471 (1979).
585. K. Ogura, *Bull. Chem. Soc. Jpn.*, **35**, 808 (1962).
586. J. B. Press and N. H. Eudy, *J. Org. Chem.*, **49**, 116 (1984).
587. S. Gronowitz and A. Svensson, *Isr. J. Chem.*, **27**, 25 (1987).
588. C. R. Wagner, U.S. Patent 2,560,610.
589. J. F. McMahon, Fr. Patent 1,500,632.
590. A. V. Mashkina and N. B. Vorontsova, *Khim. Seraorg. Soedin. Soderch. Neftyakh. Nefteprod.*, **8**, 119 (1968).
591. E. M. Smolin, K. Matsuda, and D. S. Goffenberg, *Ind. Eng. Chem., Prod. Res. Develop.*, **3**, 16 (1964).
592. O. A. Kazakova, M. N. Volkov, and V. V. Zelentsov, *Zh. Org. Khim.*, **20**, 2015 (1984).
593. D. N. Ridge, J. W. Hanifin, L. A. Harten, B. D. Johnson, J. Menschik, G. Nicolau, A. E. Sloboda, and D. E. Watts, *J. Med. Chem.*, **22**, 1385 (1979).
594. M. Dandarova, D. Vegh, J. Kovac, I. Goljer, and K. Spirkova, *Top. Furan. Chem., Proc. Symp. Furan. Chem., 4th.*, 121 (1983).
595. D. Vegh. J. Kovac, and M. Dandarova, *Tetrahedron Lett.*, **21**, 969 (1980).

596. Ph. L. Kelly, S. F. Thames I, and J. E. McCleskey, *J. Heterocyl. Chem.*, **9**, 141 (1972).
597. A. N. Scott, B. E. Hoogenboom, and H. R. Snyder, *J. Org. Chem.*, **29**, 2165 (1964).
598. E. J. D. Brown and J. Harley-Mason, *J. Chem. Soc., C*, 1390 (1966).
599. U. Pindur and B. Unterhalt, *Arch. Pharm.*, **312**, 282 (1979).
600. T. Tsuchiya, M. Enkaku, and H. Sawanishi, *Chem. Pharm. Bull. (Tokyo)*, **27**, 2188 (1979).
601. S. Brenner and E. Dunkelblum, *Tetrahedron Lett.*, **14**, 2487 (1973).
602. R. R. Victor, R. Ben-Shoshan, and S. Sarel, *Tetrahedron Lett.*, **11**, 4253 (1970).
603. O. Meth-Cohn and G. van Vuuren, *Tetrahedron Lett.*, **27**, 1105 (1986).
604. N. Kawabata, J. Yoshida, H. Funahashi, and H. Iwasaki, *Tetrhedron Lett.*, **27**, 4469 (1986).
605. T. M. Brown and W. Carruthers, *J. Chem. Soc., Perkin Trans. I*, 2904 (1981).
606. M. G. Voronkov, A. N. Pereferkovich, M. P. Gavar, and G. V. Ozolin', *Chem. Het. Comp. USSR*, 1103 (1970).
607. M. Hrytsak and T. Durst, *Heterocycles*, **26**, 2393 (1987).
608. M. Makosza and A. Tyrala, *Synthesis*, 1142 (1987).
609. S. Fukuda, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles*, **20**, 1793 (1983).
610. W. P. Trompen and H. O. Huisman, *Rec. Trav. Chim.*, **85**, 175 (1966).
611. R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *J. Chem. Soc.*, 7109 (1965).
612. F. Bohlmann, H. Bornowski, and H. Schoenowsky, *Chem. Ber.*, **95**, 1733 (1962).
613. F. Carrock and M. Szwarc, *J. Am. Chem. Soc.*, **81**, 4138 (1959).
614. R. R. Burtner, U.S. Patent 2,734,904.
615. E. Crescenzi, E. Marazii-Uberti, and G. Coppi, *J. Pharm. Sci.*, **55**, 290 (1966).
616. L. Fontanella, E. Occelli, and E. Testa, *Farm. Ed. Sci.*, **30**, 742 (1975).
617. G. Alberghina, M. E. Amato, S. Fisichella, and S. Occhipinti, *Gazz. Chim. Ital.*, **111**, 231 (1981).
618. M. A. Vasyanina and V. K. Khairullin, *J. Gen. Chem.*, **44**, 45 (1974).
619. J. D. Ramanathan and Y. K. Jani, *Curr. Sci.*, **40**, 464 (1971).
620. M. Lipp, F. Dallacker, and G. Koenen, *Chem. Ber.*, **91**, 1660 (1958).
621. H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **88**, 1566 (1968).
622. H. C. Caldwell, J. A. Finkelstein, P. P. Goldman, A. J. Sivak, J. Schlosser, C. Pelikan, and W. G. Groves, *J. Med. Chem.*, **13**, 1076 (1970).
623. G. Alberghina, A. Arcoria, and S. Fisichella, *J. Org. Chem.*, **43**, 1122 (1978).
624. H. K. Kim and R. E. Bambury, *J. Med. Chem.*, **14**, 366 (1971).
625. W. K. Wapburton and M. J. Wilson, *J. Chem. Soc., Perkin Trans. I*, 2241 (1973).
626. H. C. Caldwell and W. L. Nobles, *J. Am. Chem., Soc.*, **76**, 1159 (1954).
627. E. Utterback and E. V. Bergstrom, U.S. Patent 2,477,502.
628. Z. M. Garashchenko, G. G. Skovortsova, and N. S. Krishtal, *Khim. Geterot. Soedin*, **7**, 1626 (1971).
629. G. Pappalardo, *Gazz. Chim. Ital.*, **89**, 1736 (1959).
630. M. A. McCall, *J. Org. Chem.*, **27**, 2433 (1962).
631. W. Opitz, M. Schwiertz, S. Raddatz, and P. R. Imeerge, *Arzneim-Forsch-Drug Res.*, **31**, 402 (1981).
632. A. F. Popov, L. I. Kostenko, V. V. Kravchenko, D. Vegh, and J. Kovac, *Ukr. Khim. Zh. USSR*, **48**, 526 (1982).
633. J. P. Verge and P. Roffey, *J. Med. Chem.*, **18**, 794 (1975).
634. E. Campaigne and R. L. White, Jr., *J. Heterocycl. Chem.*, **25**, 367 (1988).
635. S. B. Britton, H. C. Caldwell, and W. L. Nobles, *J. Am. Pharm. Assoc.*, **43**, 644 (1954).
636. S. B. Britton and W. L. Nobles, *J. Am. Pharm. Assoc.*, **44**, 717 (1955).

637. S. B. Britton, H. C. Caldwell, and W. L. Nobles, *J. Am. Pharm. Assoc.*, **43**, 641 (1954).
638. G. Karminskizamola and M. Bajic, *Heterocycles*, **23**, 1497 (1985).
639. G. M.Badger, J. H. Bowie, J. A. Elix, G. E. Lewis, and U. P. Singh, *Aust. J. Chem.*, **20**, 2669 (1967).
640. F. Bottari, G. Lippi, and B. Macchia, *Gazz. Chim. Ital.*, **99**, 762 (1969).
641. R. I. Pogonina, N. S. Pivnenko, V. P. Izvekov, and V. F. Lavrushin, *Chem. Het. Comp. USSR*, 24 (1971).
642. V. F. Lavrushin, R. I. Pogonina, N. S. Pivnenko, and V. P. Izvekov, *Chem. Het. Comp. USSR*, 1498 (1970).
643. J. B. Carr, P. Kirby, M. H. Goodrow, H. G. Durham, D. K. Hass, and J. J. Boudreau, *J. Med. Chem.*, **15**, 1231 (1972).
644. P. Pedaja and S. Gronowitz, *Chem. Scripta*, **22**, 53 (1983).
645. M. W. Majchrzak. *J. Hetrocycl. Chem.*, **22**, 1205 (1985).
646. Yu. D. Churkin and N. I. Putokhin, *Zh. Org. Khim.*, **1**, 596 (1965).
647. Ya. L. Go'dfarb, B. P. Fabrichnyi, and V. I. Rogovik, *Bull. Acad. Sci. USSR*, 492 (1965).
648. J. Skramstad, *Chem. Scripta*, **4**, 81 (1973).
649. R. Grafing and L. Brandsma, *Rec. Trav. Chim.—J. Roy. Neth. Chem.*, **99**, 23 (1980).
650. A. T. Jeffries III and S. Gronowitz, *Chem. Scripta*, **4**, 183 (1973).
651. M. J. Frazer and W. Gerrard, *Nature*, **204**, 1299 (1964).
652. O. Dann and H. Distler, *Chem. Ber.*, **87**, 365 (1954).
653. M. Nishio and T. Ito, *Chem. Pharm. Bull. (Tokyo)*, **13**, 1392 (1965).
654. T. Ito, M. Nishio, and H. Ogawa, Jpn. Patent 68,03,774.
655. M. Nishio and T. Ito, *Agr. Biol. Chem. (Tokyo)*, **29**, 732 (1965).
656. M. Nishio and T. Ito, *Agr. Biol. Chem. (Tokyo)*, **29**, 1119 (1965).
657. C. D. Mason and F. F. Nord, *J. Org. Chem.*, **16**, 1869 (1951).
658. A. M. Derijckere and F. G. F. Eloy, Ger. Patent. 2,059,386.
659. J. P. Maffrand and F. Eloy, *Eur. J. Med. Chem.-Chim. Ther.*, **9**, 483 (1974).
660. F. Eloy and A. Deryckere, *Extrait. Bull. Chim. Ther.*, **6**, 466 (1969).
661. C. L. Hickson and H. McNab, *Synthesis*, 464 (1981).
662. L. H. Klemm and J. N. Louris, *J. Heterocycl. Chem.*, **21**, 785 (1984).
663. V. K. Khairullin, R. R. Shagidullin, M. A. Vasyanina, I. K. Pokrovskaya, and A. N. Chernov, *Zh. Obshch. Khim. USSR*, **54**, 79 (1984).
664. A. A. Zimmerman, C. M. Orlando, Jr., M. H. Gianni, and K. Weiss, *J. Org. Chem.*, **34**, 73 (1969).
665. E. Maccarone, A. Mamo, G. Scarlata, and M. Torre, *J. Org. Chem.*, **44**, 2896 (1979).
666. E. Maccarone, A. Mamo, G. Scarlata, and M. Torre, *Tetrahedron*, **34**, 3531 (1978).
667. A. Josse, M. Stavaux, and N. Loza'ch, *Bull. Soc. Chim. Fr.*, **7–8**, 1723 (1974).
668. M. Sy, Ng. Ph. Buu-Hoi, and N. D. Xuong, *J. Chem. Soc.*, 1975 (1954).
669. Ng. Ph. Buu-Hoi and N. Hoan, *Rec. Trav. Chim.*, **68**, 441 (1949).
670. E. Campaigne, L. Fedor, and R. E. Johnson, *Heterocycl. Chem.*, **1**, 242 (1964).
671. H. Keskin, C. Mason, and F. Nord, *J. Org. Chem.*, **16**, 199 (1951).
672. N. Latif, N. Mishriky, and N. S. Girgis, *Indian J. Chem., Sect. B*, **15**, 118 (1977).
673. L. V. Panfilova, M. Y. Antipin, Y. D. Churkin, and Y. T. Struchkov, *Khim. Geterot. Soedin*, 1201 (1979).
674. A. I. Sitkin, V. I. Klimenko, and A. L. Fridman, *Zh. Org. Khim., USSR*, **13**, 2623 (1977).
675. Y. D. Churkin, L. V. Panfilova, V. D. Lugovoi, and N. V. Boiko, *Khim. Geterot. Soedin, USSR*, 913 (1981).

676. Y. D. Churkin, L. V. Panfilova, A. S. Shashkov, and K. Y. Burshtein, *Khim. Geterot. Soedin, USSR*, 325 (1981).

677. Y. D. Churkin, L. V. Panfilova, A. S. Shashkov, and K. Y. Burshtein, *Khim. Geterot. Soedin, USSR*, 753 (1981).

678. M. Hori, T. Kataoka, H. Shimizu, and S. Yoshimura, *J. Pharm. Soc. Jpn.*, **94**, 1445 (1974).

679. W. Carruthers and H. N. M. Stewart, *Tetrahedron Lett.*, 301 (1965).

680. S. Gronowitz and T. Dahlgren, *Chem. Scripta*, **12**, 57 (1977).

681. R. A. Crochet, J. T. Boatright, C. D. Blanton, C. T. Wie, and W. E. Hochholzer, *J. Heterocycl. Chem.*, **11**, 143 (1974).

682. J. G. Stuart, M. J. Quast, G. E. Martin, V. M. Lynch, S. H. Simonsen, M. L. Lee, R. N. Castle, J. L. Dallas, B. K. John, and L. F. Johnson, *J. Heterocycl. Chem.*, **23**, 1215 (1986).

683. V. H. Rawal, R. J. Jones, and M. P. Cava, *Tetrahedron Lett.*, **26**, 2423 (1985).

684. G. De Luca, G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. C*, 2504 (1970).

685. C. C. Leznoff, W. Lilie, and C. Manning, *Can. J. Chem.*, **52**, 132 (1974).

686. K. Maruyama, K. Mitsui, and T. Otsuki, *Chem. Lett.*, 853 (1977).

687. K. Maruyama, T. Otsuki, K. Mitsui, and M. Tojo, *J. Heterocycl. Chem.*, **17**, 695 (1980).

688. S. W. Schneller and J. D. Petru, *Syn. Commun.*, **4**, 29 (1974).

689. B. Capron and C. Paulmier, *Compt. Rend. Acad. Sci., Ser. C*, **279**, 947 (1974).

690. R. H. Everhardus, H. G. Eeuwhorst, and L. Brandsma, *J. Chem. Soc., Chem. Commun.*, 801 (1977).

691. B. D. Wilson, G. M. Haist, and I. A. Olwares, U.S. Patent 3,751,255.

692. P. Molina, P. M. Fresneda, and F. Hurtado, *Syn. Commun.*, **17**, 485 (1987).

693. P. Molina, P. M. Fresneda, and F. Hurtado, *Synthesis*, 45 (1987).

694. S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand.*, **B30**, 391 (1976).

695. R. S. Gairns, R. D. Grant, C. J. Moody, C. W. Rees, and S. C. Tsoi, *J. Chem. Soc., Perkin Trans. I*, 483 (1986).

696. R. S. Gairns, C. J. Moody, C. W. Rees, and S. C. Tsoi, *J. Chem. Soc., Perkin Trans. I*, 497 (1986).

697. R. D. Grant, C. W. Rees, and D. J. Williams, *J. Chem. Soc., Chem., Commun.*, 1060 (1982).

698. C. J. Moody, C. W. Rees, and S. C. Tsoi, *J. Chem. Soc., Chem. Commun.*, 550 (1981).

699. R. S. Gairns, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1818 (1985).

700. L. Cavara, F. Gerson, D. O. Cowan, and K. Lerstrup, *Helv. Chim. Acta*, **69**, 141 (1986).

701. M. Farnier, M. Brost, B. Hanquet, and R. Guilard, *J. Heterocycl. Chem.*, **23**, 513 (1986).

702. K. K. Balasubramnian, *Indian J. Chem., Sect. B*, **20**, 271 (1981).

703. S. Gronowitz and I. Ander, *Chem. Scripta*, **15**, 135 (1980).

704. M. J. S. Dewar and P. A. Marr, *J. Am. Chem. Soc.*, **84**, 3782 (1962).

705. J. T. Suk and B. M. Puma, *J. Org. Chem.*, **30**, 2253 (1965).

706. A. Foucaud, *Bull. Soc. Chim. Belg.*, **90**, 545 (1981).

707. M. C. Rebstock and Ch. D. Stratton, *J. Am. Chem. Soc.*, **77**, 3082 (1955).

708. A. L. Poot, R. G. Lemahieu, W. Janssens, and A. A. De Jaeger, Ger. Patent 2,362,956.

709. D. R. Shridhar, C. V. R. Sastry, and B. Lal, *Indian J. Chem., Sect. B*, **24**, 1102 (1985).

710. A. De, J. S. A. Brunskill, and H. Jeffrey, *Indian J. Chem., Sect. B*, **23**, 918 (1984).

711. S. Liljefors and S. Gronowitz, *Chem. Scripta*, **15**, 102 (1980).

712. N. Latif, N. Mishriky, and N. S. Girgis, *Indian J. Chem., Sect. B*, **20**, 147 (1981).

713. K. Matsumoto, T. Ochida, Y. Yagi, H. Tahara, and R. M. Acheson, *Heterocycles*, **23**, 2041 (1985).

714. G. E. H. Elgemeie, E. A. A. Hafez, G. A. M. Nawar, and M. H. Elnagdi, *Heterocycles*, **22**, 2829 (1984).
715. G. E. H. Elgemeie and F. A. Abdelaal, *Heterocycles*, **24**, 349 (1986).
716. E. Degny, S. Z. Zard, R. Pastor, and A. Cambon, *Tetrahedron Lett.*, **22**, 2169 (1981).
717. E. A. Aripov, D. A. Usmanova, and Y. A. El'tekov, *Dokl. Akad. Nauk Uzb. SSR*, **26**, 36 (1969).
718. J. Sam and A. C. Thompson, *J. Pharm. Sci.*, **52**, 898 (1963).
719. L. K. Freidlin, E. F. Litvin, and V. M. Chursina, *Khim. Geterot. Seodin. USSR*, 14 (1967).
720. S. Gronowitz, L. Svensson, M. Herslöf, and O. Karlsson, *Acta Pharm. Suecica*, **16**, 353 (1979).
721. S. Gronowitz, L. Svensson, N. Stjernström, and S. O. Ögren, *Acta Pharm. Suecica*, **16**, 365 (1979).
722. S. Gronowitz, L. Svensson, M. Herslöf, A. Tjörnebo, N. Stjernström, and S. O. Ögren, *Acta Pharm. Suecia*, **16**, 376 (1979).
723. C. Cativiela, J. A. Mayoral, E. Meléndez, L. A. Oro, M. T. Pinillos, and R. Uson, *J. Org. Chem.*, **49**, 2502 (1984).
724. J. M. Hoffman, Jr. and R. H. Schlessinger, *J. Chem. Soc. D*, **20**, 1245 (1971).
725. Ng. Ph. Buu-Hoi and M. Sy, *Compt. Rend.*, **242**, 2011 (1956).
726. D. Papa, E. Schwenk, and A. F. Ginsberg, *J. Org. Chem.*, **14**, 723 (1949).
727. A. W. Horton, *J. Org. Chem.*, **14**, 761 (1949).
728. S. Gronowitz and S. Liljefors, *Chem. Scripta*, **13**, 39 (1978–79).
729. S. Gronowitz, T. Dahlgren, J. Namtvedt, C. Roos, B. Sjöberg, and U. Forsgren, *Acta Pharm. Suecica*, **8**, 377 (1971).
730. E. E. Campaigne and W. C. McCarthy, *J. Am. Chem. Soc.*, **76**, 4466 (1954).
731. T. Kametani, Y. Ito, and S. Aonuma, *J. Pharm. Soc. Jpn.*, **74**, 1301 (1954).
732. R. T. Gilsdorf and F. F. Nord, *J. Am. Chem. Soc.*, **74**, 1837 (1952).
733. L. Lunazzi, A. Mangini, G. Placucci, P. Spagnolo, and M. Tiecco, *J. Chem. Soc., Perkin Trans. II*, 192 (1972).
734. K. Ankner, B. Lamm, B. Thulin, and O. Wennerström, *J. Chem. Soc., Perkin Trans. II*, 1301 (1980).
735. W. S. Emerson and T. M. Patrick, Jr., U.S. Patent 2,612,506.
736. A. Attia and M. Michael, *Acta Chim. Hung.*, **114**, 337 (1983).
737. H. S. Kachi and V. Taniguchi, *Yakugaku Zasshi*, **87**, 704 (1967).
738. W. W. Emerson and T. M. Patrick, Jr., U.S. Patent 2,503,197.
739. D. J. Donnelly, J. A. Donnelly, and E. M. Philbin, *Tetrahedron*, **28**, 53 (1972).
740. V. F. Belyaev and A. I. Abrazhevich, *Chem. Het. Comp. USSR*, 170 (1967).
741. A. Arcoria, F. P. Ballistreri, A. Cantone, G. Musumarra, and M. Tripolone, *Gazz. Chim. Ital.*, **110**, 267 (1980).
742. M. F. Shostakovskii, A. S. Nakhmanovich, and V. N. Elokhina, *Khim. Geterot. Soedin, Sb.*, 31 (1971).
743. R. Guilard and B. Hanquet, *Compt. Rend. Acad. Sci., Ser. C*, **278**, 295 (1974).
744. B. Haquet and R. Guilard, *Compt. Rend. Acad. Sci., Ser. C*, **287**, 515 (1978).
745. B. Hanquet, R. Guilard, and P. Fournari, *Bull. Soc. Chim. Fr., Part 2*, 571 (1977).
746. B. Hanquet, R. Guilard, and Y. Dusausoy, *J. Chem. Soc., Perkin Trans. I*, 983 (1985).
747. B. Hanquet and R. Guilard, *Can. J. Chem.*, **64**, 1360 (1986).
748. H. C. Brown, J. V. N. V. Prasad, and S. H. Zee, *J. Org. Chem.*, **51**, 439 (1986).
749. K. Mizuno, S. Toda, and Y. Otsuji, *Chem. Lett.*, 203 (1987).
750. L. N. Koikov, P. B. Terent'ev, and N. S. Kulikov, *Zh. Org. Khim.*, **17**, 1087 (1981).

751. C. R. Crane, Jr., *Chem. Abstr.*, **52**, 8892i.
752. H. Yanagisawa, S. Ishihara, A. Ando, T. Kanazaki, S. Miyamoto, H. Koike, Y. Iijima, K. Oizumi, Y. Matsushita, and T. Hata, *J. Med. Chem.*, **30**, 1984 (1987).
753. G. H. Berezin and G. H. Harris, U.S. Patent 3,219,679.
754. G. Soldati, *J. Pharm. Sci.*, **64**, 355 (1975).
755. E. Abad, J. Fayn, B. Bertaina, and A. Cambon, *J. Fluorine Chem.*, **24**, 233 (1984).
756. P. Messinger and J. Gompertz, *Arch. Pharm.*, **308**, 737 (1975).
757. W. Ried and G. Dankert, *Chem. Ber.*, **90**, 2707 (1957).
758. M. M. Elkerdawy, A. A. Samour, and A. A. Elagamey, *Pharmazie*, **30**, 76 (1975).
759. A. M. Abouof, M. Elkerdawy, H. Ragab, and M. Moustafa, *Pharmazie*, **34**, 798 (1979).
760. A. M. Islam, K. A. M. El-Bayouki, and H. H. Moharram, *Pharmazie*, **39**, 382 (1984).
761. G. V. Dmitrieva, F. N. Mazitova, and V. K. Khairullin, *Zh. Org. Khim.*, **13**, 419 (1977).
762. A. Mustafa and A. H. E. Harhash, *J. Am. Chem. Soc.*, **78**, 1649 (1956).
763. Y. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Obshch. Khim.*, **34**, 1078 (1964).
764. D. M. Torikov, L. G. Ol'khina, and A. Z. Bikkulov, *Dokl. Neftekhim. Sekts. Bashkir. Respub. Praol. Vses. Khim. Obshchest.*, **6**, 220 (1971).
765. T. Metchkov, Z. Demireva, and E. Tontcheva, *Zh. Chem.*, **25**, 62 (1985).
766. M. Bolourtchian and A. Saednya, *Bull. Soc. Chim. Fr., Part 2*, 170 (1978).
767. P. Kocovsky and D. Dvorak, *Tetrahedron Lett.*, **27**, 5015 (1986).
768. G. E. H. Elgemeie, A. E.-K. M. Gohar, H. A. Regaila, and H. A. Elfahham, *Arch. Pharm.*, **321**, 131 (1988).
769. D. T. Connor and M. V. Strandtmann, *J. Org. Chem.*, **38**, 1047 (1973).
770. M. M. Zobacheva and V. V. Perekalin, *Nauch. Dokl. Vysshei Shkoly. Khim. i Khim. Tekhnol.*, 740 (1958).
771. Y. D. Churkin and N. I. Putokhin, *Zh. Org. Khim. USSR*, **1**, 1015 (1965).
772. Y. D. Churkin and N. I. Putokhin, *Zh. Org. Khim. USSR*, **1**, 599 (1965).
773. A. Minato, K. Tamao, K. Suzuki, and M. Kumada, *Tetrahedron Lett.*, **21**, 4017 (1980).
774. H. Wynberg, M. B. Groen, and R. M. Kellogg, *J. Org. Chem.*, **35**, 2828 (1970).
775. J. Bernstein, S. Green, and M. Rejto, *J. Am. Chem. Soc.*, **102**, 323 (1980).
776. H. Lumbroso, D. M. Bertin, J. Morel, and C. Paulmier, *Bull. Soc. Chim. Fr.*, 1924 (1973).
777. G. Jones and P. Rafferty, *Tetrahedron*, **35**, 2027 (1979).
778. W. A. Pryor, J. H. Coco, W. H. Daly, and K. N. Houk, *J. Am. Chem. Soc.*, **96**, 5591 (1974).
779. W. E. Noland, B. A. Langager, J. W. Manthey, and A. G. Zacchei, *Can. J. Chem.*, **45**, 2969 (1967).
780. M. Matsumoto, S. Dobashi, and K. Kondo, *Tetrahedron Lett.*, 4471 (1975).
781. Y. P. Porshney, E. M. Tershchenko, and V. B. Mochalin, *Khim. Geterot. Soedin*, 1329 (1974).
782. M. A. Fox and J. R. Hurst, *J. Am. Chem. Soc.*, **106**, 7626 (1984).
783. A. Foucaud, C. Razorilalana-Rabearivony, E. Loukakou, and H. Person, *J. Org. Chem.*, **48**, 3639 (1983).
784. Y. Yamashita, Y. Miyauchi, and M. Masumura, *Chem. Lett.*, 489 (1983).
785. G. B. Bachman, L. J. Filar, R. W. Finholt, L. V. Heisey, H. M. Hellman, L. L. Lewis, and D. D. Micucci, *Ind. Eng. Chem.*, **43**, 997 (1951).
786. E. C. Pitzer, U.S. Patent 2,505,204.
787. C. Aso, T. Kunitake, M. Shinsenji, and H. Miyazaki, *J. Polymer Sci., A-1*, **7**, 1497 (1969).
788. I. V. Andreeva and M. M. Koton, *Zh. Fiz. Khim.*, **32**, 1847 (1958).
789. S. Murahashi, S. Nozakura, and K. Hatada, *Bull. Chem. Soc. Jpn.*, **34**, 939 (1961).

790. K. Kuwata, H. Kawazura, and K. Hiroto, *Nippon Kagaku Zasshi*, **81**, 1770 (1960).

791. T. Fueno, T. Tsuruta, and J. Furukawa, *J. Polym. Sci.*, **40**, 499 (1959).

792. A. S. Nakhmanovich, G. G. Skvortsova, L. A. Shulyak, and G. V. Parshakova, *Chem. Het. Comp. USSR*, **3**, 356 (1967).

793. D. L. Trumbo, T. Suzuki, and H. J. Harwood, *Polym. Bull.*, **4**, 677 (1981).

794. D. L. Trumbo, T. Suzuki, and H. J. Harwood, *Polym. Prep.*, **24**, 360 (1983).

795. S. Yamada, S. Tokito, T. Tsutsui, and S. Saito, *J. Chem. Soc., Chem. Commun.*, 1448 (1987).

796. L. Corre, M. De Clercq, Ng. Ph. Buu-Hoi, and A. Lacassagne, *Bull. Soc. Chim. Biol.*, **30**, 674 (1948).

797. P. Gley, Ng. Ph. Buu-Hoi, N. H. Nam, N. D. Xuong, and J. Delor, *Bull. Soc. Chim. Biol.*, **36**, 1249 (1954).

798. Ng. Ph. Buu-Hoi, J. M. Gazace, N. D. Xuong, G. Dufraisse, and N. H. Nam, *Bull. Soc. Chim. Biol.*, **38**, 223 (1956).

799. J. M. Gazace, Ng. Ph. Buu-Hoi, N. D. Xuong, and H. Clédiére, *Bull. Soc. Chim. Biol.*, **39**, 1343 (1957).

800. Ng. Ph. Buu-Hoi, *Acta Unio. Intn. Contra Cancrum.*, **13**, 442 (1957).

801. M. Bellenghi and A. Wittgens, *Arzneimittel-Forsch.*, **8**, 263 (1958).

802. M. T. Timbal, *Antibiot. Chemother.*, **8**, 93 (1958).

803. F. Fujikawa, K. Hirai, O. Sawada, J. Goto, M. Naito, and S. Tsukuma, *Yakugaku Zasshi*, **88**, 728 (1963).

804. P. Roffey and J. P. Verge, Br. Patent 1,317,257.

805. Farbenfarbriken Bayer A.-G., Br. Patent 708,013.

806. E. Testa, A. Bonati, and G. Pagani, *Chimia (Switz.)*, **15**, 314 (1961).

807. G. Carrara, E. Ginoulhiac, G. Rolland, and M. T. Timbal, *II. Farmaco (Pavia) Ed. Sci.*, **9**, 39 (1954).

808. E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *Arch. Ital. Sci. Farmacol.*, **4**, 267 (1964).

809. H. C. Caldwell and W. L. Nobles, *J. Am. Pharm. Assoc.*, **45**, 729 (1956).

810. M. Janda and J. Kure, *Sb. Vys. Sk. Chem.—Technol. Praze. Org. Technol.*, **11**, 5 (1967).

811. G. Carrara and E. Testa, Br. Patent 759,378.

812. W. C. Austin, R. L. Cornwell, R. M. Jones, and M. Robinson, *J. Med. Chem.*, **15**, 281 (1972).

813. C. Rufer. H. J. Kessler, and A. Damerius, *Chim. Ther.*, **7**, 122 (1972).

814. J. G. Strong, U.S. Patent 3,696,199.

815. J. B. Carr, P. Kirby, M. H. Goodrow, H. G. Durham, D. K. Hass, and J. J. Boudreau, *J. Med. Chem.*, **15**, 1231 (1972).

816. C. Pfizer and Inc. Co., Br. Patent 1,191,372.

817. R. Cavier, J. Cenac, R. Royer, and L. Rene, *Chim. Ther.*, **5**, 270 (1970).

818. A. Clitheroe, D. Green, A. B. A. Jansen, P. C. Phillips, and A. W. Rule, *J. Pharm. Pharmacol.*, **17**, 167 (1965).

819. W. Drenth and M. J. Handele, *Rec. Trav. Chim. Pays-Bas*, **91**, 688 (1972).

820. N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).

821. T. Meshi, S. Nakamura, and T. Kanno, *Chem. Pharm. Bull (Tokyo)*, **21**, 1709 (1973).

822. Y. Kase and T. Yuizono, *Chem. Pharm. Bull. (Tokyo)*, **7**, 378 (1959).

823. N. Sugimoto, K. Okumura, N. Shigematsu, and G. Hayashi, *Chem. Pharm. Bull. (Tokyo)*, **10**, 1061 (1962).

824. Y. Sasaki, J. Sugihara, A. Watanabe, M. Sakuma, M. Otsuka, and Y. Sato, *Yakugaku Zasshi*, **89**, 345 (1969).

825. J. A. Gautier, C. L. Combet-Farnoux, H. Nakjima, and J. Thuillier, *Med. Pharmacol. Exp.*, **13**, 325 (1965).
826. A. F. Green, *Br. J. Pharmacol.*, **8**, 2 (1953).
827. Tanabe Seiyaku Co., Ltd., Jpn. Patent 4243 (1962).
828. T. Tamura, *Yakkyoku*, **6**, 1269 (1955).
829. S. B. Binkley and L. C. Cheney, U.S. Patent 2,703,324.
830. A. H. Beckett and A. F. Casy, *Nature*, **173**, 1231 (1954).
831. Smith Kline & French Laboratories, Neth. Patent 6,507,155.
832. R. Ziegler, B. Ho, and N. Castagnoli, *J. Med. Chem.*, **24**, 1133 (1981).
833. A. Ricci, A. Fravolini, and D. Balucani, *Ann. Chim. (Rome)*, **58**, 1238 (1969).
834. H. Berger, K. Stach, and W. Voemel, S. Afr. Patent 67 06.255.
835. H. C. Caldwell, P. N. Craig, and W. G. Groves, *J. Med. Chem.*, **13**, 1079 (1970).
836. T. H. Haskell, F. F. Peterson, D. Watson, N. R. Plessas, and T. Culbertson, *J. Med. Chem.*, **13**, 697 (1970).
837. A. Serban and L. G. Webber, S. Afr. Patent 72 06.590.
838. Z. Vasela and S. Truchlik, Czech. Patent 152,838.
839. Sankyo Co., Ltd., Fr. Patent 1,366,363.
840. S. Minakami and K. Nagata, Jpn. Patent 68 27.842.
841. J. S. Sörensen and N. A. Sörensen, *Acta Chem. Scand.*, **12**, 771 (1958).
842. R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *Tetrahedron Lett.*, **5**, 3159 (1964).
843. F. Bohlmann, C. Arndt, K. M. Kleine, and M. Wotschokowsky, *Chem. Ber.*, **98**, 1228 (1965).
844. T. B. Waggoner, *Univ. Microfilms; Diss. Abstr.*, **25**, 2244 (1964).
845. F. Bohlmann, C. Arndt, K. M. Kleine, and H. Bornowski, *Chem. Ber.*, **98**, 155 (1965).
846. F. Bohlmann, K. M. Kleine, and C. Arndt, *Chem. Ber.*, **97**, 2125 (1964).
847. E. Winterfeldt, *Chem. Ber.*, **96**, 3349 (1963).
848. F. Bohlmann and R. Jente, *Chem. Ber.*, **99**, 995 (1966).
849. F. Bohlmann, K. M. Kleine, C. Arndt, and S. Koehn, *Chem. Ber.*, **98**, 1616 (1965).
850. E. Guddal and N. A. Sörensen, *Acta Chem. Scand.*, **13**, 1185 (1959).
851. K. E. Schulte, G. Ruecker, and F. P. Dressen, *Planta Med.*, **14**, 162 (1966).
852. J. S. Sörensen, J. T. Mortensen, and N. A. Sörensen, *Acta Chem. Scand.*, **18**, 2182 (1964).
853. C. Parkanyi and W. C. Herndon, *Phosphorus Sulfur*, **4**, 1 (1978).
854. H. Guesten, L. Klasinc, and O. Volkert, *Z. Naturforsch., B*, **24**, 12 (1969).
855. J. Fabian and H. Hartmann, *Z. Chem.*, **18**, 145 (1978).
856. J. P. Pinan-Lucarre, J. Loisel, and J. Vincent-Geisse, *Chem. Phys.*, **62**, 251 (1981).
857. C. C. Prince and E. A. Dudley, *J. Am. Chem. Soc.*, **78**, 68 (1956).
858. H. Hopff and A. Krieger, *Helv. Chim. Acta*, **44**, 1058 (1961).
859. S. Gruttadauria, G. C. Pappalardo, G. Scarlata, and M. Torre, *J. Chem. Soc. Perkin Trans. II*, 1580 (1974).
860. H. Lumbroso, C. Liegeois, N. Dereu, L. Christiaens, and A. Luxen, *J. Mol. Struct.*, **67**, 251 (1980).
861. S. V. Tsukerman, V. M. Nikitchenko, V. D. Orlov, and V. F. Lavrushin, *Chem. Het. Comp. USSR*, 173 (1967).
862. V. I. Savin, S. A. Flegontov, and Y. P. Kitaev, *Khim. Geterot. Soedin*, 1331 (1972).
863. V. I. Savin, S. A. Flegontov, and Y. P. Kitaev, *Chem. Het. Comp. USSR*, 1109 (1970).
864. J. Hrabovsky, J. Kovac, and M. Kaprinayova, *Coll. Czech. Chem. Commun.*, **51**, 1127 (1986).
865. J. Tirouflet and A. Corvaisier, *Bull. Soc. Chim. Fr.*, 535 (1962).

866. C. Caullet, *Bull. Soc. Chim. Fr.*, 3532 (1965).
867. C. Caullet, *Bull. Soc. Chim. Fr.*, 3459 (1965).
868. G. C. Pappalardo, *Boll. Sedute. Accad. Gioenia Sci. Natur. Catania*, **9**, 466 (1968).
869. H. Satonaka, *Magn. Reson. Chem.*, **24**, 265 (1986).
870. M. Dandarova, J. Kovac, D. Vegh, and V. Zvak, *Coll. Czech. Chem. Commun.*, **47**, 3412 (1982).
871. M. Dandarova, D. Vegh, J. Kovac, I. Goljer, N. Pronayova, and K. Spirkova, *Coll. Czech. Chem. Commun.*, **51**, 889 (1986).
872. T. N. Huckerby, *Tetrahedron Lett.*, **12**, 353 (1971).
873. A. F. Cockerill, D. M. Rackham, and N. C. Franklin, *J. Chem. Soc., Perkin Trans. II*, 509 (1973).
874. F. A. Bottino, G. Scarlata, D. Sciotto, and M. Torre, *Spectrochim. Acta, Part A*, **36A**, 205 (1980).
875. A. Arcoria, F. A. Bottino, and D. Sciotto, *J. Heterocycl. Chem.*, **14**, 1353 (1977).
876. H. Satonaka and M. Watanabe, *Bull. Chem. Soc. Jpn.*, **58**, 3651 (1985).
877. K. Fujieda, K. Takahashi, and T. Sone, *Bul. Chem. Soc. Jpn.*, **58**, 1587 (1985).
878. F. P. Ballistreri, G. Musumarra, and G. Scarlata, *Chem. Scripta*, **18**, 214 (1981).
879. G. Musumarra and F. P. Ballistreri, *Chem. Scripta*, **18**, 209 (1981).
880. S. P. Bhattacharyya, A. De, A. K. Chakravarty, J. S. A. Brunskill, and D. F. Ewing, *J. Chem. Soc., Perkin Trans. II*, 473 (1985).
881. N. S. Pivnenko, L. M. Grin, R. I. Pogonina, and V. F. Lavrushin, *Teor. Eksp. Khim.*, **8**, 78 (1972).
882. J. Skramstad, *Chem. Scripta*, **4**, 77 (1973).
883. C. K. Coogan, D. H. S. Horn, and J. A. Lamberton, *Aust. J. Chem.*, **18**, 723 (1965).
884. M. P. Trompen, C. Kruk, P. J. van der Haak, and H. O. Huisman, *Rec. Trav. Chim.*, **85**, 185 (1966).
885. T. Olsson, D. Tanner, B. Thulin, O. Wennerström, and T. Liljefors, *Tetrahedron*, **37**, 3473 (1981).
886. A. Bellino, M. L. Marino, and P. Venturella, *Heterocycles*, **20**, 2203 (1983).
887. K. E. Schulte, A. Kreutzberger, and G. Bohn, *Chem. Ber.*, **97**, 3263 (1964).
888. A. Hidalgo, *J. Phys. Radium*, **16**, 366 (1955).
889. I. H. Rosatzin, *Spectrochim. Acta*, **19**, 1107 (1963).
890. A. Hidalgo, *Compt. Rend.*, **239**, 253 (1954).
891. T. Marey, P. Fournari, and J. Tirouflet, *Compt. Rend.*, **260**, 4340 (1964).
892. A. Arcoria, S. Fisichella, G. Scarlata, and M. Torre, *J. Heterocycl. Chem.*, **10**, 643 (1973).
893. C. Caullet, *Compt. Rend.*, **260**, 1599 (1965).
894. S. Fisichella, G. Scarlata, and M. Torre, *Gazz. Chim. Ital.*, **104**, 1237 (1974).
895. S. Millefiori, G. Scarlata, A. Millefiori, and D. Carbone, *Z. Phys. Chem.*, **128**, 63 (1981).
896. A. Perjéssy, P. Temkowitz, and D. W. Boykin, Jr., *Coll. Czech. Chem. Commun.*, **44**, 2832 (1979).
897. S. V. Tsukerman, L. A. Kutulya, Y. N. Surov, V. F. Lavrushin, and Y. K. Yur'ev, *Dokl. Akad. Nauk SSSR*, **164**, 354 (1965).
898. S. V. Tsukerman, L. A. Kutulya, and V. F. Lavrushin, *Khim. Geterot. Soedin*, 803 (1965).
899. S. V. Tsukerman, V. M. Nikitchenko, Y. S. Rozum, and V. F. Lavrushin, *Chem. Het. Comp. USSR*, 361 (1967).
900. C. Caullet, *Compt. Rend.*, **260**, 2457 (1965).
901. E. G. Treshchova, D. Ekkhardt, and Y. K. Yur'ev, *Zh. Fiz. Khim.*, **38**, 295 (1964).
902. M. J. Janssen and J. W. van Reijendam, *Z. Chem.*, **10**, 261 (1970).

903. J. W. van Reijendam and M. J. Janssen, *Tetrahedron*, **26**, 1303 (1970).
904. K. Schloegl and H. Egger, *Liebigs Ann.*, **676**, 76 (1964).
905. V. F. Lavrushin, S. V. Tsukerman, and V. M. Nikitchenko, *Zh. Obshch. Khim.*, **32**, 2677 (1962).
906. V. F. Lavrushin, S. V. Tsukerman, and V. M. Nikitchenko, *Zh. Obshch. Khim.*, **32**, 3971 (1962).
907. H. H. Szmant and H. J. Planinsek, *J. Am. Chem. Soc.*, **76**, 1193 (1954).
908. V. M. Nikitchenko, S. V. Tsukerman, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **33**, 2563 (1963).
909. S. V. Tsukerman, V. M. Nikitchenko, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **33**, 1255 (1963).
910. L. E. Coleman, *J. Org. Chem.*, **21**, 1193 (1956).
911. S. V. Tsukerman, I.-S. Chang, and V. F. Lavrushin, *Zh. Prikl. Spectroskopii Akad. Nauk Belorussk. SSR*, **4**, 554 (1966).
912. S. V. Tsukerman, V. D. Orlov, and V. F. Lavrushin, *Chem. Het. Comp. USSR*, 55 (1969).
913. C. Hanna and F. W. Schueler, *J. Am. Chem. Soc.*, **75**, 741 (1953).
914. A. Ancona, S. Casadio, and S. Fantelli, *II Farmaco (Pavia), Ed. Sci.*, **9**, 438 (1954).
915. M. Picon, *Compt. Rend.*, **227**, 1381 (1948).
916. S. V. Tsukerman, L. A. Kutulya, V. M. Nikitchenko, and V. F. Lavrushin, *Org. Khim., Tartu.*, **1**, 309 (1962).
917. S. V. Tsukerman, L. A. Kutulya, V. F. Lavrushin, and M. T. Nguyen, *Zh. Fiz. Khim.*, **42**, 1930 (1968).
918. S. V. Tsukerman, L. A. Kutulya, Y. N. Surov, V. F. Lavrushin, and Y. K. Yur'ev, *Dokl. Akad. Nauk SSSR*, **164**, 354 (1965).
919. S. V. Tsukerman, L. A. Kutulya, V. F. Lavrushin, and Y. K. Yur'ev, *Khim. Geterot. Soedin*, 376 (1966).
920. S. V. Tsukerman, L. A. Kutulya, Y. N. Surov, and V. F. Lavrushin, *Chem. Het. Comp. USSR*, 1097 (1979).
921. V. M. Tolmachov, O. F. Boberov, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **35**, 1841 (1965).
922. O. F. Boberov, V. M. Tolmachov, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **35**, 2130 (1965).
923. V. M. Tomachov, O. F. Boberov, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **35**, 1841 (1965).
924. T. Liljefors, U. Michael, B. Yom-Tov, and S. Gronowitz, *Acta Chem. Scand.*, **27**, 2485 (1973).
925. T. Wismontski-Knittel and P. K. Das, *J. Phys. Chem.*, **88**, 1168 (1984).
926. C. Julienlarose, M. Guerret, D. Lavene, and J. R. Kiechel, *Biomed. Mass. Spectrom.*, **10**, 136 (1983).
927. D. V. Ramana and M. Vairamani, *Indian, J. Chem., Sect. B*, **17**, 369 (1979).
928. G. K. Musorin, V.Y. Vitkovskii, S. V. Amosova, and B. A. Trofimov, *Zh. Org. Khim.*, **21**, 1320 (1985).
929. M. E. Amato, S. Fisichella, S. Occhipinti, and G. Scarlata, *Phosphor Sulfur Relat. Elem.*, **29**, 35 (1987).
930. J. R. McCarthy, C. Barney, D. P. Matthews, and T. M. Bargar, *Tetrahedron Lett.*, **28**, 2207 (1987).
931. V. R. Kuhn and J. Jahn, *Chem. Ber.*, **86**, 759 (1953).
932. B. D. Tilak and A. M. Malte, *Indian J. Chem.*, **7**, 1175 (1969).
933. P. Cadiot, B. Rutimeyer, and A. Willemart, *Compt. Rend.*, **231**, 659 (1950).
934. P. Cadiot and A. Willemart, *Bull. Soc. Chim. Fr.*, 100 (1951).
935. P. Cadiot, *Ann. Chim. (Paris)*, **1**, 214 (1956).
936. A. Vaitiekunas and F. F. Nord, *J. Org. Chem.*, **19**, 902 (1954).
937. K. E. Schulte and G. Bohn, *Arch. Pharm.*, **297**, 179 (1964).
938. A. J. Osbahr, A. Vaitiekunas, and F. F. Nord, *J. Am. Chem. Soc.*, **77**, 1911 (1955).
939. F. Bohlmann, H. Bornowski, and D. Kramer, *Chem. Ber.*, **96**, 584 (1963).

940. J. C. Craig and M. Moyle, *J. Chem. Soc.*, 3907 (1963).
941. L. Skatteboel, *Acta Chem. Scand.*, **13**, 1460 (1959).
942. J. Kagan, G. Chan, S. N. Dhawan, S. K. Arora, and I. Prakash, *Lloydia—J. Nat. Prod.*, **46**, 646 (1983).
943. J. P. Beny and J. Kagan, *J. Label. Comp. Radiopharm.*, **19**, 313 (1982).
944. M. Dauria, A. Demico, F. Donofrio, and G. Piancatelli, *Syn. Commun*, **17**, 491 (1987).
945. M. Dauria, A. Demico, F. Donofrio, and G. Piancatelli, *J. Chem. Soc., Perkin Trans. I*, 1777 (1987).
946. J. Kagan, S. K. Arora, I. Prakash, and A. Ustunol, *Heterocycles*, **20**, 1341 (1983).
947. T. B. Patrick and J. L. Honegger, *J. Org. Chem.*, **39**, 3791 (1974).
948. C. Wentrup and H. W. Winter, *Angew. Chem.*, **90**, 643 (1978).
949. T. B. Patrick, J. M. Disher, and W. J. Probst, *J. Org. Chem.*, **37**, 4467 (1972).
950. Y. Xin, X. Wu, and Y. Shen, *J. Fluorine Chem.*, **40**, 15 (1988).
951. G. F. Nazvanova, V. V. Moskva, T. S. Sitdikova, and F. A. Kashfarova, *Izv. Vyssh. Uchebn. Zaved., Khim. Tekhnol.*, **25**, 37 (1982).
952. R. Raap, *Can. J. Chem.*, **49**, 2155 (1971).
953. R. Raap and R. G. Micetich, *Can. J. Chem.*, **46**, 1057 (1968).
954. D. H. Wadsworth, S. M. Geer, and M. R. Detty, *J. Org. Chem.*, **52**, 3662 (1987).
955. R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *Chem. Ind. (London)*, 2101 (1964).
956. F. Bohlmann, M. Wotschokowsky, U. Hinz, and W. Lucas, *Chem. Ber.*, **99**, 984 (1966).
957. R. E. Atkinson and R. F. Curtis, *Tetrahedron Lett.*, **6**, 297 (1965).
958. M. D. Rausch, A. Siegel, and L. P. Klemann, *J. Org. Chem.*, **31**, 2703 (1966).
959. R. E. Atkinson, R. F. Curtis, and J. A. Taylor, *J. Chem. Soc. C.*, 578 (1967).
960. R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *Chem. Commun.*, 718 (1967).
961. R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *J. Chem. Soc. C.*, 2173 (1969).
962. F. Bohlmann and W. Skuballa, *Chem. Ber.*, **106**, 497 (1973).
963. F. Bohlmann and P. D. Hopf, *Chem. Ber.*, **106**, 3621 (1973).
964. F. Bohlmann, C. Zdero, and H. Kapteyn, *Chem. Ber.*, **106**, 2755 (1973).
965. A. Carpita, A. Lezzi, R. Rossi, F. Marchetti, and S. Merlino, *Tetrahedron*, **41**, 621 (1985).
966. D. Brown, J. Craig, N. H. Dyson, and J. W. Westley, *J. Chem. Soc., Org.*, 89 (1966).
967. R. Rossi, A. Carpita, and A. Lezzi, *Tetrahedron*, **40**, 2773 (1984).
968. A. Carpita, R. Rossi, and C. A. Veracini, *Tetrahedron*, **41**, 1919 (1985).
969. J. K. Stille and J. H. Simpson, *J. Am. Chem. Soc.*, **109**, 2138 (1987).
970. T. X. Neenan and G. M. Whitesides, *J. Org. Chem.*, **53**, 2489 (1988).
971. A. S. Zanina, G. N. Khabibulina, V. V. Legkoderya, and I. L. Kotlyarevskii, *Zh. Org. Khim.*, **8**, 1527 (1972).
972. F. Boberg, *Angew. Chem.*, **73**, 579 (1961).
973. K. Schlögl and H. Pelousek, *Monatsh. Chem.*, **92**, 51 (1961).
974. Sankyo Co., Ltd., Jpn. Patent 11.123 (1961).
975. K. Tanaka, I. Iwai, Y. Yura, and K. Tomita, *Chem. Pharm. Bull. (Tokyo)*, **8**, 252 (1960).
976. M. C. Verploegh, L. Donk, H. J. T. Bos, and W. Drenth, *Rec. Trav. Chim. Pays-Bas*, **90**, 765 (1971).
977. A. Carpita, D. Neri, and R. Rossi, *Gazz. Chim. Ital.*, **117**, 481 (1987).
978. P. J. Elving and C. M. Callahan, *J. Am. Chem. Soc.*, **77**, 2077 (1955).
979. F. Bohlmann and A. Suwita, *Chem. Ber.*, **108**, 515 (1975).

980. W. T. Smith, Jr. and R. W. Shelton, *J. Am. Chem. Soc.*, **76**, 2731 (1954).
981. P. Cagniant and G. Merle, *Compt. Rend. Acad. Sci. (Paris) Ser. C*, **264**, 112 (1967).
982. F. Bohlmann and J. Kocur, *Chem. Ber.*, **107**, 2115 (1974).
983. B. S. Tanaseichuk and S. V. Yartseva, *Zh. Org. Khim.*, **7**, 1299 (1971).
984. S. F. Birch, T. V. Cullum, R. A. Dean, and R. L. Denyer, *Ind. Eng. Chem.*, **47**, 240 (1955).
985. J. T. Suh, U.S. Patent 3,381,006.
986. D. G. Fletcher, K. H. Gibson, H. R. Moss, D. R. Sheldon, and E. R. H. Walker, *Prostaglandins*, **12**, 493 (1976).
987. A. Clearfield, R. Gopal, M. D. Rausch, E. F. Tokas, F. A. Higbie, and I. Bernal, *J. Organomet. Chem.*, **135**, 229 (1977).
988. A. C. Brouwer and H. J. T. Bos, *Rec. Trav. Chim. Pays-Bas*, **103**, 152 (1984).
989. T. Teide, D. Wells, and W. H. F. Sasse, *Aust. J. Chem.*, **26**, 2129 (1973).
990. P. J. Kocienski, J. M. Ansell, and B. E. Norcross, *J. Org. Chem.*, **41**, 3650 (1976).
991. L. V. Timokhima, A. S. Nakhmanovich, and A. I. Borisova, *Izv. Sib. Old. Akad. Nauk SSSR, Soc. Khim. Nauk*, 109 (1973).
992. P. A. Cadby, M. T. W. Hearn, and A. D. Ward, *Aust. J. Chem.*, **26**, 557 (1973).
993. J. Nakayama, R. Yomoda, and M. Hoshino, *Heterocycles*, **26**, 2215 (1987).
994. I. Iwai, H. Shindo, Y. Okajima, T. Konotsune, and K. Tomita, *Yakugaku Zasshi*, **80**, 1588 (1960).
995. R. A. Baldwin, *Univ. Microfilms, Diss. Abstr.*, **22**, 734 (1961).
996. F. Bohlmann and C. Zdero, *Chem. Ber.*, **101**, 2062 (1968).
997. F. Bohlmann and C. Arndt, *Chem. Ber.*, **99**, 135 (1966).
998. F. Bohlmann and K. M. Kleine, *Chem. Ber.*, **97**, 1193 (1964).
999. F. Bohlmann and E. Berger, *Chem. Ber.*, **98**, 883 (1965).
1000. F. Bohlmann and K. H. Knoll, *Phytochemistry*, **18**, 1060 (1979).
1001. A. Selva, A. Arnone, R. Mondelli, V. Sprio, and L. Ceraulo, *Phytochemistry*, **17**, 2097 (1978).
1002. F. Bohlmann and U. Hinz, *Chem. Ber.*, **98**, 876 (1965).
1003. F. Bohlmann, M. Wotschokowsky, U. Hinz, and W. Lucas, *Chem. Ber.*, **99**, 984 (1966).
1004. F. Bohlmann, C. Zdero, and M. Grenz, *Phytochemistry*, **15**, 1309 (1976).
1005. F. Bohlmann and W. R. Abraham, *Phytochemistry*, **18**, 839 (1979).
1006. F. Bohlmann and C. Zdero, *Chem. Ber.*, **109**, 901 (1976).
1007. E. R. H. Jones, C. M. Piggin, V. Thaller, and J. L. Turner, *J. Chem. Res.*, 744 (1977).
1008. F. Bohlmann and C. Zdero, *Chem. Ber.*, **108**, 739 (1975).
1009. F. Bohlmann and C. Zdero, *Chem. Ber.*, **103**, 2095 (1970).
1010. F. Bohlmann and C. Zdero, *Chem. Ber.*, **103**, 2856 (1970).
1011. F. Bohlmann, C. Arndt, K. M. Kleine, and H. Bornowski, *Chem. Ber.*, **98**, 155 (1965).
1012. K. Szendrei, J. Reisch, and E. Varga, *Phytochemistry*, **23**, 901 (1984).
1013. D. McLachlan, T. Arnason, and J. Lam, *Photochem. Photobiol.*, **39**, 177 (1984).
1014. S. Gronowitz and I. Ander, *Acta Chem. Scand.*, **B29**, 513 (1975).
1015. Ng. Ph. Buu-Hoi and N. Hoan, *J. Org. Chem.*, **16**, 874 (1951).
1016. T. Itahara and F. Ouseto, *Synthesis*, 488 (1984).
1017. G. H. Badger, J. A. Elix, and G. E. Lewis, *Aust. J. Chem.*, **18**, 70 (1965).
1018. S. Linke, J. Kurz, D. Lipinski, and W. Gau, *Liebigs Ann. Chem.*, 542 (1980).
1019. F. D. Popp and A. Catala, *J. Org. Chem.*, **26**, 2738 (1961).
1020. R. S. Bradley and A. D. Care, *J. Chem. Soc.*, 1688 (1953).

1021. F. Outuquin, C. Paulmier, and P. Pastour, *Bull. Soc., Chem. Fr., Part 2*, 3039 (1974).
1022. C. K. Sha and C. P. Tsou, *J. Chem. Soc., Chem. Commun.*, 310 (1986).
1023. B. P. Asthana and P. I. Ittyrah, *Agra (India) Univ. J. Res.*, **12**, 81 (1963).
1024. P. Ribereau, G. Queguiner, and P. Pastour, *Bull. Soc. Chim. Fr.*, 1581 (1972).
1025. D. N. Nicolaides, *Synthesis*, 127 (1977).
1026. D. N. Nicolaides, *Synthesis*, 675 (1976).
1027. K. Sindelar, J. Metysova and M. Protiva, *Coll. Czech. Chem. Commun.*, **36**, 3404 (1971).
1028. V. I. Rogovik and Y. L. Gol'dfarb, *Chem. Het. Comp. USSR*, 439 (1965).
1029. S. Gronowitz and B. Maltesson, *Acta Chem. Scand.*, **26**, 2982 (1972).
1030. P. Tintillier, G. Dupas, J. Bourguignon, and G. Queguiner, *Tetrahedron Lett.*, **27**, 2357 (1986).

CHAPTER II

Organometallic Derivatives of Thiophenes

Torbjörn Frejd

Department of Organic Chemistry
University of Umeå
Umeå, Sweden

I. Introduction 258
II. Lithium Derivatives and Thenylic Grignard Reagents 669
1. Reactions of α-Thienyllithium Derivatives Obtained via Metalation 671
A. Alkylations and Arylations 671
B. Halogenations 679
C. Oxidation and Amination 680
D. Introduction of Groups Carrying Nonoxygen and Nonnitrogen Heteroatoms . . 681
E. Metalations of Nonthienylic or Nonthenylic Positions 683
2. Reactions of β-Thienyllithium Derivatives Obtained via Metalation 684
3. Reactions of α-Thienyllithium Derivatives Obtained via Halogen–Metal Exchange . . 688
4. Reactions of β-Thienyllithium Derivatives Obtained via Halogen–Metal Exchange . . 692
5. Thenyllithium and Thenylmagnesium Halide Derivatives 697
A. Lithiations 698
B. Thenylic Grignard Reagents 703
6. Reactions of Di- and Polylithium Derivatives 705
7. Directed Metalation 709
8. Halogen Migration and Rearrangements 717
9. Ring-Opening Reactions 721
10. Mechanisms and Physical Chemistry 728
A. Metalation 729
B. NMR Data 732
C. Constitution of Thenyllithium Derivatives 735
D. Acidity of Thienylic Protons 736
E. Halogen–Metal Exchange 736
References 738

The Chemistry of Heterocyclic Compounds, Volume 44: Thiophene and Its Derivatives, Part Five, Edited by Salo Gronowitz.
ISBN 0-471-52944-3 © 1992 John Wiley & Sons, Inc.

TABLE 1. α-Thienyllithium Derivatives via Metalation 259
TABLE 2. β-Thienyllithium Derivatives via Metalation 328
TABLE 3. α-Thienyllithium Derivatives via Halogen–Metal Exchange 339
TABLE 4. β-Thienyllithium Derivatives via Halogen–Metal Exchange 373
TABLE 5. Thenylmetal Derivatives 430
TABLE 6. Di- and Polylithiated Thiophenes 444
TABLE 7. Directed Metalations 458
TABLE 8. Rearrangements 488
TABLE 9. Ring-Opening Reactions 494
TABLE 10. Sodium, Potassium, Cesium, and Rubidium Derivatives. 503
TABLE 11. Reactions of 2-Thienylmagnesium Halides. 510
TABLE 12. Reactions of 3-Thienylmagnesium Halides. 537
TABLE 13. Calcium and Strontium Derivatives. 542
TABLE 14. Boron Derivatives 543
TABLE 15. Al, Ga, In, and Tl Derivatives 564
TABLE 16. Si Derivatives. 565
TABLE 17. Ge, Sn, and Pb Derivatives. 578
TABLE 18. Te, As, Sb, and Bi Derivatives 586
TABLE 19. Zn and Cd Derivatives 588
TABLE 20. Mercury Derivatives. 591
TABLE 21. Copper, Silver, and Gold Derivatives. 604
TABLE 22. Transition Metal Derivatives. 622

I. INTRODUCTION

The review presented in this chapter is a compilation of literature references published between 1949 and 1985 and concerns metal derivatives of thiophene and its derivatives. The period 1986–1989 is covered only to a minor extent. The thenylic position has been included, but cases where the metal is placed further away from the thiophene ring are omitted. A major part of the metal introducing reactions is based on the use of halothiophenes, and the reader should consult the chapters devoted to this area in the series.[1] Thienyllithium and thienyl Grignard reagents have been reviewed on a regular basis,[2,3] and further reviews of these and other areas of metallothiophene chemistry, including some transition-metal chemistry of thiophene, are available.[4–9]

In the present review data on the metal-related reactions are covered in tables, which are organized according to increasing molecular weight of the starting thiophene derivative (see Tables 1–22, pp. 259–668). Only the area of thienyllithium derivatives is discussed in some detail, since thienyllithium derivatives are used as reactive intermediates in an increasing number of cases.

TABLE 1. α-Thienyllithium Derivatives via Metalation

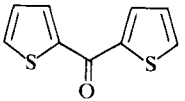
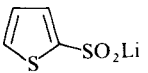
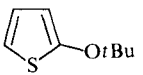
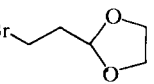
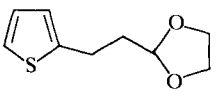
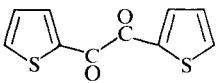
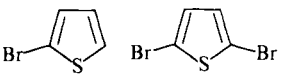
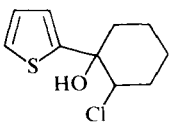
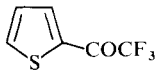
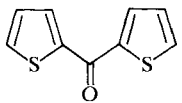
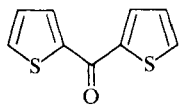
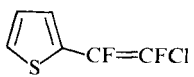
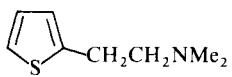
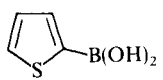
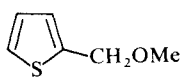
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi/ether 2. CO_2			64
	1. BuLi 2. SO_2			106
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		72	93
	1. BuLi 2. 		75	35
	1. EtLi 2. $(COOMe)_2$		12	248
	1. BuLi 2. $Br(CF_2)_3Br$	 70% 8%		88
	1. BuLi 2. 2-Chlorocyclohexanone		76	40

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CF_3CONMe_2		55	69
	1. EtLi 2. Me_2NCO_2Et		92	65
	1. EtLi 2. Me_2NCOCl		90	65
	1. BuLi, $-40°C$, 6 h 2. $CF_2{=}CFCl$		82	45
	1. BuLi 2. $Me_2NCH_2CH_2Cl$		7–21	18
	1. BuLi 2. $B(OBu)_3$			96
	1. BuLi 2. $ClCH_2OMe$		76	249

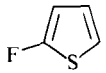
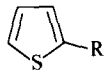
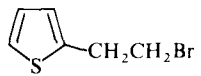
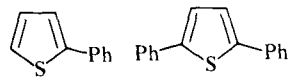
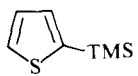
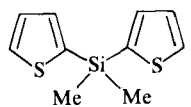
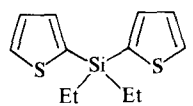
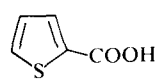
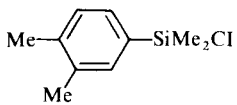
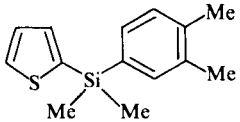
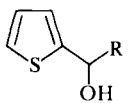
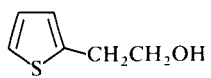
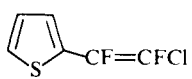
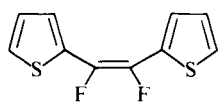
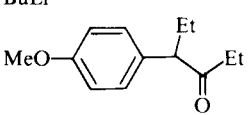
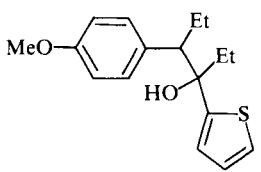
	1. BuLi, ether 2. $FClO_3$		48	91
	1. BuLi, ether 2. DMS or RBr		47–65	36
	1. BuLi, ether 2. $BrCH_2CH_2Br$		5.6	36
	1. BuLi, THF, heat 2. PhBr	 31% 22%		36
	1. BuLi, ether 2. $ClCH_2COOEt$		Polymer	36
	1. BuLi, ether 2. TMSCl		65	250
	1. BuLi, ether 2. Me_2SiCl_2		71	250
	1. BuLi, ether 2. Et_2SiCl_2		60	250
	1. Li–polystyrene 2. CO_2		43	24

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, ether 2. 		36	251
	1. BuLi/ether 2. RCHO		53–76	252
	1. BuLi 2. Ethylene oxide		78	112
	1. BuLi, $-80°C$ 2. $ClFC{=}CF_2$		55	44
	1. BuLi 2. $F_2C{=}CF_2$		30	44
	1. BuLi 2. 		60	253

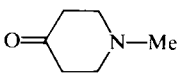
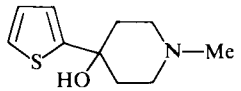
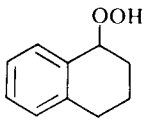
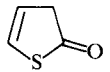
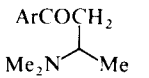
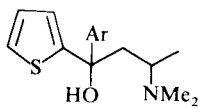
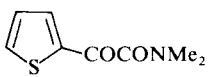
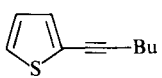
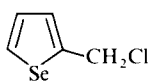
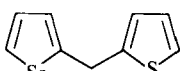
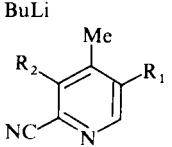
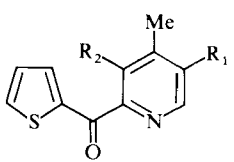
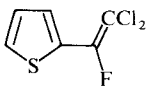
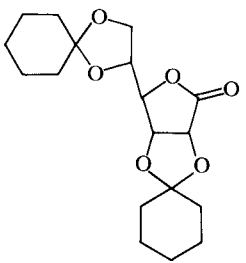
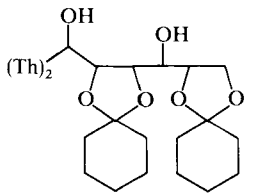
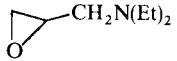
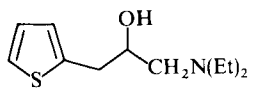
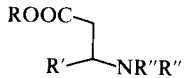
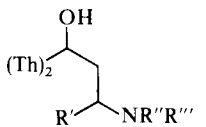
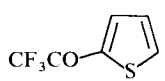
	1. PhLi 2. 		73	254
	1. BuLi 2. 		10	95
	1. BuLi 2. 			255
	1. BuLi 2. $Me_2NCOCONMe_2$		52	76
	1. BuLi 2. BuC═COEt		33	50
	1. BuLi 2. 		30	256
	1. BuLi 2. 		70–90	78

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $F_2C{=}CCl_2$		81	46
	1. BuLi 2. 		90	257
	1. BuLi 2. 		71	258
	1. BuLi 2. 		72	259
	1. BuLi 2. CF_3CONEt_2		82	68

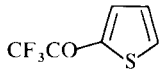
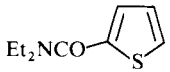
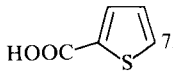
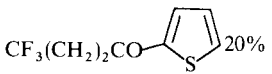
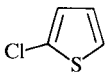
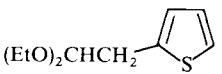
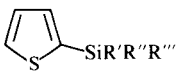
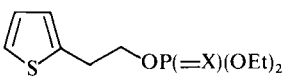
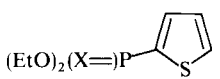
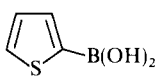
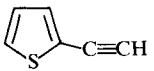
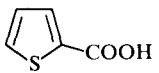
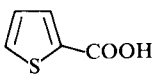
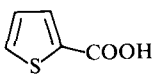
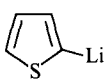
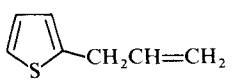
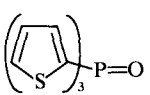
	1. BuLi 2. CF_3COOH		87	68
	1. BuLi 2. $CF_3(CF_2)_2CONEt_2$		20	68
	1. BuLi 2. $CF_3(CF_2)_2COOH$	 73%  20%		68
	1. BuLi 2. CCl_3CN		40	80
	1. BuLi 2. $BrCH_2CH(OEt)_2$		40	48
	1. BuLi 2. R′R″R‴Si			110
	1. BuLi 2. Ethylene oxide 3. $ClP(=X)(OEt)_2$		51–62	110
	1. BuLi 2. $ClP(=X)(OEt)_2$			110
	1. BuLi 2. $B(OBu)_3$		32	97

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. FC≡CH		55	51
	1. Li, THF 2. CO_2		12	25
	1. Li, THF, naphthalene 2. CO_2		41	25
	1. Li, THF, $PhC(R)=CH_2$ 2. CO_2		80–100	25
	1. BuLi, hexane 2. CO_2		0	32
	BuLi, hexane, NEt_3 (0.5 eq)		Quantitative	32
	1. BuLi 2. $CH_2=CHCH_2Br$			260
	1. BuLi 2. $POCl_3$		24	261

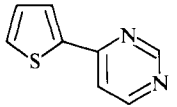
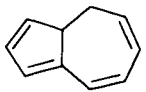
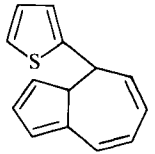
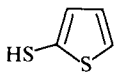
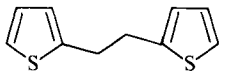
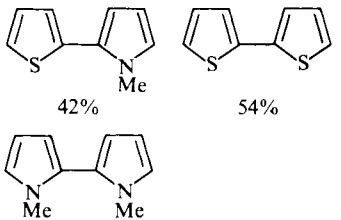
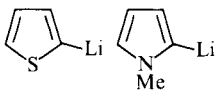
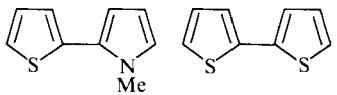
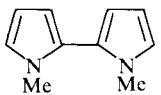
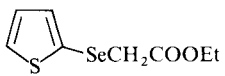
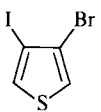
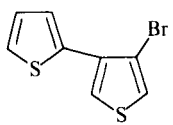
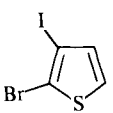
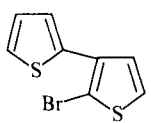
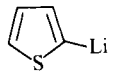
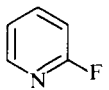
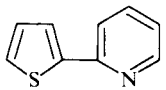
	1. BuLi 2. Pyrimidine 3. $KMnO_4$, chloranil, or $K_2(FeCN)_6$		45	63
	1. BuLi 2. 		22	262
	1. BuLi 2. S		70	103
	1. BuLi 2. $BrCH_2CH_2Br$		5.6	36
	1. BuLi 2. CuBr 3.	 42% 54% 1%		13

TABLE 1. (*Continued*)

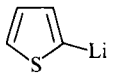
Starting Material	Reagent	Product	Yield (%)	Ref.
	CuBr	 45% 15%  40%		13
	1. BuLi 2. Se 3. $ClCH_2COOEt$		45	107
	1. BuLi 2. CuBr 3. 		55	56
	1. BuLi 2. CuBr 3. 		53	56

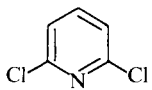


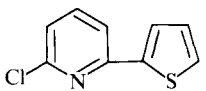




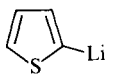
58 59



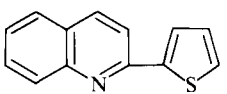




36 59

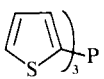


Quinoline



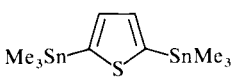
75 59

1. BuLi
2. PBr_3



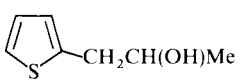
66 263

1. BuLi, TMEDA
2. Me_3SnCl



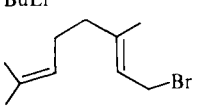
82 27

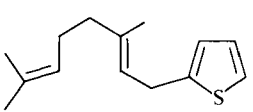
1. BuLi
2. Propenoxide



38

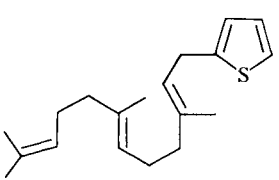
1. BuLi
2.





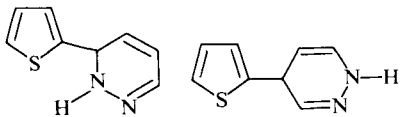
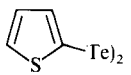
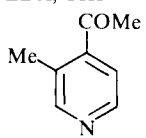
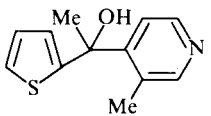
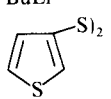
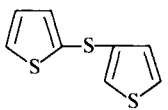
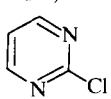
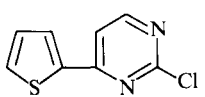
89 264

1. BuLi
2. Geranylbromide



79 265

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2.			62
	1. BuLi, THF 2. Te 3. O_2		74	108
	1. LDA, THF 2. 		78	266
	1. BuLi 2. 		79	54
	1. BuLi, hexane/ether 2.  then $KMnO_4$		79	61

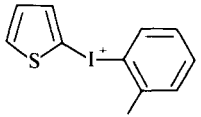
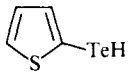
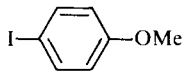
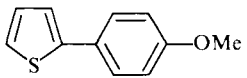
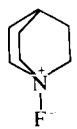
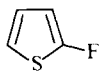
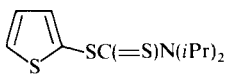
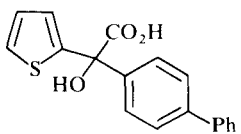
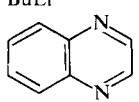
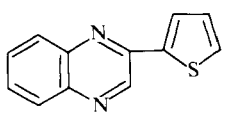
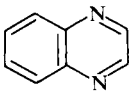
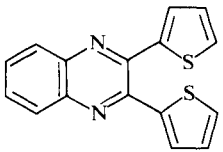
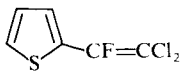
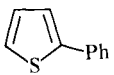
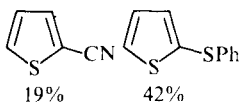
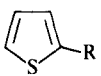
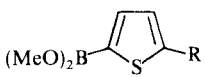
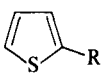
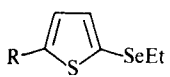
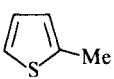
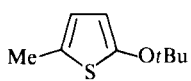
	1. 2. *t*Bu—≡—I$^+$-*o*-Tol		62–64	90
	1. BuLi 2. Te 3. PhNHPh/TFA			267
	1. BuLi 2. CuI 3. 		37–50	52
	1. BuLi 2. 		10	92
	1. BuLi 2. [(*i*Pr)$_2$NC(=S)S]$_2$—		96	105
	1. BuLi 2. *p*-PhPhCOCO$_2$Et		62	41
	1. BuLi 2. 		79	60

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. 		49	60
	1. BuLi 2. $CF_2{=}CCl_2$			46
	1. BuLi or PhLi 2. CuI 3. PhI, quinoline $< 240°C$		41	247
	1. BuLi 2. PhSCN	 19% 42%		268
	1. BuLi THF/Hex 2. $(MeO)_3B$			98
	1. BuLi 2. Se 3. EtI		73	107
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		51	93

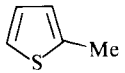
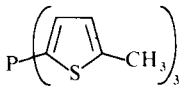
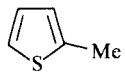
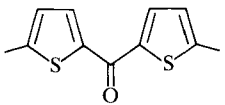
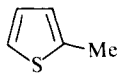
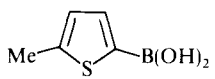
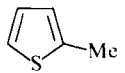
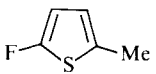
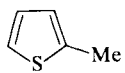
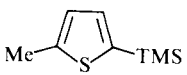
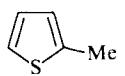
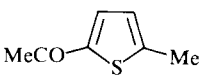
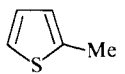
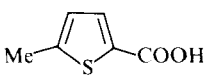
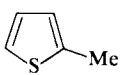
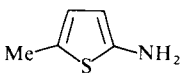
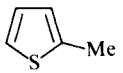
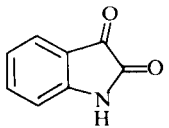
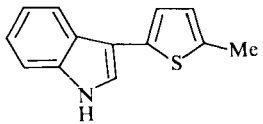
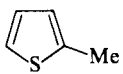
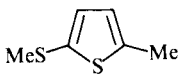
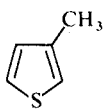
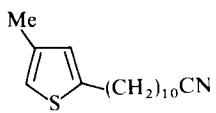
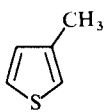
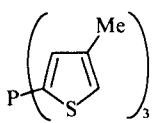
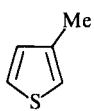
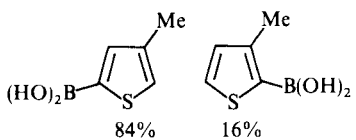
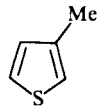
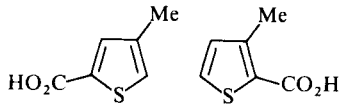
	1. BuLi 2. PBr_3		66	109
	1. EtLi 2. Me_2NCO_2Et		60	65
	1. BuLi 2. $B(OBu)_3$			96
	1. BuLi, ether 2. $FClO_3$		44	91
	1. BuLi, ether 2. TMSCl		72	250
	1. BuLi, ether 2. Ac_2O		33	70
	1. BuLi, TMEDA, and various reagents 2. CO_2		29–66	31
	1. BuLi, THF 2.		58	101

TABLE 1. (*Continued*)

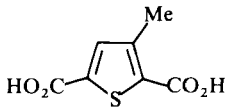
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, TMEDA 2.  3. $LiAlH_4$		37	28
	1. BuLi 2. MeSSMe		75	269
	1. BuLi 2. $Br(CH_2)_{10}CN$		Not given	81
	1. BuLi 2. PBr_3		Mixture	109
	1. BuLi 2. $B(OBu)_3$	 84% 16%		96



1. BuLi, ether
2. CO_2

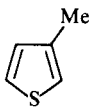


68% 19%

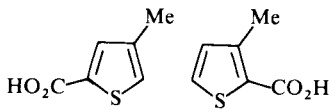


0%

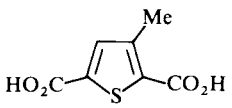
36



1. PhLi
2. CO_2

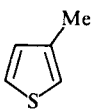


61% 29%

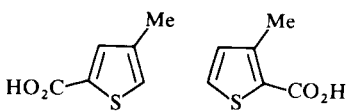


0%

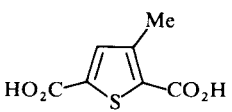
36



1. PhNa
2. CO_2



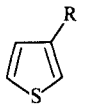
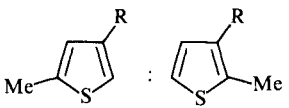
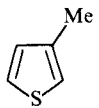
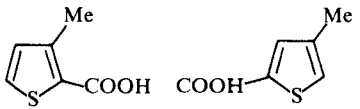
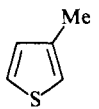
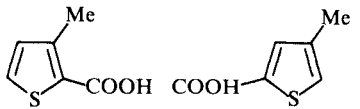
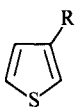
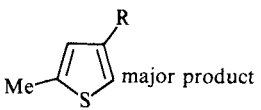
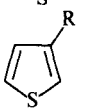
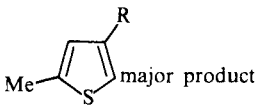
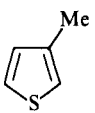
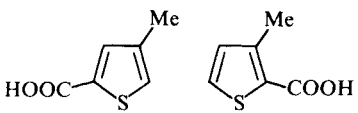
58% 0%



11%

36

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, TMEDA, LDA 2. Me_2SO_4			29
	1. BuLi, TMEDA, 0°C 2. CO_2	 1 : 3.5		31
	1. LDA 2. CO_2	 1 : 9		31
	1. BuLi 2. DMS	 major product		29
	1. LDA 2. DMS	 major product		29
	1. BuLi 2. CO_2	 3.5 : 1	24	31

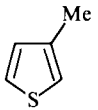
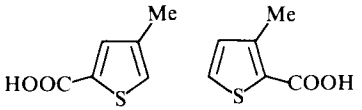
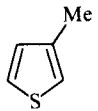
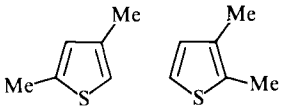
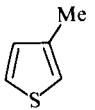
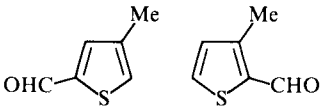
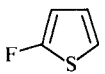
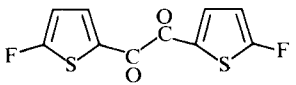
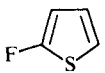
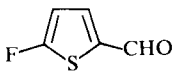
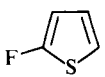
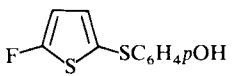
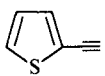
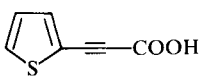
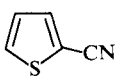
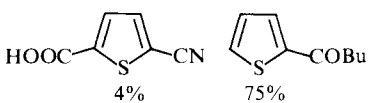
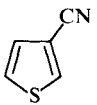
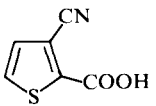
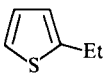
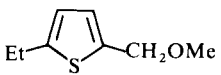
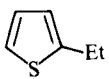
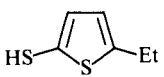
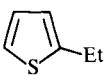
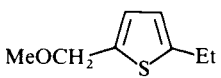
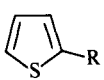
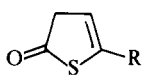
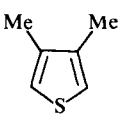
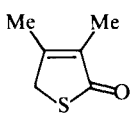
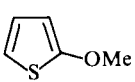
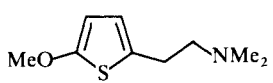
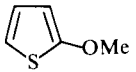
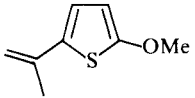
	1. LDA 2. CO_2	 24 : 1	2	31
	1. EtLi 2. DMS	 80 : 20	73 total	271
	1. BuLi 2. DMF	 83 : 17	59	269
	1. BuLi 2. $(COOMe)_2$		34	77
	1. BuLi 2. DMF		63	272
	1. BuLi 2. $[p\text{-}(OH)C_6H_4\text{-}S]_2$			273
	1. BuLi 2. CO_2		73	111
	1. BuLi, $-70°C$ 2. CO_2	 4% 75%		162

TABLE 1. (*Continued*)

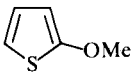
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, $-70°C$ 2. CO_2		68	162
	1. BuLi 2. $ClCH_2OMe$		65	249
	1. BuLi 2. S		73	103
	1. BuLi 2. $ClCH_2OMe$		65	249
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		30–66	274
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		46	275
	1. BuLi 2. $Me_2CH_2CH_2Cl$		40–60	18



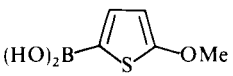
1. BuLi or PhLi
2. MeCOMe



42

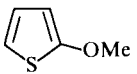


1. BuLi
2. $B(OBu)_3$

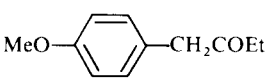


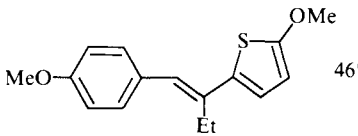
72

96

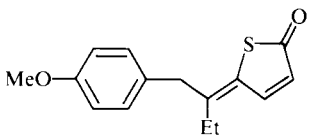


1. BuLi or PhLi
2.



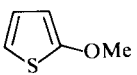


46%

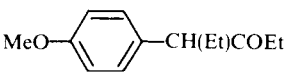


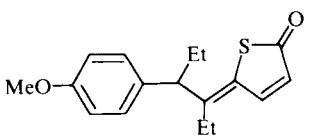
16%

43



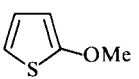
1. BuLi
2.



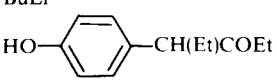


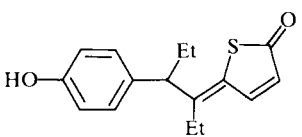
30

43



1. BuLi
2.

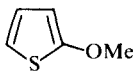
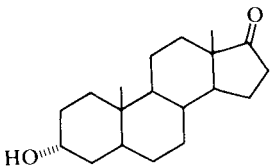
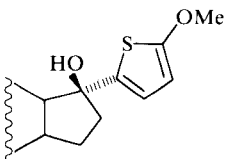
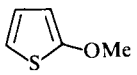
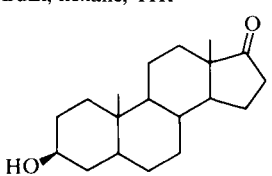
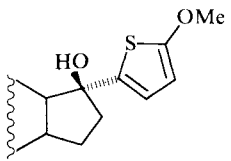
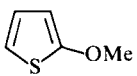
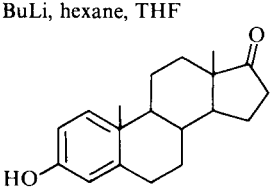
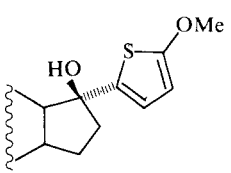
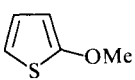
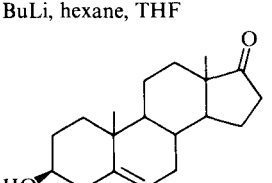
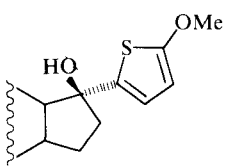




49

43

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, hexane, THF 2. 		56	276
	1. BuLi, hexane, THF 2. 		56	276
	1. BuLi, hexane, THF 2. 			276
	1. BuLi, hexane, THF 2. 			276

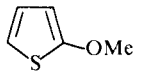
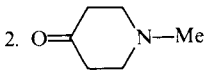
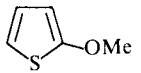
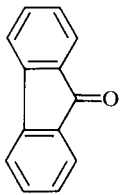
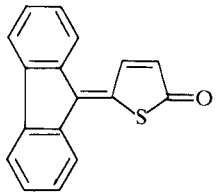
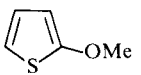
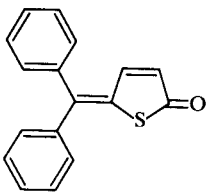
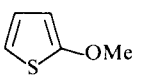
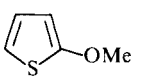
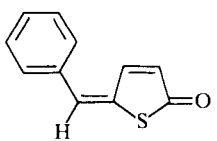
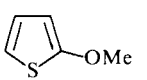
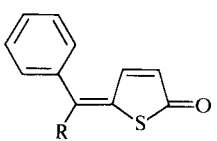
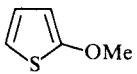
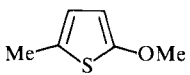
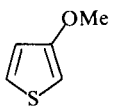
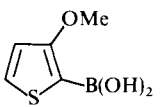
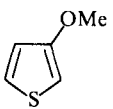
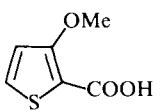
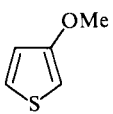
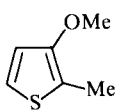
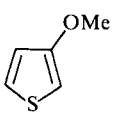
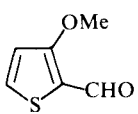
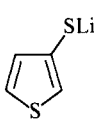
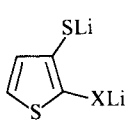
	1. PhLi 2. 		Resin	254
	1. BuLi or PhLi 2. 		58	42
	1. BuLi or PhLi 2. PhCOPh		72	42
	1. BuLi or PhLi 2. $(p\text{MeOPh})_2\text{CO}$		No reaction	42
	1. BuLi or PhLi 2. PhCHO		17	42
	1. BuLi or PhLi 2. RCOMe		11	42

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. MeO_3STol		78	269
	1. BuLi 2. $B(OBu)_3$		80	96
	1. BuLi 2. CO_2		86	26
	1. BuLi, LDA, or BuLi–TMEDA 2. DMS		78–54	29
	1. BuLi 2. DMF			277
	1. BuLi 2. S or Se			190

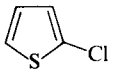
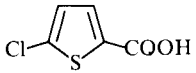
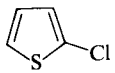
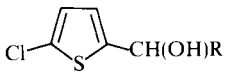
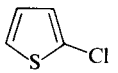
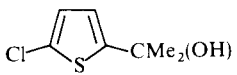
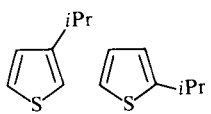
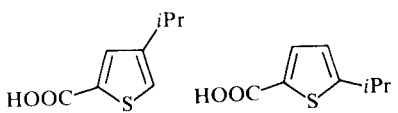
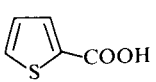
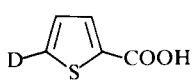
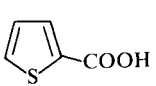
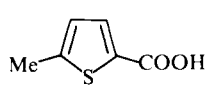
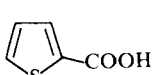
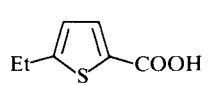
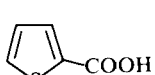
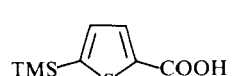
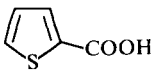
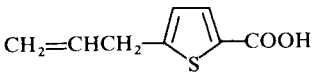
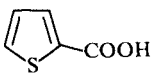
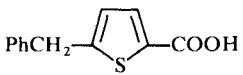
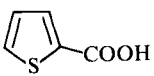
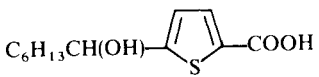
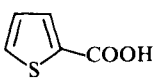
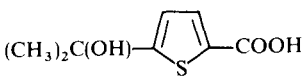
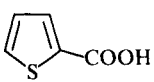
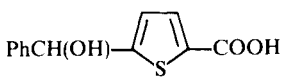
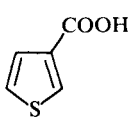
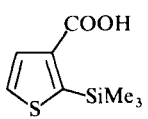
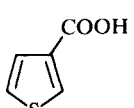
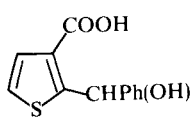
	1. BuLi 2. CO_2		65	159
	1. BuLi 2. RCHO		81–68	159
	1. BuLi 2. MeCOMe		67	159
	1. BuLi. 2. CO_2		75	200
	1. LDA 2 eq 2. D_2O		80	37
	1. LDA 2 eq, $-78°C$ 2. MeI		80	37
	1. LDA 2 eq 2. EtI		80	37
	1. LDA 2 eq 2. TMSCl		85	37

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA 2 eq, TMEDA 2. $CH_2{=}CHCH_2Br$		50	37
	1. LDA 2 eq 2. $PhCH_2Br$		57	37
	1. LDA 2 eq 2. $C_6H_{13}CHO$		50	37
	1. LDA 2 eq 2. MeCOMe		50	37
	1. LDA 2 eq 2. PhCHO		50	37
	1. LDA 2. TMSCl			14
	1. LDA 2 eq 2. PhCHO		43	37

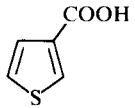
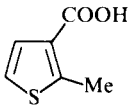
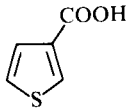
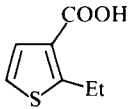
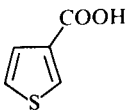
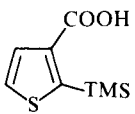
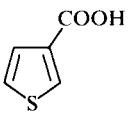
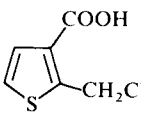
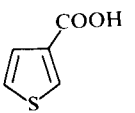
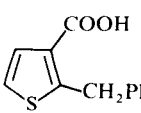
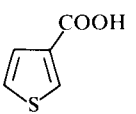
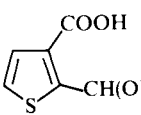
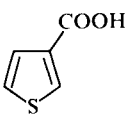
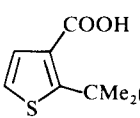
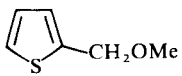
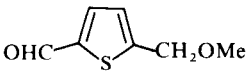
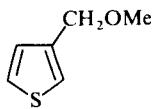
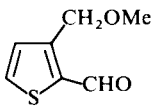
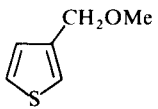
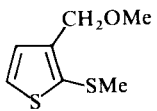
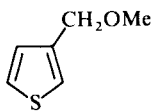
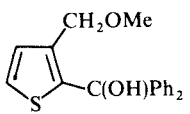
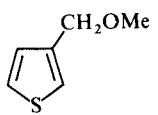
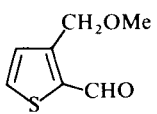
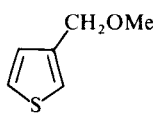
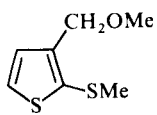
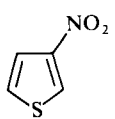
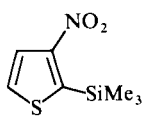
	1. LDA 2 eq 2. MeI		87	37
	1. LDA 2 eq 2. EtI		31	37
	1. LDA 2 eq 3. TMSCl		55	37
	1. LDA 2 eq 2. CH_2=$CHCH_2Br$		22	37
	1. LDA 2 eq 2. $PhCH_2Br$		0	37
	1. LDA 2 eq 2. $C_6H_{13}CHO$		55	37
	1. LDA 2 eq 2. MeCOMe		65	37

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhLi 2. DMF			278
	1. BuLi 2. DMF		72	74
	1. BuLi 2. MeSSMe		66	74
	1. BuLi 2. Ph_2CO		46	74
	1. BuLi 2. DMF		54	74
	1. BuLi 2. Me_2S_2		61	74
	1. LDA 2. TMSCl			14

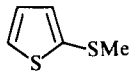
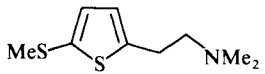
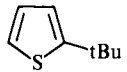
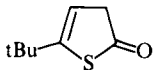
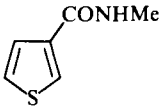
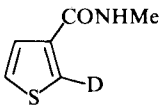
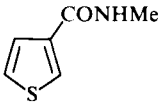
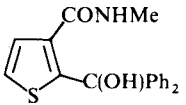
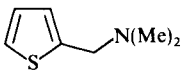
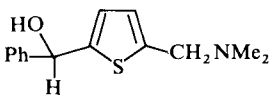
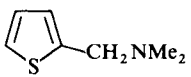
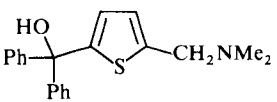
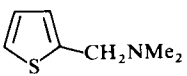
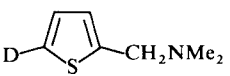
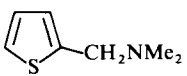
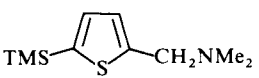
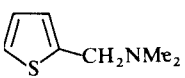
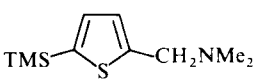
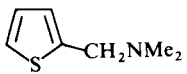
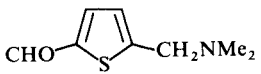
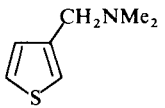
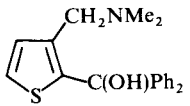
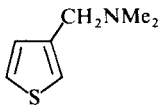
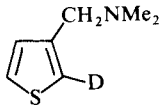
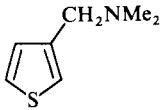
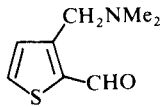
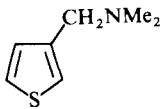
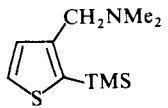
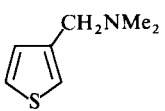
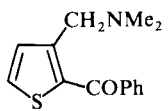
	1. BuLi 2. $Me_2CH_2CH_2Cl$		11	18
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		62	279
	1. BuLi 2. D_2O		55	74
	1. BuLi 2. Ph_2CO		23	74
	1. BuLi 2. PhCOPh		47	280
	1. BuLi 2. PhCHO		50	280
	1. BuLi 2. D_2O		88	74
	1. BuLi 2. TMSCl		71	74
	1. BuLi 2. TMSCl		71	74

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. DMF		40	74
	1. BuLi 2. Ph_2CO		67	74
	1. BuLi 2. D_2O		67	74
	1. BuLi 2. DMF		75	74
	1. BuLi 2. TMSCl		71	74
	1. BuLi 2. PhCN		54	74

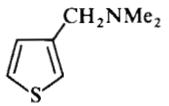
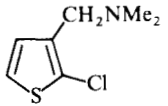
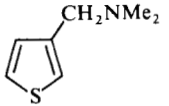
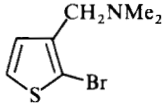
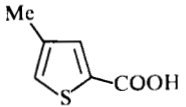
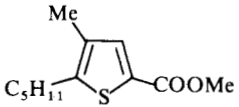
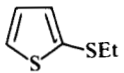
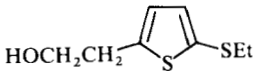
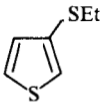
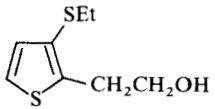
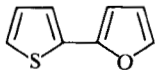
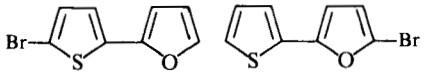
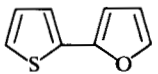
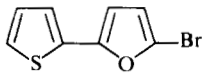
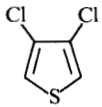
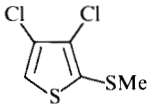
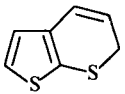
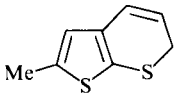
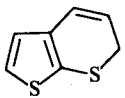
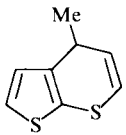
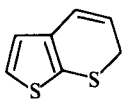
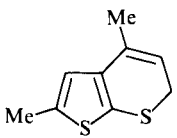
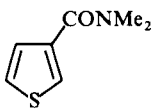
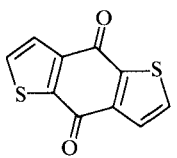
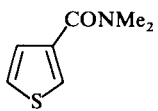
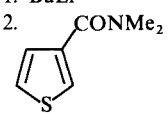
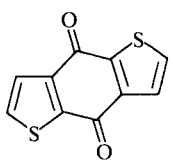
	1. BuLi 2. pTolSO$_2$Cl		25	74
	1. BuLi 2. pTolSO$_2$Br		32	74
	1. LDA 2 eq, THF, 2. $C_5H_{11}Br$		48	164
	1. BuLi 2. Ethylene oxide		79	191
	1. BuLi 2. Ethylene oxide		48	191
	1. BuLi, THF 2. Br_2	 68% 1.4%		83
	1. BuLi, hexane 2. Br_2		4.5	83
	1. BuLi 2. Me_2S_2		81	218

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, THF, − 10°C 2. MeI		85	172
	1. BuLi, THF + HMPA, − 10°C 2. MeI		80	172
	1. BuLi, THF + HMPA, − 10°C 2. MeI		Not given	172
	1. BuLi 2. Air		41	74
	1. BuLi 2. 		56	75

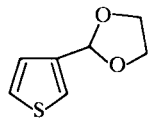
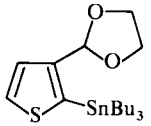
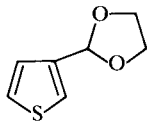
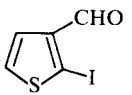
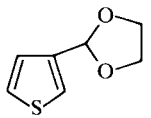
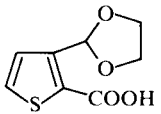
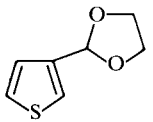
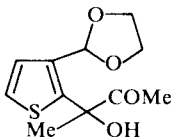
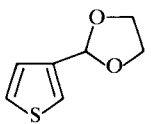
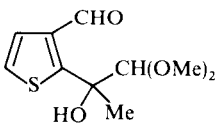
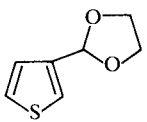
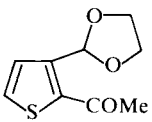
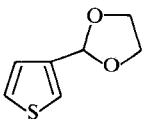
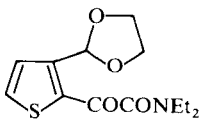
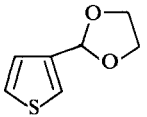
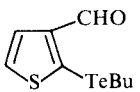
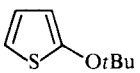
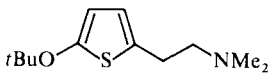
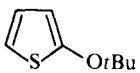
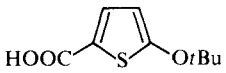
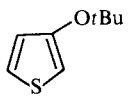
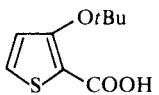
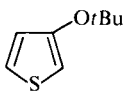
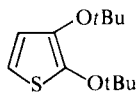
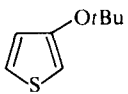
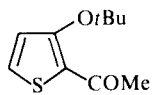
	1. LDA 2. CO_2		77	281
	1. BuLi, room temp. 2. I_2		63	84
	1. BuLi 2. CO_2		78	282
	1. BuLi 2. MeCOCOMe			283
	1. BuLi 2. $MeCOCH(OMe)_2$		72	284
	1. BuLi 2. DMA		40	71

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $(Et_2NCO)_2$		55	71
	1. BuLi 2. Te		34	72
	1. BuLi 2. $Me_2CH_2CH_2Cl$		48	18
	1. BuLi 2. CO_2		68	269
	1. BuLi, ether 2. CO_2		62	285
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		70	66
	1. BuLi 2. Ac_2O		75	66

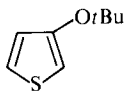
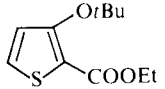
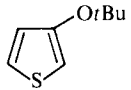
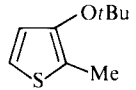
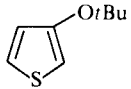
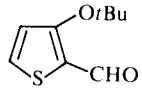
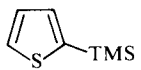
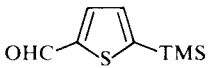
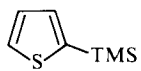
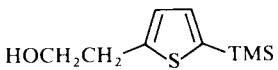
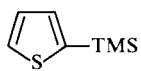
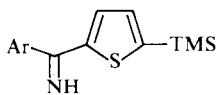
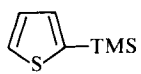
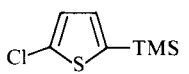
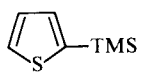
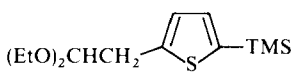
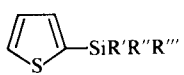
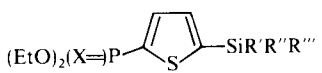
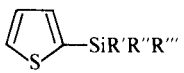
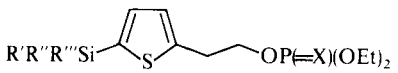
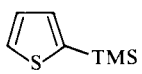
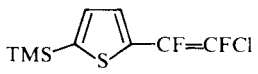
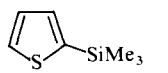
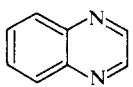
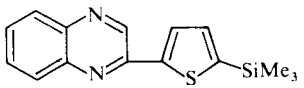
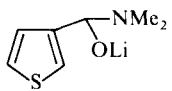
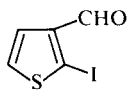
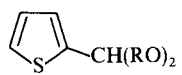
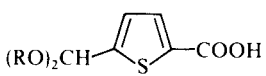
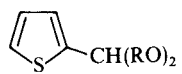
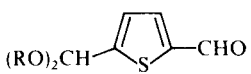
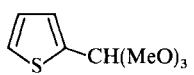
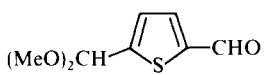
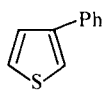
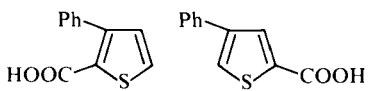
	1. BuLi 2. ClCOOEt		75	66
	1. BuLi 2. DMS		87	66
	1. BuLi 2. DMF		62	277
	1. BuLi, ether 2. DMF		69	250
	1. BuLi, ether 2. Ethylene oxide		50	250
	1. BuLi 2. ArCN		30–75	80
	1. BuLi 2. CCl_3CN		40–50	80
	1. BuLi 2. $BrCH_2CH(OEt)_2$		30	48
	1. BuLi 2. $ClP(=X)(OEt)_2$		31–66	110

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. Ethylene oxide 3. $ClP(=X)(OEt)_2$			110
	1. BuLi 2. $CF_2=CFCl$		70	286
	1. BuLi 2. 		4	287
	1. BuLi 2. I_2		29	84
	1. BuLi 2. CO_2			288
	1. BuLi 2. DMF			288
	1. BuLi 2. DMF		45	89
	1. BuLi, room temp., ether 2. CO_2	 55% 45%	72	235

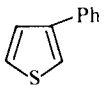
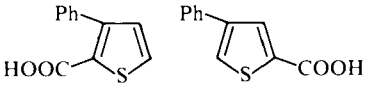
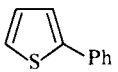
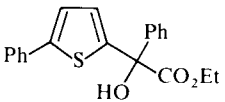
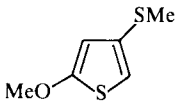
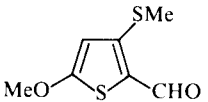
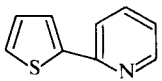
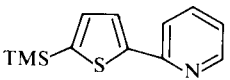
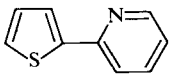
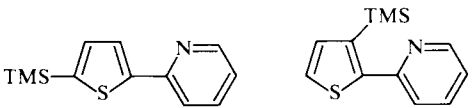
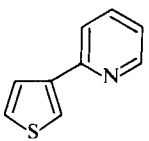
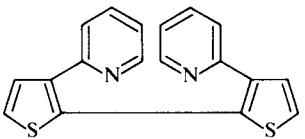
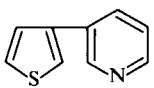
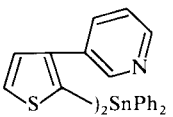
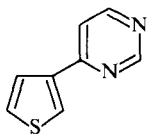
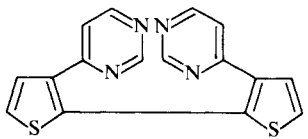
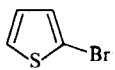
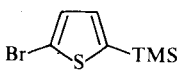
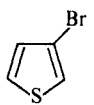
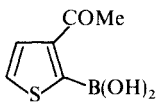
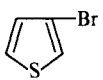
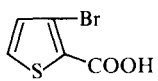
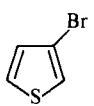
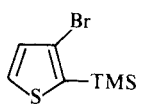
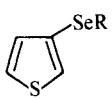
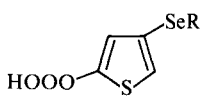
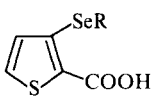
	1. EtLi, − 50°C., ether 2. CO_2	 6% 4%		235
	1. BuLi 2. $PhCOCO_2Et$		71	41
	1. BuLi 2. DMF		77	87
	1. LDA or BuLi in THF 2. TMSCl		Mostly	59
	1. BuLi, THF 2. TMSCl	 95 : 5		126
	1. BuLi 2. $CuCl_2$		51	55
	1. BuLi 2. Ph_2SnBr_2			289

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA 2. $CuCl_2$		28	55
	1. LDA 2. TMSCl			14
	1. EtLi 2. DMA 3. EtLi 4. $B(OBu)_3$		13	100
	1. PhLi 2. CO_2		72	12
	1. LDA 2. TMSCl		63	15
	1. BuLi 2. CO_2	 40%  60%	79	193

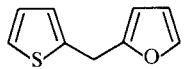
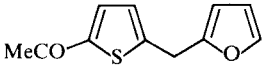
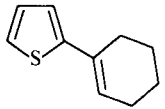
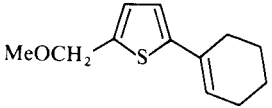
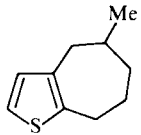
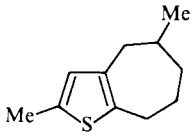
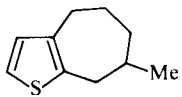
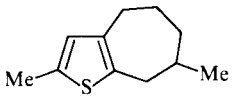
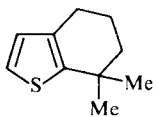
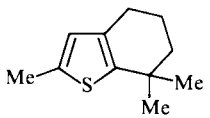
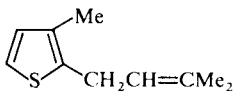
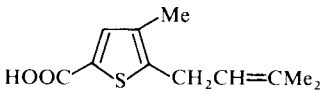
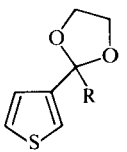
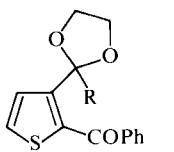
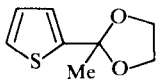
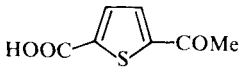
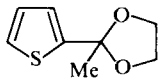
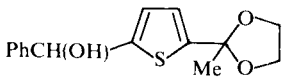
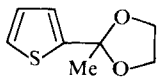
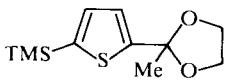
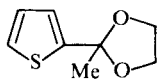
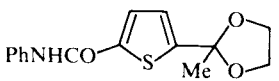
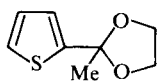
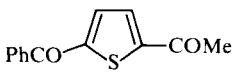
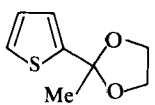
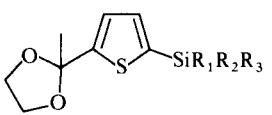
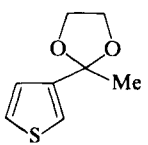
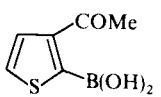
	1. BuLi, ether, 0–2°C 2. Ac_2O		12–16	70
	1. BuLi 2. $ClCH_2OMe$		78	249
	1. BuLi 2. DMS		70	209
	1. BuLi 2. DMS		69	209
	1. BuLi 2. DMS		68	210
	1. BuLi 2. CO_2			290
	1. BuLi 2. PhCN	 R = Me, H	16–27	291

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, ether/hexane 2. CO_2		70	67
	1. BuLi, ether/hexane 2. PhCHO		60	67
	1. BuLi, ether/hexane 2. TMSCl		96	67
	1. BuLi, ether/hexane 2. PhNCO		65	67
	1. BuLi, ether/hexane 2. PhCN		66	67
	1. BuLi 2. $R_1R_2R_3SiCl$		49–96	292
	1. EtLi 2. $B(OBu)_3$		20	100

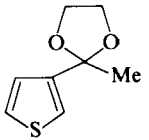
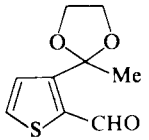
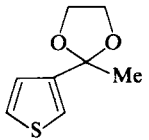
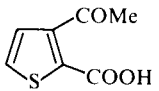
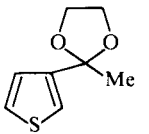
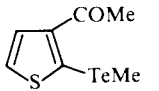
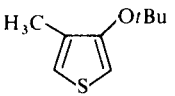
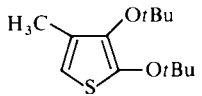
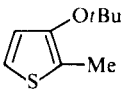
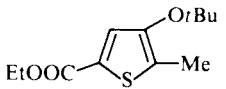
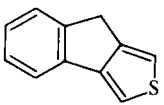
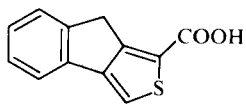
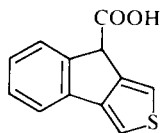
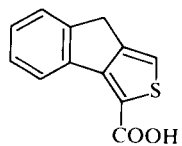
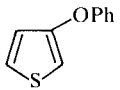
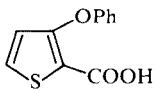
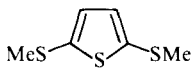
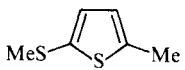
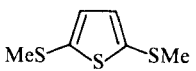
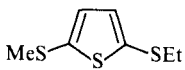
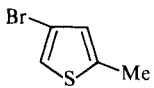
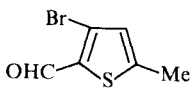
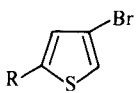
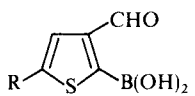
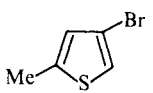
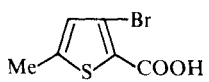
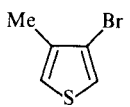
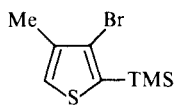
	1. BuLi 2. DMF		70	71
	1. BuLi 2. CO_2		70	71
	1. BuLi 2. Te 3. MeI		42	72
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		79	94
	1. BuLi 2. ClCOOEt		66	66
	1. BuLi 2. CO_2	 14%  38%		165
		 48%		

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhLi 2. CO_2		98	192
	1. BuLi, HMPT, $-40°C$ 2. MeI		77–80	115
	1. BuLi, THF, $-70°C$ 2. MeI		80	115
	1. LDA 2. DMF		65	16
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		18–32	100
	1. LDA 2. CO_2		56	17
	1. LDA 2. TMSCl		77	15

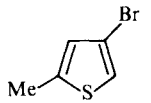
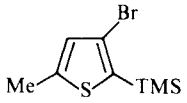
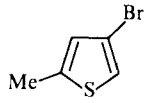
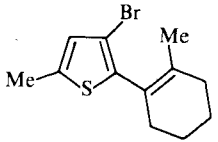
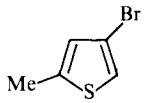
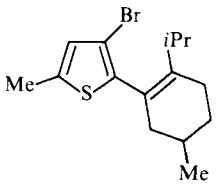
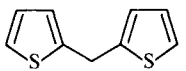
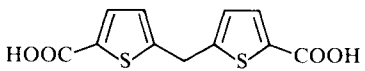
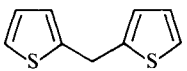
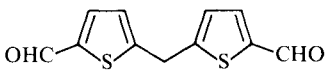
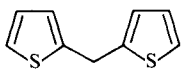
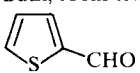
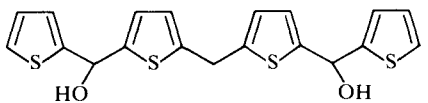
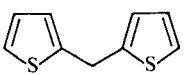
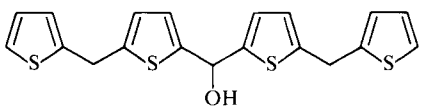
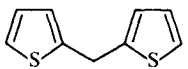
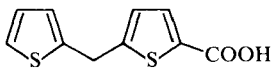
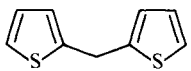
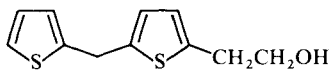
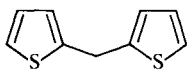
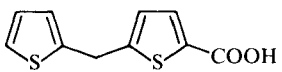
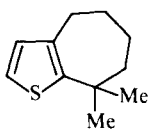
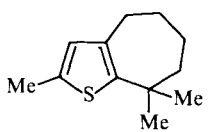
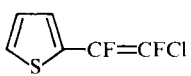
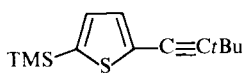
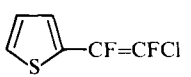
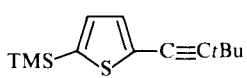
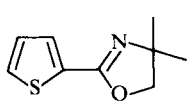
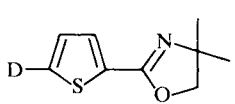
	1. LDA 2. TMSCl		74	15
	1. LDA 2. 2-Me–cyclohexanone 3. *p*TsOH		67	212
	1. LDA 2. (–)-Menthone 2. *p*TsOH		44	212
	1. BuLi 2. CO_2			114, 170
	1. BuLi 2. DMF		75	114, 170
	1. BuLi, room temp. 2. 		53	114, 169, 170
	1. BuLi, room temp. 2. HCOOMe		46	114, 169, 170

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, $< -10°C$ 2. CO_2			170
	1. BuLi 2. Ethylene oxide		74	112
	1. BuLi 2. CO_2			112
	1. BuLi 2. DMS		56	210
	1. *t*BuLi 2. TMSCl			51
	1. *t*BuLi 3 eq 2. TMSCl		86	293
	1. LDA, THF 2. MeOD			102

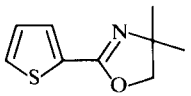
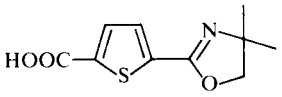
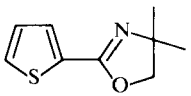
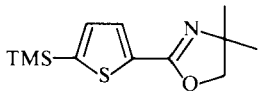
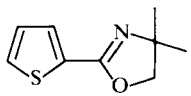
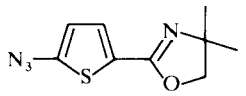
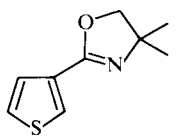
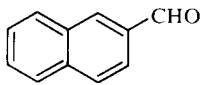
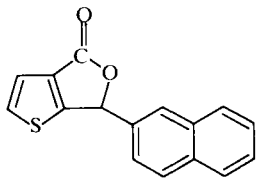
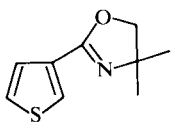
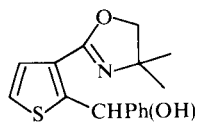
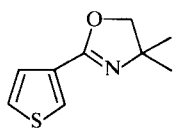
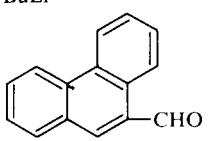
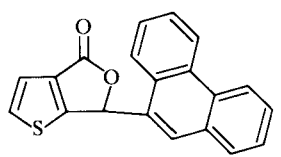
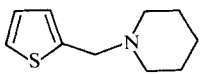
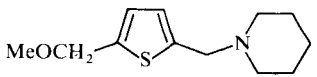
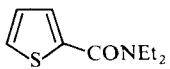
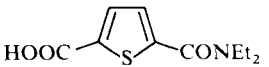
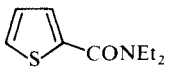
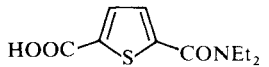
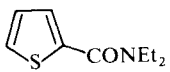
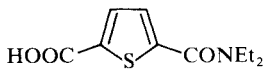
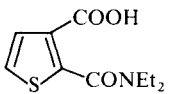
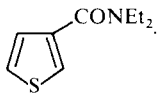
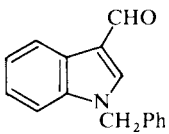
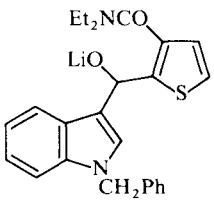
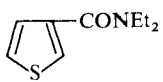
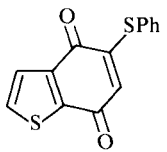
	1. LDA, THF 2. CO_2		67	102
	1. LDA, THF 2. TMSCl		95	102
	1. LDA, THF 2. TsN_3		57	102
	1. BuLi 2. 		56	196
	1. BuLi, hexane 2. ArCHO			196
	1. BuLi 2. 		21	197

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $ClCH_2OMe$		50	249
	1. LDA, THF 2. CO_2		85	129
	1. *sec*BuLi, DME, or ether 2. CO_2		82	129
	1. *sec*BuLi, THF 2. CO_2	 41%  50%	99 total	129
	1. *sec*BuLi 2. Air oxidation 3. 		>67	194
	1. *sec*BuLi, TMEDA 2. PhSCH=CHCHO		44	49

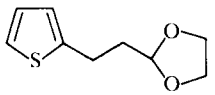
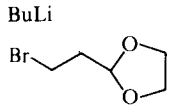
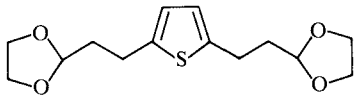
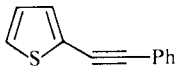
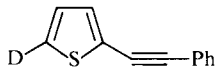
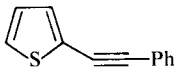
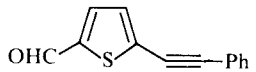
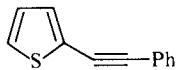
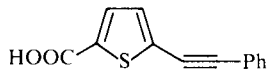
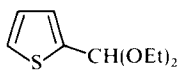
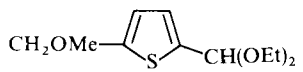
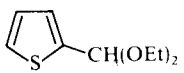
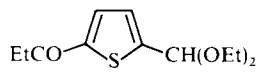
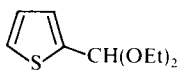
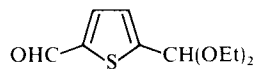
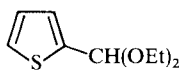
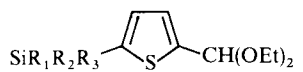
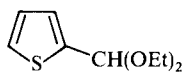
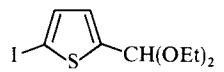
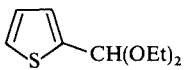
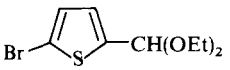
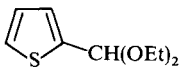
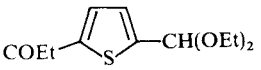
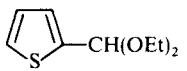
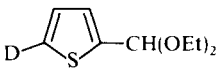
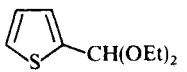
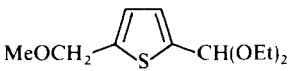
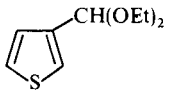
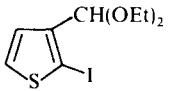
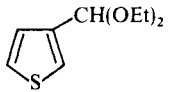
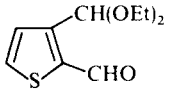
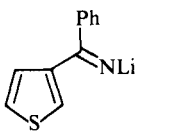
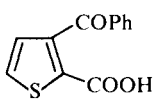
	1. BuLi 2. 		42	35
	1. BuLi 2. D_2O		84	294
	1. BuLi 2. DMF		20	294
	1. BuLi 2. CO_2		63	294
	1. BuLi 2. $ClCH_2OMe$		56	249
	1. BuLi, ether 2. $(EtCO)_2O$		Low	73
	1. BuLi, ether 2. DMF			295
	1. BuLi 2. $R_1R_2R_3SiCl$		49–96	292
	1. BuLi 2. $IC{\equiv}CCH_3$		70	89

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. BrC≡CMe		65	89
	1. BuLi 2. $(EtCO)_2O$			296
	1. BuLi, $-40°C$ 2. D_2O		73	297
	1. BuLi 2. $ClCH_2OMe$		56	249
	1. BuLi 2. I_2		30	85
	1. BuLi 2. DMF		85	298
	1. BuLi 2. CO_2		70	79

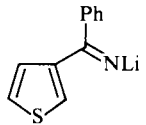
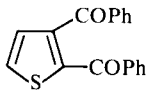
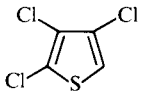
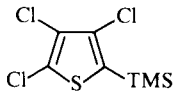
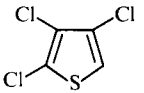
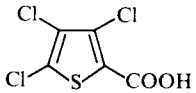
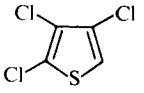
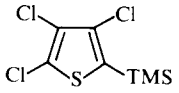
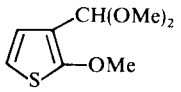
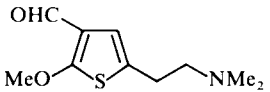
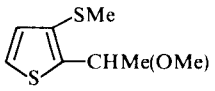
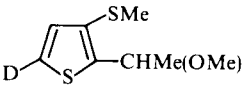
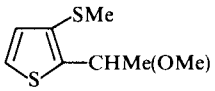
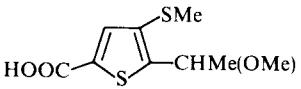
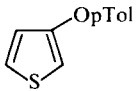
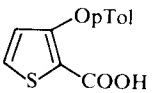
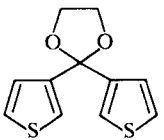
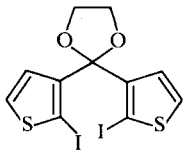
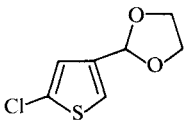
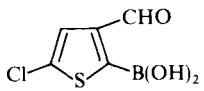
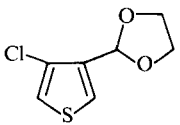
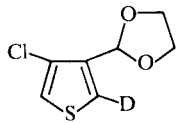
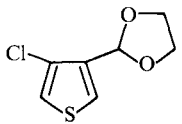
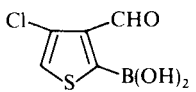
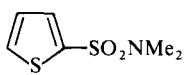
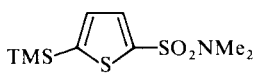
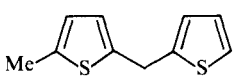
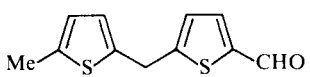
	1. BuLi 2. PhCN		52	79
	1. BuLi, THF, − 70°C 2. TMSCl		87	186
	1. BuLi, THF, − 70°C 2. CO_2		91	186
	1. *t*BuLi, THF, − 78°C 2. TMSCl			186
	1. BuLi 2. $Me_2NCH_2CH_2Cl$		0	18
	1. BuLi 2. D_2O			20
	1. BuLi 2. CO_2			20
	1. PhLi 2. CO_2		65	192

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. I_2		56	86
	1. EtLi 2. $B(OBu)_3$		39	100
	1. EtLi 2. MeCOOD		66	100
	1. BuLi 2. $B(OBu)_3$		50	100
	1. BuLi 2. TMSCl		41	128
	1. BuLi 2. DMF		50	113

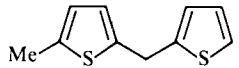
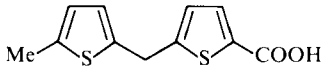
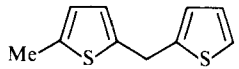
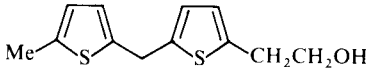
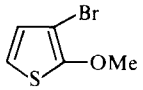
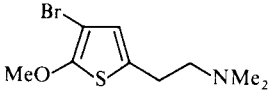
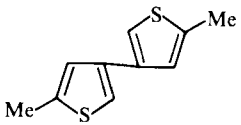
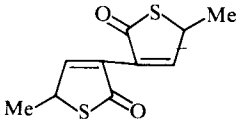
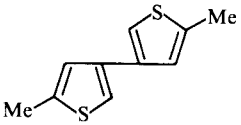
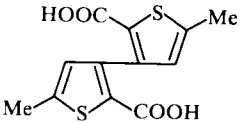
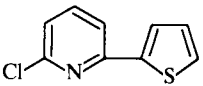
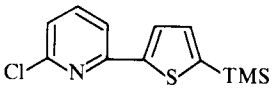
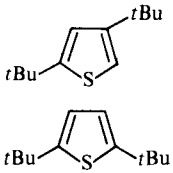
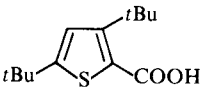
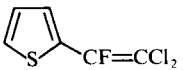
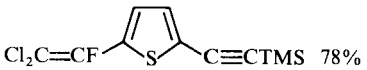
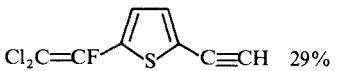
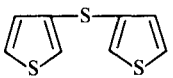
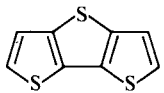
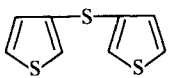
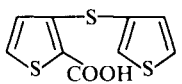
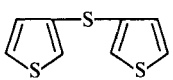
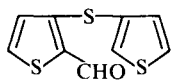
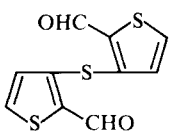
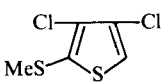
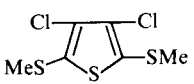
	1. BuLi 2. CO_2		55	113
	1. BuLi 2. Etylene oxide		75	113
	1. LDA 2. $Me_2CH_2CH_2Cl$		11	18
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		17	279
	1. BuLi 2. CO_2		45	299
	1. LDA or BuLi in ether 2. TMSCl			59
	1. BuLi 2. CO_2			300

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $CF_2{=}CCl_2$ 3. TMSCl or H_2O	 78% or  29%		47
	1. BuLi 2 eq 2. $CuCl_2$		50	54
	1. BuLi 2. CO_2		25	54
	1. BuLi 2. DMF	 16%  22%		54
	1. BuLi 2. Me_2S_2		75	218

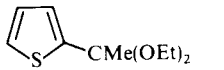
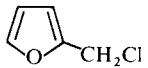
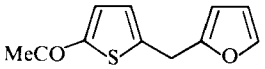
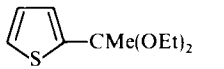
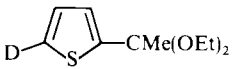
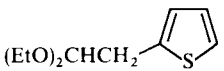
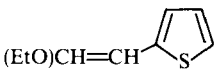
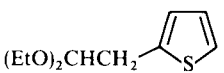
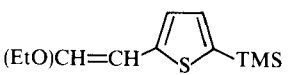
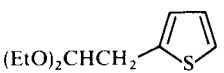
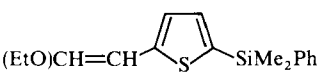
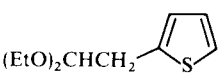
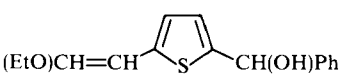
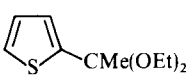
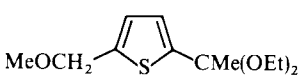
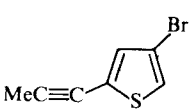
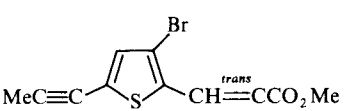
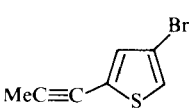
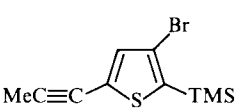
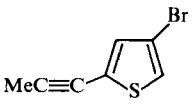
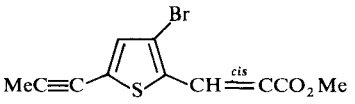
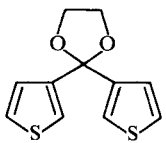
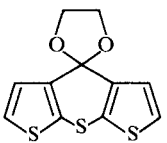
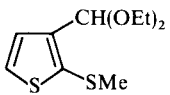
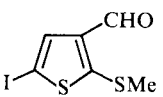
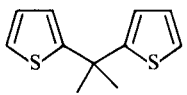
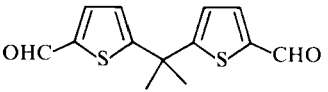
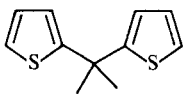
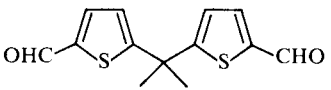
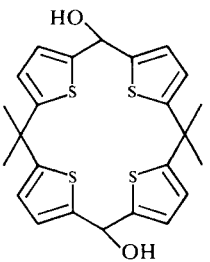
	1. BuLi, ether 2. 		22	70
	1. BuLi, $-40^{\circ}C$ 2. D_2O		70	297
	1. BuLi 2 eq 2. H_2O		78	48
	1. BuLi 2 eq 2. TMSCl		87	48
	1. BuLi 2 eq 2. $PhMe_2Cl$		62	48
	1. BuLi 2 eq 2. PhCHO		66	48
	1. BuLi 2. $ClCH_2OMe$		50	249
	1. LDA 2. $ZnCl_2$ 3. $Pd(PPh_3)_4$ 4. $BrCH{=}CHCO_2Me$			19
	1. LDA 2. TMSCl			19

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA 2. $ZnCl_2$ 3. $Pd(PPh_3)_4$ 4. $BrCH{=}CHCO_2Me$			19
	1. BuLi 2. S		60	104
	1. BuLi 2. I_2		59	87
	1. BuLi, room temp. 2. DMF		82	114, 168
	1. BuLi, room temp. 2. 		4	114, 168

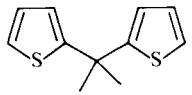
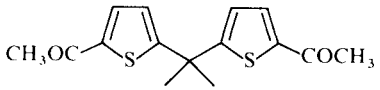
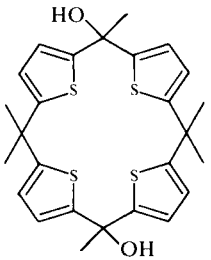
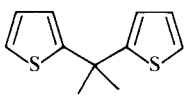
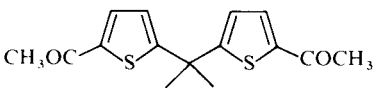
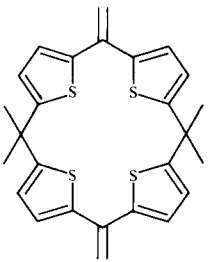
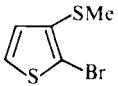
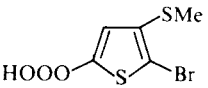
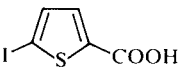
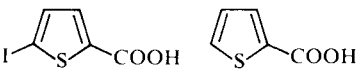
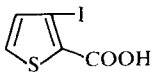
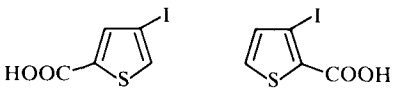
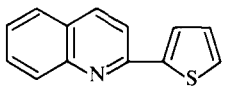
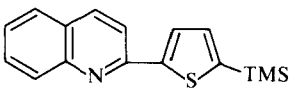
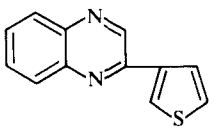
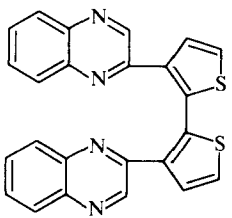
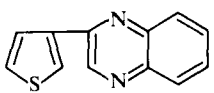
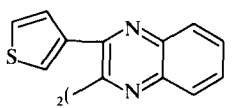
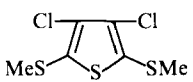
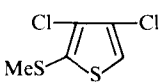
	1. BuLi, room temp. 2. 		2.5	114
	1. BuLi 2. 		0.8	168
	1. LDA, −78°C 2. CO_2		80	20
	1. PhLi, TMEDA 2. CO_2		30	13
	1. N-Me-pyrrolyl-Li, TMEDA 2. CO_2	 30 : 70		13

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA 2. CO_2		63	189
	1. N-Me-pyrrolyl-Li, TMEDA 2. CO_2	 1 : 4	33	13
	1. LDA or BuLi in ether 2. TMSCl			59
	1. LDA 2. $CuCl_2$		48	55
	1. LDA, ether			301
	1. BuLi 2. H_2O		62	218

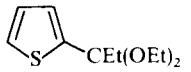
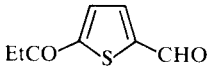
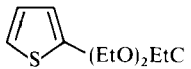
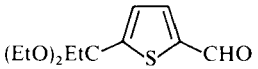
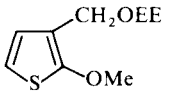
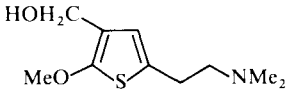
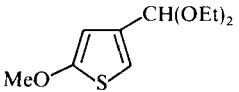
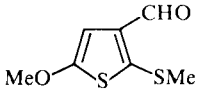
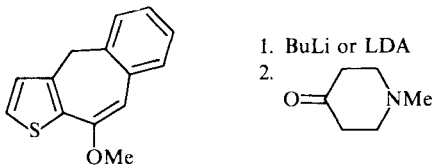
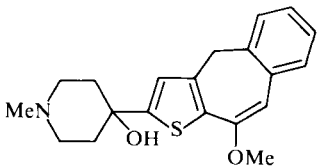
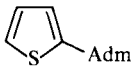
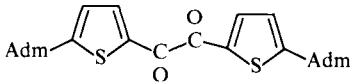
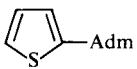
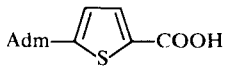
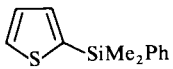
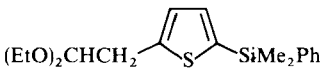
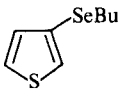
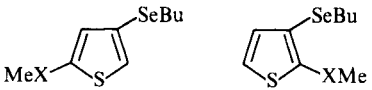
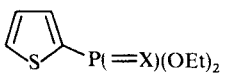
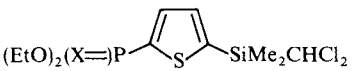
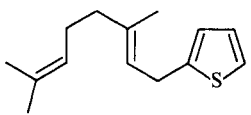
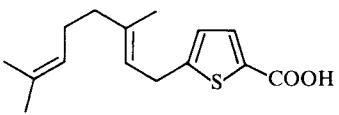
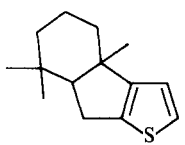
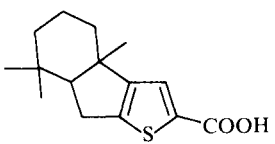
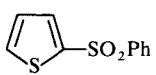
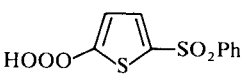
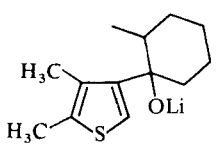
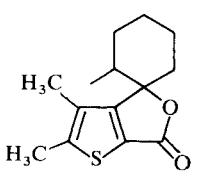
	1. BuLi, ether 2. DMF		66	73
	1. BuLi 2. DMF		75	296
	1. BuLi 2. $Me_2NCH_2CH_2Cl$		0	18
	1. BuLi 2. Me_2S_2		57	87
	1. BuLi or LDA 2.		71	302
	1. BuLi 2. $(COOMe)_2$		22	77
	1. BuLi 2. CO_2		70	303
	1. BuLi 2 eq 2. $BrCH_2CH(OEt)_2$		36	48

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. S or Se 3. MeI		67–76	193
	1. BuLi 2. $Cl_2CHSiClMe_2$		44	110
	1. BuLi 2. CO_2		79	264
	1. BuLi 2. CO_2			264
	1. BuLi 2. CO_2		60	304
	1. BuLi 2. CO_2			305

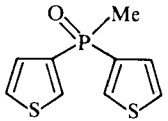
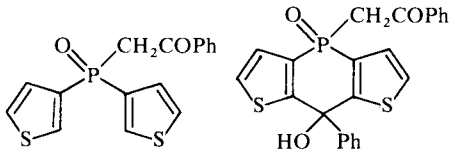
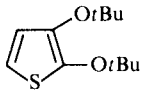
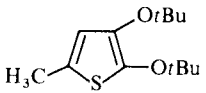
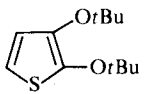
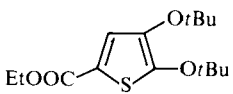
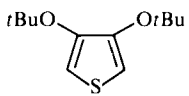
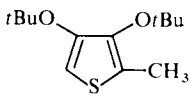
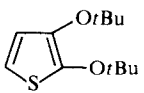
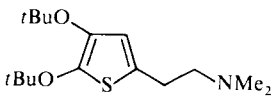
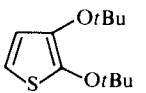
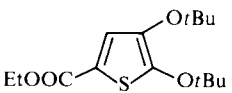
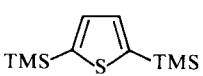
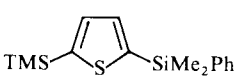
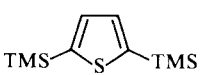
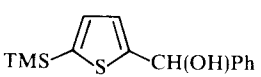
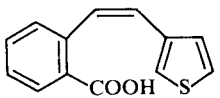
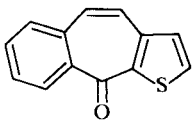
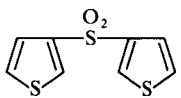
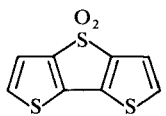
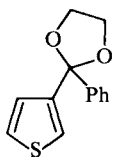
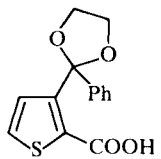
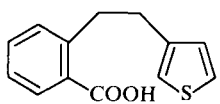
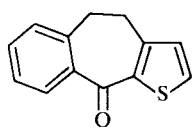
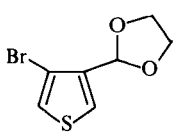
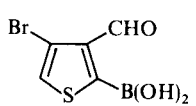
	1. BuLi, THF 2. PhCOOEt			53
		10 : 20		
	1. BuLi 2. Me_2SO_4		69	94
	1. BuLi 2. ClCOOEt			94
	1. BuLi 2. Me_2SO_4		91	94
	1. BuLi 2. $Me_2CH_2CH_2Cl$		13	18
	1. BuLi 2. ClCOOEt		51	66
	1. BuLi, THF 2. $PhMe_2SiCl$		30	116
	1. BuLi, THF 2. PhCHO		30	116

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	LDA 2 eq		59	195
	1. BuLi 2. $CuCl_2$		33	54
	1. BuLi 2. CO_2		43	291
	LDA 2 eq		4	195
	1. LDA 2. $B(OEt)_3$		65	21

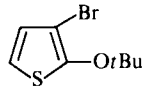
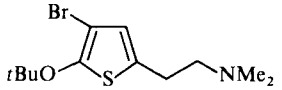
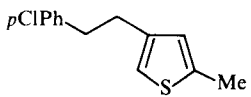
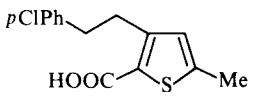
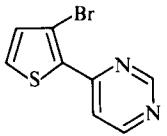
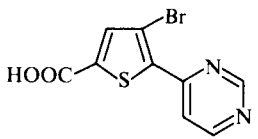
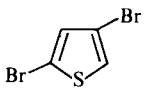
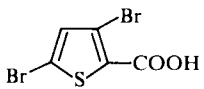
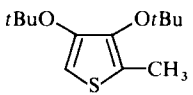
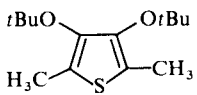
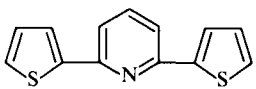
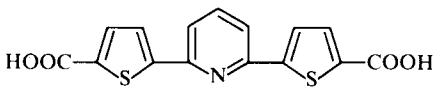
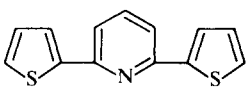
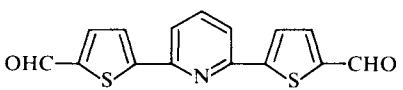
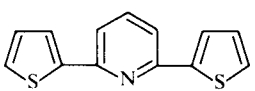
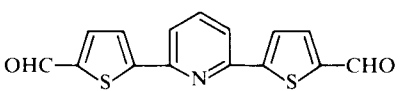
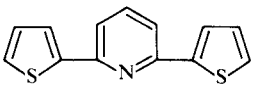
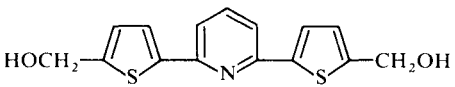
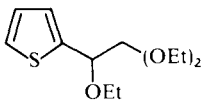
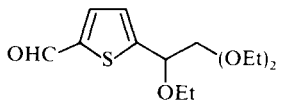
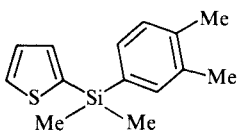
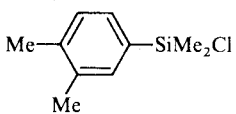
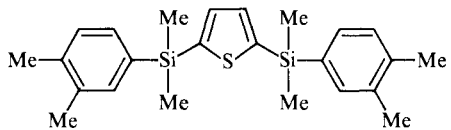
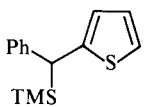
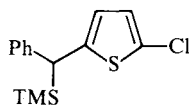
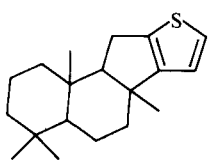
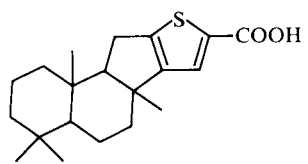
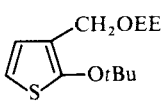
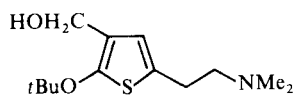
	1. LDA 2. $Me_2NCH_2CH_2Cl$		21	18
	1. BuLi 2. CO_2		90	146
	1. BuLi 2. CO_2		29	63
	1. BuLi, room temp. 2. CO_2		28	135
	1. BuLi 2. Me_2SO_4		81	94
	1. BuLi, TMEDA 2. CO_2		89	306
	1. BuLi, TMEDA 2. PhNCHO(Me)		69	306
	1. BuLi, TMEDA 2. DMF		69	306

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, TMEDA 2. CH_2O		20	306
	1. BuLi 2. DMF		37	89
	1. BuLi, ether 2. 		77	251
	1. BuLi 2. CCl_3CN			82
	1. BuLi 2. CO_2		82	265
	1. BuLi 2. $Me_2NCH_2CH_2Cl$		0	18

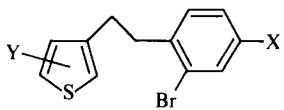
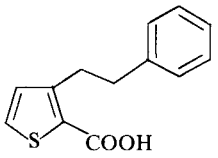
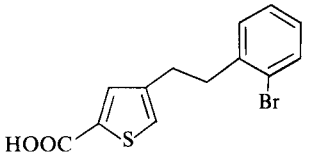
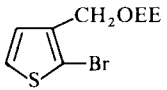
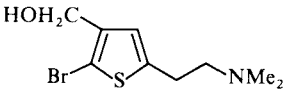
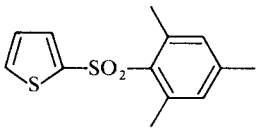
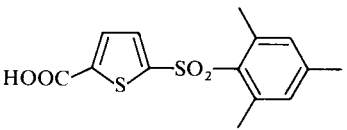
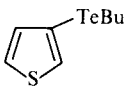
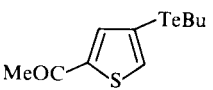
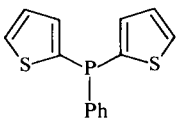
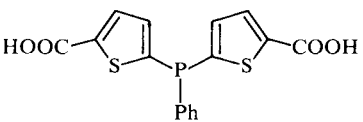
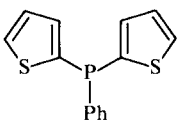
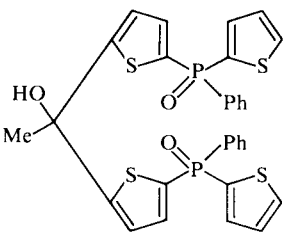
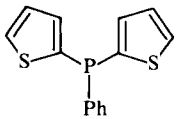
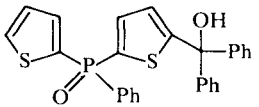
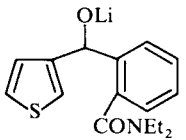
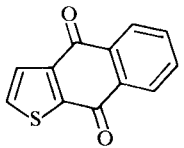
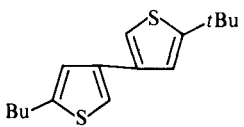
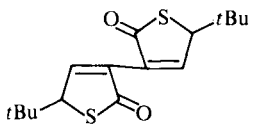
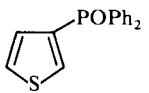
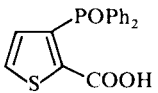
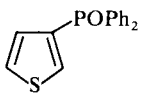
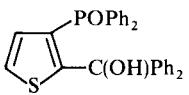
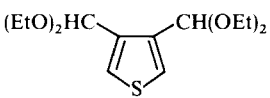
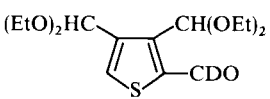
	1. BuLi or LDA 2. CO_2	 (with BuLi)  (with LDA)	X, Y = H[a]	22
	1. LDA 2. $Me_2NCH_2CH_2Cl$		14	18
	1. BuLi 2. CO_2		41	199
	1. LDA 2. DMA		34	72
	1. BuLi, THF 2. CO_2		40	53
	1. BuLi, THF 2. MeCOOEt 3. H_2O_2		30	53

TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, THF 2. PhCOPh 3. H_2O_2		35	53
	1. *sec*BuLi 2. Air oxidation		35	194
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		15	279
	1. BuLi 2. CO_2			53
	1. BuLi 2. PhCOPh			53
	1. BuLi 2. DMF-d_7			307

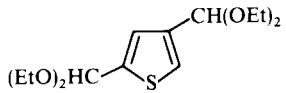
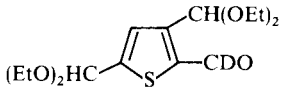
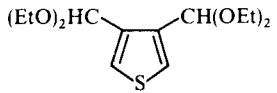
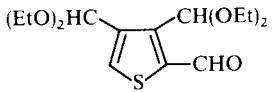
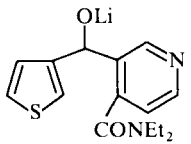
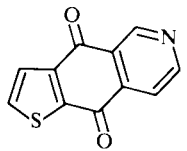
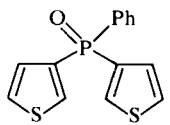
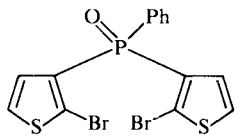
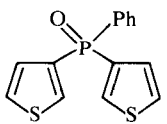
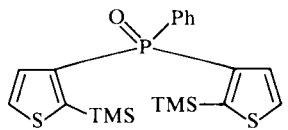
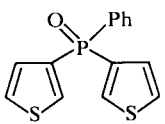
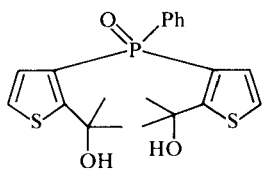
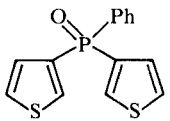
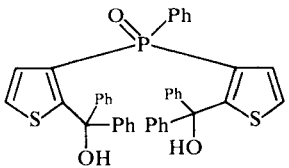
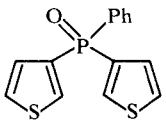
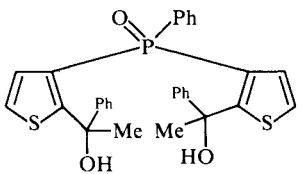
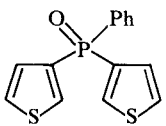
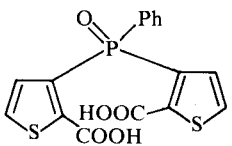
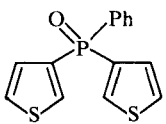
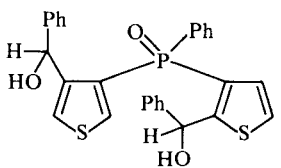
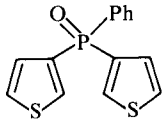
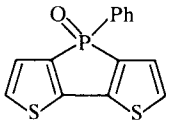
	1. BuLi 2. DMF-d_7			307
	1. BuLi 2. DMF			308
	1. *sec*BuLi 2. Air oxidation		20	194
	1. BuLi, THF 2. Br_2		65	53
	1. BuLi, THF 2. TMSCl		30	53
	1. BuLi, THF 2. MeCOMe		45	53

TABLE 1. (*Continued*)

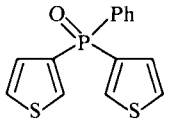
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, THF 2. PhCOPh		80	53
	1. BuLi, THF 2. PhCOMe		50	53
	1. BuLi, THF 2. CO_2		75	53
	1. BuLi, THF 2. PhCHO		70	53



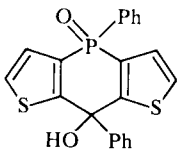
1. BuLi, THF
2. $CuCl_2$



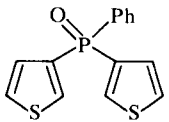
10 53



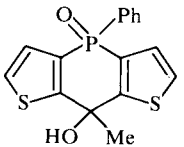
1. BuLi, THF
2. PhCOOEt



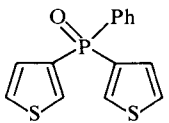
68 53



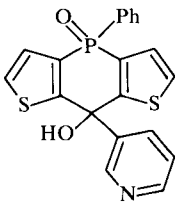
1. BuLi, THF
2. MeCOOEt



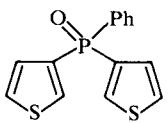
35 53



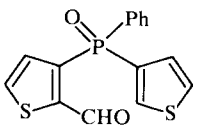
1. BuLi, THF
2. 3-COOEt–pyr



35 53

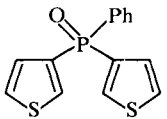
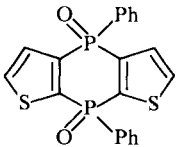
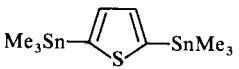
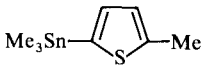
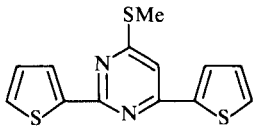
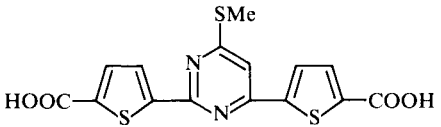
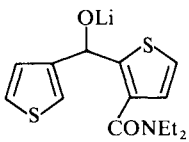
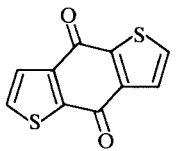
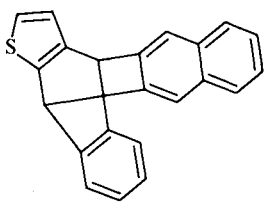
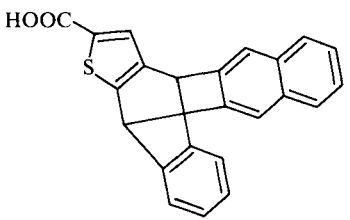


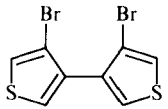
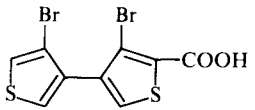
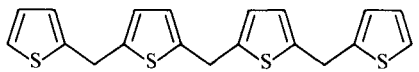
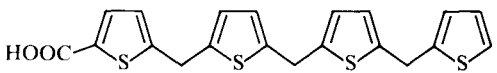
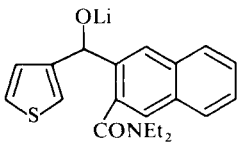
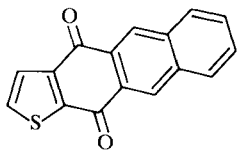
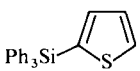
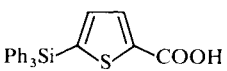
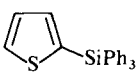
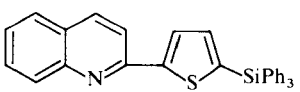
1. BuLi, THF
2. HCOOEt



48 53

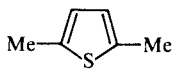
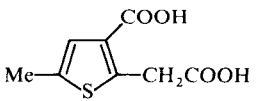
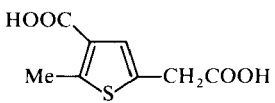
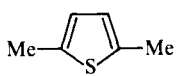
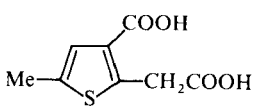
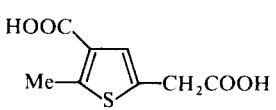
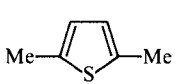
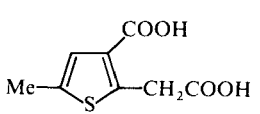
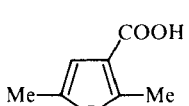
TABLE 1. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, THF 2. $PhPCl_2$ 3. H_2O_2		6–10	53
	1. MeLi, TMEDA 2. MeI		51	27
	1. BuLi, TMEDA 2. CO_2		41	306
	1. *sec*BuLi 2. Air oxidation		77	194
	1. BuLi, $-50°C$ 2. CO_2			309

	1. EtLi or BuLi 2. CO_2		47	310
	1. BuLi, room temp. 2. CO_2		15	114, 169
	1. *sec*BuLi 2. Air oxidation		37	194
	1. BuLi 2. CO_2		45	311
	1. BuLi 2. Quinoline		40	58

[a] Several other examples and conditions are discussed in Ref. 22.

TABLE 2. β-Thienyllithium Derivatives via Metalation

Starting Material	Reagent	Product		Yield (%)	Ref.
	1. BuLi, TMEDA, ether 2. CO_2	 : 	9 1	14	31
	1. BuLi, TMEDA, hexane 2. CO_2	 : 	0.43 1	17	31
	1. EtLi, TMEDA, ether 2. CO_2	 : 	3 1	8	30

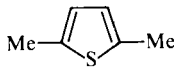
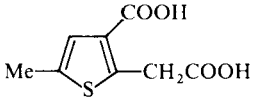
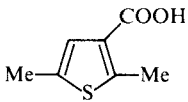
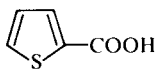
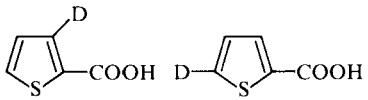
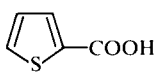
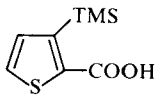
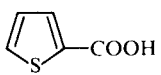
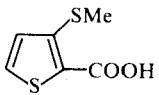
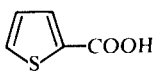
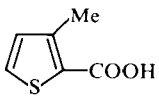
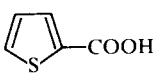
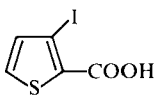
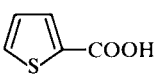
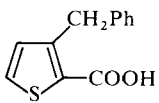
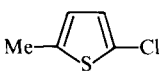
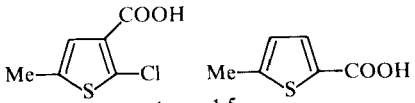
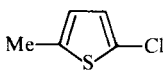
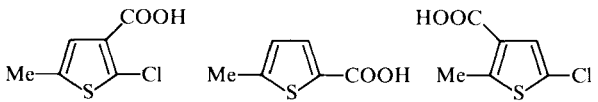
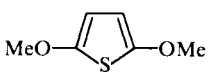
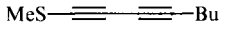
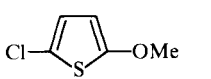
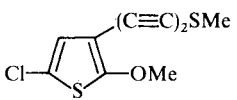
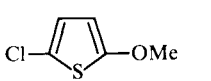
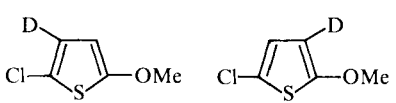
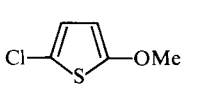
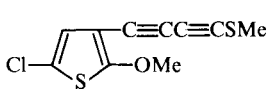
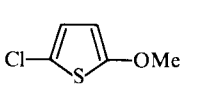
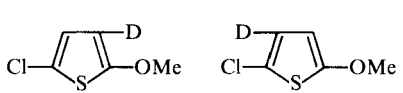
	1. EtLi, TMEDA, hexane 2. CO_2	 10 :  1	16	30
	1. BuLi, THF, − 78°C 2. MeOD	 93% 5%		125
	1. BuLi, THF, − 78°C 2. TMSCl		85	125
	1. BuLi, THF, − 78°C 2. Me_2S_2		94	125
	1. BuLi, THF, − 78°C 2. MeI		83	125
	1. BuLi, THF, − 78°C 2. I_2		92	125
	1. BuLi, THF, − 78°C 2. $PhCH_2Br$		70	125

TABLE 2. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, TMEDA 2. CO_2	 1 : 1.5		31
	1. LDA 2. CO_2	 1 : 1.5 : 1.8		31
	1. BuLi 2eq 2. Me_2SO_4		45	121
	1. BuLi, 25°C 2. Me_2SO_4		20	122
	1. BuLi, 25°C 2. D_2O	 1 : 2		122
	1. BuLi, 25°C, 4 h 2. DMS		20	122
	1. BuLi, 25°C, 10 min 2. D_2O	 2 : 1	20	122

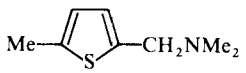
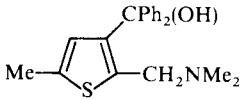
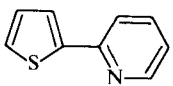
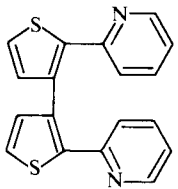
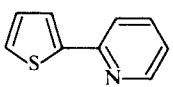
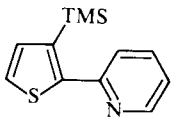
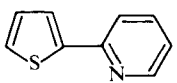
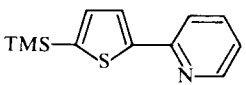
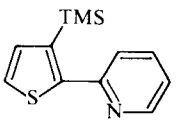
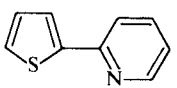
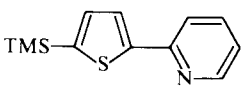
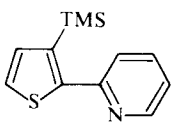
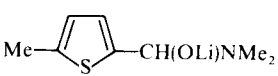
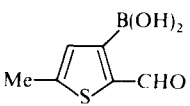
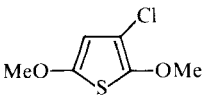
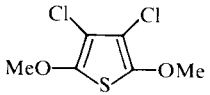
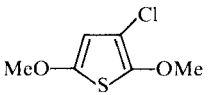
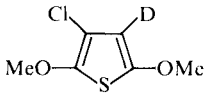
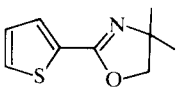
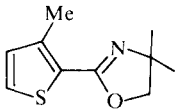
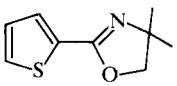
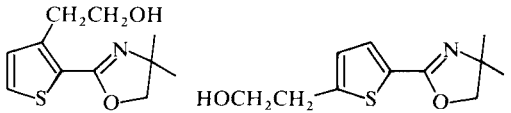
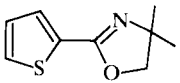
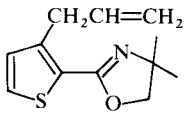
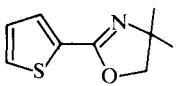
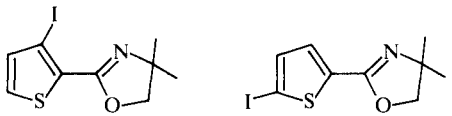
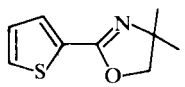
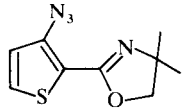
	1. BuLi 2. Ph_2CO		65	74
	1. *t*BuLi 2. $CuCl_2$		54	55
	1. *t*BuLi or BuLi, ether 2. TMSCl		Mostly	59
	1. BuLi, ether 2. TMSCl	  17 : 83		126
	1. BuLi, ether, TMEDA 2. TMSCl	  17 : 83		126
	1. EtLi 2. $B(OBu)_3$		28	100

TABLE 2. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. C_2C_{16}		60	218
	1. BuLi 2. D_2O		—	218
	1. BuLi, ether 2. MeI		90	102
	1. BuLi, ether 2. Ethyleneoxide	 33 : 11		
	1. BuLi, ether 2. AllylBr		81	102
	1. BuLi, ether 2. I_2	 53 : 12		102

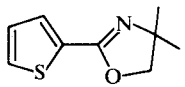


1. BuLi, ether
2. $TosN_3$

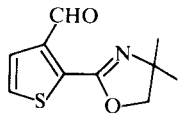


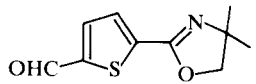
90

102



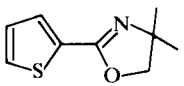
1. BuLi, ether
2. DMF



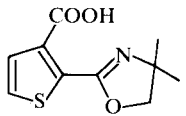


94 : 3

102

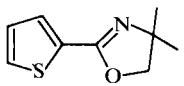


1. BuLi, ether
2. CO_2

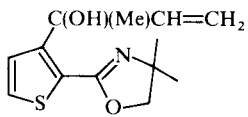


90

102

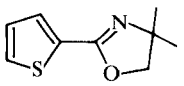


1. BuLi, ether
2. MVK

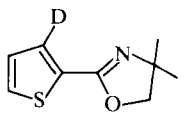


26

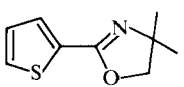
102



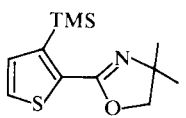
1. BuLi, ether
2. D_2O



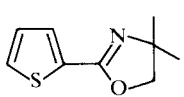
102



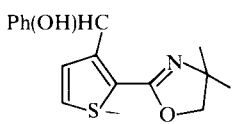
1. BuLi, ether
2. TMSCl



102

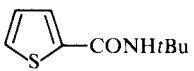
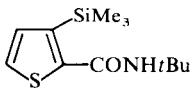
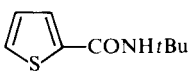
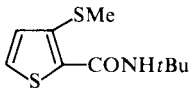
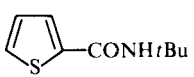
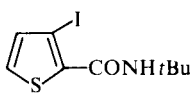
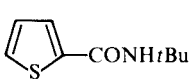
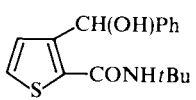
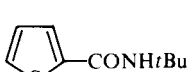
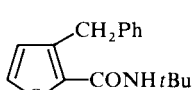
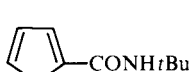
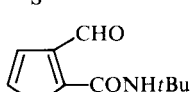
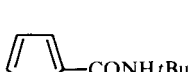
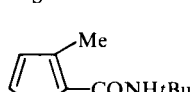


1. BuLi
2. PhCHO



127

TABLE 2. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi/DME 2. Me_3SiCl		95	129
	1. BuLi/DME 2. MeSSMe		93	129
	1. BuLi/DME 2. I_2		72	129
	1. BuLi/DME 2. PhCHO		77	129
	1. BuLi/DME 2. $PhCH_2Br$		76	129
	1. BuLi/DME 2. DMF		63	129
	1. BuLi/DME 2. MeI		88	129

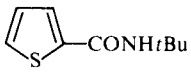
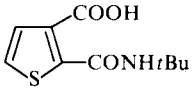
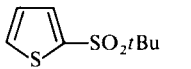
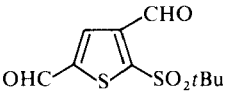
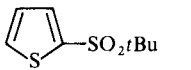
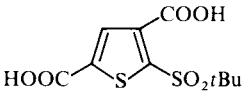
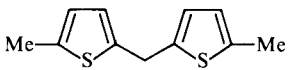
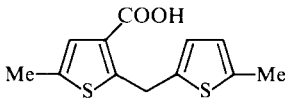
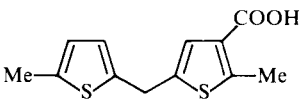
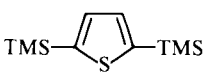
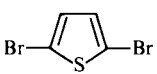
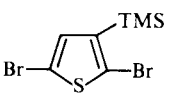
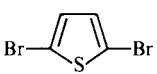
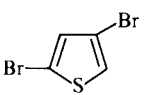
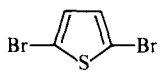
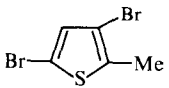
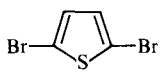
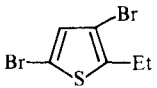
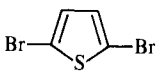
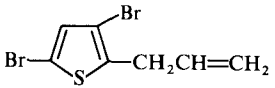
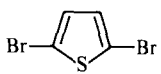
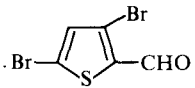
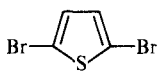
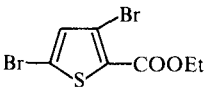
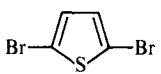
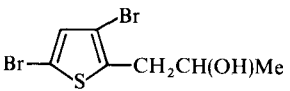
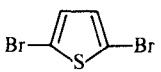
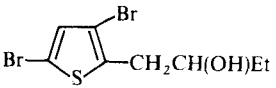
	1. BuLi/DME 2. CO_2		74	129
	1. BuLi 4 eq, THF, $-15°C$ 2. DMF		59	130
	1. BuLi 4 eq, THF, $-15°C$ 2. CO_2		68	130
	1. BuLi 2. CO_2	 or 	Low	113
	BuLi, THF			116
	1. LDA 2. TMSCl			14
	1. LDA, THF, $-78°C$ 2. H_2O		100	124

TABLE 2. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA, THF, − 78°C 2. MeI		100	124
	1. LDA, THF, − 78°C 2. EtI		95	124
	1. LDA, THF, − 78°C 2. AllylBr		68	124
	1. LDA, THF, − 78°C 2. DMF		85	124
	1. LDA, THF, − 78°C 2. ClCOOEt		72	124
	1. LDA, THF, − 78°C 2. Propene oxide		73	124
	1. LDA, THF, − 78°C 2. 1-Butene oxide		68	124

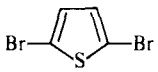
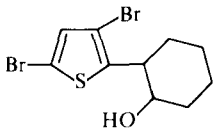
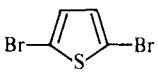
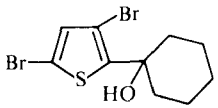
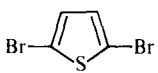
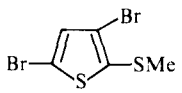
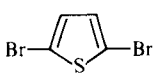
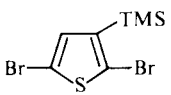
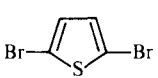
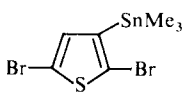
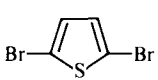
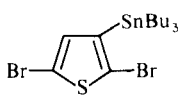
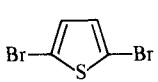
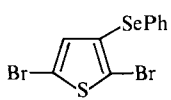
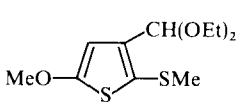
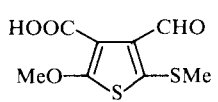
	1. LDA, THF, − 78°C 2. Cyclohexene oxide		63	124
	1. LDA, THF, − 78°C 2. Cyclohexanone		77	124
	1. LDA, THF, − 78°C 2. MeSSMe		45	124
	1. LDA, THF, − 78°C 2. TMSCl		91	123
	1. LDA, THF, − 78°C 2. Me_3SnCl		74	123
	1. LDA, THF, − 78°C 2. Bu_3SnCl		84	123
	1. LDA, THF, − 78°C 2. PhSeCl		78	123
	1. BuLi 2. CO_2		85	131

TABLE 2. (*Continued*)

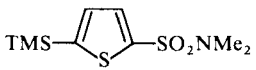
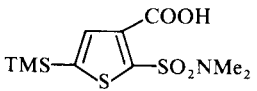
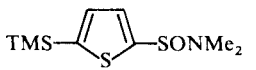
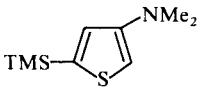
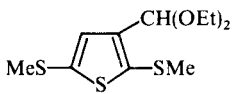
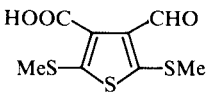
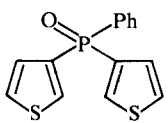
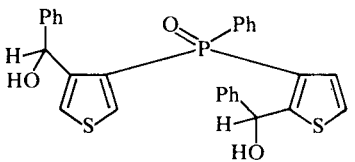
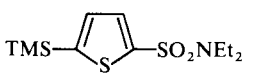
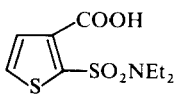
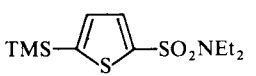
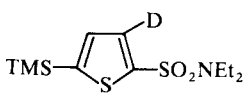
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, 0°C 2. CO_2		10	128
	1. BuLi, TMEDA 2. CO_2		39	128
	1. BuLi 2. CO_2		83	131
	1. BuLi, THF 2. PhCHO		70	53
	1. BuLi, TMEDA 2. CO_2		44	128
	1. BuLi, TMEDA 2. D_2O		70	128

TABLE 3. α-Thienyllithium Derivatives via Halogen–Metal Exchange

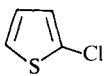
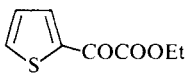
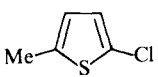
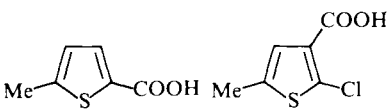
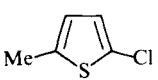
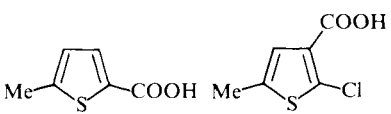
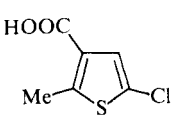
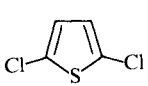
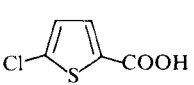
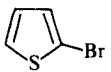
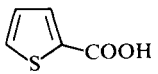
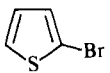
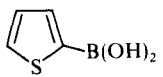
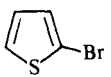
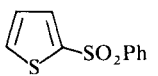
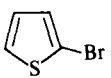
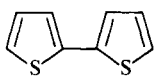
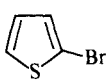
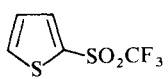
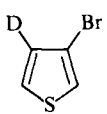
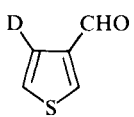
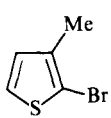
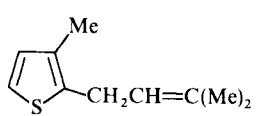
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, THF/hexane 2. $(COOEt)_2$		84	221
	1. BuLi, TMEDA 2. CO_2	 1.5 : 1	90	31
	1. LDA 2. CO_2	 1 : 5.1 1.8 : 	12 total	31
	1. BuLi 2. CO_2		63	159

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Poly-*p*-Li-styrene 2. CO_2		66	24
	1. BuLi 2. $B(OBu)_3$		62	140
	1. BuLi 2. $PhSO_2OPh$		88	346
	1. Li 2. $CoCl_2$, PhBr		30	347
	1. BuLi 2. $(CF_3SO_2)_2O$		High yield	348
	1. BuLi 2. DMF		70	349
	1. BuLi 2. $BrCH_2CH{=}C(Me)_2$		75	290

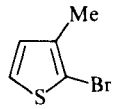
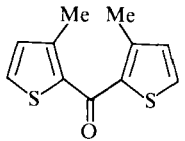
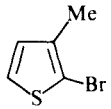
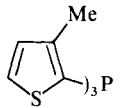
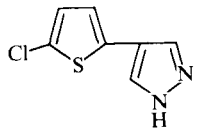
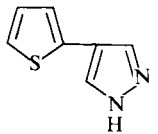
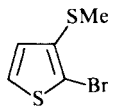
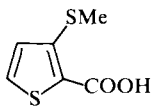
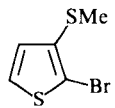
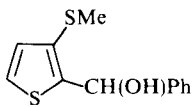
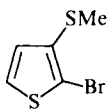
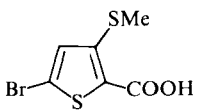
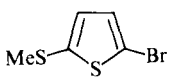
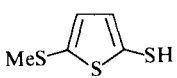
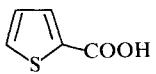
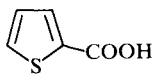
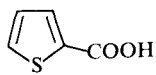
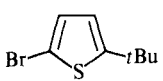
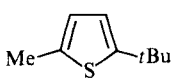
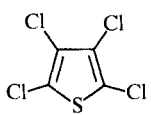
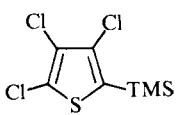
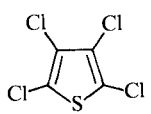
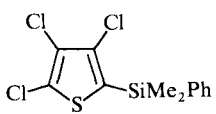
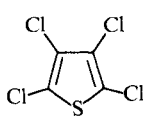
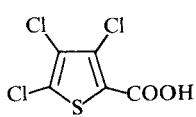
	1. EtLi 2. $Me_2NCOOEt$		75	65
	1. BuLi 2. PBr_3		28	109
	1. BuLi 3 eq, THF 2. H_2O		73	350
	1. BuLi 2. CO_2			20
	1. BuLi 2. MeCHO			20
	1. LDA 2. CO_2		41	20
	1. BuLi 2. S		64	351

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhLi 2. CO_2		58	352
	1. Li 2. CO_2		69	150
	1. PhLi 2. CO_2		55	13
	1. BuLi 2. DMS		76	353
	1. BuLi, PhLi, MeLi, or *t*BuLi in THF 2. TMSCl		50	354
	1. *t*BuLi in THF 2. $PhMe_2SiCl$		56	354
	1. *t*BuLi in THF 2. CO_2		94	354

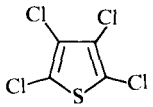
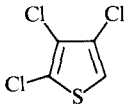
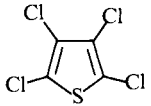
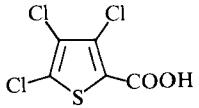
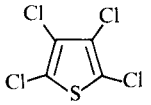
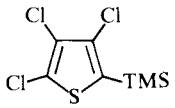
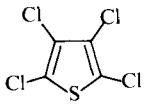
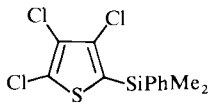
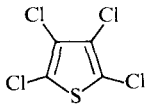
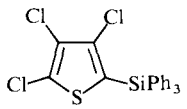
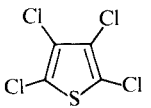
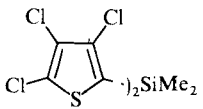
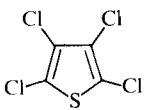
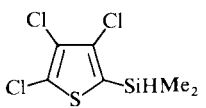
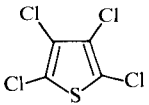
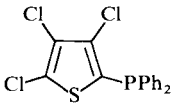
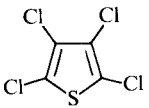
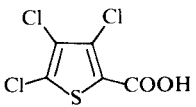
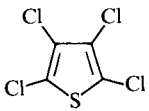
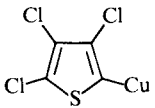
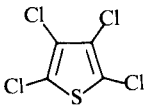
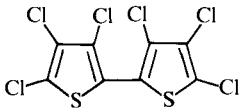
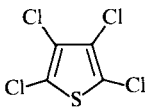
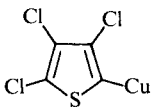
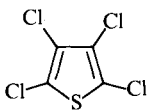
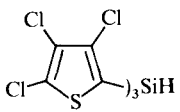
	1. BuLi 2. H_2O		99	355
	1. BuLi 2. CO_2		99	355
	1. BuLi 2. TMSCl		91	355
	1. BuLi 2. $PhMe_2SiCl$		89	355
	1. BuLi 2. Ph_3SiCl		39	355
	1. BuLi 2. Me_2SiCl_2		76	355
	1. BuLi 2. HMe_2SiCl		88	355

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. Ph_2PCl		49	355
	1. *t*BuLi 2. CO_2		91	355
	1. *t*BuLi, THF or BuLi, monoglyme 2. CuCl or CuI		70	356
	1. BuLi, ether 2. CuCl		67–73	356
	1. BuLi, ether 2. CuI		63	356
	1. BuLi 2. Cl_3SiH		65	357

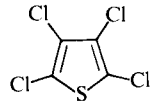
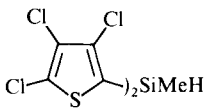
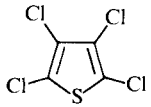
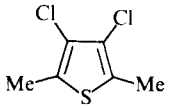
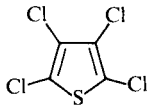
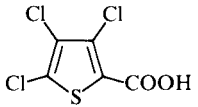
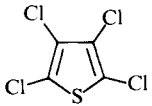
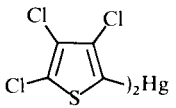
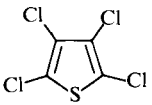
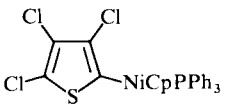
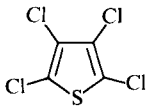
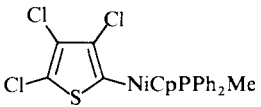
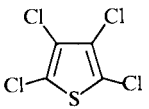
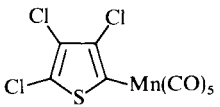
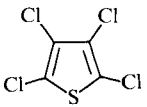
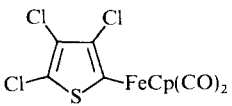
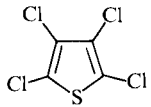
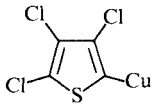
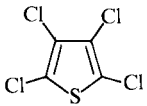
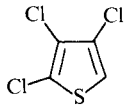
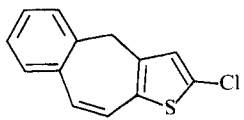
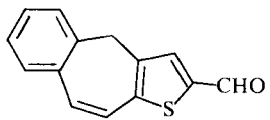
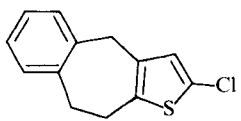
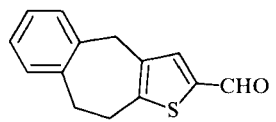
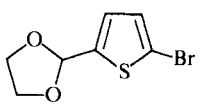
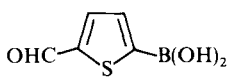
	1. BuLi 2. $MeCl_2SiH$		91.5	357
	1. BuLi 2. DMS		72	30
	1. BuLi 2. CO_2		55	159
	1. BuLi 2. $HgCl_2$		40	358
	1. BuLi 2. CpNiCl 3. PPh_3		29	358
	1. BuLi 2. CpNiCl 3. PPh_2Me		36	358
	1. BuLi 2. $Mn(CO)_5Br$		13	358

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $CpFe(CO)_2I$		17	358
	1. BuLi, $-30°C$ 2. CuI			359
	1. BuLi 2. H_2O		62	218
	1. BuLi 2. DMF		58	146
	1. BuLi 2. DMF		45	146
	1. BuLi 2. $B(OBu)_3$		57	156

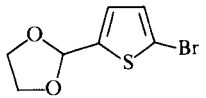
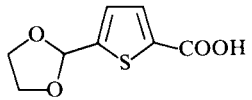
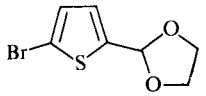
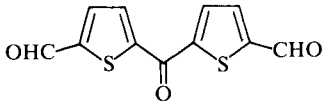
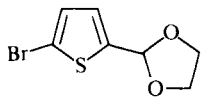
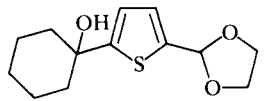
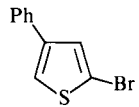
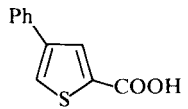
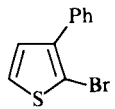
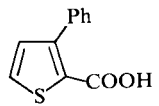
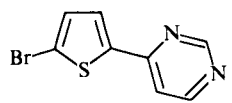
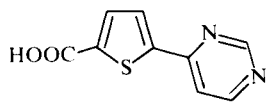
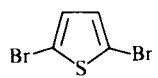
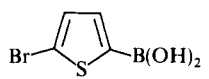
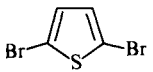
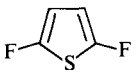
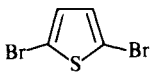
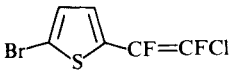
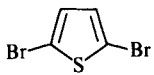
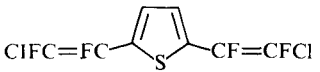
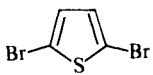
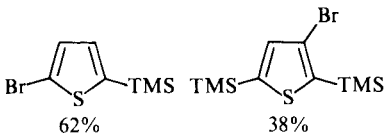
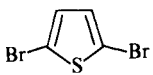
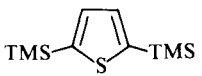
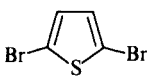
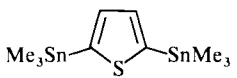
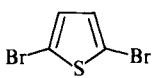
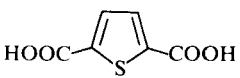
	1. BuLi 2. CO_2		78	158
	1. BuLi 2. $Me_2NCOOEt$		49	360
	1. BuLi 2. Cyclohexanone		75	361
	1. EtLi, – 70°C 2. CO_2		85	235
	1. EtLi, – 70°C 2. CO_2		82	235
	1. BuLi 2. CO_2		50	63
	1. BuLi 2. $B(OBu)_3$		58	140

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. $FClO_3$		—	184
	1. BuLi 2. CF_2=CFCl		60	286
	1. BuLi 2 eq 2. CF_2=CFCl 2 eq		76	286
	1. BuLi, THF 2. TMSCl	 62% 38%		123
	1. BuLi, THF, − 55°C 2. TMSCl		89	123
	1. BuLi, THF, − 55°C 2. TMSnCl		92	123
	1. BuLi, THF, − 55°C 2. CO_2		95	123

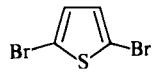
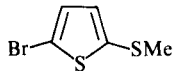
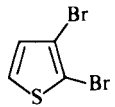
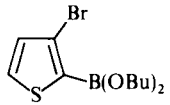
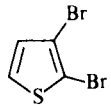
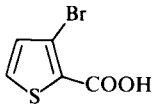
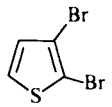
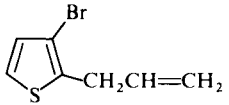
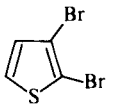
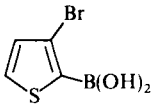
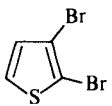
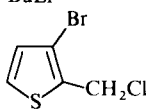
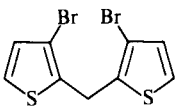
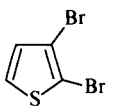
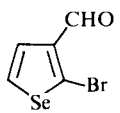
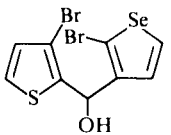
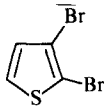
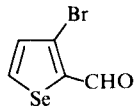
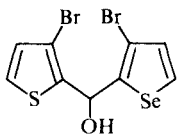
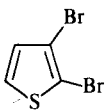
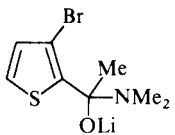
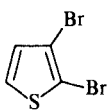
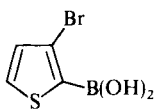
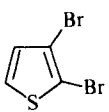
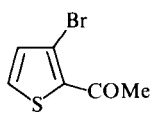
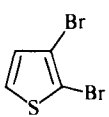
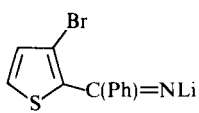
	1. BuLi 2. MeSSMe		82	369
	1. EtLi, ether 2. $B(OBu)_3$		—	362
	1. BuLi 2. CO_2		85	157
	1. BuLi 2. AllylBr		85	35
	1. BuLi 2. $B(OBu)_3$		80	96
	1. BuLi 2. 		16	363
	1. BuLi 2. 		71	364

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. 		78	364
	1. EtLi 2. DMA			100
	1. BuLi 2. $B(OBu)_3$		51	140
	1. BuLi 2. DMA		40	365
	1. BuLi 2. PhCN		—	79

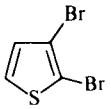
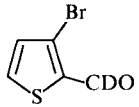
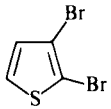
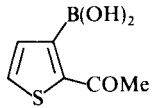
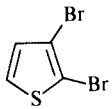
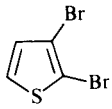
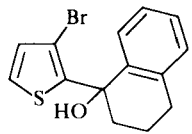
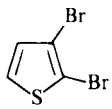
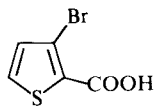
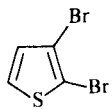
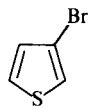
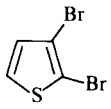
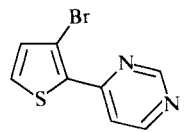
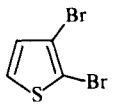
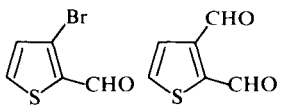
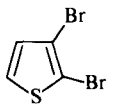
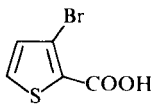
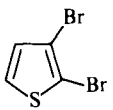
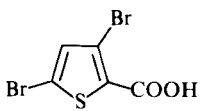
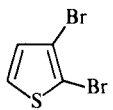
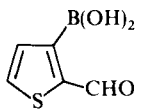
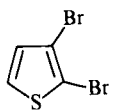
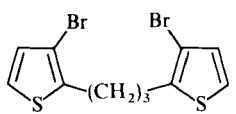
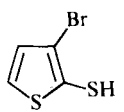
	1. BuLi 2. DMF-d_7		—	366
	1. EtLi 2. DMA 3. BuLi 4. $B(OBu)_3$		35	100
	1. EtLi 2. $FClO_3$		67	184
	1. BuLi 2. 1-Tetralone		60	367
	1. BuLi 1 eq 2. CO_2		70	138
	1. BuLi 1 eq 2. H_2O		58	138
	1. BuLi 2. Pyrimidine		29	63

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2 eq 2. DMF			142
	1. BuLi, − 70°C, 5 min 2. CO_2		70	137
	1. BuLi, 5 h, room temp. 2. CO_2		47	137
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		35	143
	1. BuLi 2. $(TosOCH_2)CH_2$		31	368
	1. BuLi 2. S		59	351

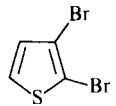
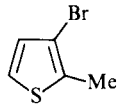
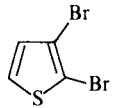
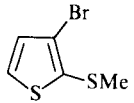
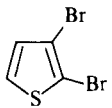
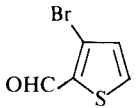
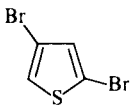
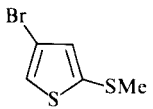
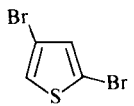
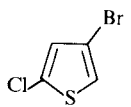
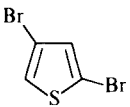
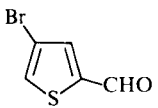
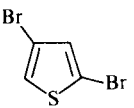
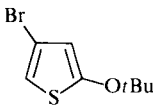
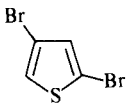
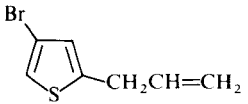
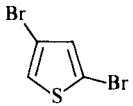
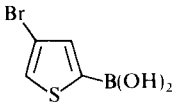
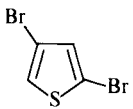
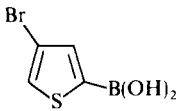
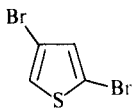
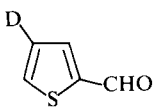
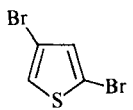
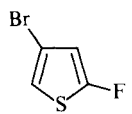
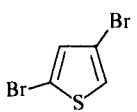
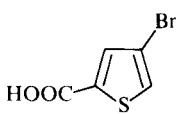
	1. BuLi 2. MeTos		84	369
	1. BuLi 2. MeSSMe		73	369
	1. BuLi 2. DMF		70	269
	1. BuLi 2. MeSSMe		76	369
	1. BuLi 2. C_2Cl_6		44	370
	1. BuLi 2. DMF		55	269
	1. BuLi 2. $MgBr_2$ 3. *t*BuOOCOPh			94

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. AllylBr		56	35
	1. BuLi 2. $B(OBu)_3$		80	96
	1. BuLi 2. $B(OBu)_3$		56	140
	1. BuLi 2. DMF 3. BuLi 4. MeOD		41	349
	1. EtLi 2. $FClO_3$		67	184
	1. BuLi 2. CO_2		75	135

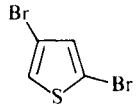
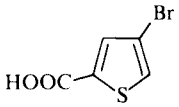
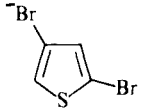
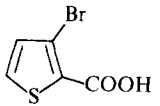
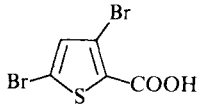
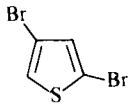
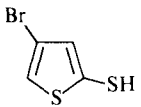
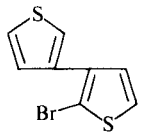
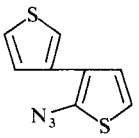
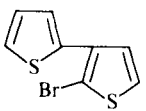
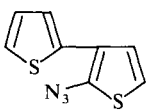
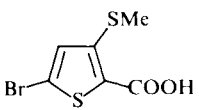
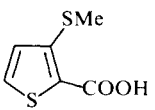
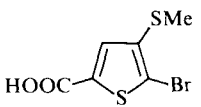
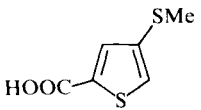
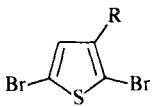
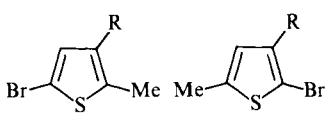
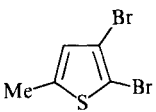
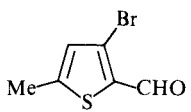
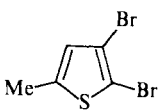
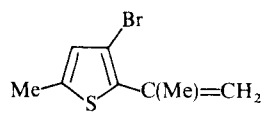
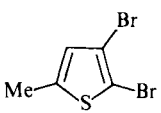
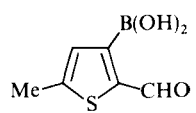
	1. BuLi, −70°C, 5 min 2. CO_2		81	137
	1. BuLi, 12 h, room temp. 2. CO_2	 36%  36%	81	137
	1. BuLi 2. S		51	351
	1. BuLi 2. $ToSN_3$		41	56
	1. BuLi 2. $TosN_3$		33	56
	1. BuLi, 2 eq 2. H_2O		58	20

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, 1.5 eq 2. HCl		70	20
	1. BuLi, 2. BuLi–TMEDA, EtMgBr, or Mg 3. DMS			29
	1. EtLi 2. DMF		65	100
	1. EtLi 2. MeCOMe 3. $(COOH)_2$		77	353
	1. BuLi 2. DMF 3. BuLi 4. $B(OBu)_3$		28	100

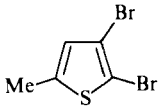
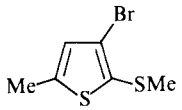
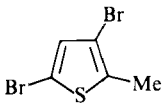
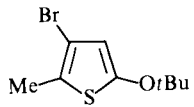
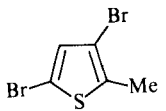
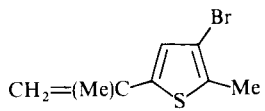
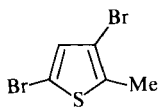
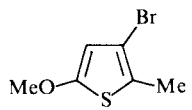
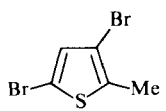
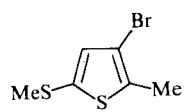
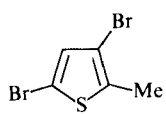
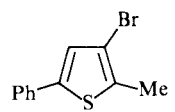
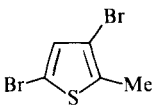
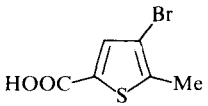
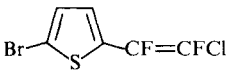
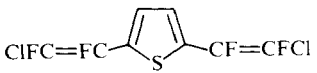
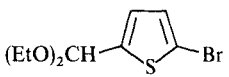
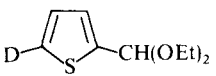
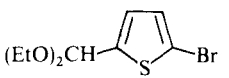
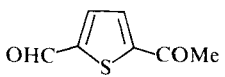
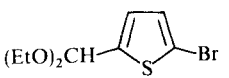
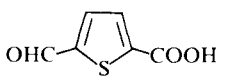
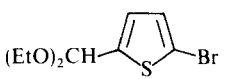
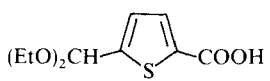
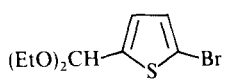
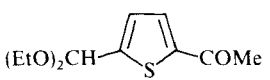
	1. BuLi 2. Me_2S_2		66	145
	1. BuLi 2. $MgBr_2$ 3. *t*BuOOCOPh			94
	1. EtLi 2. MeCOMe 3. $(COOH)_2$		65	353
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2 4. DMS		32	145
	1. BuLi 2. Me_2S_2		70	213
	1. BuLi 2. Cyclohexanone 3. DDQ		51	17

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CO_2		75	17
	1. BuLi 2. CF_2=CFCl		39	286
	1. BuLi 2. D_2O		—	371
	1. BuLi 2. Ac_2O		Low	73
	1. BuLi 2. CO_2		83	73
	1. BuLi 2. CO_2		85	296
	1. BuLi 2. Ac_2O		Low	296

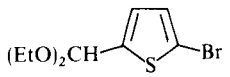
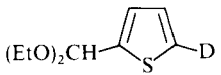
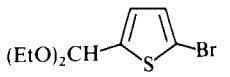
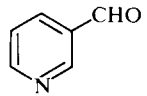
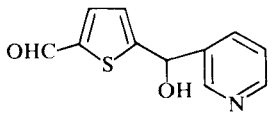
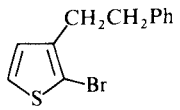
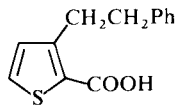
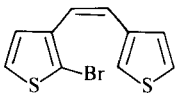
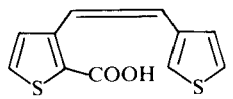
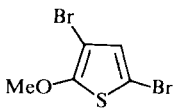
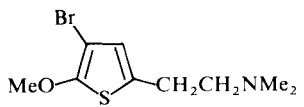
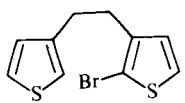
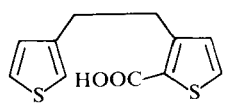
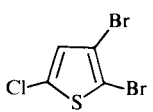
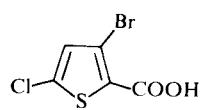
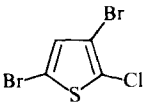
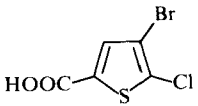
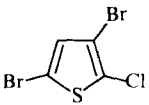
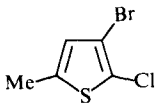
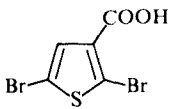
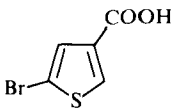
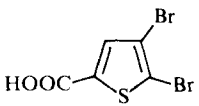
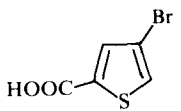
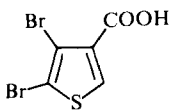
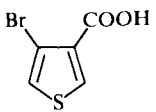
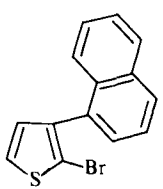
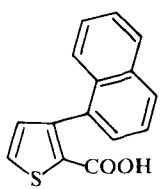
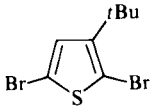
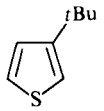
	1. BuLi 2. D_2O		50	372
	1. BuLi 2. 		87	373
	1. BuLi, $-70°C$ 2. CO_2		39	22
	1. BuLi or EtLi 2. CO_2		84 or 64	374, 375
	1. BuLi 2. $Cl(CH_2)_2NMe_2$		7	18
	1. EtLi or BuLi 2. CO_2		90–95, 80	160, 376
	1. BuLi 2. CO_2		67	141

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CO_2		62	141
	1. BuLi 2. DMS		85	145
	1. BuLi 2. H_2O		49	144
	1. BuLi 2. H_2O		55	377
	1. BuLi 2. H_2O		53	144
	1. BuLi 2. CO_2		84	367

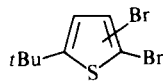


1. BuLi
2. H_2O

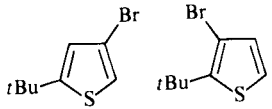


82

29



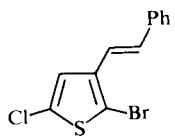
1. BuLi
2. H_2O



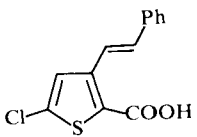
76 : 24

75

279

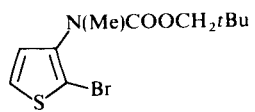


1. BuLi
2. CO_2

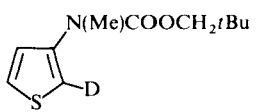


82

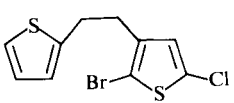
146



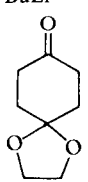
1. BuLi
2. D_2O

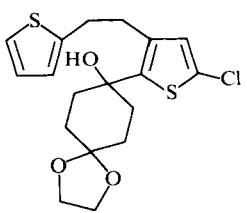


378



1. BuLi
2.

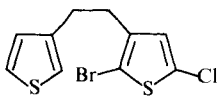
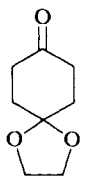
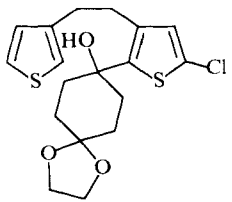
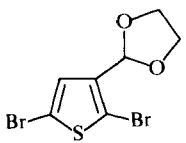
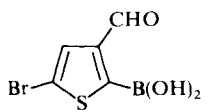
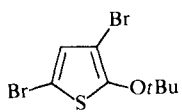
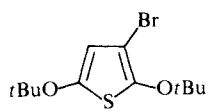
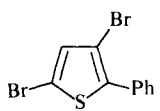
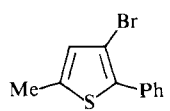
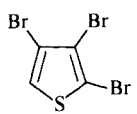
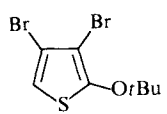




77

147

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. 		52	148
	1. BuLi 2. $B(OEt)_3$		95	21
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		90	154
	1. BuLi 2. DMS		56	17
	1. BuLi 2. $MgBr_2$ 3. $tBuOOCOPh$			94

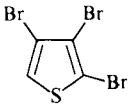
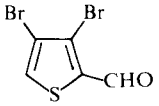
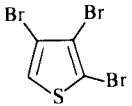
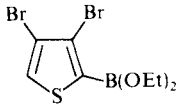
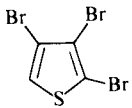
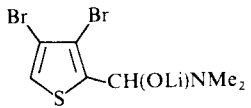
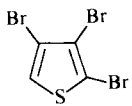
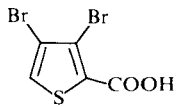
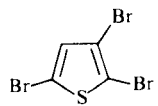
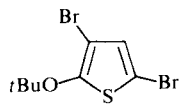
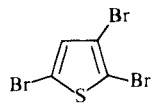
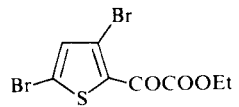
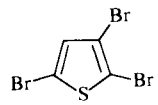
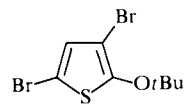
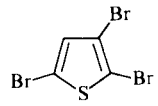
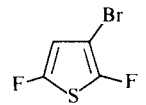
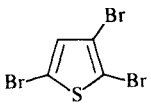
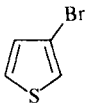
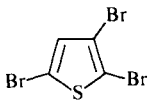
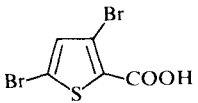
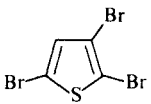
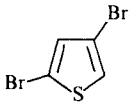
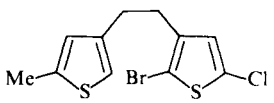
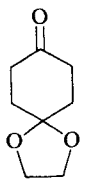
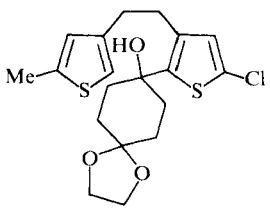
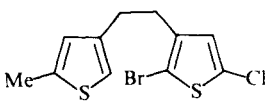
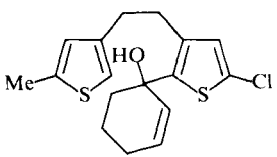
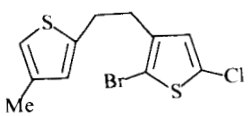
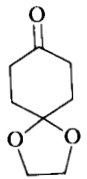
	1. BuLi 2. DMF			307
	1. BuLi 2. $B(OEt)_3$			21
	1. BuLi 2. DMF			21
	1. BuLi 2. CO_2		62	136
	1. BuLi 2. $MgBr_2$ 3. *t*BuOOCOPh			94
	1. BuLi, THF/hexane 2. $(COOEt)_2$		75	221
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		95	154
	1. EtLi 2. $FClO_3$			184

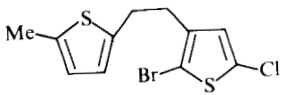
TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2 eq 2. H_2O		65	138
	1. BuLi 1 eq 2. CO_2		36	138
	1. BuLi 2. H_2O		75	135
	1. BuLi 2. 		46	148
	1. BuLi 2. 2-cyclohexenone		95	148

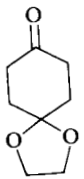


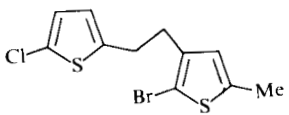
1. BuLi
2.



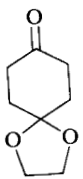


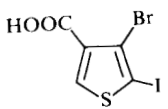
1. BuLi
2.



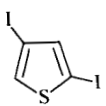


1. BuLi
2.

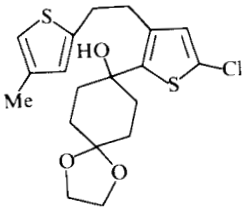




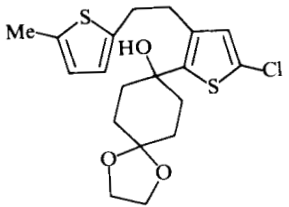
1. BuLi
2. CO_2



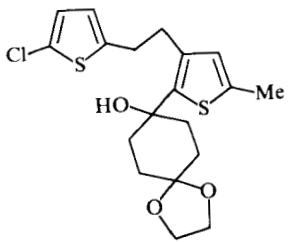
1. BuLi
2. Br_2



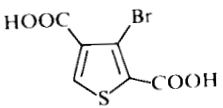
87 147



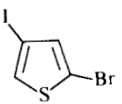
87 147



44 148

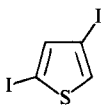
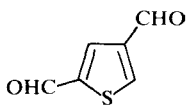
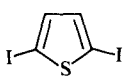
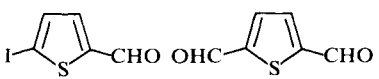
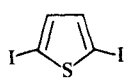
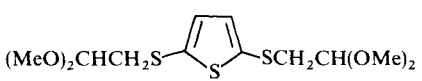
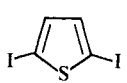
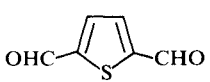
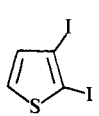
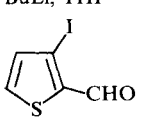
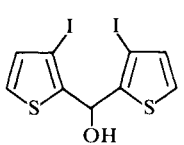
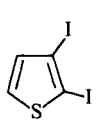
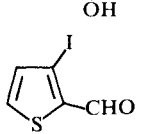
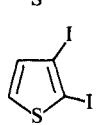
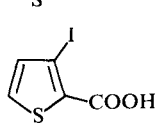


64 379



36 141

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2 eq 2. DMF			142
	1. BuLi 2. DMF	 34 : 5		85
	1. PhLi 2. $(MeO)_2(CHCH_2S)_2$—		58	380, 381
	1. BuLi 2 eq 2. DMF			142
	1. BuLi, THF 2. 		69	86
	1. BuLi 2. DMF		60	85
	1. EtLi 2. CO_2		45	141

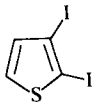
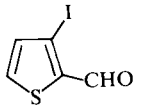
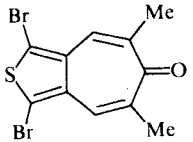
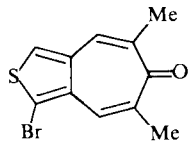
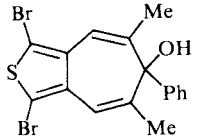
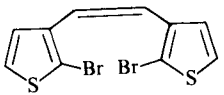
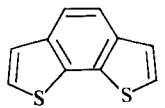
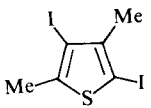
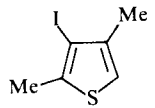
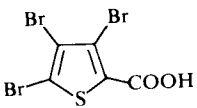
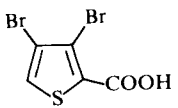
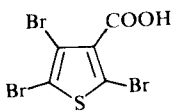
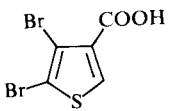
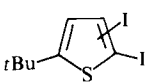
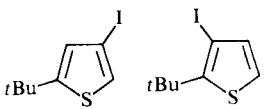
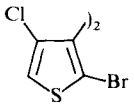
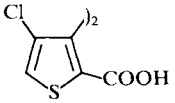
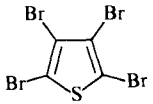
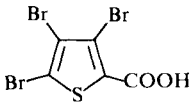
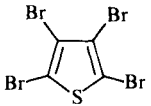
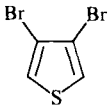
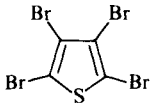
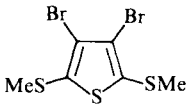
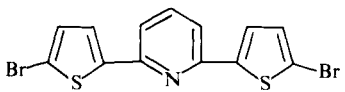
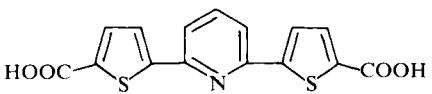
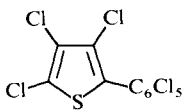
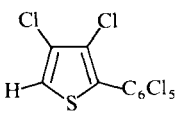
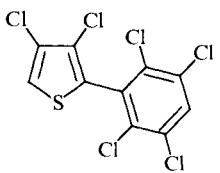
	1. BuLi 2 eq 2. DMF		142
	1. PhLi 2. H_2O	 	382
	1. EtLi 2. $CuCl_2$		56 84
	1. EtLi 2. H_2O		89 271
	1. BuLi 2. H_2O		57 144
	1. BuLi 2. H_2O		47 144
	1. BuLi 2. H_2O	 97 : 3	79 279

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CO_2		84	383
	1. BuLi 2. CO_2		73	144
	1. BuLi 2 eq 2. H_2O		74	136
	1. BuLi 2 eq 2. Me_2S_2		73	384
	1. BuLi 2. CO_2		39	306
	1. BuLi 2 eq, THF, $-78°C$ 2. H_2O	  76 : 24		149

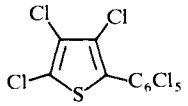
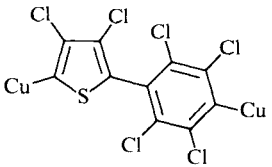
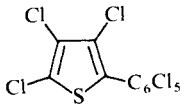
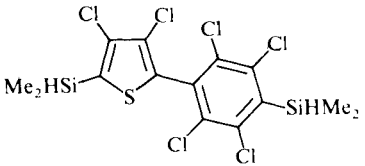
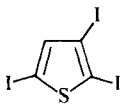
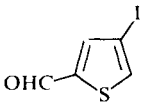
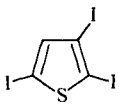
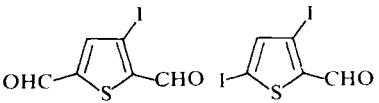
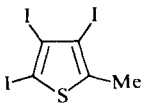
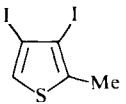
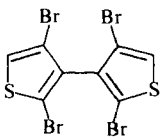
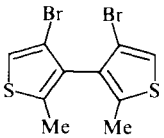
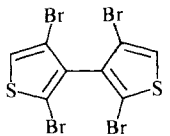
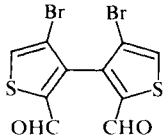
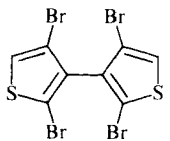
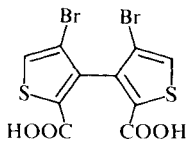
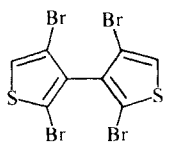
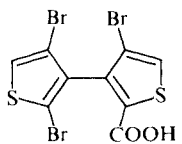
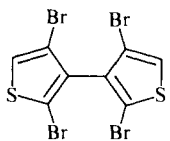
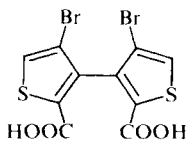
	1. BuLi 3 eq, THF 2. CuI		63	149
	1. BuLi 3 eq, THF 2. Me_2HSiCl		67	149
	1. BuLi 2. H_2O 3. BuLi 4. DMF		55	85
	1. BuLi 2. DMF	 13 : 30		85
	1. BuLi 2. H_2O		78	207
	1. BuLi 2. DMS		86	385

TABLE 3. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, − 70°C 2. DMF		86	386
	1. EtLi 4 eq, − 70°C 2. CO_2		70	241
	1. EtLi 2 eq, − 70°C 2. CO_2		Optically active	241
	1. BuLi 2 eq 2. CO_2		59	387

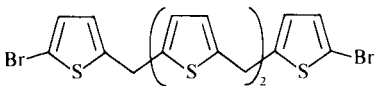
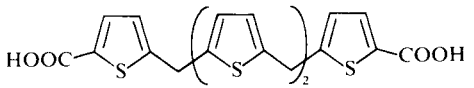
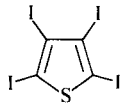
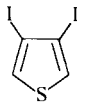
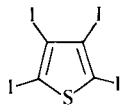
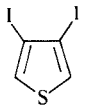
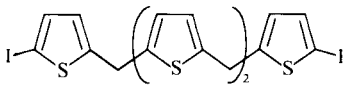
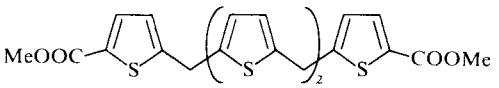
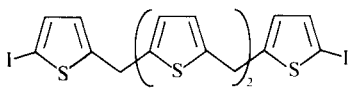
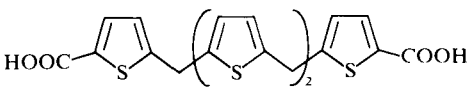
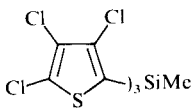
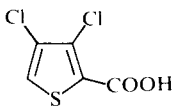
	1. BuLi 2. CO_2		170
	1. BuLi 2. H_2O		85
	1. BuLi 2. H_2O		48 139
	1. BuLi 2. H_2O 3. CH_2N_2		42 114
	1. BuLi 2. CO_2		378
	1. BuLi or MeLi 2. CO_2 3. H_2O		59 357

TABLE 3. (*Continued*)

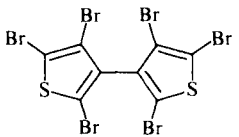
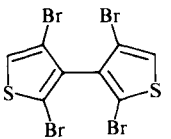
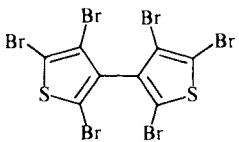
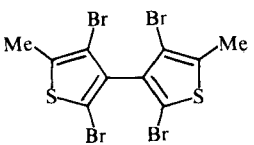
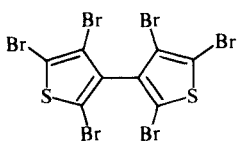
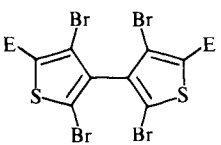
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, < 35°C 2. H_2O		75	386
	1. BuLi, −40°C 2. DMS		Optically active	242
	1. BuLi 2. H_2O or CO_2		61% E=H	387

TABLE 4. β-Thienyllithium Derivatives via Halogen–Metal Exchange

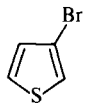
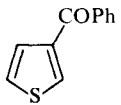
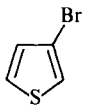
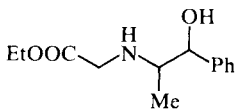
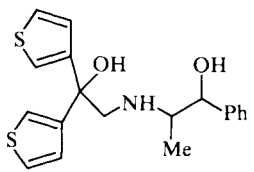
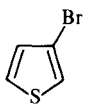
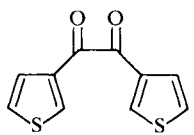
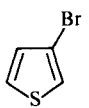
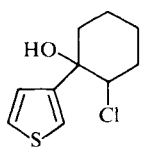
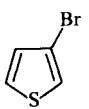
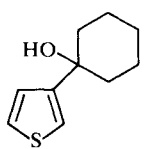
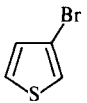
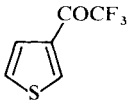
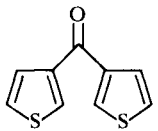
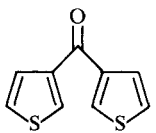
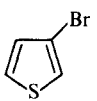
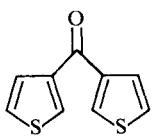
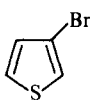
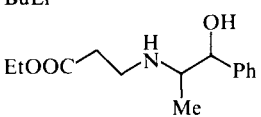
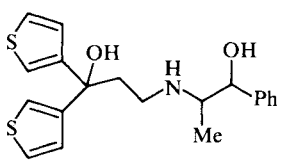
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. PhCN			291
	1. BuLi 2. 			659
	1. EtLi 2. $(MeOOC)_2$		28	248
	1. BuLi 2. 2-Chlorocyclohexanone		80	40
	1. BuLi 2. Cyclohexanone		—	40

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CF_3CONMe_2		50	69
	1. BuLi 2. $EtOOCNMe_2$		45	65
	1. BuLi 2. $PhOOCNMe_2$		57	65
	1. BuLi 2. $ClOCNMe_2$		89	65
	1. BuLi 2. 		78	388

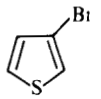
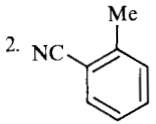
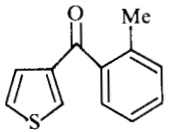
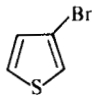
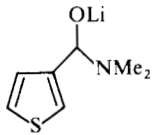
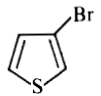
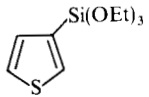
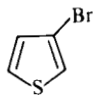
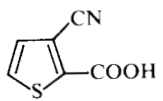
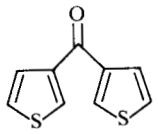
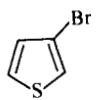
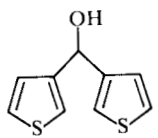
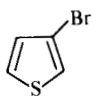
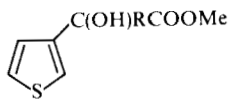
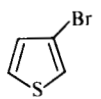
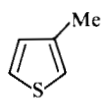
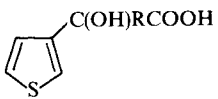
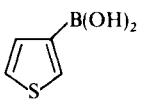
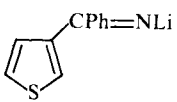
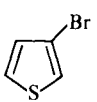
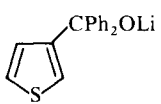
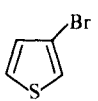
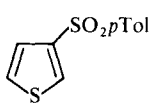
	1. BuLi 2. 		46	389
	1. BuLi 2. DMF			84
	1. BuLi 2. $SiCl_4$ 3. EtOH		15	330
	1. BuLi 2. 3-Cyanothiophene 3. CO_2	 80%  10%		162
	1. BuLi 2. 3-Thiophenealdehyde		75	162
	1. BuLi 2. RCOCOOMe			390
	1. BuLi 2. DMS			29

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. Me_2CO 3. H^+ 4. $RhCl(PPh_3)_3$, H_2			29
	1. BuLi 2. RCOCOOH		50–70	391
	1. BuLi 2. $B(OBu)_3$		57	140
	1. BuLi 2. PhCN			79
	1. BuLi 2. PhCOPh			79
	1. BuLi 2. $pTolSO_3CH_2Cy$		55	346

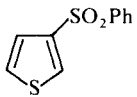
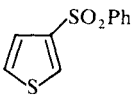
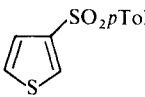
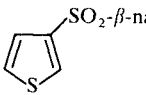
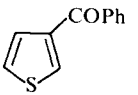
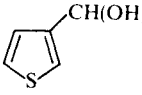
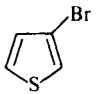
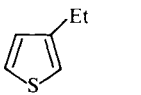
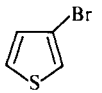
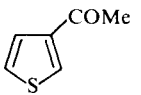
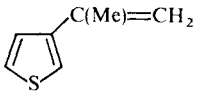
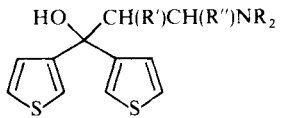
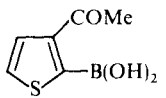
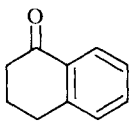
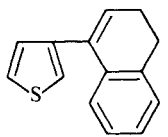
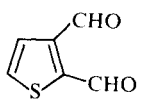
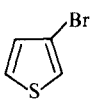
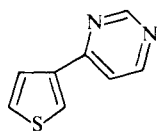
	1. BuLi 2. $PhSO_3CH_2Cy$		50	346
	1. BuLi 2. $PhSO_3Ph$		85	346
	1. BuLi 2. *p*TolSO$_3$Ph		96	346
	1. BuLi 2. 2-Naphth-SO_3Ph		76	346
	1. BuLi 2. PhCOOH		2	392
	1. BuLi 2. *p*CN-benzaldehyde		11	392
	1. BuLi 2. Et_2SO_4		60	29
	1. BuLi 2. DMA		> 71	29

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. Me_2CO 3. H^+		54	29
	1. BuLi 2. $ROOCCH(R')CH(R'')NR_2$		—	393
	1. EtLi 2. DMA 3. EtLi 4. $B(OBu)_3$		13	100
	1. BuLi, $-70°C$ 2. 		88	367
	1. BuLi excess 2. DMF		40	71
	1. BuLi 2. Pyrimidine 3. $KMnO_4$, chloranil, or $K_3(FeCN)_6$		36	63

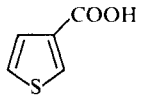
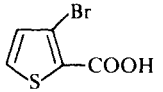
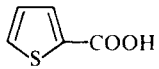
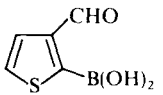
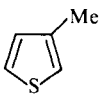
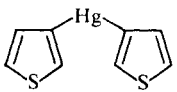
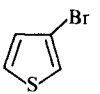
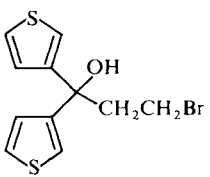
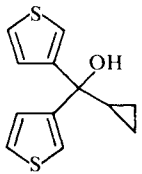
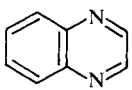
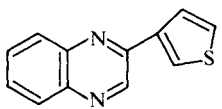
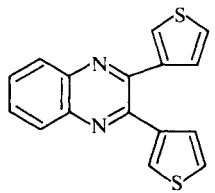
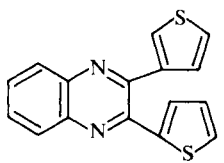
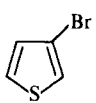
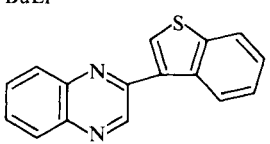
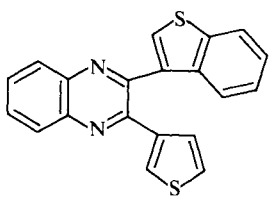
	1. BuLi, − 70°C, 5 min 2. CO_2		78	137
	1. BuLi, room temp., 16 h 2. CO_2	 15%  29%	78	137
	1. BuLi, room temp., 24 h 2. CO_2		Oil	137
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		44	143
	1. EtLi 2. DMS		70	271
	1. BuLi, − 70°C 2. $HgCl_2$		—	394
	1. BuLi, diisopropyl ether 2. $EtOOCCH_2CH_2Br$		96	395, 396

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, diisopropyl ether 2. Ethyl cyclopropylcarboxylate		52	396
	1. BuLi 2. 	 58 or 16%  14 or 51%  11 or 0%		60
	1. BuLi 2. 		22	60

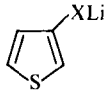
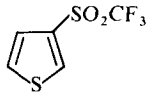
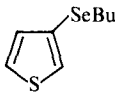
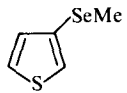
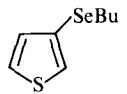
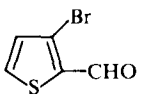
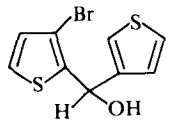
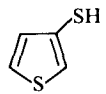
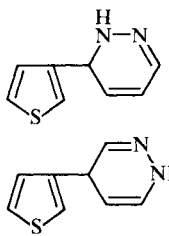
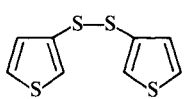
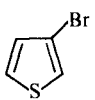
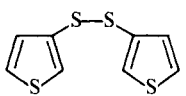
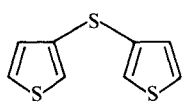
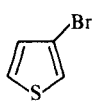
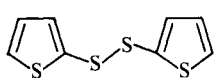
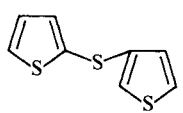
	1. BuLi 2. R_3B 3. Br_2		> 54	151
	1. BuLi 2. S or Se		—	190
	1. BuLi 2. $(CF_3SO_2)O$		Good yield	348
	1. BuLi 2. Se 3. BuBr		74	193
	1. BuLi 2. Me_2Se_2		81	193
	1. BuLi 2. Se 3. $ClCH_2COOEt$		—[a]	193
	1. BuLi 2. 		97	75
	1. BuLi 2. S		63	397

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. I_2		59	397
	1. BuLi 2.			62
	1. BuLi 2. S 3. $K_3Fe(CN)_6$		74	54
	1. BuLi 2. 		57	54
	1. BuLi 2. 		47	54

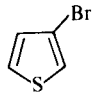
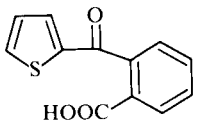
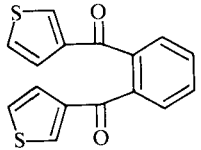
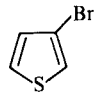
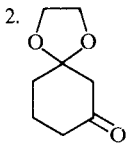
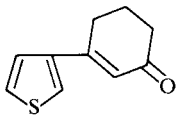
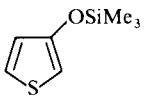
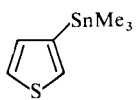
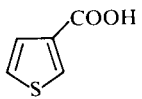
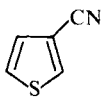
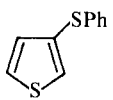
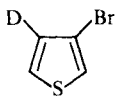
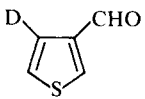
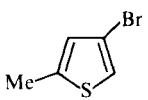
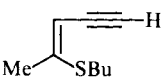
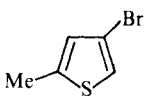
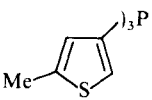
	1. BuLi 2. Phthalic anhydride	 38%  30%		152
	1. BuLi 2.  3. HCl		41	398
	1. BuLi 2. $(Me_3SiO)_2$		60	155
	1. BuLi 2. Me_3SnCl		—	399
	1. BuLi 2. CO_2		79	12
	1. EtLi, $-70°C$ 2. MeCOOD		68	369

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. PhSCN	 24%  34%		268
	1. BuLi 2. DMF		70	349
	1. BuLi 2. BuBr		15	205
	1. BuLi, $-70°C$ 2. PBr_3		50	109

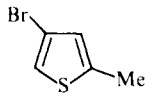
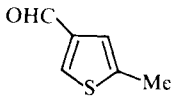
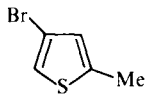
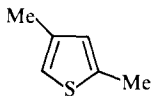
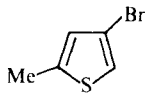
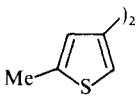
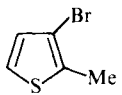
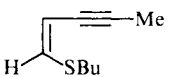
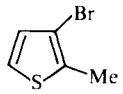
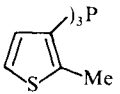
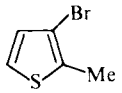
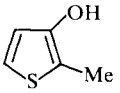
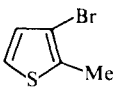
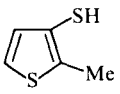
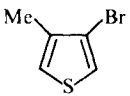
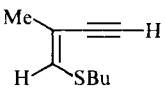
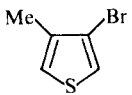
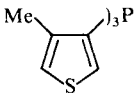
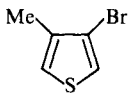
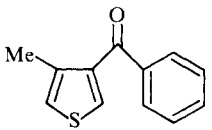
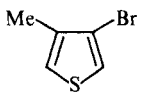
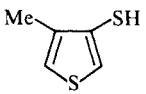
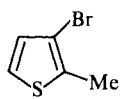
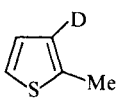
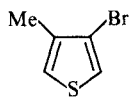
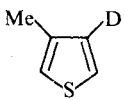
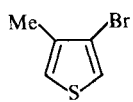
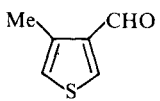
	1. BuLi, − 70°C 2. DMF		—	400
	1. EtLi 2. DMS		65	271
	1. BuLi 2. $CuCl_2$		27	299
	1. BuLi 2. BuBr		95	205
	1. BuLi, − 70°C 2. PBr_3		64	109
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		49	401
	1. BuLi 2. S		67	351
	1. BuLi 2. BuBr		26	205

TABLE 4. *(Continued)*

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, $-70°C$ 2. PBr_3		54	109
	1. BuLi 2. NC		46	389
	1. BuLi 2. S		50	351
	1. EtLi, $-70°C$ 2. MeCOOD		63	369
	1. EtLi, $-70°C$ 2. MeCOOD		31	369
	1. BuLi 2. DMF		25	269

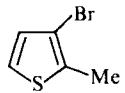
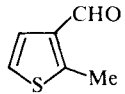
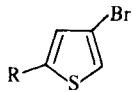
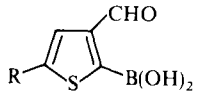
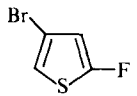
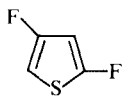
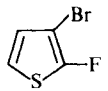
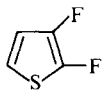
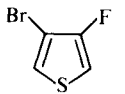
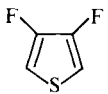
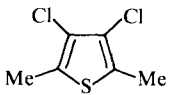
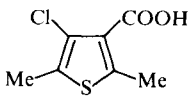
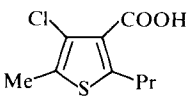
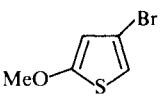
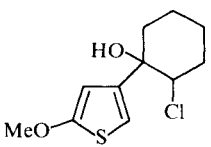
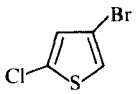
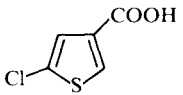
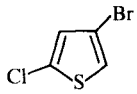
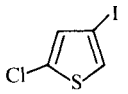
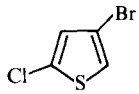
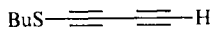
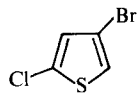
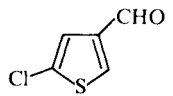
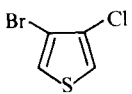
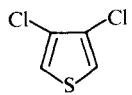
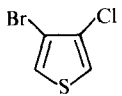
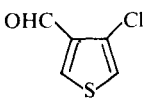
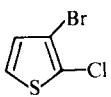
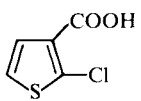
	1. BuLi 2. DMF		44	269
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		18–32	100
	1. EtLi 2. $FClO_3$		—	184
	1. EtLi 2. $FClO_3$		—	184
	1. EtLi 2. $FClO_3$		—	184
	1. EtLi, TMEDA, ether, reflux 2. CO_2	 3 : 4 	Low yield	30
	1. BuLi 2. 2-Chlorocyclohexanone		—	402

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, − 70°C 2. CO_2		47	141
	1. BuLi, − 70°C 2. I_2		44	141
	BuLi, − 51°C, then room temp.		—[b]	141
	1. BuLi 2. DMF		70	100
	1. BuLi 2. Cl_3CCCl_3		—	218
	1. BuLi 2. DMF		73	100
	1. BuLi, − 70°C 2. CO_2 (gas)		58	141

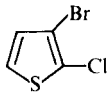
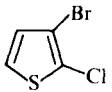
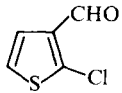
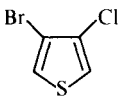
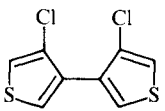
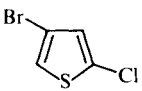
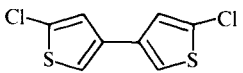
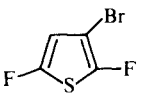
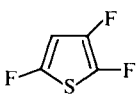
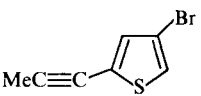
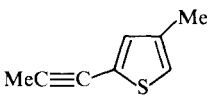
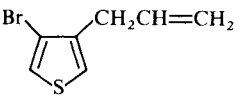
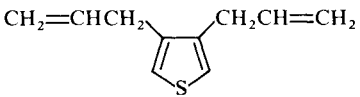
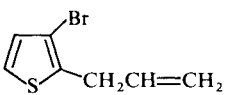
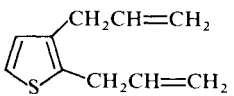
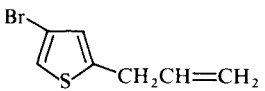
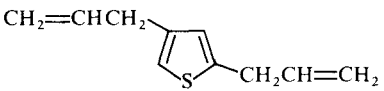
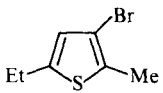
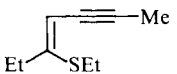
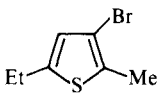
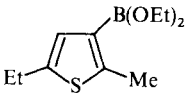
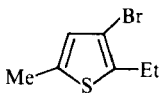
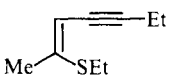
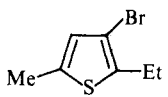
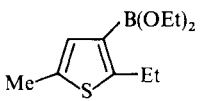
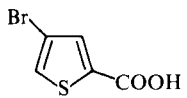
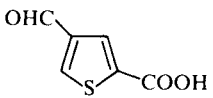
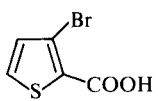
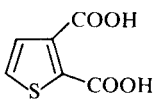
	1. BuLi, − 70°C 2. Room temp., overnight 3. CO_2 (gas)		—[c]	141
	1. EtLi, − 70°C 2. DMF		92	160
	1. BuLi 2. $CuCl_2$		55	370
	1. BuLi 2. $CuCl_2$		36	370
	1. EtLi 2. $FClO_4$		—	184
	1. BuLi 2. MeI		60	19
	1. BuLi 2. CH_2=$CHCH_2Br$		56	35
	1. BuLi 2. CH_2=$CHCH_2Br$		37	35

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CH_2=$CHCH_2Br$		52	35
	1. EtLi, + 21°C, 4 h 2. EtI		64	208
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. EtLi, + 21°C, 4 h 2. EtI		60	208
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. BuLi 2 eq 2. DMF		Low yield	158
	1. BuLi 3 eq 2. CO_2		72	157

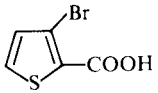
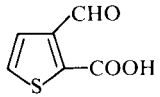
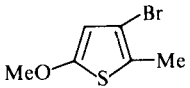
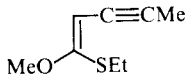
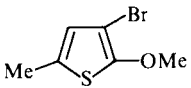
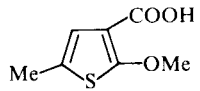
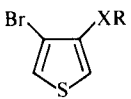
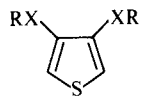
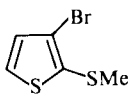
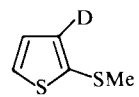
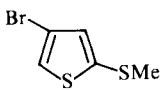
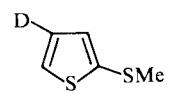
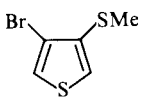
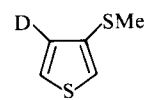
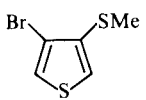
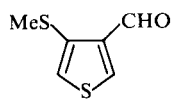
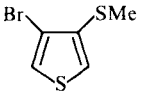
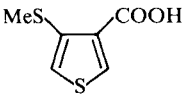
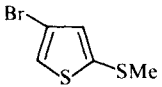
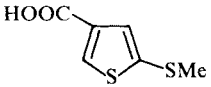
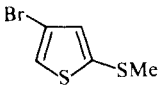
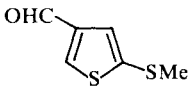
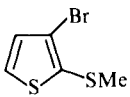
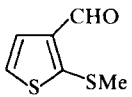
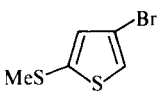
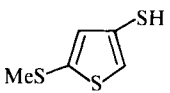
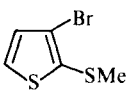
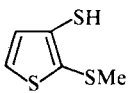
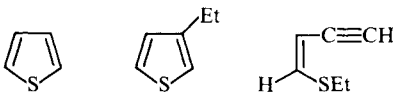
	1. BuLi 2 eq 2. DMF		75	158
	1. EtLi 2. EtBr, HMPA		33	145
	1. EtLi 2. CO_2		70	145
	1. BuLi 2. RSSR or RSeSeR		—	190
	1. BuLi, − 70°C 2. D_2O, MeCOOD		70	369
	1. BuLi, − 70°C 2. D_2O, MeCOOD		46	369
	1. BuLi, − 70°C 2. D_2O, MeCOOD		55	369
	1. BuLi 2. DMF		46	269

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CO_2		60	269
	1. BuLi 2. CO_2		69	269
	1. BuLi 2. DMF		58	269
	1. BuLi 2. DMF		68	269
	1. BuLi 2. S		55	351
	1. BuLi 2. S			351
	1. EtLi 2. EtBr, room temp., 5 h	 65% 12% 16%		206

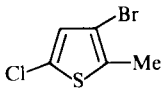
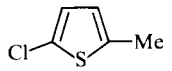
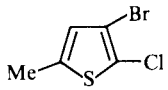
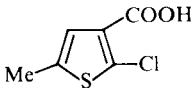
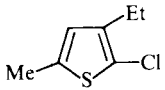
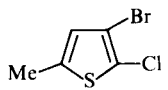
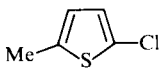
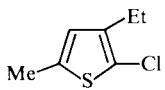
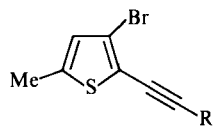
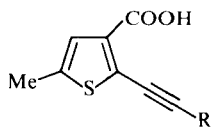
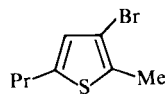
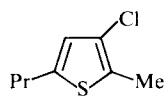
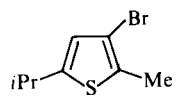
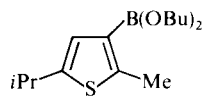
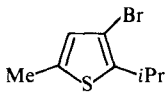
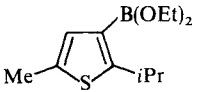
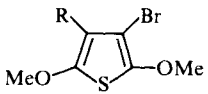
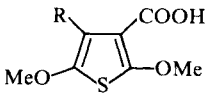
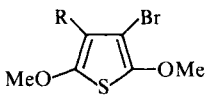
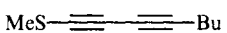
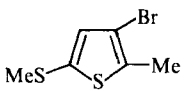
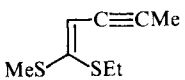
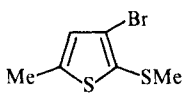
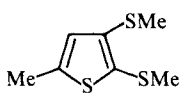
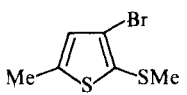
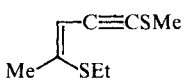
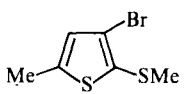
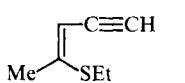
	1. EtLi 2. EtBr	EtSC≡CC≡CMe 37%  42%		145
	1. EtLi 2. CO_2	 36%  6%		145
	EtLi	 4% 	51	145
	1. BuLi, 0°C 2. CO_2		60	212
	1. EtLi, ether 2. C_2Cl_6		21	30
	1. EtLi 2. $B(OBu)_3$		Not isolated	353

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. BuLi, $-70°C$, 2. CO_2		56–60	121
	1. BuLi, room temp., 2 h 2. DMS		67	121
	1. EtLi 2. EtBr, room temp., 5 h		50	213
	1. BuLi 2. Me_2S_2		38	145
	1. EtLi 1 eq 2. EtBr		Major	145
	1. EtLi 2 eq 2. EtBr		Major	145

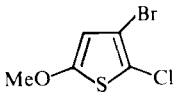
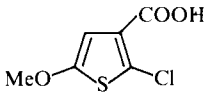
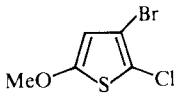
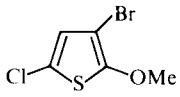
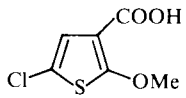
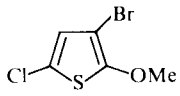
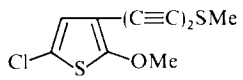
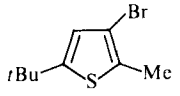
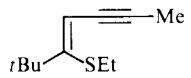
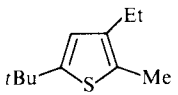
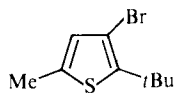
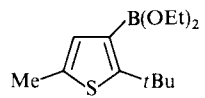
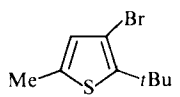
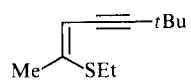
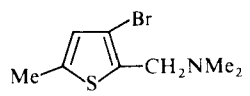
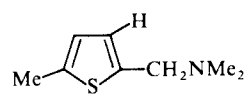
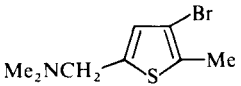
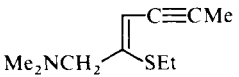
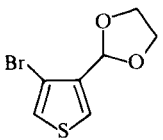
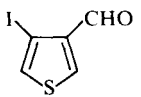
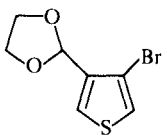
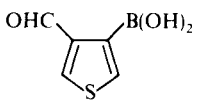
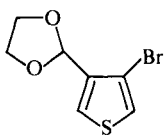
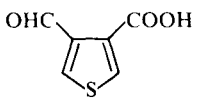
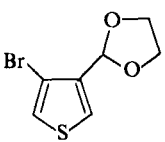
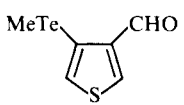
	1. BuLi, − 70°C 2. CO_2		57	122
	1. BuLi, room temp. 2. DMS		—	122
	1. BuLi, − 70°C 2. CO_2		61	122
	1. BuLi, room temp. 2. DMS		20	122
	1. EtLi, + 21°C, 4 h 2. EtI	 35%  33%	80	208
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. EtLi, + 21°C, 4 h 2. EtI		80	208
	1. EtLi 2. EtBr 3. H_2O			17

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. EtBr		49	17
	1. BuLi 2. I_2		71	84
	1. BuLi, $-70°C$ 2. $B(OBu)_3$		49	156
	1. BuLi 2. CO_2		75	158
	1. BuLi 2. Me_2Te_2		50	72

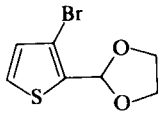
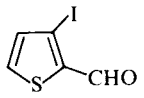
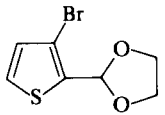
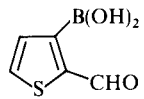
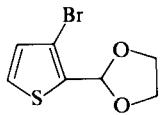
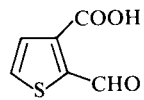
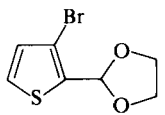
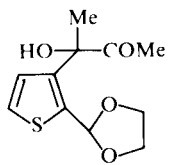
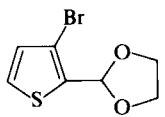
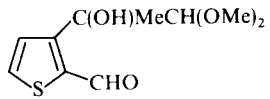
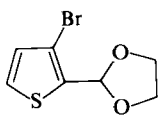
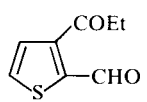
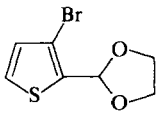
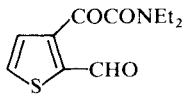
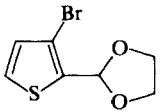
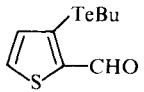
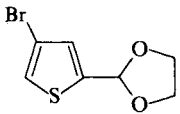
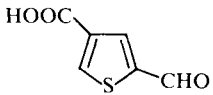
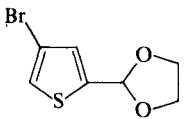
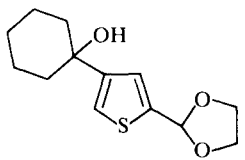
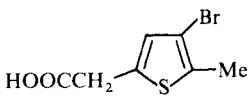
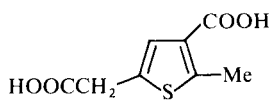
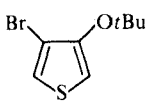
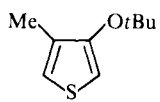
	1. BuLi 2. I_2		67	84
	1. BuLi, − 70°C 2. $B(OBu)_3$		66	156
	1. BuLi 2. CO_2		75	158
	1. BuLi 2. MeCOCOMe			283
	1. BuLi, − 70°C 2. $MeCOCH(OMe)_2$ 3. HCl		81	284
	1. BuLi 2. EtCN		40	71

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $Et_2NCOCONEt_2$		55	71
	1. BuLi 2. Te		34	72
	1. BuLi 2. CO_2		86	158
	1. BuLi 2. Cyclohexanone		42	361
	1. BuLi 2 eq 2. CO_2		0	30
	1. BuLi 2. DMS		90	94

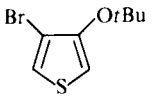
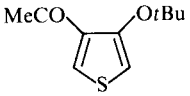
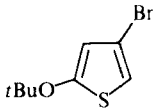
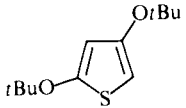
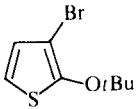
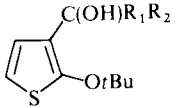
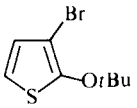
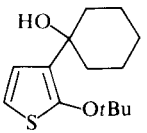
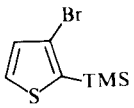
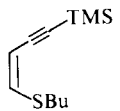
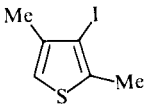
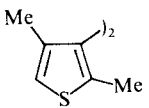
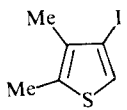
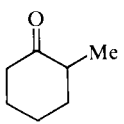
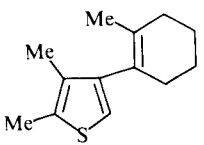
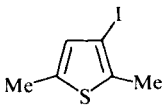
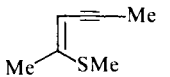
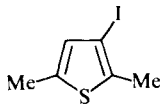
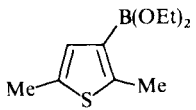
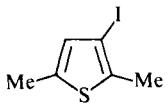
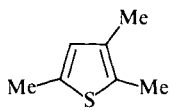
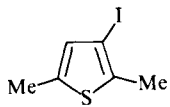
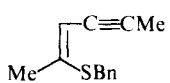
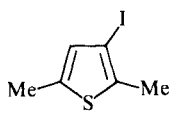
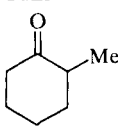
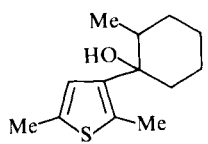
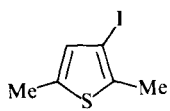
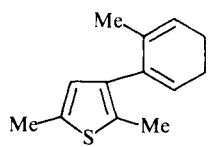
	1. BuLi 2. $MgBr_2$ 3. Ac_2O		70	66
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		60	94
	1. BuLi 2. R_1R_2CO		19–84	403
	1. BuLi 2. Cyclohexanone		Not stable	403
	1. BuLi 2. BuBr		68	15, 19
	1. EtLi 2. $CuCl_2$		64	271
	1. BuLi 2. 		—[d]	305

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. MeLi or PhLi, 20–35°C 2. MeI		42	204
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. EtLi 2. DMS		63	271
	1. PhLi 2. BnBr		--	404
	1. BuLi 2. 		Good yield	305
	1. BuLi 2. 2-Methylcyclohexenone		Good yield	305

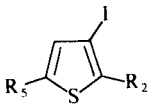
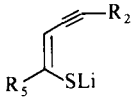
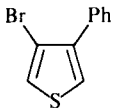
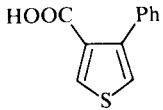
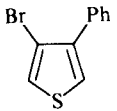
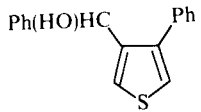
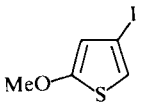
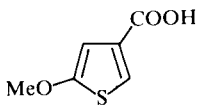
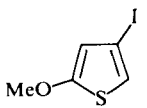
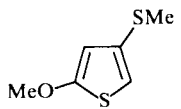
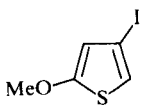
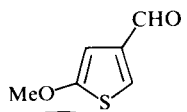
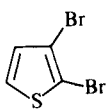
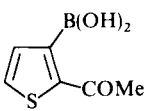
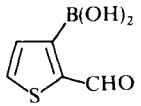
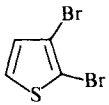
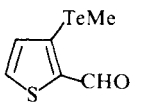
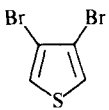
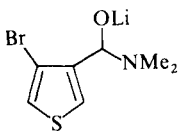
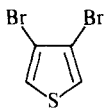
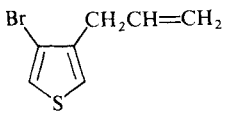
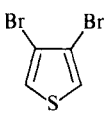
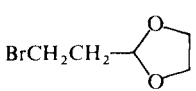
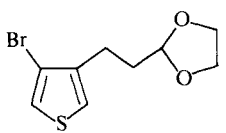
	PhLi			214
	1. BuLi 2. CO_2		84	165
	1. BuLi 2. PhCHO		—	405
	1. BuLi 2. CO_2		67	87
	1. BuLi 2. Me_2S_2		83	87
	1. BuLi 2. DMF		62	87
	1. EtLi 2. DMA 3. BuLi 4. $B(OBu)_3$		35	100

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		35	143
	1. BuLi 2. DMF 3. BuLi 4. Me_2Te_2		10	72
	1. BuLi 2. DMF		—	84
	1. BuLi 2. $CH_2{=}CHCH_2Br$		77	35
	1. BuLi 2. 		15	35

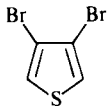
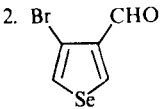
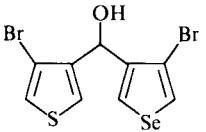
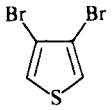
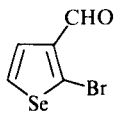
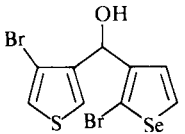
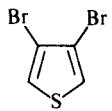
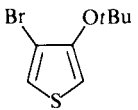
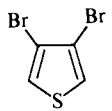
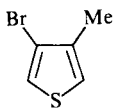
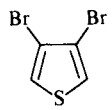
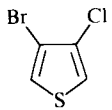
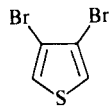
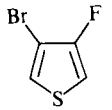
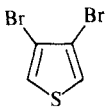
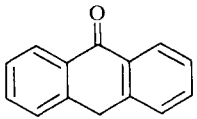
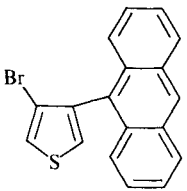
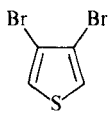
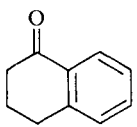
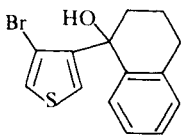
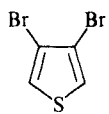
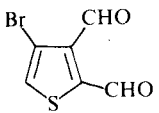
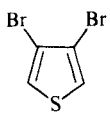
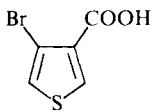
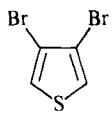
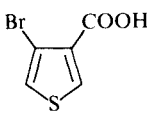
	1. BuLi 2. 		70	364
	1. BuLi 2. 		54	364
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		63	66
	1. BuLi, $-70°C$ 2. DMS		77	160
	1. BuLi 2. Cl_2		55	100
	1. EtLi 2. $FClO_3$		—	184

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, − 70°C 2. 		65	367
	1. BuLi, − 70°C 2. 		53	367
	1. BuLi 2 eq, − 30°C 2. DMF			142
	1. BuLi, − 70°C 2. CO_2		73	136
	1. BuLi, room temp. 2. CO_2		31	136

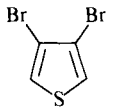
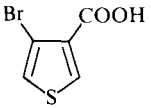
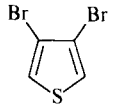
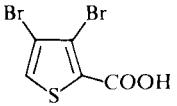
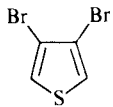
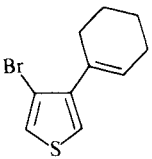
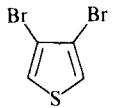
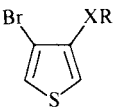
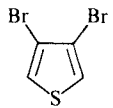
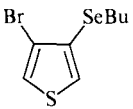
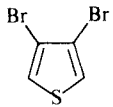
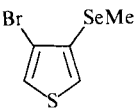
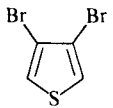
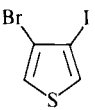
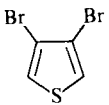
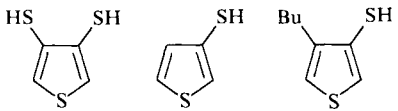
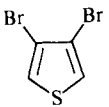
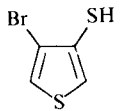
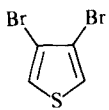
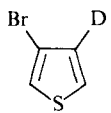
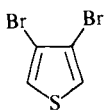
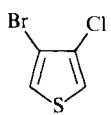
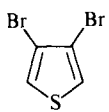
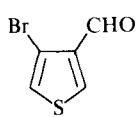
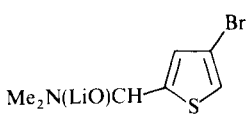
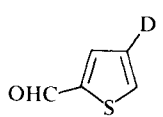
	1. BuLi, − 70°C, 5 min 2. CO_2		80	137
	1. BuLi, room temp., 6 h 2. CO_2		24	137
	1. BuLi 2. Cyclohexanone 3. TosOH		86	165
	1. BuLi 2. RSSR or RSeSeR		—	190
	1. BuLi 2. Se 3. BuBr		55	193
	1. BuLi 2. Me_2Se_2		79	193
	1. BuLi 2. I_2		76	56

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2 eq, − 70°C 2. S			406
	1. BuLi 2. S		—	351
	1. BuLi, − 70°C 2. MeCOOD		55	369
	1. BuLi 2. C_2Cl_6		65	370
	1. BuLi 2. DMF		77	269
	1. BuLi 2. MeOD		41	349

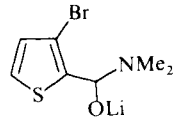
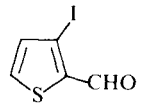
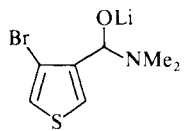
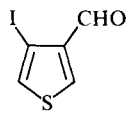
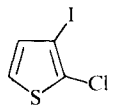
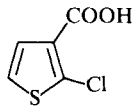
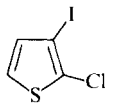
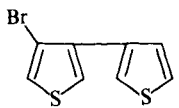
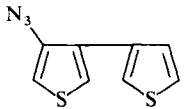
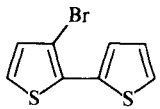
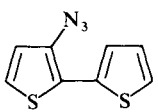
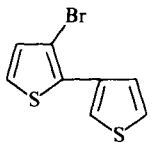
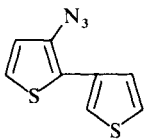
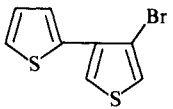
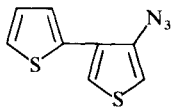
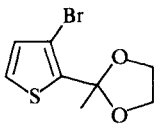
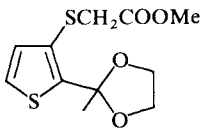
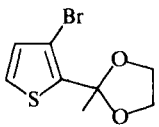
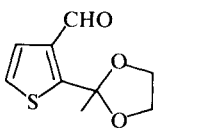
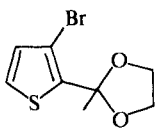
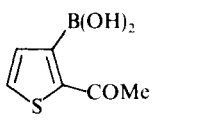
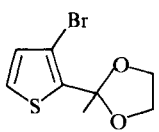
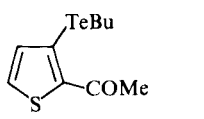
	1. BuLi 2. I_2		25	84
	1. BuLi 2. I_2		30	84
	1. BuLi, $-70°C$ 2. CO_2 (gas)		51	141
	1. BuLi, $-70°C$ 2. Room temp., overnight 3. CO_2 (gas)		—[c]	141
	1. BuLi 2. $TosN_3$		77	56
	1. BuLi 2. $TosN_3$		72	56
	1. BuLi 2. $TosN_3$		73	56

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $TosN_3$		75	56
	1. BuLi 2. S 3. $ClCH_2COOMe$		64	407
	1. BuLi 2. DMF		85	365
	1. BuLi, $-70°C$ 2. $B(OBu)_3$		32	100
	1. BuLi 2. Te		56	72

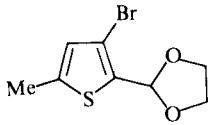
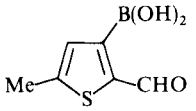
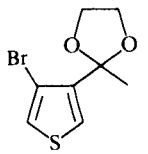
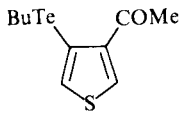
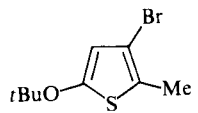
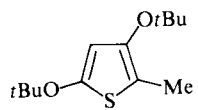
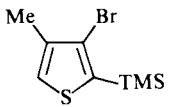
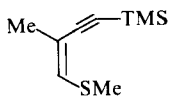
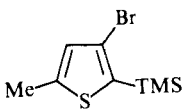
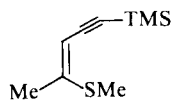
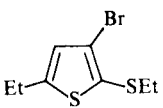
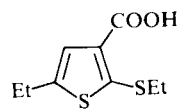
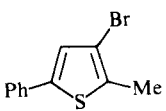
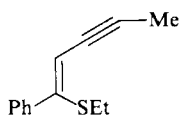
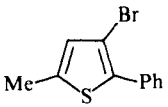
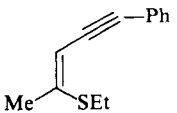
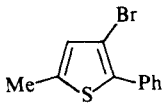
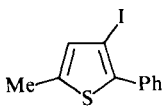
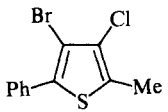
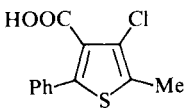
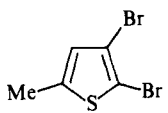
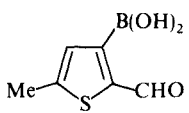
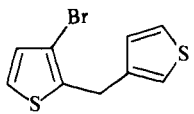
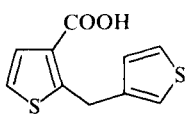
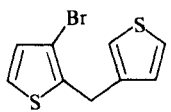
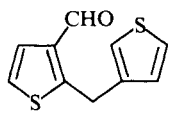
	1. BuLi 2. $B(OBu)_3$		25	100
	1. BuLi 2. Te		45	72
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		92	94
	1. BuLi 2. BuBr		67	15, 19
	1. BuLi 2. BuBr		57	15, 19
	1. BuLi 2. CO_2		62	103
	1. EtLi 2. EtBr		12	17

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. EtBr		47	17
	1. BuLi 2. I_2		54	17
	1. BuLi, ether, hexane 2. CO_2		67	30
	1. BuLi 2. DMF 3. BuLi 4. $B(OBu)_3$		28	100
	1. BuLi 2. CO_2		79	408
	1. BuLi 2. DMF		99	75

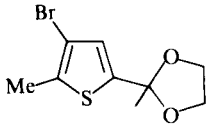
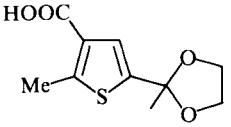
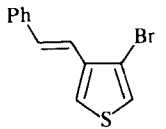
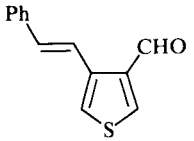
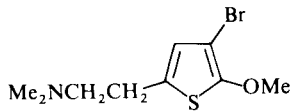
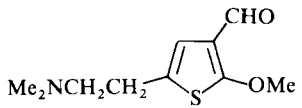
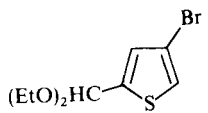
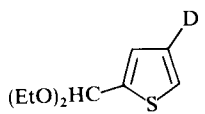
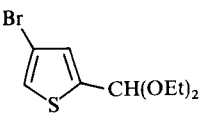
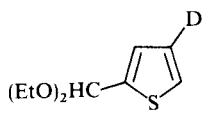
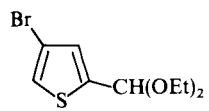
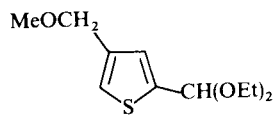
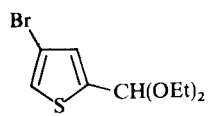
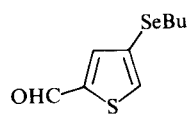
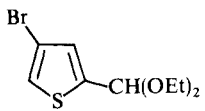
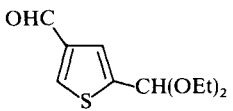
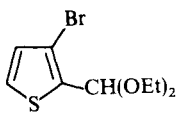
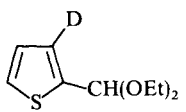
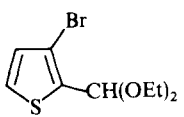
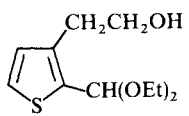
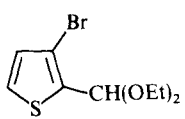
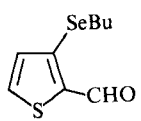
	1. BuLi 2. CO_2		56	30
	1. BuLi 2. DMF		53	409
	1. BuLi 2. DMF		61	18
	1. BuLi 2. D_2O		50	372
	1. BuLi 2. D_2O		42	297
	1. BuLi 2. $ClCH_2OMe$		67	249
	1. BuLi 2. Bu_2Se_2		55	193

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, $-70°C$ 2. DMF		74	400
	1. BuLi 2. D_2O		80	372
	1. BuLi 2. Ethylene oxide		—	410
	1. BuLi 2. Bu_2Se_2		60	193

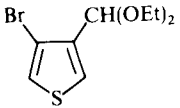
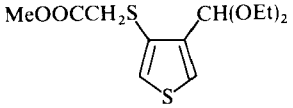
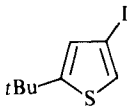
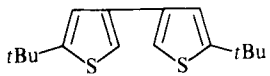
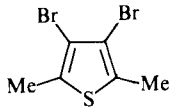
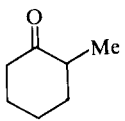
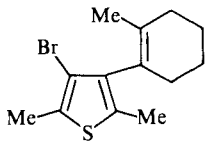
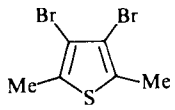
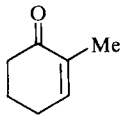
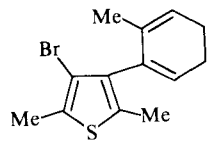
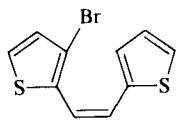
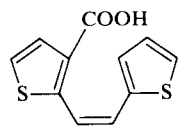
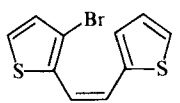
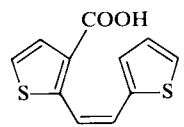
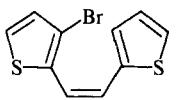
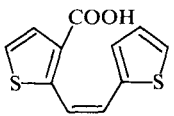
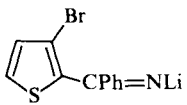
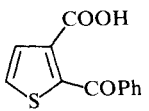
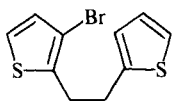
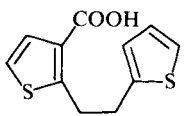
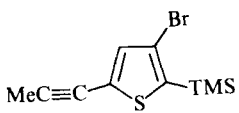
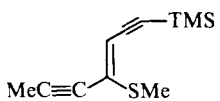
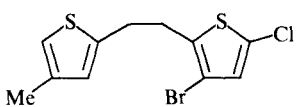
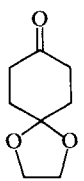
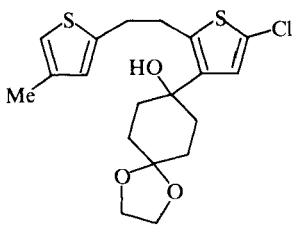
	1. BuLi 2. S 3. $ClCH_2COOMe$		64	407
	1. BuLi, − 70°C 2. $CuCl_2$		48	279
	1. EtLi 2. 		55	305
	1. BuLi 2. 		—	305
	1. BuLi 2. CO_2		High	374
	1. EtLi, − 70°C 2. CO_2		63	375

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. CO_2		—	374
	1. BuLi 2. CO_2		58	79
	1. EtLi, $-70°C$ 2. CO_2		90–95	160
	1. BuLi 2. MeI		84	19
	1. BuLi 2. 		83	16

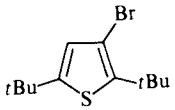
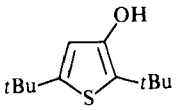
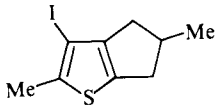
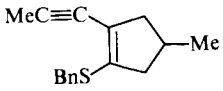
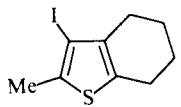
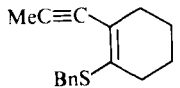
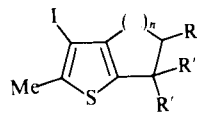
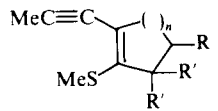
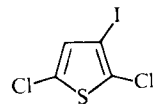
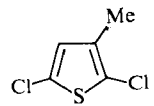
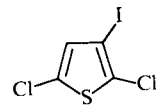
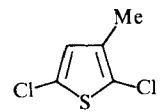
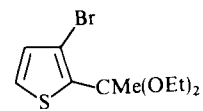
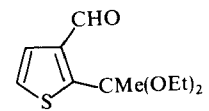
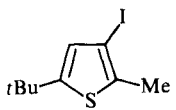
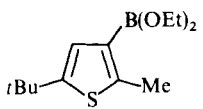
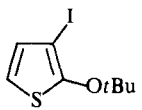
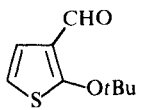
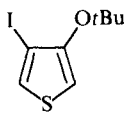
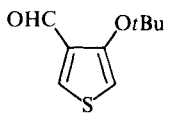
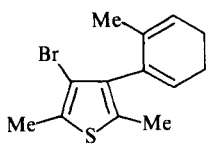
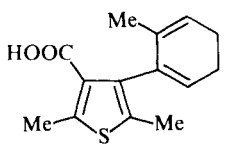
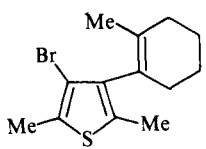
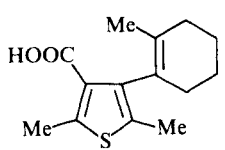
	1. EtLi, −70°C 2. $B(OEt)_3$ 3. H_2O_2			411
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. DMS			210
	1. MeLi, 2 h 2. MeI		55	145
	1. PhLi 2. DMS		40	145
	1. BuLi 2. DMF		> 61	412

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. BuLi 2. DMF		37	277
	1. BuLi 2. DMF		70	277
	1. EtLi 2. CO_2		Good yield	305
	1. BuLi 2. CO_2		81	305

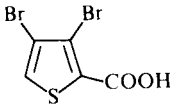
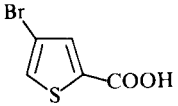
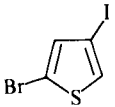
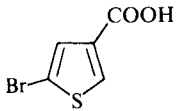
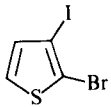
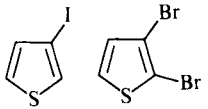
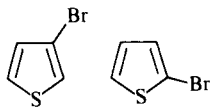
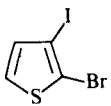
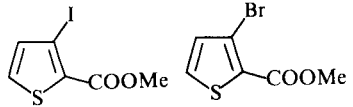
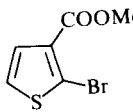
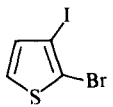
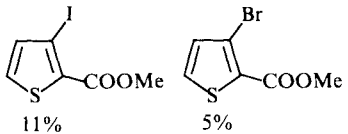
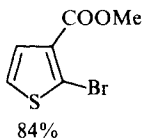
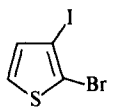
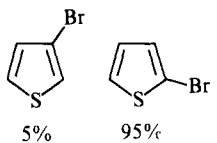
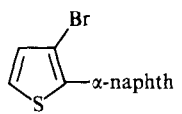
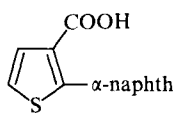
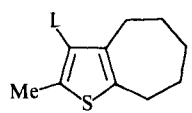
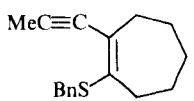
	1. BuLi, − 20°C 2. H_2O		50	144
	1. BuLi, − 100°C 2. CO_2 (gas)		—[e]	141
	1. EtLi, − 60°C 2. EtOH	 20% 20%		161
		 55% 2%		
	1. EtLi, − 60°C 2. CO_2 3. Ester formation	 26% 71%		161
		 3%		

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 1.5 eq, − 100°C 2. CO_2 3. Ester formation	 11% 5%		161
		 84%		
	1. EtLi 1.5 eq, − 100°C 2. EtOH	 5% 95%		161
	1. BuLi, − 70°C 2. CO_2		74	367
	1. PhLi 2. BnCl		44–63	209

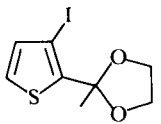
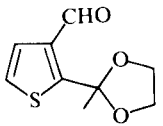
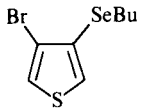
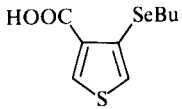
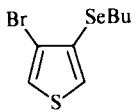
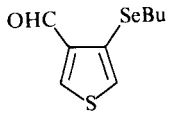
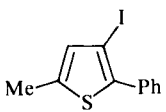
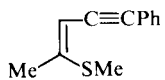
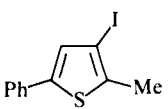
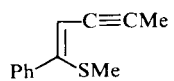
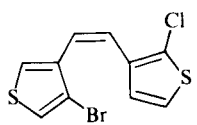
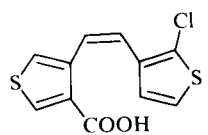
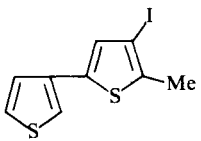
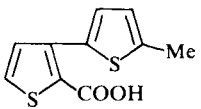
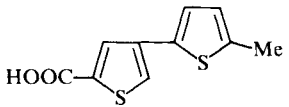
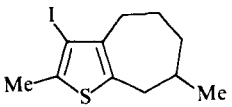
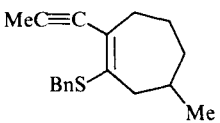
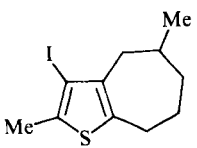
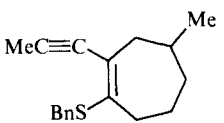
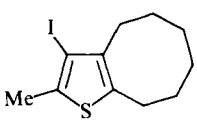
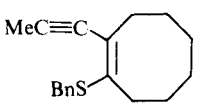
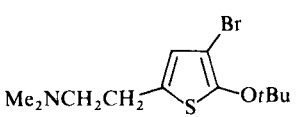
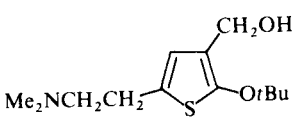
	1. BuLi, −70°C 2. DMF		72	413
	1. BuLi 2. CO_2		64	193
	1. BuLi 2. DMF		69	193
	1. PhLi 2. DMS		69	17
	1. PhLi 2. DMS		50	17
	1. EtLi, −70°C 2. CO_2		90–95	160

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhLi, room temp. 2. CO_2	 	55 mix	207
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. BnCl		44–63	209
	1. BuLi 2. $(HCHO)_x$		30	18

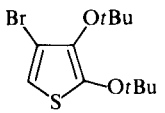
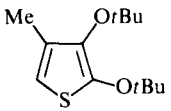
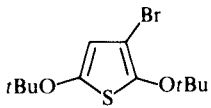
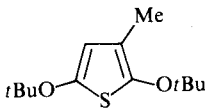
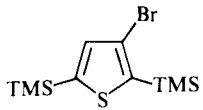
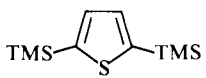
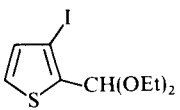
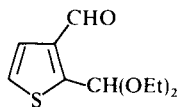
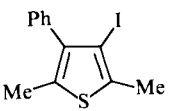
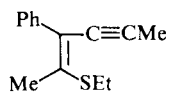
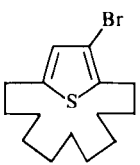
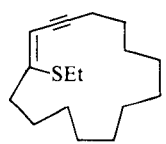
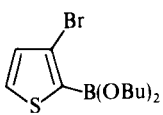
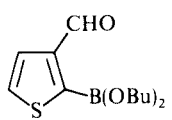
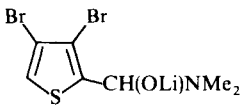
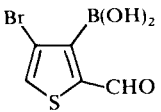
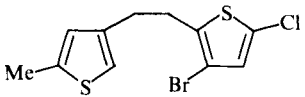
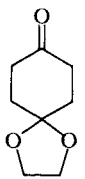
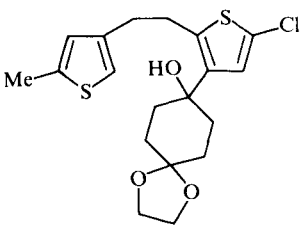
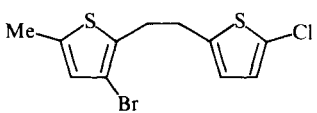
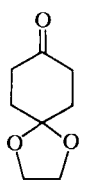
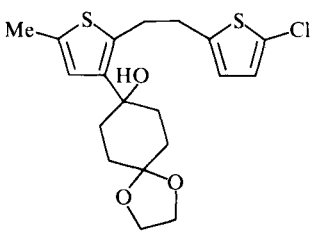
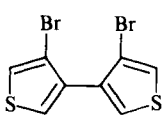
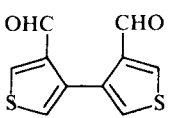
	1. BuLi 2. DMS		40	94
	1. BuLi 2. DMS		91	94
	1. BuLi, THF 2. H_2O		44	123
	1. BuLi, $-70°C$ 2. DMF		91	413
	1. EtLi 2. EtBr		55	17
	1. EtLi 2. EtI, room temp., 5 h		45	211
	1. EtLi, ether 2. DMF		56	362

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $B(OEt)_3$ 3. Hydrolysis		65	21
	1. BuLi 2. 		92	16
	1. BuLi 2. 		89	16
	1. EtLi, THF, $-70°C$ 2. DMF		58	414

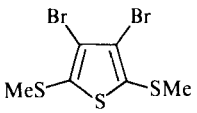
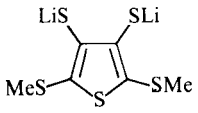
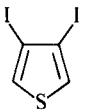
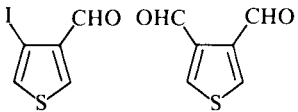
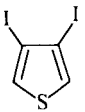
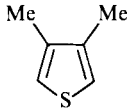
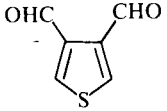
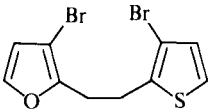
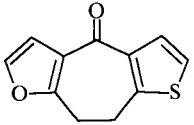
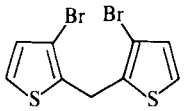
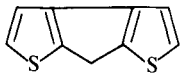
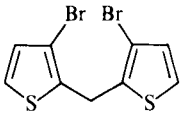
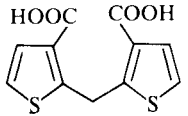
	1. *t*BuLi 2. S 3. *t*BuLi 4. S		> 45	384
	1. BuLi, – 70°C 2. DMF	 22% 10%		85
	1. BuLi 2. MeI, – 40°C to room temp.		Low yield	415
	1. BuLi 2 eq 2. DMF			142
	1. BuLi 2. $Me_2NCOOEt$		38	416
	1. BuLi 2. $CuCl_2$		38	363
	1. BuLi 2. CO_2		54	363

TABLE 4. (*Continued*)

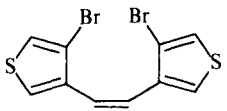
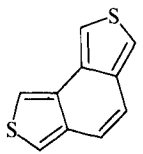
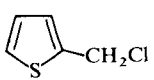
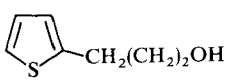
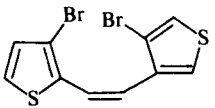
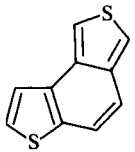
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. $CuCl_2$		19	84
			88	385

TABLE 5. (*Continued*)

Starting Material	Reagent	Product	Yield (%)		Ref.
	1. Mg 2. Ethylene oxide		Ether (%) 11	DME (%) > 99	176

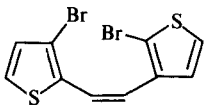


1. EtLi
2. $CuCl_2$

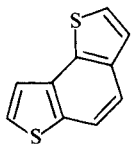


Unstable

84

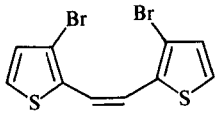


1. EtLi
2. $CuCl_2$

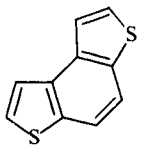


60

84

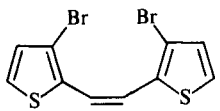


1. EtLi
2. $CuCl_2$

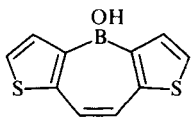


70

84

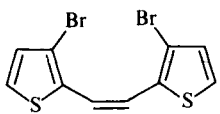


1. EtLi
2. $B(OEt)_3$

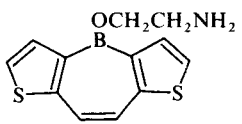


25

417

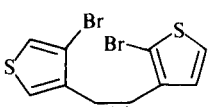


1. BuLi
2. Et_2NBCl_2
3. $HOCH_2CH_2NH_2$

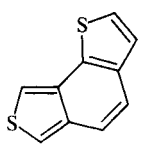


85

418



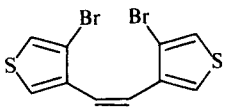
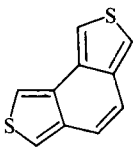
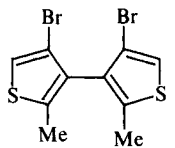
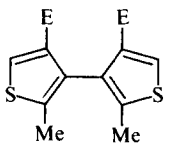
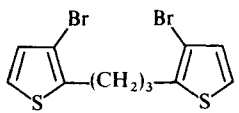
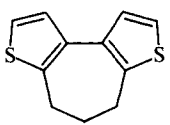
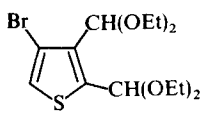
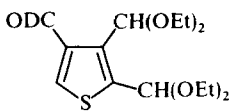
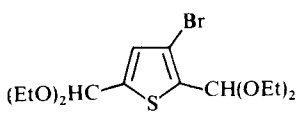
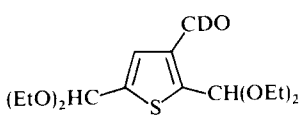
1. EtLi
2. $CuCl_2$



Unstable

84

TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. $CuCl_2$		19	84
	1. BuLi 2. DMF or CO_2		88	385
	1. EtLi, $-70°C$ 2. $CuCl_2$		10	368
	1. BuLi 2. DMF-d_7			307
	1. BuLi 2. DMF-d_7			307

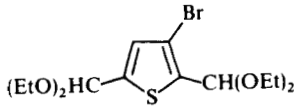
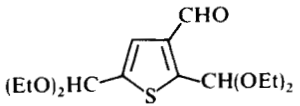
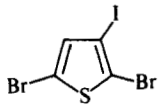
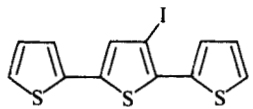
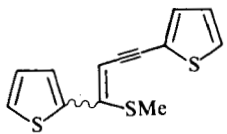
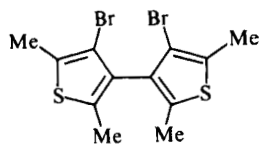
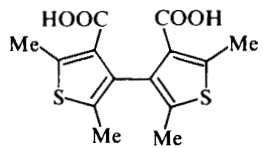
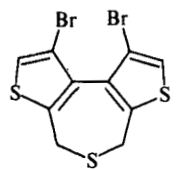
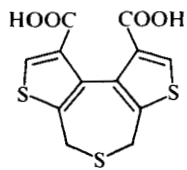
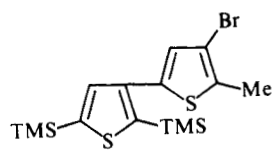
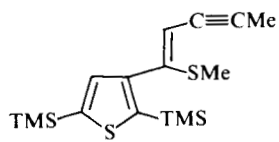
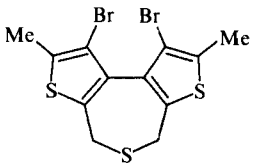
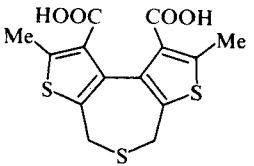
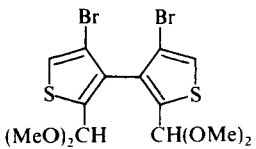
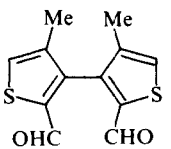
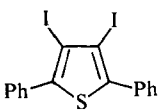
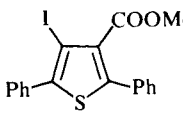
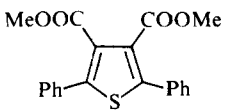
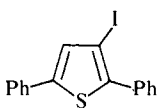
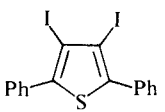
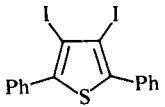
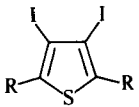
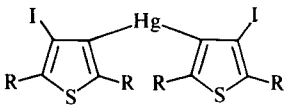
	1. BuLi 2. DMF			308
	1. BuLi, − 70°C 2. H_2O		—[g]	141
	1. PhLi, room temp. 2. MeI		44[h]	207
	1. EtLi, 2 min, − 70°C 2. CO_2		—[i]	242
	1. BuLi 2. CO_2		73	419
	1. PhLi, room temp. 2. MeI		45	207

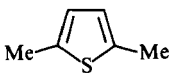
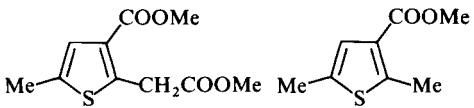
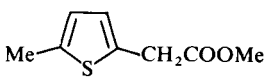
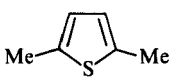
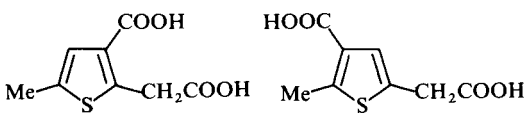
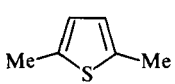
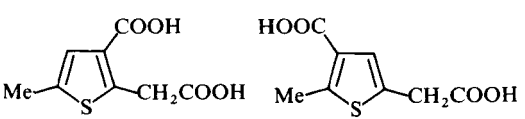
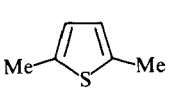
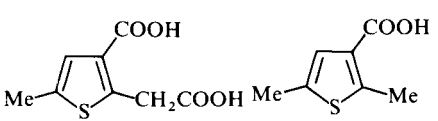
TABLE 4. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi, excess, − 70°C 2. CO_2		—	240
	1. BuLi 2. DMS 3. HCl		93	385
	1. BuLi, − 70°C 2. CO_2	 24%  27%  29%  17%		139

	BuLi, higher temp.	$Ph(C{\equiv}C)_2Ph$	60–70	139
	1. BuLi 2. $HgCl_2$		60–70	139

[a] The expected product was not formed.
[b] Not isolated.
[c] Rearrangement products after CO_2 treatment.
[d] 80 : 20 mixture of olefine isomers.
[e] Major product but rearrangement occurred at higher temp.
[f] Tellurium–lithium exchange.
[g] Several products; not a useful reaction.
[h] *E* : *Z* 7 : 3.
[i] The starting material was optically active but the product was optically inactive.

TABLE 5. Thenylmetal Derivatives

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, TMEDA, hexane 2. CO_2	 39% 19%  5%		117
	1. BuLi, TMEDA, ether 2. CO_2	 9 : 1	14 total	31
	1. BuLi, TMEDA, hexane 2. CO_2	 0.43 : 1	17 total	31
	1. EtLi, TMEDA, ether 2. CO_2	 3 : 1	8	30

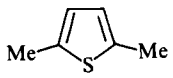
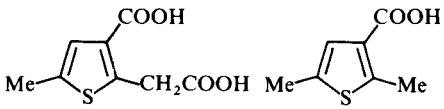
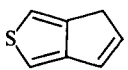
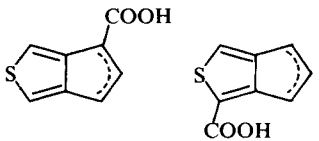
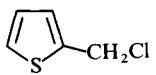
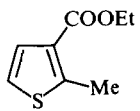
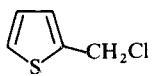
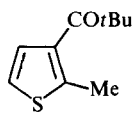
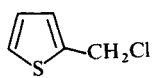
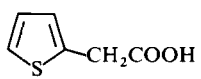
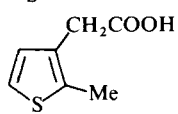
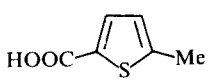
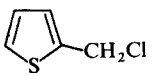
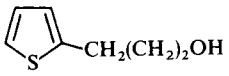
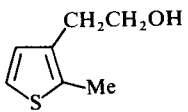
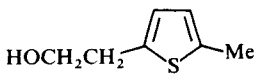
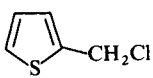
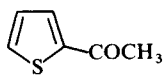
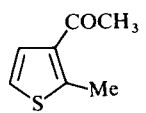
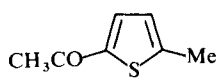
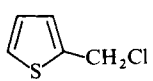
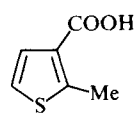
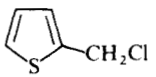
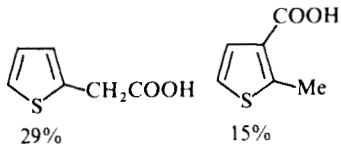
	1. EtLi, TMEDA, hexane 2. CO_2	 10 : 1	16		30
	1. BuLi, $-10°C$ 2. CO_2	 70% 30%			166
	1. Mg 2. ClCOOEt				176
	1. Mg 2. ClCO*t*Bu				176
	1. Mg 2. CO_2		Ether (%) 61	DME (%) 100	176
			36	—	
			3	—	

TABLE 5. (*Continued*)

Starting Material	Reagent	Product	Yield (%)		Ref.
	1. Mg 2. Ethylene oxide		Ether (%) 11	DME (%) > 99	176
			75	—	
			14	—	
	1. Mg 2. CH_3COCl		Ether (%) 17.5	DME (%) 54.6	176
			82.5	45.4	
			—	—	
	1. Hg(Mg) 2. ClCOOEt		72		174

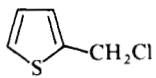


1. Hg(Mg)
2. CO_2

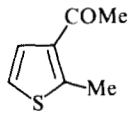


29% 15%

174

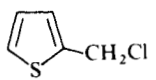


1. Hg(Mg)
2. CH_3COCl, or Ac_2O

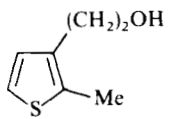


25–34[a]

174

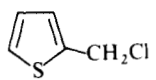


1. Hg(Mg)
2. Ethylene oxide

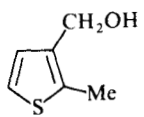


39

174

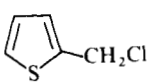


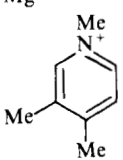
1. Hg(Mg)
2. CH_2O

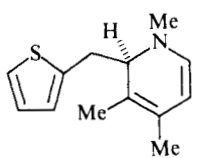


49

174

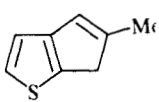


1. Mg
2. 

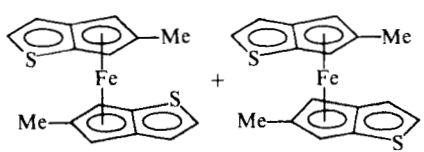


> 66

420

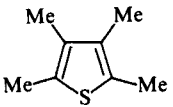
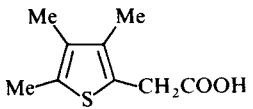
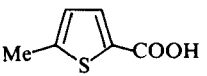
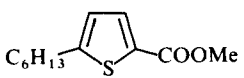
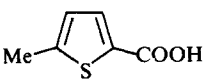
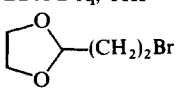
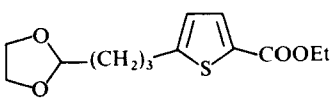
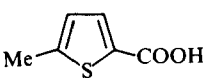
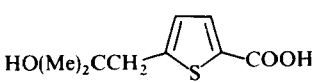
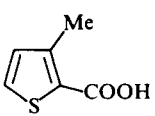
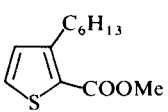
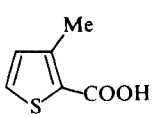
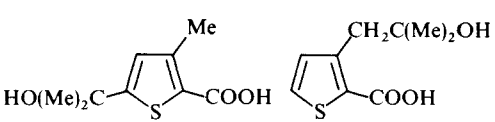


1. BuLi
2. $FeCl_2$



167

TABLE 5. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi, TMEDA, ether 2. CO_2		5	30
	1. LDA 2 eq, THF 2. $C_5H_{11}Br$		65	164
	1. LDA 2 eq, THF 2. 		69	164
	1. LDA 2 eq, THF 2. Acetone		61	164
	1. LDA 2 eq, THF, 2. $C_5H_{11}Br$		66	164
	1. LDA 2 eq, THF 2. Acetone	 38% 62%		164

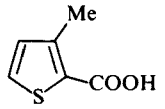
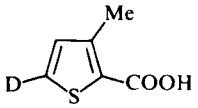
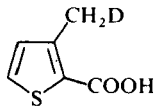
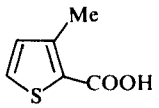
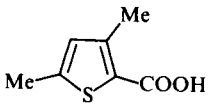
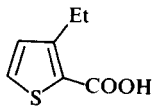
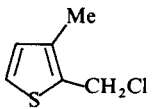
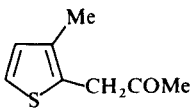
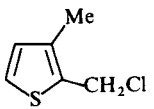
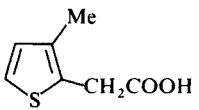
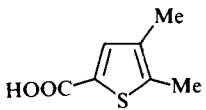
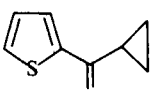
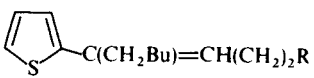
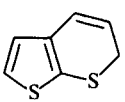
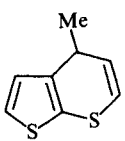
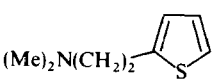
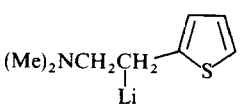
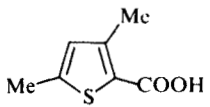
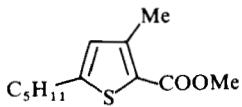
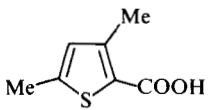
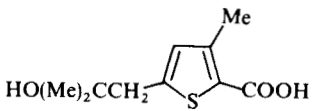
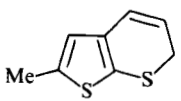
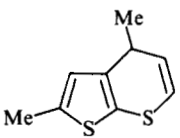
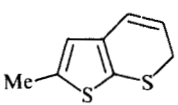
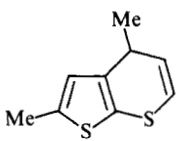
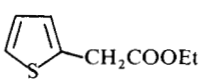
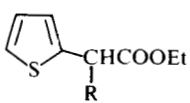
	1. LDA 2 eq, THF 2. D_2O	 26%  74%		164
	1. LDA 2 eq, THF 2. MeI	 35%  65%		164
	1. Mg 2. CH_3COCl			176
	1. Mg 2. CO_2	 67%  33%		176
	1. BuLi, TMEDA 2. H_2O or TMSCl			163
	1. $NaNH_2$, NH_3(l) 2. CH_3I		80	172
	2-Thienyllithium			18

TABLE 5. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA 2 eq, THF 2. C_4H_9Br		72	164
	1. LDA 2 eq, THF 2. Acetone		60	164
	1. $NaNH_2$, NH_3(l) 2. CH_3I		80	172
	1. BuLi, THF, HMPA 2. CH_3I			172
	1. LDA 2. RX		—[a]	38

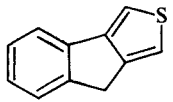
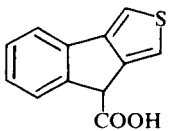
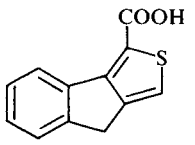
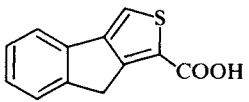
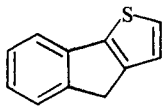
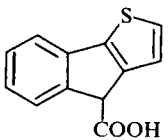
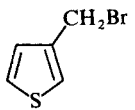
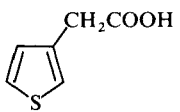
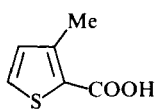
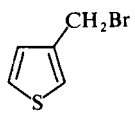
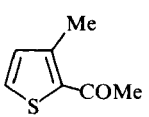
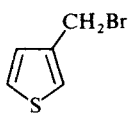
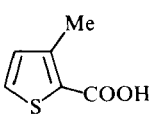
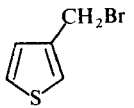
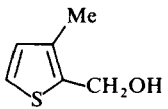
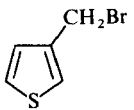
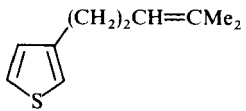
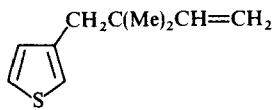
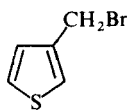
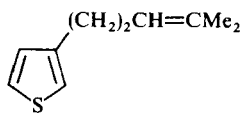
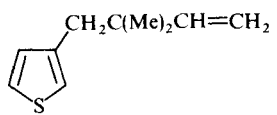
	1. BuLi 2. CO_2	 38%  48%  14%		165
	1. BuLi 2. CO_2		53	165
	1. Mg 2. CO_2	 23%  34%		175
	1. Mg 2. CH_3COCl		50	175
	1. Mg 2. ClCOOEt		53	175

TABLE 5. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. CH_2O		40	175
	1. Mg, THF 2. $(Me)_2C{=}CHCH_2OP(=O)(OEt)_2$	 99%  1%	71	179
	1. Mg, THF 2. $(Me)_2C{=}CHCH_2OP(=O)(OEt)_2$, CuI	 18%  82%	78	179

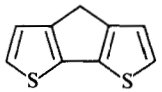
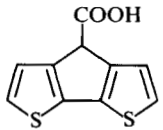
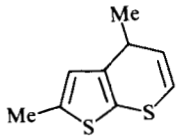
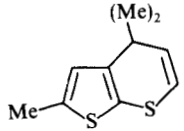
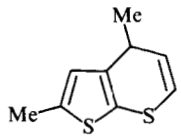
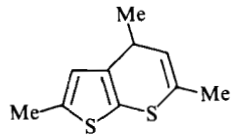
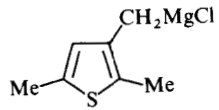
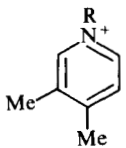
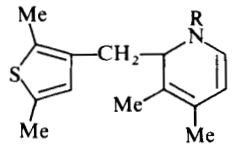
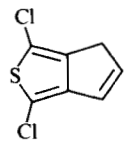
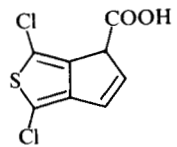
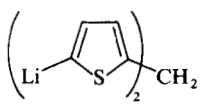
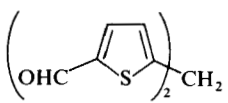
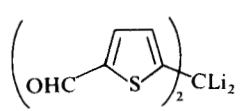
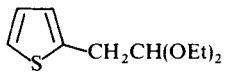
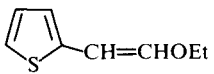
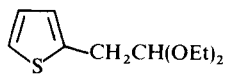
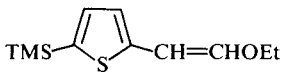
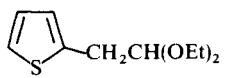
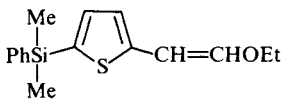
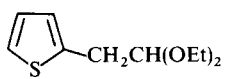
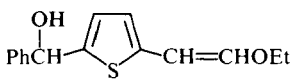
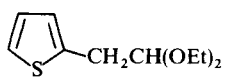
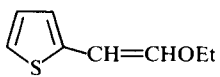
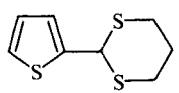
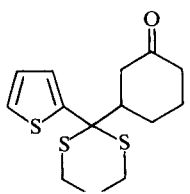
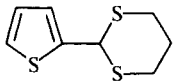
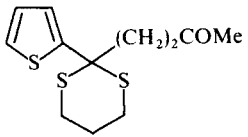
	1. BuLi 2. CO_2			41
	1. KNH_2, NH_3(l) 2. CH_3I		86	172
	1. BuLi, ether, THF 2. CH_3I		87	172
			36–57	421
	1. BuLi, − 50°C 2. CO_2		50	166
				168

TABLE 5. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. H_2O		78	48
	1. BuLi 2. TMSCl		87	48
	1. BuLi 2. $Ph(CH_3)_2SiCl$		62	48
	1. BuLi 2. PhCHO		66	48
	1. $NaNH_2$, $NH_3(l)$ 2. $PhMe_2SiCl$			48
	1. BuLi 2. 2-Cyclohexenone		90	171

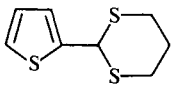


1. BuLi
2. MVK

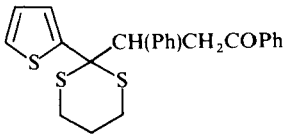


34

171

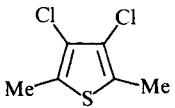


1. BuLi
2. PhCH=CHCOPh

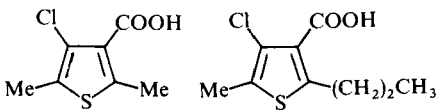


60

171

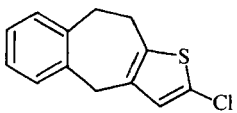


1. EtLi, TMEDA, ether
2. CO_2

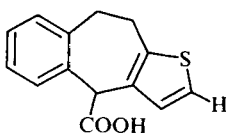


3 : 4

30

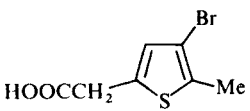


1. LDA, THF: HMPA (6 : 1), + 20°C
2. CO_2

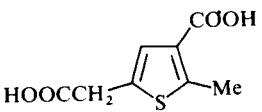


29

146

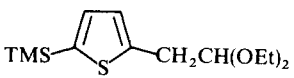


1. BuLi 2 eq
2. CO_2

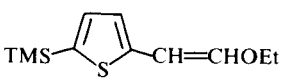


0

30



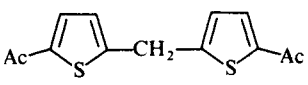
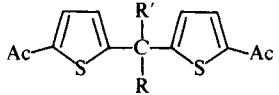
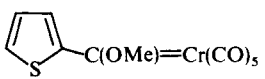
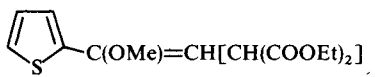
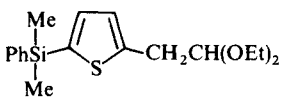
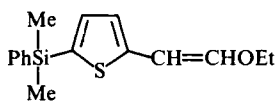
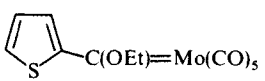
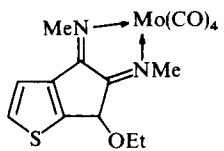
1. BuLi
2. H_2O

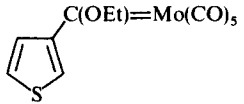
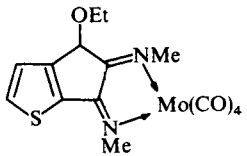
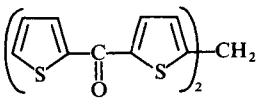
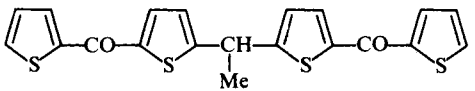
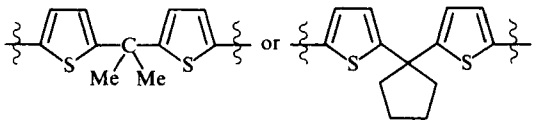


90

48

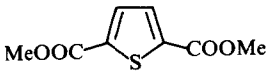
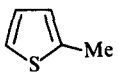
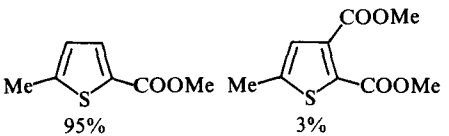
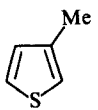
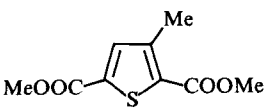
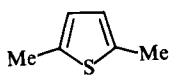
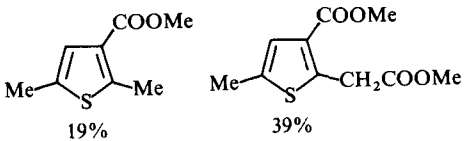
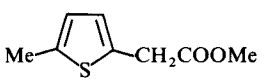
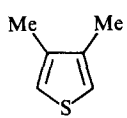
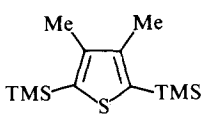
TABLE 5. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. NaH 2. RBr 3. NaH 4. R'Br			170
	$HC{\equiv}CCOOEt$, EtOH		81	422
	BuLi, H_2O		62	48
	CH_3NC		42	423

	CH_3NC		30	423
	NaH. THF, CH_3hal, or $hal(CH_2)_4hal$			169
				

[a] Lowest yield with Ac_2O.

TABLE 6. Di- and Polylithiated Thiophenes

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, TMEDA, hexane 2. CO_2		Quantitative	117
	1. BuLi, TMEDA, hexane 2. CO_2	 95% 3%		117
	1. BuLi, TMEDA, hexane 2. CO_2		Quantitative	117
	1. BuLi, TMEDA, hexane 2. CO_2	 19% 39%  5%		117
	1. BuLi 2.6 eq reflux hexane/ether 2. TMSCl		78	424

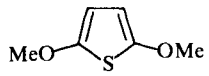
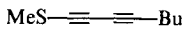
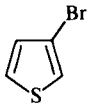
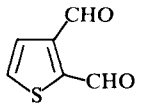
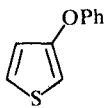
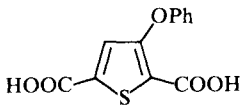
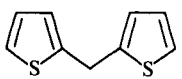
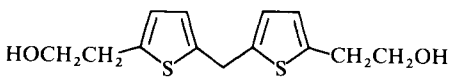
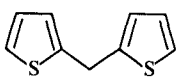
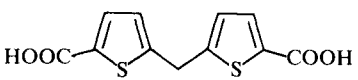
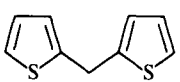
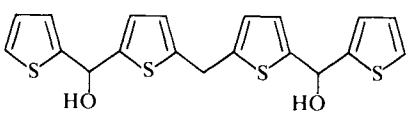
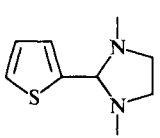
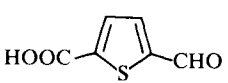
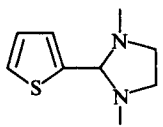
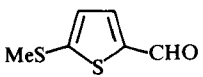
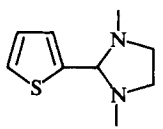
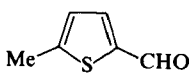
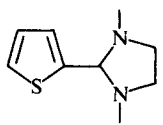
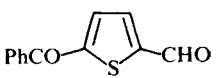
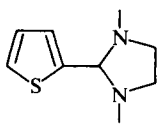
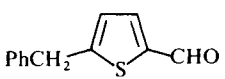
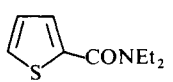
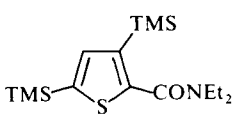
	1. BuLi 2 eq 2. Me_2SO_4		45	121
	1. BuLi excess 2. DMF		40	71
	1. BuLi 2 eq 2. CO_2		23	192
	1. BuLi 2 eq 2. Ethyleneoxide		77	112
	1. BuLi 2 eq 2. CO_2			112
	1. BuLi > 0°C 2. 2-ThCHO			169
	1. BuLi, TMEDA, THF 2. CO_2 3. Hydrolysis		95	181

TABLE 6. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, TMEDA, THF 2. Me_2S_2 3. Hydrolysis		88	181
	1. BuLi, TMEDA, THF 2. MeI 3. Hydrolysis		82	181
	1. BuLi, TMEDA, THF 2. PhCHO 3. Air oxidation 4. Hydrolysis		51	181
	1. BuLi, TMEDA, THF 2. $PhCH_2Br$ 3. Hydrolysis		98	181
	1. *sec*BuLi, TMEDA, $-78°C$, THF 2. TMSCl		82	182

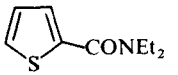
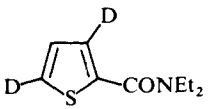
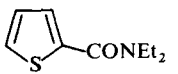
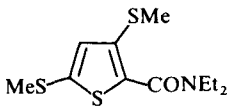
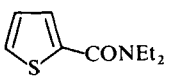
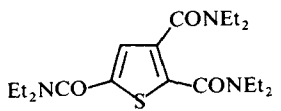
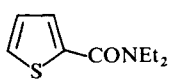
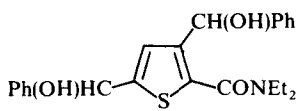
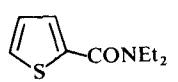
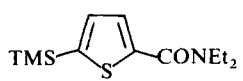
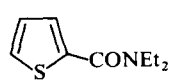
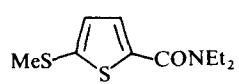
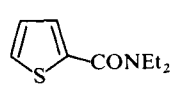
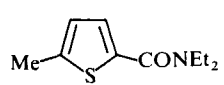
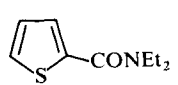
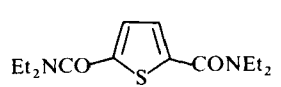
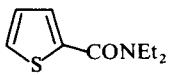
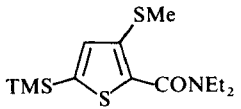
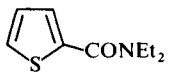
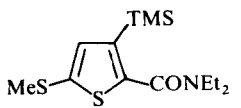
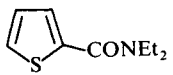
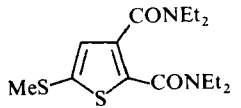
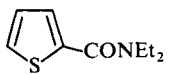
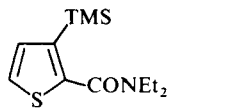
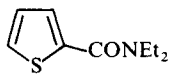
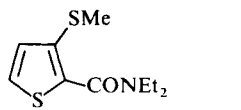
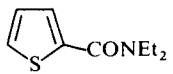
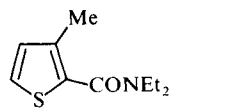
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. EtOD		83	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. Me_2S_2		65	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. $ClCONEt_2$		82	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. PhCHO		48	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. TMSCl 3. MeOH		40	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. Me_2S_2 3. MeOH		34	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. MeI 3. MeOH		57	182
	1. *sec*Buli, TMEDA, − 78°C, THF 2. $ClCONEt_2$ 3. MeOH		38	182

TABLE 6. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. TMSCl 3. Me_2S_2		35	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. Me_2S_2 3. TMSCl		30	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. Me_2S_2 3. $ClCONEt_2$		26	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. TMSCl 3. MeOH		40	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. Me_2S_2 3. MeOH		34	182
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. MeI 3. MeOH		57	182

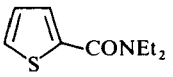
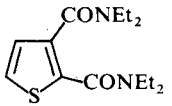
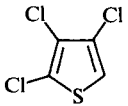
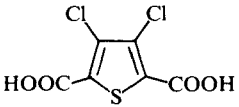
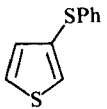
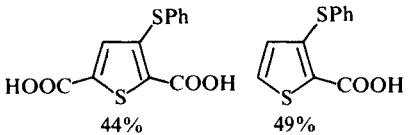
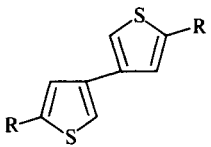
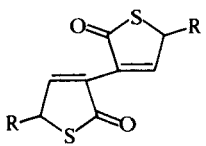
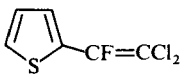
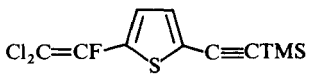
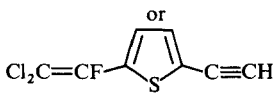
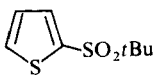
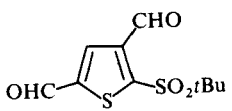
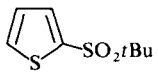
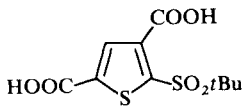
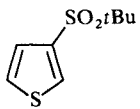
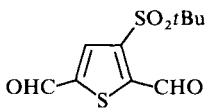
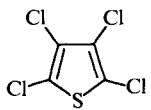
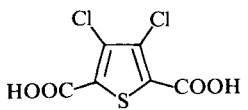
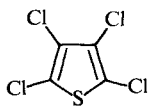
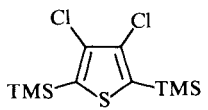
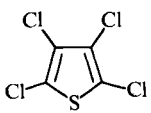
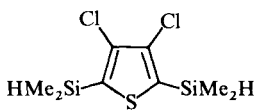
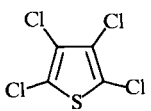
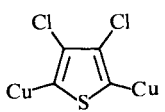
	1. *sec*BuLi, TMEDA, − 78°C, THF 2. $ClCONEt_2$ 3. MeOH		38	182
	1. BuLi 2 eq, THF, − 78°C 2. CO_2		96	186
	1. BuLi, 2 eq 2. CO_2	 44% 49%		192
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		15–17	279
	1. BuLi 2. $CF_2{=}CCl_2$ 3. TMSCl or H_2O	 78% or  29%		47
	1. BuLi 4 eq, THF, − 15°C 2. DMF		59	130

TABLE 6. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 4 eq, THF, $-15°C$ 2. CO_2		68	130
	1. BuLi 4 eq, THF, $-15°C$ 2. DMF		36	130
	1. BuLi 2 eq, ether 2. CO_2		87–96	185
	1. BuLi 2 eq, ether 2. TMSCl		80	185
	1. BuLi 2 eq, ether 2. Me_2HSiCl		82	185
	1. BuLi 2 eq, ether 2. CuCl or CuI		—	185

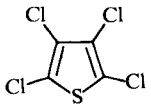
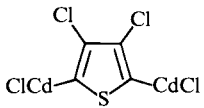
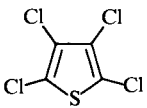
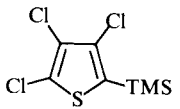
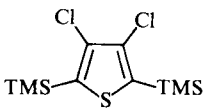
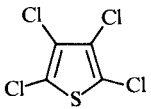
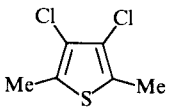
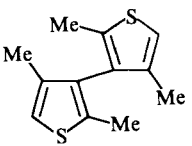
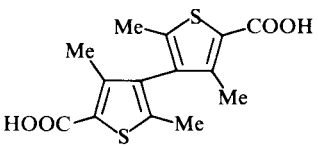
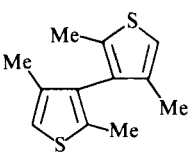
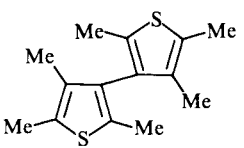
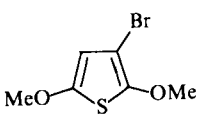
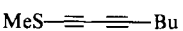
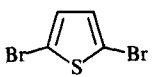
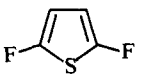
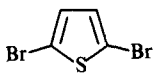
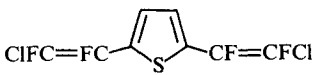
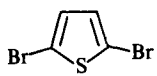
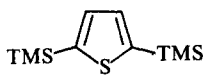
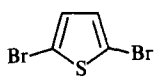
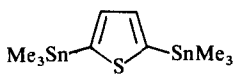
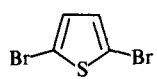
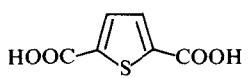
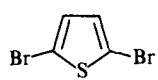
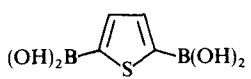
	1. BuLi 2 eq, ether 2. $CdCl_2$		—	185
	1. Mg, EtBr, 2 eq, THF 2. TMSCl	 50–55%  25–30%		425
	1. BuLi 2. DMS		72	30
	1. EtLi 2. CO_2		77	271
	1. EtLi 2. DMS		84	271
	1. BuLi, room temp., 2 h 2. DMS		67	121

TABLE 6. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. $FClO_3$		—	184
	1. BuLi 2 eq 2. $CF_2{=}CFCl$ 2 eq		76	286
	1. BuLi, THF, − 55°C 2. TMSCl		89	123
	1. BuLi, THF, − 55°C 2. TMSnCl		92	123
	1. BuLi, THF, − 55°C 2. CO_2		95	123
	1. Mg, THF 2. $B(OMe)_3$		62	188

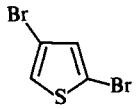
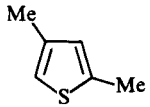
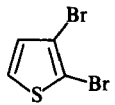
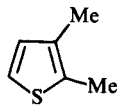
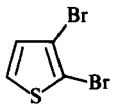
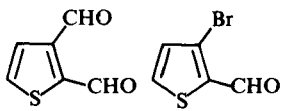
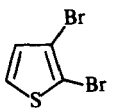
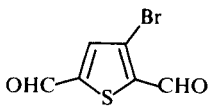
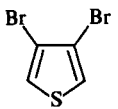
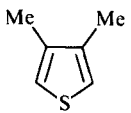
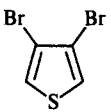
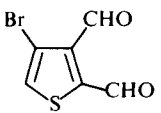
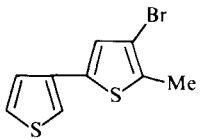
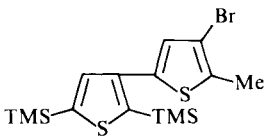
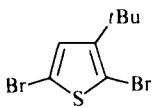
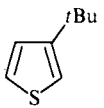
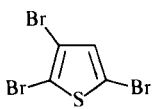
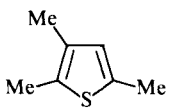
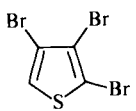
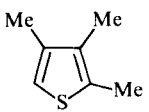
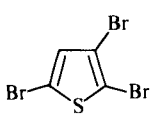
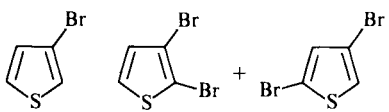
	1. BuLi 2.5 eq 2. DMS		75	183
	1. BuLi 2.5 eq 2. DMS		70	183
	1. BuLi, − 70 to − 10°C 2. DMF	 20%	40	142
	1. BuLi, − 20°C → reflux 2. DMF		35	142
	1. BuLi 2.5 eq 2. DMS		80	183
	1. BuLi, − 40°C 2. DMF		20[a]	142

TABLE 6. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA 2. TMSCl		38	207
	1. BuLi 2. H_2O		82	29
	1. BuLi 20 eq 2. DMS		75	183
	1. BuLi 20 eq 2. DMS		92	183
	1. Mg, EtBr 2.5 eq 2. H_2O	 51% 24%		187

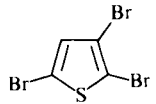
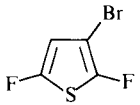
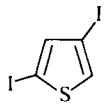
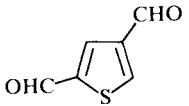
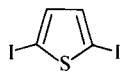
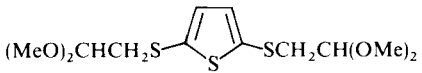
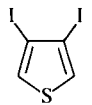
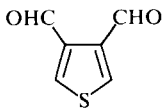
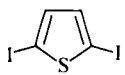
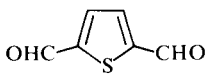
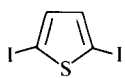
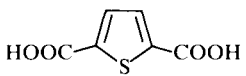
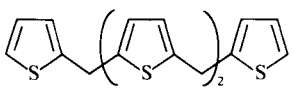
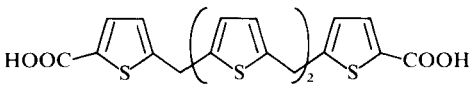
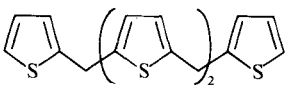
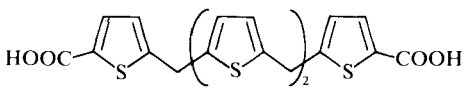
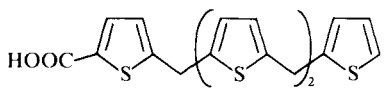
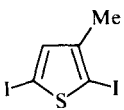
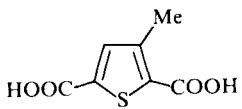
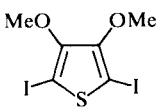
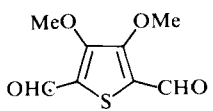
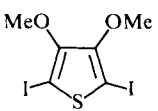
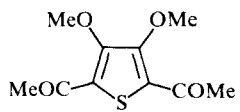
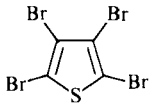
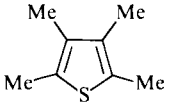
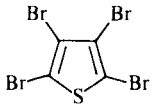
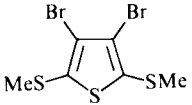
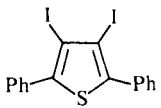
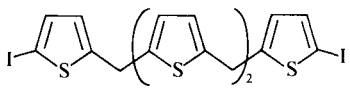
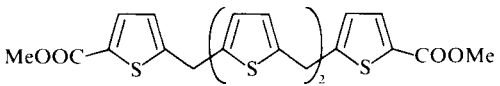
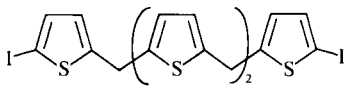
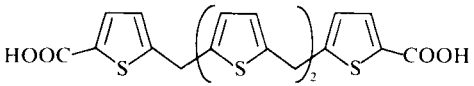
	1. EtLi 2. $FClO_3$		--	184
	1. BuLi 2 eq, − 30°C 2. DMF		20	142
	1. PhLi 2. $((MeO)_2CHCH_2S)_2$—		58	380, 381
	1. BuLi, − 60°C 2. DMF		58	142
	1. BuLi, − 30°C 2. DMF		70	142
	1. PhLi 2. CO_2		53	352
	1. BuLi, room temp. 2. CO_2		29	114

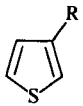
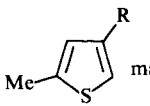
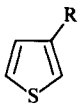
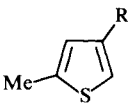
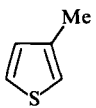
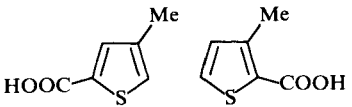
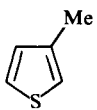
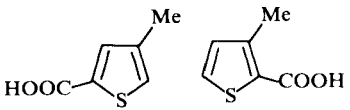
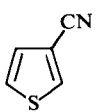
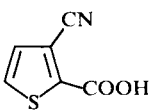
TABLE 6. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CO_2	 		169
	1. PhLi, 5 eq 2. CO_2		75	36
	1. BuLi 2. DMF		85	426
	1. BuLi 2. DMA		35	426

	1. BuLi 30 eq 2. DMS		75	183
	1. BuLi 2 eq 2. Me_2S_2		73	384
	BuLi, higher temp.	$Ph{\cdot}(C{\equiv}C)_2Ph$	67–70	139
	1. BuLi 2. CO_2		42	114
	1. BuLi 2. CO_2		—	378

[a] 3,4-Diformylthiophene was not formed.

TABLE 7. Directed Metalations

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. DMS	 major product		29
	1. LDA 2. DMS	 major product		29
	1. BuLi 2. CO_2	 3.5 : 1	24	31
	1. LDA 2. CO_2	 24 : 1	2	31
	1. BuLi, $-70°C$ 2. CO_2		68	162

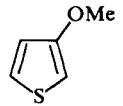
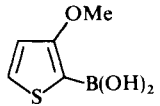
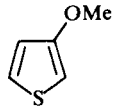
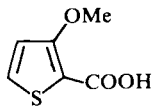
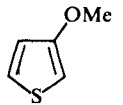
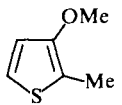
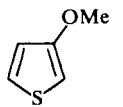
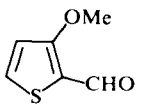
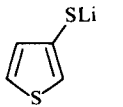
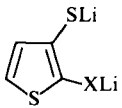
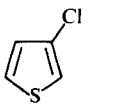
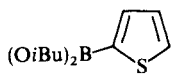
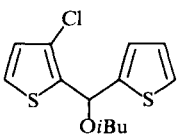
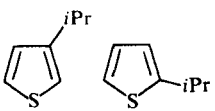
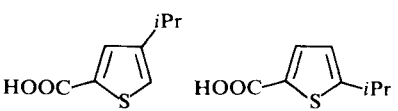
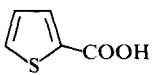
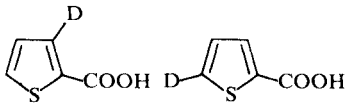
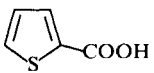
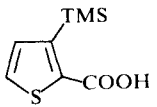
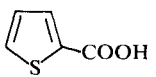
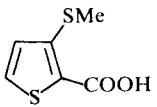
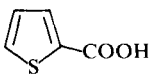
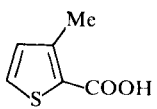
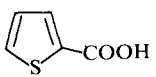
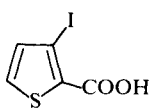
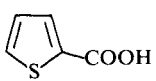
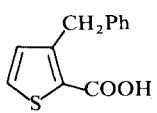
	1. BuLi 2. $B(OBu)_3$		80	96
	1. BuLi 2. CO_2		86	26
	1. BuLi, LDA, or BuLi–TMEDA 2. DMS		78–54	29
	1. BuLi 2. DMF			277
	1. BuLi 2. S or Se			190
	1. BuLi 2. 			99
	1. BuLi 2. CO_2		75	200

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, THF, − 78°C 2. MeOD	 93 : 5		125
	1. BuLi, THF, − 78°C 2. TMSCl		85	125
	1. BuLi, THF, − 78°C 2. Me_2S_2		94	125
	1. BuLi, THF, − 78°C 2. MeI		83	125
	1. BuLi, THF, − 78°C 2. I_2		92	125
	1. BuLi, THF, − 78°C 2. $PhCH_2Br$		70	125

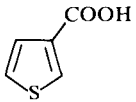
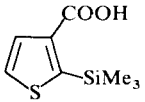
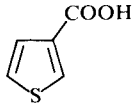
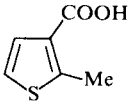
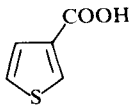
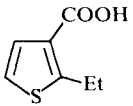
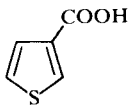
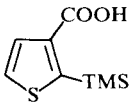
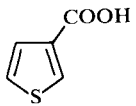
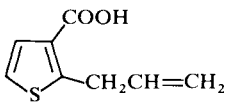
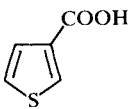
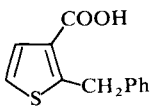
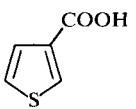
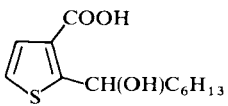
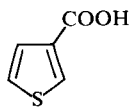
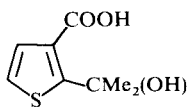
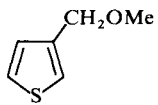
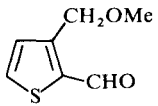
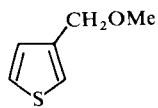
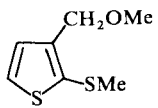
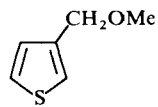
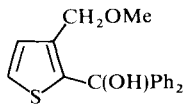
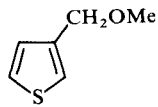
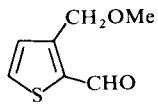
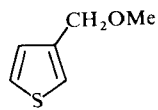
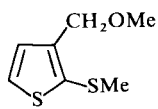
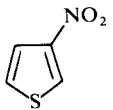
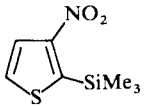
	1. LDA 2. TMSCl			14
	1. LDA 2 eq 2. MeI		87	37
	1. LDA 2 eq 2. EtI		31	37
	1. LDA 2 eq 2. TMSCl		55	37
	1. LDA 2 eq 2. CH_2=$CHCH_2Br$		22	37
	1. LDA 2 eq 2. $PhCH_2Br$		0	37
	1. LDA 2 eq 2. $C_6H_{13}CHO$		55	37

TABLE 7. (*Continued*)

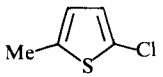
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA 2 eq 2. MeCOMe		65	37
	1. BuLi 2. DMF		72	74
	1. BuLi 2. MeSSMe		66	74
	1. BuLi 2. Ph_2CO		46	74
	1. BuLi 2. DMF		54	74
	1. BuLi 2. Me_2S_2		61	74



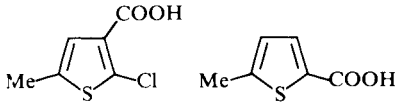
1. LDA
2. TMSCl



14

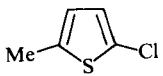


1. BuLi, TMEDA
2. CO_2

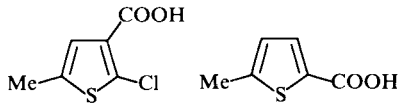


1 : 1.5

31

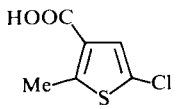


1. LDA
2. CO_2

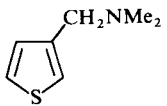


1 : 1.5

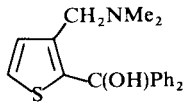
31



1.8

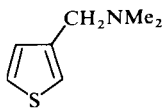


1. BuLi
2. Ph_2CO

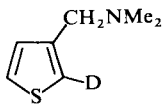


67

74

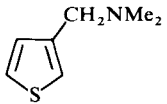


1. BuLi
2. D_2O

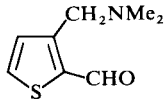


67

74



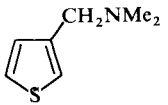
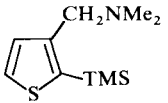
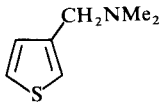
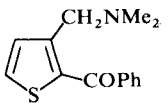
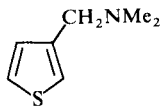
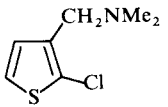
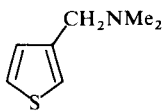
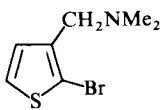
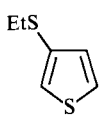
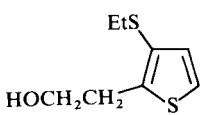
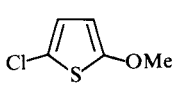
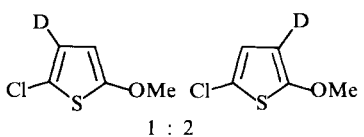
1. BuLi
2. DMF



75

74

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. TMSCl		71	74
	1. BuLi 2. PhCN		54	74
	1. BuLi 2. pTolSO$_2$Cl		25	74
	1. BuLi 2. pTolSO$_2$Br		32	74
	1. BuLi 2. Ethylene oxide		48	191
	1. BuLi, 25°C 2. D_2O	 1 : 2		122

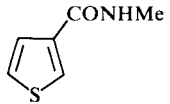
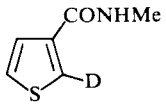
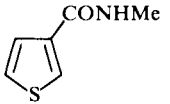
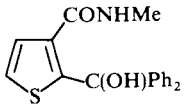
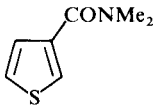
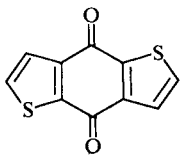
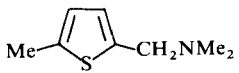
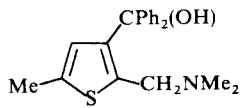
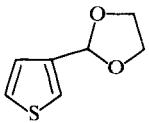
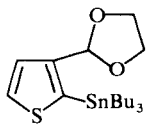
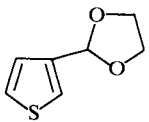
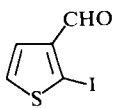
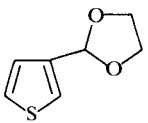
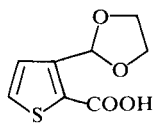
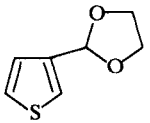
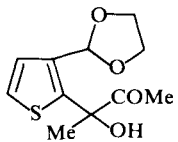
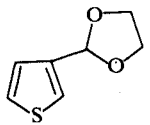
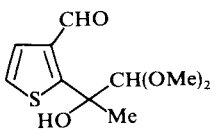
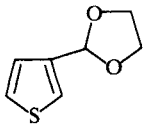
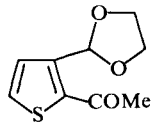
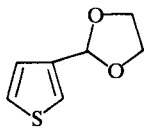
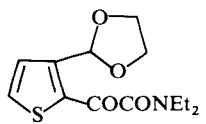
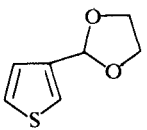
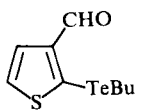
	1. BuLi 2. D_2O		55	74
	1. BuLi 2. Ph_2CO		23	74
	1. BuLi 2. Air oxidation		41–56	74, 75
	1. BuLi 2. Ph_2CO		65	74
	1. LDA 2. CO_2		77	281
	1. BuLi, room temp. 2. I_2		63	84
	1. BuLi 2. CO_2		78	282

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. MeCOCOMe			283
	1. BuLi 2. $MeCOCH(OMe)_2$		72	284
	1. BuLi 2. DMA		40	71
	1. BuLi 2. $(Et_2NCO)_2$		55	71
	1. BuLi 2. Te		34	72

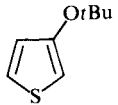
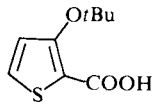
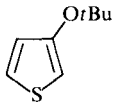
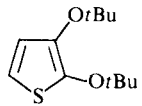
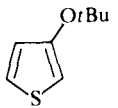
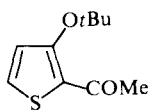
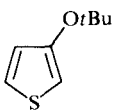
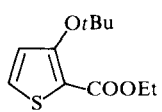
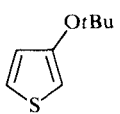
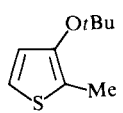
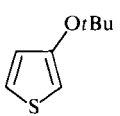
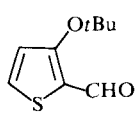
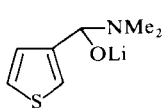
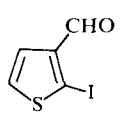
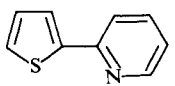
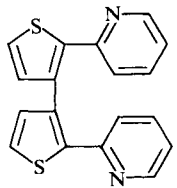
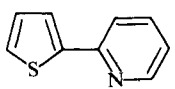
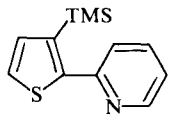
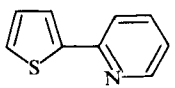
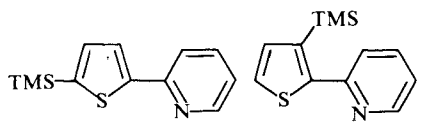
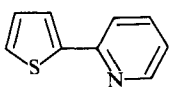
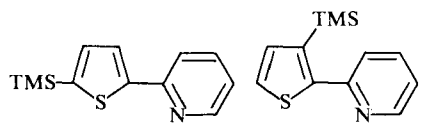
	1. BuLi, ether 2. CO_2		62	285
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$		70	66
	1. BuLi 2. Ac_2O		75	66
	1. BuLi 2. ClCOOEt		75	66
	1. BuLi 2. DMS		87	66
	1. BuLi 2. DMF		62	277
	1. BuLi 2. I_2		29	84

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. *t*BuLi 2. $CuCl_2$		54	55
	1. *t*BuLi or BuLi, ether 2. TMSCl		Major	59
	1. BuLi, THF 2. TMSCl	 96 : 4	98	126
	1. BuLi, ether, TMEDA 2. TMSCl	 17 : 83	80	126

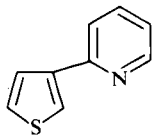
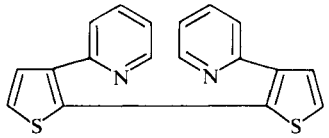
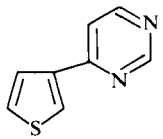
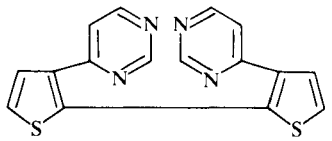
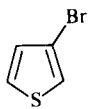
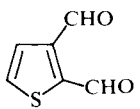
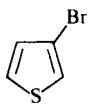
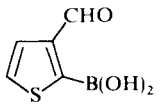
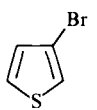
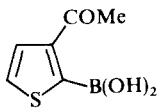
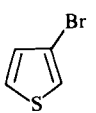
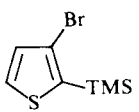
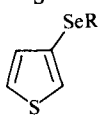
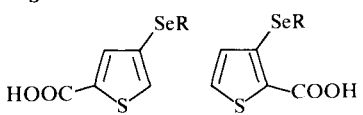
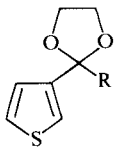
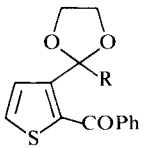
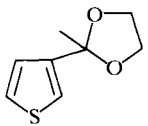
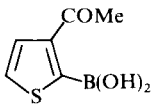
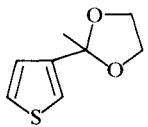
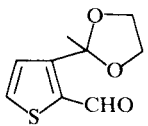
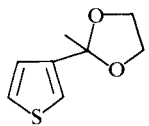
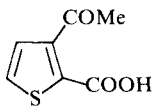
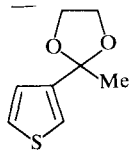
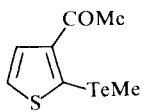
	1. BuLi 2. $CuCl_2$		51	55
	1. LDA 2. $CuCl_2$		28	55
	1. BuLi excess 2. DMF			71
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$			143
	1. EtLi 2. DMA 3. EtLi 4. $B(OBu)_3$		13	100
	1. LDA 2. TMSCl		63	15
	1. BuLi 2. CO_2	 40 : 60	79	193

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. PhCN	 R = Me, H	16–27	291
	1. EtLi 2. $B(OBu)_3$		20	100
	1. BuLi 2. DMF		70	71
	1. BuLi 2. CO_2		70	71
	1. BuLi 2. Te 3. MeI		42	72

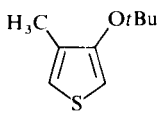
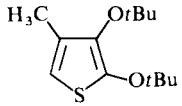
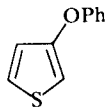
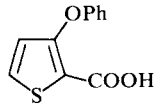
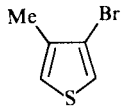
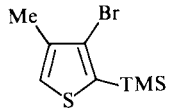
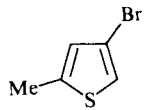
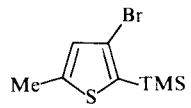
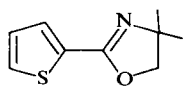
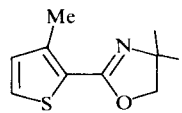
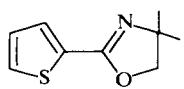
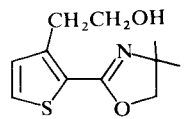
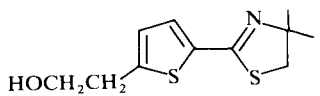
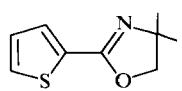
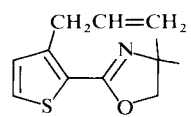
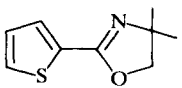
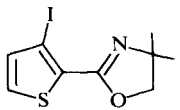
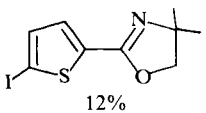
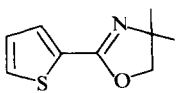
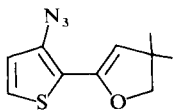
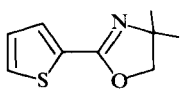
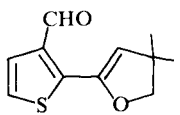
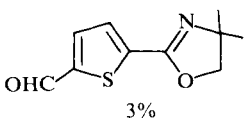
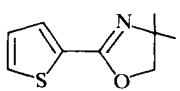
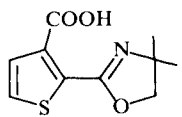
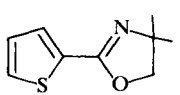
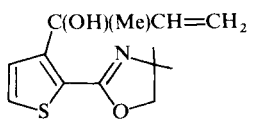
	1. BuLi 2. $MgBr_2$ 3. $PhCO_3tBu$			94
	1. PhLi 2. CO_2		98	192
	1. LDA 2. TMSCl		77	15
	1. LDA 2. TMSCl		74	15
	1. BuLi, ether 2. MeI		90	102
	1. BuLi, ether 2. Ethyleneoxide	 33%  11%		102
	1. BuLi, ether 2. AllylBr		81	102

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, ether 2. I_2	 53%  12%		102
	1. BuLi, ether 2. $TosN_3$		90	102
	1. BuLi, ether 2. DMF	 94%  3%		102
	1. BuLi, ether 2. CO_2		90	102
	1. BuLi, ether 2. $CH_2{=}CHCOCH_3$		26	102

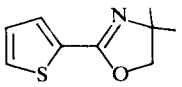
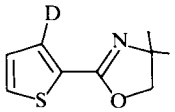
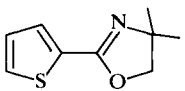
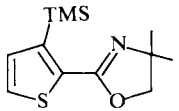
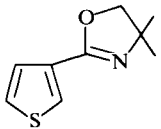
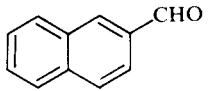
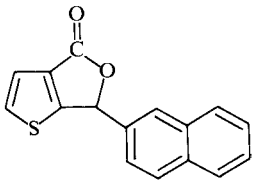
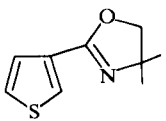
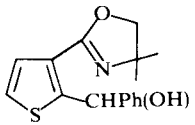
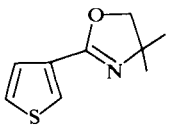
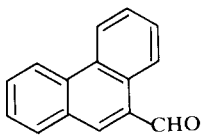
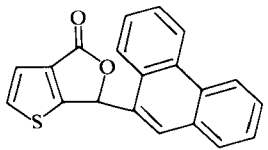
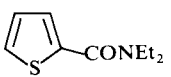
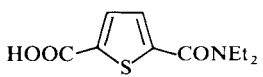
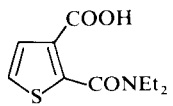
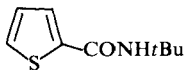
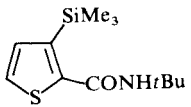
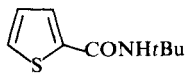
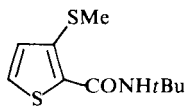
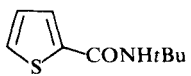
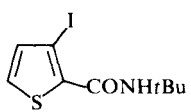
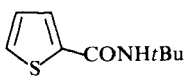
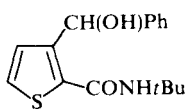
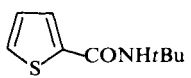
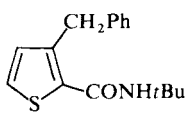
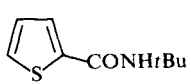
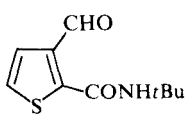
	1. BuLi, ether 2. D_2O		—	102
	1. BuLi, ether 2. TMSCl		—	102
	1. BuLi 2. 		56	196
	1. BuLi, hexane 2. ArCHO			196
	1. BuLi 2. 		21	197
	1. *sec*BuLi, THF 2. CO_2	  41 : 50	99 total	129

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi/DME 2. Me_3SiCl		95	129
	1. BuLi/DME 2. MeSSMe		93	129
	1. BuLi/DME 2. I_2		72	129
	1. BuLi/DME 2. PhCHO		77	129
	1. BuLi/DME 2. $PhCH_2Br$		76	129
	1. BuLi/DME 2. DMF		63	129

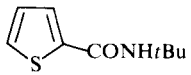
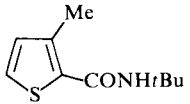
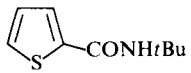
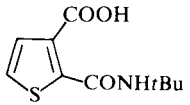
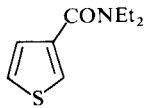
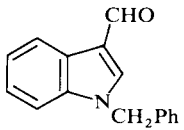
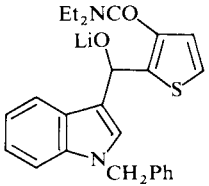
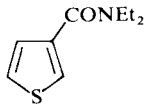
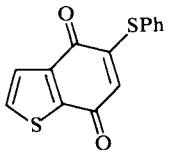
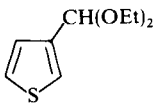
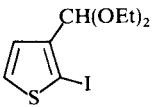
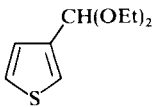
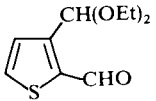
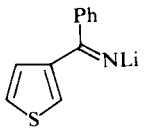
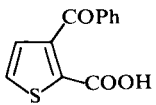
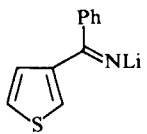
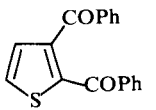
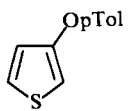
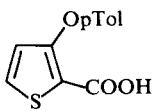
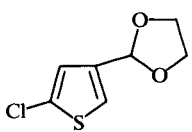
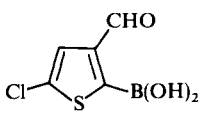
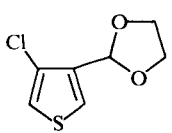
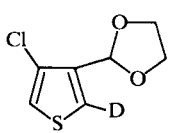
	1. BuLi/DME 2. MeI		88	129
	1. BuLi/DME 2. CO_2		74	129
	1. *sec*BuLi 2. Air oxidation 3. 		> 67	194
	1. *sec*BuLi, TMEDA 2. PhSCH=CHCHO		44	49
	1. BuLi 2. I_2		30	85
	1. BuLi 2. DMF		85	298

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CO_2		70	79
	1. BuLi 2. PhCN		52	79
	1. PhLi 2. CO_2		65	192
	1. EtLi 2. $B(OBu)_3$		39	100
	1. EtLi 2. MeCOOD		66	100

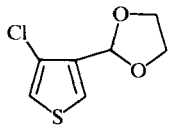
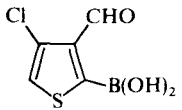
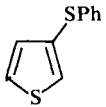
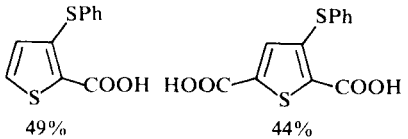
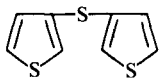
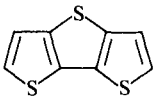
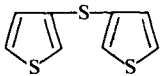
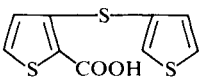
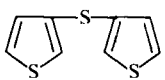
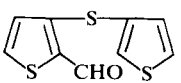
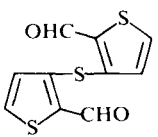
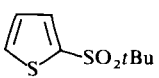
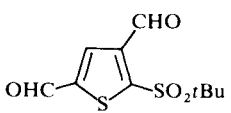
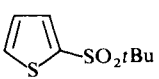
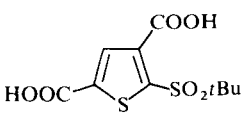
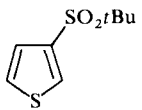
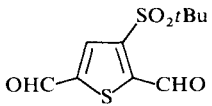
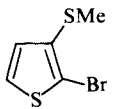
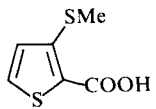
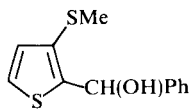
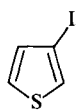
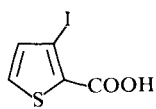
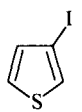
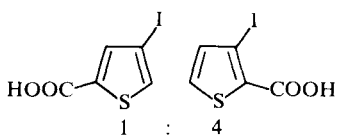
	1. BuLi 2. $B(OBu)_3$		50	100
	1. BuLi 2 eq 2. CO_2	 49% 44%		192
	1. BuLi 2 eq 2. $CuCl_2$		50	54
	1. BuLi 2. CO_2		25	54
	1. BuLi 2. DMF	 16%  22%		54
	1. BuLi 4 eq, THF, $-15°C$ 2. DMF		59	130
	1. BuLi, 4 eq, THF, $-15°C$ 2. CO_2		68	130

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 4 eq, THF, − 15°C 2. DMF		36	130
	1. BuLi 2. CO_2			20
	1. BuLi 2. MeCHO			20
	1. LDA 2. CO_2		63	189
	1. N-Me-pyrrolyl-Li, TMEDA 2. CO_2	 1 : 4	33	13

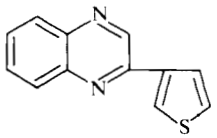
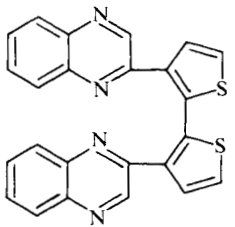
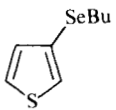
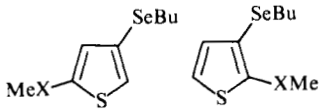
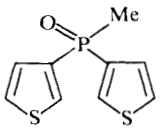
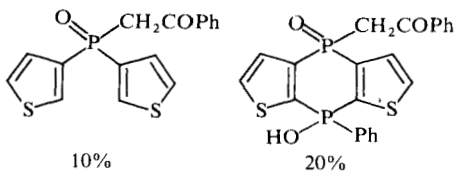
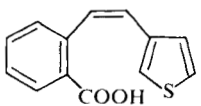
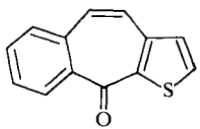
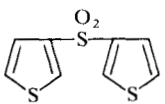
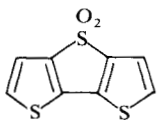
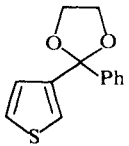
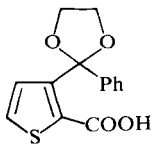
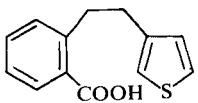
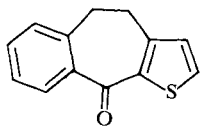
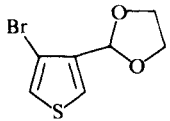
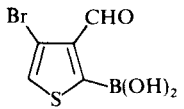
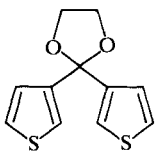
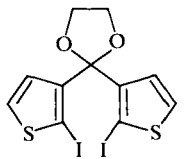
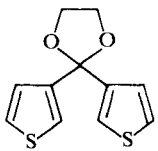
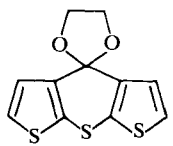
	1. LDA 2. $CuCl_2$		48	55
	1. BuLi 2. S or Se 3. MeI		67–76	193
	1. BuLi, THF 2. PhCOOEt	 10% 20%		53
	LDA 2 eq		59	195
	1. BuLi 2. $CuCl_2$		33	54

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. CO_2		43	291
	LDA 2 eq		4	195
	1. LDA, $-70°C$ 2. $B(OEt)_3$		65	21
	1. BuLi 2. I_2		56	86
	1. BuLi 2. S		60	104

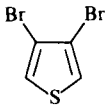
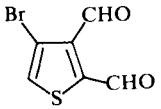
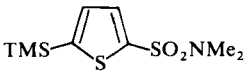
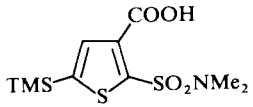
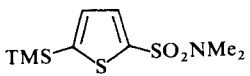
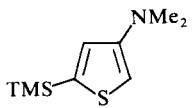
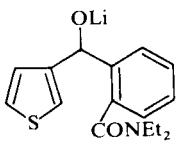
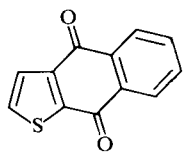
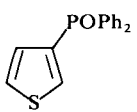
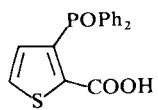
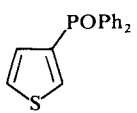
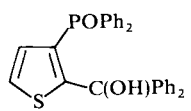
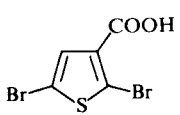
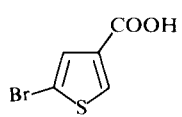
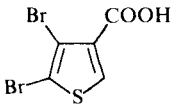
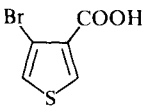
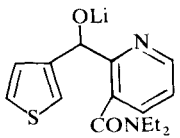
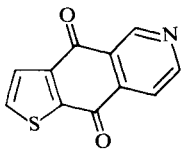
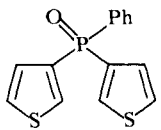
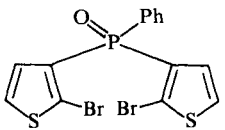
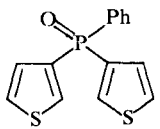
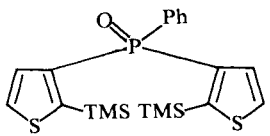
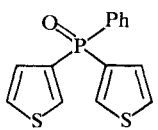
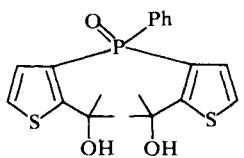
	1. BuLi, −40°C 2. DMF		20	142
	1. BuLi, 0°C 2. CO_2		10	128
	1. BuLi, TMEDA 2. CO_2		39	128
	1. *sec*BuLi 2. Air oxidation		35	194
	1. BuLi 2. CO_2			53
	1. BuLi 2. PhCOPh			53
	1. BuLi 2. H_2O			144

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. H_2O			144
	1. *sec*BuLi 2. Air oxidation		20	194
	1. BuLi, THF 2. Br_2		65	53
	1. BuLi, THF 2. TMSCl		30	53
	1. BuLi, THF 2. MeCOMe		45	53

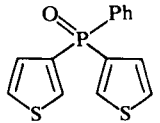
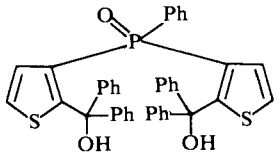
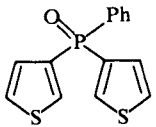
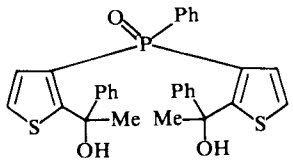
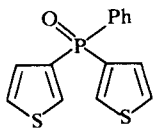
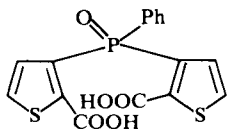
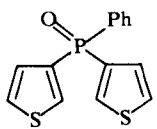
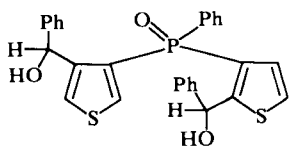
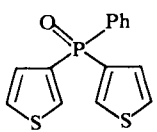
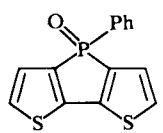
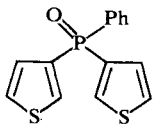
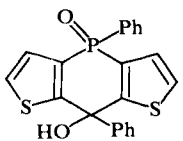
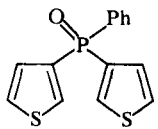
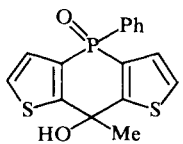
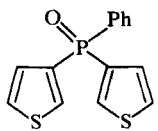
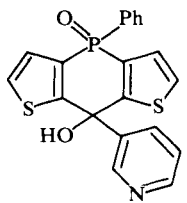
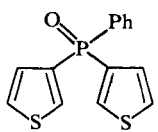
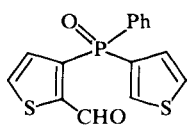
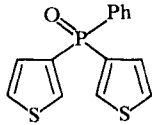
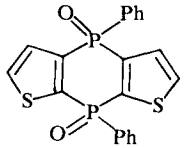
	1. BuLi, THF 2. PhCOPh		80	53
	1. BuLi, THF 2. PhCOMe		50	53
	1. BuLi, THF 2. CO_2		75	53
	1. BuLi, THF 2. PhCHO		70	53
	1. BuLi, THF 2. $CuCl_2$		10	53

TABLE 7. (*Continued*)

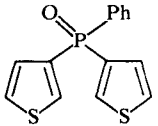
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, THF 2. PhCOOEt		68	53
	1. BuLi, THF 2. MeCOOEt		35	53
	1. BuLi, THF 2. 3-COOEt-pyridine		35	53
	1. BuLi, THF 2. HCOOEt		48	53



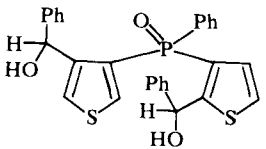
1. BuLi, THF
2. $PhPCl_2$
3. H_2O_2



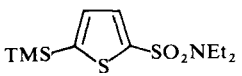
6–10 53



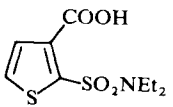
1. BuLi, THF
2. PhCHO



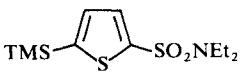
70 53



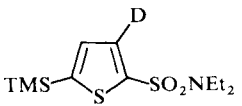
1. BuLi, TMEDA
2. CO_2



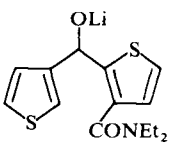
44 128



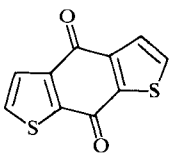
1. BuLi, TMEDA
2. D_2O



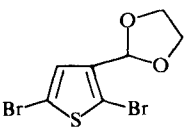
70 128



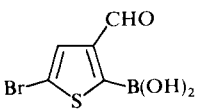
1. *sec*BuLi
2. Air oxidation



77 194

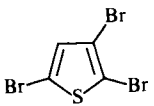
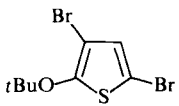
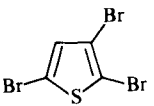
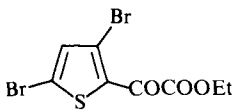
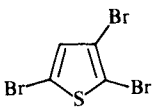
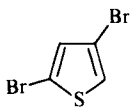
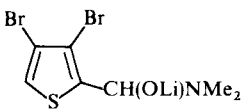
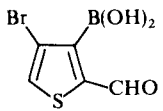
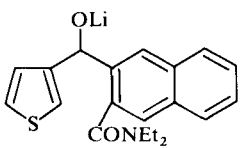
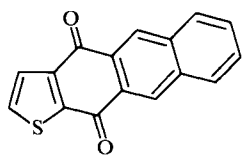


1. BuLi
2. $B(OEt)_3$



21

TABLE 7. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $MgBr_2$ 3. *t*BuOOCOPh		79	154
	1. BuLi, THF/hexane 2. $(COOEt)_2$			221
	1. BuLi 2. H_2O			135
	1. BuLi 2. $B(OEt)_3$			21
	1. *sec*BuLi 2. Air oxidation		37	194

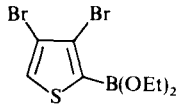
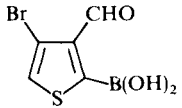
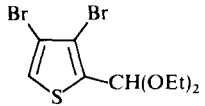
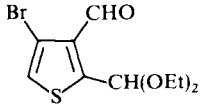
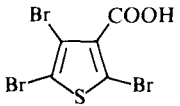
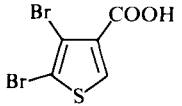
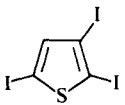
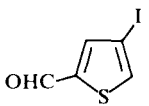
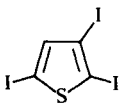
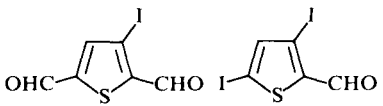
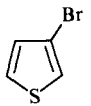
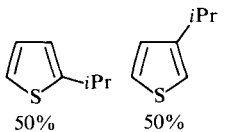
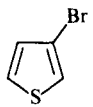
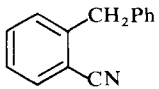
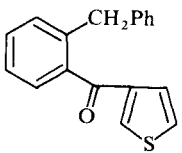
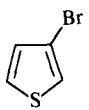
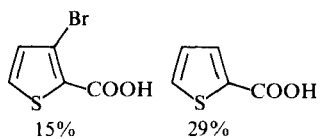
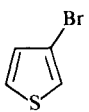
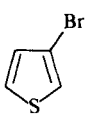
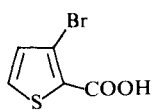
	1. BuLi 2. DMF		21
	1. BuLi 2. DMF		307
	1. BuLi 2. H_2O		144
	1. BuLi 2. H_2O 3. BuLi 4. DMF		85
	1. BuLi 2. DMF	 13% 30%	85

TABLE 8. Rearrangements

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. $PhSO_3iPr$	 50% 50%		200
	1. Mg, EtBr 2. 		58[a]	270
	1. BuLi, room temp., 16 h 2. CO_2	 15% 29%	78	137
	1. BuLi, room temp., 24 h 2. CO_2		Oil	137
	1. BuLi 2. CO_2		< 50	12

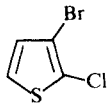
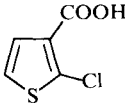
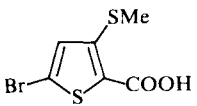
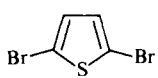
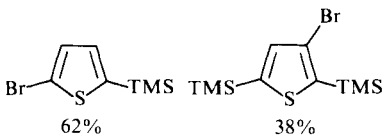
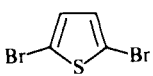
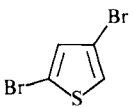
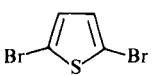
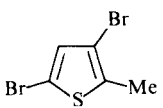
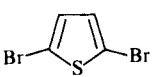
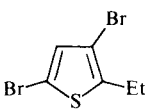
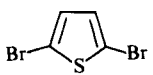
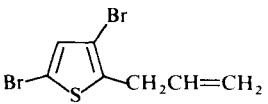
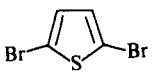
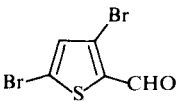
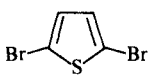
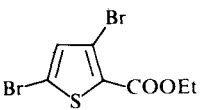
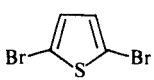
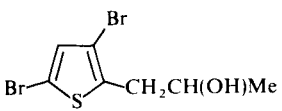
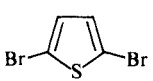
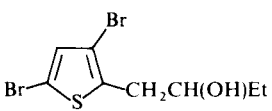
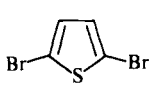
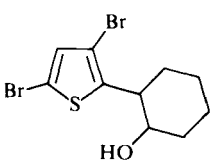
	1. BuLi, − 70°C 2. CO_2 (gas)		58	141
	1. BuLi, − 70°C 2. Room temp., overnight 3. CO_2 (gas)		—[b]	141
	1. LDA 2. CO_2		41	20
	1. BuLi, THF 2. TMSCl	 62% 38%		123
	1. LDA, THF, − 78°C 2. H_2O		100	124
	1. LDA, THF, − 78°C 2. MeI		100	124
	1. LDA, THF, − 78°C 2. EtI		95	124

TABLE 8. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. LDA, THF, − 78°C 2. AllylBr		68	124
	1. LDA, THF, − 78°C 2. DMF		85	124
	1. LDA, THF, − 78°C 2. ClCOOEt		72	124
	1. LDA, THF, − 78°C 2. Propenoxide		73	124
	1. LDA, THF, − 78°C 2. 1-Butenoxide		68	124
	1. LDA, THF, − 78°C 2. Cyclohexeneoxide		63	124

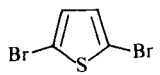
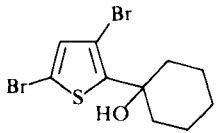
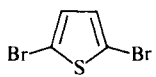
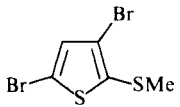
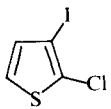
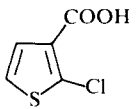
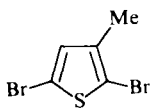
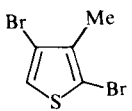
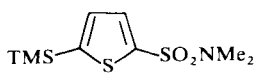
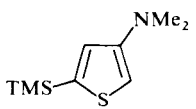
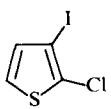
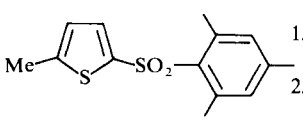
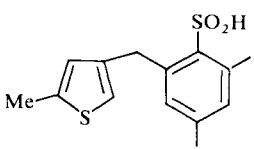
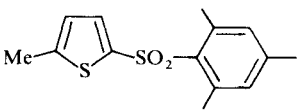
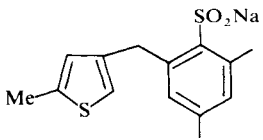
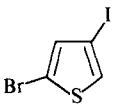
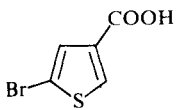
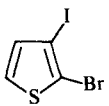
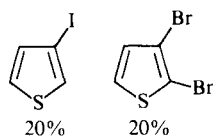
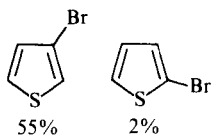
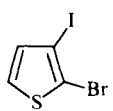
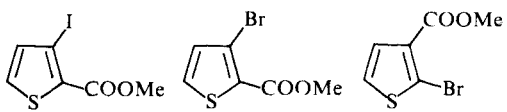
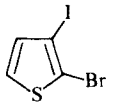
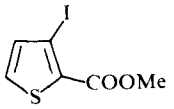
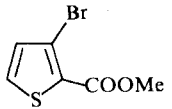
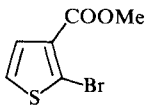
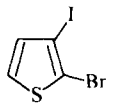
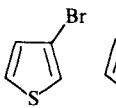
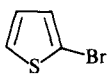
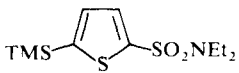
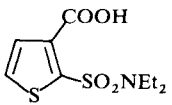
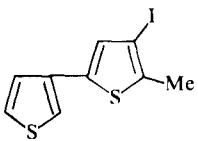
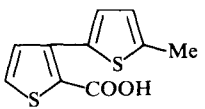
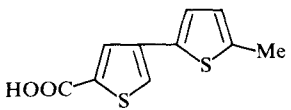
	1. LDA, THF, − 78°C 2. Cyclohexanone		77	124
	1. LDA, THF, − 78°C 2. MeSSMe		45	124
	1. BuLi, − 70°C 2. CO_2 (gas)		51	141
	1. BuLi, TMEDA 2. Me_2SO_4			29
	1. BuLi, TMEDA 2. CO_2		39	128
	1. BuLi, − 70°C 2. Room temp., overnight 3. CO_2 (gas)		—[b]	141
	1. BuLi 2 eq, THF, 4 h, room temp. 2. H^+		88	199

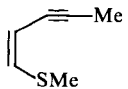
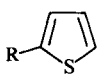
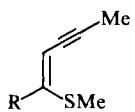
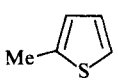
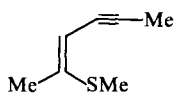
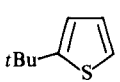
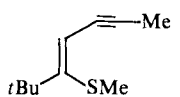
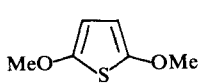
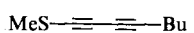
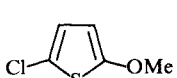
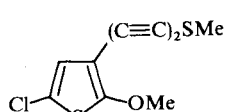
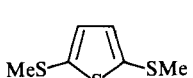
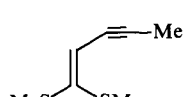
TABLE 8. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2 eq ether, 24-h reflux 2. H^+ 3. NaOH		70	199
	1. BuLi, $-100°C$ 2. CO_2 (gas)		—[c]	141
	1. EtLi, $-60°C$ 2. EtOH	 20% 20%  55% 2%		161
	1. EtLi, $-60°C$ 2. CO_2	 26% 71% 3%		161

	1. EtLi 1.5 eq, −100°C 2. CO_2	 11%  5%  84%		161
	1. EtLi 1.5 eq, −100°C 2. EtOH	 5%  95%		161
	1. BuLi, TMEDA 2. CO_2		44	128
	1. PhLi, room temp. 2. CO_2	 	55% mix	207

[a] No rearrangement was observed.
[b] Rearrangement products were obtained.
[c] Major product, but rearrangement occurred at higher temp.

TABLE 9. Ring-Opening Reactions

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, HMPA 2. MeI		80	115
	1. LiHMDS, HMPA, $18C_6$ 2. MeI		71–92	215
	1. BuLi, HMPA 2. MeI		60	115
	1. BuLi, HMPA 2. MeI		40	115
	1. BuLi 2 eq 2. Me_2SO_4		45	121
	1. BuLi, 25°C 2. Me_2SO_4		20	122
	1. LDA, HMPA or $NaNH_2(NH_3)$ 2. MeI		80	115

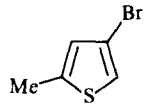
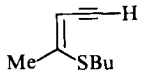
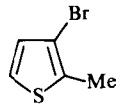
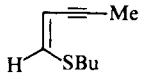
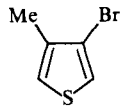
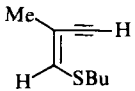
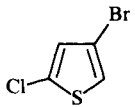
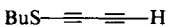
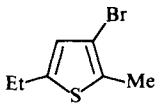
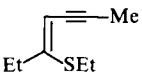
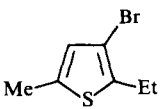
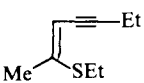
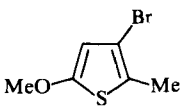
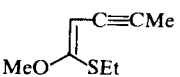
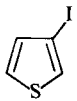
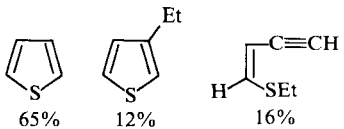
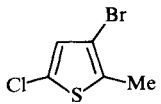
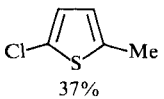
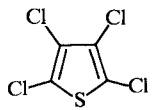
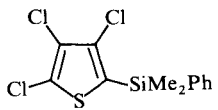
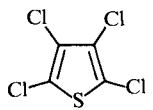
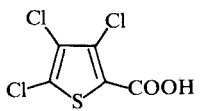
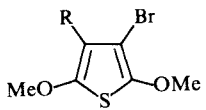
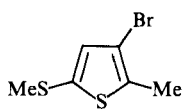
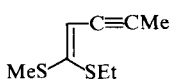
	1. BuLi 2. BuBr		15	205
	1. BuLi 2. BuBr		95	205
	1. BuLi 2. BuBr		26	205
	1. BuLi, − 51°C 2. Room temp.		—[a]	141
	1. EtLi, + 21°C, 4 h 2. EtI		64	208
	1. EtLi, + 21°C, 4 h 2. EtI		60	208
	1. EtLi 2. EtBr, HMPA		33	145

TABLE 9. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. EtBr, room temp., 5 h	 65% 12% 16%		206
	1. EtLi 2. EtBr	EtSC≡CC≡CMe 42%  37%	33	145
	1. *t*BuLi in THF 2. $PhMe_2SiCl$		56[b]	354
	1. *t*BuLi in THF 2. CO_2		94[b]	354
	1. BuLi, room temp., 2 h 2. DMS	MeS—≡—≡—Bu	R = H 67	121
	1. EtLi 2. EtBr, room temp., 5 h		50	213

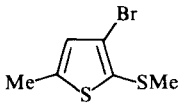
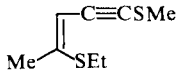
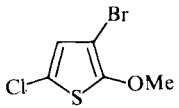
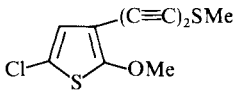
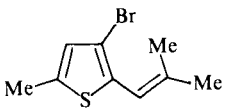
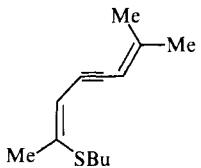
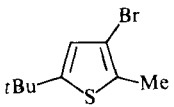
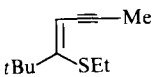
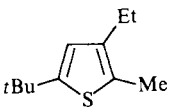
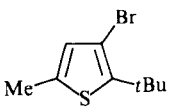
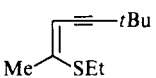
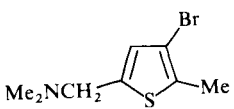
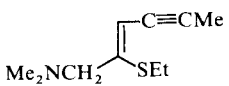
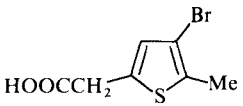
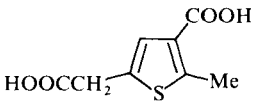
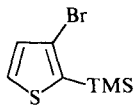
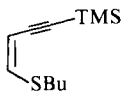
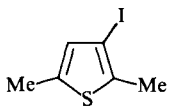
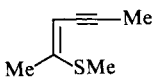
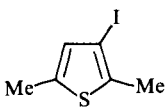
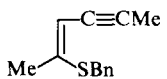
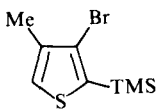
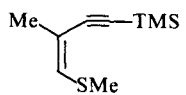
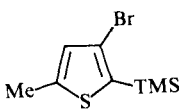
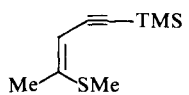
	1. EtLi 1 eq 2. EtBr		Major	145
	1. BuLi, room temp. 2. DMS		20	122
	1. BuLi, 25°C 2. BuBr		66	212
	1. EtLi, + 21°C, 4 h 2. EtI	 35%  33%	80	208
	1. EtLi, + 21°C, 4 h 2. EtI		80	208
	1. EtLi 2. EtBr		49	17

TABLE 9. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, 2 eq 2. CO_2		0	30
	1. BuLi 2. BuBr		68	15, 19
	1. MeLi or PhLi, 20–35°C 2. MeI		42	204
	1. PhLi 2. BnBr		—	404
	1. BuLi 2. BuBr		67	15, 19
	1. BuLi 2. BuBr		57	15, 19

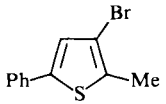
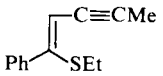
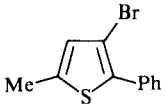
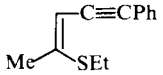
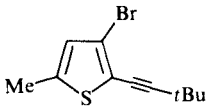
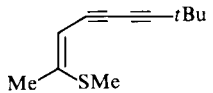
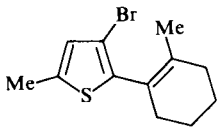
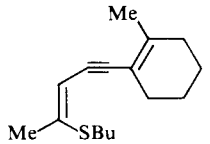
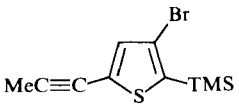
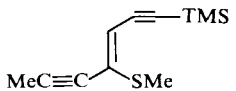
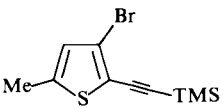
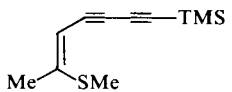
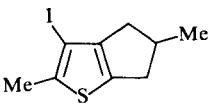
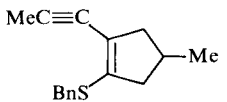
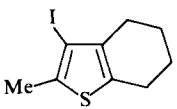
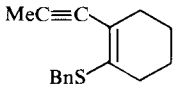
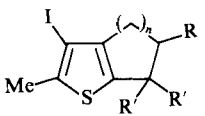
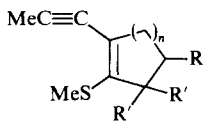
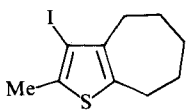
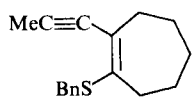
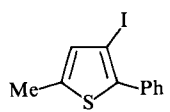
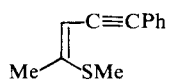
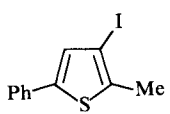
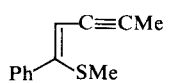
	1. EtLi 2. EtBr		12	17
	1. EtLi 2. EtBr		47	17
	1. BuLi, 25°C 2. MeI		56	212
	1. BuLi, 25°C 2. BuBr		49	212
	1. BuLi 2. MeI		84	19
	1. BuLi, 25°C 2. MeI		52	212
	1. PhLi 2. BnCl		44–63	209

TABLE 9. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. DMS			210
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. DMS		69	17
	1. PhLi 2. DMS		50	17

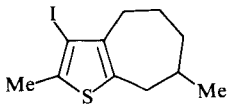
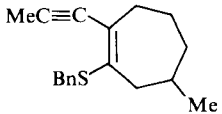
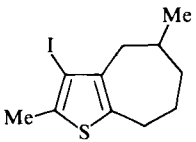
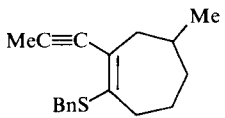
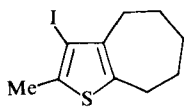
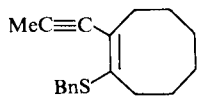
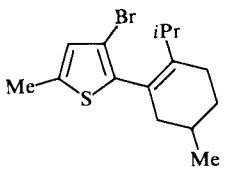
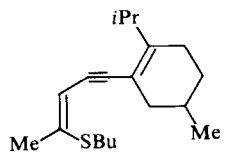
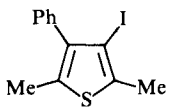
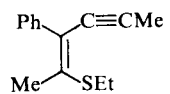
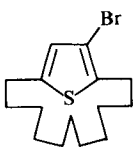
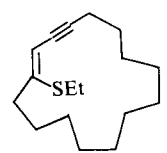
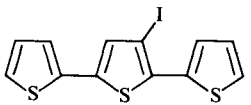
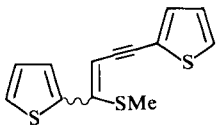
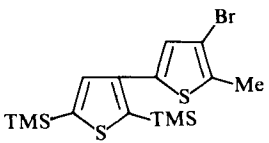
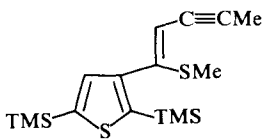
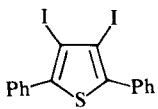
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. BnCl		44–63	209
	1. PhLi 2. BnCl		44–63	209
	1. BuLi 25°C 2. BuBr		66	212
	1. EtLi 2. EtBr		55	17
	1. EtLi 2. EtI, room temp., 5 h		45	211

TABLE 9. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhLi, room temp. 2. MeI		44[c]	207
	1. PhLi, room temp. 2. MeI		45	207
	BuLi, higher temp.	Ph·(C≡C)$_2$Ph	60–70	139

[a] Not isolated.
[b] Ring opening with MeLi or BuLi probable, but the products were not isolated.
[c] *E* : *Z* 7 : 3.

TABLE 10. Sodium, Potassium, Cesium, and Rubidium Derivatives

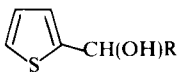
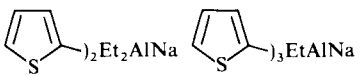
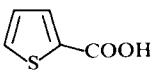
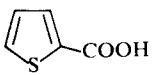
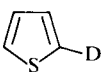
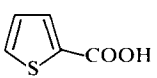
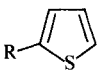
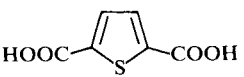
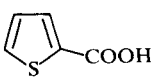
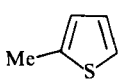
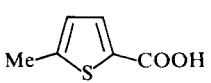
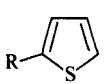
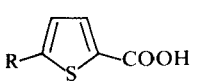
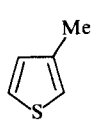
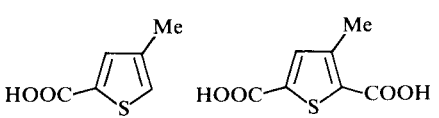
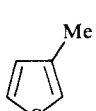
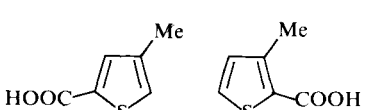
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhBr, Na(Hg) 2. RCHO		25–89	252
	1. $NaNH_2$, NH_3(l) 2. TMSCl		—[a]	48
	$NaAlEt_4$ + NaEt (catalyst), 60–80°C			312
	1. BuCs, heptane/DME, −60°C 2. CO_2		18	313
	1. BuK, heptane/DME, −60°C 2. CO_2		51	313
	1. K, vapor, 60°C 2. D_2, 1 atm.		4	314
	1. Na(Hg), EtCl, ether 2. CO_2		44	315

TABLE 10. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $NaNH_2$, NH_3(l) 2. RBr or R_2SO_4			316
	1. Amyl-Na, *t*-pentanol 2. CO_2		50	317
	1. $Et_2Zn \cdot EtNa$ complex 2. CO_2		55	318
	1. BuK, heptane/DME, $-60°C$ 2. CO_2		33	313
	1. Na(Hg), EtCl, ether 2. CO_2		44	319
	1. PhNa 2. CO_2	 58% 11%		36
	1. BuCs, heptane/DME, $-60°C$ 2. CO_2	 18 : 33		313

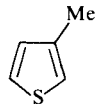
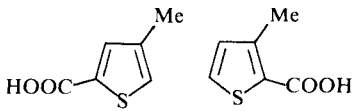
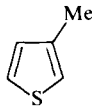
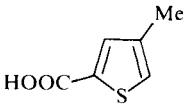
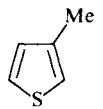
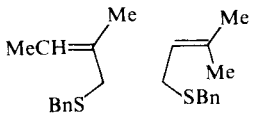
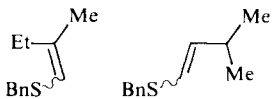
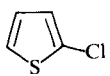
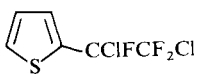
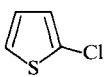
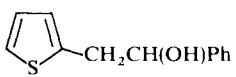
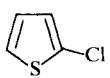
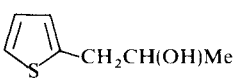
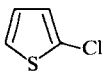
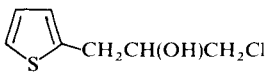
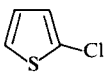
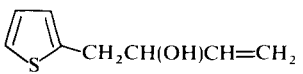
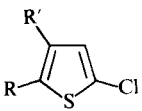
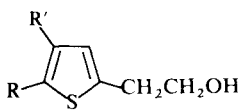
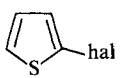
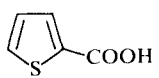
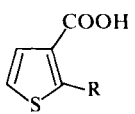
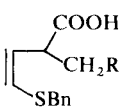
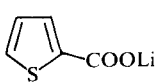
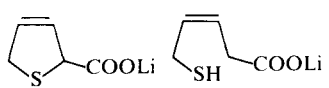
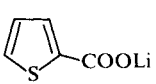
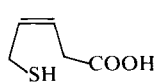
	1. BuK, heptane/DME, $-60°C$ 2. CO_2	 51 : 33		313
	1. Na, EtBr, or BuBr 2. CO_2		10–21	320
	1. Na, NH_3 (4 eq) EtOH 2. BnBr	 10 : 4  4 : 1		38
	1. Na(Hg), benzene reflux 2. $(CFCl_2)_2$		10	321
	1. Na(Hg), benzene 2. Styreneoxide		50	322
	1. Na(Hg), benzene 2. Propeneoxide		32	322

TABLE 10. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Na(Hg), benzene 2. Chloropropenoxide		32	322
	1. Na, benzene 2. Vinyloxirane		16	323
	1. Na(Hg), benezene reflux 2. Ethyleneoxide		47	319
	1. Na, 50–150°C 2. CO_2		44	319
	1. Na, NH_3 (5 eq), EtOH 2. BnBr		51–69	38
	Li, NH_3, NH_4Cl	 75% 12%		324
	1. Li, NH_3 2. MeOH		92	324

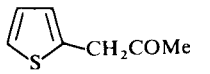
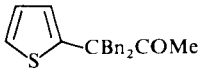
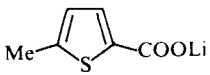
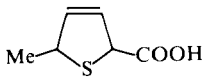
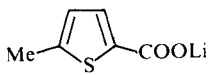
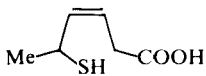
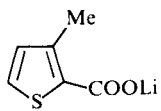
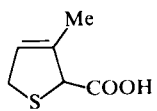
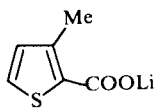
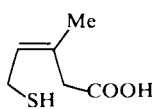
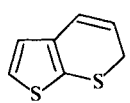
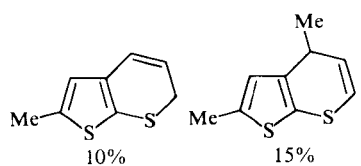
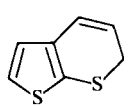
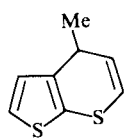
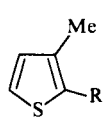
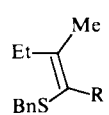
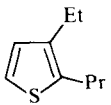
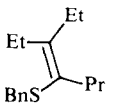
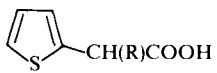
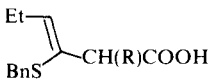
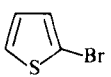
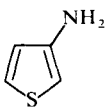
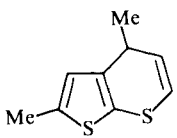
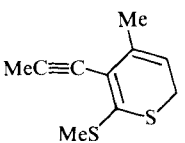
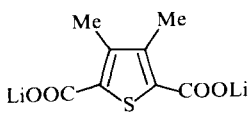
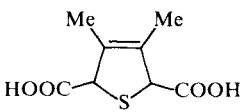
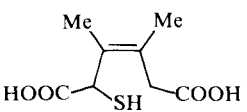
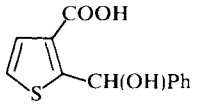
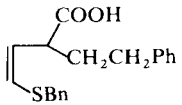
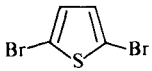
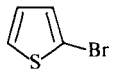
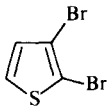
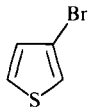
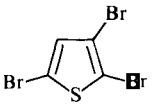
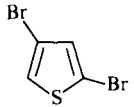
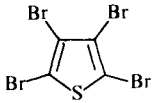
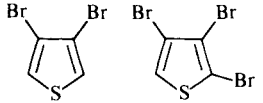
	1. Na, NH_3 (5 eq) EtOH 2. BnBr		63–77	38
	Li, NH_3, NH_4Cl			324
	1. Li, NH_3 2. MeOH		96	324
	Li, NH_3, NH_4Cl			324
	1. Li, NH_3 2. MeOH		92	324
	1. $NaNH_2(NH_3)$ 2. MeI		—[b]	172
	1. $NaNH_2(NH_3)$ 2. MeI		—[c]	172
	1. Na, NH_3 (4 eq), EtOH 2. BnBr		37–60	38

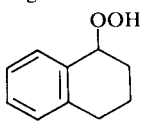
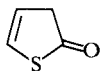
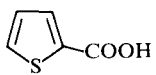
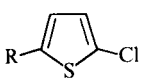
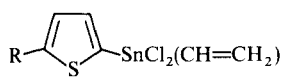
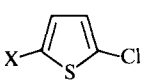
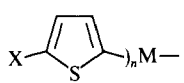
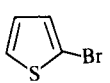
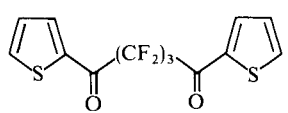
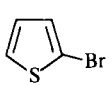
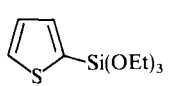
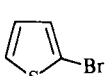
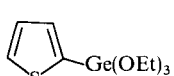
TABLE 10. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Na, NH_3 (4 eq), EtOH 2. BnBr		52	38
	1. Na, NH_3 (5 eq), EtOH 2. BnBr		63–77	38
	KNH_2, − 33°C, 60 min		60	325
	1. $KNH_2(NH_3)$ 2. MeI (− 60°C)		85	172
	Li, NH_3, NH_4Cl	 		324

	1. Na, NH_3 (5 eq), EtOH 2. BnBr		48	38
	NaOMe, DMSO		65	326
	NaOMe, DMSO		67	326
	NaOMe, DMSO		Major	326
	NaOMe, DMSO	 1 : 4		326

[a] No TMS-substituted thiophene derivative was formed.
[b] Kinetically controlled products.
[c] Thermodynamically controlled product.

TABLE 11. Reacions of 2-Thienylmagnesium Halides

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. 		5	95
	1. EtMgBr, 65 h 2. CO_2		3	327
	1. Mg 2. $CH_2{=}CHSnCl_3$		—	328
	1. Mg 2. Metal–halide derivative			329
	1. Mg 2. $HOOC(CF_2)_3COOH$		61	88
	1. Mg 2. $Si(OEt)_4$		22	330
	1. Mg 2. $Ge(OEt)_4$		< 50	330

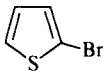
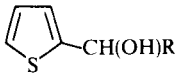
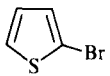
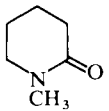
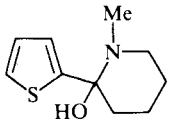
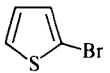
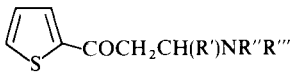
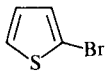
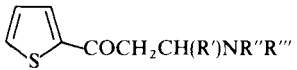
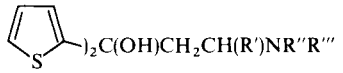
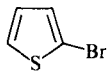
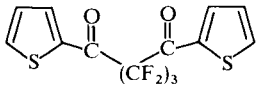
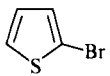
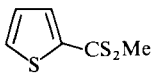
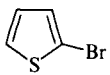
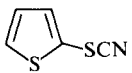
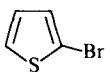
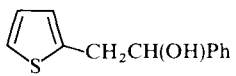
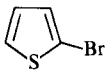
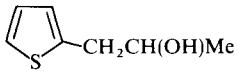
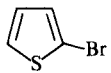
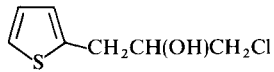
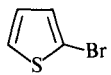
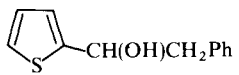
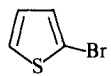
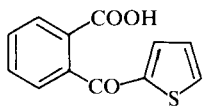
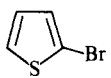
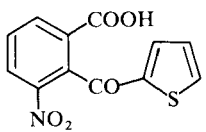
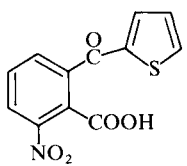
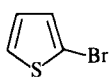
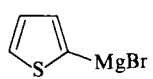
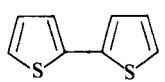
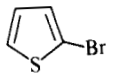
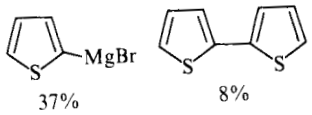
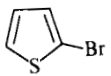
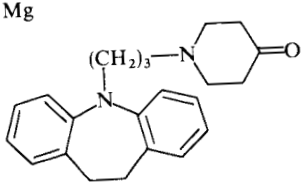
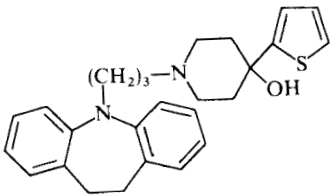
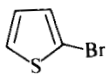
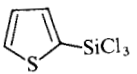
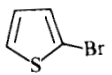
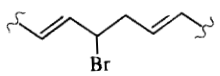
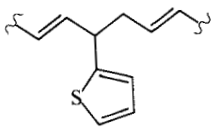
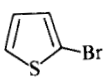
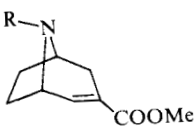
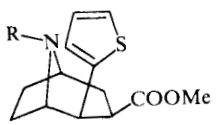
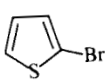
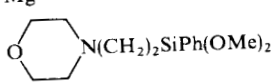
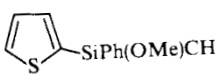
	1. Mg 2. RCHO		54–86	252
	1. Mg 2. 		43	254
	1. Mg 2. $ROOCCH_2CH(R')NR''R'''$		18	259
	1. Mg 2. 		31	259
	1. Mg 2. $ClOC(CF_2)_3COCl$		37	68
	1. Mg, THF 2. CS_2 3. MeI		68	331
	1. Mg 2. $(SCN)_2$		10–12	332
	1. Mg 2. Styrene oxide		63	322

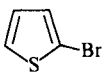
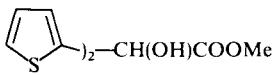
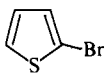
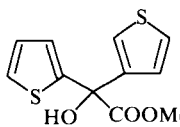
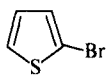
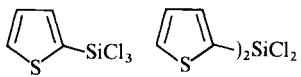
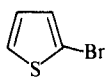
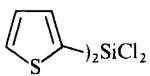
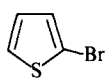
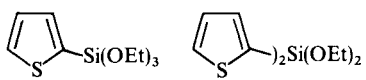
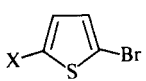
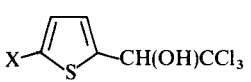
TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. Propene oxide		60	322
	1. Mg 2. 3-Chloropropene oxide		60	322
	1. Mg 2. $PhCH_2CHO$		86	322
	1. Mg 2. Phthalic anhydride		60	333
	1. Mg 2. 3-Nitrophthalic anhydride	 30%  19%		333
	Mg	 18%  3%		334

	Mg, *hv*	 37% 8%		334
	1. Mg 2. 		Good yield	335
	1. Mg 2. $SiCl_4$		—	336
	1. Mg 2. 		—	337
	1. Mg 2. 		—[a]	338
	1. Mg 2. 		52	339

[a]

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. $(COOMe)_2$		47	340
	1. Mg 2. 3-ThCOCOOMe		46	340
	1. Mg 2. $SiCl_4$	 54% 17%		341
	1. Mg 2. $SiCl_4$ 2.6 eq		40	341
	1. Mg 2. $Si(OEt)_4$	 24% 6%		341
	1. Mg 2. CCl_3CHO		50–56	342

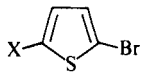
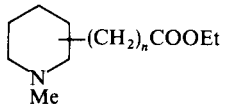
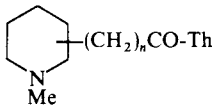
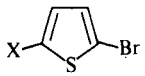
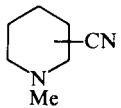
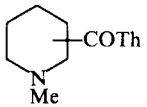
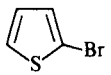
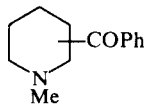
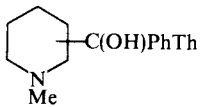
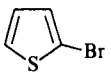
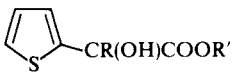
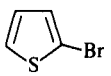
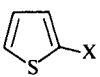
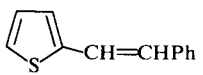
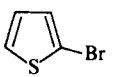
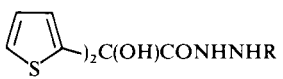
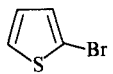
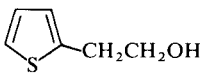
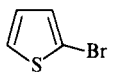
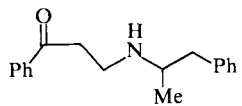
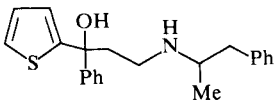
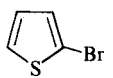
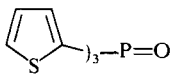
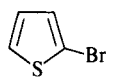
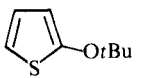
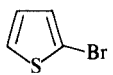
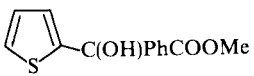
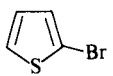
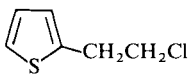
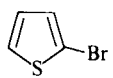
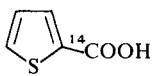
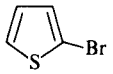
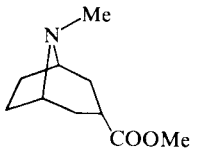
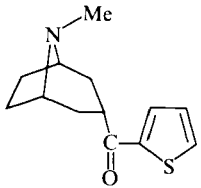
	1. Mg 2. 		50–56	343
	1. Mg 2. 		50–56	343
	1. Mg 2. 			344
	1. Mg 2. RCOCOOR′			345
	1. Mg 2. RNHNHCOCOOEt		68–99	470
	1. Mg 2. $Ni(acac)_2$ 0.2% 3. PhCH=CHBr		68–99	469
	1. Mg 2. EtOOCNHNHR		29–98	475

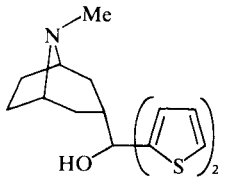
TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. Ethylene oxide		44	464
	1. Mg 2. 		67	447
	1. Mg 2. $POCl_3$		42	261
	1. Mg 2. $PhCO_3tBu$		70–76	473
	1. Mg 2. PhCOCOOMe		41	471
	1. Mg 2. $TolSO_3CH_2CH_2Cl$		60	478
	1. Mg 2. $^{14}CO_2$		75	465

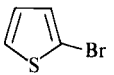


1. Mg
2. 

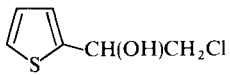

4%


8%

479

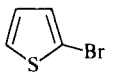


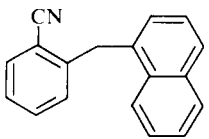
1. Mg
2. $ClCH_2CHO$

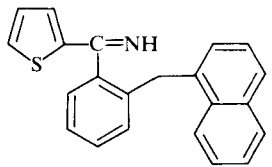


48

484

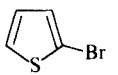


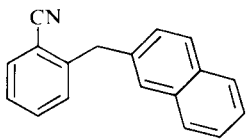
1. Mg
2. 

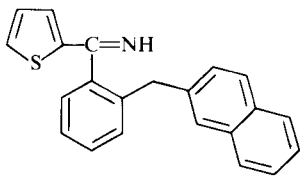


77

430

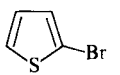


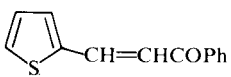
1. Mg
2. 

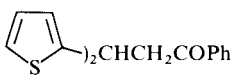


64

430

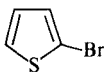
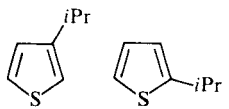
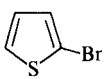
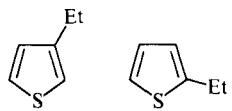
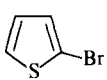
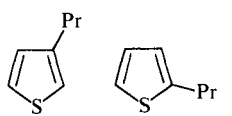
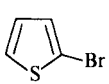
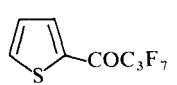
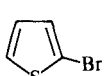
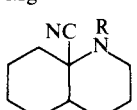
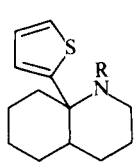


1. Mg
2. 



433

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. $PhSO_3iPr$	 45 : 55		200
	1. Mg 2. $PhSO_3Et$	 30 : 70		200
	1. Mg 2. $PhSO_3Pr$	 30 : 70		200
	1. Mg 2. C_3F_7COCl		32	437
	1. Mg 2. 		36	436

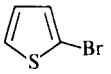
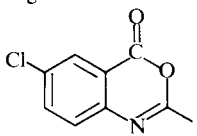
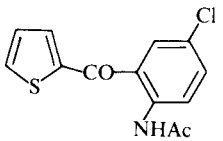
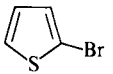
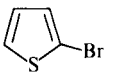
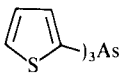
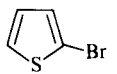
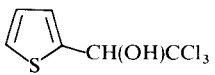
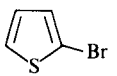
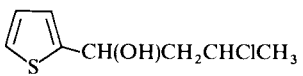
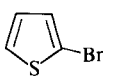
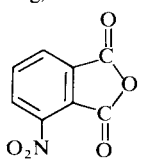
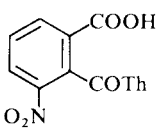
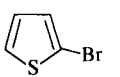
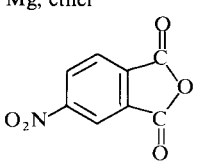
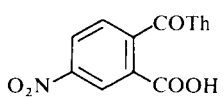
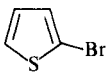
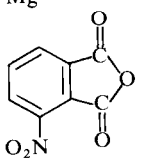
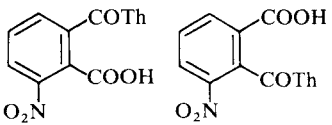
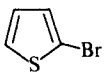
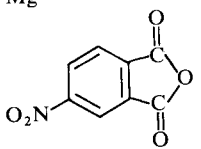
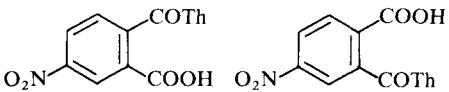
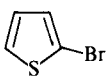
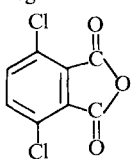
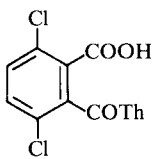
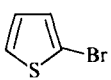
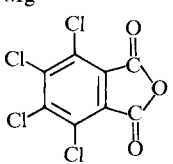
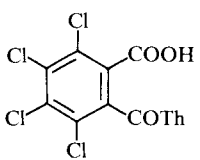
	1. Mg 2. 		50	435
	1. Mg 2. $NC(CH_2)_3NEt_2$		60	438
	1. Mg 2. $AsCl_3$		—	440
	1. Mg 2. CCl_3CHO		62	443
	1. Mg 2. $MeCH(Cl)CH_2CHO$		74	443
	1. Mg, ether 2. 		43	452
	1. Mg, ether 2. 		34	452

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. 	 31% 20%		445
	1. Mg 2. 	 33% 22%		445
	1. Mg 2. 		76	444
	1. Mg 2. 		95	444

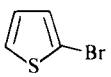
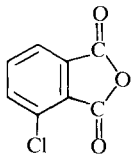
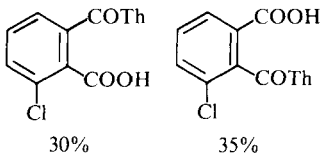
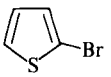
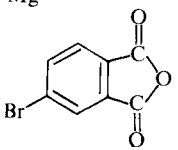
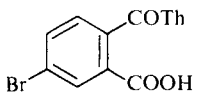
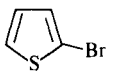
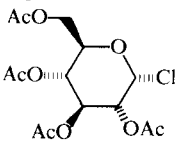
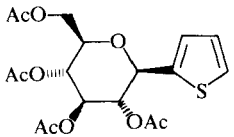
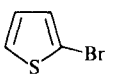
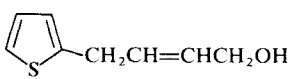
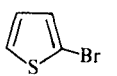
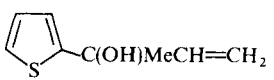
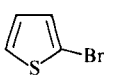
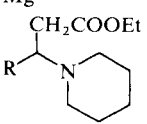
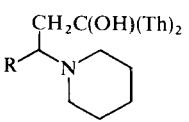
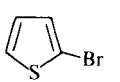
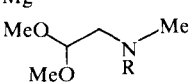
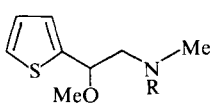
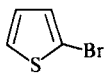
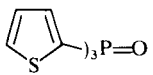
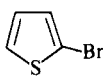
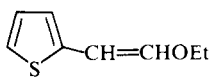
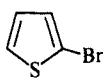
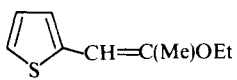
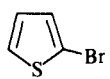
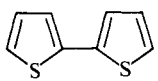
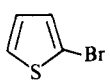
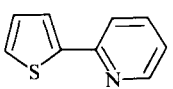
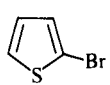
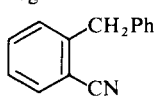
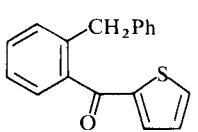
	1. Mg 2. 	 30% 35%		444
	1. Mg 2. 		42 mix	444
	1. Mg 2. 		55[b]	446
	1. Mg 2. Vinyloxirane		26	323
	1. Mg 2. Methylvinyl ketone		4.5	323
	1. Mg 2. 			448
	1. Mg 2. 		7.9–9.6	450

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. $(EtO)_2POCl$		75	449
	1. Mg, ether 2. BrCH=CHOEt, $Ni(dppp)Cl_2$		53	482
	1. Mg, ether 2. BrCH=C(Me)OEt, $Ni(dppp)Cl_2$		27	483
	1. Mg 2. $CoCl_2$ (catalyst), BuBr		25	347
	1. Mg 2. Pyridine		—	472
	1. Mg 2. 		88	270

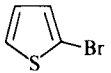
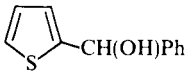
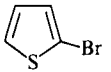
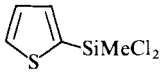
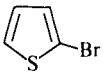
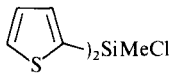
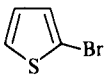
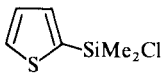
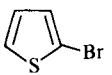
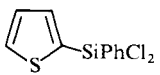
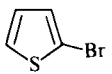
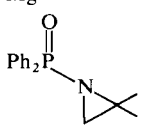
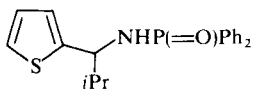
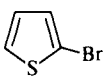
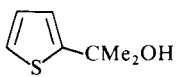
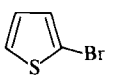
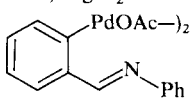
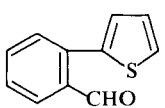
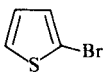
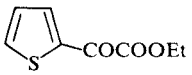
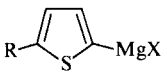
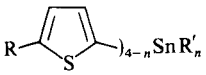
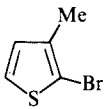
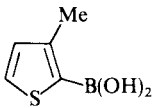
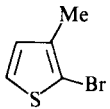
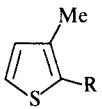
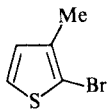
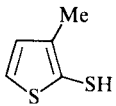
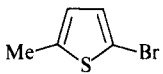
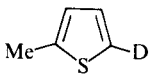
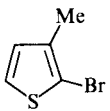
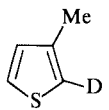
	1. Mg 2. PhCHO		75	434
	1. Mg, THF 2. $MeSiCl_3$		48	453
	1. Mg, THF 2. $MeSiCl_3$		27	453
	1. Mg, THF 2. Me_2SiCl_2		33	453
	1. Mg, THF 2. $PhSiCl_3$		56	453
	1. Mg 2. 		43	441
	1. Mg 2. Me_2CO		63	274
	1. BuLi, $MgBr_2$ 2. 		27	442

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, THF[a] 2. $(EtOOC)_2$		39	428
	R'_nSnCl_{4-n}		—[c]	461
	1. Mg 2. $B(OBu)_3$			96
	1. Mg 2. ROTs 2 eq		—[d]	38
	1. Mg 2. S		52	351
	1. Mg 2. D_2O		60	369
	1. Mg 2. D_2O		68	369

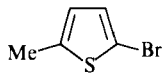
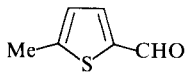
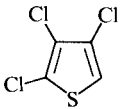
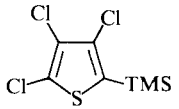
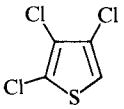
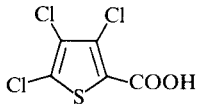
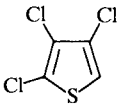
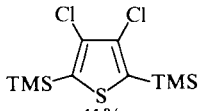
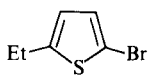
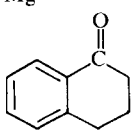
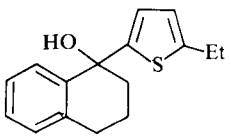
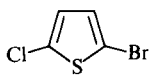
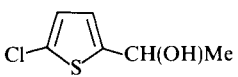
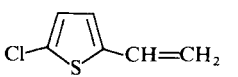
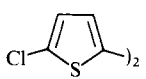
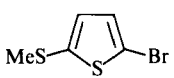
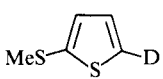
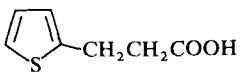
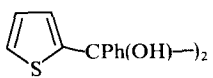
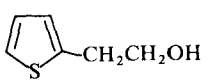
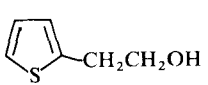
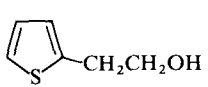
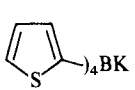
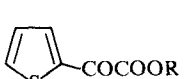
	1. Mg 2. DMF		69	269
	1. EtMgBr, 8 h 2. TMSCl		86	327
	1. EtMgBr, 8 h 2. CO_2		74	327
	1. EtMgBr 2.5 eq, 24 h 2. TMSCl	 41% 40%		327
	1. Mg 2. 		50	476
	1. Mg 2. MeCHO	  		159
	1. Mg 2. D_2O		63	369

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. $CdCl_2$, β-propiolactone		41	477
	1. Mg 2. PhCOCOPh		5.4	454
	1. Mg 2. Ethylene oxide		50	455
	1. Mg 2. Ethylene oxide		65	439
	1. Mg 2. Ethylene oxide		25	460
	1. Mg 2. KBF_4			459
	1. Mg 2. $(COOR)_2$		45–78	468
	1. Mg 2. RNHNHCOCOOEt		56–84	462

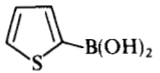
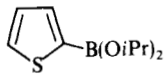
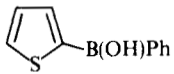
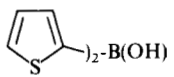
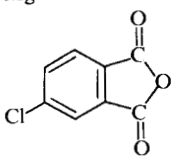
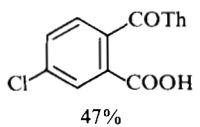
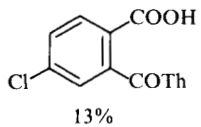
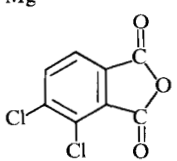
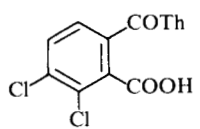
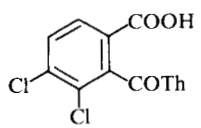
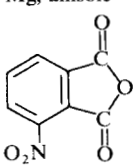
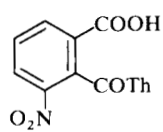
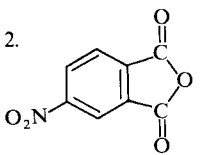
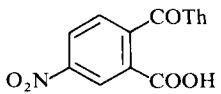
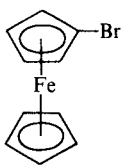
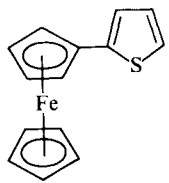
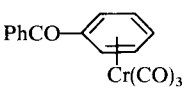
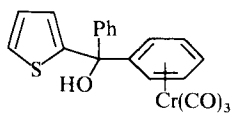
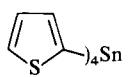
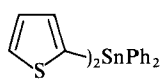
	1. Mg 2. $B(OEt)_3$		61	466
	1. Mg 2. $B(OiPr)_3$		31	466
	1. Mg 2. $PhB(OiBu)_2$		31	466
	1. Mg 2. $B(OiBu)_3$		57	466
	1. Mg 2. 	 47%  13%		444
	1. Mg 2. 	 	41 mix	444
	1. Mg, anisole 2. 		53	452

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, anisole 2. 		56	452
	1. Mg, Cu, CuBr 2. 		87	463
	1. Mg 2. 		71	458
	1. Mg 2. $SnCl_4$		90	481
	1. Mg 2. Ph_2SnCl_2		90	481

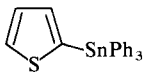
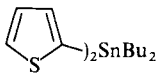
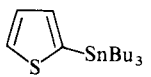
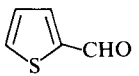
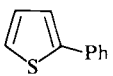
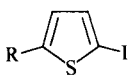
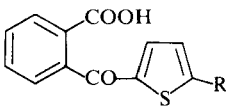
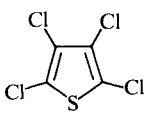
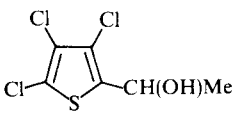
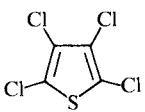
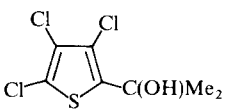
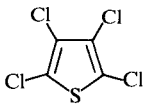
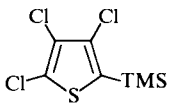
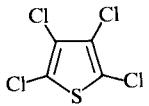
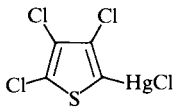
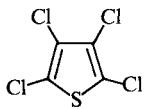
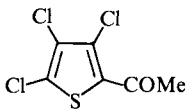
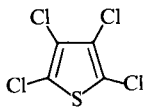
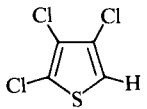
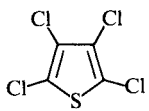
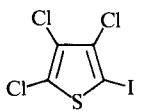
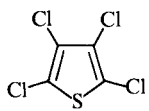
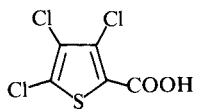
	1. Mg 2. Ph_3SnCl		90	481
	1. Mg 2. Bu_2SnCl_2		90	481
	1. Mg 2. Bu_3SnCl		90	481
	1. Mg 2. $HC(OEt)_3$		—	427
	1. Mg 2. CuI 3. PhI, quinoline > 150°C		35–50	247
	1. Mg 2. Phthalic anhydride		65–91	451
	1. Mg, EtBr 2. MeCHO		87	159
	1. Mg, EtBr 2. Me_2CO		Low yield	159

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, EtBr, THF 2. TMSCl		80	425
	1. Mg, EtBr, THF 2. $HgCl_2$		88	425
	1. Mg, EtBr, THF 2. $CdCl_2$ 3. MeCOCl		10	425
	1. Mg, EtBr, THF 2. H_2O		66	425
	1. Mg, EtBr, THF 2. I_2		65	425
	1. Mg, EtBr, THF 2. CO_2		87	425

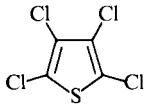
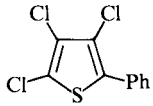
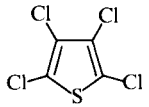
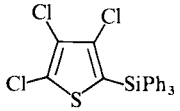
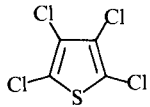
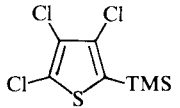
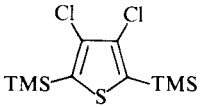
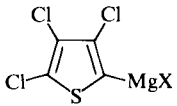
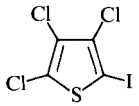
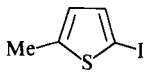
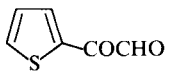
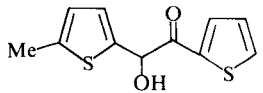
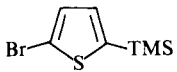
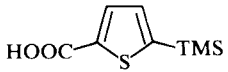
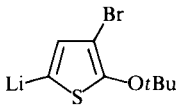
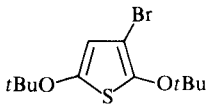
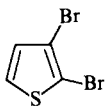
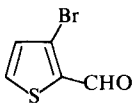
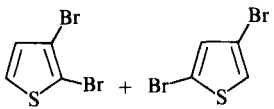
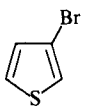
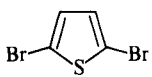
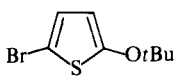
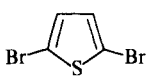
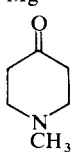
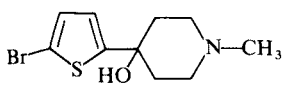
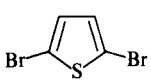
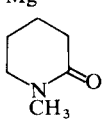
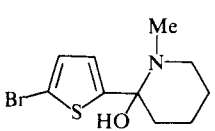
	1. Mg, EtBr, THF 2. PhI		0	425
	1. Mg, EtBr, THF 2. Ph_3SiCl		38	425
	1. Mg, EtBr, 2 eq, THF 2. TMSCl	 50–55%  25–30%		425
	1. Mg 2. $CuCl_2$ (catalyst), I_2		85	480
	1. Mg 2. 		28	77
	1. Mg 2. CO_2		—	456
	1. $MgBr_2$ 2. $PhCO_3tBu$		90	154

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, EtBr 2. DMF		73	467
	1. Mg, EtBr 2. H_2O		80	187
	1. Mg 2. $PhCO_3tBu$		64	96
	1. Mg 2. 		20	254
	1. Mg 2. 		37	254

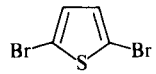
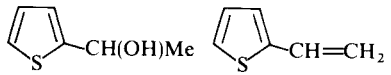
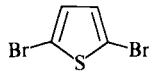
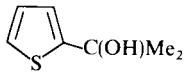
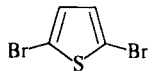
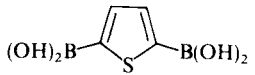
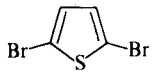
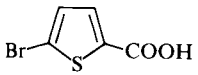
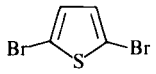
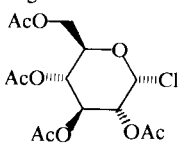
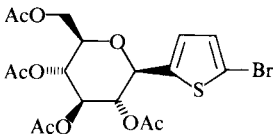
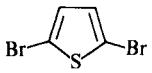
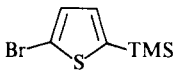
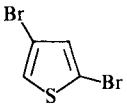
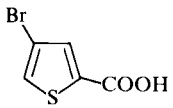
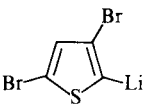
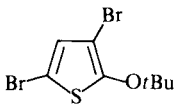
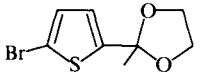
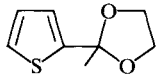
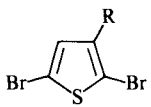
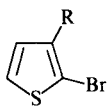
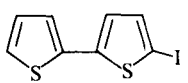
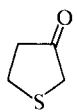
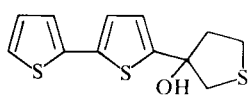
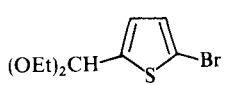
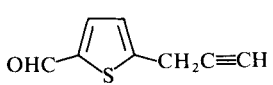
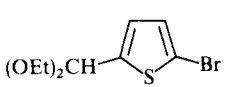
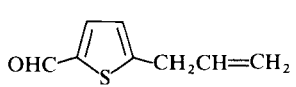
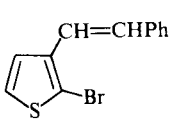
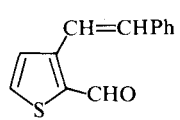
	1. Mg 2. MeCHO			159
	1. Mg 2. Me_2CO		> 53	159
	1. Mg, THF 2. $B(OMe)_3$		62	188
	1. Mg excess, ether reflux 2. CO_2		59	446
	1. Mg 2. 		47[e]	446
	1. Mg 2. TMSCl		50	456
	1. Mg, EtBr 2. CO_2		51	135
	1. $MgBr_2$ 2. $PhCO_3tBu$		95	154

TABLE 11. *(Continued)*

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, THF 2. H_2O		64	457
	1. EtMgBr 2. H_2O			29
	1. Mg 2. 		80	431
	1. Mg, THF 2. Propargyl bromide		—	474
	1. Mg, THF 2. Allyl bromide		—	474
	1. Mg, THF 2. DMF		55	409

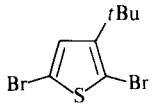
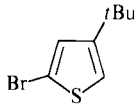
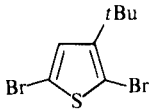
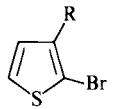
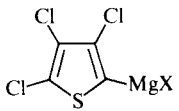
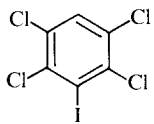
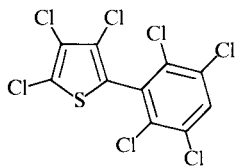
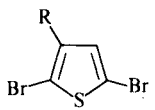
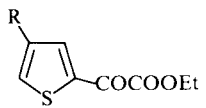
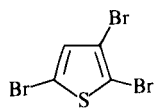
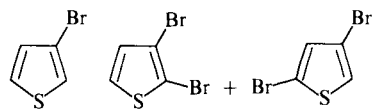
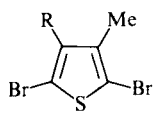
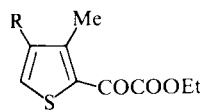
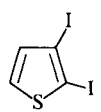
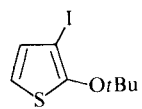
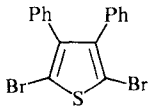
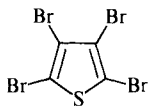
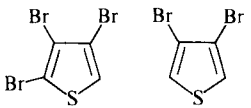
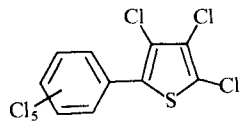
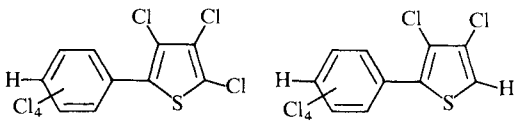
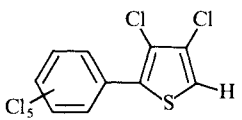
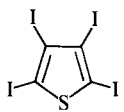
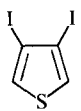
	1. EtMgBr 2. H_2O		Major	29
	1. Mg 2. H_2O			29
	1. CuCl 2. 		56	429
	1. Mg 2. $(EtOOC)_2$		27–37	432
	1. Mg, EtBr 2.5 eq 2. H_2O	 51% 24%		187
	1. Mg 2. $(EtOOC)_2$		32–35	432
	1. EtMgBr 2. $PhCO_3tBu$		30	277

TABLE 11. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. $(EtOOC)_2$		No reaction	432
	1. Mg, EtBr 2. H_2O	 44% 29%		136
	1. Mg 2. H_2O	 		149
	1. EtMgBr, THF 2. H_2O		72	382

[a] R = Me 49%, R = Bn 26%. No α-epimers were formed.
[b] 18% α-isomer.
[c] R = H, Cl; R′ = various aryl groups.
[d] R = Bu, Oct.
[e] 9% α-isomer.

TABLE 12. Reactions of 3-Thienylmagnesium Halides

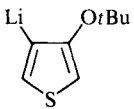
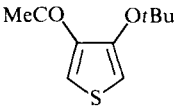
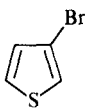
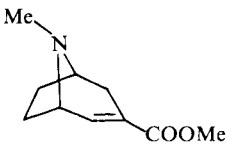
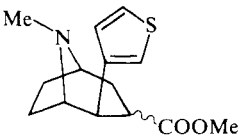
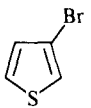
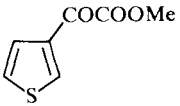
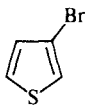
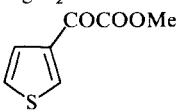
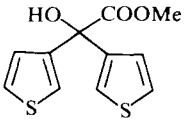
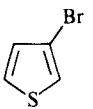
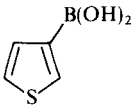
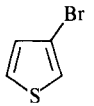
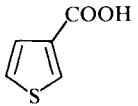
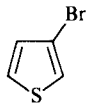
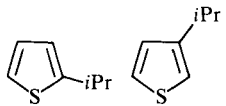
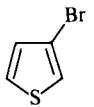
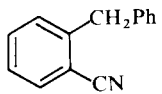
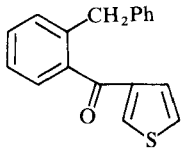
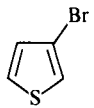
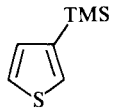
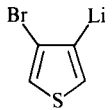
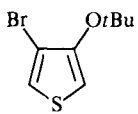
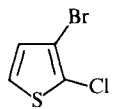
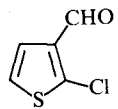
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $MgBr_2$ 2. Ac_2O		70	66
	1. Mg, EtBr 2. 		66	338
	1. EtLi 2. $MgBr_2$ 3. $(COOMe)_2$		—	340
	1. EtLi 2. $MgBr_2$ 3. 		29	340
	1. Mg, MeI 2. $B(OBu)_3$		22	140

TABLE 12. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, EtBr 2. CO_2		56	187
	1. Mg 2. $PhSO_3iPr$	 50% 50%		200
	1. Mg, EtBr 2. 		58	270
	1. Mg, EtBr 2. TMSCl		54	487
	1. $MgBr_2$ 2. $PhCO_3tBu$		63	66
	1. Mg, 1,2-dibromoethane 2. DMF		33	488

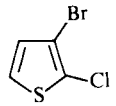
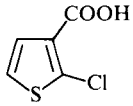
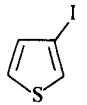
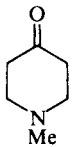
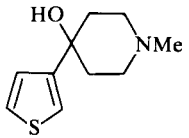
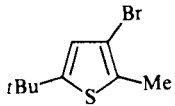
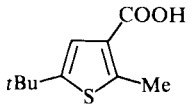
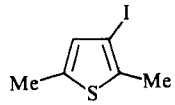
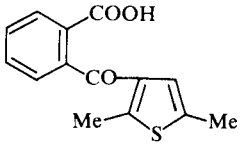
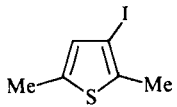
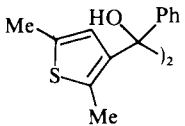
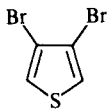
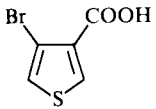
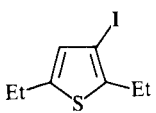
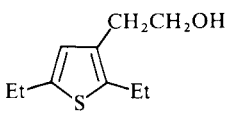
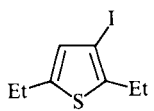
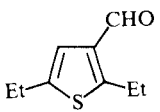
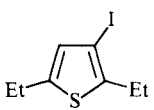
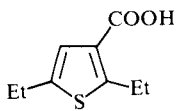
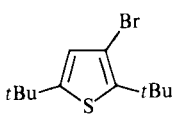
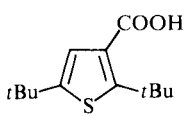
	1. Mg, 1,2-dibromoethane 2. CO_2		87	488
	1. Mg 2. 		17	254
	1. Mg, EtBr 2. CO_2		62	486
	1. Mg 2. Phthalic anhydride		62	451
	1. Mg, ether/benzene 2. PhCOCOPh		13	454
	1. Mg, EtBr 2. CO_2		38	136

TABLE 12. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, EtBr 2. Ethylene oxide		54	485
	1. Mg, EtBr 2. $HC(OEt)_3$		51	485
	1. Mg, EtBr 2. CO_2		Low yield	485
	1. Mg, EtBr 2. CO_2		57	486

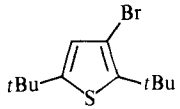
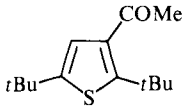
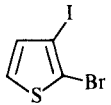
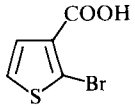
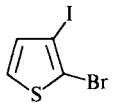
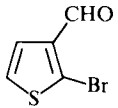
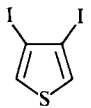
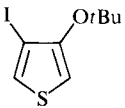
	1. Mg, EtBr 2. Ac_2O		31	486
	1. Mg, 1,2-dibromoethane 2. CO_2		81	488
	1. Mg, 1,2-dibromoethane 2. DMF		60	488
	1. EtMgBr 2. $PhCO_3tBu$		72	277

TABLE 13. Calcium and Strontium Derivatives

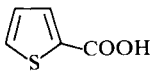
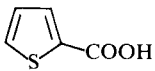
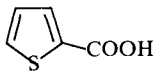
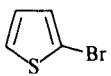
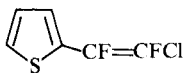
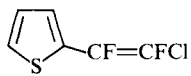
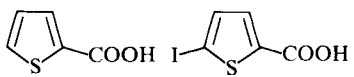
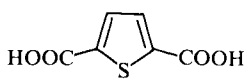
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. PhCaI·DABCO 2. CO_2		10	489
	1. MeCaI 2. CO_2		34	490
	1. MeCaI, $-30°C \rightarrow$ room temp., THF 2. CO_2		21	150
	1. Ca(Hg) 2. $CF_2{=}CFCl$		33	45
	1. Sr 2. $CF_2{=}CFCl$		8	45
	1. Ca, THF, 0–35°C 2. CO_2	 		150

TABLE 14. Boron Derivatives

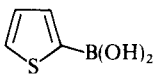
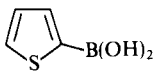
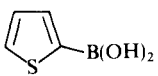
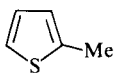
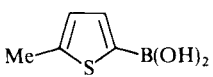
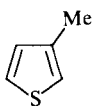
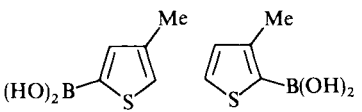
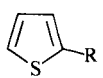
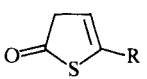
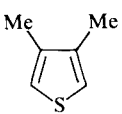
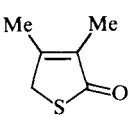
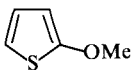
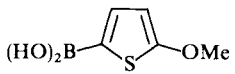
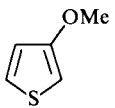
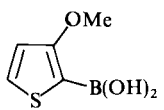
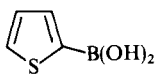
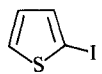
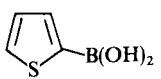
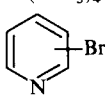
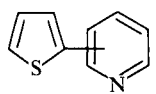
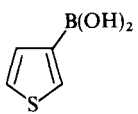
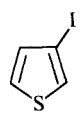
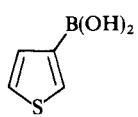
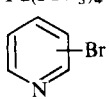
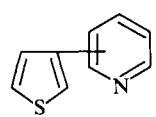
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $B(OBu)_3$			96
	1. BuLi 2. $B(OBu)_3$		32	97
	1. BuLi 2. $B(OBu)_3$		32	491
	1. BuLi 2. $B(OBu)_3$			96
	1. BuLi 2. $Bu(OBu)_3$	 84% 16%		96
	1. BuLi 2. $B(OBu)_3$, H_2O_2		30–66	274
	1. BuLi 2. $B(OBu)_3$, H_2O_2		46	275

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $B(OBu)_3$		72	96
	1. BuLi 2. $B(OBu)_3$		80	96
	1. KI, I_2 2. MeOH, H_2O			493
	1. $Pd(PPh_3)_4$ 2. 		57–67	494
	1. KI, I_2 2. MeOH, H_2O			493
	1. $Pd(PPh_3)_4$ 2. 		70	494

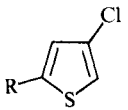
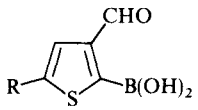
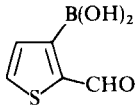
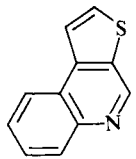
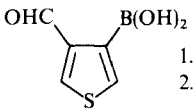
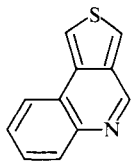
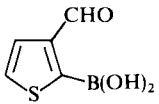
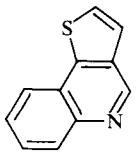
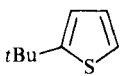
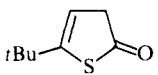
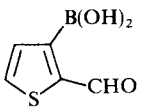
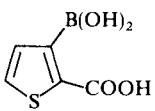
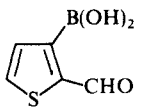
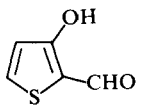
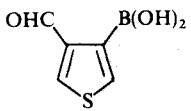
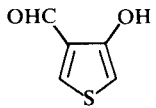
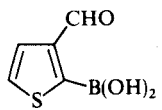
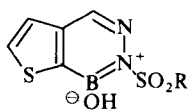
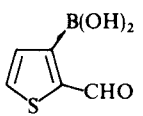
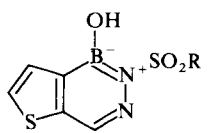
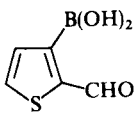
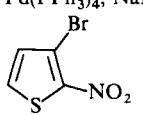
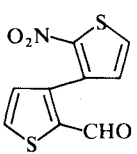
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		18–32	100
	1. *o*-Bromoacetanilid, Pd(0), DMF 2. HCl		44	503
	1. *o*-Bromoacetanilid, Pd(0), DMF 2. HCl		71	503
	1. *o*-Bromoacetanilid, Pd(0), DMF 2. HCl		38	503
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		62	279
	$NaOH, Ag_2O, AgNO_2$		29	492

TABLE 14. *(Continued)*

Starting Material	Reagent	Product	Yield (%)	Ref.
	H_2O_2, OH^-		62	492
	H_2O_2, OH^-			492
	RSO_2NHNH_2			502
	RSO_2NHNH_2		—	502
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		82	504

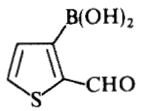
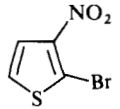
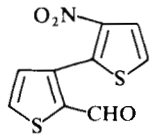
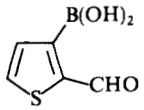
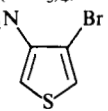
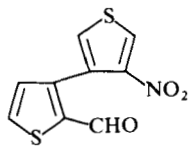
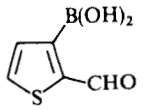
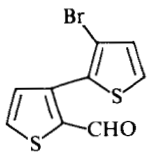
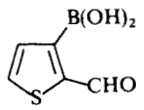
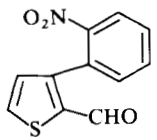
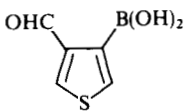
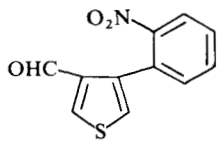
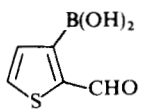
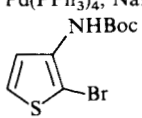
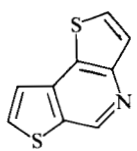
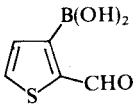
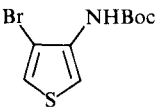
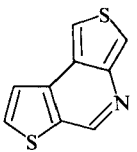
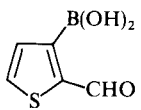
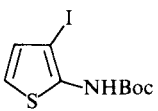
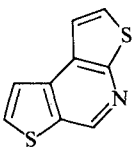
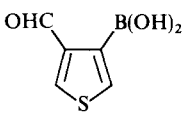
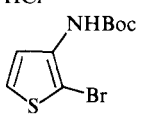
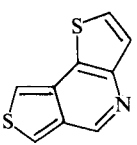
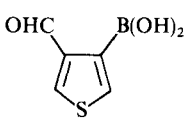
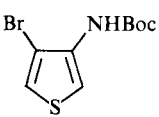
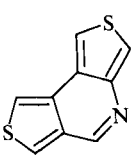
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		81	504
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		53	504
	2,3-Dibromothiophene, $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane		65	504
	*o*-Bromonitrobenzene $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane		54	536
	*o*-Bromonitrobenzene, $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane		72	536
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		81	189

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. HCl 3. 		67	189
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. HCl 3. 		50	189
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. HCl 3. 		88	189
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. HCl 3. 		65	189

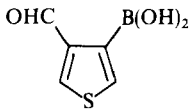
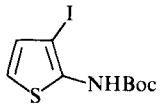
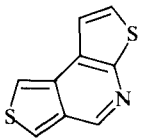
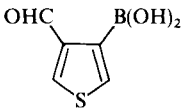
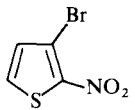
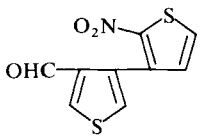
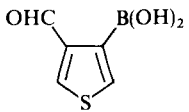
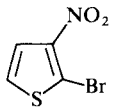
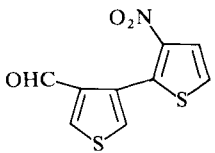
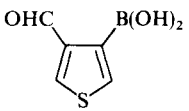
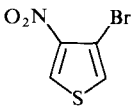
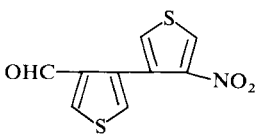
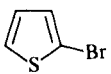
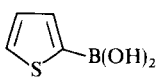
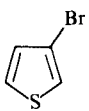
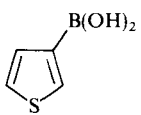
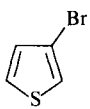
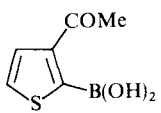
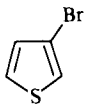
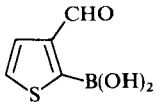
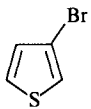
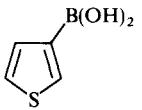
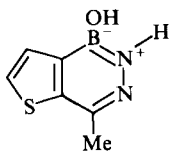
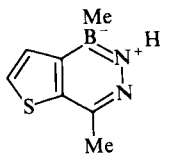
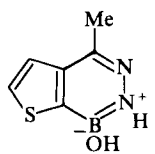
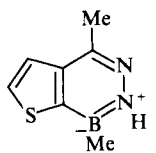
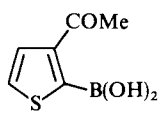
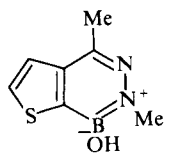
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. HCl 3. 		65	189
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		58	504
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		84	504
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		65	504
	1. BuLi 2. $B(OBu)_3$		62	140
	1. BuLi 2. $B(OBu)_3$		57	140
	1. EtLi 2. DMA 3. EtLi 4. $B(OBu)_3$		13	100

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		44	143
	1. Mg, MeI 2. $B(OBu)_3$		22	140
	1. BuOH 2. MeMgBr		62	500
	1. BuOH 2. MeMgBr		62	500
	H_2NNHMe		87	500

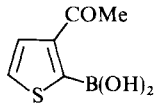
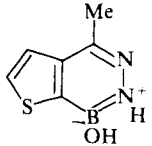
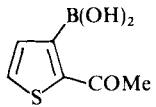
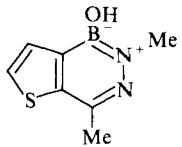
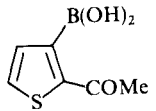
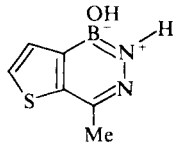
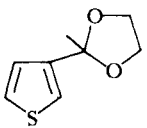
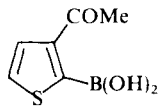
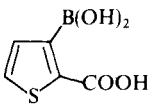
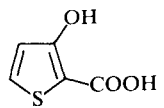
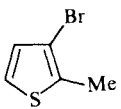
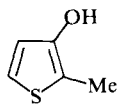
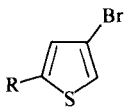
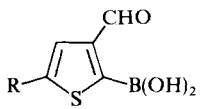
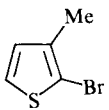
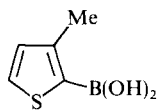
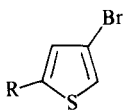
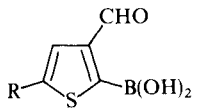
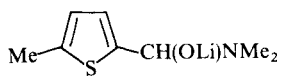
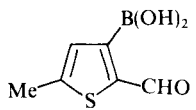
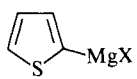
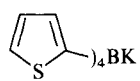
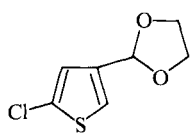
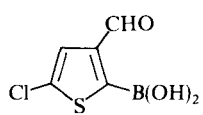
	H_2NNHH_2		86	500
	H_2NNHMe		87	500
	H_2NNH_2		88	500
	1. EtLi 2. $B(OBu)_3$		20	100
	H_2O_2, OH^-		54	492
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		49	401

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		18–32	100
	1. Mg 2. $B(OBu)_3$			96
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		18–32	100
	1. EtLi 2. $B(OBu)_3$		28	100
	KBF_4			496
	1. EtLi 2. $B(OBu)_3$		39	100

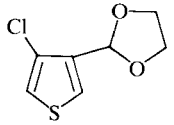
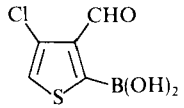
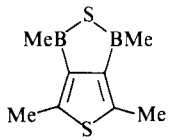
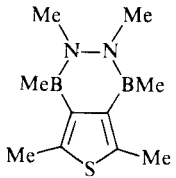
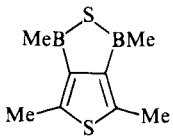
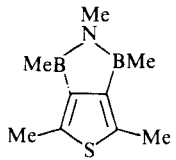
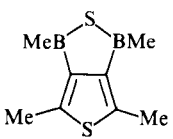
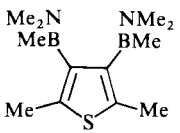
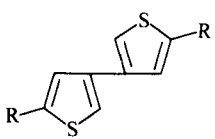
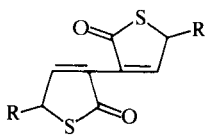
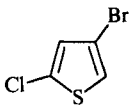
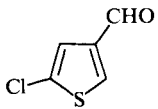
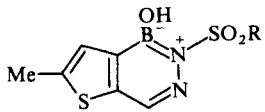
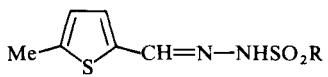
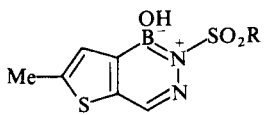
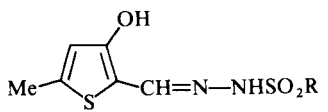
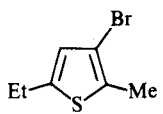
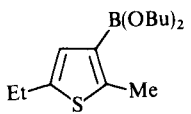
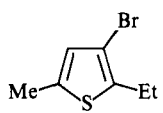
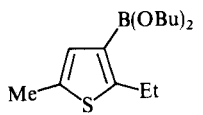
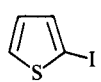
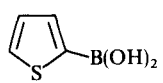
	1. BuLi 2. $B(OBu)_3$		50	100
	MeNHNHMe		84	499
	CH_3NH_2		68	499
	Me_2NH		60	499
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		15–17	279

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $B(OBu)_3$		70	100
	NaOH		—	495
	H_2O_2		100	495
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. Mg 2. $B(OEt)_3$		61	466

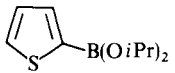
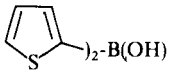
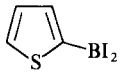
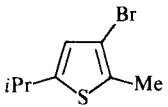
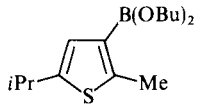
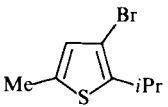
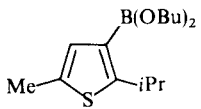
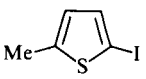
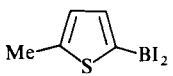
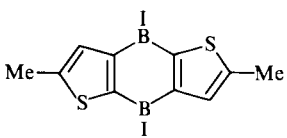
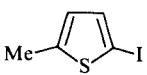
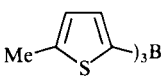
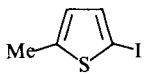
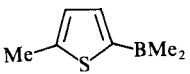
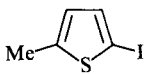
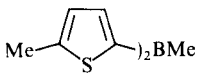
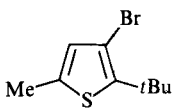
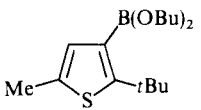
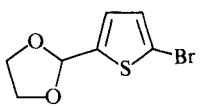
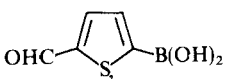
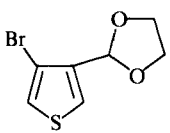
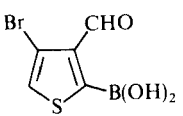
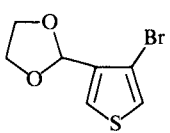
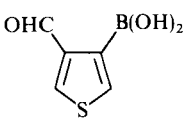
	1. Mg 2. $B(OiPr)_3$		31	466
	1. Mg 2. $B(OiBu)_3$		57	466
	BI_3		Unstable	501
	1. EtLi 2. $B(OBu)_3$		Not isolated	353
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	BI_3			501
				
	BI_3		60	501

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	Me_2BI		60	501
	$MeBI_2$		57	501
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. BuLi 2. $B(OBu)_3$		57	156
	1. LDA 2. $B(OEt)_3$		65	21
	1. BuLi, $-70°C$ 2. $B(OBu)_3$		49	156

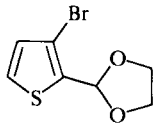
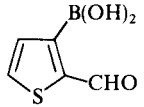
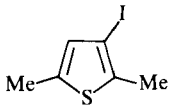
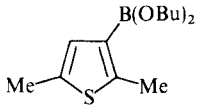
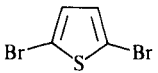
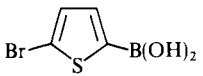
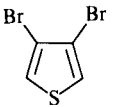
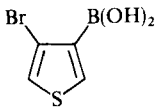
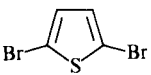
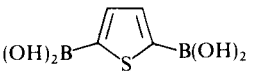
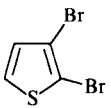
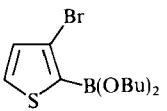
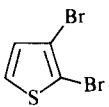
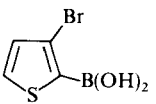
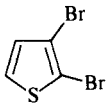
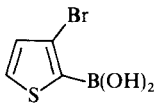
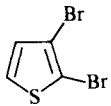
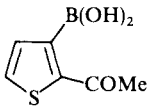
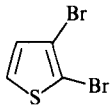
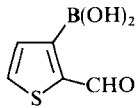
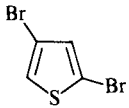
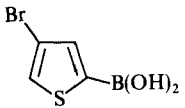
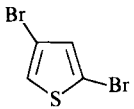
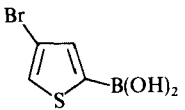
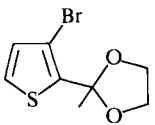
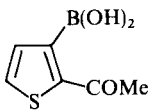
	1. BuLi, – 70°C 2. $B(OBu)_3$		66	156
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	1. BuLi 2. $B(OBu)_3$		58	140
	1. BuLi 2. $B(OBu)_3$		55	140
	1. Mg, THF 2. $B(OMe)_3$		62	188
	1. EtLi, ether 2. $B(OBu)_3$		—	362
	1. BuLi 2. $B(OBu)_3$		80	96

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $B(OBu)_3$		51	140
	1. EtLi 2. DMA 3. BuLi 4. $B(OBu)_3$		35	100
	1. EtLi 2. DMF 3. EtLi 4. $B(OBu)_3$		35	143
	1. BuLi 2. $B(OBu)_3$		80	96
	1. BuLi 2. $B(OBu)_3$		56	140
	1. BuLi, $-70°C$ 2. $B(OBu)_3$		32	100

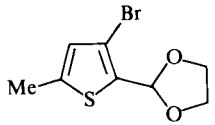
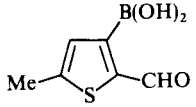
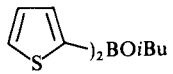
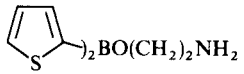
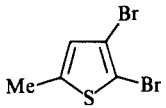
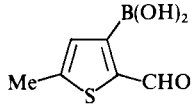
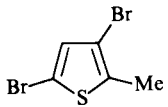
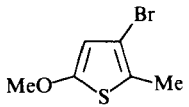
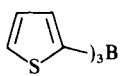
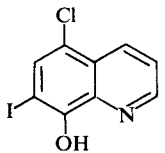
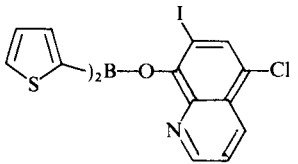
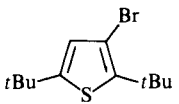
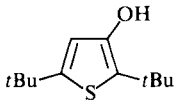
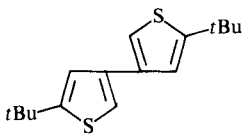
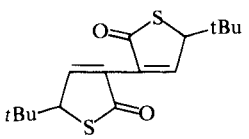
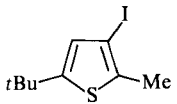
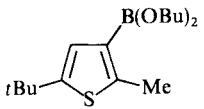
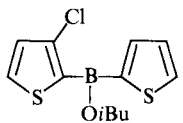
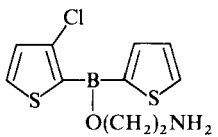
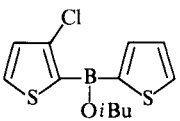
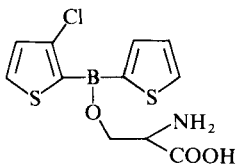
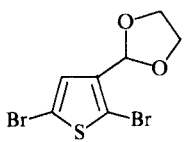
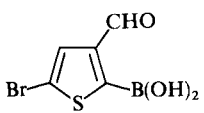
	1. EtLi 2. $B(OBu)_3$		25	100
	$HO(CH_2)_2NH_2$			497
	1. BuLi 2. DMF 3. BuLi 4. $B(OBu)_3$		28	100
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2 4. DMS		32	145
				497
	1. EtLi, $-70°C$ 2. $B(OEt)_3$			411

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $B(OBu)_3$ 3. H_2O_2		15	279
	1. EtLi 2. $B(OEt)_3$		Not isolated	353
	$HO(CH_2)_2NH_2$			99
	Serine			99
	1. BuLi 2. $B(OEt)_3$		95	21

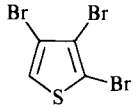
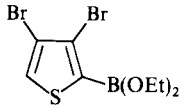
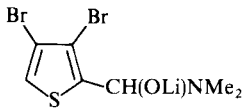
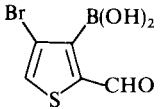
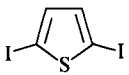
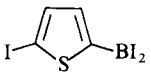
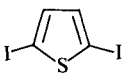
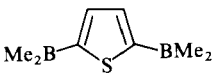
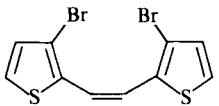
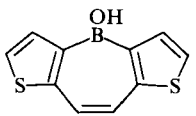
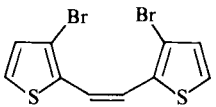
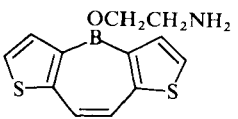
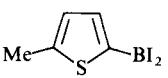
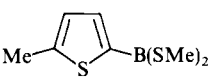
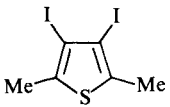
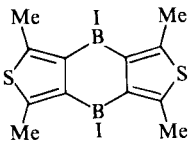
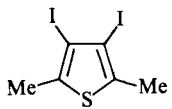
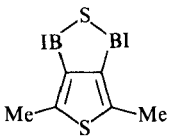
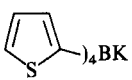
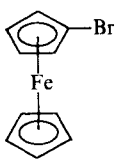
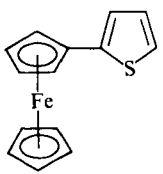
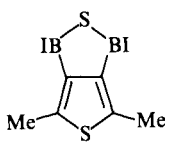
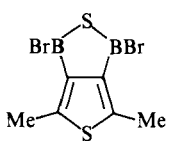
	1. BuLi 2. $B(OEt)_3$		—	21
	1. BuLi 2. $B(OEt)_3$		65	21
	BI_3		Unstable	501
	Me_2BI		67	501
	1. EtLi 2. $B(OEt)_3$		25	417
	1. BuLi 2. Et_2NBCl_2 3. $HOCH_2CH_2NH_2$		85	418
	MeSSMe		54	501

TABLE 14. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BI_3 2. 80–85°C		97	499
	BI_3, S		93	499
	1. Cu_2Br_2, 125–130°C 2. 		81	498
	Br_2		77	499

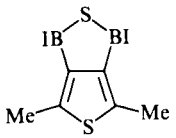
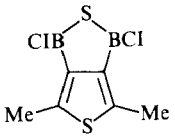
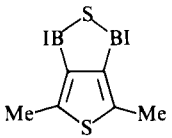
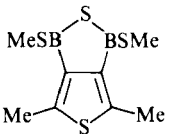
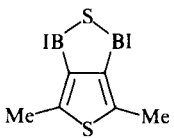
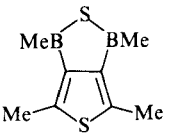
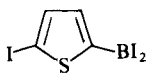
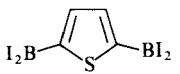
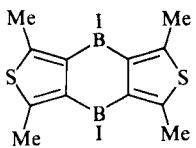
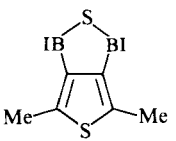
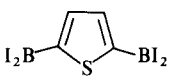
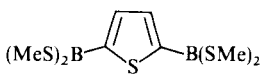
	ICl		59	499
	$(CH_3S)_2$		96	499
	$(CH_3)_4Sn$		88	499
	BI_3		82	501
	$(IBS)_3$		79	499
	MeSSMe		—	501

TABLE 15. Al, Ga, In, and Tl-Derivatives

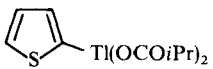
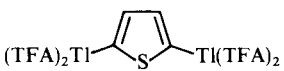
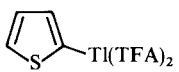
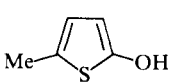
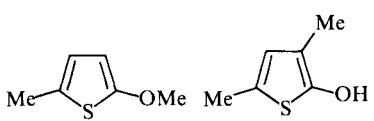
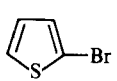
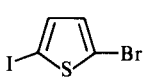
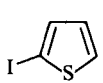
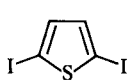
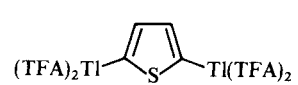
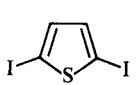
Starting Material	Reagent	Product	Yield (%)	Ref.
	$Tl(OOCiPr)_3$		88	505
	$Tl(TFA)_3$, CH_3CN			507
	$Tl(TFA)_3$, CH_3CN		82	508
	1. TlOEt 2. MeI, or DMS		—[a]	579
	1. $Tl(TFA)_3$ 2. KI			506
	1. $Tl(TFA)_3$, MeCN 2. I^-		44	507
	I^-, H_2O			507

TABLE 16. Si Derivatives

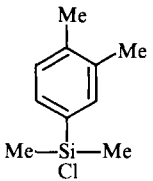
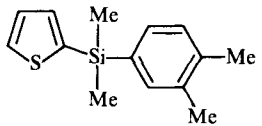
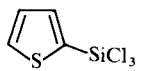
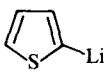
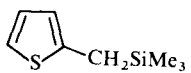
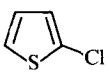
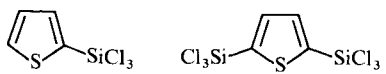
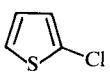
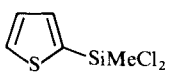
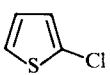
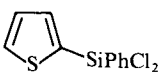
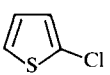
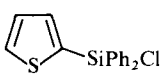
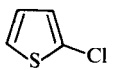
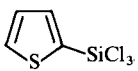
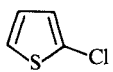
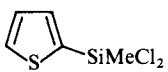
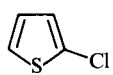
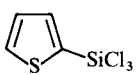
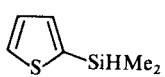
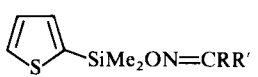
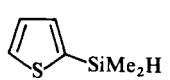
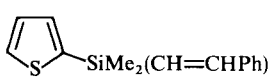
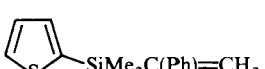
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, ether 2. 		36	251
	$HSiCl_3$, 600°C, FVP		18	528
	$TMSCH_2Br$			521
	$HSiCl_3$, 570°C, FVP	 67% 6%		528
	$MeSiHCl_2$, FVP		58	528
	$PhSiHCl_2$, FVP		45	528
	Ph_2SiHCl, FVP		20	528

TABLE 16. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$HSiCl_3$, Pd, 300°C			523
	$MeSiHCl_2$, Pd, 300°C			523
	$CH{=}CHSiCl_3$, 600°C, FVP		9	534
	$HON{=}CRR_1$			514
	1. H_2PtCl_6, 50°C, 6 h 2. $PhC{\equiv}CH$	 73%  27%	89	519

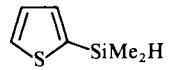
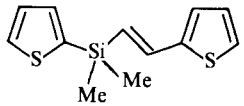
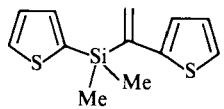
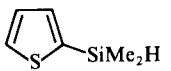
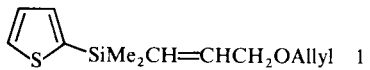
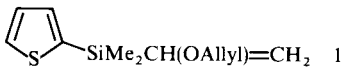
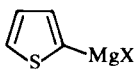
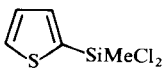
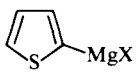
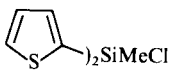
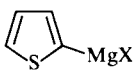
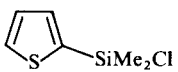
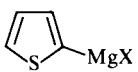
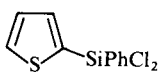
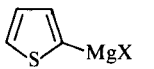
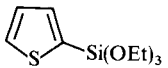
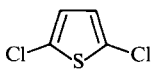
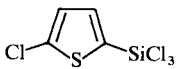
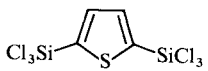
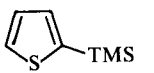
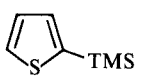
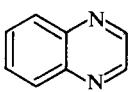
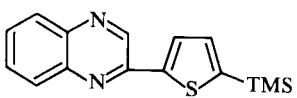
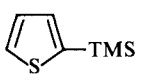
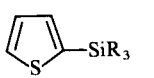
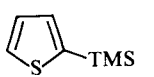
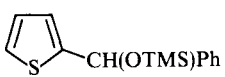
	1. H_2PtCl_6, 50°C, 6 h 2. 2-ThC≡CH	 30 %  70 %	64	519
	1. $H_2PtCl_6 : 6H_2O$ 2. HC≡CCH$_2$O Allyl	 1  1		522
	$MeSiCl_3$		48	453
	$MeSiCl_3$		27	453
	Me_2SiCl_2		33	453
	$PhSiCl_3$		56	453

TABLE 16. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$(EtO)_4Si$, 300°C		Low yield	525
	$HSiCl_3$, FVP	 26%  60%		528
	HCl, HOAc	TMSCl 37% 87%		518
	1. BuLi 2. 		4	287
	MeOH, $HClO_4$			529
	NaOMe, MeOH		—[a]	531
	1. *t*BuOK (2%), DMF 2. PhCHO		80	520

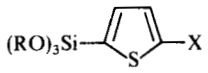
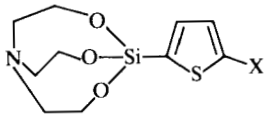
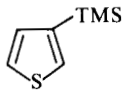
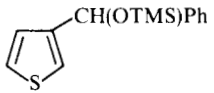
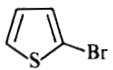
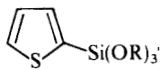
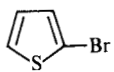
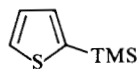
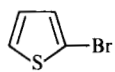
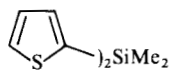
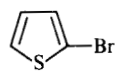
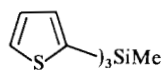
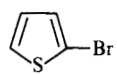
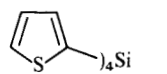
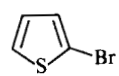
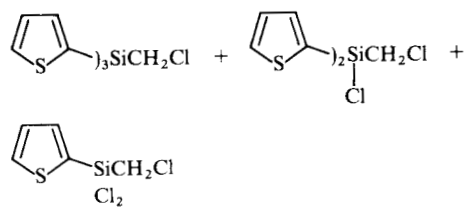
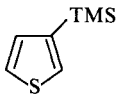
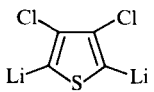
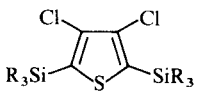
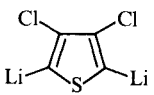
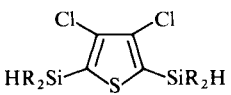
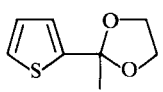
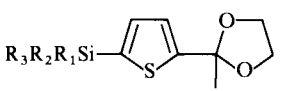
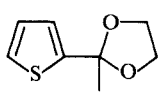
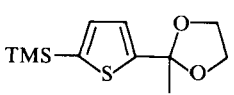
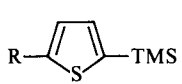
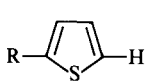
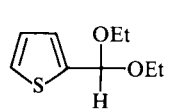
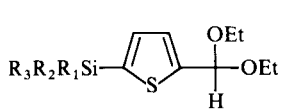
	$N(CH_2CH_2OH)_3$		75–90	533
	1. CsF, HMPA, 100°C 2. PhCHO		42	520
	1. Mg, $SiCl_4$ 2. ROH			336
	1. Mg 2. $ClSiMe_3$		72	511
	1. Mg 2. Cl_2SiMe_2		58	511
	1. Mg 2. Cl_3SiMe		9	511
	1. Mg 2. $Si(OEt)_4$ or $SiCl_4$		8	511
	1. Mg 2. Cl_3SiCH_2Cl			515

TABLE 16. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg, EtBr 2. Me_3SiCl		54	487
	R_3SiCl		80	185
	HR_2SiCl		82	185
	1. BuLi 2. $R_1R_2R_3SiCl$		49–96	292
	1. BuLi, ether 2. Me_3SiCl		96	530
	$HClO_4$, MeOH, H_2O or H_2SO_4, HOAc, H_2O			510
	1. BuLi 2. $R_1R_2R_3SiCl$		49–96	292

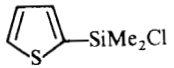
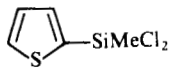
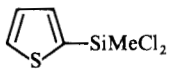
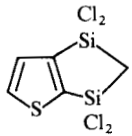
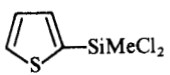
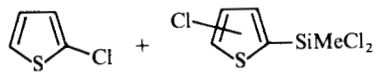
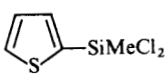
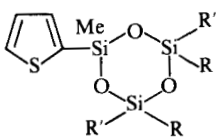
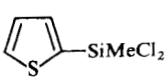
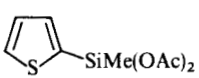
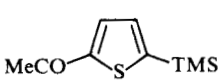
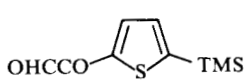
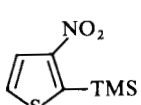
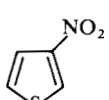
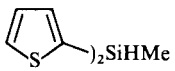
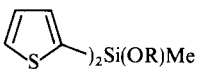
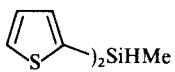
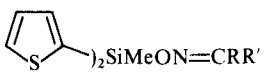
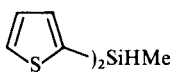
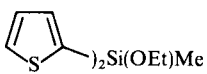
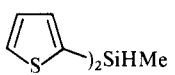
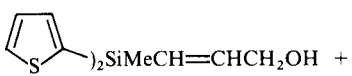
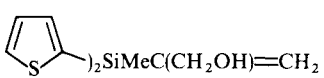
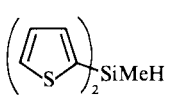
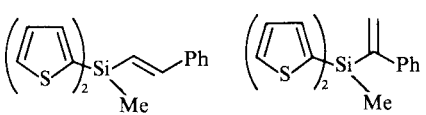
	H_2O, ether		Polymers	524
	H_2O, ether		Polymers	524
	$(SiCl_3)_2$, pyrolysis		17	532
	Cl_2			509
	$HO(SiORR')_nH$, pyridine			513
	Ac_2O		90	513
	SeO_2		40–70	287
	$HClO_4$, MeOH, H_2O or H_2SO_4, HOAc, H_2O			510

TABLE 16. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	ROH, amine			512
	$HON{=}CRR_1$			514
	EtOH		74	516
	1. H_2PtCl_6 2. $HC{\equiv}CCH_2OH$	 		516
	1. H_2PtCl_6, 50°C, 6 h 2. $PhC{\equiv}CH$	 71 % 29 %	89	519

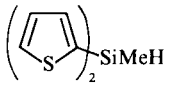
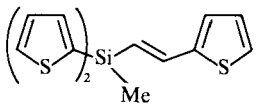
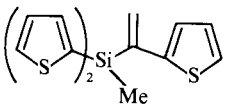
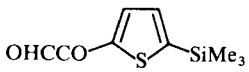
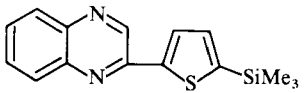
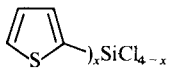
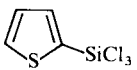
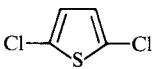
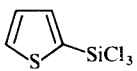
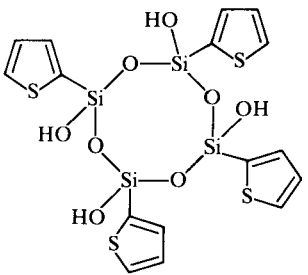
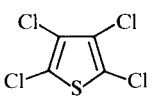
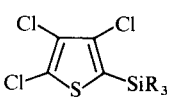
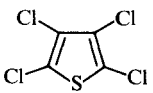
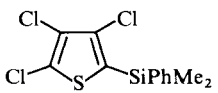
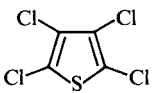
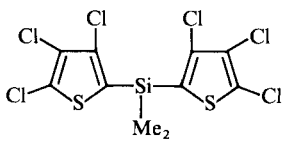
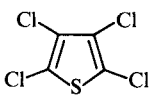
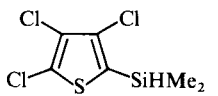
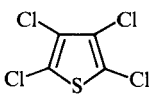
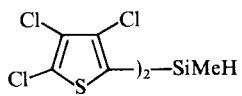
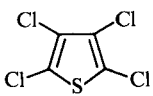
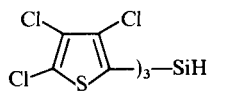
	1. H_2PtCl_6, 50°C, 6 h 2. 2-ThC≡CH	 50 %  50 %	17	519
	1,2-Diaminobenzene		92	287
	H_2O, ether		Polymers	524
	Cl_2, heat			509
	Ether, Pyridine, H_2O, 7°C			517
	1. BuLi 2. R_3SiCl			355

TABLE 16. *(Continued)*

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $PhMe_2SiCl$		89	355
	1. BuLi 2. Me_2SiCl_2		76	355
	1. BuLi 2. HMe_2SiCl		88	355
	1. BuLi 2. $MeSiCl_2H$		91.5	357
	1. BuLi 2. Cl_3SiH		65	357

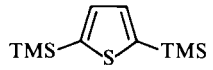
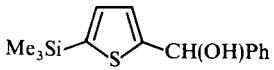
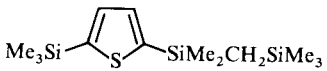
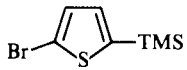
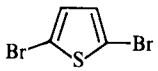
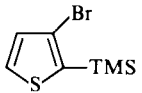
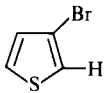
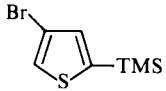
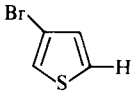
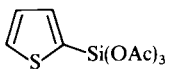
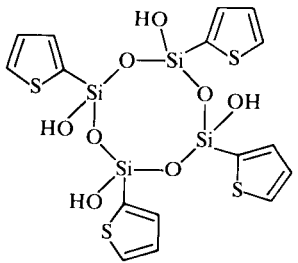
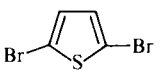
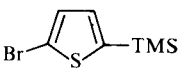
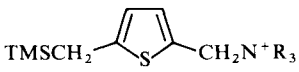
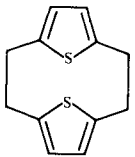
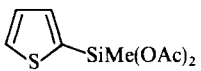
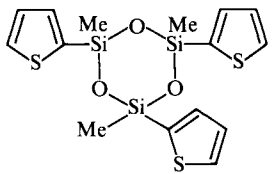
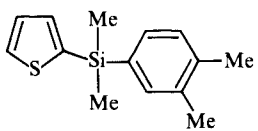
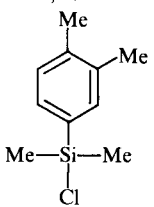
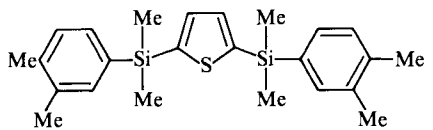
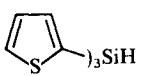
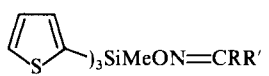
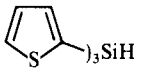
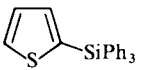
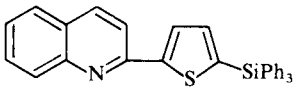
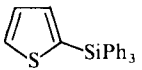
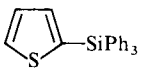
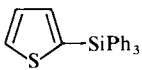
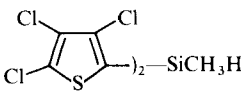
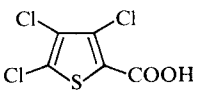
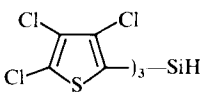
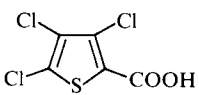
	1. BuLi, reflux THF 2. ArCHO or TMS-Cl	 30–40% or  15–20%		116
	Br_2, CCl_4		—	456
	$HClO_4$, MeOH, H_2O or H_2SO_4, HOAc, H_2O			510
	$HClO_4$, MeOH, H_2O or H_2SO_4, HOAc, H_2O			510
	1. H_2O, ether 2. + 20°C			517
	1. Mg 2. TMSCl		50	456

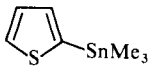
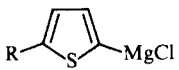
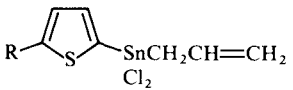
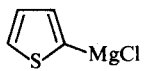
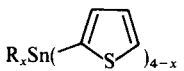
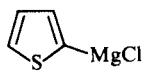
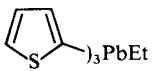
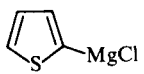
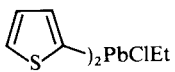
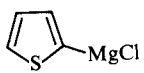
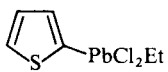
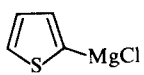
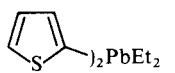
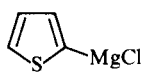
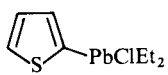
TABLE 16. *(Continued)*

Starting Material	Reagent	Product	Yield (%)	Ref.
	QF, CH_3CN		37	535
	H_2O		47	513
	1. BuLi, ether 2. 		77	251
	$HON{=}CRR_1$			514

	1. H_2PtCl_6 2. PhCH=CHCOOH *trans*	 		516
	1. BuLi 2. Quinoline		40	58
	HCl, HOAc	$HOSiPh_3$	12	518
	HCl (gas), HOAc	$HOSiPh_3$	21	526
	KOH, 85%, H_2O, ethanol	$HOSiPh_3$	69	526
	1. BuLi or CH_3Li 2. CO_2		67–89	357
	1. BuLi or CH_3Li 2. CO_2		92	357

[a] Rates compared with those of the Sn-derivatives.

TABLE 17. Ge, Sn, and Pb Derivatives

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. Me_3SnCl			521
	$CH_2{=}CHSnCl_3$			328
	R_xSnCl_{4-x}			461
	$EtPbCl_3$			329
	$EtPbCl_3$			329
	$EtPbCl_3$			329
	Et_2PbCl_2			329
	Et_2PbCl_2			329

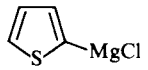
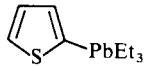
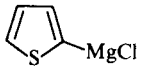
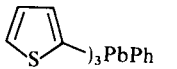
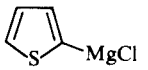
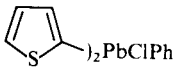
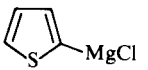
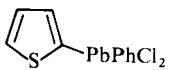
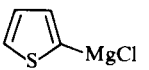
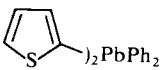
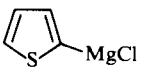
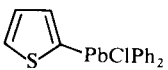
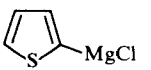
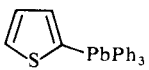
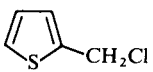
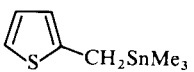
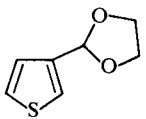
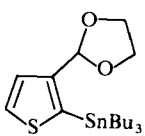
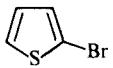
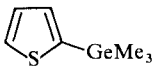
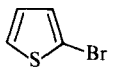
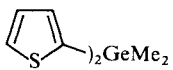
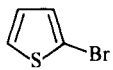
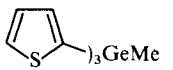
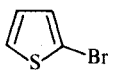
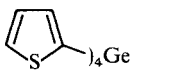
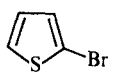
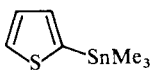
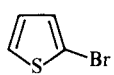
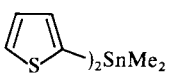
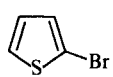
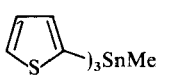
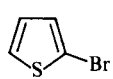
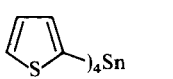
	Et_3PbCl			329
	$PhPbCl_3$			329
	$PhPbCl_3$			329
	$PhPbCl_3$			329
	Ph_2PbCl_2			329
	Ph_2PbCl_2			329
	Ph_3PbCl			329
	1. Mg 2. Me_3SnCl		75	521
	1. BuLi 2. Bu_3SnCl		77	281

TABLE 17. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Mg 2. $ClGeMe_3$		87	511
	1. Mg 2. Cl_2GeMe_2		71	511
	1. Mg 2. Cl_3GeMe		39	511
	1. Mg 2. Cl_4Ge		61	511
	1. Mg 2. $ClSnMe_3$		73	511
	1. Mg 2. Cl_2SnMe_2		64	511
	1. Mg 2. Cl_3SnMe		37	511
	1. Mg 2. $SnCl_4$		60	511

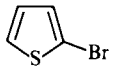
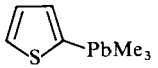
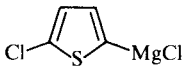
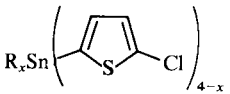
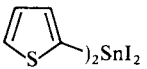
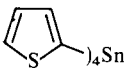
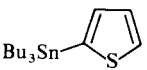
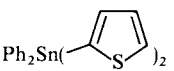
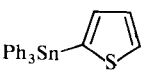
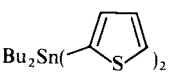
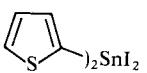
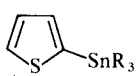
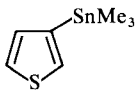
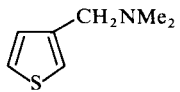
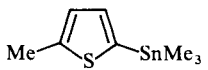
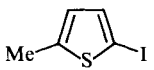
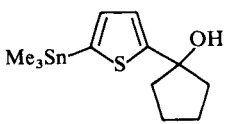
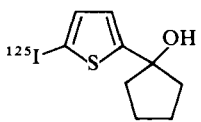
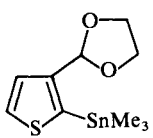
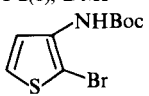
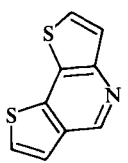
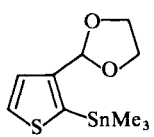
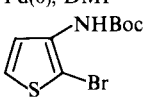
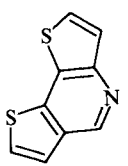
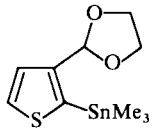
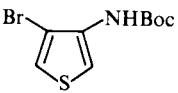
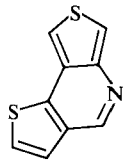
	1. Mg 2. $ClPbMe_3$		43	511
	R_xSnCl_{4-x}			461
	Sn, pyridine, HCl		2.5	539
	1. Mg 2. $SnCl_4$		90	481
	1. Mg 2. Bu_3SnCl		90	481
	1. Mg 2. Ph_2SnCl_2		90	481
	1. Mg 2. Ph_3SnCl		90	481
	1. Mg 2. Bu_2SnCl_2		90	481
	1. Sn 2. Pyridine, HCl, 150°C		90	540
	NaOMe, MeOH			531

TABLE 17. (*Continued*)

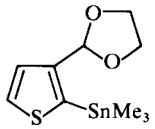
Starting Material	Reagent	Product	Yield (%)	Ref.
			66	399
	1. I_2, THF 2. KF, H_2O		93	27
	$^{125}I^-$, H_2O_2			537
	1. Pd(0), DMF 2.  3. HCl		59	542
	1. Pd(0), DMF 2.  3. HCl		43	542

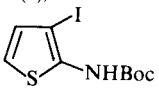


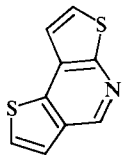
1. Pd(0), DMF
2. 
3. HCl



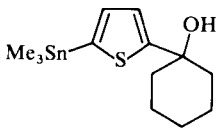
63 542



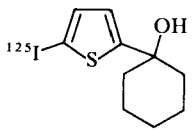
1. Pd(0), DMF
2. 
3. HCl



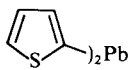
27 542

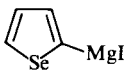


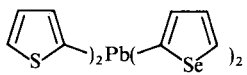
$^{125}I^-$, H_2O_2



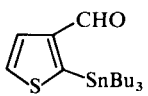
537

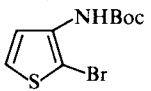


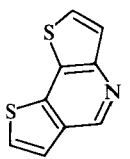




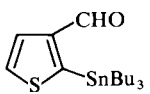
6 538

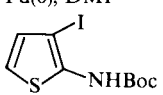


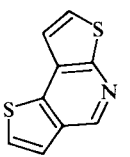
1. Pd(0), DMF
2. 



59 281

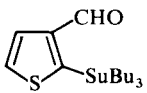
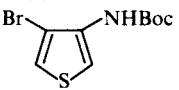
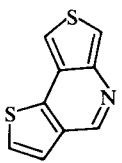
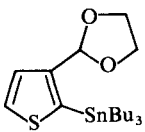
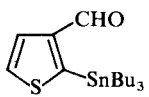
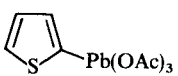
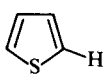
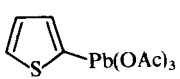
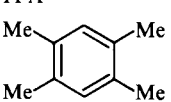
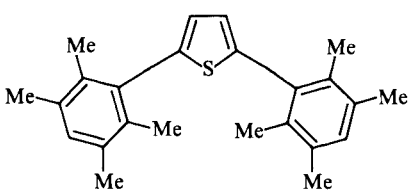


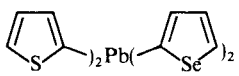
1. Pd(0), DMF
2. 



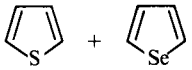
42 281

TABLE 17. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Pd(0), DMF 2. 		75	281
	HCl		85	281
	TFA			541
	1. TFA 2. 			541

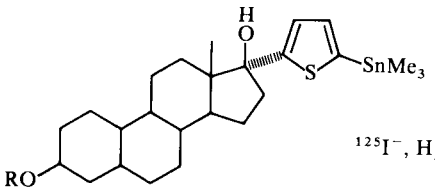


HCl

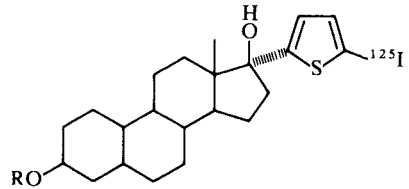


18 : 1

538



$^{125}I^-$, H_2O_2



537

TABLE 18. Te, As, Sb, and Bi Derivatives

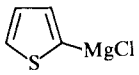
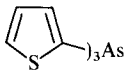
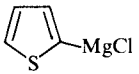
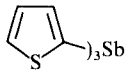
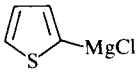
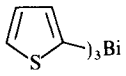
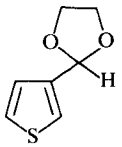
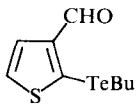
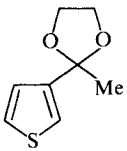
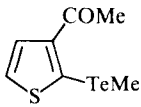
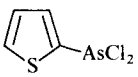
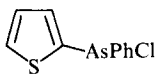
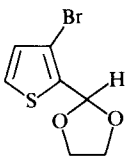
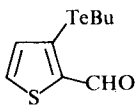
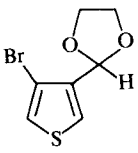
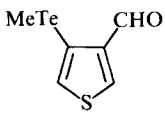
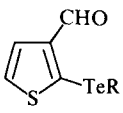
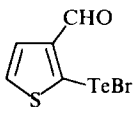
Starting Material	Reagent	Product	Yield (%)	Ref.
	$AsCl_3$			329
	$SbCl_3$			329
	$BiCl_3$			329
	1. BuLi 2. Te 3. BuI 4. H^+		34	72
	1. BuLi 2. Te 3. MeI 4. HCl		42	72
	PhHgCl			543
	1. BuLi 2. Te 3. H^+		34	72
	1. BuLi 2. Me_2Te_2 3. H^+		50	72
	1. $BrCH_2COOEt$ 2. HBr		70	72

TABLE 18. (*Continued*)

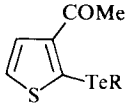
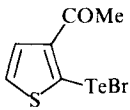
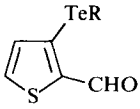
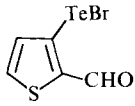
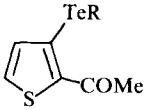
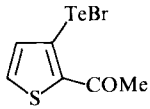
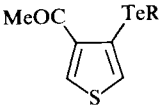
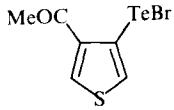
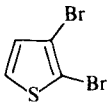
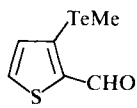
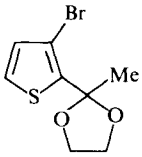
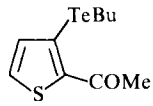
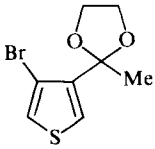
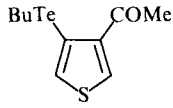
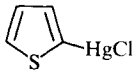
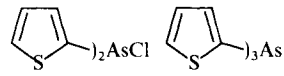
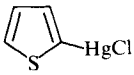
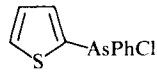
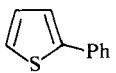
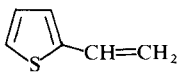
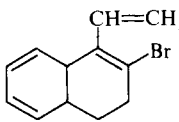
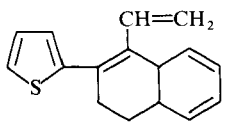
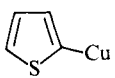
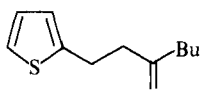
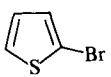
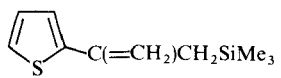
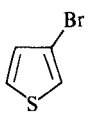
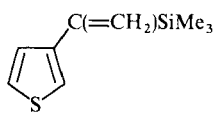
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $BrCH_2COOEt$ 2. HBr		76	72
	1. $BrCH_2COOEt$ 2. HBr		25	72
	1. $BRCH_2COOEt$ 2. HBr		67	72
	1. $BrCH_2COOEt$ 2. HBr		66	72
	1. BuLi 2. DMF 3. BuLi 4. Me_2Te_2		10	72
	1. BuLi 2. Te 3. H^+		56	72
	1. BuLi 2. Te		45	72
	$AsCl_3$			543
	$PhAsCl_2$			543

TABLE 19. Zn and Cd Derivatives

Starting Material	Reagent	Product	Yield (%)	Ref.
	BuLi, $ZnCl_2$, PhI, $Pd(PPh_3)_4$			545
	BuLi, $ZnCl_2$, $CH_2{=}CHBr$			545
	1. BuLi, $ZnBr_2$, $Pd(PPh_3)_4$ 2. 			548
	CH_2IZnI : ZnI_2, 2-bromomethyl-1-hexene			549
	$PdCl_2$·dppb, $CH_2{=}C(ZnCl)CH_2SiMe_3$			546
	$PdCl_2$·dppb, $CH_2{=}C(ZnCl)SiMe_3$			546

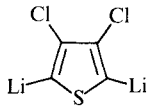
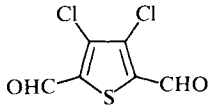
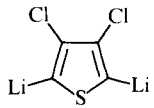
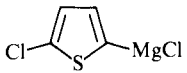
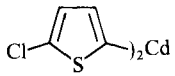
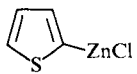
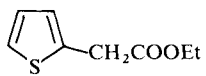
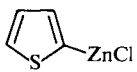
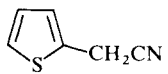
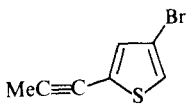
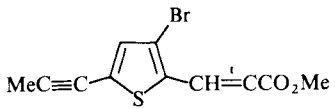
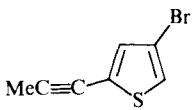
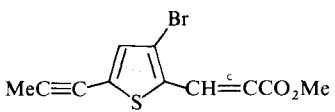
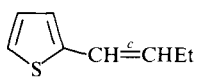
	$CdCl_2$, MeCOCl			185
	$CdCl_2$, I_2		Polymer	185
	$CdCl_2$			329
	1. $Ni(acac)_2$, PPh_3 2. $BrCH_2COOEt$			550
	1. $Ni(acac)_2$, $PCyPh_2$ 2. $BrCH_2CN$			655
	1. LDA, 2. $ZnCl_2$, 3. $Pd(PPh_3)_4$ 4. $BrCH{=}CHCO_2Me$ (*trans*)			19
	1. LDA 2. $ZnCl_2$ 3. $Pd(PPh_3)_4$ 4. $BrCH{=}CHCO_2Me$ (*cis*)			19
	$(EtCH{=}CH)_2CuLi$, $ZnBr_2$, $Pd(Ph_3)_4$			544

TABLE 19. *(Continued)*

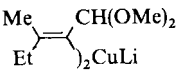
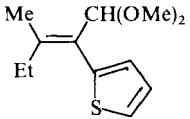
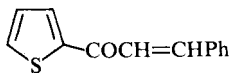
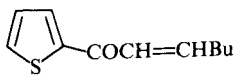
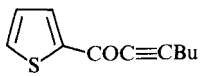
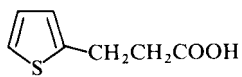
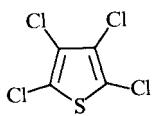
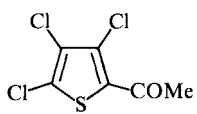
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $ZnBr_2$, $Pd(Ph_3)_4$ 2. 			544
	$Pd(PPh_3)_2Cl_2$, Zn–Cu, Cp_2TiCl_2, $PhC{\equiv}CH/CO$			547
	$Pd(PPh_3)_2Cl_2$, Zn–Cu, Cp_2TiCl_2, $C_4H_9C{\equiv}CH/CO$	 54%	 7%	547
	1. Mg 2. $CdCl_2$, β-propiolactone			477
	1. Mg, EtBr, THF 2. $CdCl_2$ 3. MeCOCl			425

TABLE 20. Mercury Derivatives

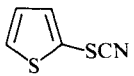
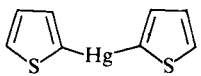
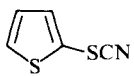
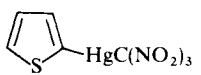
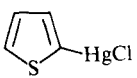
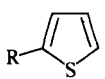
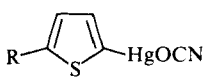
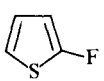
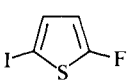
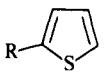
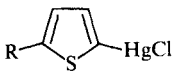
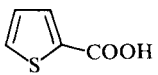
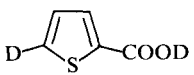
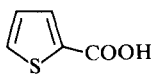
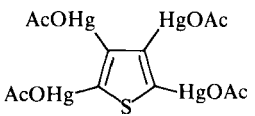
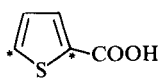
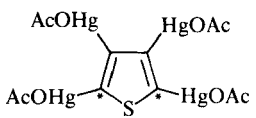
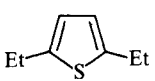
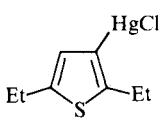
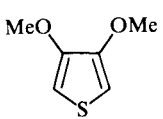
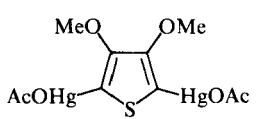
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $HgCl_2$ 2. $(SCN)_2$		30–40	332
	1. $HgCl_2$ 2. MeCOMe, NaI, H_2O	 		332
	$Hg[C(NO_2)_3]_2$			560
	$HgCl_2$, EtOH, AcONa		60	561
	$Hg(OCN)_2$, H_2O, NaOAc			562
	1. HgO 2. I_2		62	272

TABLE 20. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$HgCl_2$, NaOAc, EtOH			555
	1. $HgCl_2$ 2. DCl, D_2O			371
	HgO, HOAc		—[b]	559
	HgO, HOAc		98[c]	575
	$HgCl_2$			485
	$Hg(OAc)_2$			576

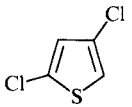
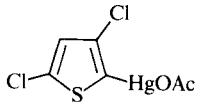
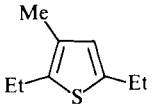
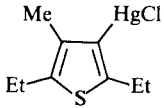
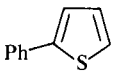
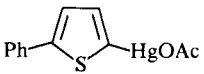
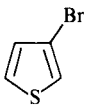
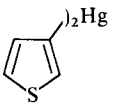
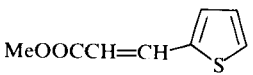
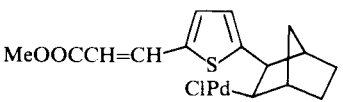
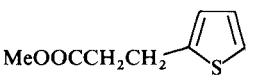
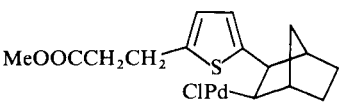
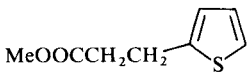
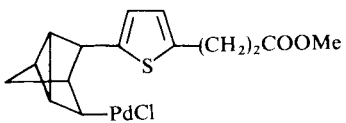
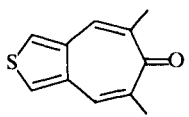
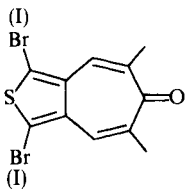
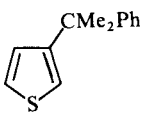
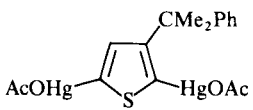
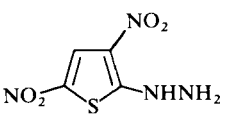
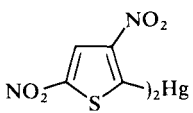
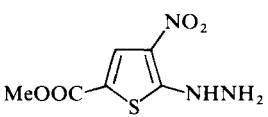
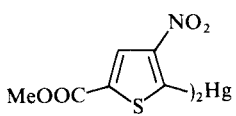
	$Hg(OAc)_2$			564
	$HgCl_2$			485
	$Hg(OAc)_2$			554
	1. BuLi, $-70°C$ 2. $HgCl_2$		—	394
	1. $HgCl_2$, $PdCl_2$; LiCl 2.		67	580
	1. $HgCl_2$, $PdCl_2$; LiCl 2.		78	580

TABLE 20. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $HgCl_2$, $PdCl_2$; LiCl 2.		74	580
	1. $Hg(OAc)_2$ 2. KBr; Br_2, or KI; I_2			382
	HgO, HOAc		—	572
	HgO, EtOH		15	567
	HgO, EtOH		49	567

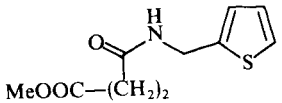
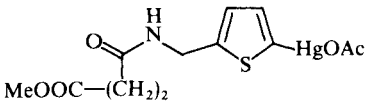
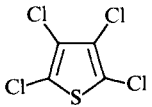
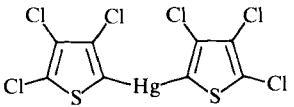
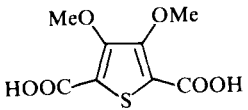
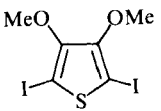
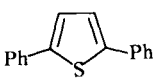
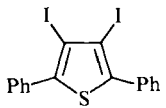
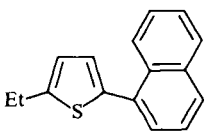
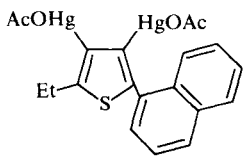
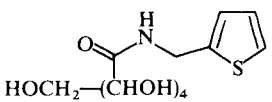
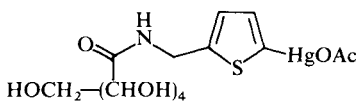
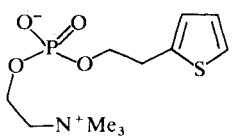
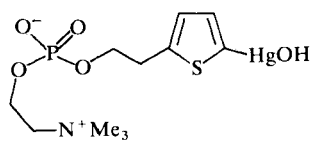
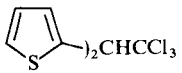
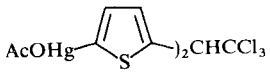
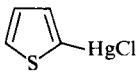
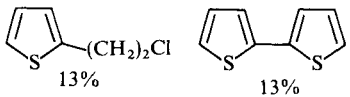
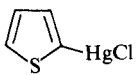
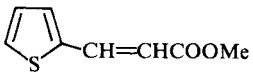
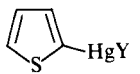
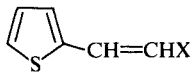
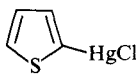
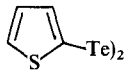
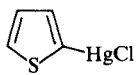
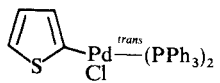
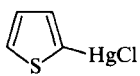
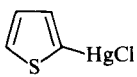
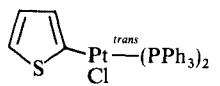
	$Hg(OAc)_2$, MeOH		557
	1. BuLi 2. $HgCl_2$		40 358
	1. $Hg(OAc)_2$ 2. I_2		19 426
	1. HgO 2. I_2		139
	HgO, HOAc		476
	$Hg(OAc)_2$, MeOH		557
	$Hg(OAc_2)$, MeOH		581

TABLE 20. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Hg(OAc)_2$, EtOH, HOAc		94	552
	1. Li_2PdCl_2 2. Ethylene	 13% 13%		569
	1. "Pd" 2. Methyl acrylate			570
	1. Li_2PdCl_4 2. CH_2=CHX			571
	$TeCl_4$		—	577
	$PdCl_2(PPh_3)_2$		68	578
	$PtCl_2(PPh_3)_2$		No reaction!	578
	$Pd(PPh_3)_4$		—	578

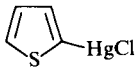
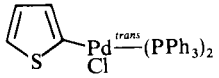
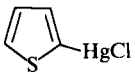
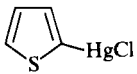
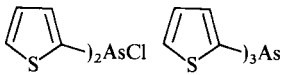
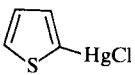
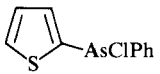
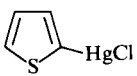
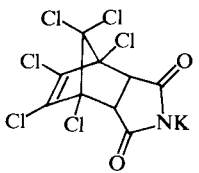
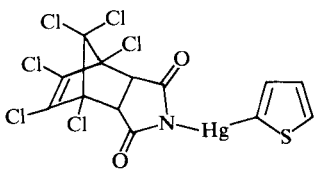
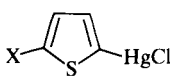
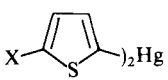
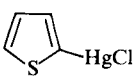
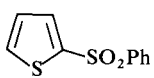
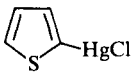
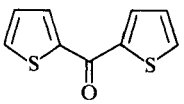
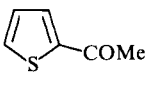
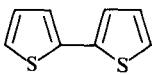
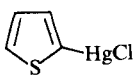
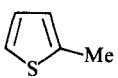
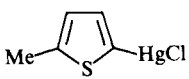
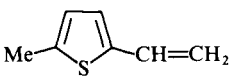
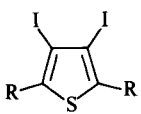
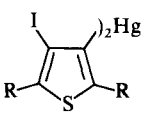
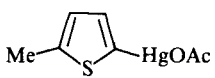
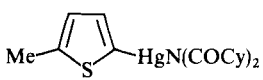
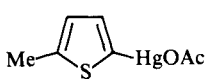
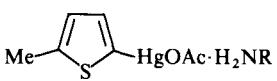
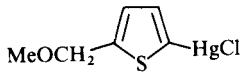
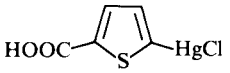
	$Pt(PPh_3)_4$		65	578
	Et_3SiH		—	566
	$AsCl_3$, Tol, reflux		—	543
	$PhAsCl_2$		—	543
				558
	N_2H_4		80–97	563
	$Cu(SO_2Ph)_2$, MeCN		24	568

TABLE 20. (*Continued*)

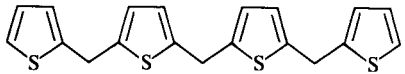
Starting Material	Reagent	Product	Yield (%)	Ref.
	Li_2PdCl_4, CO, MeOH, 50 atm	 40%  35%  10%		574
	1. Li_2CuMe_3 2. MeI, O_2		—	551
	1. LiCl, $ClRh(PPh_3)_3$, HMPA, 70°C 2. CH_2=CHBr		40	553
	1. BuLi, − 70°C 2. $HgCl_2$			139
	$(CyCO)_2NH$		—	573
	RNH_2			556



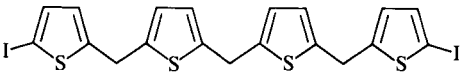
$KMnO_4$, KOH



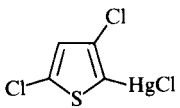
278



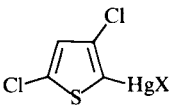
1. HgO
2. I_2



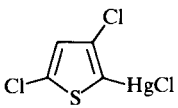
170



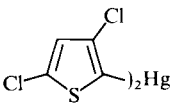
NaX



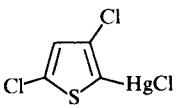
564



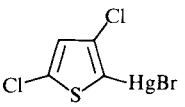
NaI, excess



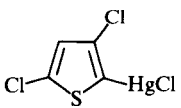
564



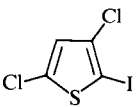
$HgBr_2$



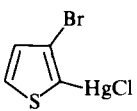
564



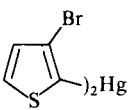
I_2, KI



564

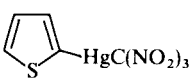


N_2H_4

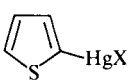


87

563

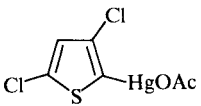
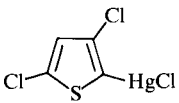
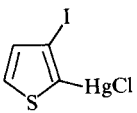
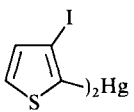
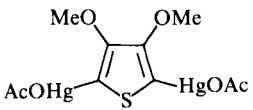
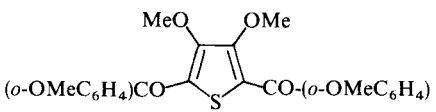
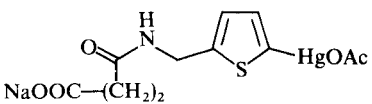
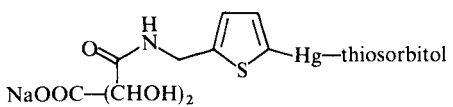
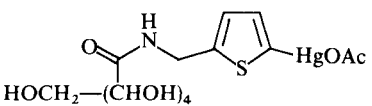
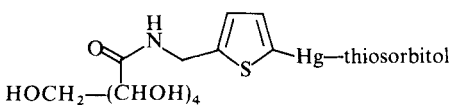


HCl or HBr



560

TABLE 20. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	NaCl			564
	NaI			139
	Anisoyl chloride			576
	Thiosorbitol			557
	Thiosorbitol			557

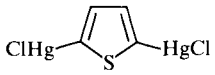
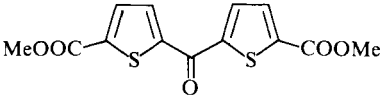
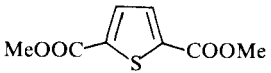
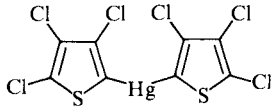
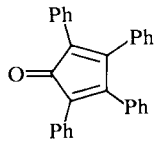
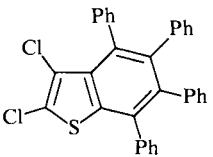
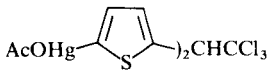
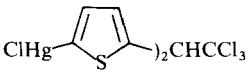
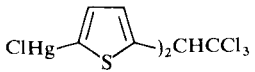
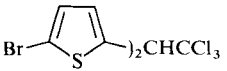
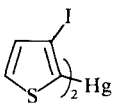
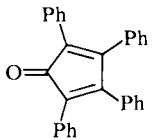
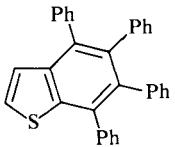
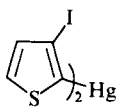
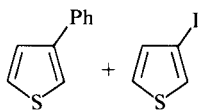
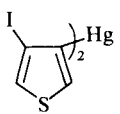
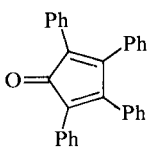
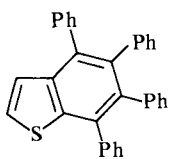
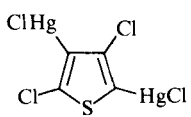
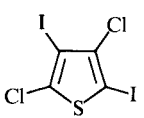
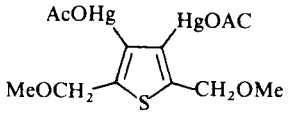
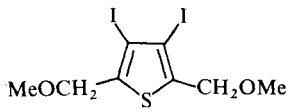
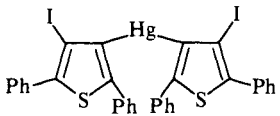
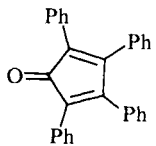
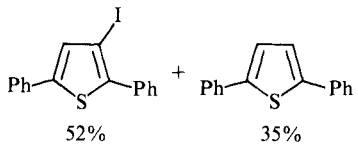
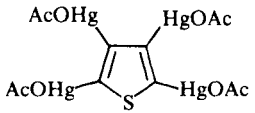
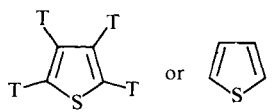
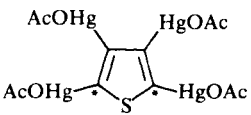
	Li_2PdCl_4, CO, MeOH, 50 atm	 36%  40%		574
	1. 245°C 2. 		68	358
	NaCl		—	552
	Br_2, CCl_4		35	552
	1. 240°C 2. 		9	139, 565

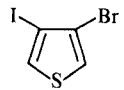
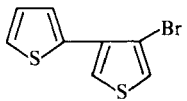
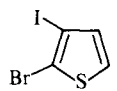
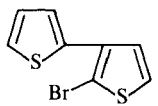
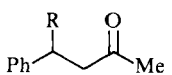
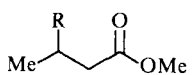
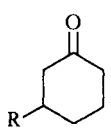
TABLE 20. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	*hv*, benzene	 6% 10%	16	139
	1. 240°C 2. 		16	139
	I_2, KI			564

	I_2		—	278
	1. 240°C 2. 	 52% 35%		139
	T_2O, TCl or H_2O, HCl		—[b]	559
	NaCl, HCl		65[c]	575

[a] MeI 32 : 65; DMS 99 : 1.
[b] ^{35}S.
[c] ^{14}C = *.

TABLE 21. Copper, Silver, and Gold Derivatives

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, CuBr 2. 		55	56
	1. BuLi, CuBr 2. 		53	56
	1. BuLi, CuI, RLi 2. PhCH=CHCOMe		35–83	586
	1. BuLi, CuI, RLi 2. MeCH=CHCOOMe			586
	1. BuLi, CuI, RLi 2. Cyclohexenone			586

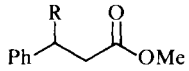
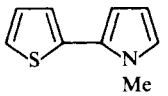
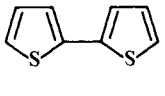
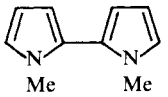
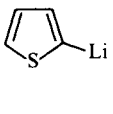
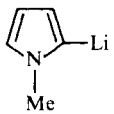
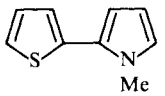
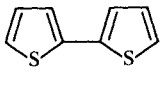
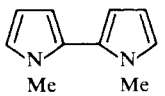
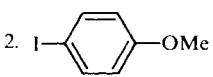
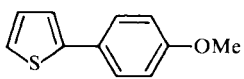
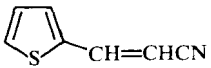
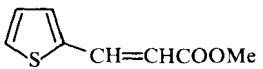
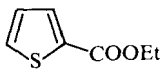
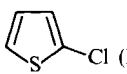
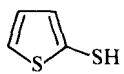
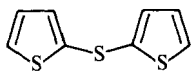
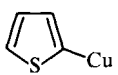
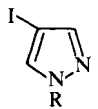
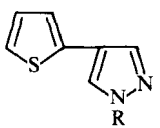
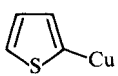
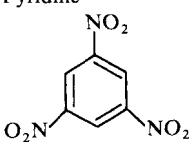
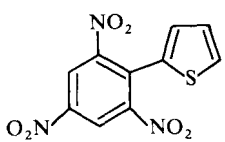
	1. BuLi, CuI, RLi 2. Methyl cinnamate		10–59	586
	1. BuLi 2. CuBr, pyridine 3. N-Methyl-2-iodopyrrole	 42%  54%  1%		13
 	CuBr	 45%  15%  40%		13
	1. BuLi, CuI 2. 		37–50	52

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Pd(OAc)_2$, $Cu(OAc)_2$, CH_2=CHCN		7	594
	$Pd(OAc)_2$, $Cu(OAc)_2$, CH_2=CHCOOMe		3	594
	$PdCl_2$, $Hg(OCOCF_3)LiBr$; $Cu(OAc)_2$, CO, EtOH		17	587
	1. Cu_2O 2. 			582
	1. Pyridine, 115°C 2. 			350
	1. Pyridine 2. 		44	593

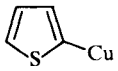
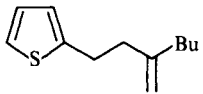
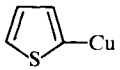
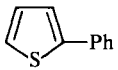
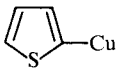
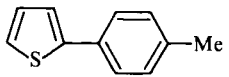
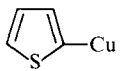
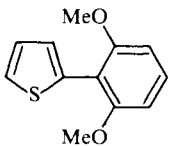
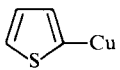
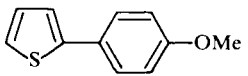
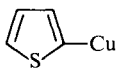
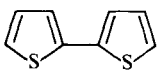
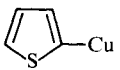
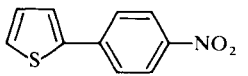
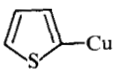
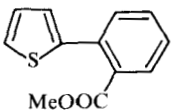
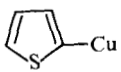
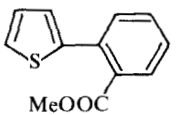
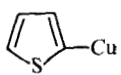
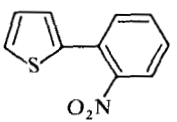
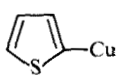
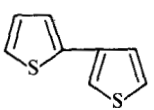
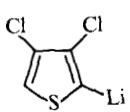
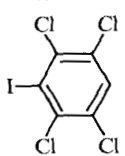
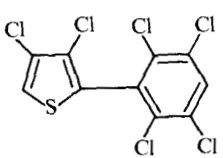
	$CH_2IZnI.ZnI_2$, 2-bromomethyl-1-hexene			549
	PhI, quinoline, heat		30–50	247
	*p*-Iodotoluene, quinoline, heat		36	247
	2,5-Dimethoxyiodobenzene, quinoline, heat		55	247
	*p*-Iodoanisol, quinoline, heat		55	247
	2-Iodothiophene, quinoline, heat		42	247
	*p*-Iodonitrobenzene, quinoline, heat		70	247

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	Methyl *o*-iodobenzoate, quinoline, heat		50	247
	Methyl *o*-bromobenzoate, quinoline, heat		13	247
	*o*-Iodonitrobenzene, quinoline, heat		56	247
	3-Bromothiophene, quinoline, heat		14	247
	1. CuCl 2. 		58	429

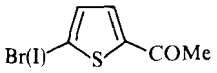
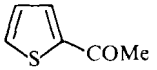
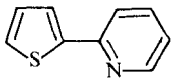
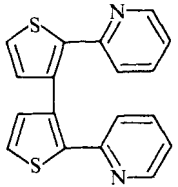
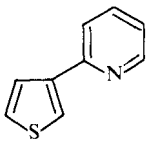
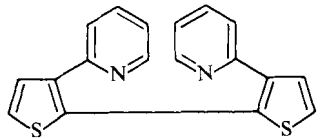
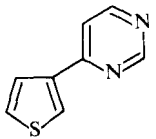
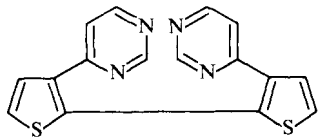
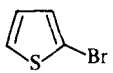
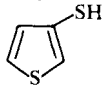
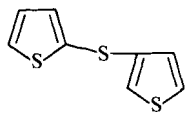
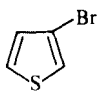
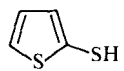
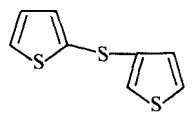
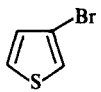
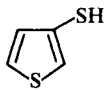
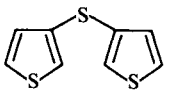
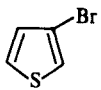
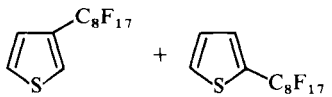
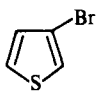
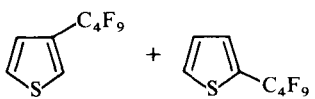
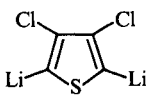
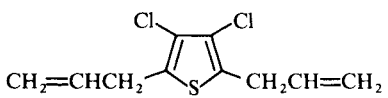
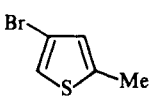
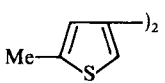
	Cu, quinoline		24–37	588
	*t*BuLi, $CuCl_2$		54	55
	BuLi, $CuCl_2$		51	55
	LDA, $CuCl_2$		28	55
	1. Cu_2O, DMF 2. 		73	582
	1. Cu_2O, DMF 2. 		63	582

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. Cu_2O, DMF 2. 		48	582
	Cu, DMF, $C_8F_{17}I$	 40% 4%		584
	Cu, DMF, C_4F_9I	 82% 18%		584
	CuI, $CH_2{=}CHCH_2Br$		66	185
	BuLi, $CuCl_2$		27	299

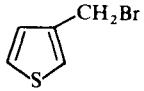
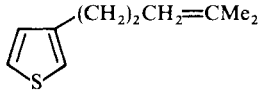
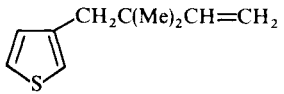
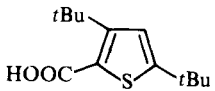
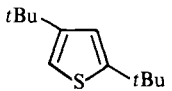
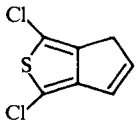
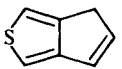
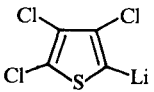
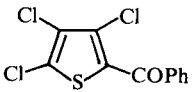
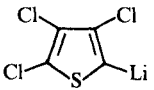
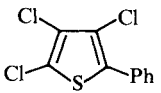
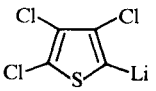
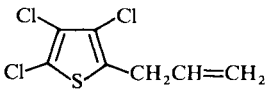
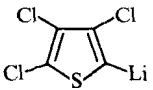
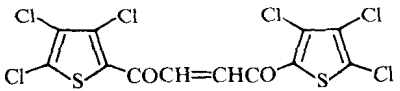
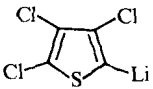
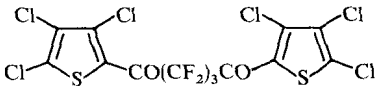
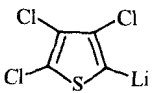
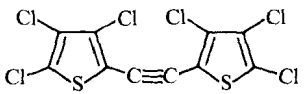
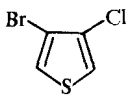
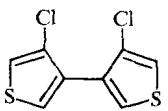
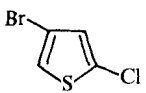
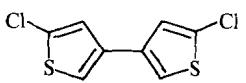
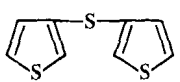
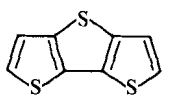
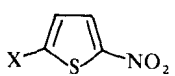
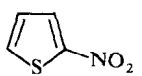
	1. Mg, THF 2. $(Me)_2C{=}CHCH_2OP(=O)(OEt)_2$, CuI	 18%  82%	78	179
	Cu, quinoline, or HBr; HOAc		88–92	300
	Cu, propionic acid, reflux 30 h		64	589
	1. CuCl or CuI in THF or THF/ether 2. PhCOCl		58	356
	1. CuCl or CuI in THF or THF/ether 2. PhI		53	356
	1. CuCl or CuI in THF or THF/ether 2. $CH_2{=}CHCH_2Br$		62	356

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. CuCl or CuI in THF or THF/ether 2. ClOCCH=CHCOCl		55	356
	1. CuCl or CuI in THF or THF/ether 2. $ClOC(CF_2)_3COCl$		22	356
	1. CuCl or CuI in THF or THF/ether 2. $CHBr{=}CBr_2$		36	356
	1. BuLi 2. $CuCl_2$		55	370
	1. BuLi 2. $CuCl_2$		36	370
	BuLi 2 eq, $CuCl_2$		50	54
	Cu, quinoline		32–14	588

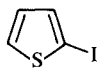
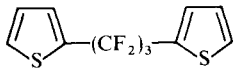
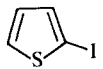
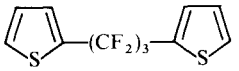
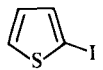
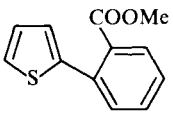
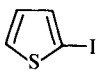
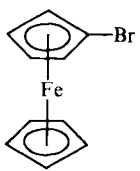
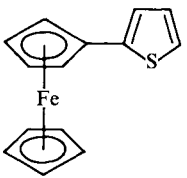
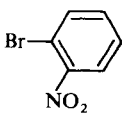
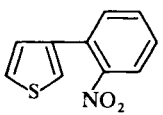
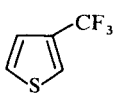
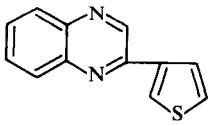
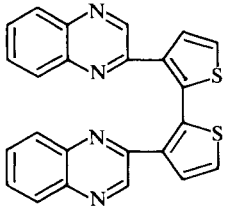
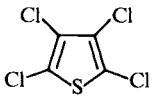
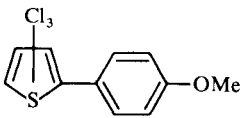
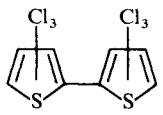
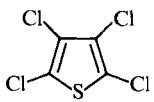
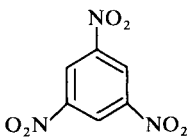
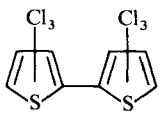
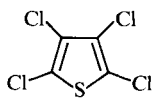
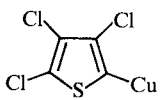
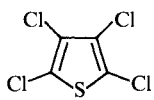
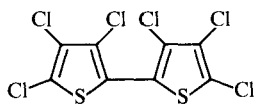
	Cu; pyridine, $I(CF_2)_3I$		25	591
	Cu; pyridine, $I(CF_2)_3I$		25	592
	Cu, methyl *o*-iodobenzoate			165
	1. Mg, Cu, CuBr 2. 		87	463
	1. Cu, 170–180°C 2. 			583
	Cu, DMF, CF_3I, 130°C		17	584

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	LDA, $CuCl_2$		48	55
	1. BuLi, CuI 2. Pyridine, *o*-iodoanisole	 65%  16%		359
	1. BuLi, CuI 2. 		75	359
	1. *t*BuLi, THF, or BuLi, monoglyme 2. CuCl or CuI		70	356
	1. BuLi ether 2. CuCl		67–73	356

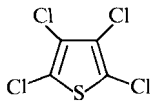
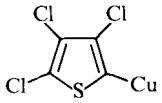
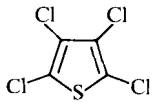
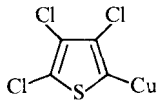
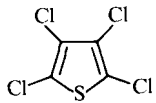
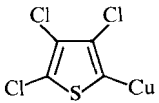
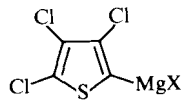
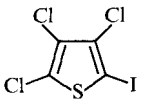
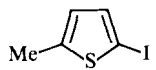
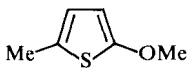
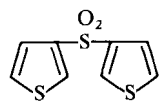
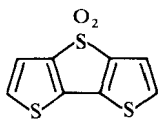
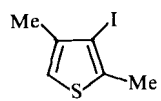
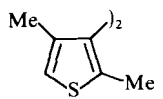
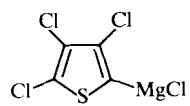
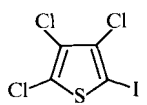
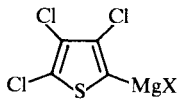
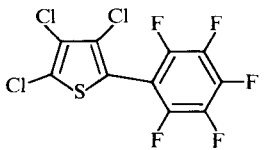
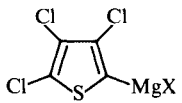
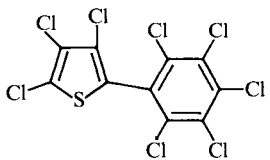
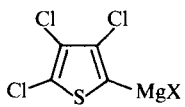
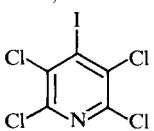
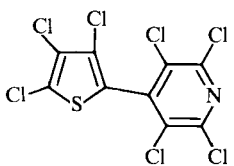
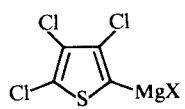
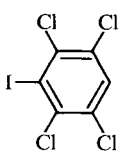
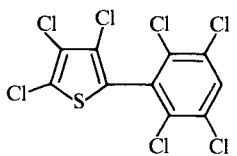
	1. BuLi ether 2. CuI		63	356
	1. BuLi, − 30°C 2. CuI			359
	1. Me_2CuLi, THF 2. MeCOCl		< 6	356
	$CuCl_2$ (catalyst), I_2		85	480
	CuO, NaOMe		54	145
	BuLi, $CuCl_2$		33	54
	EtLi, $CuCl_2$		64	271
	1. CuCl or CuI in THF or THF/ether 2. I_2		85	356

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	CuCl, dioxane, hexafluorobenzene		50	590
	CuCl, dioxane, hexachlorobenzene		56	590
	1. CuCl, dioxane 2. 		56	590
	1. CuCl 2. 		56	429

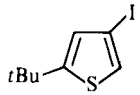
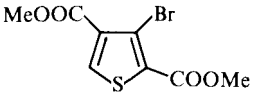
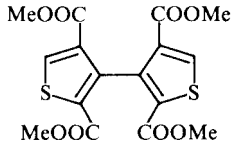
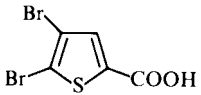
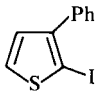
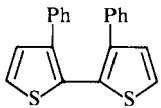
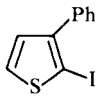
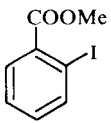
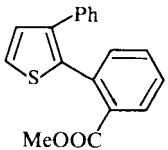
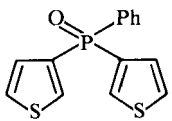
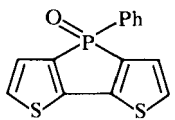
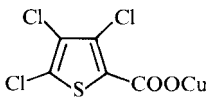
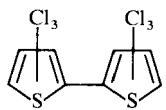
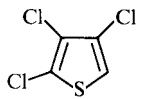
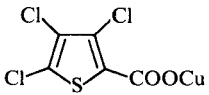
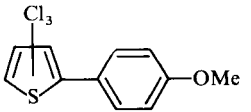
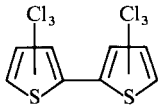
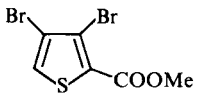
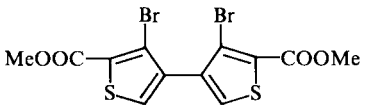
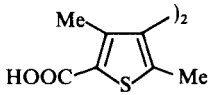
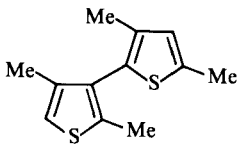
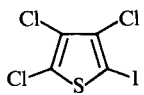
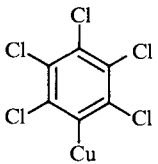
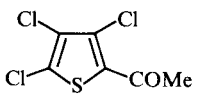
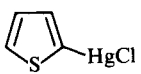
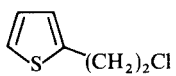
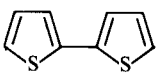
	1. BuLi, − 70°C 2. $CuCl_2$		48	279
	Cu		53	379
	Cu, quinoline			588
	Cu, Δ		13	361
	1. Cu, Δ 2. 		45	361
	1. BuLi, THF 2. $CuCl_2$		10	53
	Pyridine, Δ	 		359

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	Pyridine, Δ, *o*-iodoanisole	  13%		359
	Cu, DMF, reflux, 24 h		12	387
	Cu, quinoline		34	271
	1. MeCOCl 2. 			590
	Li_2PdCl_4, $CuCl_2$, LiCl, $CH_2{=}CH_2$	 13%  13%		569

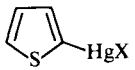
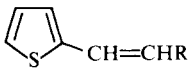
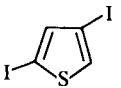
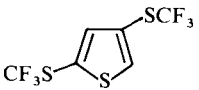
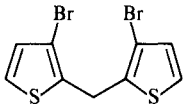
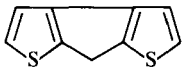
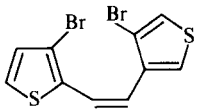
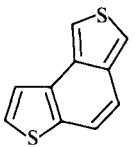
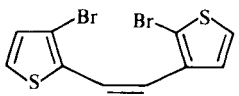
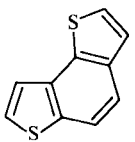
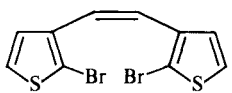
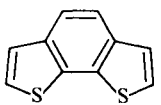
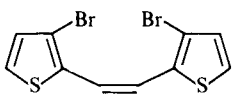
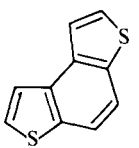
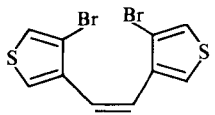
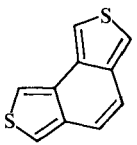
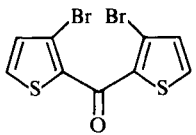
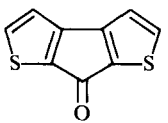
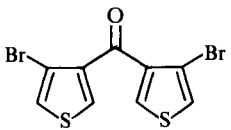
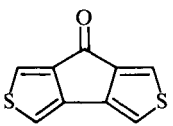
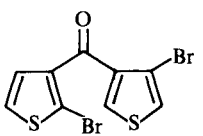
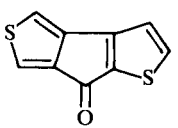
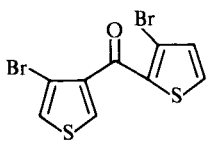
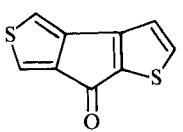
	Pd-, Cu-, Ru–salts, CH_2=CHR			571
	$CuSCF_3$, pyridine			348
	1. BuLi 2. $CuCl_2$		38	363
	1. EtLi 2. $CuCl_2$		Unstable	84
	1. EtLi 2. $CuCl_2$		60	84
	1. EtLi 2. $CuCl_2$		56	84
	1. EtLi 2. $CuCl_2$		70	84

TABLE 21. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. EtLi 2. $CuCl_2$		19	84
	Cu, DMF		49	86
	Cu, DMF		37	86
	Cu, DMF		38	86
	Cu, DMF		57	86

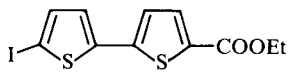
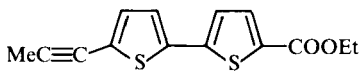
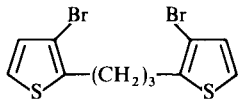
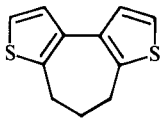
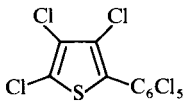
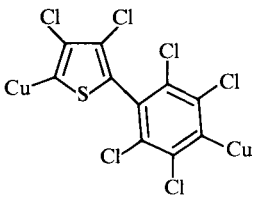
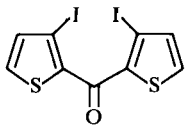
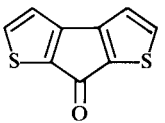
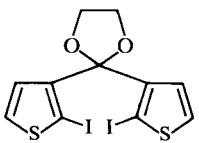
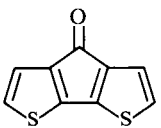
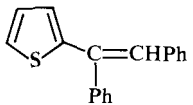
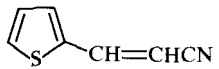
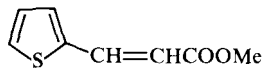
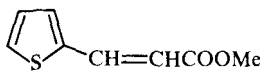
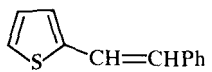
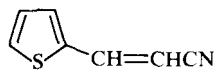
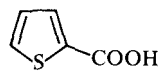
	$Pd(PPh_3)_4$, CuI, Et_3N, $MeC{\equiv}CH$		93	585
	1. EtLi, $-70°C$ 2. $CuCl_2$		10	368
	1. BuLi, THF 2. CuI			149
	Cu, DMF		99	86
	Cu, DMF		99	86

TABLE 22. Transition-Metal Derivatives

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Rh_4(CO)_{12}$, catalytic, PhC≡CPh, CO 25 kg/cm^2, 220°C		48	654
	$Pd(OAc)_2$, $Cu(OAc)_2$, CH_2=CHCN		7	594
	$Pd(OAc)_2$, $Cu(OAc)_2$, CH_2=CHCOOMe		3	594
	$Pd(OAc)_2$, CH_2=CHCOOMe		33	594
	$Pd(OAc)_2$, 1 eq, CH_2=CHPh		13	594
	$Pd(OAc)_2$, 1 eq, CH_2=CHCN		24	594
	$Pd(OAc)_2$, CO 15 atm, 100°C		18	652

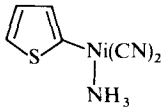
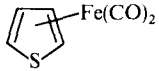
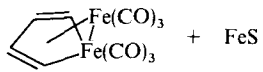
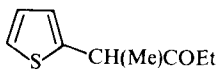
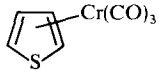
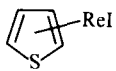
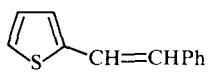
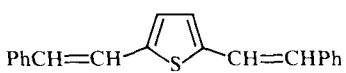
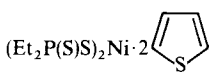
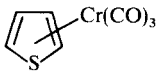
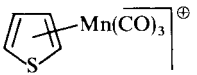
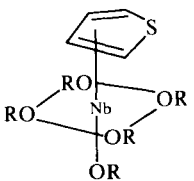
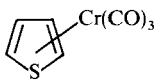
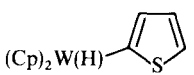
	$NiSO_4$, KCN, NH_4OH			645
	$Fe(CO)_5$			627
	$Fe_3(CO)_{12}$			630
	$Fe_2(CO)_9$, MeCH(Br)COCH(Br)Me		37	639
	$Cr(CO)_6$		2–3	628
	ReI_4			629
	$Pd(OAc)_2$, $PhCH{=}CH_2$	 13%  36%		644
	$Ni[SP(S)Et_2]_2$		blue complex	633

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Cr(CO)_6$		4.5	634
		$Cr(OP(O)(Me)Ph)2\cdot$	—[a]	636
	$AlCl_3$, 100°C, $Mn(CO)_5Cl$	 $ClO_4^{\ominus}$	3, 5	631
	$[Nb(OR)_5]_2$			640
	$(NH_3)_3Cr(CO)_3$ reflux, dioxane			641
	Cp_2WH_2, *hv*		71	648

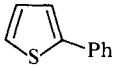
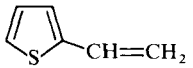
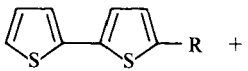
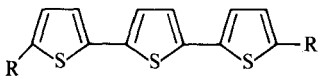
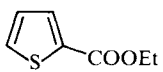
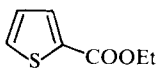
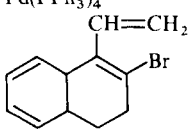
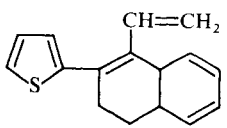
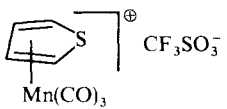
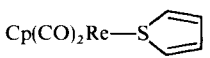
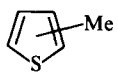
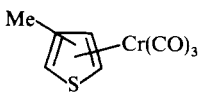
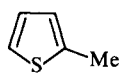
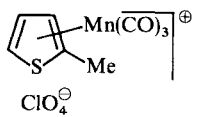
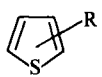
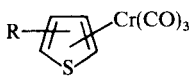
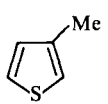
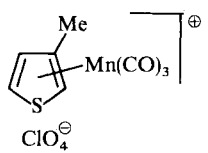
	$BuLi, ZnCl_2, PhI, Pd(PPh_3)_4$		75	545
	$BuLi, ZnCl_2, CH_2{=}CHBr, Pd(PPh_3)_4$		66	545
	$RuCl_3 \cdot H_2O$, MeOH, EtOH, PrOH	 + 	R = Me, Et, Pr	618
	$RuCl_3 \cdot H_2O$, EtOH, CO 35–40 bar		15	618
	$PdCl_2, Hg(OCOCF_3)_2$, LiBr; $Cu(OAc)_2$, CO, ROH		17	587
	1. BuLi, 2. $ZnBr_2$ 3. $Pd(PPh_3)_4$ 4. 		72	548
	$CF_3SO_3Mn(CO)_5$		74	611

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Cp(CO)_2Re \cdot THF$		38	658
	$Cr(CO)_6$, 180°C			415
	$AlCl_3$, 100°C, $Mn(CO)_5Cl$		6.5	631
	$(CH_3CN)_3 \cdot Cr(CO)_3$			637
	$AlCl_3$, 100°C, $Mn(CO)_5Cl$		18.5	631

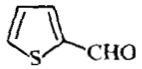
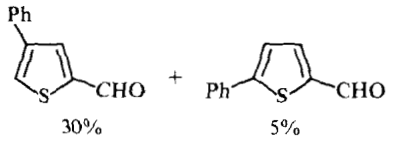
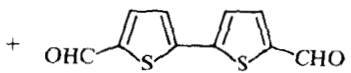
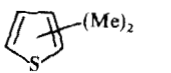
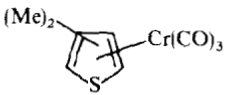
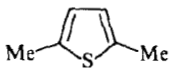
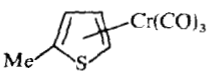
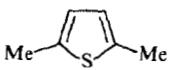
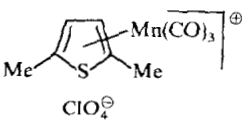
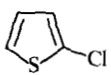
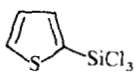
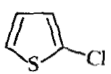
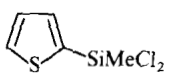
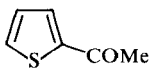
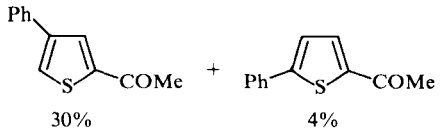
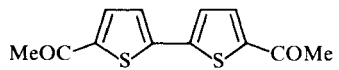
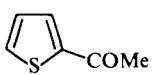
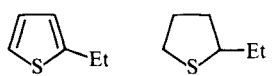
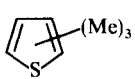
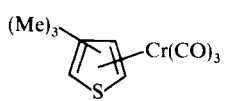
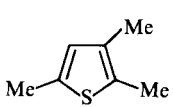
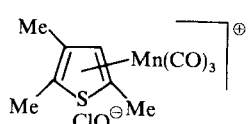
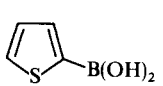
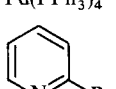
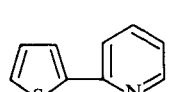
	$Pd(OAc)_2$, benzene	 30% 5% +  16%		656
	$Cr(CO)_6$, 180°C			415
	$Cr(CO)_6$		15	634
	$AlCl_3$, 100°C, $Mn(CO)_5Cl$		23.5	631
	Pd–metal, $HSiCl_3$, 500°C			523
	Pd–metal, $MeSiHCl_2$, 500°C			523

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Pd(OAc)_2$, benzene	 30% 4%		656
		+  18%		
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc	 50% 50%		624
	$Cr(CO)_6$, 180°C			415
	$AlCl_3$, 100°C, $Mn(CO)_5Cl$		28.5	631
	1. $Pd(PPh_3)_4$ 2. 		67	494

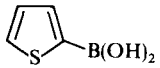
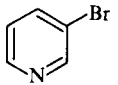
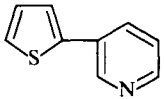
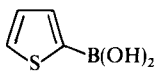
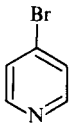
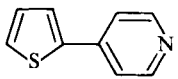
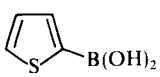
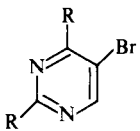
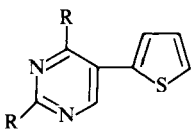
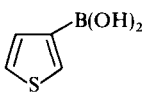
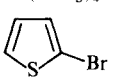
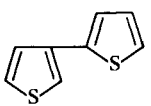
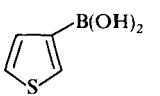
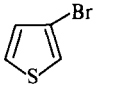
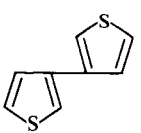
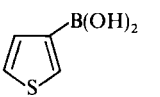
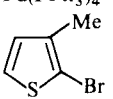
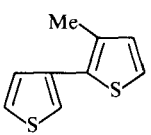
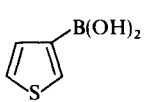
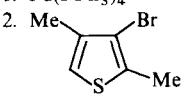
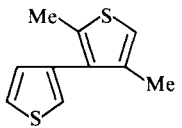
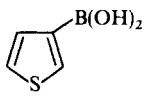
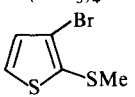
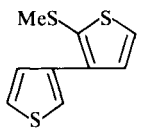
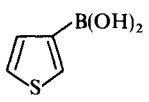
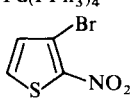
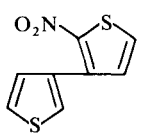
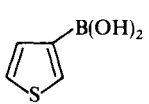
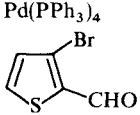
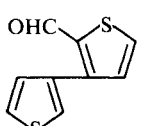
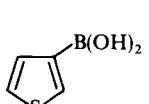
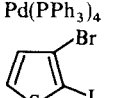
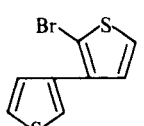
	1. $Pd(PPh_3)_4$ 2. 		68	494
	1. $Pd(PPh_3)_4$ 2. 		57	494
	1. $Pd(PPh_3)_4$, $MeO(CH_2)_2OMe$ 2. 		52--63	615
	1. $Pd(PPh_3)_4$ 2. 		72	600
	1. $Pd(PPh_3)_4$ 2. 		70	600
	1. $Pd(PPh_3)_4$ 2. 		60	600

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $Pd(PPh_3)_4$ 2. 		72	600
	1. $Pd(PPh_3)_4$ 2. 		55	600
	1. $Pd(PPh_3)_4$ 2. 		63	600
	1. $Pd(PPh_3)_4$ 2. 		67	600
	1. $Pd(PPh_3)_4$ 2. 		57	600

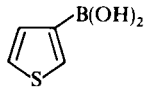
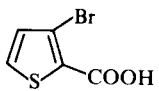
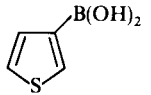
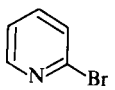
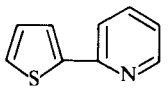
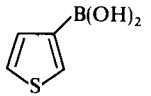
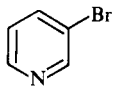
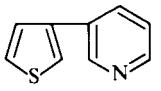
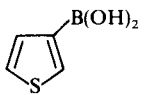
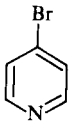
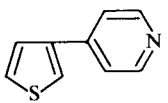
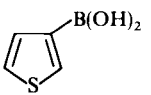
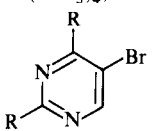
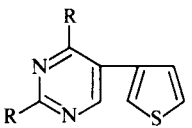
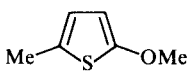
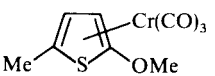
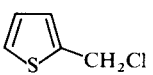
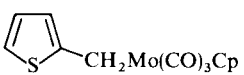
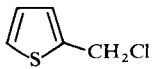
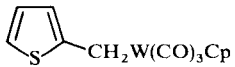
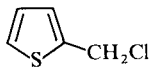
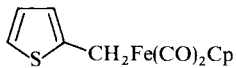
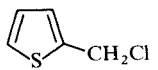
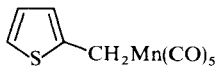
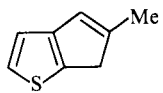
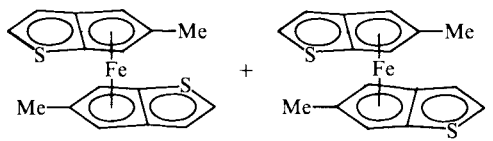
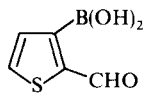
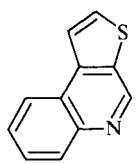
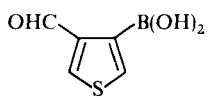
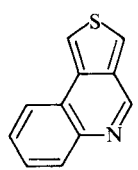
	1. $Pd(PPh_3)_4$ 2. 		0	600
	1. $Pd(PPh_3)_4$ 2. 		74	494
	1. $Pd(PPh_3)_4$ 2. 		69	494
	1. $Pd(PPh_3)_4$ 2. 		74	494
	1. $Pd(PPh_3)_4$, $MeO(CH_2)_2OMe$ 2. 		61–73	615
	$(CH_3CN)_3 \cdot Cr(CO)_3$			637
	$NaMo(CO)_3Cp$		85	527

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$NaW(CO)_3Cp$		55	527
	$NaFe(CO)_2Cp$		64	527
	$NaMn(CO)_5$		60	527
	BuLi, $-20°C$, $FeCl_2$			167
	1. *o*-Bromoacetanilid, Pd(0), DMF 2. HCl		44	503
	1. *o*-Bromoacetanilid, Pd(0), DMF 2. HCl		71	503

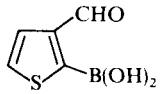
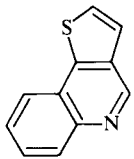
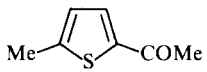
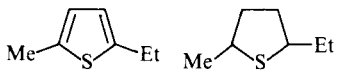
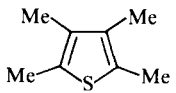
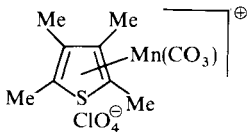
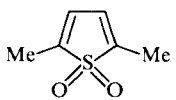
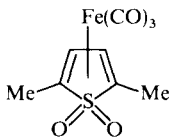
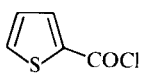
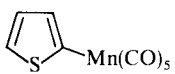
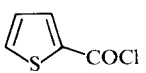
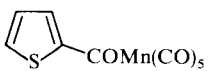
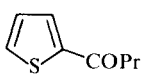
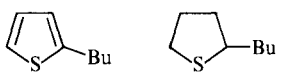
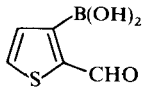
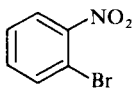
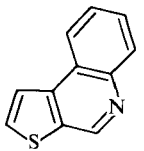
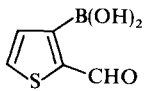
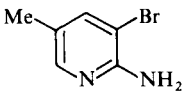
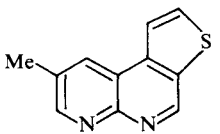
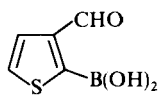
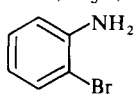
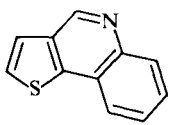
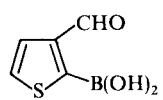
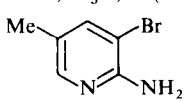
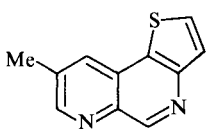
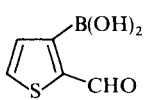
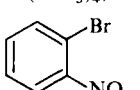
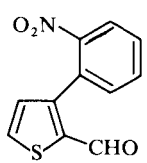
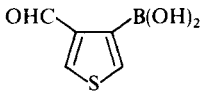
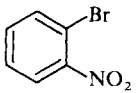
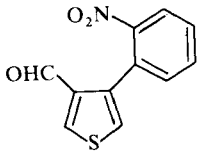
	1. *o*-Bromacetanilid, Pd(0), DMF 2. HCl		38	503
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc	 80% 15%		624
	$AlCl_3$, 100°C, $Mn(CO)_5Cl$		33	631
	$Fe_3(CO)_{12}$		58	650
	$NaMn(CO)_5$		42	358, 626
	$NaMn(CO)_5$		82	626
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc	 65% 30%		624

TABLE 22. (*Continued*)

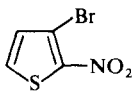
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $Pd(PPh_3)_4$ 2. 		32	614
	1. $Pd(PPh_3)_4$ 2. 		57	614
	1. DMF, Et_3N, $Pd(PPh_3)_4$ 2. 		29	614
	1. DMF, Et_3N, $Pd(PPh_3)_4$ 2. 		47	614
	1. $Pd(PPh_3)_4$, $MeO(CH_2)_2OMe$, $NaHCO_3$ 2. 		54	536

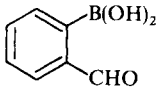


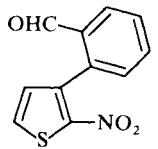
1. $Pd(PPh_3)_4$, $MeO(CH_2)_2OMe$, $NaHCO_3$
2. 



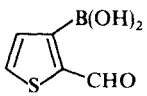
72 536

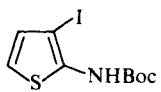


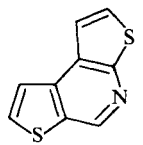
1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane
2. 



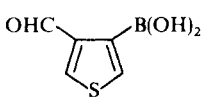
40 536

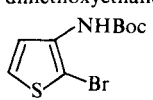


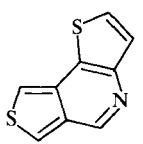
1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane
2. 
3. HCl



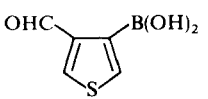
50 189

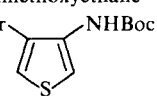


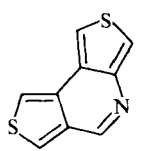
1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane
2. 
3. HCl



88 189

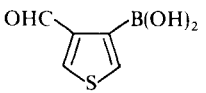
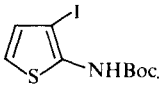
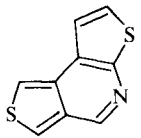
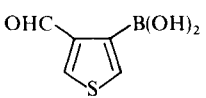
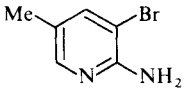
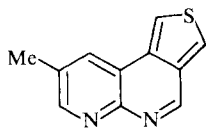
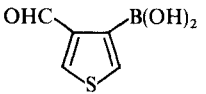
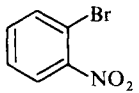
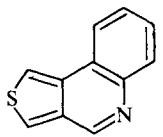
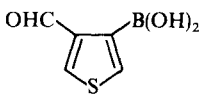
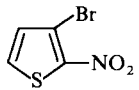
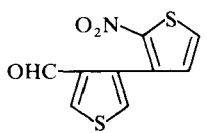
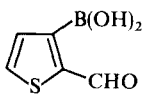
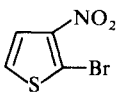
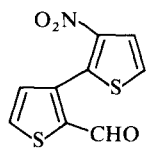


1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane
2. 
3. HCl



65 189

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2.  3. HCl		65	189
	1. $Pd(PPh_3)_4$ 2. 		72	614
	1. $Pd(PPh_3)_4$ 2. 		38	614
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		58	504
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		81	504

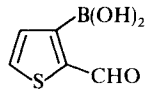
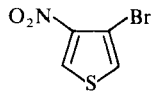
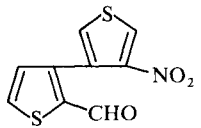
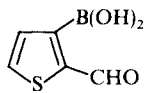
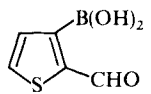
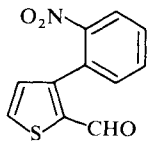
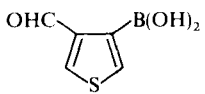
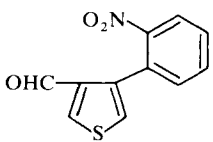
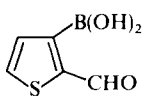
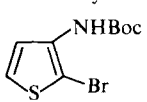
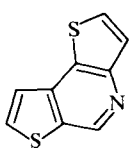
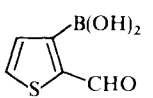
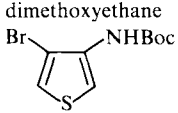
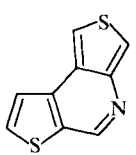
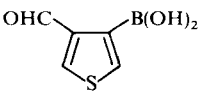
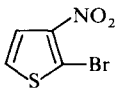
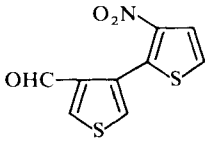
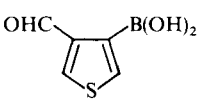
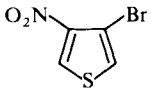
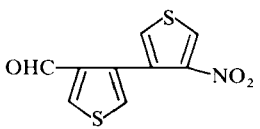
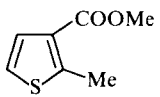
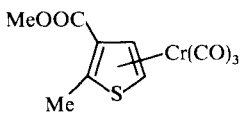
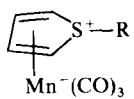
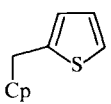
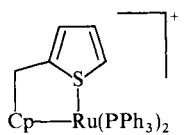
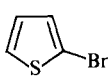
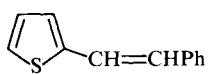
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		53	504
	2,3-Dibromothiophene, $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane		65	504
	*o*-Bromonitrobenzene, $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane		54	536
	*o*-Bromonitrobenzene, $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane		72	536
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		81	189
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2.  3. HCl		67	189

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		84	504
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		65	504
	$Cr(CO)_6$, 180°C			415
	$Mn(CO)_4SR$			638
	$RuCl_3$, PPh_3		80	612
	1. Mg 2. $Ni(acac)_2$ 0.2%, PhCH=CHBr *trans*		50–75	469

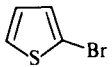
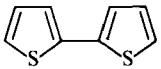
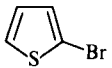
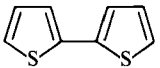
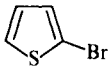
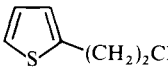
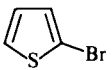
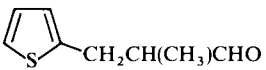
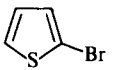
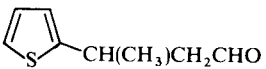
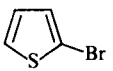
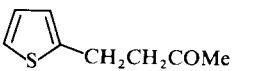
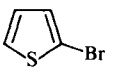
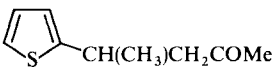
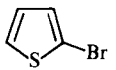
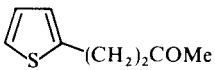
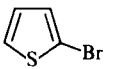
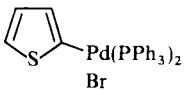
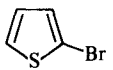
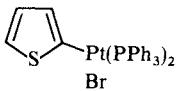
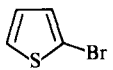
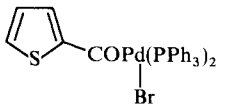
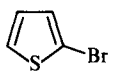
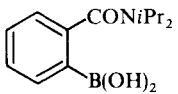
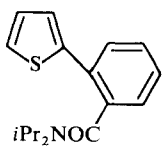
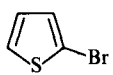
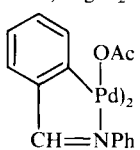
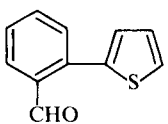
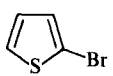
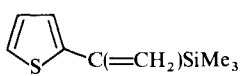
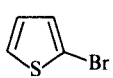
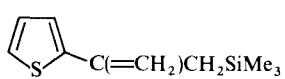
	1. Mg 2. $CoCl_2$, BuBr		25	347
	1. Li 2. $CoCl_2$, PhBr		30	347
	$Pd(OAc)_2$, NaI, HMPA, $NaHCO_3$, $CH_2{=}CHCH_2OH$		36	646
	$Pd(OAc)_2$, NaI, HMPA, $NaHCO_3$, $CH_2{=}C(CH_3)CH_2OH$		15	646
	$Pd(OAc)_2$, NaI, HMPA, $NaHCO_3$, $CH_3CH{=}CHCH_2OH$		58	646
	$Pd(OAc)_2$, NaI, HMPA, $NaHCO_3$, $CH_2{=}CHCH(CH_3)OH$		87	646
	$Pd(OAc)_2$, NaI, HMPA, $NaHCO_3$, $CH_3CH{=}CHCOMe$		37	646
	$Pd(OAc)_2$, $NaHCO_3$, DMF or HMPA, $CH_2{=}CHCH(OH)Me$		80	647
	$Pd(PPh_3)_4$		51	578

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Pt(PPh_3)_4$		74	578
	$PdCO(PPh_3)_3$		73	578
	1. $Pd(PPh_3)_4$, Na_2CO_3 2. 		92	610
	1. BuLi, $MgBr_2$ 2. 		27	442
	Mg, $CH_2{=}C(Br)SiMe_3$, $PdCl_2(dppb)_2$		81	546
	Mg, $CH_2{=}C(Br)CH_2SiMe_3$, $PdCl_2(dppb)$		78	546

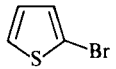
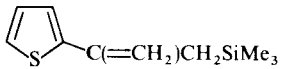
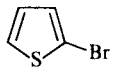
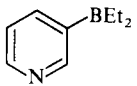
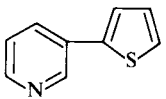
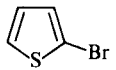
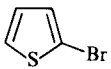
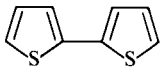
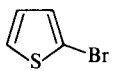
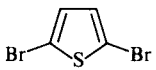
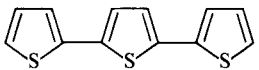
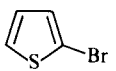
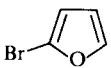
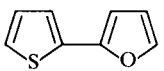
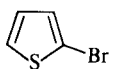
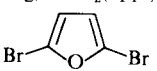
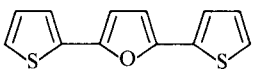
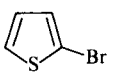
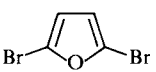
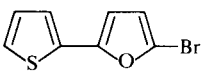
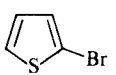
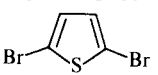
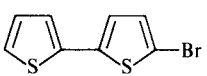
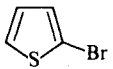
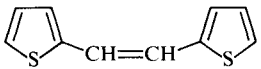
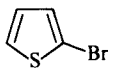
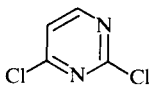
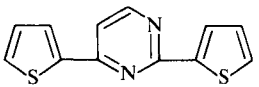
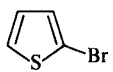
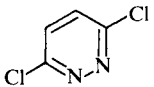
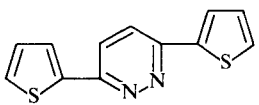
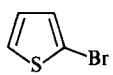
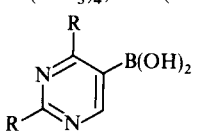
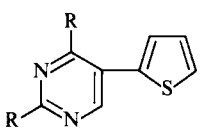
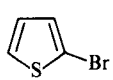
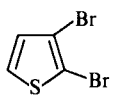
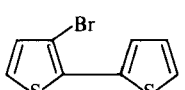
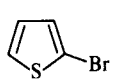
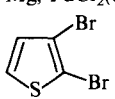
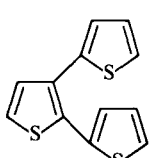
	$PdCl_2(dppb)$, $CH_2{=}C(ZnCl)CH_2SiMe_3$		66	546
	1. $Pd(PPh_3)_4$, KOH, QBr 2. 		75	605
	1. Mg, $NiCl_2(dppe)$ 2. 		90	83
	1. Mg, $NiCl_2(dppe)$ 2. 		70	83
	1. Mg, $PdCl_2(dppf)$ 2. 		98	83
	1. Mg, $PdCl_2(dppf)$ 2. 		82	83
	1. Mg, $PdCl_2(dppf)$ 2. 			83
	1. Mg, $PdCl_2(dppf)$ 2. 		58	83

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$NiCl_2(dppp)$, ClCH=CHCl *trans*		30	609
	1. $NiCl_2(dppp)$ 2. 		30	609
	1. $NiCl_2(dppp)$ 2. 		90	609
	1. $Pd(PPh_3)_4$, $MeO(CH_2)_2OMe$ 2. 		77	615
	1. Mg, $PdCl_2(dppf)$ 2. 		82	585
	1. Mg, $PdCl_2(dppf)$ 2. 		85	585

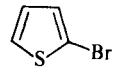
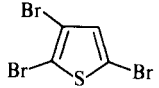
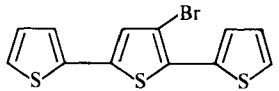
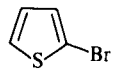
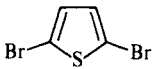
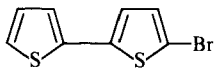
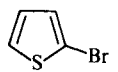
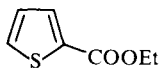
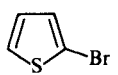
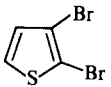
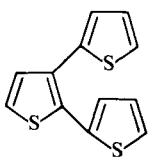
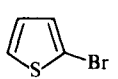
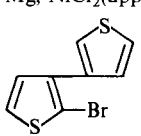
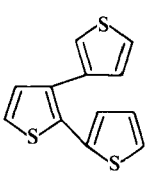
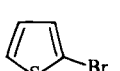
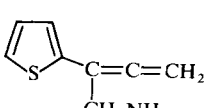
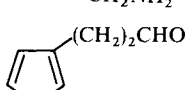
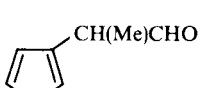
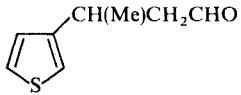
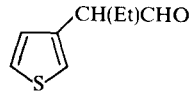
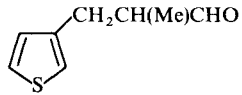
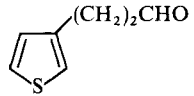
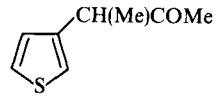
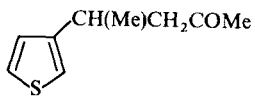
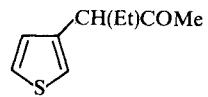
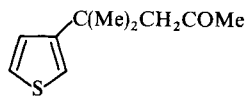
	1. Mg 2 eq, $PdCl_2(dppf)$ 2. 		89	585
	1. Mg, $PdCl_2(dppf)$ 2. 		53	585
	$Pd(PPh_3)_2Cl_2$, EtOH, CO 294 psi		96	585
	1. Mg, $NiCl_2(dppp)$ 2. 		83	616
	1. Mg, $NiCl_2(dppp)$ 2. 		93	616
	Mg, $NiCl_2(dppp)$ $MeOCH_2C{\equiv}CCH_2NTMS$		87	623
	$Pd(OAc)_2$, $CH_2{=}CHCH_2OH$	 25%  16%		644

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Pd(OAc)_2$, $MeCH{=}CHCH_2OH$	 23%  17%		644
	$Pd(OAc)_2$, $CH_2{=}C(Me)CH_2OH$	 79%		644
	$Pd(OAc)_2$, $CH_2{=}CHCH(OH)Me$	 90%  7%		644
	$Pd(OAc)_2$, $MeCH{=}CHCH(OH)Me$	 62%  16%		644
	$Pd(OAc)_2$, $(Me)_2C{=}CHCH(OH)Me$		22	644

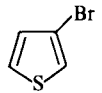
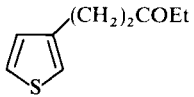
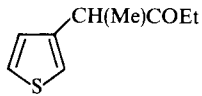
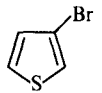
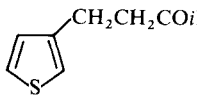
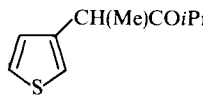
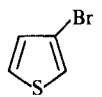
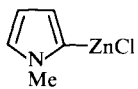
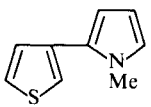
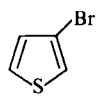
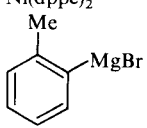
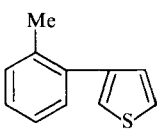
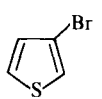
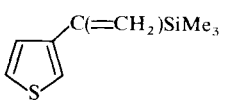
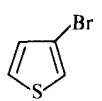
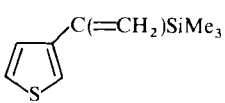
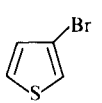
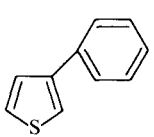
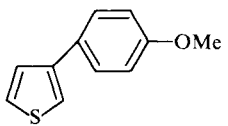
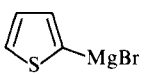
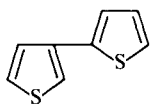
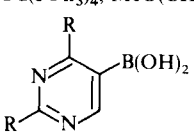
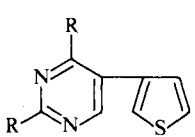
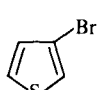
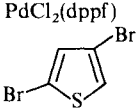
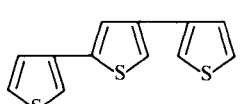
	$Pd(OAc)_2$, $CH_2{=}CHCH(OH)Et$	 79%  6%		644
	$Pd(OAc)_2$, $CH_2{=}CHCH(OH)iPr$	 87%  3%		644
	1. $PdCl_2$(dppb), THF 2. 		73	597
	1. $Ni(dppe)_2$ 2. 		67	442
	$PdCl_2$(dppb), $CH_2{=}C(MgBr)SiMe_3$		60	546
	$PdCl_2$(dppb), $CH_2{=}C(ZnCl)SiMe_3$		72	546
	PhMgBr, NiCl(dppp)		80	601

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$NiCl_2$(dppp), *p*OMePhMgBr		80	601
	1. $NiCl_2$(dppp) 2. 		80	601
	RMgBr, $NiCl_2$(dppp)		57–79	613
	1. $Pd(PPh_3)_4$, $MeO(CH_2)_2OMe$ 2. 		69–84	615
	1. Mg 2 eq, 2. $PdCl_2$(dppf) 3. 		48	585

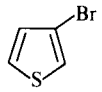
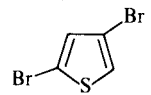
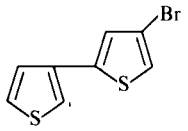
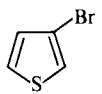
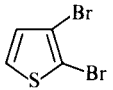
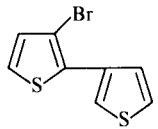
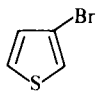
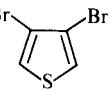
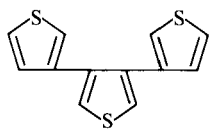
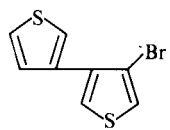
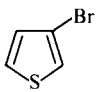
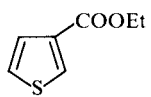
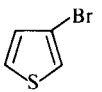
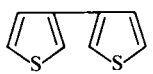
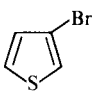
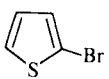
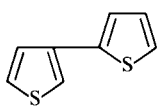
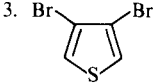
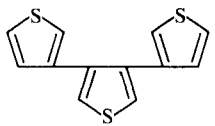
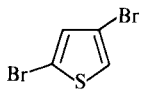
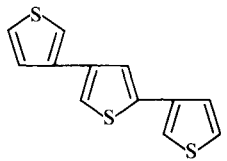
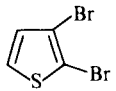
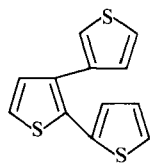
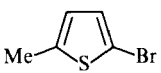
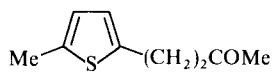
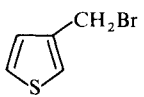
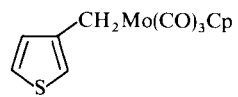
	1. Mg 1 eq, 2. $PdCl_2(dppf)$ 3. 		64	585
	1. Mg 1 eq, 2. $PdCl_2(dppf)$ 3. 		45	585
	1. Mg 1 eq, 2. $PdCl_2(dppf)$ 3. 	 50%  16%	45	585
	$Pd(PPh_3)_2Cl_2$, EtOH, CO 294 psi		55	585
	1. BuLi, $MgBr_2$, 2. $Ni(dppp)Cl_2$ 3.		88	616
	1. BuLi, $MgBr_2$, 2. $Ni(dppp)Cl_2$ 		77	616

TABLE 22. *(Continued)*

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi, $MgBr_2$ 2. $Ni(dppp)Cl_2$ 3. 		85	616
	1. BuLi, $MgBr_2$ 2. $Ni(dppp)Cl_2$ 3. 		61	616
	1. BuLi, $MgBr_2$ 2. $Ni(dppp)Cl_2$ 3. 		77	616
	$Pd(OAc)_2$, $NaHCO_3$, DMF or HMPA, CH_2=CHCH(OH)Me			647
	$NaMo(CO)_3Cp$		75	527

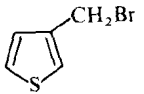
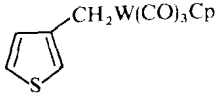
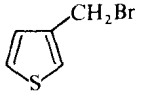
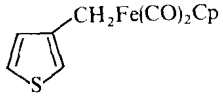
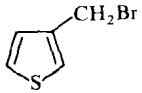
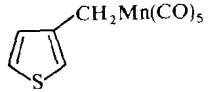
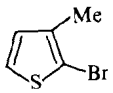
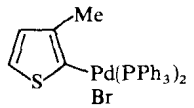
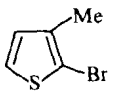
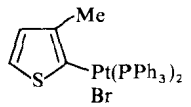
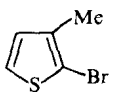
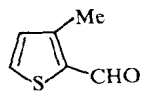
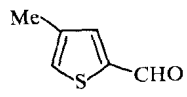
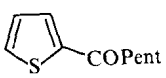
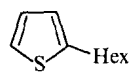
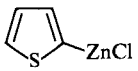
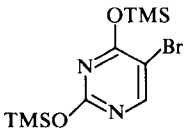
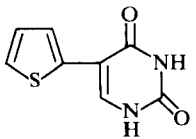
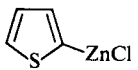
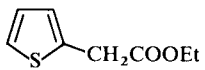
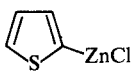
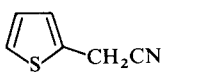
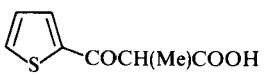
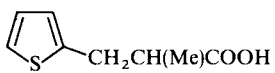
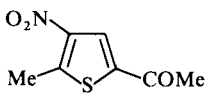
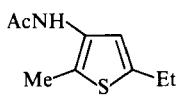
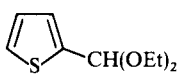
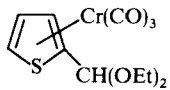
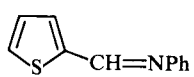
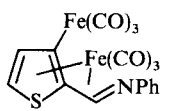
	$NaW(CO)_3Cp$		52	527
	$NaFe(CO)_2Cp$		55	527
	$NaMn(CO)_5$		66	527
	$Pd(PPh_3)_4$			578
	$Pt(PPh_3)_4$		72	578
	$PdCl_2(PPh_3)_2$, NEt_3, CO, 20 atm, 130°C	 54%	 18%	578
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc			624

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $Ni(PPh_3)_4$, THF 2.  3. 2NHCl		35	615
	$Ni(acac)_2$, PPh_3, $BrCH_2COOEt$		45	550
	$Ni(acac)_2$, $CCyPPh_2$, $BrCH_2CN$		46	655
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc			624
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc			624
	$Cr(CO)_6$		9	634
	$Fe_2(CO)_9$		21	635

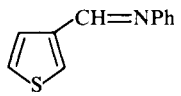
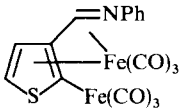
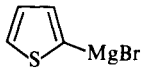
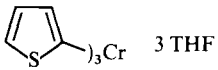
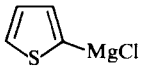
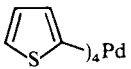
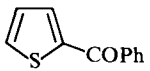
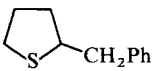
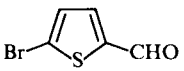
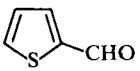
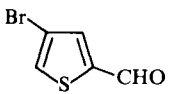
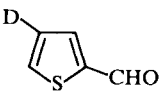
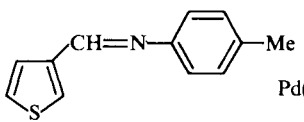
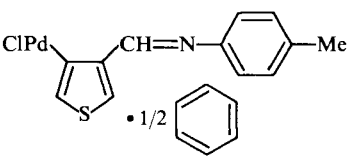
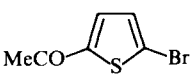
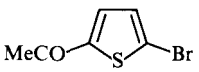
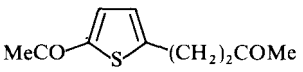
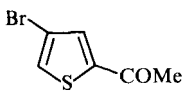
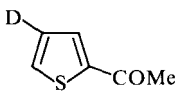
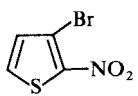
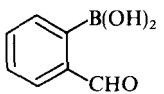
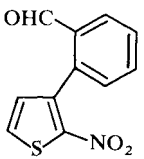
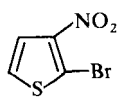
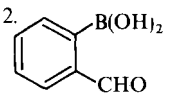
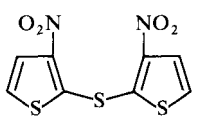
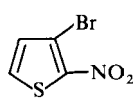
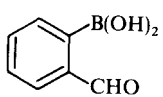
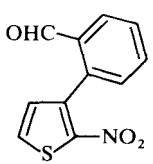
	$Fe_2(CO)_9$		25	635
	$CrCl_3 \cdot 3(THF)$		80–90	632
	$PdCl_4$			329
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc			624
	Pd complex on Si gel, H_2 or D_2			599
	Pd complex on Si gel, H_2 or D_2			599
	$Pd(PhCN)_2Cl_2$			578
	CoS_x, 200–225°C, 100–150 atm H_2, HOAc	25% 75%		624

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Pd(OAc)_2$, $NaHCO_3$, DMF or HMPA, CH_2=CHCH(OH)Me		30	647
	Pd complex on Si gel, H_2 or D_2			599
	1. $Pd(PPh_3)_4$, dimethoxy ethane, $NaHCO_3$ 2. 			536
	1. $Pd(PPh_3)_4$, dimethoxy ethane, $NaHCO_3$ 2. 			536
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		40	536

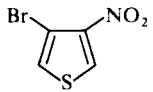
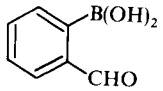
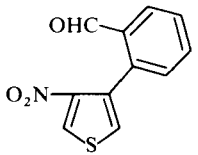
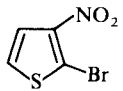
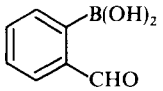
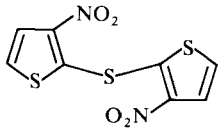
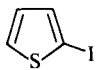
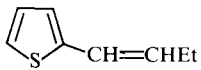
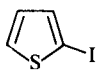
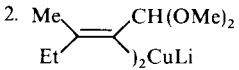
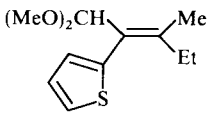
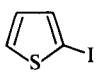
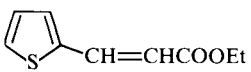
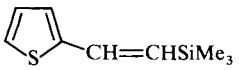
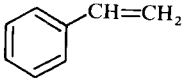
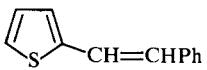
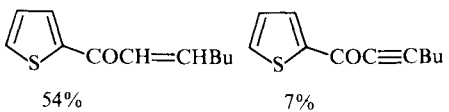
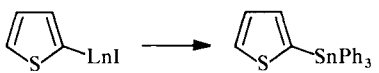
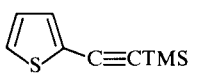
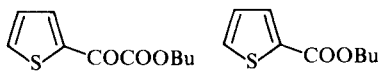
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		83	536
	1. $Pd(PPh_3)_4$, $NaHCO_3$, water, dimethoxyethane 2. 		5	536
	$(EtCH{=}CH)_2CuLi$, $ZnBr_2$, $Pd(Ph_3)_4$	 *cis*		544
	1. $ZnBr_2$, $Pd(Ph_3)_4$ 2. 			544
	$CH_2{=}CHCOOEt$, Pd (graphite), NBu_3		64	596

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Pd(OAc)_2$, $AgNO_3$, PPh_3, Et_3N, $CH_2{=}CHSiMe$		74	622
	1. $Pd(OAc)_2$, PPh_3 2. 		20	598
	$Pd(PPh_3)_2Cl_2$, Zn–Cu, Cp_2TiCl_2, $PhC{\equiv}CH/CO$		44	547
	$Pd(PPh_3)_2Cl_2$, Zn–Cu, Cp_2TiCl_2, $C_4H_9C{\equiv}CH/CO$	 54% 7%		547
	Yb, Eu, Sm, or Ce + CH_2I_2, Ph_3SnCl		< 70	604
	$Pd(PPh_3)_4$, $TMSC{\equiv}CMgBr$		98	83
	$PdCl_2(PCy_3)_2$, CO 70 atm, BuOH, Et_3N, 70°C, 96 h	 64% 36%		606

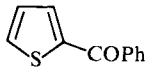
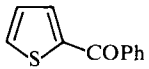
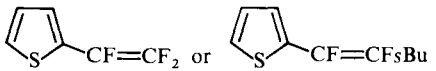
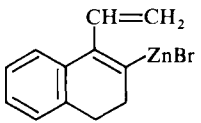
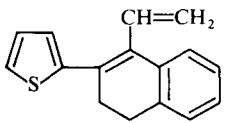
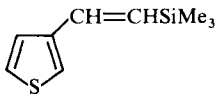
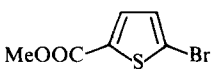
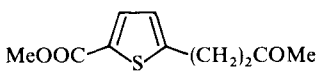
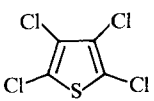
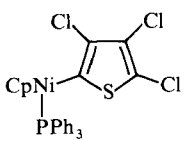
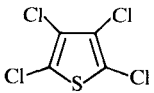
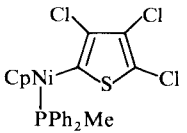
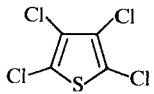
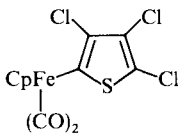
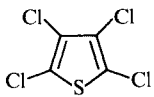
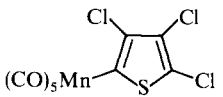
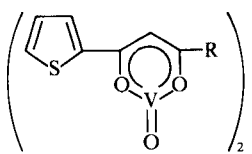
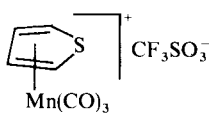
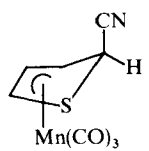
	Ph_3Al, $PdCl_2(CH_3CN)_2$, CO 1 atm, DMSO		99	608
	Ph_2Al–*i*Bu, $PdCl_2(CH_3CN)$THF, HMPA, CO 1 atm		82	608
	$Pd(PPh_3)_4$, THF, $CF_2{=}CFZnCl$ or *s*Bu$CF{=}CFZnCl$	 78% 50%		619
	1. $Pd(PPh_3)_4$ 2. 		66	548
	$Pd(OAc)_2$, $AgNO_3$, PPh_3, Et_3N, $CH_2{=}CHSiMe$		73	622
	$Pd(OAc)_2$, $NaHCO_3$, DMF or HMPA, $CH_2{=}CHCH(OH)Me$		60	647
	1. BuLi 2. $CpNi(PPh_3)Cl$		29	358

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. BuLi 2. $CpNi(PPh_2Me)Cl$		36	358
	1. BuLi 2. $CpFe(CO)_2I$		17	358
	1. BuLi 2. $Mn(CO)_5Br$		13	358
	$VOSO_4$ or $VOSO_4 \cdot 2(H_2O)$			625
	KCN		74	611

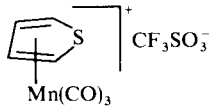
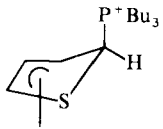
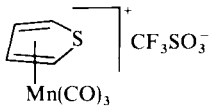
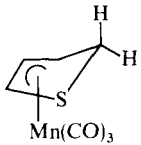
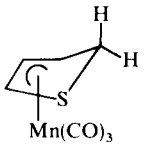
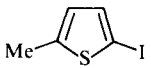
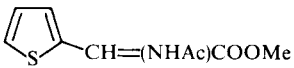
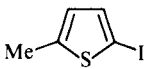
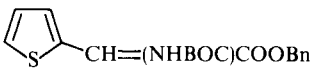
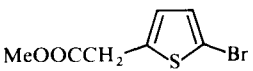
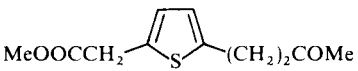
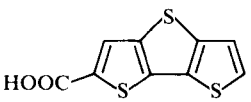
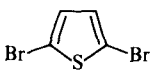
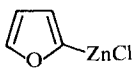
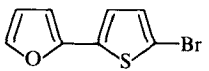
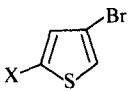
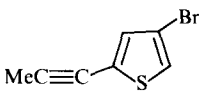
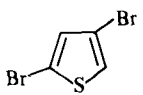
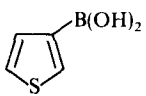
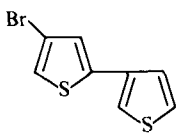
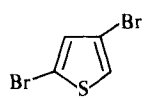
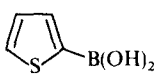
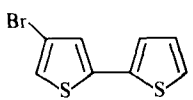
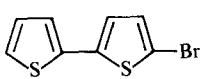
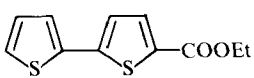
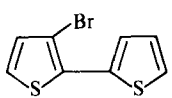
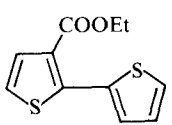
	PBu_3		74	611
	$NaBH_4$ or $HFe(CO)_4^-$ or $HW(CO)_5^-$		86	611
	HCl gas		86	611
	$Pd(OAc)_2$, QCl, CH_2=C(COOMe)NHAc		36	595
	$Pd(OAc)_2$, QCl, CH_2=C(COOBn)NHBOC		56	595
	$Pd(OAc)_2$, $NaHCO_3$, DMF or HMPA, CH_2=CHCH(OH)Me			647
	Raney Ni	$C_8H_{17}COOH$	79	54

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $PdCl_2$ dppf 2. 		67	83
	$MeC{\equiv}CZnCl$, $Pd(OAc)_2$, PPh_3			19
	1. $Pd(PPh_3)_4$, acetonylacetone 2. 		64	207
	1. $Pd(PPh_3)_4$, acetonylacetone 2. 		35	207
	$Pd(PPh_3)_2Cl_2$, EtOH, CO 294 psi		93	585
	$Pd(PPh_3)_2Cl_2$, EtOH, CO 294 psi		48	585

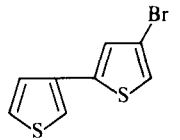
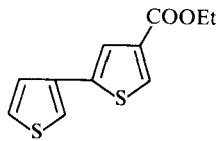
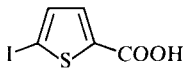
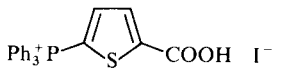
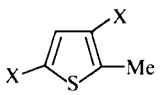
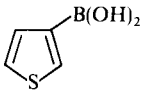
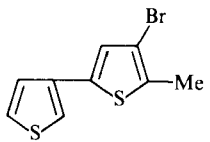
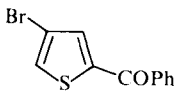
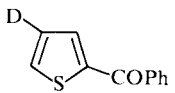
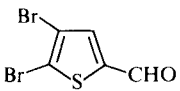
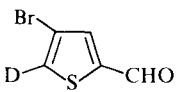
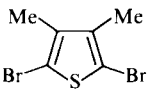
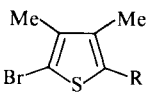
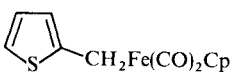
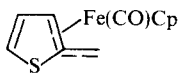
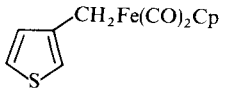
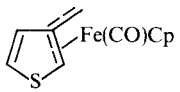
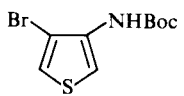
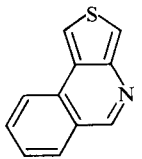
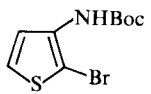
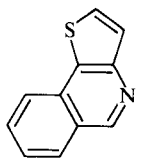
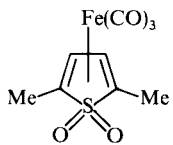
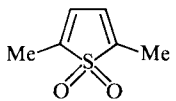
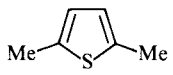
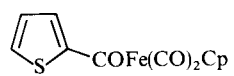
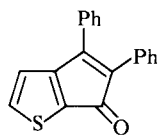
	$Pd(PPh_3)_2Cl_2$, EtOH, CO 294 psi		87	585
	$NiCl_2$, PPh_3		40	653
	1. $Pd(PPh_3)_4$, acetonylacetone 2. 		X = Br 50 X = I 37	207
	Pd complex on Si gel, H_2 or D_2			599
	Pd complex on Si gel, Zn as DBr acceptor, D_2 (H_2)			599
	Pd, RMgX			657
	*hv*		~ 1.5	527

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	*hv*		1.5	527
	1. *o*-Formylphenylboronic acid, Pd(0), DMF 2. HCl		52	503
	1. *o*-Formylphenylboronic acid, Pd(0), DMF 2. HCl		90	503
	FVP, 640–800°C	 70% 640°C	 ?	650
	*hv*, PhC≡CPh		52	651

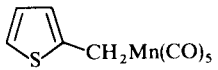
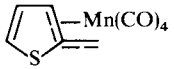
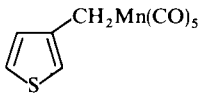
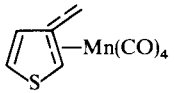
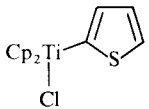
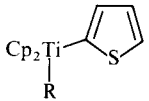
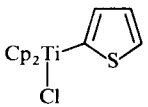
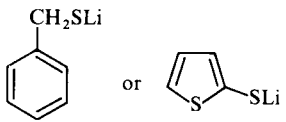
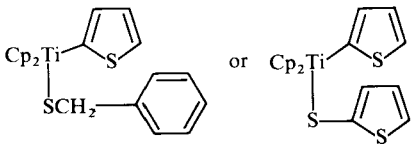
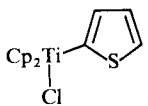
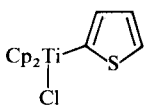
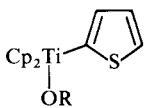
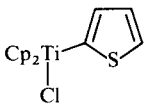
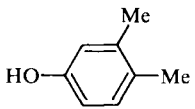
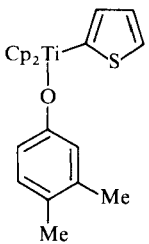
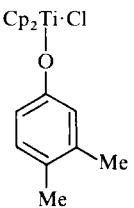
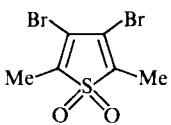
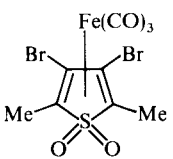
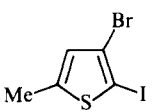
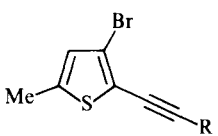
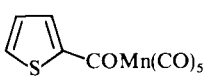
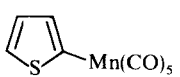
	Δ, 65°C		50	527
	Δ, 65°C		50	527
	RLi, ether			620
				603
	ROH (phenolic)	$Cp_2Ti(Cl)OR$	60–70	607
	ROLi (phenolic)		39–52	607

TABLE 22. *(Continued)*

Starting Material	Reagent	Product	Yield (%)	Ref.
	1. NEt_3 2. 	 1 : 1 	67–90	607
	*hv*, $Fe(CO)_5$			649
	1. $RC{\equiv}CZnCl$ 2. $Pd(OAc)_2$, PPh_3		57–72	212
	Δ, 70–100°C			626

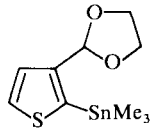
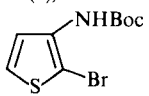
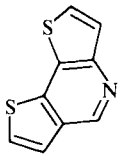
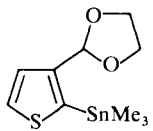
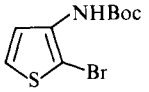
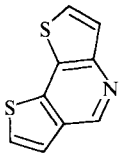
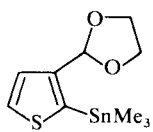
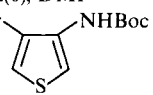
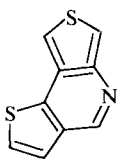
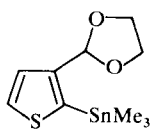
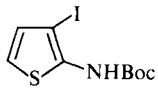
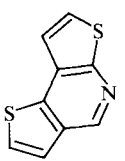
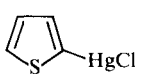
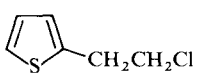
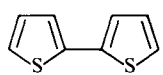
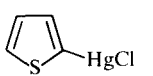
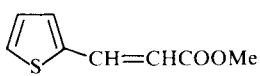
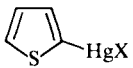
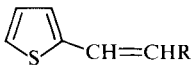
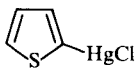
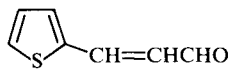
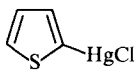
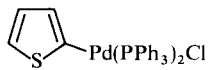
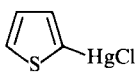
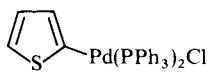
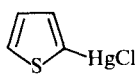
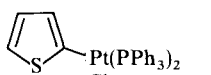
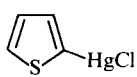
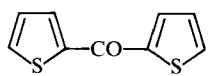
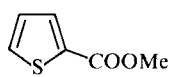
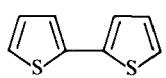
	1. Pd(0), DMF 2.  3. HCl		59	542
	1. Pd(0), DMF 2.  3. HCl		43	542
	1. Pd(0), DMF 2.  3. HCl		63	542
	1. Pd(0), DMF 2.  3. HCl		27	542
	Li_2PdCl_4, $CuCl_2$, LiCl, $CH_2{=}CH_2$	 13%  13%		569
	Pd, $CH_2{=}CHCOOMe$			570

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	Pd, Cu, Ru salts, CH_2=CHR			571
	Li_2PdCl_4, CH_2=CHCHO			643
	$Pd(PPh_3)_2Cl_2$	 *trans*	68	578
	$Pd(PPh_3)_4$			578
	$Pt(PPh_3)_4$	 *trans*	65	578
	Li_2PdCl_4, CO, 50 atm	 40%  35%  10%		574

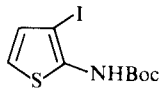
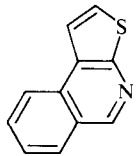
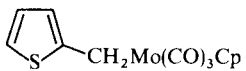
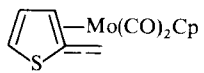
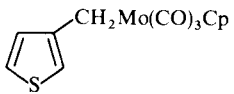
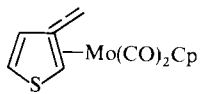
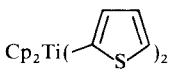
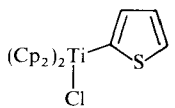
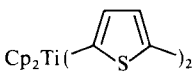
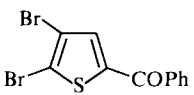
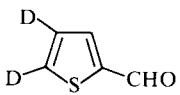
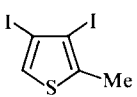
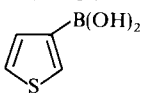
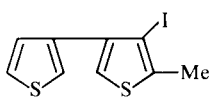
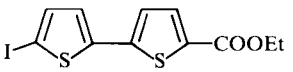
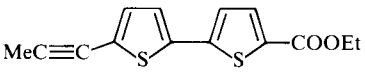
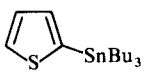
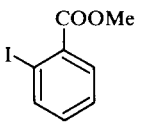
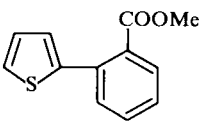
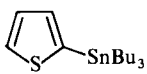
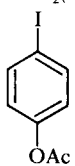
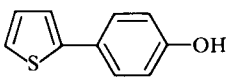
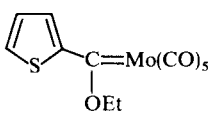
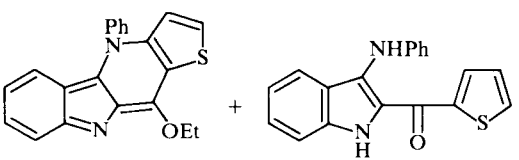
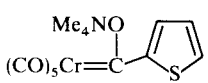
	1. *o*-Formylphenylboronic acid, Pd(0), DMF 2. HCl		75	503
	*hv*		53	527
	*hv*		35	527
	1 eq HCl			603
	ROH (phenolic)	$Cp_2Ti(OAr)_2$	67–90	607
	Pd complex on Si gel, CaO as DBr acceptor, D_2 (H_2)			599
	1. $Pd(PPh_3)_4$, acetonylacetone 2. 		36	207

TABLE 22. (*Continued*)

Starting Material	Reagent	Product	Yield (%)	Ref.
	$Pd(PPh_3)_4$, CuI, Et_3N, MeC≡CH		93	585
	1. $PdCl_2(PPh_3)_2$ 2. 		81	621
	1. $PdCl_2(PPh_3)_2$ 2. 		65	621
	3 eq PhNC			617
	110–120°C, 4h		—[b]	642

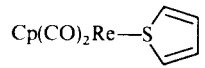
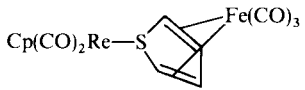
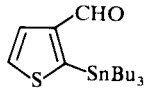
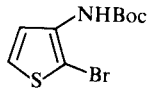
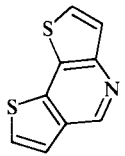
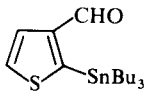
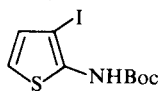
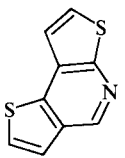
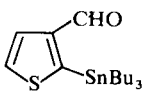
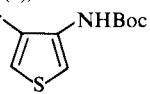
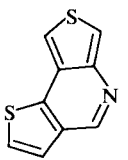
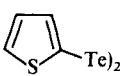
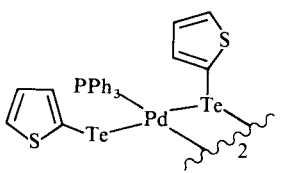
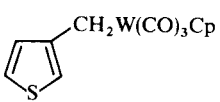
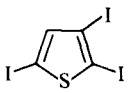
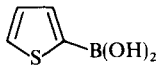
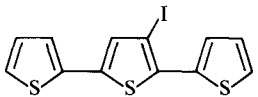
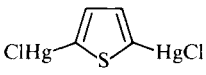
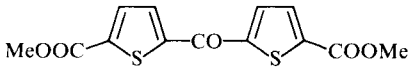
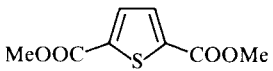
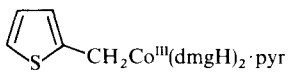
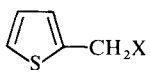
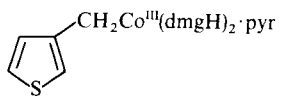
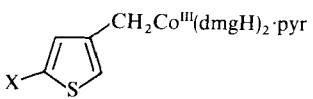
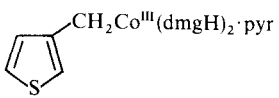
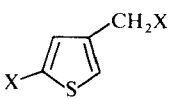
	$Fe_2(CO)_9$, THF, $-40°C$		59	658
	1. Pd(0), DMF 2. 		59	281
	1. Pd(0), DMF 2. 		42	281
	1. Pd(0), DMF 2. 		75	281
	$Pd(PPh_3)_4$			577
	*hv*		mainly unchanged starting material	527

TABLE 22. (*Continued*)

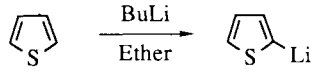
Starting Material	Reagent	Product	Yield (%)	Ref.
	1. $Pd(PPh_3)_4$, acetonylacetone 2. 		60	207
	Li_2PdCl_4, CO, 50 atm, MeOH	 36%		574
		 40%		
	Cl_2 or Br_2		> 90	602
	Cl_2 or Br_2		> 90	602
	2 eq Cl_2 or Br_2		> 90	602

[a] Sensitive in air.

[b] Polymer or dimer were also formed.

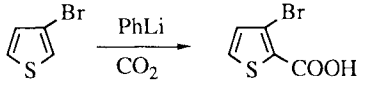
II. LITHIUM DERIVATIVES AND THENYLIC GRIGNARD REAGENTS

Introduction of substituents at the α-positions of the thiophene ring is very effectively done by metalation followed by reaction with an electrophile. In the absence of directing groups the metalation of the α-positions is much faster than that of the β-positions (see Section II.10). The prototype reaction (Eq. 1) was reported in 1948/49[10,11] and has since been extensively used and developed by many workers.



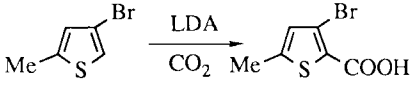
(1)

Butyl- and ethyllithium (BuLi and EtLi) or lithium diisopropyl amide (LDA) are the standard reagents for lithiation of the α-position of thiophene but also the less reactive phenyllithium (PhLi) is used successfully. Both LDA and PhLi preferably metalate the α-position even if there are halogens in the β-positions (Eqs. 2–4).[12–22] LDA is particularly useful if the thiophene ring also carries carbonyl-containing substituents, which are incompatible with the more nucleophilic BuLi, EtLi, and PhLi.



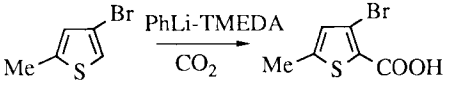
72%

(2)



56%

(3)



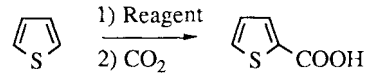
30%

(4)

It has been mentioned that one molar excess of thiophene is necessary to consume all BuLi.[23] This indicates that the reaction is an equilibrium with a significant amount of BuLi present if a stoichiometry of 1 : 1 is used. The α-lithiated thiophene derivatives are almost always used *in situ*. Methyllithium is not used to metalate the thiophene α-positions because of its lower reactivity.

An interesting application is the use of polystyryl lithium to metalate thiophene, which gives 43% yield of 2-thiophenecarboxylic acid after carbonation.[24]

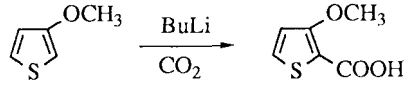
Direct treatment of thiophene derivatives with lithium metal is hardly a useful lithiation method unless naphthalene or other electron sinks are present (Eq. 5).[25]



(5)

Reagent	Yield
Li, THF	12%
Li, naphthalene	41%
Li, 1,1-diphenylethylene	92%

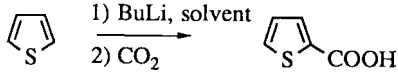
A widely applied concept is the use of directing groups placed on the thiophene ring. These groups carry electronegative elements, usually oxygen or nitrogen, which form donor complexes with the attacking lithium reagent and also stabilize the thienyllithium derivative formed, most likely through intramolecular complexation. These reactions, referred to as *directed metalations*, are exemplified in Eqs. 2 and 6.[26] Directed metalations are discussed in Section II.7.



86%

(6)

Coordinating solvents and/or some additives with Lewis base character are often beneficial for the lithiation reactions. Accordingly, the most commonly used solvents are diethyl ether and THF, but dioxane, methylal, and the glymes are also used. Enhanced reactivity of the metal introducing agent may be achieved by the coordination of TMEDA, DABCO, or other similar tertiary amine bases.[27–29] The BuLi–TMEDA reagent is reactive enough to metalate one of the methyl groups of 2,5-dimethylthiophene, although the 3-position is also metalated (Section II.5).[30,31] Another example is shown in Eq. 7, where no reaction took place in hexane, while an almost quantitative yield was obtained on addition of triethylamine.[32]



(7)

Solvent	Yield
Hexane	0%
Hexane + NEt_3	quant.

In hydrocarbon solvents the lithium reagents are most probably oligomeric or even polymeric, and it is assumed that the coordinating agents may break up these aggregates to form more reactive lower complexes.[33] This probably holds true also in ether-type solvents to some extent. While metalation of the β-positions is difficult and requires special activating groups, halogen–metal exchange at this position proceeds smoothly as is also the case for the α-positions (Sections II.3 and II.4). The stability of the β-lithiated thiophenes are not as good as for the α-lithium derivatives, since the former may undergo ring opening (Section II.9) and rearrangement reactions (Section II.8). Rearrangements may, in fact, occur with some halogenated α-lithiothiophenes as well. Therefore the halogen–metal exchange reactions are usually performed at lower temperatures (-100 to -50°C), particularly when the metal is expected to enter the β-position.

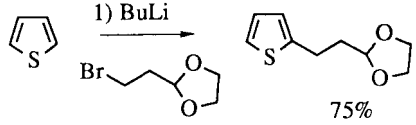
1. Reactions of α-Thienyllithium Derivatives Obtained via Metalation

In this section hydrogen–metal exchange (metalation) will be discussed, and also some cases of other exchange reactions will be included where heteroatoms such as silicon, tin, and selenium are replaced by lithium. Halogen–metal exchange reactions will be treated separately (Sections II.3 and II.4).

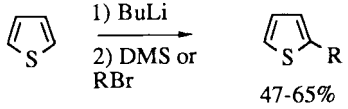
A very large variety of electrophiles have been used to trap the thienyllithium derivatives; the discussion here will exemplify only some of the different cases but also focus on the more unexpected reactions. The reader is referred to Table 1 for a compilation of reactions based on metalations of the α-position. It is convenient to make distinctions according to the following reactions: *alkylations and arylations*, *halogenations*, *acylations*, *oxidations*, and the *introduction of heteroatoms* (*including other metals*). The same reaction types apply of cause to most other thienyl and thenyl lithium derivatives as well as Grignard reagents.

A. Alkylations and Arylations

The 2-thienyllithium reagents are nucleophilic and consequently may attack most substrates generally used in nucleophilic substitution reactions. Thus, treatment of thienyllithium reagents with organohalides or sulfates may lead to alkylation of the thiophene nucleus as shown in Eqs. 8[34,35] and 9.[36] Many other examples are found in Table 1.



(8)



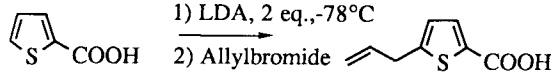
(9)

The alkylation is sometimes an unwanted reaction since the metal introducing reagent may have been prepared by a metalation reaction of the corresponding alkyl halide with lithium metal. Unreacted organohalide then reacts with thienyllithium derivatives to produce the undesired alkylated thiophenes.

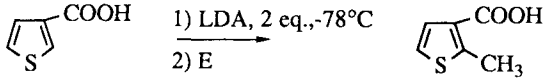
Generally, thiophene derivatives carrying carbonyl substituents are not good candidates for metalation reactions. However, 2- and 3-thiophenecarboxylic acids are metalated in the 5- and 2-positions, respectively, by the use of 2 eq of LDA without interfering addition reactions of the carbonyl group. The thienyllithium reagents were trapped with a variety of alkyl halides to give the corresponding alkyl thiophenes (Eqs. 10 and 11).[37] Prior to these results 3-thiophenecarboxylic acid was metalated with LDA and trapped with TMSCl to give 2-trimethylsilyl-3-thiophenecarboxylic acid.[14]

The lithium carboxylate moiety placed in the 3-position is obviously an efficient directing group since only products resulting from lithiation of the

adjacent 2-position are observed. Curiously, benzyl bromide did not react with this lithium derivative.[37]



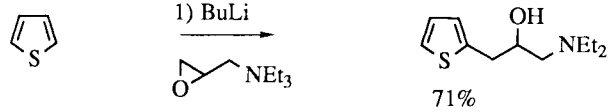
50% (10)



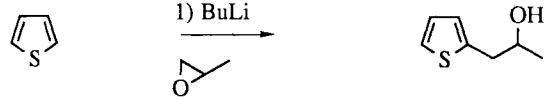
87% (11)

E	R
TMSCl	TMS 55%
MeI	Me 87%
EtI	Et 31%
AllylBr	Allyl 22%
$PhCH_2Br$	$PhCH_2$ 0%
$C_6H_{13}CHO$	$CH(OH)C_6H_{13}$ 55%
Me_2CO	$Me_2C(OH)$ 65%

Epoxides are attacked by 2-thienyllithium derivatives at the least substituted site as exemplified in Eqs. 12[38] and 13[39] to give thiophene derivatives with alkyl side chains carrying the alcohol function two carbon atoms away from the thiophene ring.

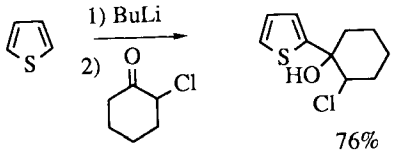


71% (12)



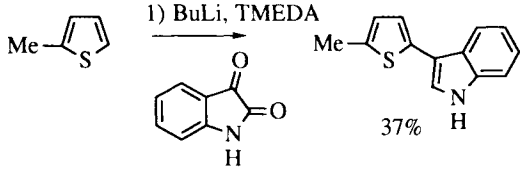
(13)

If, instead, the thienyllithium reagent is allowed to react with ketones or aldehydes, the alcohol group will be placed at the thenylic position (Eq. 14).[40] In this case the 1,2-addition to the carbonyl group is faster than the substitution of the chlorine even though the latter is placed at the usually very reactive α-position to the carbonyl group.



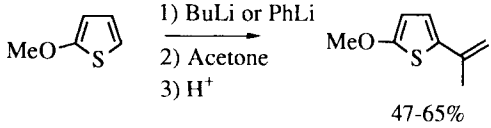
76% (14)

Although ethyl chloroacetate is an electrophile related to the one above, a polymeric material is formed on treatment with 2-thienyllithium.[36] Thus selectivity problems may be at hand in cases where the very reactive thienyllithium derivatives will attack multifunctional electrophiles. However, selective attack by 5-methyl-2-thienyllithium at the keto carbonyl group of isatin instead of the amide carbonyl group is observed (Eq. 15).[28]

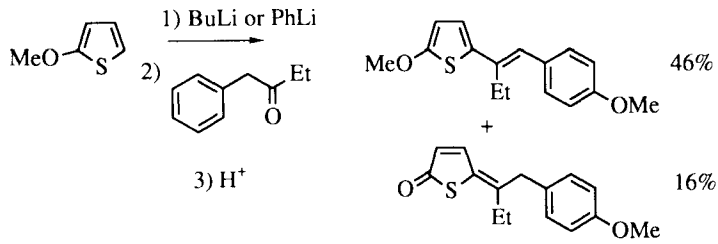


(15)

Similar selectivity is observed with ethyl phenylpyruvate.[41] The alcohols formed in this type of reaction may easily eliminate water on acid treatment, resulting in a net introduction of a vinylic group to the thiophene ring as shown in Eq. 16.[42] Other similar cases are shown in Eq. 17, but here also methanol is eliminated (1,6-elimination) to give thiolactone systems.[43]

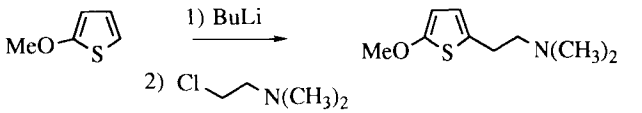


(16)



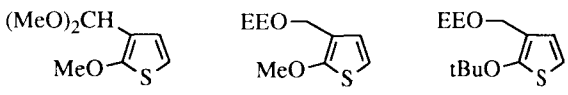
(17)

Attachment of the *N*,*N*-dimethylaminoethyl group to the thiophene nucleus has been successful by treatment of 1-chloro-2-dimethylaminoethane with some thienyllithium derivatives (Eq. 18).[18] This reaction does not work, however, with those 2-thienyllithium derivatives carrying both acetal and alkoxy groupings at the 4- and 5-positions, although the metalation reaction worked. The reason for this is suggested to be the formation of an unreactive polymeric complex between the thienyllithium molecules (Eq. 18, see also Eq. 208).



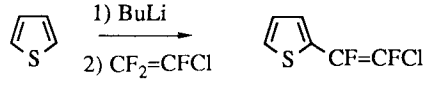
(18)

These compounds all gave 0% of *N*,*N*-dimethylaminoethyl substitution.

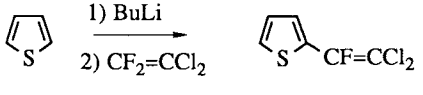


In order to introduce vinylic substituents, various kinds of vinylic halides may be used. Trifluorochloroethene is attacked by 2-thienyllithium at the most

electropositive carbon followed by elimination of fluoride ion to give the haloalkene carrying the thiophene and the chlorine substituent at different carbons (Eq. 19).[44,45] The stereochemistry is not known. Tetrafluoroethylene gave the 1,2-dithienyl-substituted ethylene derivative.[44] Also, 1,1-dichloro-2,2-difluoroethylene is attacked at the fluorine-carrying carbon, resulting in elimination of the fluoride ion (Eq. 20).[46,47]

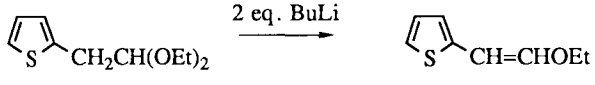


82% (19)



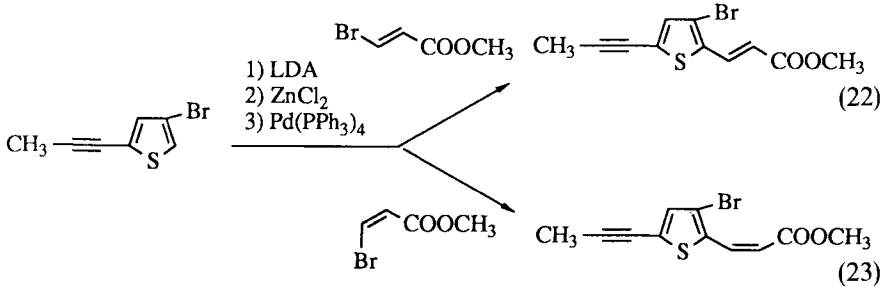
81% (20)

Thienylenol ethers were obtained by treating (2-thienyl)acetaldehyde diethylacetal with 2 eq of BuLi (Eq. 21).[48]



78% (21)

Ethanol was eliminated presumably via a thenylic anion, which, however, could not be trapped even at $-70°C$. Various enol ethers were prepared by trapping the resulting 5-thienyllithium derivative with different electrophiles such as water, TMSCl, and $Ph(CH_3)_2SiCl$. Transition-metal-catalyzed cross-coupling has been applied for the preparation of 2-thienylacrylates. *Cis-* or *trans-β-*bromoacrylates and 2-thienylzinc chlorides, obtained from the corresponding 2-thienyllithium derivatives by treatment with dry zinc chloride, were stereoselectively coupled in the presence of $Pd(PPh_3)_4$ (Eqs. 22, 23).[19]

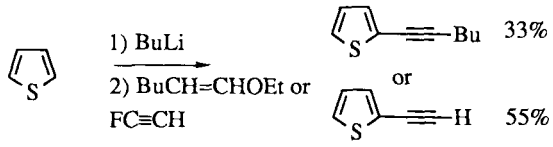


(22)

(23)

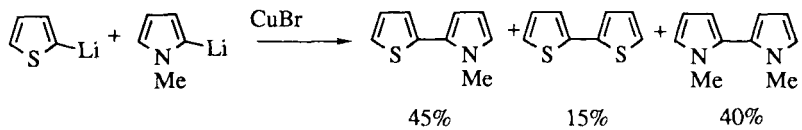
Conversion of the thienyllithium reagent to the less reactive zinc reagent was necessary since the thienyllithium derivative would be suspected to undergo addition reactions with the α,β-unsaturated carbonyl system.[49] Acetylenic

groups may be attached to the thiophene ring by reaction of 2-thienyllithium with vinyl ethers[50] or fluoroacetylenes (Eq. 24).[51]



Thienylacetylenes may also be prepared by cross-coupling of halothiophenes with acetylenic zinc derivatives under palladium catalysis (see Table 22).

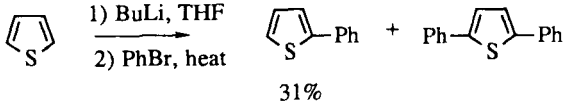
The cross-coupling technique has also been used for *arylation* of thiophene derivatives (Eq. 25, 26).[13,52]



(25)

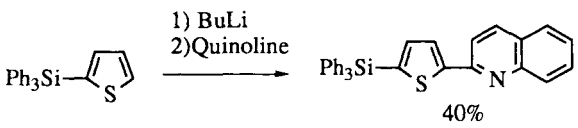
(26)

The most common catalysts or coupling agents were originally copper salts (CuCl, CuBr, $CuCl_2$, $CuBr_2$),[53–56] and this reaction is sometimes referred to as the Karasch reaction.[57] Other metal based catalysts have been developed, and Pd and Ni are now increasingly being used. The involvement of thienyl copper and thienyl transition-metal intermediates is likely, and these areas are compiled in Table 21 (copper derivatives) and Table 22 (transition-metal derivatives). The direct treatment of 2-thienyllithium with bromobenzene in refluxing THF gives a mixture of 2- and 2,5-diphenylthiophene without the use of a catalyst (Eq. 27).[36]



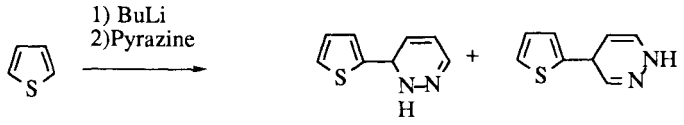
(27)

Arylation of 2-thienyllithium derivatives with halopyridenes and other electron deficient nitrogen aromatics has been successful, as exemplified in Eq. 28.[58–63]

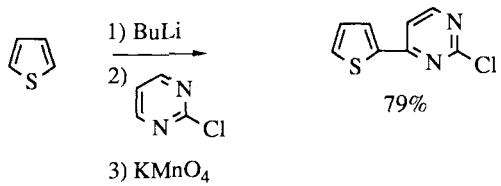


(28)

These arylations proceed via addition–elimination steps. The adduct between the thienyllithium derivative and the nitrogen heterocycle is sometimes isolated[62] and/or may be aromatized by oxidation (Eqs. 29, 30).[61]

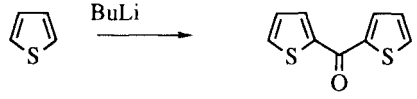


40% (29)



79% (30)

Acylations are among the most frequently used reactions of 2-thienyllithium or other thienyl metal derivatives. A number of acylating agents have been applied, such as carbon dioxide, DMF, and other carboxamides, carbonates, carbamates, acetic anhydride, and nitriles (see Table 1). Carbon dioxide usually gives good yields of thiophene carboxylic acids but has also been used to prepare dithienyl ketone (Eq. 31).[64] The latter reaction is better performed by the use of carbamates or a carbamoyl chloride.[65]

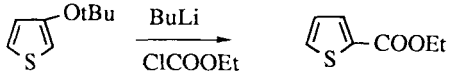


(31)

CO_2	67%
Me_2NCO_2Et	92%
Me_2NCOCl	90%

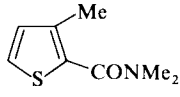
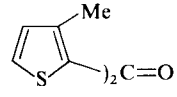
In the carbamate related reactions 2 eq of the thienyllithium reagent were used; with only 1 eq the amide was also observed (Table 23). It was discussed whether a stepwise addition of different lithium reagents could lead to unsymmetric ketones, but no definite conclusions were made.

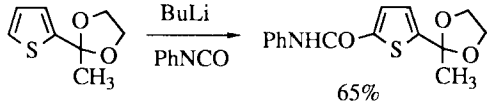
The direct introduction of the ester functionality has been achieved by reacting 2-thienyllithium with chloroformates[66] and amidation has been done by the use of phenylisocyanate[67] and *N,N*-diethylperfluoropropanecarboxamide (Eqs. 32–34).[68]



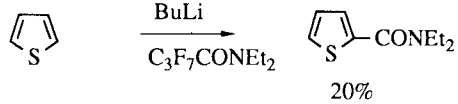
75% (32)

TABLE 23. Product Distribution (g.l.c.) of Amide to Ketone in the Reaction of 3-Methyl-2-thienyllithium and 1 eq of Carbamate Derivatives Me_2NCOX

X		
OEt	10.5	89.5
SEt	7.5	92.5
OPh	55	45
Cl	> 98	< 2

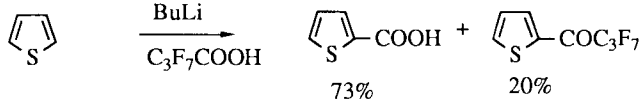


(33)



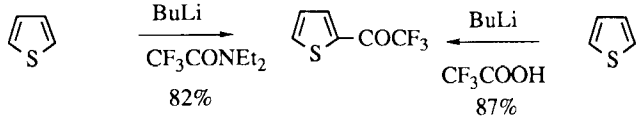
(34)

The latter case is rather unexpected since the tetrahedral intermediate obviously decomposes by losing the fluorocarbon moiety, carrying the negative charge, instead of the diethylamide ion. Perfluorobutyric acid behaves in a similar way by producing mostly 2-thiophenecarboxylic acid on reaction with 2-thienyllithium (Eq. 35).[68]



(35)

On the other hand, trifluoroacetic acid, *N*,*N*-diethyltrifluoroacetamide,[68] and *N*,*N*-dimethyltrifluoroacetamide[69] give high yields of 2-trifluoroacetylthiophene in their reactions with 2-thienyllithium (Eq. 36).

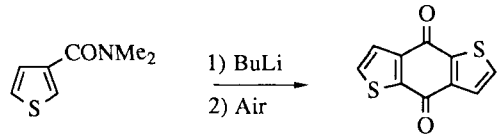


(36)

In this case the tetrahedral intermediate apparently does not lose the trifluoromethyl anion. The explanation for this difference may be that the longer fluorocarbon chain can lose a fluoride ion, perhaps in a concerted manner, to give

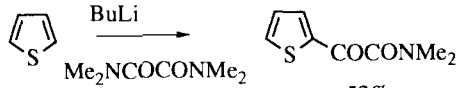
the corresponding perfluoro olefin, while the trifluoromethyl anion has no such possibility.

Methyl thienyl ketones have been synthesized by trapping 2-thienyllithium with acetic anhydride[66,70] or *N*,*N*-dimethylacetamide.[71,72] Only a low yield of the propanoyl derivative was formed in the reaction of propionic anhydride with the α-thienyllithium reagent obtained from the diethylacetal of 2-thiophene carbaldehyde.[73] Thiophene carbaldehydes are conveniently prepared by trapping 2-thienyllithium derivatives by DMF, a reaction that is abundantly exemplified in Table 1 and seems to give generally better yields than the methyl ketone syntheses, although good yield has been obtained in one case.[66] Other *N*,*N*-dimethylcarboxamides behave similarly as shown in Eq. 37 where a dithienoquinone is obtained in an elegant way.[74,75]

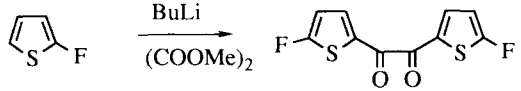


56% (37)

1,2-Dicarbonyl derivatives of thiophene are obtained on treating 2-thienyllithium reagents with various derivatives of oxalic acid. Thus, oxalic bisamides give 2-thienylglyoxylamides,[71,76] and the dimethylester gives diketones (Eqs. 38, 39).[77]

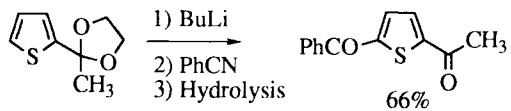


52% (38)



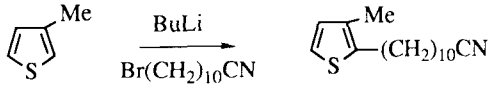
34% (39)

The reaction of 2-thienyllithium derivatives with nitriles normally gives imines or ketones after aqueous acidic workup as shown in Eq. 40.[60,78–80]

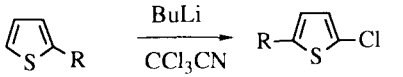


66% (40)

Interestingly, there is sufficient difference in reactivity of a primary bromine and a cyano group, so that the bromine carrying end reacts faster, resulting in an alkylation of the thiophene ring (Eq. 41).[81] In contrast, trichloroacetonitrile is attacked on the chlorine atoms to give 2-chlorothiophenes (Eq. 42).[80,82]



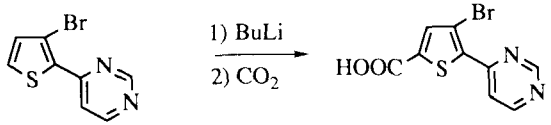
(41)



(42)

40-50%

An unexpected α-metalation was observed for 3-bromo-2-(4-pyrimidinyl) thiophene instead of halogen–metal exchange of the 3-positioned bromine atom (Eq. 43).[63] Steric hindrance at the 3-position and activation of the 5-position by the pyrimidinyl group was suggested as an explanation for this anomalous result.

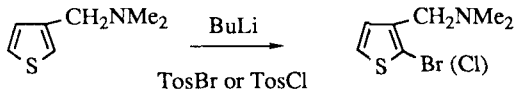


(43)

29%

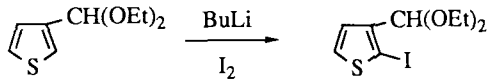
B. Halogenations

In addition to the chlorination using trichloroacetonitrile mentioned above (Eq. 42), halogenation may be achieved in moderate yields by treating 2-thienyllithium derivatives with tosylchloride or tosylbromide.[74] Halogenations of 2-lithiothiophenes may also be done by reactions with the elemental halogens Br_2[53,83], I_2[84–87] or halocarbons such as 1,3-dibromohexafluoropropane.[88] The halogen atoms in iodo- and bromoacetylenes are likewise susceptible to nucleophilic attack to give the halothiophenes.[89] It should be noted that fluoroacetylene did not give the fluorothiophene on treatment with 2-thienyllithium, but instead the acetylenic group was transferred in contrast to the bromo- and iodoacetylenes (cf. Eqs. 48 and 24).[51] Some examples are shown in Eqs. 44–48.



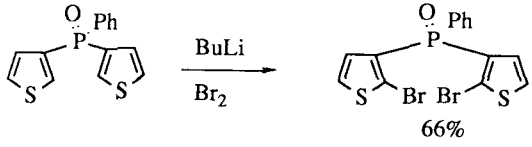
(44)

25-32%

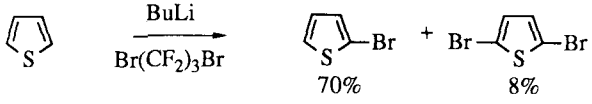


(45)

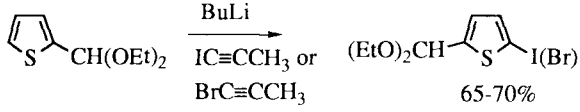
30%



(46)

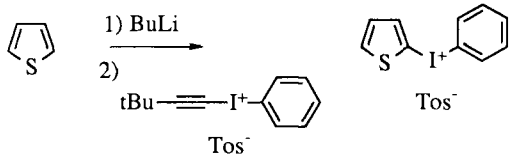


(47)



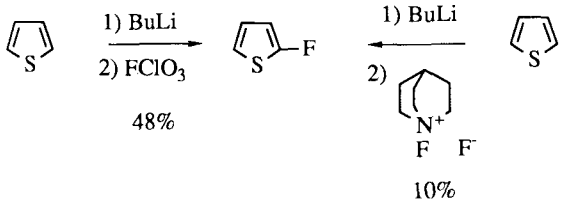
(48)

A related reaction is the attack on iodine of the iodonium salt to form the thiophene iodonium compound shown in Eq. 49.[90]



(49)

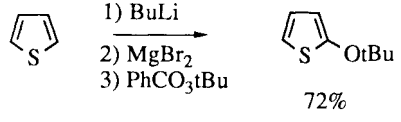
Fluorine can be introduced by the use of perchloryl fluoride,[91] or *N*-fluoroquinuclidinium fluoride[92] (Eqs. 50, 51).



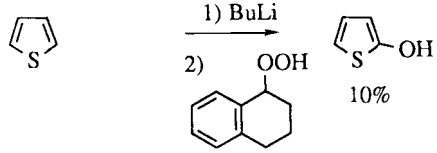
(50, 51)

C. *Oxidation and Amination*

Oxidation of thienyllithium derivatives with O_2 is not an efficient reaction for the preparation of oxygenated thiophenes. Instead, peroxo compounds seem to be the more versatile oxidation reagents, but in combination with the thienylic Grignard reagents, which, in turn, may be obtained from the thienyllithium reagents. In particular, *t*-butyl perbensoic acid ($PhCO_3tBu$) is a convenient oxidation reagent and is used to introduce the *t*-butoxy group (Eq. 52).[93,94] The 1-hydroperoxide of tetraline has also been used but resulted in only 10% yield of the 2-hydroxythiophene system on oxidation of 2-thienyllithium (Eq. 53).[95]



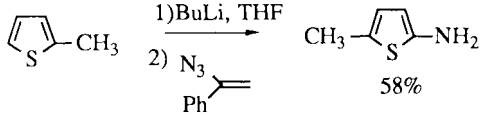
(52)



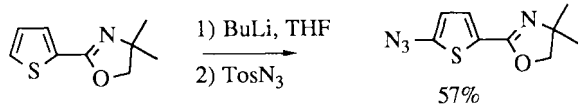
(53)

The hydroxythiophenes are treated in another part of this series (Part 3, Chapter 1), but it could be mentioned here that they may be obtained in higher yields by acid treatment of the *t*-butoxythiophenes and via oxidation of thienylboronic acids with hydrogen peroxide (see Table 14, boron compounds). Thienyl boronic esters are synthesized by trapping the thienyllithium reagents with a trialkylborate, and the related boronic acids are formed by subsequent hyrolysis.[21,96–100] Bistrimethylsilyl peroxide should also be useful for oxy-functionalization at the α-position (cf. Eq. 94).

Examples of the introduction of nitrogen-containing substituents, giving thiophene derivatives with the nitrogen atom directly attached to the thiophene ring, are not so frequent, but some advances have recently been made in this respect. Thus, styrylazide has been used successfully to trap 5-methyl-2-thienyllithium to give 5-methyl-2-aminothiophene after hydrolysis of the originally formed triazene (Eq. 54).[101] Tosyl azide has been used similarly to produce thienyl azides,[56,102] which could be reduced with hydrogen sulfide to give the aminothiophenes (Eq. 55).[56]



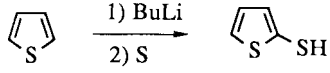
(54)



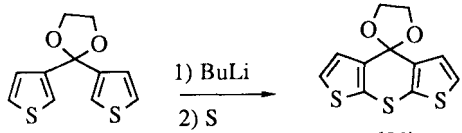
(55)

D. Introduction of Groups Carrying Nonoxygen and Nonnitrogen Heteroatoms

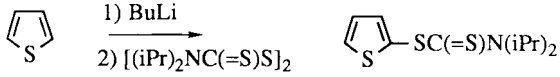
A large number of other heteroatoms has been attached to the thiophene ring by treating lithiothiophenes with halide-substituted heteroatom derivatives or disulfides, diselenides, and ditellurides as well as with the elements themselves. Thus the synthesis of thienylthiols may be done by treating lithiothiophenes with elemental sulfur followed by hydrolysis (Eq. 56).[103] The yields are not always acceptable as sulfides may also be formed, which, on the other hand, may be taken advantage of (Eq. 57).[104]



(56)

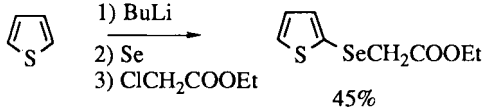


(57)

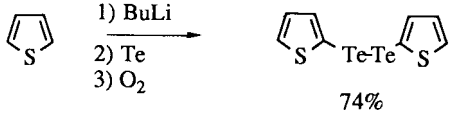


(58)

An alternative route to aromatic thiols is to treat lithioaromatics with tetraisopropylthiuram disulfide followed by basic hydrolysis of the fist formed *S*-aryl-*N*,*N*-diisopropylthiocarbamate (Eq. 58).[105] Lithium 2-thienylsulfinate was prepared by treating 2-thienyllithium with sulfur dioxide.[106] Also selenium and tellurium may be introduced via treatment of thienyllithium reagents with the elements as exemplified in Eq. 59[107] and Eq. 60.[108]

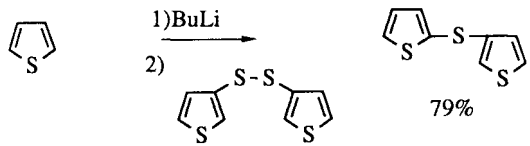


(59)



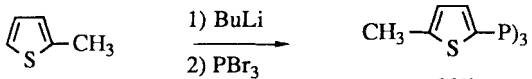
(60)

By using diorganyl disulfides, diselenides, or ditellurides, the respective unsymmetric thienyl sulfides, selenides, and tellurides may be obtained. Thus 2-thienyllithium gave 2-thienyl 3′-thienylsulfide on treatment with 3,3′-dithienyldisulfide (Eq. 61).[54]



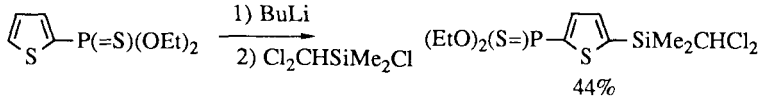
(61)

Trithienylphosphine derivatives are obtained when thienyllithium reagents are trapped with phosphorus tribromide (Eq. 62).[109]



(62)

Trimethylsilyl chloride is one of the usual trapping reagents of lithiothiophenes, and many examples where this and other silicon-containing reagents have been used are found in Tables 1–22. Interestingly, dimethyl(dichloromethyl)silyl chloride is selectively attacked at the silicon atom by the α-thienyllithium derivative prepared from 2-(diethylthiophosphonato)thiophene (Eq. 63).[110]

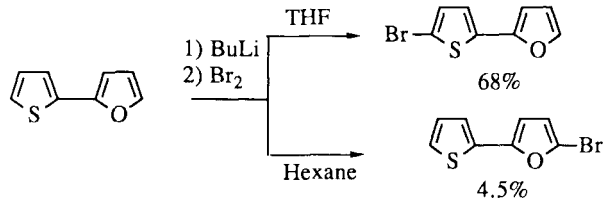


(63)

Additional examples of reactions in which heteroatoms are introduced by the use of 2-thienyllithium (prepared via metalation) are compiled in Table 1. In the case of metal derivatives the tables concerning the particular metallothiophenes should be consulted.

E. Metalations of Nonthienylic or Nonthenylic Positions

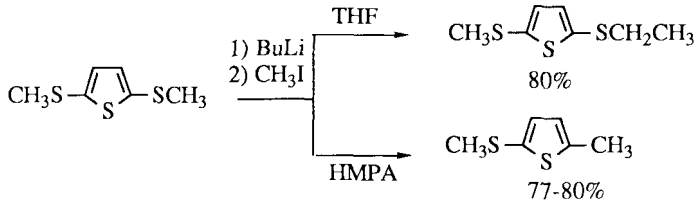
Some cases should be noted of selective metalations of positions other than those in the thiophene ring even though one or both α-positions are unsubstituted. Obviously, this may happen in cases where the acidity of other protons are higher than the thiophene protons. Thus 2-ethynylthiophene is metalated by ethereal BuLi exclusively at the acetylenic position.[111] A more complicated behavior is observed for 2*H*-thieno[2,3-*b*]thiopyran as discussed in connection with thenylic lithium reagents. An interesting solvent dependence is demonstrated for 2-(2′-furyl)thiophene (Eq. 64), where BuLi in THF metalates the thienyl α-position, while in hexane only the furyl α-position is metalated, although the yield in the latter case is very low.[83]



(64)

The thienyl α-position is also the more reactive in (2-thienyl)(2′-furyl)methane despite the presence of thenylic protons[70] as is the case also with other dithienylmethanes with free α-positions.[112–114] 5,5′-Dimethyl-2,2′-dithienylmethane was metalated to a very low degree in the thiophene ring and not in the methylene group.[113] The exact position of metalation could not be determined because of an insufficient amount of material. It seemed probable, however, that the metal was introduced in the 3-position since the corresponding carboxylic acid was the tentative product based on comparison with authentic material.

A selective metalation of a methyl group of 2,5-bis(methylthio)thiophene is achieved on treatment with BuLi in THF at $-70°C$. A different selectivity is observed when HMPA is used as solvent since now the methylthio group is exchanged for lithium (Eq. 65).[115]

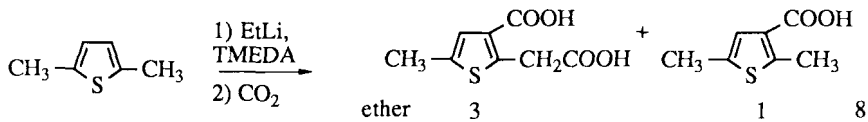


(65)

In this context it should be mentioned that the TMS group may be replaced by lithium on BuLi treatment as shown for 2,5-bis(trimethylsilyl)-thiophene (see Table 16, silicon derivatives).[116]

2. Reactions of β-Thienyllithium Derivatives Obtained via Metalation

Many reactions discussed in the preceding chapter also apply to the 3-thienyllithium reagents (Table 2). The use of 3-thienyllithium derivatives, obtained via metalation is, however, not as frequent as is the case for the 2-thienyllithium derivatives, since the β-position is not easily metalated unless strongly directing groups are placed in the α-positions. (See Section II.7 for further examples of directed metalation.) In fact, even when both α-positions are occupied by methyl groups the β-positions are not selectively metalated but also the thenylic positions are reacting with the metal introducing agent, such as the BuLi–TMEDA[31] or EtLi–TMEDA[30] complexes. Thus 2,5-dimethylthiophene was metalated by the latter reagent to give a mixture of 2,5-dimethyl-3-thiophenecarboxylic acid and 3-carboxy-5-methyl-2-thienylacetic acid after Dry Ice quenching (Eq. 66).[30] The latter compound (m.p. 217–219°C), was erroneously determined to be 3-carboxy-2-methyl-5-thienylacetic acid.[31] A small amount of 5-methyl-2-thienylacetic acid was also formed in this reaction (cf. Eq. 108).[117]

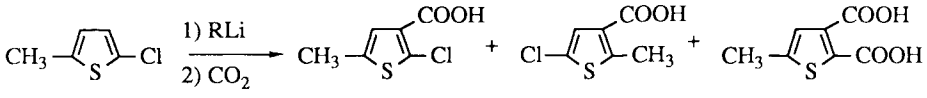


ether	3	1	8%
hexane	10	1	16%

(66)

As mentioned above, 2,5-bis(trimethylsilyl)thiophene undergoes exchange reaction of a TMS group and is not metalated in the β-position by BuLi in THF.[116]

The 2-positioned chlorine of 2-chloro-5-methylthiophene directed the metalation to the 3-position but also chlorine–lithium exchange was observed using BuLi–TMEDA in ether (Eq. 67). Changing the metalating reagent to LDA favored metalation of the 4-position, although the total yield of carboxylic acids was low.[31]

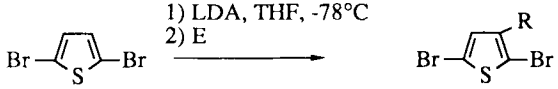


BuLi, TMEDA	1		1.5
LDA	1	1.8	1.5

(67)

Both 2-methoxy-5-methylthiophene[118] and, to a lesser extent, 5-methyl-2-methylthiothiophene[119] are metalated in the 3-position. Metalation experiments of 2,5-dimethoxythiophene with BuLi at room temperature was reported to give unidentified products.[120] It was later shown, by using 2 eq of BuLi followed by trapping the reaction mixture with dimethyl sulfate, that 1-methylthio-1,3-octadiyne was formed, which was a result of ring opening of the initially formed β-dilithio derivative of 2,5-dimethoxythiophene (see Section II.9).[121] A nonselective metalation of the β-positions of 2-chloro-5-methoxythiophene was noticed on treatment with BuLi at room temperature.[122] NMR and GC–MS (gas-chromatographic–mass spectrometric) analysis of the product obtained after deuteration showed that the 4-deutero isomer predominated over the 3-deutero isomer by 2 : 1. The lithiated thiophenes in this experiment underwent ring opening at higher temperature.

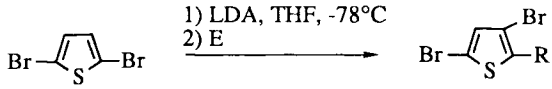
Lithiation of 2,5-dibromothiophene with LDA in ether or THF at $-70°C$ gives 2,5-dibromo-3-lithiothiophene, which could be trapped with TMSCl to give 2,5-dibromo-3-trimethylsilylthiophene.[14] This result was later confirmed, and some other electrophiles could also be used as trapping agents, such as trimethyl- and tributyltin chloride, and phenylselenenyl chloride (Eq. 68).[123]



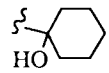
E	R	
PhSeCl	PhSe	78%
Me_3SiCl	Me_3Si	91%
Me_3SnCl	Me_3Sn	74%

(68)

In contrast, when other electrophiles such as water, dimethyldisulfide, and carbon electrophiles were used, the 2,4-dibromo-5-substituted thiophenes were formed. Some examples are shown in Eq. 69.[124]

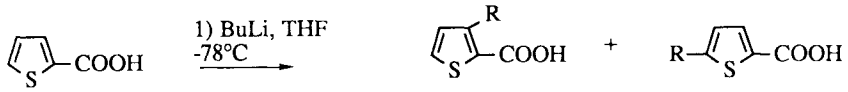


(69)

E	R	
Cyclohexanone		77%
H_2O	H	100%
CH_3I	CH_3	95%
CH_3SSCH_3	CH_3S	45%

It is possible that the electrophiles used in the latter investigation are less reactive and react with the lithiothiophene during the temperature rise after their addition. This would allow 2,5-dibromo-3-lithiothiophene to undergo a halogen migration (see Section II.8) to form the thermodynamically more stable 2,4-dibromo-5-lithiothiophene, which is the species reacting with these slower electrophiles.

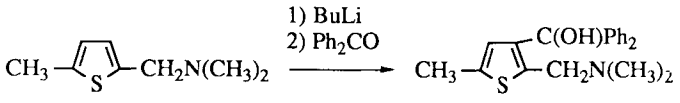
The lithium carboxylate moiety has proved to be a strong directing group of lithiation as demonstrated for 2-thiophenecarboxylic acid.[125] The electrophile enters the 3-position following metalation with 2 eq of BuLi in THF at $-78°C$ despite the access of the normally more reactive 2-position (Eq. 70). At higher reaction temperatures with the electrophile, the lithium starts to migrate to the 5-position via transmetalation. It should be noted that the use of 2 eq of LDA gave metalation only in the 5-position.[37]



2) E	R		
MeOD	D	93%	5%
Me_3SiCl	Me_3Si	85%	-
MeSSMe	MeS	94%	-
MeI	Me	83%	-
I_2	I	92%	-
$PhCH_2Br$	$PhCH_2$	70%	-
DMF	CHO	20%	-

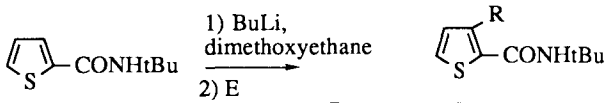
(70)

Similar β-metalations are reported for other thiophenes having electron-withdrawing substituents in the α-position, such as the 2-pyridyl,[59,55,126] oxazolinyl,[102,125,127] and sulfonamido[128] and carboxamido[129] groups (see Table 2). Although the electronic *-I,-M* (-substituent) effect is a common feature of these groups and would act to stabilize on the adjacent negatively polarized carbon of the lithium derivative formed, these thiophenes also carry electronegative atoms that may coordinate to (i.e., direct) the incoming lithium reagent. This property should be the dominating one in the case of 5-methyl-2-(dimethylaminomethyl)thiophene that is metalated selectively in the 3-position (Eq. 71).[74]



(71)

A 1 : 1 mixture of α- and β-metalation was reported for the reaction of *N,N*-diethylthiophene-2-carboxamide with *sec*-BuLi in THF, while the use of other solvents such as ether and DME resulted only in α-metalation.[129] A much better selectivity of proximal β-metalation was then achieved by replacing the tertiary amide group with the secondary *t*-butylcarboxamido function (Eq. 72). The favored metalating conditions were now BuLi in DME or THF at temperatures below 0°C. Change of base to LDA gave α-metalation as the main reaction.

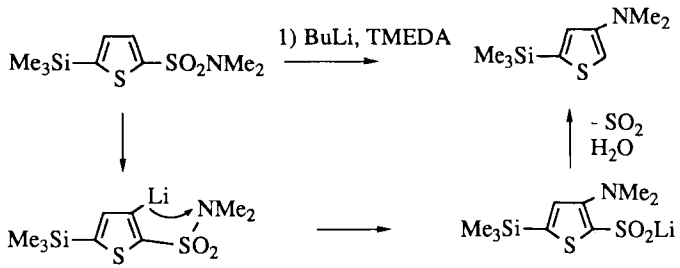


(72)

E	R
TMSCl	TMS 95%
MeSSMe	MeS 93%
I_2	I 72%
CO_2	CO_2H 74%
MeI	Me 88%
PhCHO	CH(OH)Ph 77%
$PhCH_2Br$	$PhCH_2$ 76%
DMF	CHO 63%

A drawback with this otherwise effective method is the difficulty to remove the carboxamido group. Hydrolytic conditions for preparing the free acids degraded the material in some cases.

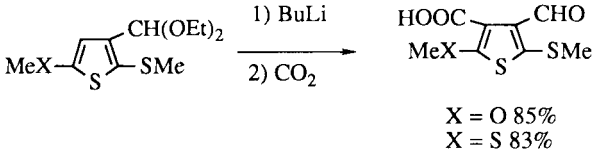
N,N-Dimethyl 5-trimethylsilyl-2-thiophenesulfonamide was metalated in the 3-position by BuLi at 0°C; a 10% yield of the 3-carboxylic acid was obtained on carbonation, leaving 75% starting material unreacted.[128] When the reaction was performed at − 30°C in the presence of TMEDA, a rearrangement took place to give 4-dimethylamino-2-(trimethylsilyl)thiophene in 39% yield. A much lower yield was obtained when the quenching was performed with water instead of Dry Ice. The proposed mechanism (Eq. 73) involves metalation of the β-position closest to the sulfonamido group followed by an intramolecular attack of the carbanionic center on the nitrogen of the sulfonamido group. The lithium sulfinate moiety acts here as a leaving group, and loss of sulfur dioxide during the workup procedure then leads to the observed product.



(73)

The use of the *N,N*-diethylsulfonamide instead of the *N,N*-dimethyl analog together with BuLi/TMEDA followed by Dry Ice treatment led not only to carboxylation of the 3-position but also to desilylation. The latter event is surprising since the 3-lithiated TMS-sulfonamide could be trapped as the deuterium derivative. These results remain to be clarified, but a rearrangement similar to the one of the *N,N*-dimethyl case was not observed. The *t*-butylsulfonyl group also allows metalation of the adjacent *β*-position as 2-*t*-butylsulfonylthiophene was bismetalated with 4 eq of BuLi at − 15–20°C to give the 3,5-bis(aldehyde) (59%) and the 3,5-dicarboxylic acid (68%) after trapping the reaction mixture with DMF and CO_2, respectively.[130]

Trisubstituted thiophenes carrying electronegative and coordinating substituents in the 2,3,5-positions may be metalated in the remaining *β*-position by BuLi (Eq. 74).[131] It should be noted that the methylthio groups were not exchanged for lithium.



(74)

X = O 85%
X = S 83%

Metalation followed by carbonation of 5,5′-dimethyl-2,2′-dithienylmethane gives a low yield of a monocarboxylic acid, the carboxyl group of which was determined to be placed in one of the *β*-positions.[113]

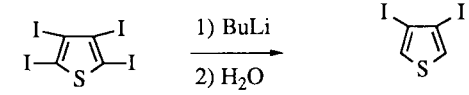
Further cases of metalation of the *β*-position may be found in Table 2 and in Section II.7, where the subject of directed metalation is discussed.

3. Reactions of *α*-Thienyllithium Derivatives Obtained via Halogen–Metal Exchange

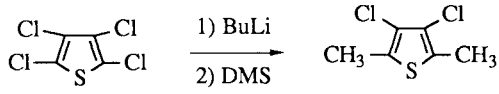
The introduction of lithium by halogen–metal exchange between halothiophenes and alkyllithium reagents is a standard route to substituted thiophenes since all of the electrophiles that were discussed elsewhere in this volume may also be applied here, and a considerable number of cases are compiled in Table 3. The lithium–halogen exchange reaction was first discovered by Gilman et al.[132,133] and Wittig et al.[134] and was later applied and developed by Gronowitz and Lawesson in the halothiophene series.[12,135–137]

A major difference between the metalation and the halogen–metal exchange reactions is that the latter are preferentially performed at lower temperatures (− 50–100°C) while the former often require room temperature or refluxing ether. It is therefore possible to get higher selectivity in the halogen–metal exchange reactions. Another halide (alkyl or aryl) may also be formed in the halogen–metal exchange reactions. Sometimes this is a problem since the newly formed halide may react with the thienyllithium to form alkylated or arylated thiophene derivatives. This occurs particularly at higher temperatures.

The selective replacement of a particular halogen with lithium at low temperature is a very useful reaction and is the major concern in this chapter. It can first be stated that the α-positioned halogens are more reactive than the β-halogens if all are of the same kind. This was recognized early and led to the synthesis of 2,4-dibromothiophene from the more easily prepared 2,3,5-tribromothiophene.[135] If an excess of BuLi is used, both α-bromines may be exchanged to give 3-bromothiophene[138] and 3,4-dibromothiophene[136] after quenching with water, starting from 2,3,5-tribromo- and tetrabromothiophene, respectively. Tetraiodothiophene[85,139] and tetrachlorothiophene[30] react similarly (Eqs. 75, 76).

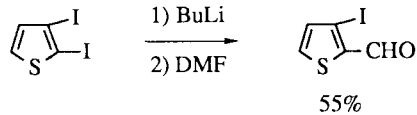


(75)

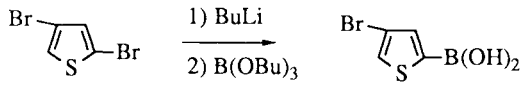


(76)

The higher α-reactivity is also manifested in the 2,3-[138] and 2,4-dibromothiophenes[140] and the corresponding diiodothiophenes[85,71,141] as shown in Eqs. 77 and 78.



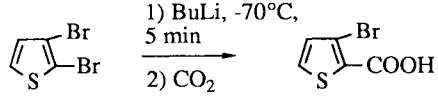
(77)



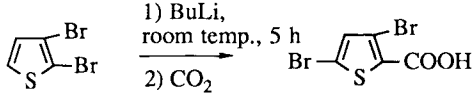
(78)

Only the α-iodine of 2,3-diiodothiophene was reacting even if 2 eq of BuLi was used.[142]

The lithium derivative initially formed in the halogen–metal exchange of 2,4-dibromothiophene is not the thermodynamically most stable one.[137] Particularly at higher temperatures there is a tendency for lithium to eventually be placed at the position where the most acidic hydrogen would have been located. This type of rearrangement, often called "halogen dance," is discussed in more detail in Section II.8. Synthetically, the reaction has found little use since the equilibrium concentration of several lithium species may be relatively high, resulting in a mixture of products. However, useful yields may be obtained as shown in Eqs. 79 and 80, where the low temperature conditions gave the expected product while higher reaction temperature resulted in halogen–lithium rearrangement.[137]

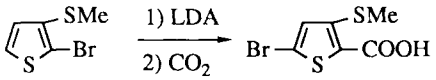


70% (79)



47% (80)

Halogen–lithium rearrangement is also involved at low temperatures as demonstrated in the reaction shown in Eq. 81, where 2-bromo-3-methylthiothiophene is rapidly added to LDA at − 78°C (cf. Eq. 182 for the mechanism).[20]

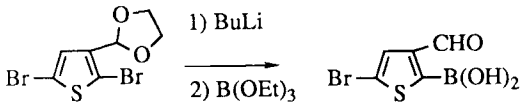


41% (81)

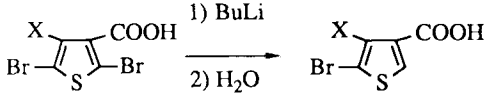
If the addition is slow halogen dance does not take place because the concentration of the starting material is not sufficient at any time to start the rearrangement.

On the basis of the different reactivities of the halogens, halogen–metal exchange reactions, one at a time, have been used to introduce two different substituents in one-pot procedures. Thus 2,3-dibromothiophene was treated in sequence with EtLi, DMF, EtLi, and $B(OBu)_3$ to give 2-formyl-3-thienylboronic acid after workup,[143] and 2,3,5-triiodothiophene gave 4-iodo-3-thiophene aldehyde by a similar sequential technique.[85] Other examples may be found in Tables 3 and 4.

Selective halogen–metal exchange of the bromine in the 2-position is observed when the 3-position carries carboxylate[144] and acetal[21] groups as shown in Eqs. 82 and 83.

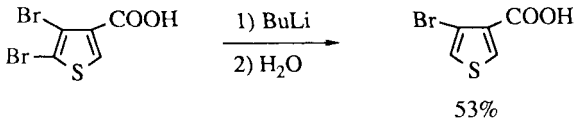


95% (82)



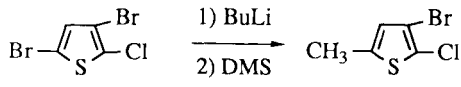
X = H 49%
X = Br 47% (83)

The reason for this is probably the coordinative character of these groups, which directs the metal introducing agent to attack the nearest bromine atom and also to stabilize the thienyllithium derivatives once formed. In 2,3-dibromo-4-thiophenecarboxylic acid, on the other hand, the α-bromine is exchanged selectively, demonstrating that the directing effect of the carboxylate group does not overtake the inherent reactivity of the α-position (Eq. 84).[144]



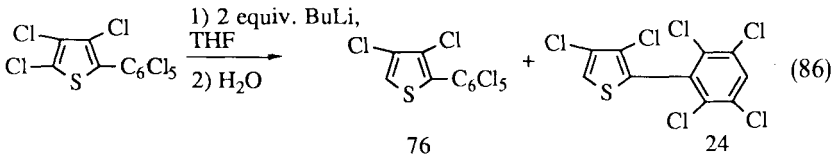
53% (84)

The different reactivity of bromine and chlorine substituents has been utilized to advantage particularly when no directing group is present in the molecule.[145–148] Thus, even though the 2-position is the more "acidic" one, the 5-Br is exchanged faster than the 2-Cl in 3,5-dibromo-2-chlorothiophene (Eq. 85).[145]

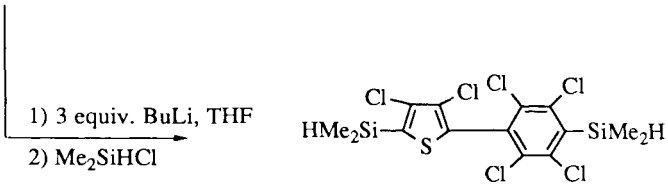


85% (85)

The thienyl α-chlorine in octachloro-2-phenylthiophene (Eqs. 86, 87) is somewhat more reactive than the phenyl *p*-chlorine,[149] as shown by the use of 2 eq of BuLi in THF at − 78°C. Both positions were exchanged with 3 eq of BuLi.



76 24 (86)



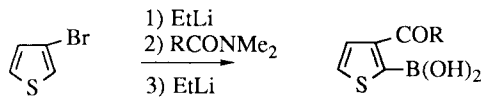
67% (87)

The direct treatment of 2-iodothiophene with lithium metal gives 2-thienyllithium.[150] Phenyllithium, which has a tendency to give metalation,[12] gives halogen–metal exchange with 2-iodothiophene, while the PhLi–TMEDA complex results in metalation.[13]

4. Reactions of β-Thienyllithium Derivatives Obtained via Halogen–Metal Exchange

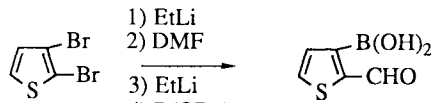
As seen in Table 4, the 3-thienyllithium reagents may be trapped with essentially all of the electrophilic reagents already mentioned. However, two properties of the 3-thienyllithium derivatives should be considered, the tendency to undergo lithium migration and the tendency to undergo ring-opening reaction. These reactions are discussed in more detail in Sections II.8 and II.9, respectively. As a rule the 3-thienyllithium reagents are stable at $-70°C$ and are treated with the electrophiles at this temperature. Although there are obvious similarities between the 2-thienyllithium and the 3-thienyllithium reagents, some of the reactions of the latter derivatives deserve some comments.

Since β-positioned bromines are exchanged faster than the α-hydrogens it is possible to use one-pot sequences to prepare 2,3-disubstituted thiophenes by first treating the appropriate β-bromothiophene derivative with BuLi followed by the first electrophile and then again with BuLi followed by the second electrophile. This requires that the first electrophile form an intermediary group that will direct the secondly introduced lithium atom to the 2-position. Examples of this technique are shown in Eq. 88. Thus, 3-bromothiophene is converted to 3-formyl-2-thienylboronic acid and 3-acetyl-2-thienylboronic acid.[100,143]



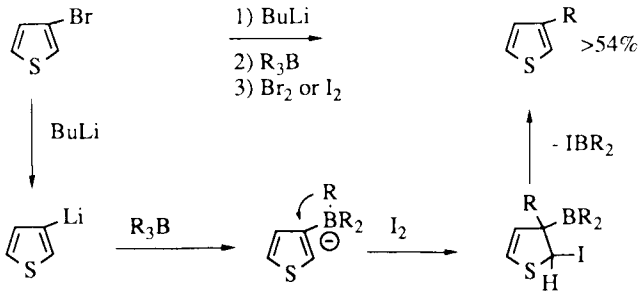
R = H 44%
R = Me 13% (88)

If 2,3-dibromothiophene is used, such a reaction sequence gives the product with the reversed order of the substituents on the thiophene ring since the α-bromine is more reactive than the β-bromine (Eq. 89).[143]



35% (89)

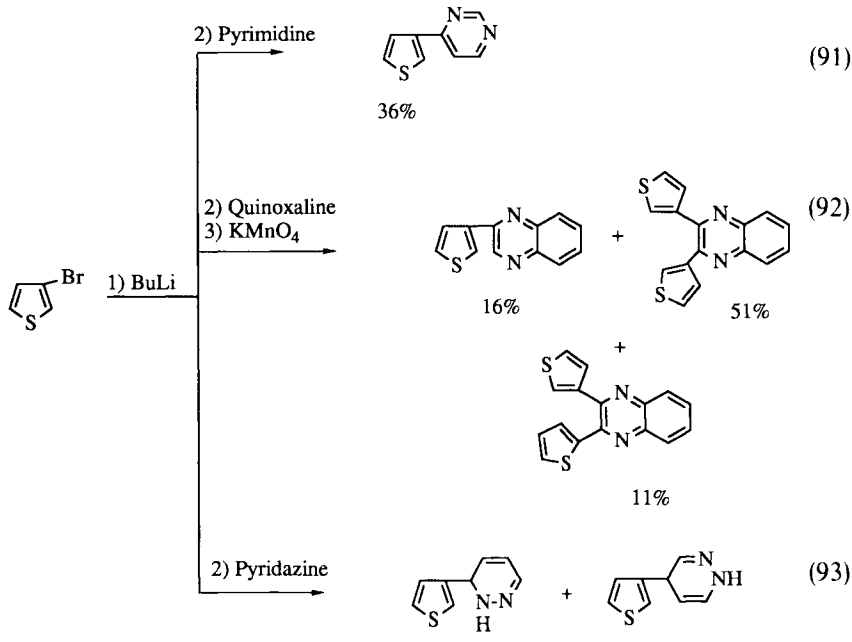
A new alkylation procedure was introduced by treating 3-thienyllithium with a trialkylborane (R_3B) and then Br_2 (or I_2).[151] The 3-alkyl thiophenes are obtained in $> 54\%$ yield. Migration of the alkyl group from boron to the 3-thiophene carbon is initiated by the halogen, which is supposed to attack the 2-position. Subsequent elimination of $halBR_2$ gives the final product (Eq. 90).



(90)

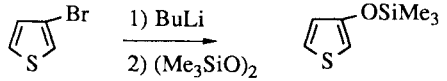
R = various alkyl groups

Thiophenes carrying aromatic nitrogen heterocycles in the 3-position may be obtained via the 3-thienyllithium derivatives.[60,62,63] Thus 3-thienyllithium was treated with pyrimidine to give 3-(4-pyrimidinyl)thiophene (36%) after aromatization with $KMnO_4$ (Eq. 91).[63] A similar reaction with pyridazine gave addition products (Eq. 92).[62] The 1,2-addition mode was preferred when ether was the solvent and pyridazine was added to the thienyllithium derivative at 0°C, but the 1,4-addition was preferred when THF was the solvent and the lithium derivative was added to the pyridazine at -75°C.[62] In these cases the aromatizations were effected with chloranil treatment. Reaction of 3-thienyllithium with quinoxaline gave the mono and di(thienyl)-substituted quinoxalines after oxidation with potassium permanganate (Eq. 93).[60] An excess of the thienyllithium reagent increased the amount of the disubstituted products.



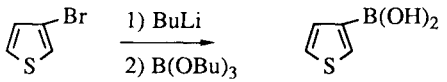
Acylation of the thiophene 3-position was achieved by the reaction of phthalic anhydride and 3-thienyllithium at $-70°C$.[152] A mixture of mono- and dithenoyl benzene derivatives was obtained in 38 respectively 30% yields. (Compare other reactions with phthalic anhydride derivatives and thienyl Grignard reagents in Tables 11 and 12.)

Oxidation of thienyllithium reagents with oxygen directly or with peroxides are generally not useful routes to oxidized thiophenes. Thienyl Grignard reagents are, on the other hand, successfully used in this respect as demonstrated by Lawesson et al.[153,154] A new development in this area was found recently, since a new siloxylation reagent, bistrimethylsilylperoxide, was used to give 3-trimethylsilyloxythiophene starting from 3-thienyllithium (Eq. 94).[155] Hydroxythiophene systems should be easily prepared by this method.

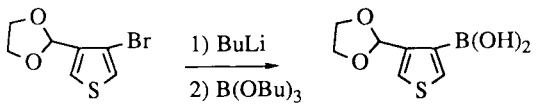


60% (94)

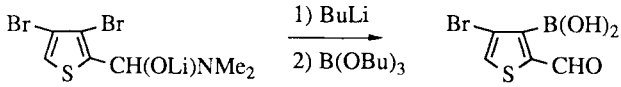
Oxidation of thienylboronic acids is another way to prepare hydroxythiophenes, which make thienylboronic acids valuable intermediates in organic synthesis. Recently this class of compounds has found use in transition-metal cross-coupling reactions as well (see Table 22). 3-Thienylboronic acids are easily synthesized by treating the appropriate thienyllithium or Grignard reagent with tributyl- or triethylborate followed by hydrolysis as shown in Eqs. 95–97.[21,140,156] Further examples of boron derivatives of thiophene are compiled in Table 14.



57% (95)



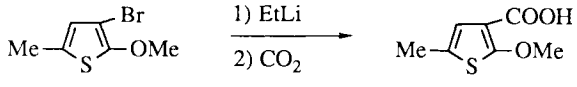
49% (96)



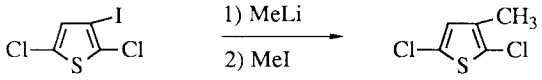
65% (97)

Similar to the situation of metalation reactions, the presence of a carboxylic acid grouping in the thiophene ring does not prevent the formation of thienyllithium derivatives. Thus good yields of 2,3-dithiophencarboxylic acid[157] and the related 3-formyl derivative[158] are obtained via halogen–metal exchange of the

β-bromine atom of 3-bromo-2-thiophenecarboxylic acid. In contrast, a similar reaction with 4-bromo-2-thiophenecarboxylic acid gives only a low yield of 4-formyl-2-thiophenecarboxylic acid.[158] The β-lithium reagents derived from 3-bromo-2-methoxy-5-methylthiophene and 2,5-dichloro-3-iodothiophene[145] appear to be stable even at room temperature for several hours, as shown by the relatively good yields of the resulting 3-substituted products (Eqs. 98, 99). This stability is also valid for 3-bromo-2-*N*,*N*-dimethylaminomethyl-5-methylthiophene.[17]

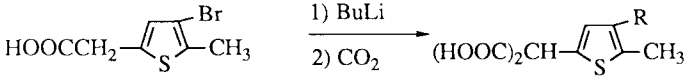


70% (98)



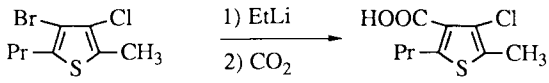
55% (99)

Treatment of the thienylacetic acid derivative shown in Eq. 100 with 2 eq of BuLi followed by Dry Ice resulted in a complicated mixture of compounds. As indicated by NMR, one of the products was a malonic acid derivative probably formed via metalation of the most acidic thenylic position.[30]



R = H or COOH (100)

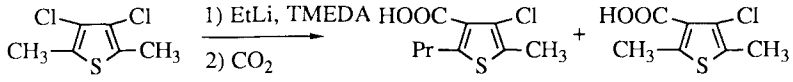
As pointed out earlier, lithium–halogen exchange with chlorothiophenes is not as easy as with the bromo and iodo derivatives. Even hydrogen exchange is faster than chlorine exchange since 2-chlorothiophene is metalated by BuLi in the 5-position.[159] The reluctant chlorine exchange is also demonstrated at the β-position with 3-bromo-4-chloro-5-methyl-2-propylthiophene, for instance, which selectively undergoes halogen–metal exchange reaction with BuLi at −70°C of the bromine atom to give 4-chloro-5-methyl-2-propyl-3-thiophenecarboxylic acid (67%) after treatment of the lithiated mixture with Dry Ice (Eq. 101).[30]



67% (101)

The slow β-chlorine exchange is also shown for 3,4-dichloro-2,5-dimethylthiophene on treatment with EtLi–TMEDA in refluxing ether,

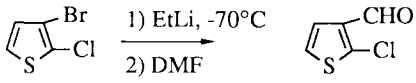
although this reagent is perhaps more suitable for metalations.[30] In any case mostly the starting material was recovered after the mixture was poured onto Dry Ice. A low yield of a mixture of two carboxylic acids were obtained in the proportions 3 : 4 (Eq. 102).



(102)

The compounds were identified as 4-chloro-2,5-dimethyl-3-thiophenecarboxylic acid and 4-chloro-5-methyl-2-propyl-3-thiophenecarboxylic acid, respectively, indicating that the thenylic position must have been metalated and then reacted with ethyl chloride formed in the halogen–metal exchange reaction. Thus metalation of α-thenylic position and the chlorine–lithium exchange at the β-position seem to occur at comparable rates with the EtLi–TMEDA reagent.

An α-positioned chlorine is less reactive than a β-positioned bromine as shown in Eq. 103.[160]



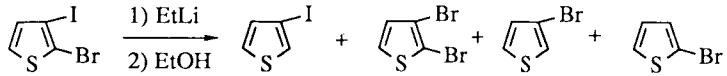
(103)

The reaction of 3,4-dibromo and 3,4-diiodothiophene with BuLi proceeds differently. When the former compound was treated with 2 eq of BuLi at − 30°C only one of the bromine atoms was exchanged and the second lithium atom entered the 2-position.[142] At this relatively low temperature it is likely that the first event is the halogen–metal exchange, which is followed by the metalation, since there are many examples of selective Br–Li exchange of 3,4-dibromothiophene (see Table 4). On the other hand, it has been suggested that by a rapid addition of this compound to a BuLi solution at room temperature a direct metalation of the 2-position may be the initial event.[137]

In contrast to the behavior of 3,4-dibromothiophene both halogens of 3,4-diiodothiophene were partly exchanged using only 1 eq of BuLi at − 70°C to give a mixture of mono- and dialdehydes after DMF treatment.[85] A similar unselective reaction was reported for 3,4-diiodo-2,5-dimethylthiophene.[139] This high reactivity of the iodines stands in marked contrast to the behavior of 2,3-diiodothiophene, which exchanges only the 2-positioned iodine even though treated with 2 eq of BuLi.[142]

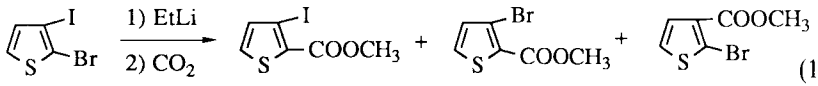
A particularly complicated situation may arise in halogen–metal exchange reactions when the initially formed lithiothiophene derivative does not have the lithium atom in the thermodynamically most favored position. At higher temperature several equilibria may transform the initially formed lithium derivative into the system of lowest energy. Thus, when 2-bromo-3-iodothiophene was treated with EtLi at − 60°C followed by trapping with Dry Ice

or EtOH, mixtures of halothiophene derivatives were produced with dominance of the compounds having bromine in the 3-position. By lowering the temperature to $-100°C$ the same treatment gave mainly the products with bromine in the 2-position (Eqs. 104, 105).[161]



(104)

-60°C	20	20	55	2
-100°C	--	--	5	95

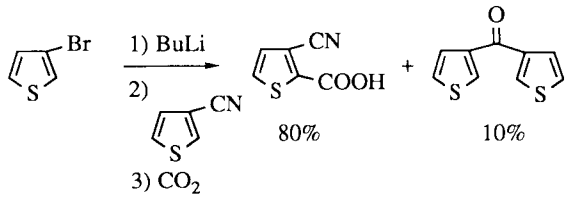


(105)

-60°C	20	71	3
-100°C	11	5	84

These results showed that the initially formed 2-bromo-3-thienyllithium is very prone to rearrange to give the thermodynamically most favourable 3-bromo-2-thienyllithium. At very low temperatures this rearrangement was hindered. A reaction scheme involving a series of halogen–metal exchange reactions similar to the ones earlier proposed for the rearrangements induced by halogen–metal exchange reactions of mono-, di- and tribromothiophenes[137] was advanced as an explanation to these results.[161] (Such rearrangements are discussed in more detail in Section II.8.) Similar rearrangements were reported for 2-bromo-4-iodothiophene, 2,5-dibromo-3-iodothiophene, and 2-chloro-3-iodothiophene.[141] One should notice that 2,5-dichloro-3-iodothiophene did not rearrange even after several hours at room temperature, again demonstrating the low reactivity of the α-chlorines.[145]

Metalation of the more acidic position was also observed in the reaction of 3-cyanothiophene with 3-thienyllithium. After quenching the reaction mixture with Dry Ice the major product was 3-cyano-2-thiophenecarboxylic acid and only minor amounts of 3,3′-dithienylketone was obtained (Eq. 106).[162]



(106)

80% 10%

5. Thenyllithium and Thenylmagnesium Halide Derivatives

The lithiation at the unactivated thenylic position is generally more difficult than at the thiophene ring α-positions. If, however, the thenylic position is

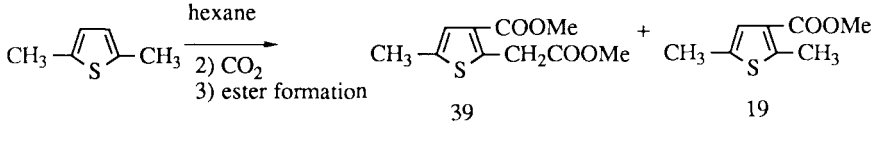
activated by acidifying groups, such as ester groupings or dithiane moieties, metalation is, of course, facilitated. For the generation of thenylic Grignard reagents a special cyclic reactor method is recommended, but even then, these Grignard reagents, tend to give reaction with electrophiles at both the thenylic and the thienylic positions. As in many other cases of metalation, the solvent may have a profound influence. A number of cases where thenyllithium and thenyl Grignard derivatives were studied are collected in Table 5.

A. Lithiations

The α-methyl group of tetramethyl thiophene may be metalated in low yield by EtLi–TMEDA in ether.[30] If the β-positions are free, as in 2,5-dimethylthiophene, unselective metalation occurs (Eqs. 107, 108).[30,31,117]

5%

(107)



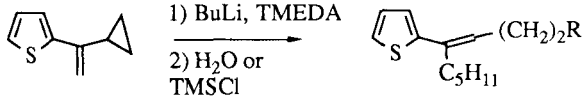
39 19

(108)

5

These reactions give generally better yields in hexane than in diethyl ether, and also the selectivity is changed somewhat (Eq. 66). Since these metalations are performed at or above room temperature, the thiophene ring may be cleaved (see Section II.9).[30]

The addition of BuLi to the double bond of the vinylcyclopropyl derivative shown in Eq. 109 supposedly generates a thenylic lithium derivative, which leads to ring opening of the cyclopropane ring instead of the thiophene ring.[163]

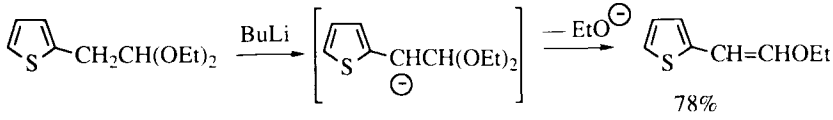


R = H or TMS

(109)

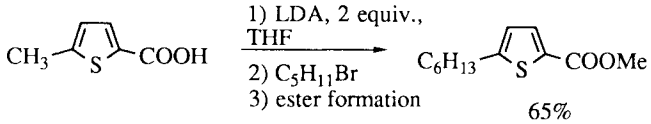
In the reaction of thenylic acetals with BuLi, one alcohol moiety is eliminated. A thenylic lithium compound has been suggested as an intermediate even if it could not be trapped with electrophiles (Eq. 110).[48] A similar metalation

was suggested as an explanation to the extensive polymerization of 2-(2-dimethylaminomethyl)thiophene on treatment with BuLi.[18]

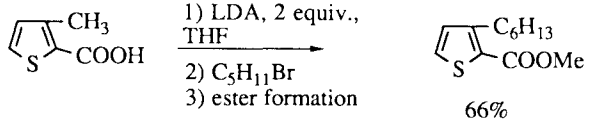


(110)

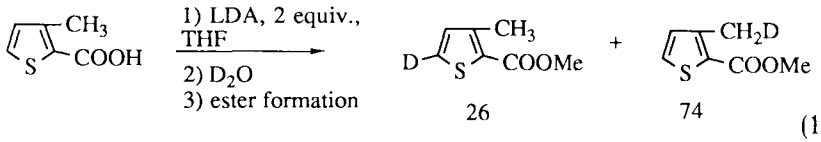
Lithiations of thenylic positions have been effectively completed when a carboxylate group is also attached to the thiophene ring.[164] Thus 5- and 3-methyl-2-thiophenecarboxylic acids gave side-chain metalation using 2 eq of LDA in THF (Eqs. 111–113).



(111)



(112)

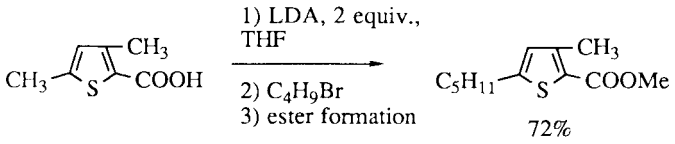


(113)

As seen in Eq. 113, the 3-methyl derivative also gave the product originating from the 5-lithiothiophenecarboxylate. This was ascribed to the presence of an equilibrium between the side chain and the nucleus metalated thiophene derivatives (Eq. 114). The faster-reacting electrophiles, such as water, were suggested to trap the equilibrium, while the slower ones gave only reactions at the side-chain center.

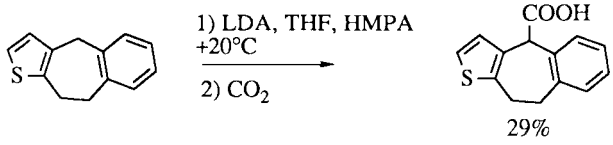
(114)

Only metalation at the 5-position was observed for 4-methyl-2-thiophenecarboxylate and at the 5-methyl group of 3,5-dimethyl-2-thiophenecarboxylate (Eq. 115).

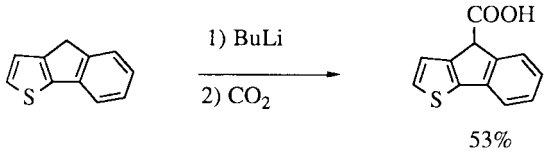


(115)

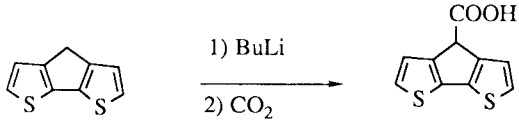
The thenylic protons in thiophene analogs of indene and related compounds are sufficiently acidic to be abstracted by bases, and in some cases only thenylic metalation is observed (Eqs. 116–118),[41,146,165] while in other cases competitive metalation of a thienylic position is also taking place (Eqs. 119, 120).[166,165] The reason for this difference is suggested to be the better stabilization of the thenylic anion when the thiophene ring can use its π-system for effective delocalization such as in Eq. 118 as compared to the arrangement in Eq. 119, where the [*c*]-annelation of the thiophene ring renders the delocalization less efficient.



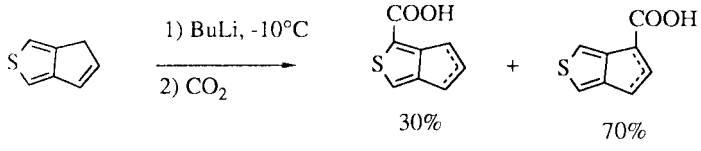
(116)



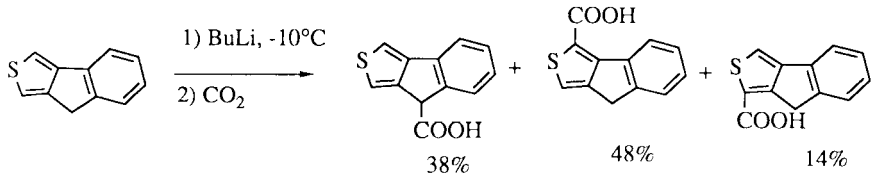
(117)



(118)

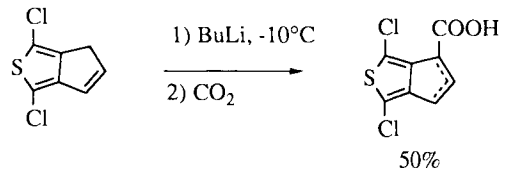


(119)



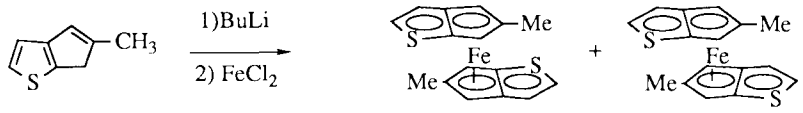
(120)

The dichlorothiophene derivative shown in Eq. 121 is selectively metalated in the thenylic position using BuLi; no halogen–metal exchange is taking place.[166]



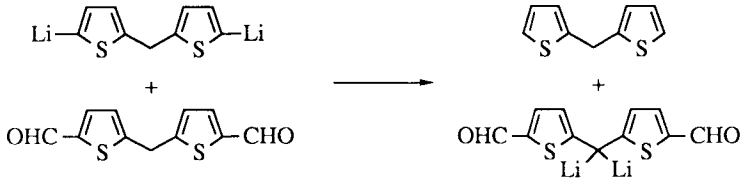
(121)

The metalation of the thenylic position of 5-methylthieno[2,3-*b*]indene has been used to prepare the two thienoferrocene derivatives (obtained as a mixture) shown in Eq. 122.[167]

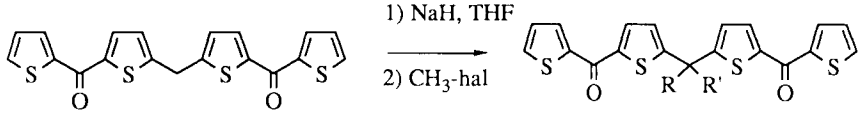


(122)

2,2′-Dithienylmethane is metalated in the 5,5′-positions and not in the methylene group, but if the 5,5′-positions carry electron-withdrawing substituents, the methylene group is metalated and may even be bis-metalated as shown in Eqs. 123 and 124.[168–170]



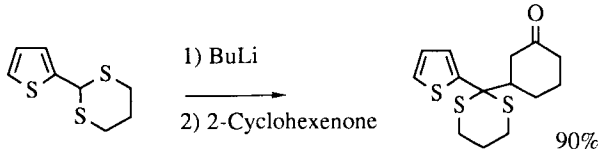
(123)



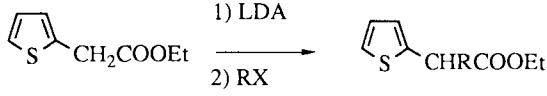
mixture of R=R'= Me and R=H, R'=Me

(124)

The anions derived from dithianes and acetic ester derivatives are used in alkylation reactions in the expected way (Eqs. 125, 126).[38,171]

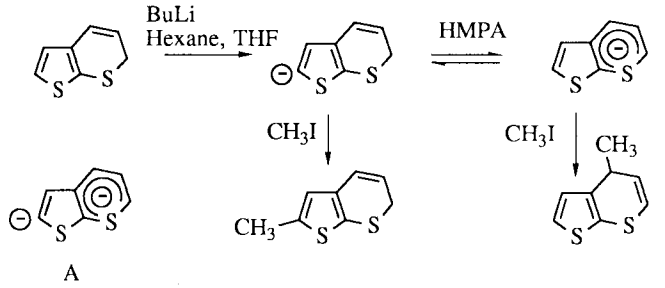


(125)



(126)

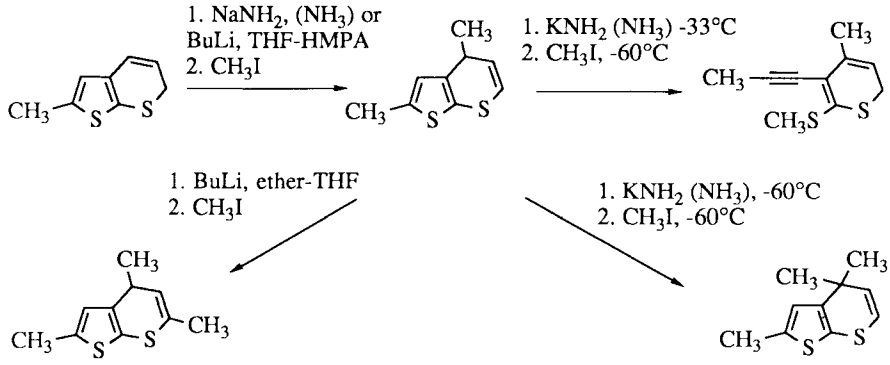
A somewhat more complicated situation is at hand in the metalation of the thiopyrane derivative shown in Eq. 127, where the α-thienylic and the pentadienylic protons of the thiopyrane ring are of comparable thermodynamic acidity.[172] Metalation of 2*H*-thieno[2,3-*b*]thiopyran by strong bases under relatively apolar conditions occurs exclusively in the 2-position of the thiophene ring. In polar media an allylic proton of the thiopyran ring is removed to give the resonance-stabilized pentadienyl anion. Conversion to the pentadienyl anion also takes place by addition of HMPA to the 2-lithiothiophene derivative. By studying the time dependence of the product formation on trapping with MeI, it was suggested that a dianion (A) may be an intermediate in this conversion under the more polar conditions in HMPA.



(127)

A

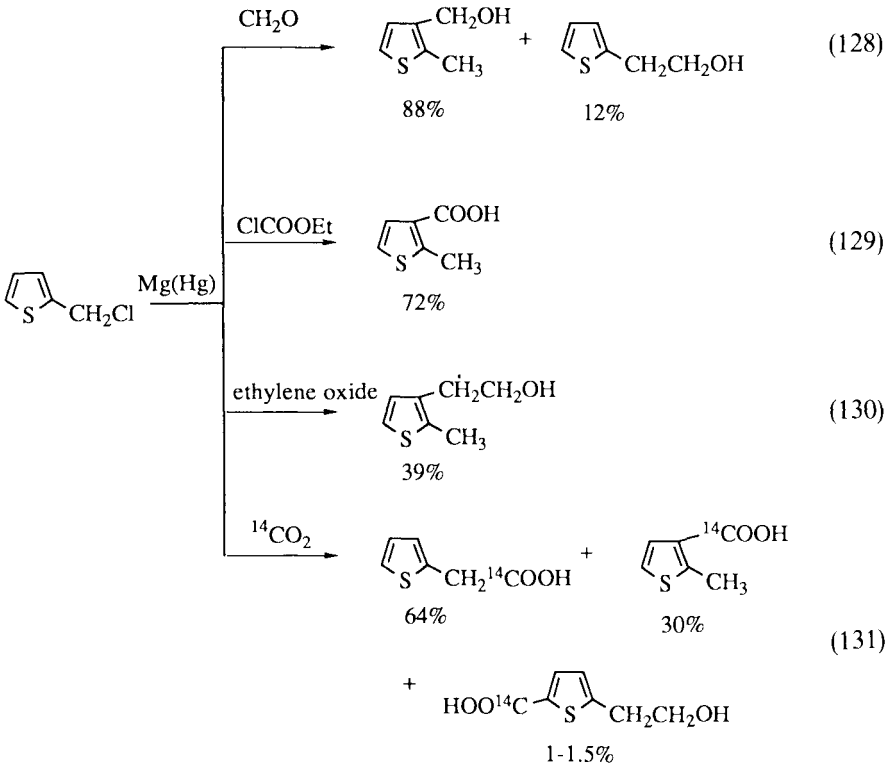
The 2-methylthienothiopyrane derivatives can be further methylated by reaction with BuLi in THF–HMPA mixtures or sodamide in liquid NH_3, followed by addition of methyl iodide. The resulting 2,4-dimethyl derivative can be converted into the compounds shown in Scheme 1 depending on the base–solvent system. Thus, the ring-opening compound is produced by KNH_2 treatment in liquid NH_3 at $-33°C$, followed by methylation at $-60°C$. If the reaction with KNH_2 is carried out at $-60°C$, however, methylation at the thenylic position (C-4) takes place. This is also the result using BuLi in THF–HMPA followed by methyl iodide. Omission of HMPA during the metalation gives rise to vinylic substitution at C-6.



Scheme 1

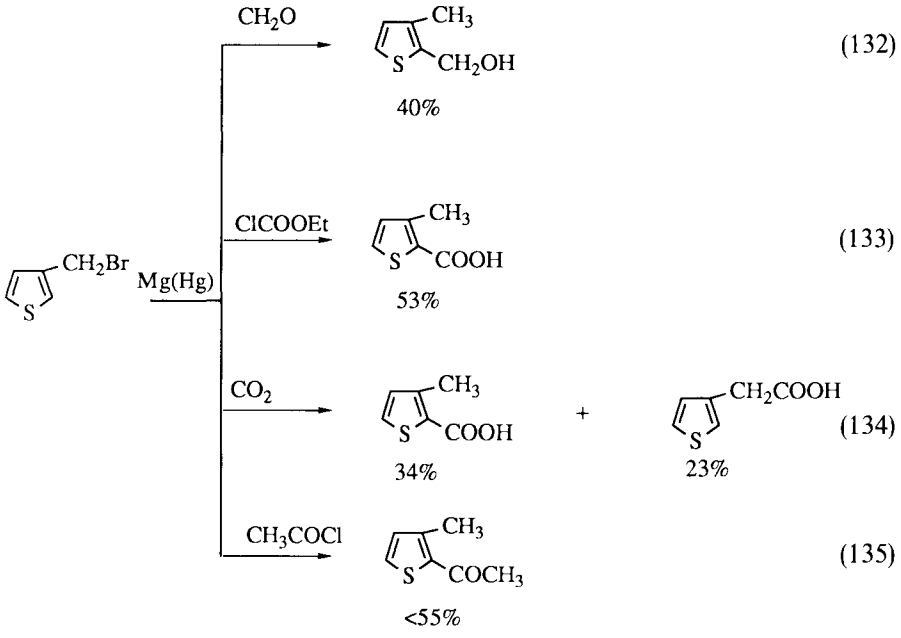
B. Thenylic Grignard Reagents

In order to circumvent the coupling reactions that accompany the formation of benzylic or allylic types of Grignard reagents, a "cyclic reactor" was developed, which allows the reaction of the organohalide and magnesium to proceed at high dilution.[173] The reactor column is loaded with magnesium, which may be amalgamated using dry mercuric bromide,[174] and the organohalide is added slowly at the top of the column into refluxing ether used as a solvent. A detailed procedure of an improved reactor including a drawing of the apparatus is described by Campaigne and Yokley.[175] Using this device it was possible to prepare thenylmagnesium halides in the high yields necessary to perform detailed studies of their reactions with electrophiles. The general reaction pattern of the 2-thenyl Grignard reagent is that the electrophile becomes attached to the ortho position relative to the thenylic site (Eqs. 128–130).[174] Only carbon dioxide and formaldehyde give some of the normal products, 2-thienyl-acetic acid, and 2-(2-thienyl)ethanol, respectively.[176] It was found, using the isotope dilution technique, that also some 5-substitution product was formed from 2-thenylmagnesium chloride on reaction with $^{14}CO_2$ (Eq. 131).[177]



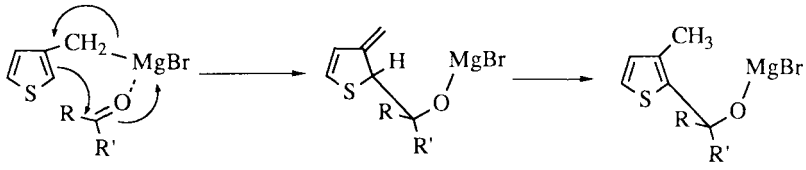
The solvent substantially affects the product distribution as demonstrated for 2-thenylmagnesium chloride in its reactions with ethylene oxide, acetyl chloride, and CO_2 in ether or dimethoxy ethane (DME).[176] In DME the thenylic products were the dominant ones, while in ether the amount of ortho-substitution products dominated. Para-substitution occurred to some extent (< 13%) in ether and amounted to 33% if the 3-position was blocked with a methyl group, as in the trapping of 3-methyl-2-thenylmagnesium chloride with CO_2. If acetyl chloride was used as trapping agent, only the thenylic product was obtained, clearly demonstrating the influence of the choice of electrophile on the product composition. The addition of magnesium perchlorate did not drastically alter the product distribution of the reaction of 2-thenylmagnesium chloride in ether, although a small increase of the amount of "ortho" product was noticed in the reaction with acetyl chloride.

3-Thenylmagnesium bromide was prepared from 3-thenylbromide using the cyclic reactor and treated with electrophilic reagents such as CO_2, formaldehyde, acetyl chloride, and ethyl chloroformate.[175] It turned out that the 3-thenyl Grignard reagent had a greater tendency to give the "ortho" products than did the 2-thenyl Grignard reagent. Thus the electrophiles entered the 2-position of the thiophene ring instead of the 3-thenylic position except with CO_2, which gave a mixture of 3-thienylacetic acid and 3-methyl-2-thiophenecarboxylic acid (Eqs. 132–135).



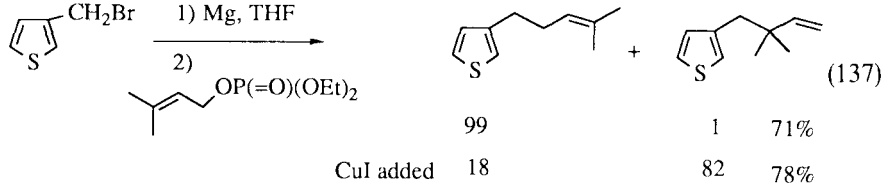
The mechanism proposed to explain the preponderance for ortho-substitution in these reactions is shown in Eq. 136.[178] It involves the coordination of the

electrophile to the metal site followed by carbon bond formation via a cyclic transition state.



(136)

It was recently reported that 3-thenylmagnesium bromide could be prepared by simply reacting 3-thenyl bromide with magnesium turnings in THF at ice–salt bath temperature.[179] The resulting solution was then used at $-70°C$ in reaction with prenyl diethylphosphate to give a good yield of the chain-extended thiophene derivatives (a 1 : 99 ratio of the two products) as shown in Eq. 137. Apparently no "ortho" product was formed, which was ascribed to the preference of the harder phosphate leaving group to react with the harder thenylic position rather than with the softer α-thienyl position. The addition of CuI to the Grignard reagent changed the ratio of the two products to 82 : 18.



(137)

The hard–soft concept has not been applied to explain the other results in this area, but may be partly responsible for the different behavior of the electrophiles.

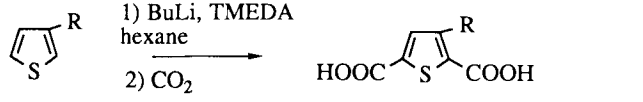
Transition-metal carbene complexes carrying thenylic ligands have been prepared and are shown in Table 22 (transition-metal derivatives).

6. Reactions of Di- and Polylithium Derivatives

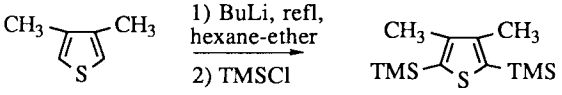
The use of an excess of the lithium introducing agent either in metalation or in halogen–metal exchange reactions allows multilithiation of thiophene derivatives (Table 6). Di-metalated and poly-metalated thiophene derivatives carrying the metals in different rings (bithienyls, dithienylmethanes, and similar compounds) are also included in Table 6 but are not commented on in the text.

As mentioned, 2,5-dimethylthiophene can be metalated both in the 3-position and in the side chain methyl group by the EtLi–TMEDA complex.[30,31,117] Although the bis-lithiated thiophene derivative is formed, nothing is known about in which order the two lithium atoms are introduced. Thiophene itself is bis-metalated in the α-positions by the use of the BuLi–TMEDA complex,[117] as

is 3-methylthiophene (Eq. 138).[117] Uncomplexed BuLi in hexane–ether is also useful as demonstrated for 3,4-dimethylthiophene (Eq. 139).[180]



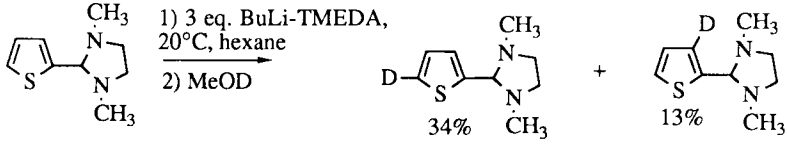
R = H, Me quant. yield (138)



78% (139)

Only a small amount (3%) of dilithiation is observed for 2-methylthiophene and then in the 4- and 5-positions.[117]

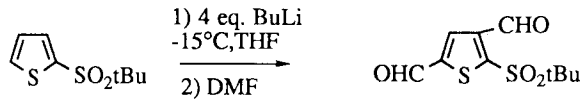
Unselective mono-metalation was observed when 1,3-dimethyl-2 (2-thienyl)imidazolidine was treated with 3 eq of the BuLi–TMEDA complex (Eq. 140).[181]



(140)

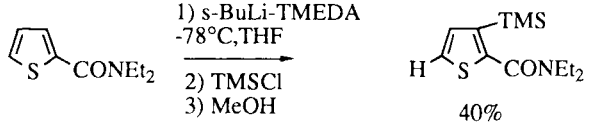
However, selective 3,5-dilthiation was obtained using an excess of THF solutions of *s*-BuLi–TMEDA or BuLi, together with diethylamido-[182] and *t*-butylsulfonyl[130]-substituted thiophenes, respectively (Eqs. 141, 142).

82% (141)



59% (142)

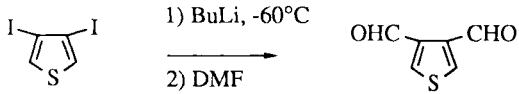
In the former case it is worth noticing that different electrophiles may be added in sequence (one-pot) to give trisubstituted thiophene derivatives carrying three different substituents. It was also found that the anionic center in the 3-position was more reactive than the 5-position, resulting in the synthesis of 2,3-disubstituted thiophene derivatives if methanol was used as the last electrophile (Eq. 143).[182]



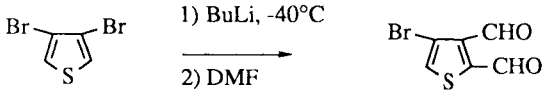
(143)

The direct metalation of 2,5-dimethoxythiophene resulted in the formation of a diacetylene derivative via ring opening of the β-lithiated thiophene derivative. It is possible that bis-lithiation of the two β-positions occurred.[121]

Several cases of dilithiation in halogen–metal exchange reactions of thiophene dihalides were observed. Dialdehydes were obtained after DMF treatment.[71] Also some cases of combined halogen–metal exchange and metalation reactions gave dialdehydes after DMF trapping. It should be noted that while 3,4-diiodothiophene gave 58% yield of the 3,4-dialdehyde via halogen–metal exchange followed by DMF treatment, the corresponding 3,4-dibromothiophene gave 4-bromo-2,3-thiophenedialdehyde (Eqs. 144, 145). Thus the metalation in the 2-position was faster than the halogen–metal exchange of the remaining bromine atom. A directing (coordinative) effect seems to be provided by the first introduced lithium atom.

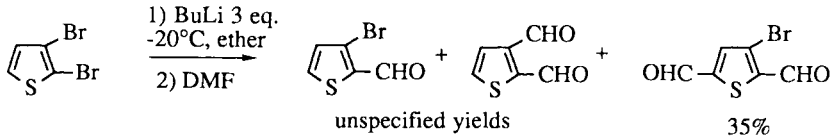


(144)



(145)

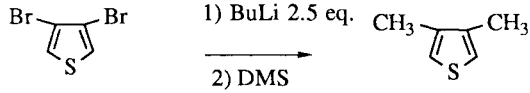
Another case of a faster metalation than halogen–metal exchange was noted when 2,3-dibromo thiophene was treated with 3 eq of BuLi in ether. In addition to 3-bromo-2-formylthiophene and 2,3-diformylthiophene, 3-bromo-2,5-diformylthiophene was obtained in 35% yield (Eq. 146).[71]



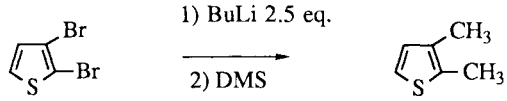
(146)

In contrast to these results it was reported that 3,4-dibromothiophene gave 3,4-dimethylthiophene after treatment with BuLi followed by DMS; likewise, 2,3-dibromothiophene gave 2,3-dimethylthiophene (Eqs. 147, 148).[183] If a large

excess of BuLi was used, tri and tetra lithiation could be achieved with 2,3,5- and 2,3,4-tribromothiophene and tetrabromothiophene.

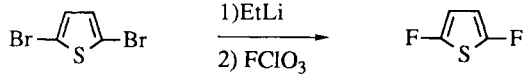


80% (147)

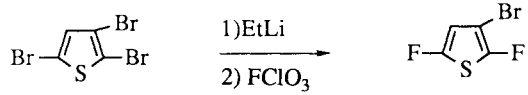


75% (148)

An improved method for the synthesis of pure 3-*t*-butylthiophene was realized by treating 2,5-dibromo-3-*t*-butylthiophene with 2 eq of BuLi followed by water.[29] The two α-bromine atoms of 2,5-dibromo and 2,3,5-tribromothiophene were used similarly to introduce fluorine substituents by treating the α-dilithiathed thiophene derivatives with perchloryl fluoride (Eqs. 149, 150).[184]

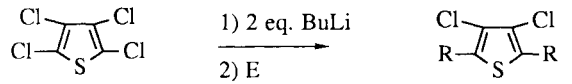


(149)



(150)

Also, the α-chlorines of tetrachlorothiophene were exchanged for lithium using 2 eq of BuLi, and the resulting dilithium derivative was then trapped with various electrophiles (Eq. 151).[185]



(151)

E	R
CO_2	CO_2H 87%
TMSCl	TMS 80%
Me_2HSiCl	Me_2HSi 82%

Starting from 2,3,4-trichlorothiophene the same method gave 3,4-dichloro-2,5-dithiophenecarboxylic acid, which again shows that the β-positioned chlorines are rather slow-reacting in comparison with metalation of the α-position.[186]

Some cases of generation of bis-magnesiumhalides of thiophene-derivatives have been reported. Thus 2,3,5-tribromothiophene gave 3-bromothiophene (together with substantial amounts of 2,3- and 2,4-dibromothiophene) on treatment with magnesium in the presence of 2.5 eq of ethyl bromide (entrainment conditions) followed by water.[187] 2,5-Dibromothiophene gave 2,5-dithiopheneboronic acid on treatment with an excess of magnesium in THF followed by trimethyl borate and hydrolysis.[188] Here the bis (Grignard reagent) was added to a solution of $B(OMe)_3$ in ether.

Although there seem to be many examples of multimetalated thiophene derivatives, these cases should be considered as preliminary ones. For example, it has been shown that dimethylsulfate may exist together with butyllithium at low temperatures, which means that lithiations and lithium-halogen exchange reactions with the aromatic reactant may take place despite the presence of the trapping reagent.[660] Accordingly, the first formed monolithiated thiophene derivative may be trapped by one equivalent of the trapping reagent and then another lithiation takes place with the excess of the lithiation reagent. It is also possible that other trapping reagents such as DMF and dimethyldisulfide behave similarly.[661] Thus, there are reasons to question whether multilithiated thiophene derivatives really are intermediates in all cases referred in the above section and in Table 6. Some results may be better explained if one assumes a stepwise lithiation-trapping process and these aspects are now being looked into.[661]

7. Directed Metalation

Substituents already present in the thiophene ring may have a directing effect on the metalation or the halogen–metal exchange. Generally, all substituents have in fact some influence in this respect. Alkyl groups, whether placed in the α-position or the β-position, direct metalation to the distant α-position due to steric hindrance as well as the + I effect. Other groups may coordinatively direct the metal to enter their ortho positions (α or β). Since the substituents responsible for the latter metalations usually are electronegative ones (carrying oxygen or nitrogen), − I effects may also be involved. The removal of these directing groups after having served their purpose may be an additional advantage.

The effect of the alkyl group of 3-alkylthiophene derivatives has been studied in both metalation and halogen–metal exchange reactions followed by quenching with dimethyl sulfate (Table 24).[29] Metalation of 3-methylthiophene with BuLi–TMEDA gave a somewhat higher selectivity than did BuLi for the 5-position. LDA was the least selective reagent. By increasing the bulk of the alkyl group at the 3-position, the selectivity for the 5-position increased. Similar results were obtained after quenching the metalated reaction mixtures of 3-methylthiophene with dry ice.[31] It is interesting to note that the preference for the 5-position was very high using LDA at + 35°C, although the yield was low (2%).

The halogen–metal exchange reactions of 2,5-dibromo-3-alkyl-substituted thiophenes with a variety of reagents showed the same selectivity, for example, the bromine in the 5-position was exchanged in preference to that in the 2-position (Table 25).[29] This was most pronounced in the reactions with magnesium and the (supposedly) large BuLi–TMEDA complex. The steric bulk of the *t*-butyl group resulted in release of steric strain so that with the uncomplexed BuLi reagent, and even more with ethylmagnesium bromide, a preference for the 2-position was observed. The directing effect of groups carrying electronegative

TABLE 24. Metalation of 3-Alkyl Substituted Thiophene Derivatives[a]

Substituent	Reagent	2-Me (%)	5-Me (%)
Me	BuLi	20	80
	BuLi–TMEDA	7	93
	BuLi–TEEDA	16	84
	LDA	24	76
	t-BuLi	10	90
	t-BuLi–TMEDA	10	90
Et	BuLi	15	85
	BuLi–TMEDA	3	97
i-Pr	BuLi	5	95
	BuLi–TMEDA	1	99
t-Bu	BuLi	1	99
	BuLi–TMEDA	0	100

[a] The isomer distributions were measured (by GC) on methyl derivatives obtained after quenching the reaction mixtures with DMS.

TABLE 25. Halogen–Metal Exchange Reactions of 2,5-Dibromo-3-alkyl-Substituted Thiophene Derivatives[a]

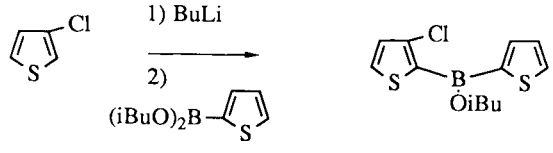
Substituent	Reagent	2-Me (%)	5-Me (%)
Me	BuLi	19	81
	BuLi–TMEDA	5	95
	EtMgBr	17	83
	Mg	15	85
Et	BuLi	23	77
	BuLi–TMEDA	7	93
	EtMgBr	20	80
	Mg	13	87
i-Pr	BuLi	28	72
	BuLi–TMEDA	10	90
	EtMgBr	23	77
	Mg	11	89
t-Bu	BuLi	57	43
	BuLi–TMEDA	13	87
	EtMgBr	64	36
	Mg	6	94

[a] The isomer distributions were measured (by GC) on methyl derivatives obtained after quenching the reaction mixtures with DMS.

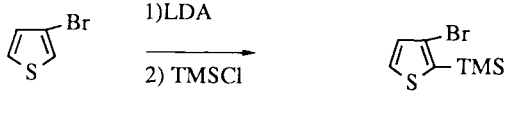
elements gives the opportunity to place the metal at the position ortho to the directing group. A large variety of such directors has been found, as is evident from Table 7, where examples of this phenomenon are compiled.

The directive effect of the halogens is quite pronounced. 3-Chloro-,[99] 3-bromo[15] and 3-idothiophene[189] are metalated in the 2-position; the former by

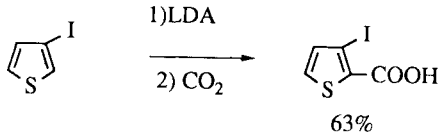
BuLi and the latter two, by LDA (Eqs. 152–154). The action of *N*-methyl-2-pyrrolyllithium on 3-iodothiophene leads to a 1 : 4 mixture of metalation of the 5- and the 2-positions, respectively, which again points to the directing effect of the iodine atom.[13]



(152)

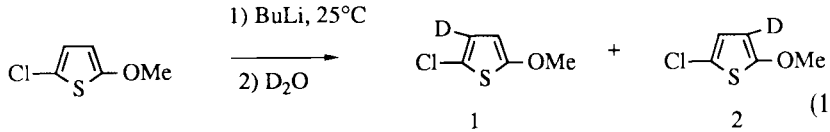


(153)



(154)

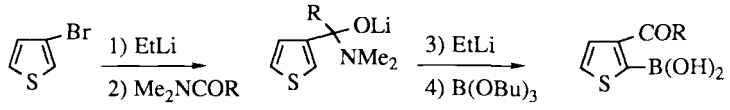
The halogen–metal-exchange reactions of 2,3,5-tribromo[135] and 2,3,5-triiodothiophene[85] preferentially give exchange of the 2-halogens, although 2,3,5-triiodothiophene also gives exchange of both iodine atoms at the 5- and 2-positions to some extent, indicating the high reactivity of the iodines. The directing effect of a methoxy group seems somewhat stronger than that of a chlorine as shown by the metalation of 2-chloro-5-methoxythiophene with BuLi followed by quenching with D_2O after a short reaction time (Eq. 155).[122] The β-hydrogen closest to the methoxy group is exchanged twice as fast as the one at the chlorine.



1 2 (155)

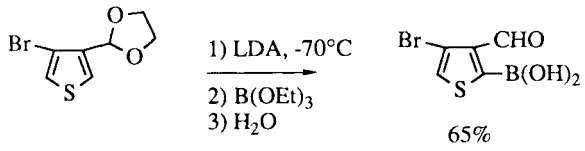
Treatment of 2-chloro-5-methylthiophene with BuLi–TMEDA at room temperature gives chlorine–metal exchange as well as metalation of the β-position next to chlorine.[31] Curiously, both β-positions were metalated by LDA in low yields.

Alkoxy groups show directing effects when attached to the thiophene ring or the thenylic positions. A large number of such cases may be found in the Table 7. It should be pointed out that the acetal function and its equivalent(s) are quite useful directing groups for metalation. Intermediates with the functional equivalence of acetal groups have been used for the *in situ* sequential synthesis of 2,3-disubstituted thiophene derivatives as exemplified in Eq. 156. The directing group is first introduced via a halogen–metal exchange reaction, and it then directs the subsequent metalation.[100,143]



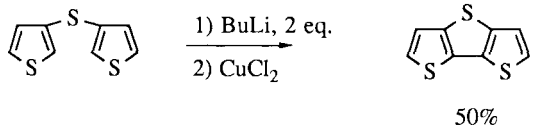
(156)

It should be noted that the acetal grouping seems to enhance the metalation reaction more than does the bromine substituent. Thus the cyclic acetal of 3-bromo-4-thiophene aldehyde is metalated by LDA in the 5-position (Eq. 157).[21]



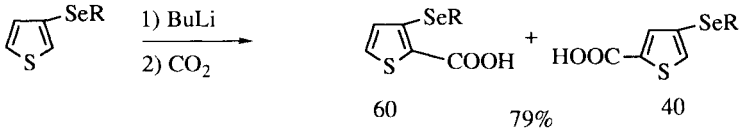
(157)

Similar to the oxygen-carrying substituents some sulfur-containing groups also show directing effects. Thus the lithium mercaptide of 3-mecaptothiophene[190] and 3-ethylthiothiophene[191] are selectively metalated in the 2-position as are 3-phenylthiothiophene[192] and 3,3′-dithienylsulfide (Eq. 158)[54] and its corresponding sulfone.



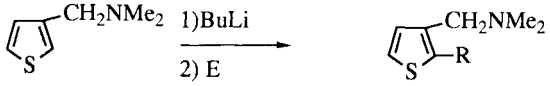
(158)

The organoseleno group is not a strong directing group, as demonstrated by the metalation of 3-methylselenothiophene; a 60 : 40 mixture of the corresponding 2- and 5-thienyl carboxylic acids was obtained after trapping the metalation mixture with Dry Ice (Eq. 159).[193]



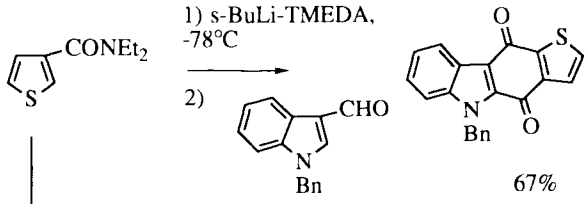
(159)

Several examples are known where the amino and amido functions show directing effects in metalation reactions. Thus 3-(*N*,*N*-dimethylaminomethyl) thiophene[74] and the *N*-methyl[74] as well as the *N*,*N*-diethylamide of 3-thiophenecarboxylic acid[49,194] give selective metalation of the 2-position (Eqs. 160–162).

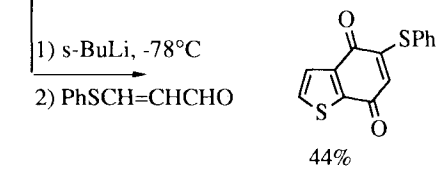


(160)

E	R
Ph_2CO	$Ph_2C(OH)$ 67%
D_2O	D 67%
DMF	CHO 75%
$pTolSO_2Cl$	Cl 25%

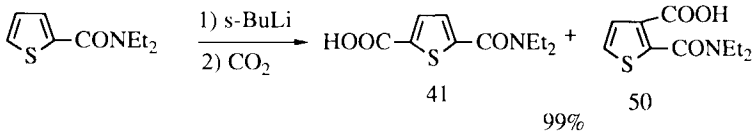


(161)



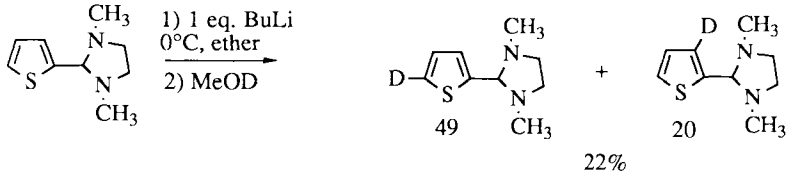
(162)

When the *N*,*N*-dimethylaminomethyl group is placed in the 2-position and the 5-position is blocked with a methyl group, the metalation takes place in the 3-position.[74] Not only is the metalation directed to the β-position next to the *N*,*N*-dimethylaminomethyl group; this position becomes more reactive than normally observed in α-alkyl substituted thiophenes. The directive effect is also shown for 2-*N*,*N*-diethylamidothiophene, although in this case the 5-position was metalated as well (Eq. 163).[129]



(163)

2-(*N*,*N*-dimethyl-2-imidazolidinyl)thiophene, a protected thienyl carbaldehyde derivative, was metalated mainly in the 5-position by a variety of reagents, one of which is shown in Eq. 164. Other metalating conditions were BuLi in the absence or presence of TMEDA and LDA, in different solvents such as hexane, DME, THF, or ether (cf. Eq. 140).[181] Metalations of the 3-position took place to only a small extent (0–20%). Thus the imidazolidine group is not a strong β-directing group.



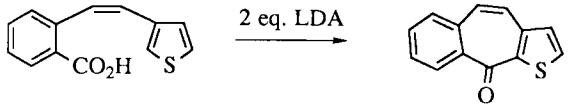
(164)

More selective metalations were achieved by using the *N*-*t*-butylamido group as a directing group;[129] in these cases no α-metalation was observed (cf. Eq. 72).

An unexpected reaction pattern was revealed when 5-trimethylsilyl-2-*N*,*N*-dialkylamidosulfonyl thiophene was investigated with respect to the directive effect of the sulfonylamido function (see Eq. 73).

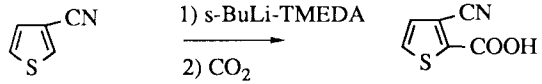
The carboxylate group shows a pronounced directing effect in metalation reactions, which was demonstrated for 2- and 3-thiophene carboxylic acid. The former gives metalation predominantly in the 3-position on metalation with BuLi at low temperature (see Eq. 70),[125] but LDA gives metalation only in the 5-position.[37] Metalation of 3-thiophene carboxylic acid gave selectively metalation of the 2-position with LDA (Eq. 11).[14,37] The directive effect of the carboxylate group was noticed in 1957 by Lawesson in the halogen–metal exchange reaction of 2,5-dibromo-3-thiophenecarboxylic acid in which the bromine in the 2-position selectively reacted with BuLi.[144]

Also, when the carboxylate group is placed at a distance remote from the thiophene ring, its directing effect may be noticed as shown for the carboxylate substituted thienylphenylethylene derivative in Eq. 165.[195] The corresponding saturated compound did not show this effect, indicating that the carboxylate group must be properly oriented in the vicinity of the thienylic position in order to function as a directing group.

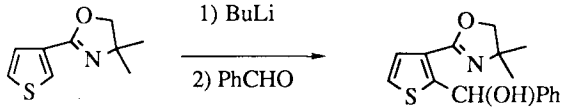


59% (165)

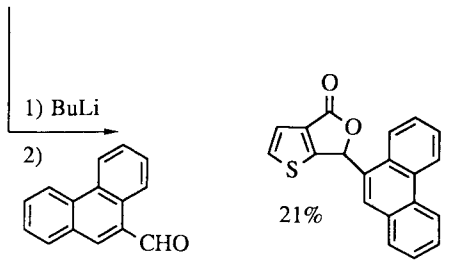
Other thiophene derivatives having substituents at the carboxylic acid oxidation state such as 3-cyanothiophene[162] and 3-(4,4-dimethyl-2-isoxazolinyl) thiophene[196,197] may be metalated in the thienylic 2-positions by BuLi (Eqs. 166–168).



68% (166)

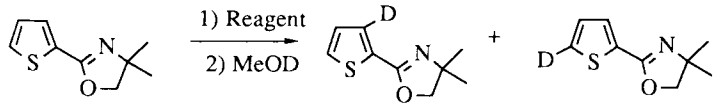


(167)



(168)

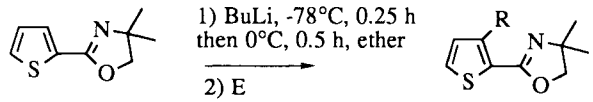
When the isoxazolinyl grouping is placed in the 2-position of the thiophene ring, the situation is more complicated, and a thorough investigation has been reported where the influence of solvents, reagents, and other reaction conditions were tested.[102] In short, the combination of BuLi in hexane at $-78°C$ gave the highest selectivity for lithiation of the 3-position (heterogeneous reaction mixture), while the use of BuLi–TMEDA gave a mixture of 5- and 3-lithiation and LDA in THF resulted in selective 5-lithiation (Eq. 169).



(169)

Reagent		
BuLi, hexane -78°C 30 min	71%	0%
BuLi-TMEDA hexane, -78°C	24%	49%
LDA, THF -78°C	0%	82%

However, the synthetic usefulness for preparing 2,3-disubstituted thiophene derivatives applying the best conditions for 3-lithiation in hexane is low, since on reaction with a variety of electrophiles mixtures of 5- and 3-substitution products were obtained. It turned out that the 3-lithio derivative was less reactive than the 5-lithio derivative and also that transmetalation may convert the former into the latter. Change of solvent from hexane to ether made the reaction mixture homogeneous, and now the 3-lithiated intermediate could be trapped with electrophiles such as CO_2, DMF, allyl bromide, and MeI to produce the 2,3-disubstituted thiophene derivatives in high yields (Eq. 170).



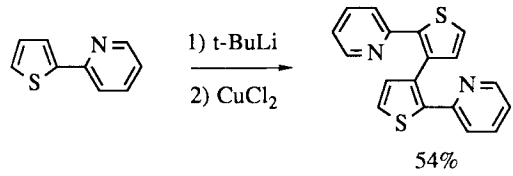
(170)

E	R
MeI	Me 90%
AllylBr	Allyl 81%
$TosN_3$	N_3 81%
DMF	CHO 94%
CO_2	CO_2H 90%

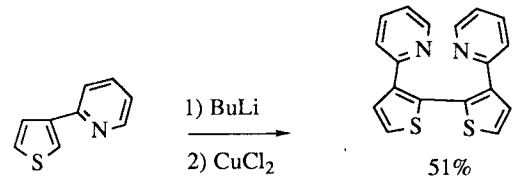
It was shown that the use of electrophiles with labile protons such as acetone, methylvinylketone, and acetonitrile results in proton abstraction to give the thienyloxazoline. The reaction with oxirane and iodine gave mixtures of the 5- and 3-substituted products.[102]

Aromatic nitrogen heterocycles, attached to the thiophene nucleus, direct lithiation into that thienylic position that is capable of forming a five-membered complex, including the nitrogen atom of the nitrogen heterocycle. As expected,

the α-hydrogens of the thiophene ring are more reactive than the β-hydrogens. This is demonstrated for thienylpyridines, thienylpyrimidine, and thienylquinazoline, which on treatment with *t*-BuLi or LDA in ether followed by $CuCl_2$ gave bithienyls with the new pivot bonds connecting the positions ortho to the nitrogen heterocycles (Eqs. 171, 172).[55]

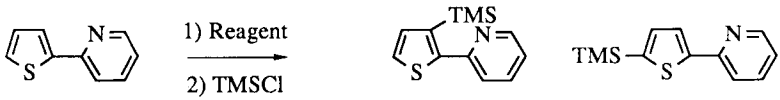


(171)



(172)

The α/β-selectivity depends on the choice of solvent as demonstrated for 2-(2-pyridyl)thiophene, which was treated with BuLi followed by TMSCl in various solvents to give a mixture of 5- and 3-substituted thiophenes (Eq. 173). In ether the 3-metalation predominated over 5-metalation, while in THF the 5-metalation predominated.[126] The use of ether with added TMEDA did not change the α/β-ratio in comparison with use of just ether.

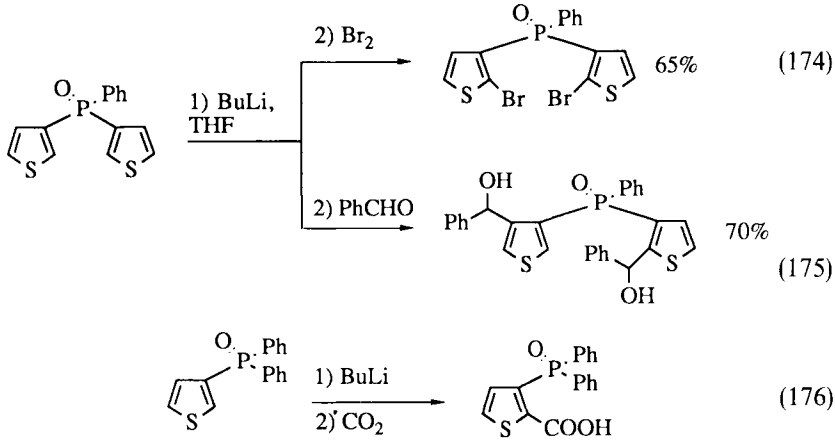


(173)

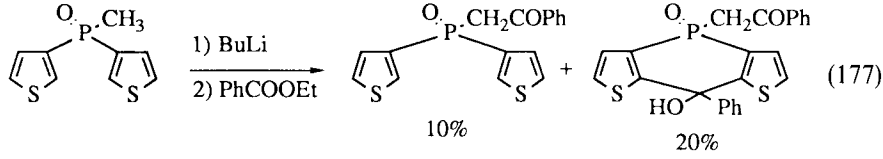
Reagent		
BuLi, ether, 0°C, 30 min	83%	17%
BuLi-TMEDA ether, -78°C, 1h	83%	17%
BuLi, THF 0°C, 30 min	5%	95%
BuLi, ether/hexane -78°C, 1 h	80%	20%

Both 3-nitrothiophene (with LDA)[14] and diphenyl(3-thienyl)phosphine oxide (with BuLi)[53] are metalated in the 2-position. Phosphinoxides carrying two thiophene rings attached at their 3-positions to the phosphorus atom show a divergent behavior toward different electrophiles.[53] Thus, when metalated with BuLi in THF followed by bromine, only the 2,2′-dibromo derivative was

isolated, but with benzaldehyde as electrophile, one of the thiophene rings was substituted in the 2-position and the other in the 3-position (Eqs. 174–176).



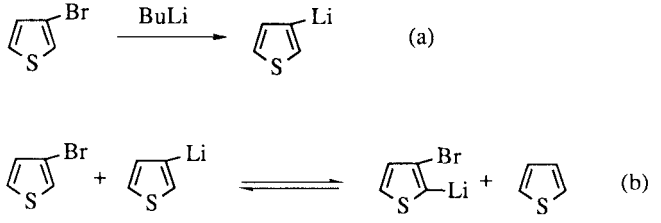
Curiously, metalation of the methyl group of 3,3′-dithienylmethylphosphine oxide was observed on treating the metalation mixture (BuLi in THF) with ethyl benzoate (Eq. 177).



8. Halogen Migration and Rearrangements

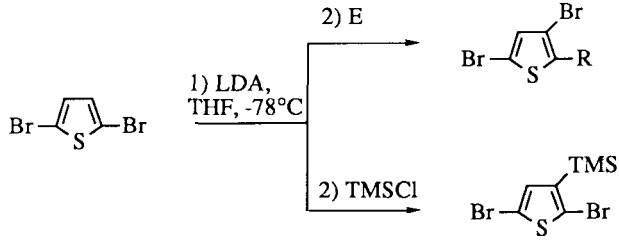
It is generally observed that BuLi gives a faster halogen–metal exchange reaction than does metalation of iodo and bromothiophenes and that the order of reaction rate is I > Br. Chlorine is rather unreactive but may be exchanged if there is no possibility of metalation, and fluorine is not reported to give any halogen–metal exchange reaction. These factors, together with the higher reactivity of the α-position in metalation reactions and the higher thermodynamic stability of the α-lithiothiophenes over the β-lithiothiophenes, make it possible to initially generate a kinetically controlled product, which may rearrange to the thermodynamically more stable lithiothiophene if the temperature of the reaction mixture is allowed to rise or the reaction time is extended. A closely related area is the halogen dance of bromothiophenes by treatment with sodium amide in liquid ammonia described in more detail in this series, Part 2, Chapter III.[198] Since all cases of halogen migration are related to halothiophenes, the reader is referred to the above-mentioned chapter for more detailed information.

Gronowitz noticed in 1954 that 3-bromothiophene gave an anomalous product, 3-bromo-2-thiophenecarboxylic acid, on treatment with BuLi at room temperature followed by trapping with Dry Ice.[12] The result was explained as an initial halogen–metal exchange reaction followed by transmetalation to give the thienyllithium derivative having the lithium at the most acidic position, i.e., the 2-position (Eq. 178). This seems to be the first paper of halogen dance in the thiophene series, although it was not called "halogen dance" at the time. At $-70°C$ only halogen–metal exchange takes place with BuLi without rearrangement.



(178)

Several other halothiophenes were investigated in this respect, and the halogen migration was shown to be a common phenomenon, particularly at temperatures in excess of $-70°C$.[29,137,141,161] Also, when the first event is supposed to be metalation, such as by using LDA, the halogen migration is observed.[124] Thus, when 2,5-dibromothiophene was treated with LDA in THF at $-78°C$ followed by various electrophilic reagents (mostly carbon electrophiles: methyl and ethyl iodide, allyl bromide, DMF, ethyl chloroformate, propylene oxide, butylene oxide, cyclohexene oxide, and cyclohexanone, but also water and dimethyl disulfide), the electrophile entered the 2-position and the bromines were rearranged to the 3,5-positions. The yields were 45–95% depending on the reagent (Eq. 179). These results are in contrast to that where the lithiation mixture was quenched with TMSCl, which gave 2,5-dibromo-3-trimethylsilylthiophene (Eq. 180).[14]

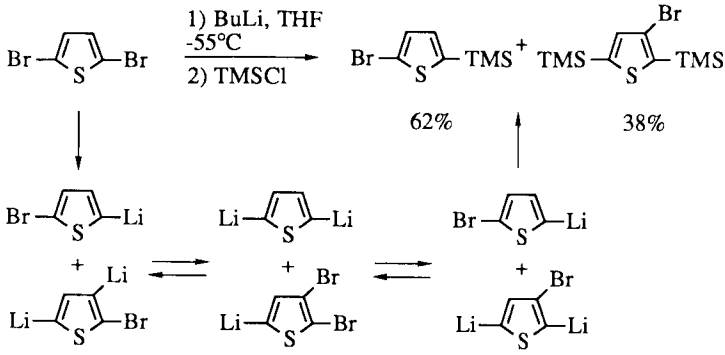


(179)

(180)

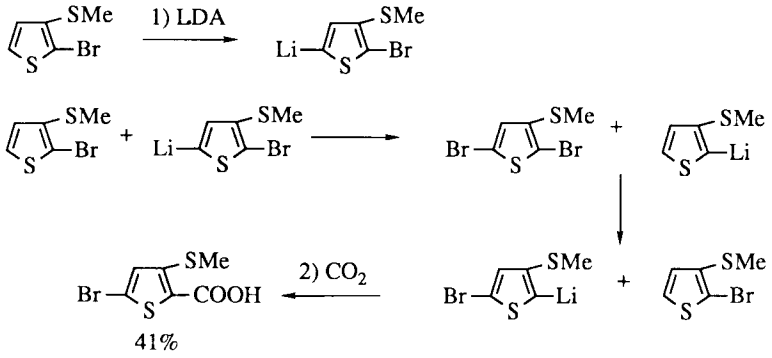
This may mean that TMSCl reacts very quickly at low temperature while all the other reagents react at higher temperature, which allows the halogen migration to take place while the reaction mixture is warming up. Changing the metal introducing reagent to BuLi in THF at -55–$50°C$ and trapping with TMSCl

gave a mixture of 2-bromo-5-trimethylsilylthiophene and 3-bromo-2,5-bis(trimethylsilyl)thiophene, again showing the halogen migration pattern (Eq. 181).[123] The rationale for these results involves the formation of 2-bromo-3,5-dilithiothiophene, which rearranges to 3-bromo-2,5-dilithiothiophene as shown in Eq. 181. Only 2,5-bis(trimethylsilyl)thiophene was formed by increasing the amount of BuLi to 2 eq and trapping with TMSCl.



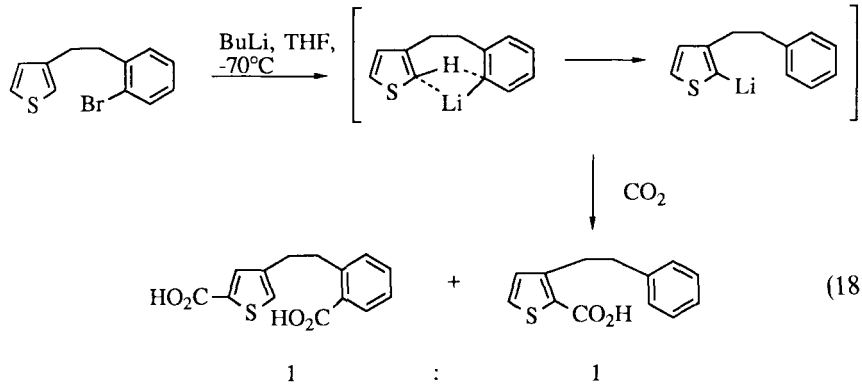
(181)

A similar sequence of metalation and halogen–metal exchange reactions was involved in the reaction when 1 eq of LDA was added to 2-bromo-3-(methylthio)thiophene. This produced the rearranged product, 2-bromo-4-methylthio-5-thiophene carboxylic acid, even at − 78°C on quenching with Dry Ice (Eq. 182).[20] The other mode of LDA addition gave the expected product, 5-bromo-4-methylthio-2-thiophenecarboxylic acid, since now there was no starting material present for any length of time to start the transmetalation reaction.



(182)

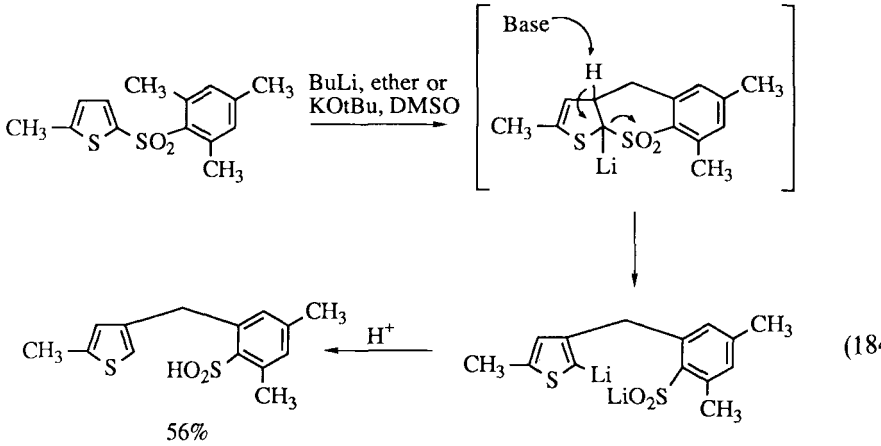
Intramolecular metalation via a cyclic arrangement was suggested as an explanation of the apparent migrations obtained when 3-[2-(2-bromophenyl)ethyl]thiophene was treated with BuLi followed by Dry Ice (Eq. 183).[22]



(183)

Since no trace of the corresponding benzoic acid derivative (mono acid) was found, it seems likely that the initially formed phenyllithium derivative (halogen–metal exchange) rearranged to the thermodynamically more stable 2-thienyllithium derivative via the cyclic transmetalation intermediate shown. This suggestion was supported by reactions of similar bromophenyl-substituted thienylethane derivatives.

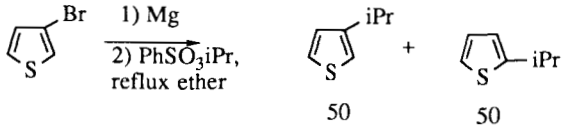
A few cases of rearrangement involving compounds carrying sulfonyl groups have been noticed. On treatment with BuLi in ether or *t*-BuOK in DMS, mesityl 2-thienyl sulfones undergo a rearrangement that moves the mesityl group to the 3-position of the thiophene ring (Eq. 184).[199] An addition–β-elimination sequence commencing with a deprotonation of a benzylic position has been proposed to explain these results (Truce–Smiles rearrangement).



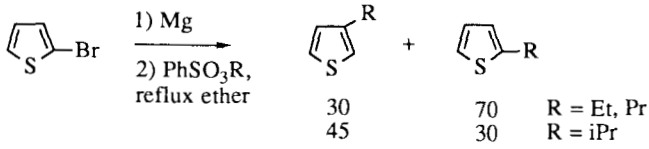
(184)

Mixtures of 2- and 3-alkylthiophenes were obtained by reacting 2- or 3-thienylmagnesium halides with alkyl *p*-toluenesulfonates (Eqs. 185, 186),[200] which may proceed by a cyclic mechanism in analogy with that of Johnson[201] for the reaction of benzylmagnesium bromide with CO_2 or with that proposed

by Dauben et al.[202] for the reaction of aromatic cadmium reagents with acid chlorides. These reactions may be classified together with the Reimer–Tiemann reaction and the Kolbe synthesis.



(185)

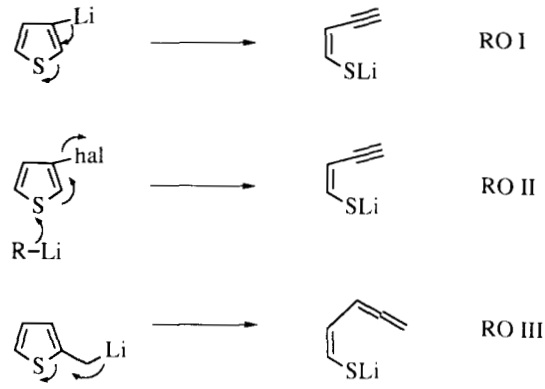


(186)

The rearrangement during lithiation of *N*,*N*-dimethyl 5-trimethylsilyl-2-thienylsulfonyl amide was mentioned earlier (see Eq. 73).[128]

9. Ring-Opening Reactions

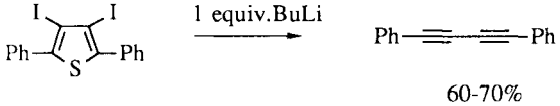
The ring-opening reactions of thiophene and other heterocyclic derivatives under metalating or basic conditions have been reviewed.[5,203] This section will therefore not include a detailed discussion of all the individual cases but rather a survey of the different modes of ring-opening reactions discernible on formal mechanistic grounds. Various ring-opening reactions of thiophene derivatives under metalation conditions are compiled in Table 9. The classification in three essentially different types of the ring opening reactions (ROI–III) may be made by simply looking at the formal mechanism of ring-opening reactions, which are each some kind of elimination. In the ROI reaction the metal is introduced in the β-position, in the ROII reaction the metal introducing agent attacks the



Scheme 2

sulfur atom as a nucleophile, and in the ROIII reaction the metal is introduced in the thenylic position. After the initial event the reactions proceed by cleavage of the thiophene ring as indicated in Scheme 2. The stepwise ring opening of the ROI and ROIII reactions are fairly well documented having trapable lithio intermediates. The ROII type may be either concerted or stepwise.

The first indication of a ring-opening reaction of the thiophene ring under metalation conditions was noticed in 1961 when 3-bromothiophene was treated with BuLi at room temperature for 24 h.[137] It was reported that the reaction product after quenching the reaction mixture with Dry Ice "might contain . . . unsaturated aliphatic products." No ring-opening products were isolated, however. Later several independent publications appeared that described ring-opening products of heterocycles when the intention was to use β-lithium derivatives as reactive intermediates. Thus 2,5-diphenyl-3,4-diiodothiophene gave 1,4-diphenyldiacetylene on treatment with 1 eq of BuLi at room temperature or higher (Eq. 187).[139]



(187)

It was proposed that a 3,4-dilithium derivative was an intermediate, although it is hard to see how the yield could exceed 50% if this is the case. Presumably other intermediates also lead to ring opening. It was shown somewhat later that monolithiated thiophene derivatives gave thioenynes (ROI-type reaction) after trapping the intermediate enynethiolate with alkylating agents,[204,205] and even 3-thienyllithium itself gave the corresponding thioenyne, although in a low yield.[206] A number of substituents, such as methylthio,[115,145] trimethylsilyl,[15,19,207] different alkyl groups,[208] annelated rings,[172,209-211] and olefinic and acetylenic,[212] aryl,[17,207] dimethylaminomethyl,[213] and methoxy[145] groups were tolerated in the ROI-type reaction. The substituent pattern was of importance particularly in the latter two cases; when the methoxy and dimethylaminomethyl groups were placed in the 2-position ring-opening was not observed. It is possible that internal complexation (Figure 1) and/or other electronic effects may stabilize the lithiothiophene against ring opening.

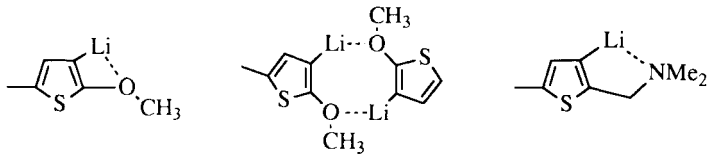
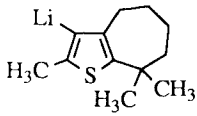
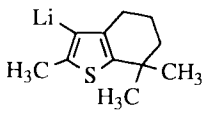
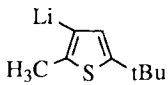
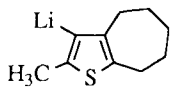
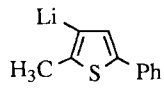
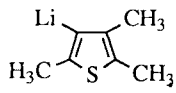
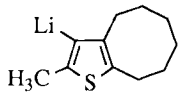
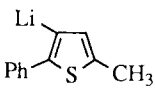
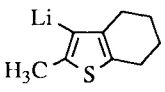
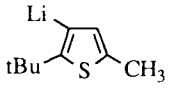
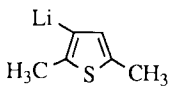
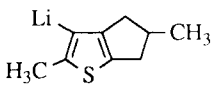


Figure 1

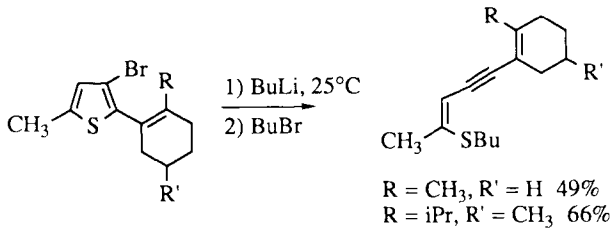
Steric effects reduced the ring-opening rate or blocked it altogether if the sterically demanding grouping was placed on the "backside" of the thiophene ring as shown in Table 26, entries 1–4.[210,214] The steric effect was not as strong

TABLE 26. Pseudo-First-Order Rate Constants ($k \times 10^3$ min^{-1}) of Ring-Opening Reactions of Various β-Thienyllithium Derivatives in Ether[a]

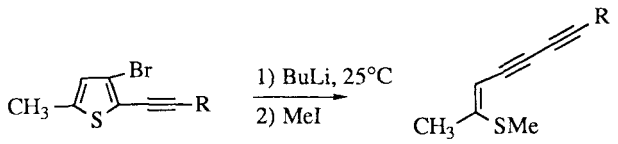
Entry	1	2	3	4
				
	no ring-opening*	0.22*	1.2	1.4*
Entry	5	6	7	8
				
	3	3.5*	5*	14
Entry	9	10	11	12
				
	20*	37	104	>8000*

[a] Values marked with an asterisk were measured at + 2°C and the others, at − 0.5°C.

if the bulky group was placed on the front side (entry 10). The cyclopenta[*b*]thiophene derivative reacted much faster than did the cyclohexa[*b*] analog (entries 12 and 9). This is possibly due to the release of ring strain in the five-membered carbocycle, but it should also be noted that the sulfur atom is placed in a staggered relation to the α-thenylic hydrogen in the cyclopenta[*b*] case, while in the cyclohexa[*b*] case there is a more eclipsed situation (buttressing effect). The 3-thienyllithium derivatives obtained from the cyclohexenyl and etynylthiophenes shown in Eqs. 188 and 189 give good yields of ring-opening products in contrast to the propynyl and phenylethynyl derivatives, which did not give any traces of ring-opened substances—a matter that is still unexplained.



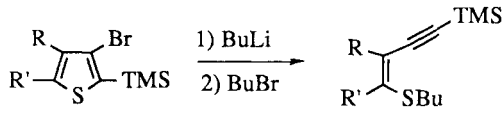
(188)



(189)

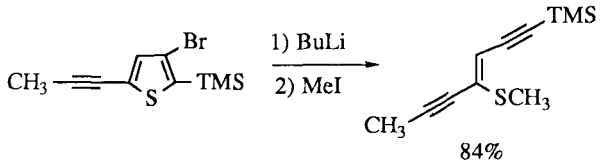
R = tBu, TMS 56%, 52%
R = Me or Ph no ring-opening

3-Thienyllithium derivatives having a TMS group in the 2-position seem to give generally good yields of ring-opening products and may be of particular synthetic interest since the TMS group may be replaced by other organic moieties after the ring opening has been performed (Eqs. 190 and 191).[15,19] A related example is shown in Eq. 192, where the TMS groups are placed in the nonreacting thiophene ring.[207] At lower temperature the TMS-substituted 3-thienyllithium derivatives are stable, as demonstrated for 2,5-bis-(trimethylsilyl)-3-thienyllithium.[123]

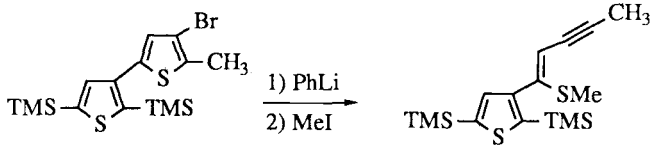


(190)

R = R' = H 68%
R = CH_3, R' = H 67%
R = H, R' = CH_3 57%



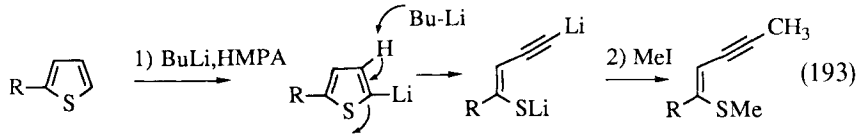
84% (191)



45% (192)

In all the cases discussed above the metal was introduced into the thienylic β-position via halogen–metal exchange reactions. The direct metalation of the thienylic β-position is generally difficult, and ring-opening reactions based on this reaction should be difficult to obtain. However, by the use of HMPA as cosolvent together with BuLi or LDA, thiophene, 2-methyl, and 2-*t*-butylthiophene were ring-opened at 25–40°C to give the thioenynes in high yields (Eq. 193).[115] It is assumed that the initially formed α-lithiothiophene derivative is attacked by the base at the β-hydrogen, and it is likely that the

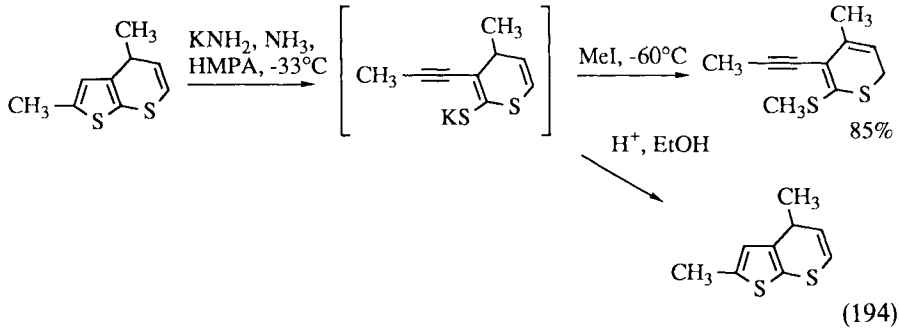
cosolvent has its strongest influence of action in this step by increasing the base strength of the reagents.



(193)

The ring opening of thiophene, 2-methyl, and 2-*t*-butylthiophene occurred even at $-60°C$ if lithium (bistrimethylsilyl)amide was used in the presence of HMPA and 18-crown-6.[215]

Another example of base-induced ring opening in the presence of HMPA is the reaction of the thienothiopyrane derivative shown in Eq. 194 with potassium amide in boiling liquid ammonia ($-33°C$).[172] See also Scheme 1, page 702.

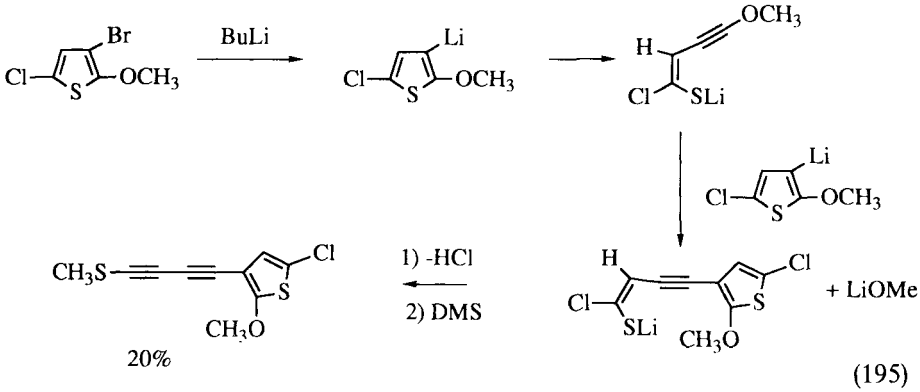


(194)

Ring opening takes place at $-33°C$, and the thiolate is alkylated at $-60°C$ with methyl iodide in THF. If the alkylation is replaced with a protonation, the thienothiopyrane is recovered completely, which indicates that the enyne thiol adds intramolecularly over the tripple bond to give the thiophene ring back as has earlier been observed for monocyclic thiophene[204] as well as benzo[*b*]-thiophene[216,217] cases.

Thiophene derivatives carrying electronegative substituents such as chloro and methoxy groups show a more complicated behavior toward organometallic agents. As mentioned above, neither 2-methoxy-5-methyl-3-thienyllithium nor 2-chloro-5-methyl-3-thienyllithium undergo ring opening at room temperature, in contrast to the isomers 5-methoxy-2-methyl-3-thienyllithium and 5-chloro-2-methyl-3-thienyllithium. The methoxy and chloro substituents seem to stabilize the thienyllithium derivatives in former cases. This effect is counteracted by replacing the methyl group with a chloro or methoxy group as shown for 5-chloro-2-methoxy-3-thienyllithium and 2-chloro-5-methoxy-3-thienyllithium, both of which are unstable at room temperature, although it is only from the former lithium derivative that a ring-opening compound has been isolated

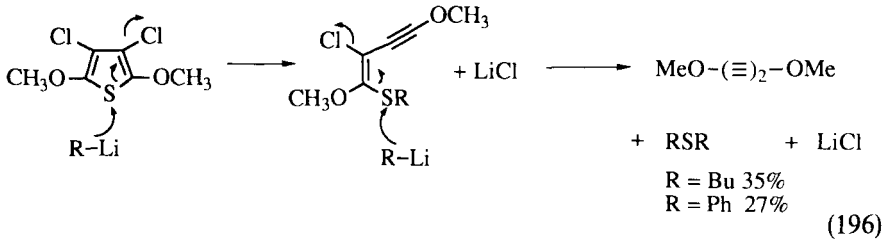
(Eq. 195).[122] Lithiation was accomplished via both halogen–metal exchange and metalation. The endproduct, the diactylenic thiophene derivative, is supposedly formed in a reaction between the original thienyllithium derivative and the initial ring-opening product. Here the acetylenic carbon carrying the methoxy group is attacked by the thienyllithium derivative. Subsequently, the resulting enyne derivative eliminates HCl (or methanol) and is finally alkylated at sulfur by the addition of dimethyl sulfate.



(195)

The 2,5-dimethoxy-3-thienyllithium system behaved similarly, although in this case a butyl group originating from BuLi was attached to the diacetylenic product instead of a 3-thienyl unit. This may be because 2 eq of BuLi was used in order to isolate any well-behaved substance.[121]

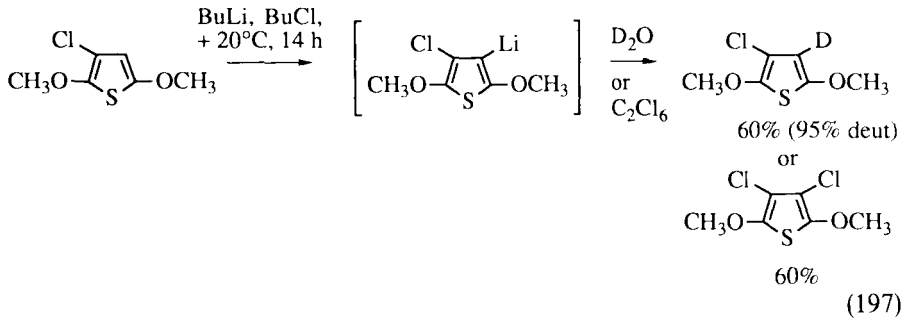
Hitherto no evidence has been obtained for a ROII-type ring opening of a monocyclic thiophene derivative except in the reaction of 3,4-dichloro-2,5-dimethoxythiophene with BuLi or PhLi at room temperature. These reactions produced dibutyl sulfide and diphenyl sulfide, respectively, which is explained by an initial attack of the organometallic reagent on the sulfur of the thiophene ring followed by a second attack on sulfur of the thus formed ring-opening product, the enyne sulfide (Eq. 196).[218]



(196)

This requires that at least 2 eq of the organometallic reagent is used. The fate of the dimethoxy diacetylene is not known. It was also shown that the ROI-type reaction via 4-chloro-2,5-dimethoxy-3-thienyllithium is not possible since this compound is stable under the reaction conditions and gives a good yield of

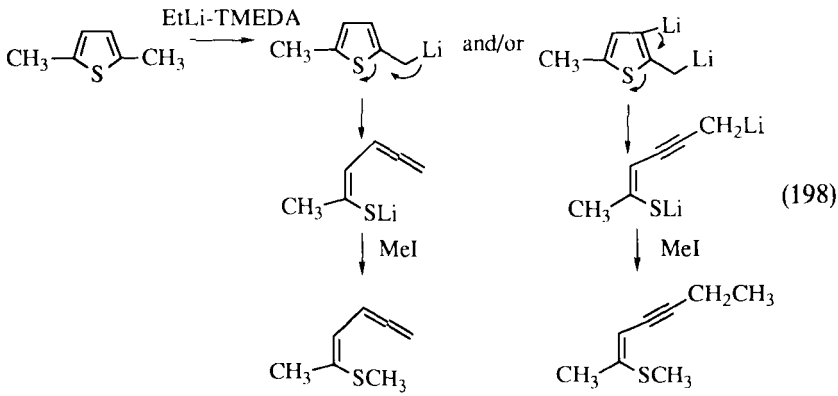
trapping products on treatment with electrophiles (D_2O and hexachloroethane) (Eq. 197).[218]



(197)

A number of ROII reactions have been recorded for other heterocyclic systems.[121]

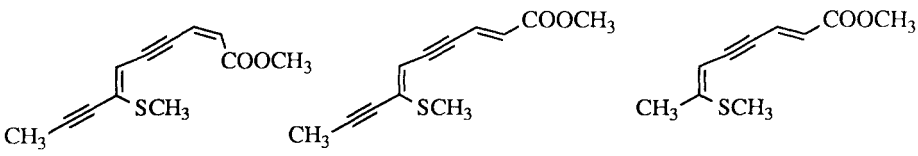
Some indications have been found for ROIII-type ring openings of thenyllithium derivatives.[30] When 2,5-dimethylthiophene was metalated with EtLi–TMEDA in ether and hexane and the lithiated reaction mixtures were poured on Dry Ice, low yields (8 resp. 16%) of 2,5-dimethyl-3-thiophenecarboxylic acid and 2-carboxymethyl-5-methyl-3-thiophenecarboxylic acid (1 : 3); were obtained. This showed that the methyl group as well as the β-position could be metalated. In the neutral phase acetylenes and allenes were found but not isolated in their pure states. The presence of allenic compounds was explained by ring-opening reactions of intermediate thenyllithium derivatives (Eq. 198). Base-induced rearrangements of the initially formed products resulted in a number of unidentified compounds as well.



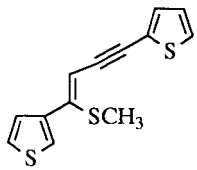
(198)

Ring opening of thiophene derivatives has been used to prepare some acetylenic natural products occurring in plants belonging to Anthemis,[19,212] Berkheya, and Cullumia[207] species (Figure 2).

Some cases of ring opening of thiophene, 1,1-dioxides are discussed in Volume 44, Part 1, Chapter VII.



Anthemis



Berkheya/ Cullumia

Figure 2

Ring opening of the thiophene ring during Birch reduction conditions and Raney nickel desulfurizations are discussed in Volume 44, Part 1, Chapter VI, and recent metalorganic aspects of the catalytic desulfurization of the thiophene nucleus are compiled in Table 22 (transition-metal derivatives and catalysis).

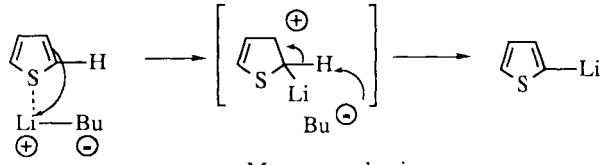
10. Mechanisms and Physical Chemistry

Physical chemistry of organolithium compounds as well as the mechanisms of their formation have been discussed previously.[219,220] It is generally observed that halogen–metal exchange reactions involving organic iodides and bromides are much faster reactions than lithium exchange (metalations). While the former reaction is performed at low temperatures (typically at $-70°C$), metalation frequently requires room temperature or refluxing solvent temperatures to go to completion. 2-Chlorothiophene is, however, metalated in the 5-position by BuLi in ether,[159] while halogen–metal exchange takes place in THF/hexane,[221] showing the profound effect of the reaction conditions. The interplay of the solvent and the degree of aggregation of the organolithium reagents as well as the coordination of the organolithium reagents to various groups of the substrate must be considered in all mechanistic aspects of metalation and halogen–metal exchange reactions. This has been pointed out earlier,[222,223] but there seems to be no mechanistic study of the lithiation of thiophene derivatives where such aspects have been examined in detail. The stability of 3-thienyllithium derivatives and the rearrangement tendency of halogenated thienyllithium derivatives have been discussed above. It should be mentioned that the elimination of lithium halide from orthohalothienyllithium derivatives to form thiophyne has not been observed despite several attempts in that direction.

A. Metalation

The first event in metalation of thiophene with organolithium reagents, such as BuLi, is suggested to be a coordination of the lithium reagent to the sulfur atom.[12] One piece of evidence for this is that both thiophene and benzo[*b*]thiophene are metalated in the 2-positions while electrophilic aromatic substitutions take place in the 3-position of benzo[*b*]thiophene and in the 2-position of thiophene. Thus the sulfur atom coordinates to the lithium atom of BuLi by *p*-electron donation, a situation that is obviously not important in electrophilic aromatic substitution. One may infer, however, that it is hardly likely that thiophene should compete effectively with ether or other coordinating solvents usually employed in metalation reactions, for the place around the lithium atom. Indeed, thiophene is metalated much more slowly in hexane than in ether, which is probably due to the ability of the coordinating solvent (and not thiophene) to break down the oligomeric organometallic reagent.

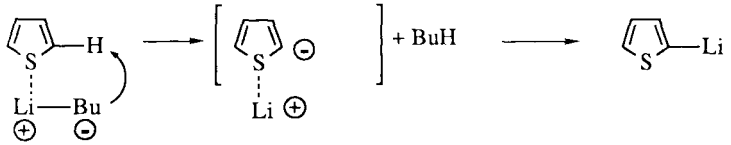
In any case two different suggestions (Morton and Roberts–Curtin) have been made for the second event. Thus the Morton mechanism, as applied to thiophene, would be that the lithium cation coordinates to the α-carbon (reminiscent of an electrophilic aromatic substitution), followed by proton abstraction by butyl anion to give butane and 2-thienyllithium (Eq. 199).[224]



(199)

Morton mechanism

In the other suggestion, made earlier by Roberts and Curtin, the reverse sequence of events is advocated, that is, the butyl anion is first abstracting the most acidic hydrogen, as in an acid–base reaction, followed by formation of the carbon–lithium bond (Eq. 200).[225] These steps may occur more or less synchronously.



(200)

Roberts-Curtin mechansim

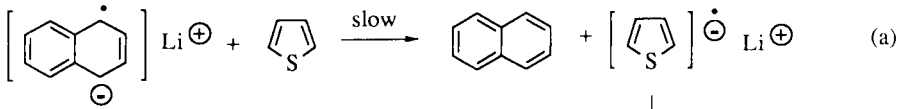
By studying the substituent effects in the metalation of 3-methyl and 3-bromothiophene, Gronowitz concluded that the Roberts–Curtin mechanism is the more likely one.[12] Thus 3-bromothiophene is preferentially metalated in the 2-position by phenyllithium, and 3-methylthiophene is metalated in the

5-position by BuLi. If the electrophilic mechanism (the Morton mechanism) were acting, one would expect the 2-position of 3-methylthiophene to be more reactive than the 5-position. Again, if the Morton mechanism would be valid, *N*-methylpyrrole should be metalated faster than thiophene, since it is also more reactive in electrophilic aromatic substitutions. The reverse is true, however, as shown by a competitive metalation experiment where essentially only thiophene was metalated by BuLi.[226] Furthermore, 3-methylthiophene is metalated at a slower rate than thiophene as determined in a competitive experiment with BuLi in ether; after carbonation of the reaction mixture with Dry Ice, 75% of 2-thiophenecarboxylic acid and 25% of 4-methyl-2-thiophene carboxylic acid were obtained. It has been mentioned that one molar excess of thiophene is necessary to ensure that all BuLi is consumed.[227] This indicates that the reaction is an equilibrium with a significant amount of BuLi present if a 1 : 1 stoichiometry is used. Substituent effects are discussed in Volume 44, Part 2, Chapter I, Section 3 and in the present chapter, Section II.7. It is to be expected that the breakage of the carbon–hydrogen bond would be involved in the rate-determining step, which is indeed indicated by the isotope effects $k_H/k_T = 16 \pm 4$ (an earlier value of 5.9 was reported[228]) and $k_H/k_D = 6.6 \pm 0.3$ for the α-position in metalation of thiophene by BuLi.[229] The high values indicate the complete loss of carbon–hydrogen stretching vibration at the transition state. However, it has been disputed that a single temperature measurement of isotope effects really is an indicator of the bond making or breaking at the transition state.[230]

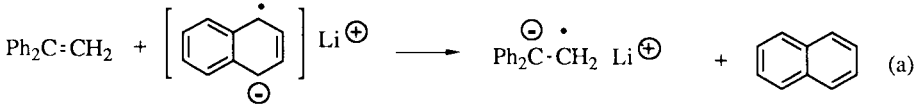
The reaction between thiophene and lithium dihydronaphthylide in THF was studied using magnetic titration to determine the amount of thiophene required to bring about complete discharge of paramagnetism.[25] This occurred at a thiophene : reagent ratio of 1 : 2, indicating that the reaction, in which 2-thienyllithium is formed, is a two-electron process. In agreement with this observation, the yield of 2-thiophenecarboxylic acid never exceeded 50% after quenching the reaction mixture, containing an excess of thiophene, with Dry Ice. When the reaction was performed in the presence of 1,1-diphenylethylene or α-methylstyrene the yield of 2-thiophenecarboxylic acid was 80–100%, that is, with 1 : 1 stoichiometry. This result indicated that the reaction became a one-electron process in the presence of substances that may dimerize under the reaction conditions. A mechanism that was proposed to explain these observations involves an initial slow formation of a thiophene radical anion that rapidly decomposes to a hydrogen radical and 2-thienyllithium. The second electron is required in the subsequent reaction of the hydrogen radical with the solvent (THF) to form lithium butoxide (Eq. 201).

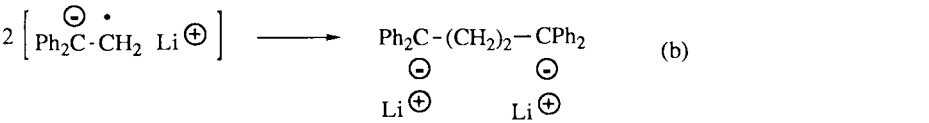
In the presence of 1,1-diphenylethylene, the first electron transfer takes place between this compound and lithium dihydronaphthylide to form the radical anion of 1,1-diphenylethylene, which may dimerize to give a dianion capable of lithiating thiophene (Eq. 202). The net result is, that 1 eq of 2-thienyllithium is formed by 1 eq of lithium dihydronaphthylide.

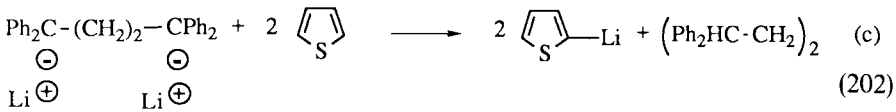
It is suggested that also this "normal" lithiation, using organolithium reagents, involves an initial electron transfer to form the thiophene anion radical.



(201)

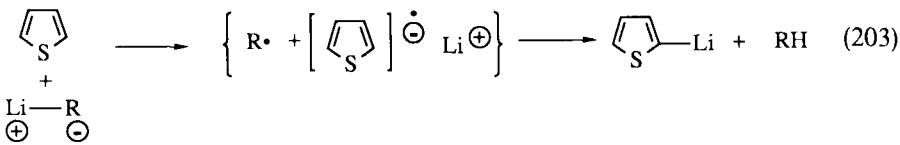






(202)

In this process a radical of the organic part of the lithium reagent is also formed, which then abstracts a hydrogen from the anion radical to give 2-thienyllithium and the hydrocarbon (Eq. 203).[25]



	Reactivity of Positions on the Basis of		
	Superdelocalizability	Localization Energy	Experiment
Thiophene	2 > 3	2 > 3	2 > 3
2-Me	5 > 3 > 4	5 > 3 > 4	5 > 3 > 4
3-Me	5 > 2 > 4	5 > 2 > 4	5 > 2 > 4
2,3-DiMe	5 > 4	5 > 4	5 > 4

Scheme 3

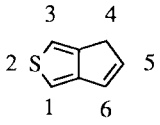
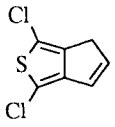
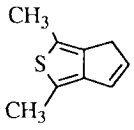
However, the anion radical mechanism has not been supported by CIDNP results but cannot, on the other hand, be ruled out.[222] The reactivities in metalations of different positions of some methylthiophenes were estimated by the use of superdelocalizabilities and localization energies obtained by HMO calculations.[231] It was found that the experimental observations were reproduced by the calculations as seen in Scheme 3.

B. NMR Data

NMR data (in THF) for the anion of 4*H*-cyclopenta[*c*]thiophene (A) and its 1,3-dimethyl (B) and 1,3-dichlorosubstituted (C) analogs were recorded (Table 27) and in the former case compared with the calculated electron densities obtained by the HMO-ω-method.[166]

For A and B it was found that the chemical shifts of the 1,3- and 6-protons moved upfield, while the 4- and 6-protons moved downfield. As seen in Figure 3, there is a positive correlation of the electron densities and the recorded relative chemical shifts ($\Delta\delta$, as expressed by the difference in chemical shifts of the parent compound and the anion) for A and its anion. The large downfield shift of the

TABLE 27. Relative ^{1}H Chemical Shifts ($\Delta\delta_n$) of Anion of 4*H*-cyclopenta[*c*]thiophene and Its 1,3-Dichloro and 1,3-Dimethyl Analogs in THF at 60 MHz ($\Delta\delta = \delta_{\text{parent compound}} - \delta_{\text{anion}}$)

Anion of	*H*1	*H*3	*H*4	*H*5	*H*6
 A	+ 0.7	+ 0.8	− 2.1	− 0.3	+ 1.3
 B			− 1.8	− 0.3	+ 1.6
 C			− 1.9	+ 0.9	+ 2.6

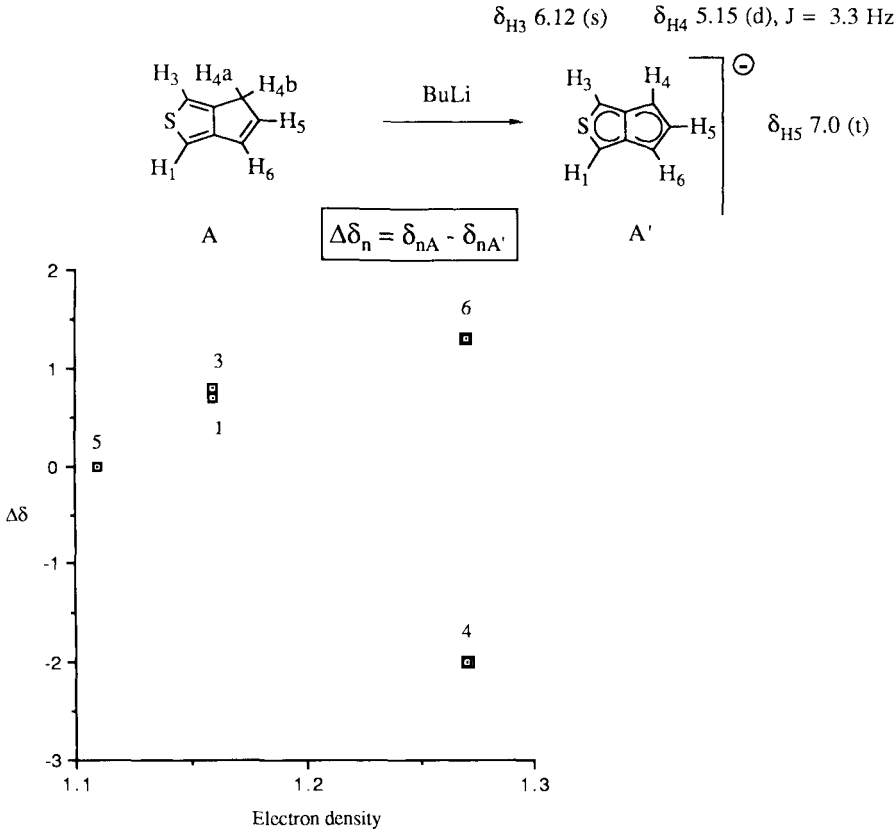


Figure 3. Correlations of $\Delta\delta$ (60 MHz, THF) and electron densities for the different positions of the anion of compound A.

4-proton was ascribed to the change of hybridization from sp^3 to sp^2 character of C-4, and the smaller downfield shift of the 5-proton was ascribed to the occurrence of a ring-current effect in the anion. Similar changes in chemical shifts were noticed for the 1,3-dichloro analog B. An upfield shift was recorded for the 5-proton of the 1,3-dimethyl analog C, which was explained by the electron-donating effect of the methyl groups, which obviously overrides the ring-current effect in this case.

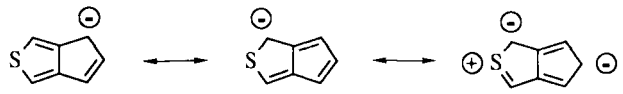


Figure 4. Major resonance forms for the anion of 4*H*-cyclopenta[*c*]thiophene.

The calculated bond orders of the anion of 4*H*-cyclopenta[*c*]thiophene indicated that the resonance hybrid should be composed of three reasonably important structures: I, II, and III (Figure 4).

The ^{1}H NMR spectra of some thienyllithium derivatives were recorded in diethyl ether.[232] It was found that the lithium atom caused an unexpected downfield chemical shift as compared with a proton and that the lithium derivatives showed smaller coupling constants than did the normal thiophenes (Table 28).

Moreover, the usually diagnostic intervals of the coupling constants for the substitution pattern became invalid. No satisfactory explanation of these results has been proposed, although it has been suggested that the structure of a possible dimeric complex may have such an arrangement that the ring current of one ring influences the chemical shifts of the protons of the other ring. The thienyllithium derivatives behave differently as compared to phenyllithium, in which only the signal of the ortho protons is moved toward lower field while the meta and para proton signals are moved toward higher field.[233, 234] Also the chemical shifts of 5-lithio- and 2-lithio-3-pentadeuterophenylthiophene are moved toward lower field as compared to the parent compound (Table 28).[235] The 53 : 47 mixture of these two thenyllithium derivatives, respectively, were obtained by EtLi treatment of 3-pentadeuterophenylthiophene in ether.

TABLE 28. Chemical Shifts (δ ppm) and Coupling Constants (Hz) of Thienyllithium Derivatives and Some Comparative Thiophene Derivatives in Ether Solution (60 MHz)

	Chemical Shifts				Coupling Constants			
Substituent	*H*2	*H*3	*H*4	*H*5	J_{23}	J_{24}	J_{25}	J_{34}
None	7.33	7.08	7.08	7.33				
2-Li	—	7.52	7.18	7.66	4.3	0.5	—	2.8
3-Li	Strongly coupled; largest peaks at 7.69 and 7.06 ppm							
2-Br	—	7.04	6.83	7.26	5.5	1.7	—	3.7
3-Br	7.32	—	7.01	7.32	—	—	—	—
5-Br, 2-Li	—	7.29	7.06	—	—	—	—	2.6
4-Br, 2-Li	—	7.27	—	7.56	—	0	—	—
3-Br, 2-Li	—	—	7.04	7.59	4.4	—	—	—
4-Br, 3-Li	7.32	—	—	7.27	—	—	2.7	—
2-Br, 5-Br	—	6.88	6.88	—	—	—	—	—
2-Br, 4-Br	—	—	7.02	7.38	5.8	—	—	—
3-Br, 4-Br	7.49	—	—	7.49	—	—	—	—
3-Ph, 2-Li[a]	—	—	7.66[b]	7.52[b]	4.3[c]	—	—	—
3-Ph, 5-Li[a]	7.80[b]	—	7.77[b]	—	—	0.7	—	—
3-Ph	7.35	—	7.25	7.25	—	—	—	—

[a] Ph = C_6D_6.

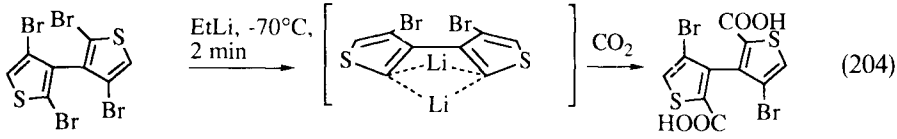
[b] These signals could be interchanged.

[c] J_{45}.

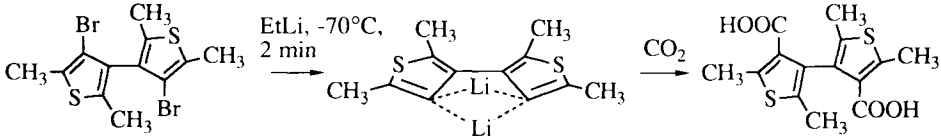
C. Constitution of Thienyllithium Derivatives

Although no X-ray structure determination has been made on thienyllithium derivatives, evidence has been accumulated indicating that these compounds are aggregated, presumably dimeric or tetrameric, in solution. The lithium atom should have a tendency to compensate its electron deficiency by surrounding itself with electron-rich molecules, carrying oxygen and nitrogen. This is one of the factors involved in directed metalation as discussed in Section II.7. Moreover, the lithium atom seems to participate in bridge formation. The bonding situation for the thienyllithium derivatives may be similar to those found for phenyllithium, that is either dimeric complexes as in the presence of TMEDA[236] (or in THF[237]) or a tetrameric structure as has been found in the crystals obtained from PhLi in ether[238] and PhLi in ether–cyclohexane.[239]

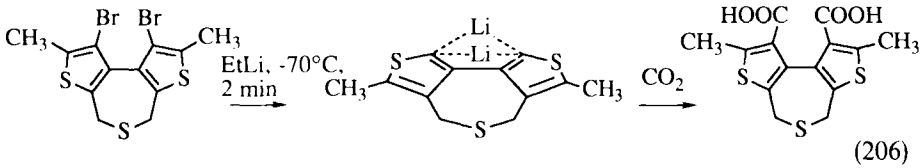
Intramolecular lithium bridging has been proposed as an explanation for the rapid, if not momentaneous, racemization of optically active bromobithienyls on treatment with alkyllithium reagents.[240] Optically inactive products were obtained when optically active 2,2′,4,4′-tetrabromo-3,3′-bithienyl[241] and 4,4′-dibromo-2,2′,5,5′-tetramethyl-3,3′-bithienyl[242] were treated with alkyllithium reagents (EtLi) at − 70°C for 2 min followed by quenching with Dry Ice (Eqs. 204, 205). Also, an optically active sulfur bridged dibromo bithienyl gave optically inactive dicarboxylic acid after a similar treatment (Eq. 206). In this case the racemization must have occurred via a cis–coplanar arrangement required by the lithium bridging.[242]



optically active racemate (204)

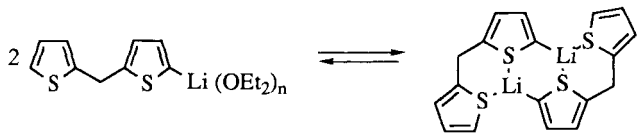


optically active racemate (205)



optically active racemate (206)

The metalation of 2,2′-dithienylmethane by BuLi shows an interesting temperature dependence. Thus at $-10°C$ or below only mono metalation takes place regardless of the amount of BuLi added, while dimetalation is easily accomplished at $+5°C$ or higher. This was explained by a temperature-dependent equilibrium between the ether solvate and the dimeric complex shown in Eq. 207.[114]

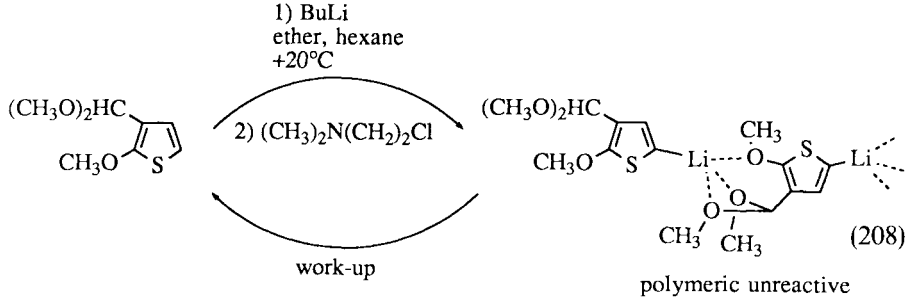


(207)

above +5°C below -10°C

At lower temperatures the dimeric complex would predominate and thus sterically shield the remaining α-position from further lithiation. At the intermediate temperatures mixtures of di- and monolithiated compounds are obtained.[112]

Complex formation was also inferred as an explanation for the unreactivity of the 5-thienyllithium derivatives carrying both a 2-methoxy group and a 3-acetal grouping (Eq. 208).[18]



(208)

D. Acidity of Thienylic Protons

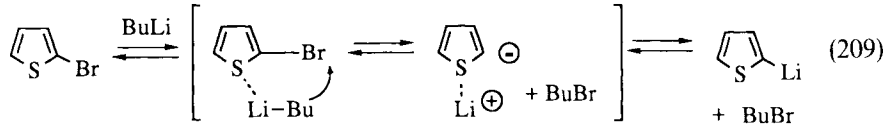
The thermodynamic pK_a of the thiophene α-hydrogen is reported to be 38.42 ± 0.06 as determined by reacting thiophene with cesium cyclohexylamide in a cyclohexylamine solution in the presence of *p*-phenyltoluen as indicator.[243] By using triphenylmethyllithium in THF a thermodynamic pK_a was determined to be 32.0 ± 0.2 for thiophene and 31.8 ± 0.2 for selenophene.[244]

Both acid- and base-catalyzed hydrogen exchange reactions have been reviewed in Volume 44, Part 2, Chapter I, Section IV.

E. Halogen–Metal Exchange

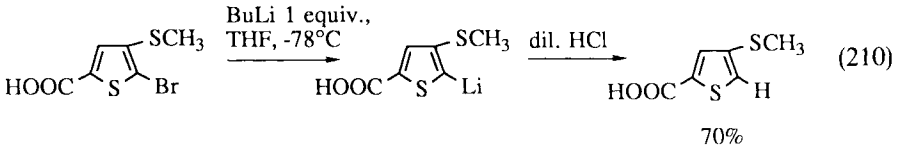
No detailed mechanistic investigation of this reaction has been done, but it is generally believed that the butyl anion attacks the halogen atom and lithium

enters, more or les concertedly, the position that the halogen leaves in an equilibrium reaction (Eq. 209)[245] Thus, this mechanism is very similar to the one presented above for the metalation reaction.



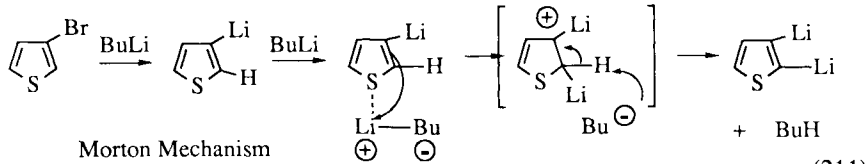
(209)

The halogen–metal exchange reaction of halothiophenes is usually very fast when the halogens are iodine or bromine. In fact, it has been demonstrated the halogen–metal exchange (Br–Li) using BuLi may be faster than the proton removal from a carboxylic acid. Thus when 2-bromo-3-methylthio-5-thiophenecarboxylic acid was treated with only 1 eq of BuLi at $-78°C$ followed by dilute hydrochloric acid, only 4-methylthio-2-thiophencarboxylic acid was formed (Eq. 210).[20] A similar result was obtained with 2-bromo-4-methylthio-5-thiophenecarboxylic acid.



(210)

A faster halogen–metal exchange reaction than metalation of 3-bromothiophene was suggested in order to explain the increased amount of dilithiation on increasing the amount of BuLi or EtLi used (reaction temperature -30 to $-40°C$).[246] If the lithium enters the 3-position first, there seems to be little reason for a second lithium to enter the 2-position via another protophilic attack since now the thiophene ring would carry some negative charge due to the polarization of the carbon–lithium bond. Instead, it is suggested that the mechanism is changed in the electophilic direction; thus the Morton mechanism may be valid on introducing the second lithium atom.[246] The reaction sequence may then be described as shown in Eq. 211.



(211)

REFERENCES

1. M. G. Reinecke and P.Pedaja, "Thiophene and its Derivatives," in *The Chemistry of Heterocyclic Compounds*, A. Weissberger and E. C. Taylor, eds., Vol. 44, Part 2, Interscience, New York, 1986, p. 159.
2. S. Gronowitz, *Thiophenes and their Selenium and Tellurium Analogues in Organic Compounds of Sulfur, Selenium, and Tellurium*, Vol. 2, 1973, p. 352; Vol. 3, 1975, p. 400; Vol. 4, 1977, p. 244; Vol. 5, 1978, p. 247; The Royal Society of Chemistry, London.
3. S. Gronowitz, in *Five-Membered Ring Systems.* Part I: *Thiophenes and their Selenium and Tellurium Analogues, Heterocyclic Chemistry*, Vol. 1, 1980, p. 67; Vol. 2, 1981, p. 73; Vol. 3, 1982, p. 63; Vol. 4, 1985, p. 71; Vol. 5, 1986, p. 73; The Royal Society of Chemistry, London.
4. H. D. Hartough, *Thiophene and Its Derivatives*, Interscience, New York, 1952, pp. 439–457.
5. B. Iddon, *Heterocycles*, **20**, 1127 (1983).
6. S. Gronowitz, *Adv. Heterocycl. Chem.*, **1**, 1–125 (1963).
7. R. M. Kellogg, in *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, A. R. Katritzky and C. W. Rees, eds., Pergamon Press, New York, 1984, Vol. 4, p. 713.
8. S. Rajappa, in *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, A. R. Katritzky and C. W. Rees, eds., Pergamon Press, New York, 1984, Vol. 4, p. 741.
9. E. Campaigne, in *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*, A. R. Katritzky and C. W. Rees, eds., Pergamon Press, New York, 1984, Vol. 4, p. 863.
10. R. R. Benkeser and R. B. Currie, *J. Am. Chem. Soc.*, **70**, 1780 (1948).
11. H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **71**, 1870 (1949).
12. S. Gronowitz, *Arkiv Kemi*, **7**, 361 (1954).
13. N. Gjös and S. Gronowitz, *Acta Chem. Scand.*, **25**, 2596 (1971).
14. G. M. Davies and P. S. Davies, *Tetrahedron Lett.*, 3507 (1972).
15. S. Gronowitz, T. Frejd, O. Karlsson, K. Lawitz, P. Pedaja, and K. Pettersson, *Chem. Scripta*, **18**, 192 (1981).
16. S. Gronowitz, L. Svensson, M. Herslöf, A. Tjörnebo, N. Stjernström, and S. O. Ögren, *Acta Pharm. Suecica*, **16**, 376 (1979).
17. S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **B30**, 485 (1976).
18. A. Hallberg and S. Gronowitz, *Chem. Scripta*, **16**, 42 (1980).
19. J. O. Karlsson, S. Gronowitz, and T. Frejd, *J. Org. Chem.*, **47**, 374 (1982).
20. E. C. Taylor and D. E. Vogel, *J. Org. Chem.*, **50**, 1002 (1985).
21. S. Gronowitz and C. Glennow, *Chem. Scripta*, **11**, 76 (1977).
22. S. Gronowitz, K. Stenhammar, and L. Svensson, *Heterocycles*, **15**, 947 (1981).
23. M. Nilsson and C. Ullenius, *Acta Chem. Scand.*, **24**, 2370 (1970).
24. D. Braun and E. Seelig, *Berichte*, **97**, 3098 (1964).
25. C. G. Screttas, *J. Chem. Soc. Perkin II*, 745 (1974).
26. S. Gronowitz, *Arkiv Kemi*, **12**, 239 (1958).
27. D. E. Seitz, S.-H. Lee, R. N. Hanson, and J. C.Bottaro, *Synth. Comm.*, **13**, 121 (1983).
28. B. Abarca, R. Ballesteros and G. Jones, *Ann. Quim.*, **79**, 23 (1983).
29. S. Gronowitz, B. Cederlund, and A.-B. Hörnfeldt, *Chem. Scripta*, **5**, 217 (1974).
30. S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **B29**, 818 (1975).
31. A. J. Clarke, S. M. McNamra, and O. Meth-Cohn, *Tetrahedron Lett.*, **27**, 2373 (1974).

32. C. G. Screttas and J. F. Eastham, *J. Am. Chem. Soc.*, **87**, 3276 (1965).
33. A. W. Langer, Jr., *Trans. N.Y. Acad. Sci.*, **27**, 741 (1965); see also M. Schlosser, *Struktur und reaktivität polarer Organometalle*, Springer-Verlag, 1973.
34. A. Covers, J. H. van Mil, M. M. E. Sap, and H. M. Buck, *Recueil*, **96**, 18 (1977).
35. C. G. M. Janssen, A. A. Macco, H. M. Buck, and E. F. Godefroi, *Recueil*, **98**, 448 (1979).
36. V. Ramanathan and R. Levine, *J. Org. Chem.*, **27**, 1667 (1962).
37. D. W. Knight and A. P. Nott, *Tetrahedron Lett.*, **21**, 5051 (1980); *J. Chem. Soc. Perkin I*, 791 (1983).
38. T. Kumamoto, K. Hosoya, S. Kanazaki, K. Masuko, M. Watanabe, and K. Shirai, *Bull. Soc. Chem. Jpn.*, **59**, 3097 (1986).
39. L. F. Cason and P. H. Seay. U.S. Patent 3,122,561 (1964).
40. D. Binder, C. R. Noe, and W. Bilek, *Arch. Pharm.*, **313**, 883 (1980).
41. A. T. Jeffries, K. C. Moore, D. M. Ondeyka, A. W. Springsteen, and D. W. K. MacDowell, *J. Org. Chem.*, **46**, 2885 (1981).
42. W. R. Biggerstaff and K. L. Stevens, *J. Org. Chem.*, **28**, 733 (1963).
43. W. R. Biggerstaff, H. Arzoumanian, and K. L. Stevens, *J. Med. Chem.*, **7**, 110 (1964).
44. S. Dixon, *J. Org. Chem.*, **21**, 400 (1956).
45. T. A. Starostina, I. E. Paleeva, L. F. Kozhemyakina, L. F. Rybakova, R. R. Shifrina, V. A. Chernoplekova, and K. A. Kocheskov, *J. Org. Chem. USSR*, **14**, 2600 (1978).
46. K. Okuhara, *J. Org. Chem.*, **41**, 1487 (1976).
47. K. Okuhara, *Bull. Chem. Soc. Jpn.*, **54**, 2045 (1981).
48. P. L. Kelly, S. F. Thames, and J. E. McClesky, *J. Heterocycl. Chem.*, **9**, 141 (1972).
49. M. Iwao and T. Kuraishi, *Tetrahedron Lett.*, **26**, 6213 (1985).
50. J. G. A. Kooyman, H. P. G. Hendricks, P. P. Montijn, L. Brandsma, and J. F. Arens, *Recueil*, **878**, 69 (1968).
51. R. Sauvetre and J. F. Normant, *Tetrahedron Lett.*, 4325 (1982).
52. L. J. Baldwin, S. Pakray, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **22**, 1667 (1985).
53. J.-P. Lampin and F. Mathey, *J. Organometal. Chem.*, **71**, 239 (1974).
54. F. M. Stoyanovich and B. P. Fedorov, *J. Org. Chem. USSR*, **1**, 1269 (1965).
55. T. Kauffmann, R. Otter, B. Greving, J. König, A. Mitschker, and E. Wenihöfer, *Chem. Ber.*, **116**, 479 (1983).
56. P. Spagnolo, P. Zanirato, and S. Gronowitz, *J. Org. Chem.*, **47**, 3177 (1982).
57. M. S. Karasch and O. Reinmuth, *Grignard Reactions of Non-Metallic Substances*, Prentice-Hall, New York, 1954.
58. H. Gilman and M. A. Plunkett, *J. Am. Chem. Soc.*, **71**, 1117 (1949).
59. T. Kauffmann, A. Mitschker, and A. Woltermann, *Berichte*, **116**, 992 (1983).
60. T. Kauffman, M. Ghanem, and R. Otter, *Berichte*, **115**, 459 (1982).
61. D. J. Brown, W. B. Cowden, and L. Strekovski, *Aust. J. Chem.*, **35**, 1209 (1982).
62. J. Bourguinon, C. Becue, and G. Queguiner, *J. Chem. Res.* (*S*), **104**, (1981); (*B*) 1401 (1981).
63. S. Gronowitz and J. Böler, *Arkiv Kemi*, **28**, 587 (1968).
64. N. Löfgren and C. Tegnér, *Acta Chem. Scand.*, **6**, 1020 (1952).
65. U. Michael and A.-B. Hörnfeldt, *Tetrahedron Lett.*, 5219 (1970).
66. H. J. Jacobsen and S.-O. Lawesson, *Tetrahedron*, **21**, 3331 (1965).
67. S. F. Thames and J. E. McClesky, *J. Heterocycl. Chem.*, **3**, 104 (1966).
68. E. Jones and I. M. Moodie, *J. Chem. Soc.* (*C*), 1195 (1968).
69. W. S. DiMenna, *Tetrahedron Lett.*, 2129 (1980).
70. Ya. L. Goldfarb and Ya. L. Danyushevskii, *Bull. Acad. Sci. USSR*, **3**, 540 (1963).

71. M. Robba, B. Roques, and M. Bonhomme, *Bull. Soc. Chim. Fr.*, **7**, 2495 (1967).
72. N. Dereu and J. L. Piette, *Bull. Soc. Chim. Fr.*, **11–12**,, II-623 (1979).
73. B. P. Fabrichnyi, Yu. B. Volkenshtein, V. I. Rogovik, I. B. Karmanova, and Ya. L. Goldfarb, *Chem. Heterocycl. Comp.*, **1**, 504 (1965).
74. D. W. Slocum and P. L. Gierer, *J. Org. Chem.*, **42**, 3668 (1976); *J. Chem. Soc., D*, 305 (1971).
75. G. Kossmehl, P. Beimling, and G. Manecke, *Makromol. Chem.*, **184**, 627 (1983).
76. E. Campaigne, G. Skowronski, and R. B. Rogers, *Synth. Commun.*, **3**, 325 (1973).
77. R. D. Schuetz and G. P. Nilles, *J. Org. Chem.*, **36**, 2486 (1971).
78. J. Bosch, R. Granados, and F. Lopez, *J. Heterocycl. Chem.*, **12**, 651 (1975).
79. D. W. H. MacDowell and F. L. Ballas, *J. Org. Chem.*, **42**, 3717 (1977).
80. F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.*, **9**, 725 (1972).
81. G. Catoni, C. Galli, and L. Mandolini, *J. Org. Chem.*, **45**, 1906 (1980).
82. C. Eaborn and A. Ricci, *J. Organometal. Chem.*, **192**, 339 (1980).
83. A. Carpita, R. Rossi, and C. A. Veracini, *Tetrahedron*, **41**, 1919 (1985).
84. S. Gronowitz and T. Dahlgren, *Chem. Scripta*, **12**, 57 (1977).
85. R. Guilard, P. Fournari, and M. Person, *Bull. Chim. Soc. Fr.*, **11**, 4121 (1967).
86. P. Jordens, G. Rawson, and H. Wynberg, *J. Chem. Soc. C*, 273 (1970).
87. Ya. L. Goldfarb, M. A. Kalik, and V. K. Zavyalova, *Chem. Heterocycl. Comp.*, 126 (1981).
88. E. Jones and I. M. Moodie, *J. Chem. Soc. C*, 2051 (1969).
89. V. I. Rogovik and Ya. L. Goldfarb, *Chem. Heterocycl. Comp.*, **1**, 439 (1965).
90. A. J. Margida and G. F. Koser, *J. Org. Chem.*, **49**, 4703 (1984).
91. R. D. Schuetz, D. O. Taft, J. P. O'Brien, J. L. Shea, and H. M. Mork, *J. Org. Chem.*, **28**, 1420 (1963).
92. R. E. Banks, R. AS. DuBoisson, and E. Tsiliopoulis, *J. Fluor. Chem.*, **32**, 461 (1986).
93. E. B. Pedersen and S.-O. Lawesson, *Tetrahedron*, **27**, 3861 (1971).
94. J. Z. Mortensen, B. Hedegaard, and S.-O. Lawesson, *Tetrahedron*, **27**, 3839 (1971).
95. C. D. Hurd and H. J. Andersson, *J. Am. Chem. Soc.*, **75**, 5124 (1953).
96. A.-B. Hörnfeldt and S. Gronowitz, *Arkiv Kemi*, **21**, 239 (1963).
97. J. Namtvedt, *Acta Chem. Scand.*, **22**, 1611 (1968).
98. R. T. Hawkins, *J. Heterocycl. Chem.*, **11**, 291 (1974).
99. ICI, Fr. Patent, 2,140,127 (1973); *Chem. Abstr.*, **79**, 42677n.
100. S. Gronowitz, T. Dahlgren, J. Namtvedt, C. Roos, G. Rosen, B. Sjöberg, and U. Forsgren, *Acta Pharm. Suecica*, **8**, 623 (1971).
101. H. Hassner, P. Munger, and B. A. Belinka, *Tetrahedron Lett.*, **23**, 699 (1982).
102. A. J. Carpenter and D. J. Chadwick, *J. Chem. Soc. Perkin I*, 173 (1985).
103. Ya. L. Goldfarb, M. A. Kalik, and M. L. Kurmalova, *J. Gen. Chem. USSR*, **32**, 222 (1962).
104. C. J. Grol, *Tetrahedron*, **30**, 3621 (1974).
105. K. Y. Jen and M. P. Cava, *Tetrahedron Lett.*, **23**, 2001 (1982).
106. W. E. Truce and E. Wallisch, *J. Am. Chem. Soc.*, **74**, 5177 (1952).
107. Ya. L. Goldfarb and V. P. Litvinov, *Bull. Acad. Sci. USSR*, **11**, 1987 (1964).
108. L. Engman and M. P. Cava, *Organometallics*, **1**, 470 (1982).
109. H. J. Jacobsen, *Acta Chem. Scand.*, **24**, 2661 (1970).
110. S. F. Thames, L. H. Edwards, T. N. Jacobs, P. L. Grube, and F. H. Pinkerton, *J. Heterocycl. Chem.*, **9**, 1259 (1972).
111. T. B. Patrick, J. M. Disher, and W. J. Probst, *J. Org. Chem.*, **37**, 4467 (1972).

112. Ya. L. Goldfarb and M. L. Kirmalova, *J. Gen. Chem. USSR*, **25**, 1321 (1955).
113. Ya. L. Goldfarb and M. L. Kirmalova, *J. Gen. Chem. USSR*, **29**, 881 (1959).
114. M. Ahmed and O. J. Meth-Cohn, *J. Chem. Soc. C*, 2104 (1971); O. Meth-Cohn, *Q. Rep. Sulfur Chem.*, **5**, 129 (1970).
115. R. Gräfing and L. Brandsma, *Recueil*, **95**, 264 (1976).
116. F. H. Pinkerton and S.-F. Thames, *J. Organometal. Chem.*, **29**, C4 (1971).
117. D. J. Chadwick and C. Willbe, *J. Chem. Soc. Perkin I*, 887 (1977).
118. J. Sicé, *J. Am. Chem. Soc.*, **75**, 3697 (1953).
119. Ya. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *J. Gen. Chem. USSR*, **29**, 3592 (1959).
120. J. M. Barker, P. R. Huddleston, and S. W. Shutler, *J. Chem. Soc. Perkin I*, 2483 (1975).
121. A. Hallberg, T. Frejd, and S. Gronowitz, *J. Chem. Soc. Perkin I*, 1390 (1980).
122. S. Gronowitz, A. Hallberg, and T. Frejd, *Chem. Scripta*, **1**, 15 (1980).
123. C. V. Pham, R. S. Macomber, H. B. Mark, and H. Zimmer, *J. Org. Chem.*, **49**, 5250 (1984).
124. S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibuya, *Heterocycles*, **20**, 2035 (1983).
125. A. J. Carpenter and D. J. Chadwick, *Tetrahedron Lett.*, **26**, 1777 (1985).
126. P. Ribeneaux and G. Quequiner, *Tetrahedron*, **39**, 3593 (1983).
127. W. Friedrichsen and A. Schöning, *Heterocycles*, **24**, 307 (1986).
128. D. W. Slocum and P. L. Gierer, *J. Org. Chem.*, **38**, 4189 (1973).
129. A. J. Carpenter and D. J. Chadwick, *J. Org. Chem.*, **50**, 4362 (1985).
130. F. M. Stoyanovich and B. P. Fedorov, *Chem. Heterocycl. Comp.*, **3**, 823 (1967).
131. Ya. L. Goldfarb, M. A. Kalik, and V. K. Zavyalova, *Bull. Acad. Sci USSR*, **12**, 2308 (1981).
132. H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938).
133. H. Gilman, W. Langham, and A. L. Jacoby, *J. Am. Chem. Soc.*, **61**, 106 (1939).
134. G. Wittig, U. Pockels, and H. Dröge., *Berichte*, **71**, 1903 (1938).
135. S. O. Lawesson, *Arkiv Kemi*, **11**, 317 (1957).
136. S. O. Lawesson, *Arkiv Kemi*, **11**, 325 (1957).
137. P. Moses and S. Gronowitz, *Arkiv Kemi*, **18**, 119 (1961).
138. S.-O. Lawesson, *Acta Chem. Scand.*, **10**, 1020 (1956).
139. G. Wittig and M. Rings, *Justus Liebigs Ann. Chem.*, **719**, 127 (1968).
140. S.-O. Lawesson, *Arkiv Kemi*, **11**, 387 (1957).
141. S. Gronowitz and B. Holm, *Acta Chem. Scand.*, **B30**, 505 (1976).
142. M. Robba, R. C. Moreau, and B. Roques, *Comput. Rend. Acad. Sci. (Paris)*, **259**, 3568 (1964).
143. U. Michael and S. Gronowitz, *Acta Chem. Scand.*, **22**, 1353 (1968).
144. S.-O. Lawesson, *Arkiv Kemi*, **11**, 345 (1957).
145. S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **B30**, 439 (1976).
146. S. Gronowitz, L. Svensson, M. Herslöf, and O. Karlsson, *Acta Pharm. Suecica*, **16**, 353 (1979).
147. S. Gronowitz and L. Svensson, *Chem. Scripta*, **15**, 169 (1980).
148. S. Gronowitz, L. Svensson, N. Stjernström, and S. O. Ögren, *Acta Pharm. Suecica*, **16**, 365 (1979).
149. M. T. Rahman and H. Gilman, *J. Indian Chem. Soc.*, **56**, 346 (1979).
150. D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc.*, 577 (1963).
151. I. Akimoto, M. Sano, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **54**, 1587 (1981).
152. M. W. Majchrak, *J. Heterocycl. Chem.*, **22**, 1203 (1985).
153. S.-O. Lawesson and C. Frisell, *Arkiv Kemi*, **17**, 393 (1961).
154. J. Z. Mortensen and S.-O. Lawesson, *Acta Chem. Scand.*, **22**, 1056 (1968).

155. L. Damici, A. Ricci, and M. Taddei, *Tetrahedron Lett.*, **27**, 5155 (1986).
156. S. Gronowitz and A. Bugge, *Acta Chem. Scand.*, **19**, 1271 (1965).
157. M. G. Reinecke, J. G. Newson, and K. A. Almqvist, *Synthesis*, 327 (1980).
158. S. Gronowitz, A. Biezais, and B. Mathiasson, *Arkiv Kemi*, **21**, 265 (1963).
159. G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.*, **70**, 2378 (1948).
160. B. Yom-Tov and S. Gronowitz, *Chem. Scripta*, **3**, 37 (1973).
161. S. Gronowitz and B. Holm, *Acta Chem. Scand.*, **23**, 2207 (1969).
162. S. Gronowitz and B. Eriksson, *Arkiv Kemi*, **21**, 335 (1963).
163. S. Brenner and E. Dunkelblum, *Tetrahedron Lett.*, **27**, 2487 (1973).
164. N. P. Gould and T.-J. Lee, *J. Org. Chem.*, **45**, 4530 (1980).
165. D. W. H. MacDowell and A. T. Jeffries, *J. Org. Chem.*, **35**, 871 (1970).
166. J. Skramstad, *Chem. Scripta*, **4**, 81 (1973).
167. H. Volz and H. Kowarsch, *J. Organometal. Chem.*, **136**, C27 (1977).
168. M. Ahmed and O. Meth-Cohn, *Tetrahedron Lett.*, **19**, 1493 (1969).
169. M. Ahmed and O. Meth-Cohn, *J. Chem. Soc. Chem. Commun.*, 82 (1968).
170. O. Meth-Cohn, *Q. Rep. Sulfur Chem.*, **5**, 129 (1970).
171. P. C. Ostrowski and V. V. Kane, *Tetrahedron Lett.*, 3549 (1977).
172. R. Gräfing and L. Brandsma, *Recueil*, **99**, 23 (1980).
173. D. C. Rowlands, K. W. Greenlee, and C. Boord, *Abstract of Papers*, 117th National Meeting of the American Chemical Society, April, 1950, p. 8L.
174. R. Gaertner, *J. Am. Chem. Soc.*, **73**, 3935 (1951).
175. E. Campaigne and O. E. Yokley, *J. Org. Chem.*, **28**, 914 (1963).
176. E. Campaigne and R. E. Johnson, *J. Heterocycl. Chem.*, **5**, 235 (1968).
177. E. Campaigne and C. J. Collins, *J. Heterocycl. Chem.*, **2**, 136 (1965).
178. J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 3029 (1933).
179. S. Araki and Y. Butsugan, *Bull. Chem. Soc. Jpn.*, **56**, 1446 (1983).
180. C. Hoogzand, J. Nielsen, and E. H. Braye, *J. Chem. Soc. Chem. Commun.*, 1520 (1971).
181. A. J. Carpenter and D. J. Chadwick, *Tetrahedron*, **41**, 3803 (1985).
182. E. G. Doadt and V. Snieckus, *Tetrahedron Lett.*, **26**, 1149 (1985).
183. M. Janda, J. Strogl, I. Stiboe, M. Nemec, and P. Vopatrana, *Synthesis*, 545 (1972).
184. H. Christiansen, S. Gronowitz, B. Rodmar, S. Rodmar, U. Rosen, and M. K. Sharma, *Arkiv Kemi*, **30**, 561 (1969).
185. M. R. Smith, Jr. and H. Gilman, *J. Organometal. Chem.*, **42**, 1 (1972).
186. M.-T. Rahman, *Monatsh. Chemie*, **114**, 249 (1983).
187. S. Gronowitz, *Arkiv Kemi*, **7**, 267 (1954).
188. I. G. C. Coutts, H. R. Goldschmid, and O. C. Musgrave, *J. Chem. Soc. C*, 488 (1970).
189. Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *Chem. Scripta*, **28**, 275 (1988).
190. V. P. Litvinov and I. A. Dzhumaev, *Bull. Acad. Sci. USSR*, **3**, 642 (1982).
191. Ya. L. Goldfarb, M. B. Ibrazimova, and O. A. Kalinovskii, *Bull. Acad. Sci. USSR*, 1029 (1962).
192. J. W. H. Watthey and M. Desai, *J. Org. Chem.*, **47**, 1755 (1982).
193. Ya. L. Goldfarb, V. P. Litvinov, and A. N. Sakisayan, *Bull. Acad. Sci. USSR*, **6**, 1199 (1971).
194. M. Watanabe and V. Snieckus, *J. Am. Chem. Soc.*, **102**, 1457 (1980).
195. A. Hallberg and P. Pedaja, *Tetrahedron*, **39**, 819 (1983).
196. M. Iwao, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **17**, 1259 (1980).
197. R. Pratap, M. L. Lee, and R. N. Castle, *J. Heterocycl. Chem.*, **18**, 1457 (1981).

198. M. G. Reinecke and P. Pedaja, "Thiophene and Its Derivatives," in *The Chemistry of Heterocyclic Compounds*, A. A. Weissberger and E. C. Taylor, eds., Vol. 44, Part 2, Interscience, New York, 1986, p. 319.
199. W. E. Truce, B. Van Gemert, and W. W. Brand, *J. Org. Chem.*, **43**, 101 (1978).
200. A.-B. Hörnfeldt and S. Gronowitz, *Acta Chem. Scand.*, **17**, 1163 (1963).
201. J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 3029 (1933).
202. W. G. Dauben and J. W. Collette, *J. Am. Chem. Soc.*, **81**, 967 (1959).
203. S. Gronowitz and T. Frejd, *Chem. Heterocycl. Comp. USSR*, **14**, 353 (1978).
204. S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **24**, 2656 (1970).
205. H. J. Jacobsen, *Acta Chem. Scand.*, **24**, 2663 (1970).
206. S. Gronowitz and T. Frejd, *Int. J. Sulfur Chem.*, **A2**, 165 (1972).
207. S. Gronowitz and A. Svensson, *Isr. J. Chem.*, **27**, 25 (1986).
208. S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **B30**, 287 (1976).
209. T. Frejd, J. O. Karlsson, and S. Gronowitz, *J. Org. Chem.*, **46**, 3132 (1981).
210. T. Frejd and J. O. Karlsson, *Acta Chem. Scand.*, **B37**, 895 (1983).
211. S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **B30**, 341 (1976).
212. J. O. Karlsson, A. Svensson, and S. Gronowitz, *J. Org. Chem.*, **49**, 2018 (1984).
213. S. Gronowitz and T. Frejd, *Acta Chem. Scand.*, **27**, 2242 (1973).
214. T. Frejd, *J. Heterocycl. Chem.*, **14**, 1085 (1977).
215. H. G. Woo and S. Y. Han, *Indian J. Chem.*, **21B**, 803 (1982).
216. R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 2592 (1970).
217. R. P. Dickinson and B. Iddon, *Int. J. Sulfur Chem. C*, **6**, 59 (1971).
218. A. Hallberg, T. Frejd, and S. Gronowitz, *Chem. Scripta*, **13**, 186 (1978).
219. M. Schlosser, *Struktur und reaktivität polarer Organometalle*, Springer-Verlag, Berlin, 1973.
220. B. J. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon Press, New York, 1974.
221. R. G. Micetich and R. Raap, *Org. Prep. Proc. Int.*, **3**, 169 (1971).
222. D. A. Shirley, T. E. Harmon, and C. F. Cheng, *J. Organometal. Chem.*, **69**, 327 (1974).
223. T. E. Hasrmon and D. A. Shirley, *J. Org. Chem.*, **39**, 3164 (1974).
224. A. A. Morton, *J. Am. Chem. Soc.*, **69**, 969 (1947).
225. J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, **68**, 1658 (1946).
226. D. A. Shirley and J. C. Goan, *J. Organomet. Chem.*, **2**, 304 (1964).
227. M. Nilsson and C. Ullenius, *Acta Chem. Scand.*, **24**, 2370 (1970).
228. S. Gronowitz and K. Halvarson, *Arkiv Kemi*, **8**, 343 (1955).
229. D. A. Shirley and K. R. Barton, *Tetrahedron*, **22**, 515 (1966).
230. A. V. Willi and M. Wolfsberg, *Chem. Ind.*, 2097 (1964).
231. M. Janda, J. Srogl, I Stibor, P. Trska, and P. Vopatrna, *Coll. Czech. Chem.*, **39**, 3522 (1974).
232. S. Gronowitz and A. Bugge, *Acta Chem. Scand.*, **22**, 59 (1968).
233. J. A. Ladd, *Spectrochim. Acta*, **22**, 1157 (1966).
234. J. A. Ladd and R. G. Jones, *Spectrochim. Acta*, **22**, 1964 (1966).
235. N. Gjös and S. Gronowitz, *Arkiv Kemi*, **30**, 225 (1968).
236. D. Thoennes and E. Weiss, *Berichte*, **111**, 3157 (1978).
237. D. Seebach, R. Hässig, and J. Gabriel, *Helv. Chim. Acta*, **66**, 308 (1983).
238. H. Hope and P. P. Power, *J. Am. Chem. Soc.*, **105**, 5320 (1983).
239. L. M. Jackman and L. M. Scaramoutzos, *J. Am. Chem. Soc.*, **106**, 4627 (1984).
240. R. Håkansson, *Chem. Scripta*, **2**, 109 (1972).

241. R. Håkansson and E. Wiklund, *Acta Chem. Scand.*, **25**, 2109 (1971).
242. R. Håkansson, A. Ask, and A. Almqvist, *Chem. Scripta*, **2**, 72 (1972).
243. A. Streitwiesser, Jr. and P. J. Scannon, *J. Am. Chem. Soc.*, **95**, 6273 (1973).
244. A. I. Shatenshtein, E. A. Kovrizhnykh, and I. O. Shapiro, *Chem. Heterocycl. Comp.*, **7**, 938 (1971).
245. R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951).
246. B. Östman, *Arkiv Kemi*, **22**, 551 (1964).
247. M. Nilsson and C. Ullenius, *Acta Chem. Scand.*, **24**, 2379 (1970).
248. K. Nyberg, *Acta Chem. Scand.*, **23**, 1087 (1969).
249. Ya. L. Goldfarb, B. P. Fabrichnyi, and V. I. Rogovik, *Bull. Acad. Sci. USSR*, 492 (1965).
250. P. A. Konstantinov and R. I. Shupik, *J. Gen. Chem. USSR*, **33**, 1223 (1963).
251. J. R. Pratt and S. F. Thames, *J. Org. Chem.*, **38**, 4271 (1973).
252. G. Van Zyl, R. J. Langenberg, H. H. Tam, and R. N. Schut, *J. Am. Chem. Soc.*, **78**, 1955 (1956).
253. R. R. Morgan, P. Tannhauser, P. J. Pratt, T. C. Myers, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 5658 (1955).
254. S. Ohshiro, *J. Pharm. Soc. Jpn.*, **75**, 658 (1955); *Chem. Abstr.*, **50**, 3436 (1956).
255. I. Hirao, K. Mizunuma, and M. Hayashi, *J. Pharm. Soc. Jpn.*, **74**, 105 (1954); *Chem. Abstr.*, **49**, 1696 (1955).
256. P. A. Konstantinov, N. M. Koloskova, O. D. Kireeva, and E. M. Malakhaev, *J. Gen. Chem. USSR*, **42**, 1780 (1972); *Chem. Abstr.*, **78**, 29541y (1973).
257. Yu. A. Zhdanov, N. G. Alekseeva, and V. N. Fomina, *Proc. Acad. Sci. USSR*, **219**, 825 (1974).
258. L. F. Cason and P. H. Seay, U.S. Patent 3,122,561 819649; *Chem. Abstr.*, **60**, P13225 (1964).
259. D. W. Adamson, *J. Chem. Soc.*, 885 (1950).
260. C. G. M. Janssen, *Recueil*, **98/7**, 448 (1979).
261. C. E. Griffin, R. P. Peller, K. R. Martin, and J. A. Peters, *J. Org. Chem.*, **30**, 97 (1965).
262. K. Hafner, C. Bernard, and R. Müller, *Liebigs Ann. Chem.*, **650**, 35 (1961).
263. Ya. L. Goldfarb, A. A. Dudinov, V. P. Litvinov, D. S. Yurit, and Yu. P. Struchkov, *Chem. Heterocycl. Comp.*, **10**, 1021 (1982).
264. A. N. Semenovskii and N. M. Emelyanov, *Bull. Acad. Sci. USSR*, **11**, 1833 (1980).
265. A. N. Semenovskii and N. M. Emelyanov, *Bull. Acad. Sci. USSR*, **6**, 1086 (1980).
266. S. Kano, N. Mochizuki, S. Hibino, and S. Shibuya, *J. Org. Chem.*, **47**, 3566 (1982).
267. M. Akiba and M. P. Cava, *Synth. Commun.*, **14**, 1119 (1984).
268. S. Gronowitz and R. Håkansson, *Arkiv Kemi*, **17**, 73 (1960).
269. S. Gronowitz, P. Moses, and A.-B. Hörnfeldt, *Arkiv Kemi*, **17**, 165 (1961).
270. F. A. Vingiello. S.-G. Quo, P. Polss, and P. Henson, *J. Med. Chem.*, **7**, 832 (1964).
271. E. Wiklund and R. Håkansson, *Chem. Scripta*, **3**, 220 (1973).
272. R. D. Schuetz and G. P. Nilles, *J. Org. Chem.*, **36**, 2188 (1971).
273. G. L. Walford, T. Y. Shen, and B. E. Wifzel, Fr. Patent 2,053,009 (1970); *Chem. Abstr.*, **76**, 113053 (1972).
274. A.-B. Hörnfeldt, *Arkiv Kemi*, **22**, 211 (1964).
275. R. Kreiswetter and P. Margaretha, *Helv. Chim. Acta*, **68**, 2350 (1985).
276. W. R. Biggerstaff, N. Sugisaka, and R. Albers, *J. Med. Chem.*, **12**, 1 (1968).
277. J.-M. Meunier and P. Fournari, *Bull. Soc. Chim. Fr.*, 3343 (1971).
278. Y. Matsumoto and T. Sone, *Kogyo Kagaku Zasshi*, **62**, 1559 (1959); *Chem. Abstr.*, **57**, 8528e (1962).
279. A.-B. Hörnfeldt, *Acta Chem. Scand.*, **21**, 1952 (1967).

280. R. T. Hawkins and D. B. Stroup, *J. Org. Chem.*, **34**, 1173 (1969).
281. S. Gronowitz, A.-B. Hörnfeldt, and Y. Yang, *Chem. Scripta*, **28**, 281 (1988).
282. S. Gronowitz, B. Gestblom, and B. Mathiasson, *Arkiv Kemi*, **20**, 407 (1963).
283. E. Sandberg. *Chem. Scripta*, **7**, 223 (1975).
284. E. Sandberg. *Chem. Scripta*, **2**, 241 (1972).
285. S. Gronowitz, *Arkiv Kemi*, **16**, 363 (1960).
286. T. A. Starostina, L. F. Rybakova, and R. R. Shifrina, *J. Org. Chem. USSR*, **16**, 1968 (1980).
287. R. A. Benkeser and H. Landesman, *J. Am. Chem. Soc.*, **71**, 2493 (1949).
288. Ya. L. Goldfarb and V. I. Rogovik, USSR Patent 184,876 (1966); *Chem. Abstr.*, **66**, 115591y (1967).
289. V. G. K. Das, L. K. Mun, C. Wei, and T. C. W. Mark, *Organometallics*, **6**, 10 (1987).
290. Z. M. Ismail and H. M. Hoffmann, *Heterocycles*, **24**, 325 (1986).
291. P. Pirson, A. Schonne, and L. Christiaens, *Bull. Soc. Chim. Belges*, **79**, 575 (1970).
292. S. F. Thames and J. F. McClesky, *J. Heterocycl. Chem.*, **4**, 146 (1967).
293. S. Martin, R. Sauvetre, and J. K. Normant, *Tetrahedron Lett.*, **23**, 4329 (1982).
294. A. Siegel and M. D. Rausch, *Synth. React. Inorg. Met.-Org. Chem.*, **8**, 209 (1978).
295. Ya. L. Goldfarb, B. P. Fabrichnyi, and V. I. Rogovik, *Bull. Acad. Sci. USSR* (transl.), 2001 (1963).
296. B. P. Fabrichnyi, Yu. B. Volkenshtein, V. I. Rogovik, I. B. Karmanova, and Ya. L. Goldfarb, *Chem. Heterocycl. Comp. USSR*, **1**, 336 (1965).
297. L. I. Belenkii, I. B. Karmanova, Yu. B. Volkenshtein, P. V. Petrovskii, L. A. Fedorov, and Ya. L. Goldfarb, *Bull. Acad. Sci. USSR*, **8**, 1648 (1974).
298. P. Pastour, P. Savalle, and P. Eymery, *Compt. Rend.*, **260**, 6130 (1965).
299. S. Gronowitz and H. Frostling, *Acta Chem. Scand.*, **16**, 1127 (1962).
300. S. Gronowitz and G. Borgen, *Acta Chem. Scand.*, **19**, 1180 (1965).
301. T. Kauffmann and R. Otter, *Chem. Ber.*, **115**, 1825 (1982).
302. M. W. Majchrzak, *J. Heterocycl. Chem.*, **22**, 1205 (1985).
303. W. Hoek, H. Wynberg, and J. Strating, *Recueil*, **85**, 1054 (1966).
304. W. E. Truce and M. F. Amos, *J. Am. Chem. Soc.*, **73**, 3013 (1951).
305. A. Svensson and R. Håkansson, *Chem. Scripta*, **18**, 202 (1981).
306. K. T. Potts and M. J. Cipullo, *J. Org. Chem.*, **47**, 3038 (1982).
307. B. Decroix, J. Morel, C. Paulmier, and P. Pastour, *Compt. Rend. Acad. Sci. (Paris) Ser. C*, **272**, 1878 (1971).
308. J. Morel, C. Paulmier, and P. Pastour, *Compt. Rend. Acad. Sci. (Paris) Ser. C*, **267**, 1842 (1968); *Bull Soc. Chim. Fr.*, 2511 (1969).
309. J. DeWitt and H. Wynberg, *Tetrahedron*, **28**, 4617 (1972).
310. R. Håkansson, *Acta Chem. Scand.*, **25**, 1313 (1971).
311. H. Gilman, R. A. Benkeser, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 1689 (1950).
312. L. I. Zakharkin and V. V. Gavrilenko, *Bull. Acad. Sci. USSR*, **10**, 1737 (1963).
313. P. Benoit and N. Collington, *Bull. Soc. Chim. Fr.*, **5–6**, 1302 (1975).
314. T. Nakamura, M. Soma, T. Onishi, and K. Tamaru, *Z. Phys. Chem.*, **89**, 130 (1974).
315. J. W. Schick and H. D. Hartough, U.S. Patent 2,492,658 (1949); *Chem. Abstr.*, **44**, 3031g (1950).
316. W. J. Zimmerschied and R. C. Arnold, U.S. Patent 2,585,292 (1952); *Chem. Abstr.*, **47**, 2776i (1953).
317. A. A. Morton and C. E. Claff, Jr., *J. Am. Chem. Soc.*, **76**, 4935 (1954).
318. J. H. Ludwig and H. Schulze, *J. Org. Chem.*, **24**, 1573 (1959).

319. J. W. Schick, U.S. Patent 2,492,659 (1949); 2,492,663 (1949); 2,492,660 (1949); *Chem. Abstr.*, **44**, 3031i; *Chem. Abstr.*, **44**, 3032f; *Chem. Abstr.*, **44**, 3032a (1950).
320. J. A. Blanchette and E. V. Brown, *J. Am. Chem. Soc.*, **74**, 1848 (1952).
321. W. A. Stover and A. N. Sachanen, U.S. Patent 2,515,139 (1950); *Chem. Abstr.*, **44**, 9483h (1950).
322. G. van Zyl, J. F. Zack, Jr., E. S. Huyser, and P. L. Cook, *J. Am. Chem. Soc.*, **76**, 707 (1954).
323. G. T. Gmitter and F. L. Benton, *J. Am. Chem. Soc.*, **72**, 4586 (1950).
324. W. G. Blenderman, M. M. Joullie, and G. Petri, *J. Org. Chem.*, **48**, 3206 (1983).
325. H. C. van der Plas, D. A. de Bie, G. Geurtsen, M. G. Reinecke, and H. W. Adickes, *Recueil*, **93**, 33 (1974).
326. J. M. Barker, I. G. C. Coutts, and P. R. Huddleston, *J. Chem. Soc.*, 615 (1972).
327. M. T. Rahman, *J. Indian Chem. Soc.*, **58**, 21 (1981).
328. H. E. Ramsden, U.S. Patent 2,965,661 (1960); *Chem. Abstr.*, **55**, 6377c (1961).
329. H. E. Ramsden, Br. Patent 824,944 (1959); *Chem. Abstr.*, **54**, 17238d (1960).
330. E.- Lukevits, O. A. Pudova, and N. P. Erchak, *J. Gen. Chem. USSR*, **50**, 1348 (1980).
331. J. Meijer, P. Vermeer, and L. Brandsma, *Recueil*, **92**, 601 (1973).
332. E. Cherbuliez and C. Giddy, *Helv. Chim. Acta*, **35**, 160 (1952).
333. V. Weinmayr, *J. Am. Chem. Soc.*, **74**, 4355 (1952).
334. B. Gandha and J. K. Sugden, *Synth. Commun.*, **9**, 845 (1979).
335. M. Nakanishi, T. Yokobe, M. Abe, and T. Seki, Jpn. Patent 7,372,175 (1973); *Chem. Abstr.*, **80**, 95768v (1974).
336. R. Breslow and D. Heyer, *J. Am. Chem. Soc.*, **104**, 2045 (1982).
337. K. Hummel, O. A. Wedam, W. Kathan, and H. Demel, *Makromol. Chem.*, **179**, 1159 (1978).
338. R. L. Clarke, M. L. Heckeler, A. J. Gambino, and S. J. Daum, *J. Med. Chem.*, **21**, 1243 (1978).
339. R. Tacke, E. Zimonyi-Hegedüs, and M. Strecker, *Arch. Pharm.*, **313**, 515 (1980).
340. K. Nyberg, B. Östman, and G. Wallerberg, *Acta. Chem. Scand.*, **24**, 1590 (1970).
341. A. C. Byrns, U.S. Patent 2,636,883 (1953); *Chem. Abstr.*, **48**, 7064a (1954).
342. R. C. Blinn, F. A. Gunther, and R. L. Metcalf, *J. Am. Chem. Soc.*, **76**, 37 (1954).
343. N. Sugimoto, S. Saito, and S. Ohshiro, *J. Pharm. Soc. Jpn.*, **74**, 714 (1954).
344. N. Sugimoto and H. Kugita, Jpn. Patent 4422 (1954); *Chem. Abstr.*, **50**, 4237 (1956).
345. I. I. Lapkin and Yu. V. Ionov, *Uch. Zap. Derm. Gos. Univ.*, **178**, 248 (1968); *Chem. Abstr.*, **61**, 3055a (1964).
346. W. H. Baarschers, *Can. J. Chem.*, **54**, 3056 (1976).
347. J. P. Morizur, *Bull. Soc. Chim. Fr.*, 1331 (1963).
348. P. Hurtel, B. Decroix, J. Morel, and F. Terrier, *J. Chem. Res. (S)*, 58 (1983).
349. S. Gronowitz, B. Yom-Tov, and U. Michael, *Acta Chem. Scand.*, **27**, 2257 (1973).
350. S. Liljefors and S. Gronowitz, *Chem. Scripta*, **15**, 102 (1980).
351. S. Gronowitz, P. Moses, and A.-B. Hörnfeldt, *Arkiv Kemi*, **17**, 237 (1961).
352. E. Campaigne and W. D. Foye, *J. Am. Chem. Soc.*, **70**, 3941 (1948).
353. R. Lantz and A.-B. Hörnfeldt, *Chem. Scripta*, **2**, 9 (1972).
354. I. Haiduc and H. Gilman, *Revue Roumaine de Chemie*, **16**, 305 (1971).
355. M. R. Smith, Jr., and H. Gilman, *Organometal. Org. Synth.*, **1**, 265 (1971).
356. M. R. Smith, Jr., M. T. Rahman, and H. Gilman, *Organometal. Org. Synth.*, **1**, 295 (1971).
357. R. D. Howells and H. Gilman, *J. Organometal. Chem.*, **77**, 177 (1974).
358. M. D. Rausch, T. R. Criswell, and A. K. Ignatowicz, *J. Organometal. Chem.*, **13**, 419 (1968).
359. M. Nilsson and C. Ullenius, *Acta Chem. Scand.*, **25**, 2428 (1971).
360. T. M. Cresp and M. V. Sargent, *J. Chem. Soc. Perkin I*, 2961 (1973).

361. A. L. Johnson, *J. Org. Chem.*, **41**, 1320 (1976).
362. S. Gronowitz and A. Maltesson, *Acta Chem. Scand.*, **25**, 2435 (1971).
363. H. Wynberg and A. Kraak, *J. Org. Chem.*, **29**, 2455 (1964).
364. C. Maletras, B. DeCroix, J. Morel, and P. Pastour, *Bull. Soc. Chim. Fr.*, **7–8**, 1575 (1974).
365. B. Hanquet, R. Guilard, and P. Fournari, *Bull. Soc. Chim. Fr.*, **5–6**, 571 (1977).
366. D. J. Chadwick, J. Chambers, H. E. Hargraves, and G. D. Meakins, *J. Chem. Soc. Perkin I*, 2327 (1973).
367. D. W. H. MacDowell, R. A. Jourdenais, and G. E. Paulovicks, *J. Org. Chem.*, **36**, 2683 (1971).
368. S. Gronowitz and P. Pedaja, *Chem. Scripta*, **15**, 187 (1980).
369. S. Gronowitz, P. Moses, and R. Håkansson, *Arkiv Kemi*, **16**, 267 (1960).
370. A. Almqvist and R. Håkansson, *Chem. Scripta*, **11**, 57 (1977).
371. D. J. Chadwick, G. D. Chambers, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc. Chem. Commun.*, 742 (1972).
372. D. J. Chadwick, J. Chambers, P. K. G. Hogson, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc. Perkin I*, 1141 (1974).
373. T. Tanouchi, M. Kawamura, I. Okyama, I. Kajiwara, Y. Iguchi, T. Okada, T. Miyamoto, K. Taniguchi, and H. Hayashi, *J. Med. Chem.*, **24**, 1149 (1981).
374. S. Gronowitz and B. Yom-Tov, *Z. Chem.*, **10**, 389 (1970).
375. B. Yom-Tov and S. Gronowitz, *Chem. Scripta*, **3**, 165 (1973).
376. B. Yom-Tov and S. Gronowitz, *J. Heterocycl. Chem.*, **15**, 285 (1978).
377. S. Gronowitz, *Arkiv Kemi*, **12**, 87 (1955).
378. E. W. Brunnett and W. C. McCarthy, *J. Heterocycl. Chem.*, **5**, 417 (1968).
379. R. Håkansson and A. Svensson, *Chem. Scripta*, **10**, 117 (1976).
380. L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Res.*, **18B**, 371 (1959).
381. L. J. Pandya and B. D. Tilak, *J. Chem. Soc. Chem. Commun.*, **98**, 382 (1958).
382. M. Hori, T. Kataoka, H. Shimizu, and S. Yoshimura, *Yakugaku Zasshi*, **94**, 1429 (1974).
383. A. Almqvist and R. Håkansson, *Chem. Scripta*, **11**, 186 (1977).
384. K. Kobayashi, *Chem. Lett.*, 1423 (1985).
385. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 174 (1974).
386. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 76 (1974).
387. R. Håkansson and E. Wiklund, *Arkiv Kemi*, **31**, 101 (1969).
388. K. Thiele, K. Posselt, and H. Offermanns, *Arzneim.-Forsch./Drug Res.*, **28**, 2047 (1978).
389. D. R. Arnold and C. P. Hadjiantoniou, *Can. J. Chem.*, **56**, 1970 (1978).
390. A. L. A. Pons, M. F. Robba, and P. H. F. Laurent, Fr. Patent 1,402,863 (1965); *Chem. Abstr.*, **63**, 11502d (1965).
391. M. Robba and Y. LeGuen, *Chim. Therp.* (May–June), 239 (1966); *Idem*, *ibid.*, (March–April), 120 (1967).
392. D. R. Arnold and R. J. Birtwell, *J. Am. Chem. Soc.*, **95**, 4599 (1973).
393. M. Robba and D. Duval, *Chim. Therap.*, **1**, 22 (1973).
394. L. Lunazzi, M. Tiecco, O. A. Boicelli, and F. Taddei, *J. Mol. Spectr.*, **35**, 190 (1970).
395. J. Engel, A. V. Schlichtegroll, and W. S. Sheldrick, *Drug. Res.*, **32**, 475 (1982).
396. A. Kleemann, J. Heese, and J. Engel, *Drug. Res.*, **31**, 1178 (1981).
397. S. Gronowitz and R. Håkansson, *Arkiv Kemi*, **16**, 309 (1960).
398. L. J. Baldwin, S. Pakray, R. N. Castle, and M. L. Lee, *J. Heterocycl. Chem.*, **22**, 1667 (1985).
399. M. S. Cooper and H. Heaney, *Tetrahedron Lett.*, **27**, 5011 (1986).
400. Ya. L. Goldfarb, Yu. B. Volkenshtein, and B. V. Lopatin, *J. Gen. Chem. USSR*, **34**, 961 (1964).
401. A.-B. Hörnfeldt, *Acta Chem. Scand.*, **19**, 1249 (1965).

402. D. Binder, C. R. Noe, W. Bilek, and M. Kubjacek, *Arch. Pharm.*, **314**, 228 (1981).
403. E. B. Pedersen and S.-O. Lawesson, *Tetrahedron*, **26**, 2959 (1970).
404. J. O. Karlsson, S. Gronowitz, and A. Hallberg, *Chem. Scripta*, **20**, 37 (1982).
405. T. Sone, H. Kawasaki, S. Nagasawa, N. Takahashi, K. Tabe, and K. Sato, *Chem. Lett.*, 399 (1981).
406. B. L. Chenard, R. L. Harlow, A. L. Johnson, and S. A. Vladuchick, *J. Am. Chem. Soc.*, **107**, 3871 (1985).
407. V. P. Litvinov and G. Fraenkel, *Bull. Acad. Sci. USSR*, 1828 (1968).
408. N. Aggarwal and D. W. H. MacDowell, *Org. Prep. Proc. Int.*, **11**, 247 (1979).
409. D. P. Munro and J. T. Sharp, *J. Chem. Soc. Perkin I*, 1718 (1980).
410. D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc. Perkin I*, 523 (1975).
411. A.-B. Hörnfeldt and P. O. Sundberg, *Acta Chem. Scand.*, **26**, 31 (1972).
412. S. G. Mairanovskii, N. V. Kondratova, I. B. Karmanova, and Yu. B. Volkenshtein, *Bull. Acad. Sci. USSR*, **11**, 2307 (1971).
413. R. Guilard and P. Fournari, *Bull. Soc. Chim. Fr.*, 1437 (1971).
414. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 137 (1974).
415. R. Guilard, J. Tirouflet, and P. Fournari, *J. Organomet. Chem.*, **33**, 195 (1971).
416. U. Michael and S. Gronowitz, *Chem. Scripta*, **4**, 126 (1973).
417. S. Gronowitz, P. Gassne, and B. Yom-Tov, *Acta Chem. Scand.*, **23**, 2927 (1969).
418. A. T. Jeffries III and S. Gronowitz, *Chem. Scripta*, **4**, 183 (1973).
419. A. Almqvist and R. Håkansson, *Chem. Scripta*, **11**, 180 (1977).
420. J. Bosch, M. Alvarez, and R. Granados, *J. Heterocycl. Chem.*, **17**, 745 (1980).
421. M. Ban, Y. Baba, K. Mura, Y. Kondo, K. Suzuki, and M. Hori, *Chem. Pharm. Bull.*, **24**, 1679 (1976).
422. A. Yamashita and T. A. Scahill, *Tetrahedron Lett.*, **23**, 3765 (1982).
423. R. Aumann and H. Heinen, *Chem. Ber.*, **118**, 4186 (1985).
424. C. Hoogzand, J, Nielsen, and E. H. Braye, *J. Chem. Soc. Chem. Commun.*, 1520 (1971).
425. M. T. Rahman, M. R. Smith, Jr., A. F. Webb, and H. Gilman, *Organomet. Chem. Synth.*, **1**, 105 (1970/71).
426. M. Morel and P. Pastour, *Bull. Chim. Soc. Fr.*, 737 (1968).
427. P. Cagniant, *Bull. Chim. Soc. Fr.*, 847 (1949).
428. L. M. Weinstock, R. B. Currie, and A. V. Lovell, *Synth. Commun.*, **11**, 943 (1981).
429. M. T. Rahman, *Monatsh. Chemie*, **113**, 91 (1982).
430. F. A. Vingiello, S. G. Quo, and P. Polss, *J. Org. Chem.*, **30**, 266 (1965).
431. J. Kagan, S. K. Arora, I. Prakash, and A.Üstünol, *Heterocycles*, **20**, 1341 (1983).
432. Yu. V. Shklyaev, Yu. P. Dornidontov, and I. I. Lapkin, *Chem. Heterocycl. Comp.*, **6**, 569 (1982).
433. Yu. D. Churkin and N. I. Putokhin, *J. Org. Chem. USSR*, **1**, 599 (1964).
434. G. M. Badger, P. Chenychit, and W. H. F. Sasse, *J. Chem. Soc.*, 3235 (1962).
435. S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).
436. E. F. Godefroi and L. H. Simanyi, *J. Org. Chem.*, **27**, 3882 (1962).
437. S. Portnoy and H. Gisser, *J. Org. Chem.*, **27**, 3331 (1962).
438. W. J. Humphlett, M. J. Weiss, and C. R. Hausser, *J. Am. Chem. Soc.*, **70**, 4020 (1948).
439. P. Cagniant, D. Cagniant, and A. Deluzarche, *Bull. Soc. Chim. Fr.*, 1083 (1948).
440. A. Etienne, *Mém. services chim. etat*, **33**, 405 (1947); *Chem. Abstr.*, **43**, 6102f (1949).
441. W. Buchowiecki, Z. Grosman-Zjawiona, and J. Zjaviony, *Tetrahedron Lett.*, **26**, 1245 (1985).

442. G. D. Hartmann, W. Halczenko, and B. T. Phillips, *J. Org. Chem.*, **51**, 142 (1986).
443. V. W. Floutz. *J. Am. Chem. Soc.*, **71**, 2859 (1949).
444. H. R. Lee and V. Weinmayr, U.S. Patent 2,513,572 (1950); *Chem. Abstr.*, **45**, 664i (1951).
445. H. R. Lee and V. Weinmayr, U.S. Patent 2,513,573 (1950); *Chem. Abstr.*, **45**, 665e (1951).
446. C. D. Hurd and R. P. Holysz, *J. Am. Chem. Soc.*, **72**, 1732 (1950).
447. K. Thiele and K. Posselt, Belg. Patent 640,572 (1964); *Chem. Abstr.*, **62**, 16194e (1965).
448. D. W. Adamson, U.S. Patent 2,561,899 (1951); *Chem. Abstr.*, **46**, 3085e (1952).
449. A. Burger and N. D. Dawson, *J. Org. Chem.*, **16**, 1250 (1951).
450. W. Beck, I. A. Kaye, I. C. Kogon, H. C. Klein, and W. J. Burlant, *J. Org. Chem.*, 1434 (1951).
451. R. Gonclaves and E. V. Brown, *J. Org. Chem.*, **17**, 698 (1952).
452. R. Gonclaves, M. Kegelman, and E. V. Brown, *J. Org. Chem.*, **17**, 705 (1952).
453. P. D. George, U.S. Patent 2,640,833 (1953); *Chem. Abstr.*, **48**, 5227a (1954).
454. M. R. Kegelman and E. V. Brown, *J. Am. Chem. Soc.*, **75**, 5961 (1953).
455. J. F. Scully and E. W. Brown, *J. Am. Chem. Soc.*, **75**, 6329 (1953).
456. R. A. Benkeser and A. Torkelson, *J. Am. Chem. Soc.*, **76**, 1252 (1954).
457. Cl. Feugeas, *Bull. Chim. Soc. Fr.*, 2579 (1963).
458. J. D. Holmes, D. A. K. Jones, and R. Pettit, *J. Organometal. Chem.*, **4**, 324 (1965).
459. V. A. Sazonova, E. P. Sererjakov, and L. S. Kovaleva, *Dokl. Akad. Nauk*, **113**, 1295 (1957) (Russ.).
460. I. V. Andreeva and M. M. Koton, *Zh. Obshch. Khim.* (transl.), **27**, 997 (1957); *Chem. Abstr.*, **52**, 4598b (1958).
461. H. E. Ramsden, Br. Patent 825,093 (1959); *Chem. Abstr.*, **54**, 18438a (1960).
462. I. S. Berdinskii, *Zh. Obshch. Khim.* (transl.), **34**, 1786 (1964).
463. A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Proc. Acad. Sci. USSR*, **165**, 1121 (1965).
464. H. C. van der Plas and C. J. Persoons, *Recueil*, **83**, 701 (1964).
465. C. D. Hurd, R. V. Levetan, and A. R. Macon, *J. Am. Chem. Soc.*, **84**, 4515 (1962).
466. H. J. Roth and B. Miller, *Arch. Pharm.*, **297**, 513 (1964).
467. W. C. Austin, L. H. Conover, and J. W. McFarland, Br. Patent 1,145,867 (1969); *Chem. Abstr.*, **71**, 30487x (1969).
468. L. I. Lapkin, N. A. Karavanov, and Yu. P. Dormidontov, *Met. Poluch. Khim. Reakt. Prep.*, **18**, 162 (1969); *Chem. Abstr.*, **74**, 141425g (1971).
469. R. J. P. Corriu and J. P. Masse, *J. Chem. Soc. Chem. Commun.*, 144 (1972).
470. I. S. Berdinskii, L. A. Vorontsova, L. I. Berdinskaya, and N. K. Mochalova, *Zh. Org. Khim.*, **7**, 2497 (1971); *Chem. Abstr.*, **76**, 72180a (1972).
471. M. J. Martell, Jr. and T. O. Soine, *J. Pharm. Sci.*, **52**, 331 (1963).
472. K. Kahmann, E. Class, and H. Erlenmeyer, *Experientia*, **20**, 297 (1964).
473. C. Frisell and S.-O. Lawesson, *Org. Synth.*, **43**, 55 (1963).
474. T. Kunishinge, K. Sugii, and H. Ishikawa, Jpn. Patent 7,240,791 (1972); *Chem. Abstr.*, **78**, 16023f (1973).
475. I. S. Berdinskii and O. P. Pilipenko, *Khim. Geterots. Soedin Sb.*, **68** (1971); *Chem. Abstr.*, **78**, 15937v (1973).
476. N. V. Stulin and N. I. Putokhin, *Chem. Heterocycl. Comp.*, **1**, 555 (1965).
477. C. G. Stuckwisch and J. V. Bailey, *J. Org. Chem.*, **28**, 2362 (1963).
478. M. Lora-Tamayo, R. Madronero, and M. G. Perez, *Chem. Ber.*, **95**, 2188 (1962).
479. C. L. Zirkle, E. L. Anderson, P. N. Craig, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Med. Pharm. Chem.*, **5**, 341 (1962).

480. M. T. Rahman and H. Gilman, *J. Indian Chem. Soc.*, **51**, 1018 (1974).
481. S. Gopinathan, C. Gopinanthan, and J. Gupta,.*Indian J. Chem.*, **12**, 623 (1974).
482. K. Tamao, M. Zembayashi, and M. Kumada, *Chem. Lett.*, 1237 (1976).
483. K. Tamao, M. Zembayashi, and M. Kumada, *Chem. Lett.*, 1239 (1976).
484. H. Hopff and R. Wandeler, *Helv. Chim. Acta*, **45**, 982 (1962).
485. M. P. Cagniant and P. Cagniant, *Bull. Soc. Chim. Fr.*, 713 (1953).
486. Ya. L. Goldfarb and P. A. Konstantinov, *Bull. Acad. Sci. USSR*, 113 (1957).
487. F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 2303 (1959).
488. S. Gronowitz and K. Pettersson, *J. Heterocycl. Chem.*, **13**, 1099 (1976).
489. M. A. Zemlyanichenko, N. I. Sheverdina, and K. A. Kocheshkov, *Proc. Acad. Sci. USSR*, **202**, 70 (1972).
490. M. Chastrette and R. Gauthier, *Compt. Rend. Acad. Sci. (Paris)*, **277**, 805 (1973).
491. J. Namtvedt, *Acta Chem. Scand.*, **22**, 1611 (1968).
492. S. Gronowitz and A. Bugge, *Acta Chem. Scand.*, **20**, 261 (1966).
493. R. D. Brown, A. S. Buchanan, and A. A. Humffray, *Aust. J. Chem.*, **18**, 1527 (1965).
494. S. Gronowitz and K. Lawitz, *Chem. Scripta*, **24**, 5 (1984).
495. M. A. Grassberger, *Liebigs Ann. Chem.*, 683 (1985).
496. V. A. Sazonova and E. P. Serebryakov, U.S.S.R. Patent 106,396 (1957); *Chem. Abstr.*, **52**, 2667b (1958).
497. G. M. Davies and T. Liegh, Ger. Patent 2,050,470 (1971); *Chem. Abstr.*, **75**, 10416w (1971).
498. A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Proc. Acad. Sci. USSR*, **154**, 30 (1964).
499. B. Asgarouladi, R. Full, K.-J. Schaper, and W. Siebert, *Chem. Ber.*, **107**, 34 (1974).
500. S. Gronowitz and C. Roos, *Acta Chem. Scand.*, **B29**, 990 (1975).
501. W. Siebert, *Chem. Ber.*, **103**, 2308 (1970).
502. S. Gronowitz, T. Dahlgren, J. Namtvedt, C. Roos, B. Sjöberg, and U. Forsgren, *Acta Pharm. Suecica*, **8**, 377 (1971).
503. Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, **26**, 865 (1989).
504. S Gronowitz, A.-B. Hörnfeldt, and Y. Yang, *Croatica Chem. Acta*, **59**, 313 (1986).
505. V. P. Glotchkova and K. A. Kocheskov, *Proc. Acad. Sci. USSR*, **103**, 615 (1955).
506. E. C. Taylor and A. N. McKillop, Ger. Patent 2,000,880 (1970); *Chem. Abstr.*, **73**, 66240s (1970).
507. G. B. Deacon, D. Tunaley, and R. N. M. Smith, *J. Organomet. Chem.*, **144**, 111 (1978).
508. A. N. McKillop, J. S. Fowler, M. J. Zelesko, and J. D. Hunt, *Tetrahedron Lett.*, **29**, 2423 (1969).
509. G. V. Motsarev, V. I. Savushina, V. T. Iushakova, B. M. Tabenko, and E. A. Chesnychev, *J. Gen. Chem. USSR*, **52**, 2440 (1982).
510. G. Seconi and C. Eaborn, *J. Chem. Soc. Perkin II*, 931 (1981).
511. E. Lukevits, D. A. Pudova, Yu. Popelin, and N. P. Ershak, *J. Gen. Chem. USSR*, **51**, 115 (1981).
512. E. Lukevits and M. Dzintara, *J. Gen. Chem. USSR*, **51**, 1761 (1981).
513. L. M. Kananashvili, E. A. Chesnyshev, B. N. Vardnosanidze, E. G. Markarashvili, M. G. Kantaiya, V. I. Savushkina, and M. O. Labartkova, *J. Gen. Chem. USSR*, **53**, 1421 (1983).
514. E. Lukevits, M. Dzintara, and O. A. Pudova, *J. Gen. Chem. USSR*, **53**, 1854 (1983).
515. E. Lukevits, N. P. Erchak, V. F. Matorykina, I. B. Mazheika, and S. Kh. Rozite, *J. Gen. Chem. USSR*, **53**, 1857 (1983).
516. E. Lukevits, O. A. Pudova, and M. Dzinmara, *J. Gen. Chem. USSR*, **54**, 303 (1984).
517. L. M. Kananashvili, E. A. Chesnykov, G. V. Tsitsishvili, Ts. N. Vardosanidze, E. G. Markarashvili, M. L. Kantariya, V. I. Savushkina, and M. O. Labartkova, *J. Gen. Chem. USSR*, **54**, 318 (1984).

518. H. Gilman and F. J. Marshall, *J. Am. Chem. Soc.*, **71**, 2066 (1949).
519. E. Lukevics, R. Ya. Sturkovich, and O. A. Pudova, *J. Organometal. Chem.*, **292**, 151 (1985).
520. F. Effenberger and W. Spiegler, *Chem. Ber.*, **118**, 3872 (1985).
521. P. Dembeck, G. Seconi, C. Eaborn, J. A. Rodriguez, and J. G. Stamper, *J. Chem. Soc. Perkin II*, 197 (1986).
522. E. Lukevics, R. Ya. Sturkovits, O. A. Pudova, and A. P. Gaukhman, *J. Gen. Chem. USSR*, **56**, 123 (1986).
523. D. Mohler and J. E. Sellers, U.S. Patent 2,598,436 (1952); *Chem. Abstr.*, **47**, 3875g (1953).
524. P. A. George, U.S. Patent 2,640,818 (1953) *Chem. Abstr.*, **47**, 9055b (1953).
525. Br. Patent 694,440 (1953); *Chem. Abstr.*, **48**, 10775h (1954).
526. R. H. Meen and H. Gilman, *J. Org. Chem.*, **20**, 73 (1955).
527. R. B. King and R. N. Kapoor, *Inorg. Chem.*, **8**, 2535 (1969).
528. E. A. Chernyshev and N. G. Tolstikova, *Bull. Acad. Sci. USSR*, **9**, 1606 (1964).
529. C. Eaborn and J. A. Sperry, *J. Chem. Soc.*, 4921 (1961).
530. S. F. Thames and J. F. McClesky, *J. Heterocycl. Chem.*, **3**, 104 (1966).
531. C. Eaborn and G. Seconi, *J. Chem. Soc. Perkin II*, 925 (1976).
532. E. A. Chernyshev, N. G. Komalenkova, S. A. Bashkirova, and T. A. Zavoronkova, *J. Gen. Chem. USSR*, **46**, 1258 (1974).
533. M. G. Voronkov, G. I. Zelchan, V. I. Savushkina, B. M. Tabenko, and E. A. Chernyshev, *Chem. Heterocycl. Comp.*, **6**, 646 (1976).
534. V. G. Nosenko, V. G. Lakhtin, V. D. Sheludyakov, and V. F. Mironov, *J. Gen. Chem. USSR*, **50**, 1437 (1981).
535. Y. Ito, S. Miyata, M. Nakatsuka, and T. Saegusa, *J. Org. Chem.*, **46**, 1043 (1981).
536. S. Gronowitz, A.-B. Hörnfeldt, and Y. Yang, *Chem. Scripta*, **26**, 383 (1986).
537. R. N. Hanson, R. Franke, S. H. Lee, and D. E. Seitz, *Appl. Radiak. Isot.*, **38**, 641 (1987).
538. Yu. K. Urev, M. A. Galbershtam, and I. I. Kandor, *J. Gen. Chem. USSR*, **34**, 4176 (1964).
539. J. Gupta, C. Gopinathan, S. Gopinathan, and P. A. Awasarkar, *Indian J. Chem.*, **11**, 596 (1973).
540. C. Gopinathan, S. K. Pandit, S. Gopinathan, A. Y. Sonsale, and P. A. Awasarkar, *Indian J. Chem.*, **13**, 516 (1975).
541. H. C. Bell, J. R. Kalman, J. T. Pinhey, and S. Sternhell, *Aust. J. Chem.*, **32**, 1531 (1979).
542. Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *Chem. Synthesis*, 130 (1989).
543. L. J. Goldsworthy, W. H. Hook, J. A. John, S. G. P. Plant, J. Rushton, and L. M. Smith, *J. Chem. Soc.*, 2208 (1948).
544. N. Jabri, A. Alexakis, and J. F. Normant, *Tetrahedron Lett.*, **22**, 3851 (1981).
545. E. Negishi, F. T. Luo, R. Frisbee, and H. Matashita, *Heterocycles*, **18**, 117 (1982).
546. A. Minato, K. Suzuki, K. Tamao, and M. Kumada, *Tetrahedron Lett.*, **25**, 83 (1984).
547. Y. Tamaru, H. Ochiai, and Z. Yoshida, *Tetrahedron Lett.*, **25**, 3861 (1984).
548. T. L. Gilchrist and R. J. Summersell, *Tetrahedron Lett.*, **28**, 1469 (1987).
549. P. Knochel, N. Jeong, M. J. Rozema, and M. C. P. Yeh, *J. Am. Chem. Soc.*, **111**, 6474 (1989).
550. T. Klingstedt and T. Frejd, *Organometallics*, **2**, 598 (1983).
551. R. C. Larock and D. R. Leach, *Organometallics*, **1**, 74 (1982).
552. J. F. Freeman, J. R. Dove, and E. D. Amshutz, *J. Am. Chem. Soc.*, **70**, 3136 (1948).
553. R. C. Larcock, K. Narayanan, and S. S. Hershberger, *J. Org. Chem.*, **48**, 4377 (1983).
554. A. W. Horton, *J. Org. Chem.*, **14**, 761 (1949).
555. H. Pines, B. Kvetinskas, and J. A. Vesley, *J. Am. Chem. Soc.*, **72**, 1568 (1950).
556. F. J. Sorva, U.S. Patent 2,668,170 (1954); *Chem. Abstr.*, **49**, 3267c (1955).

557. L. H. Wesner and C. E. Sholz, *J. Am. Chem. Soc.*, **76**, 2453 (1954).
558. M. Kleiman, U.S. Patent 2,697,101 (1954); *Chem. Abstr.*, **49**, 15974d (1955).
559. N. P. Buu-Hoi, *Bull. Soc. Chim. Fr.*, 1407 (1958).
560. S. S. Novikov, T. I. Godovikova, and V. A. Tartakovskii, *Proc. Acad. Sci. USSR*, **124**, 834 (1959).
561. Y. Takeshita, Y. Ionoue, Jpn. Patent 7810 (1958); *Chem. Abstr.*, **54**, 3838h (1960).
562. E. Söderbäck, *Acta Chem. Scand.*, **13**, 1221 (1959).
563. D. Spinelli and A. Salvenini, *Ann. Chim. (Rome)*, 1423 (1960); *Chem. Abstr.*, **55**, 10360 (1961).
564. E. Profft and A. Kubat, *Wiss. Z. Tech. Hochsch. Chem. Leuna-Meresburg*, **2**, 243 (1959/60); *Chem. Abstr.*, **55**, 1573 (1961).
565. G. Wittig and V. Wahl, *Angew. Chem.*, **73**, 492 (1961).
566. E. Lukevics and S. Hillers, *Latvijas PSR Zin. Akad. Vestis*, **4**, 99 (1961); *Chem. Abstr.*, **56**, 10178e (1962).
567. H. Beyer and S. Melde, *J. Prakt. Chem.*, **24**, 91 (1964).
568. V. A. Nefedov, *Zh. Obshch. Khim.*, **38**, 2184 (1968); *Chem. Abstr.*, **70**, 37902s (1969).
569. R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5538 (1968).
570. Hercules Inc., Fr. Patent 1,553,822 (1969); *Chem. Abstr.*, **72**, 54973z (1970).
571. R. F. Heck, U.S. Patent 3,705,919 (1972); *Chem. Abstr.*, **78**, 58627m (1973).
572. E. C. Kooyman and J. B. H. Kroon, *Recueil*, **82**, 464 (1963).
573. S. Tanabe, Jpn. Patent 4130 (1958); *Chem. Abstr.*, **39**, 2858f (1945).
574. T. Izumi, T. Iino, and A. Kasahara, *Bull. Chem. Soc. Jpn.*, **46**, 2251 (1973).
575. J.-L. Chanal, M.-T. Calmette, B. Bonnaud, and H. Cousse, *Eur. J. Med. Chem.*, **9**, 641 (1974).
576. G. Henrio and J. Morel, *Tetrahedron Lett.*, **25**, 2167 (1974).
577. L.-Y. Ohia and W. R. Whinnie, *J. Organometal. Chem.*, **148**, 165 (1978).
578. L.-Y. Ohia and W. R. Whinnie, *J. Organometal. Chem.*, **188**, 121 (1980).
579. B. Cederlund and A.-B. Hörnfeldt, *Acta Chem. Scand.*, **25**, 3546 (1971).
580. R. C. Larock, D. R. Leach, and S. M. Bjorge, *Tetrahedron Lett.*, **23**, 715 (1982).
581. T. F. Spande, *J. Org. Chem.*, **45**, 3081 (1980).
582. E. Jones and I. M. Moodie, *Tetrahedron*, **21**, 2413 (1965).
583. J. W. Barton, D. J. Lapham, and D. J. Rowe, *J. Chem. Soc. Perkin I*, 131 (1985).
584. J. Leroy, M. Rubinstein, and C. Wakselman, *J. Fluorine Chem.*, **27**, c91 (1985).
585. A. Carpita and R. Rossi, *Gazz. Chim. Ital.*, **115**, 575 (1985).
586. E. L. Lindstedt and M. Nilsson, *Acta Chem. Scand.*, **B40**, 466 (1986).
587. R. Jaruhari, P.-H. Dixneuf, and S. Lecolier, *Tetrahedron Lett.*, **27**, 6315 (1986).
588. R. Motoyama, S. Nishimura, and J. Ogawa, *Nippon Kagaku Zasshi*, **78**, 950 (1957); *Chem. Abstr.*, **54**, 14223i, 14224e (1960).
589. J. Skramstad, *Acta Chem. Scand.*, **23**, 703 (1969).
590. M. T. Rahman and H. Gilman, *J. Indian Chem. Soc.*, **56**, 299 (1979).
591. J. P. Critchley, V. C. R. McLoughlin, J. Thrower, and I. M. White, *Chem. Ind.*, 934 (1969).
592. V. C. R. McLoughlin and J. Thrower, *Tetrahedron*, **25**, 5921 (1969).
593. M. Nilsson, C. Ullenius, and O. Wennerström, *Tetrahedron Lett.*, **29**, 2713 (1971).
594. Y. Fujiwara, O. Maruyama, M. Yoshidomi, and H. Toniguchi, *J. Org. Chem.*, **46**, 851 (1981).
595. A.-S. Carlström and T. Frejd, *Synthesis*, 414 (1989).
596. D. Savoia, C. Grombini, A. Umani-Ronchi, and G. Verardo, *J. Chem. Soc. Chem. Commun.*, 541 (1981).
597. A. Minato, K. Tamas, T. Hayashi, K. Suzuki, and M. Kumada, *Tetrahedron Lett.*, **22**, 5319 (1981).

598. T. N. Sidarenko, G. A. Terenteva, O. S. Andrienko, Yu. V. Savinykh, and V. S. Aksenov, *Chem. Heterocycl. Comp.*, **2**, 156 (1982).
599. V. Z. Sharf, L. I. Belenkii, A. S. Gurovets, and I. B. Karamanova, *Chem. Heterocycl. Comp.*, **2**, 134 (1981).
600. S. Gronowitz and K. Lawitz, *Chem. Scripta*, **22**, 265 (1983).
601. J. P. Montheard, J. F. Delzant, and M. Gazard, *Synth. Commun.*, **14**, 289 (1984).
602. B. D. Gupta and S. Roy, *Tetrahedron Lett.*, **25**, 3255 (1984).
603. V. A. Knizhnikov and Yu. A. Oldekop, *J. Gen. Chem. USSR*, **54**, 2032 (1984).
604. O. P. Syutkina, L. F. Rybakova, E. S. Petrov, and I. P. Beletskaya, *J. Organomet. Chem.*, **280**, C67 (1985).
605. M. Ishikura, M. Kumada, and M. Terashima, *Synthesis*, 936 (1984).
606. F. Osawa, N. Kawasaki, T. Yamamoto, and A. Yamamoto, *Chem. Lett.*, 567 (1985).
607. V. A. Knizhnikov and Yu. A. Oldekop, *J. Gen. Chem. USSR*, **55**, 1385 (1985).
608. N. A. Bumagin, A. B. Ponomaryov, and I. P. Beletskaya, *Tetrahedron Lett.*, **26**, 4819 (1985).
609. J.-P. Montheard and J.-C. Dubois, *J. Heterocycl. Chem.*, **22**, 719 (1985).
610. M. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, **26**, 5997 (1985).
611. D. A. Lesh, J. W. Richardson, R. A. Jacobson, and R. J. Angelici, *J. Am. Chem. Soc.*, **106**, 2901 (1984).
612. M. Draganjac, C. J. Ruffing, and T. B. Rauchfuss, *Organometallics*, **4**, 1909 (1985).
613. C. V. Pham. H. B. Mark, and H. Zimmer, *Synth. Commun.*, **16**, 689 (1986).
614. S. Gronowitz, A.-B. Hörnfeldt, and Y.-H. Yang, *Chem. Scripta*, **26**, 311 (1986).
615. S. Gronowitz, A.-B. Hörnfeldt, V. Kristjansson, and T. Musil, *Chem. Scripta*, **26**, 305 (1986).
616. N. Jayasuriya and J. Kagan, *Heterocycles*, **24**, 2261 (1986).
617. R. Aumann, H. Heinen, C. Krüger, and Y. H. Tsay, *Chem. Ber.*, **119**, 3141 (1986).
618. R. Jaouhari, P. Guenot, and P. H. Dixneuf, *J. Chem. Soc. Chem. Commun.*, 1255 (1986).
619. J. P. Gillet, R. Sauvêtre, and J. F. Normant, *Bull. Chem. Soc. Jpn.*, 538 (1986).
620. V. A. Knizhnikov and Yu. A. Oldekop, *J. Gen. Chem. USSR*, **56**, 1836 (1985).
621. T. R. Bailey, *Tetrahedron Lett.*, **27**, 4407 (1986).
622. K. Karabelas and A. Hallberg, *J. Org. Chem.*, **51**, 5286 (1986).
623. J. R. McCarthy, C. L. Barney, D. P. Matthews, and T. M. Barger, *Tetrahedron Lett.*, **28**, 2207 (1987).
624. E. Campaigne and J. L. Diedrich, *J. Am. Chem. Soc.*, **73**, 5240 (1951).
625. M. M. Jones, *J. Am. Chem. Soc.*, 5995 (1954).
626. A. N. Nesmeyanov, K. N. Anisimov, and N. E. Kolobova, *Bull. Acad. Sci. USSR Ser. Khim.* (transl.), **12**, 2153 (1964).
627. R. Burton, M. L. H. Green, E. W. Abel, and G. Wilkinson, *Chem. Ind.*, 1592 (1958).
628. E. O. Fischer and K. Öfele, *Chem. Ber.*, **91**, 2395 (1958).
629. R. Colton and G. Wilkinson, *Chem. Ind.*, 1314 (1959).
630. H. D. Kaesz, R. B. King, T. A. Manuel, L. D. Nichols, and F. G. A. Stone, *J. Am. Chem. Soc.*, **82**, 4749 (1960).
631. H. Singeo, *Z. Naturforsch.*, **21**, 810 (1966); *J. Organomet. Chem.*, **9**, 135 (1967).
632. G. Stolze and J. Hähle, *J. Organomet. Chem.*, **5**, 545 (1966).
633. W. Kuchen and J. Judat, *Chem. Ber.*, **100**, 991 (1967).
634. E. O. Fischer and K. Öfele, Ger. Patent 1,239,703; *Chem. Abstr.*, **67**, 64542u (1967).
635. W. T. Flannigan, G. R. Knox, and P. L. Pauson, *J. Chem. Soc. C*, 2077 (1969).
636. J. P. King and B. P. Block, U.S. Patent 3,449,367; *Chem. Abstr.*, **71**, 91655x (1969).
637. C. Segard, B. Roques, and C. Pommier, *Compt. Rend Acad. Sci. (Paris)*, **272**, 2179 (1971).

638. M. J. Barrow, J. L. Davidson, W. Harrison, D. W. A. Sharp, G. A. Sim, and F. B. Nilson, *J. Chem. Soc. Chem. Commun.*, 583 (1973).

639. R. Noyon, Y. Baba, S. Makino, and H. Takaya, *Tetrahedron Lett.*, **20**, 1741 (1973).

640. J. G. Riess and L. G. Hubert-Pfalzgraf, *J. Chim. Phys.*, **4**, 646 (1973).

641. G. A. Moser and M. D. Rausch, *Synth. React. Inorg. Metalorg. Chem.*, **4**, 37 (1974); *Chem. Abstr.*, **81**, 1362e (1974).

642. J. A. Connor and E. M. Jones, *J. Organomet. Chem.*, **60**, 77 (1973).

643. A. Kasahara, T. Izumi, G. Saito, and T. Tokeda, *Asahi Garasu Kogyo Gijutsu Shoreihai Kenkyu Hokoku*, **22**, 95 (1973); *Chem. Abstr.*, **81** 135859e (1974).

644. R. Asano, I. Moritani, Y. Fujiwara, and Teranishi, *Bull. Chem. Soc. Jpn.*, **46**, 663 (1973).

645. V. M. Bhatnagar, *Chemical Age of India*, **14**, 540 (1963).

646. Z. Yoshida, Y. Yamada, and Y. Tamaru, *Chem. Lett.*, 423 (1977).

647. Y. Tamaru, Y. Yamada, and Z. Yoshida, *Tetrahedron Lett.*, 919 (1978).

648. A. Samat, J. Sala-Pala, R. Guglielmotti, and J. Guerchais, *Noveau J. Chem.*, **2**, 13 (1978).

649. V. Usieli, S. Gronowitz, and I. Andersson, *J. Organomet. Chem.*, **165**, 357 (1979).

650. W. J. M. van Tilborg and R. Plomp, *Recueil*, **96**, 282 (1977).

651. N. E. Kolobova and L. V. Gonoharenko, *Chem. Heterocycl. Comp.*, **11**, 1173 (1979).

652. Y. Fujiwara, T. Kawanchi, and H. Taniguchi, *J. Chem. Soc. Chem. Commun.*, 220 (1980).

653. O. M. Bukachuk, I. V. Megera, and M. I. Shevchuk, *J. Gen. Chem. USSR*, **50**, 1404 (1980).

654. P. Hong, B. R. Cho, and H. Yamazaki, *Chem. Lett.*, **5**, 507 (1980).

655. T. Klingstedt and T. Frejd, *Synthesis*, 40 (1987).

656. T. Itahara, *J. Org. Chem.*, **50**, 5272 (1985).

657. A. Minato, K. Tamao, T. Hayashi, K. Suzuki, and M. Kumada, *Tetrahedron Lett.*, **21**, 845 (1980).

658. M.-G. Choi and R. J. Angelici, *J. Am. Chem. Soc.*, **111**, 8753 (1989).

659. A. Saus and K. Posselt, *Arzneim.-Forsch/Drug Res.*, **30**, 917 (1980).

660. G. C. Nwokogu and H. Hart, *Tetrahedron Lett.*, **24**, 5725 (1983).

661. L. Brandsma, personal communication.

CHAPTER III

Syntheses, Reactions, and Physical Properties of Bithienyls and Polythienyls and Closely Related Compounds

Rolf Håkansson

University College of Kalmar
Kalmar, Sweden

I. Introduction 757
II. Preparation of Bithienyls 758
1. Preparation of 2,2′-Bithienyls 758
A. Coupling of 2-ThMgBr or 2-ThLi Derivatives with $CuCl_2$ 759
B. Ullmann-Type Coupling 765
C. Coupling Catalyzed by Co, Ni, Pd, Rh, and Te 768
D. Coupling under Friedel–Crafts Conditions 769
E. Coupling of Organoboron Reagents 771
F. Coupling Initiated by Free Radicals 772
G. Miscellaneous Types of Coupling 774
H. Ring-Closure Methods 776
2. Preparation of 3,3′-Bithienyls 778
A. Coupling of 3-ThLi Derivatives with $CuCl_2$ 779
B. Ullmann-Type Coupling 779
C. Coupling Catalyzed by Pd and Ni 783
D. Various Preparations of the 3,3′-Bithienyl System 784
3. Preparation of 2,3′-Bithienyls 784
A. Reaction of 2-ThLi Derivatives with 3-Ketotetrahydrothiophene 785
B. Coupling of 2-ThCu with 3-Halothiophenes 785
C. Coupling Catalyzed by Pd and Ni 787
D. Miscellaneous Types of Coupling 787
E. Ring-Closure Methods 788
4. Preparation of Some Bithienyls with Annelated Rings 789
III. Preparation of Polythienyls 791
1. Preparation of Terthienyls 791
A. Preparation of α-Terthienyls 791
B. Preparation of α-Terthienyl Isomers 796
2. Preparation of Polythienyls with Four or More Units 799

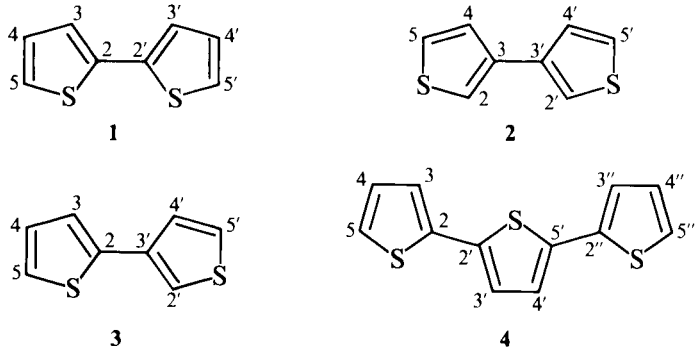
The Chemistry of Heterocyclic Compounds, Volume 44: Thiophene and Its Derivatives, Part Five, Edited by Salo Gronowitz.
ISBN 0-471-52944-3 © 1992 John Wiley & Sons, Inc.

IV. Reactions of Bi- and Polythienyls . . . 803
1. Electrophilic Substitution . . . 804
A. Nitration . . . 804
a. 2,2′-Bithienyl . . . 804
b. 3,3′-Bithienyl . . . 805
c. 2,3′-Bithienyl . . . 815
d. Polythienyls . . . 816
B. Acylation . . . 817
a. 2,2′-Bithienyl . . . 817
b. 3,3′-Bithienyl . . . 818
c. 2,3′-Bithienyl . . . 819
d. Polythienyls . . . 819
C. Halogenation . . . 819
a. 2,2′-Bithienyl . . . 819
b. 3,3′-Bithienyl . . . 820
c. 2,3′-Bithienyl . . . 824
2. Reactions via Organometallic Compounds . . . 825
A. 2,2′-Bithienyl . . . 825
B. 3,3′-Bithienyl . . . 827
C. 2,3′-Bithienyl . . . 828
3. Photochemical Rearrangements . . . 829
V. Bridged Bithienyls . . . 830
1. Zero-Atom Bridge . . . 831
2. One-Atom Bridge . . . 831
A. Cyclopentadithiophenes . . . 831
B. Dithienothiophenes . . . 833
C. Dithienopyrroles . . . 833
3. Two-Atom Bridge . . . 834
A. Benzodithiophenes . . . 834
B. Dithienopyridines . . . 835
C. Dithienopyridazines . . . 836
D. Borazarobenzodithiophenes or Dithienoazaborines . . . 836
4. Three-Atom Bridge . . . 837
A. Cycloheptadithiophenes . . . 837
B. Dithienazepines . . . 837
C. Dithienoxepines and Dithienothiepines . . . 838
5. Four-Atom Bridge . . . 839
6. Doubly Bridged Bithienyls . . . 839
VI. Optical Activity of 3,3′-Bithienyls . . . 840
1. Preparations and Absolute Configurations . . . 847
2. Optical Stabilities . . . 859
A. Racemization on Halogen–Metal Exchange; Structures of 2,2′- and 4,4′-Dilithio-3,3′-bithienyls . . . 859
B. Racemization of Carboxylic Acids . . . 861
C. Barriers to Inversion of Bridged Compounds . . . 863
3. Circular Dichroism Spectra . . . 865
VII. Physical Properties of Bi- and Polythienyls . . . 883
1. Conformational Analyses . . . 884
2. UV Spectroscopy . . . 890
3. IR Spectroscopy . . . 893
4. NMR Spectroscopy . . . 893
5. Miscellaneous Investigations . . . 895
References . . . 896

I. INTRODUCTION

Prior to 1960 bi- and polythienyls and their derivatives were not easily attainable, and consequently there were few investigations of these compounds. As to their preparation, Hartough[1] in his book from 1952 on thiophene and its derivatives states: "Indeed, methods are such that the compounds, particularly the polythienyls, are no more than laboratory curiosities, which occur in many cases as by-products in standard reactions."

For some systems this may be true even today, but in 1960 2,2′-bithienyl (**1**) and 3,3′-bithienyl (**2**) (Scheme 1) became easily available through the work of Gronowitz and Karlsson.[2] Since then, extensive studies of 3,3′-bithienyls in particular have been performed, and special attention has been given to the stereochemistry of these compounds.



Scheme 1

Bithienyls also include 2,3′-bithienyl (**3**), but comparatively few derivatives of this system are known.

Great interest has been devoted to 2,2′-bithienyl (**1**), 2,2′ : 5′,2″-terthienyl (**4**), and other polythienyls, owing to their occurrence in certain plants, often in the form of acetylenic derivatives. These natural substances, as well as similar synthetic compounds, exhibit biological activity, which further enhances their attraction for researchers. (For naturally occurring thiophenes and bithienyls, see Vol. 44, Part 1, Chapter III).

The nomenclature and numbering of the positions of bi- and polythienyls may be apparent from the above and from Scheme 1. Sometimes the term *thiophene oligomers* is used for the lower members of the polythienyl series.

To specify the number of thiophene rings, the prefixes bi-, ter-, quater-, quinque-, sexi-, septi-, etc. are used. The numbering of the positions of, for example, the fourth ring in quaterthienyl will be 2‴, 3‴, 4‴, and 5‴. Apparently, when many rings are involved, the nomenclature system exemplified here will be rather cumbersome to use, verbally as well as in writing. However, for quaterthienyl and higher polythienyls, only those with the rings connected by bonds between the 2- and 5-positions, i.e., the α-positions, are best known. In these

cases, the names may be simplified to α,α,α-quaterthienyl or, better, α-quaterthienyl, α-quinquethienyl, etc.

In the case of bithienyls, the bond connecting the rings, the pivot bond, is in the following always considered to be attached to a 2- or 3-position, which simplifies the discussion and the presentation of tables. In some original papers the terms 4,4′- and 5,5′-bithienyl may be found. For the same reason the numbering of 2,3′-bithienyls is presumed to be as in formula **3**, although derivatives of 2′,3-bithienyls can be found in the literature.

This chapter also includes discussion of bridged and doubly bridged bithienyls, such as dithienoxepines, dithienazepines, and the thiophene analogs of fluorene, phenanthrene, phenanthridine, and similar compounds. The relationship with bithienyls is seldom directly obvious from the rational names of these compounds, as the term *bithienyl* is not included in the nomenclature. However, bithienyl derivatives are often precursors in the syntheses, and although it might be questionable whether, for example, a dithienothiophene (Section V.2.B) should be considered a bithienyl, such compounds have been included here. Indeed, as soon as a bond connecting two thiophene rings can be identified, the compound is considered a bithienyl derivative.

II. PREPARATION OF BITHIENYLS

In principle, a bithienyl may be formed in two ways. A ring-closure reaction in the side chain of a suitably substituted thiophene may yield a second ring of a similar kind, or the two rings may be connected in some coupling reaction. (The possibility of forming both thiophene nuclei by ring-closure reactions also exists, of course, and some examples are given below.) The ring-closure methods have been more often used in the case of thiophene oligomers than for the preparation of bithienyls. Except for a few compounds, bithienyls are obtained in coupling reactions.

A particular substituted bithienyl may be synthesized by either the connection of two appropriately constructed thiophene rings or the subsequent introduction and/or transformation of substituents in the bithienyl framework. Usually, a combination of these strategies is utilized.

This section focuses primarily on methods (see Table 1) involving the formation of the pivot bond, i.e., the connection of two thiophene units to give a bithienyl. For the preparation of bithienyls obtained in subsequent reactions, the reader is referred to Sections IV, V, and VI.

1. Preparation of 2,2′-Bithienyls

2,2′-Bithienyl was formed, probably for the first time, in 1884 as one component in a mixture of bithienyls and other products, obtained on pyrolysis of thiophene.[3] A brief study of the reaction was done in 1894 by Auwers and Bredt.[4]

Much later Wynberg and Bantjes[5] reinvestigated it more closely and found an overall yield of the three isomeric bithienyls of 7–8% and the occurrence of a variety of condensation products. The pyrolysis of thiophene has also been studied by Fields and Meyerson.[6]

An early preparation of 2,2′-bithienyl, pure enough to enable the determination of its melting point as 33°C, was made by Töhl[7] on treatment of thiophene with fuming sulfuric acid. At about this time, Eberhard[8] also obtained the same compound, together with thiophene oligomers, in a reaction reminiscent of those used today: coupling of 2-iodothiophene by means of metallic silver. This type of reaction, coupling of a halothiophene with a metal, usually copper (Ullmann reaction), and the coupling of a Grignard-type reagent (ThMgBr or ThLi, Th = thienyl) with a metallic salt, or a Pd or Ni catalyst, are the methods most widely used thus far for the syntheses of 2,2′-bithienyls.

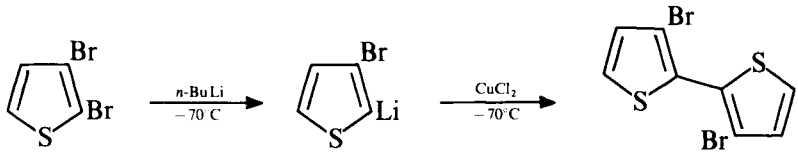
A. Coupling of 2-ThMgBr or 2-ThLi Derivatives with $CuCl_2$

The earliest preparation of 2,2′-bithienyl of synthetic value was made in 1930 by Steinkopf and Roch,[9] who obtained the compound in 44% yield by coupling 2-thienylmagnesium bromide with cupric chloride in dry ether. Lipkin[10] increased the yield to 50% by a modification.

Gronowitz and Karlsson[2] exchanged the Grignard reagent for 2-thienyllithium, which is readily available by the metalation of thiophene with *n*-butyllithium, and a yield of 54% of 2,2′-bithienyl was attained. They found that using less than equimolar amounts of cupric chloride lowered the yield; thus the role of the copper salt is more than catalytic. They also found that the reaction could be performed at − 70°C without lowering the yield.

In the thiophene series, organolithium compounds are easily obtained through halogen–metal interconversion as well (see Vol. 44, Part 2, Chapter III, Section 5). Rearrangements may occur under certain conditions, but the stability is good at − 70°C. On treatment of 3-bromo-2-thienyllithium (**6**) with $CuCl_2$ at this temperature, 3,3′-dibromo-2,2′-bithienyl (**7**) was obtained in 61% yield[11] (Scheme 2).

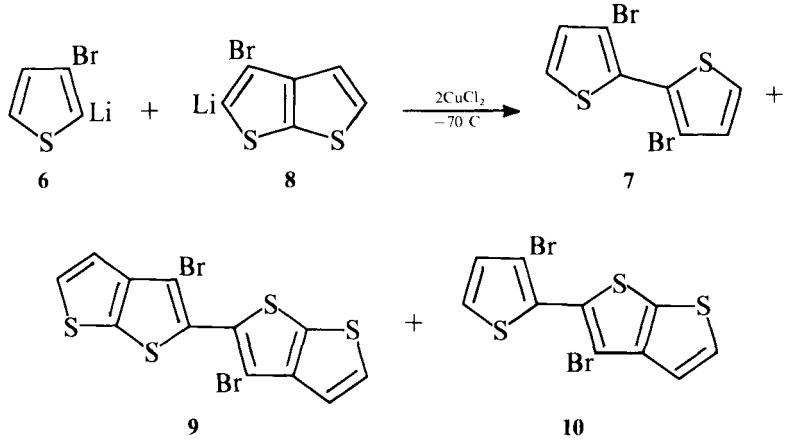
The corresponding 2,3-diiodothiophene gave only 25% of 3,3′-diiodo-2,2′-bithienyl, and a still poorer yield (8%) was obtained by coupling 3,5-diiodo-2-thienyllithium to 3,3′,5,5′-tetraiodo-2,2′-bithienyl.[12]



5 6 7

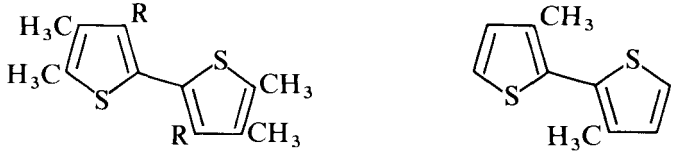
Scheme 2

Compound **6** was also used by Meunier[13] in a cross-reaction with the 2-lithium derivative of 3-bromothieno[2,3-*b*]thiophene (**8**), in order to prepare the thienylthienothiophene **10** (Scheme 3). As expected, a mixture was obtained. The overall yield was 48%, and the relative amounts of **7**, **9**, and **10** were 45 : 45 : 10. Reaction in a similar manner with **8** alone and an equimolar amount of $CuCl_2$ gave an excellent yield (72%) of **9**. Compounds of types **9** and **10** are further treated in Section II.4.



Scheme 3

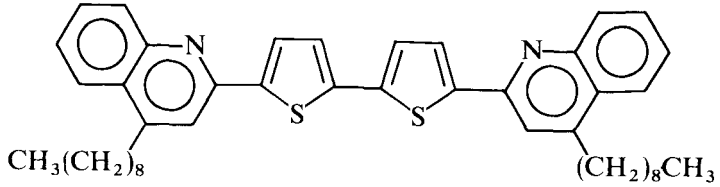
4,4′,5,5′-Tetramethyl-2,2′-bithienyl (**11**) from 4,5-dimethyl-2-thienyllithium and 3,3′-diiodo-4,4′,5,5′-tetramethyl-2,2′-bithienyl (**12**) from 3-iodo-4,5-dimethyl-2-thienyllithium are further examples of biaryls obtained by the same coupling method,[14] and this is valid for 3,3′-dimethyl-2,2′-bithienyl (**13**) from 3-methyl-2-thienyllithium as well[15] (Scheme 4).



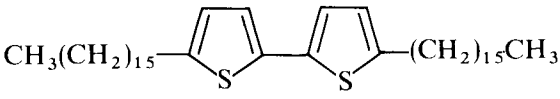
11 R = H
12 R = I

13

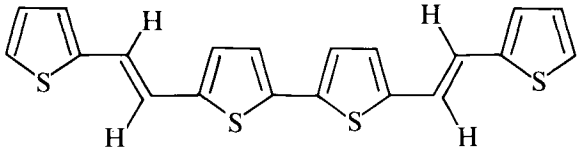
Scheme 4



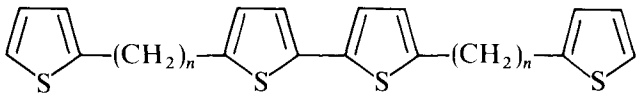
14



15

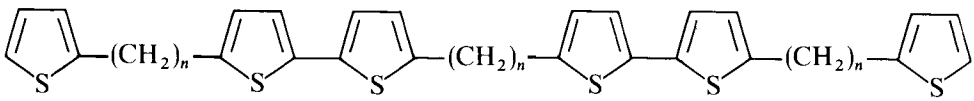


16



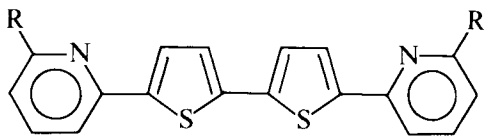
$n = 2, 6, 9$

17

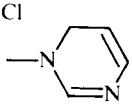


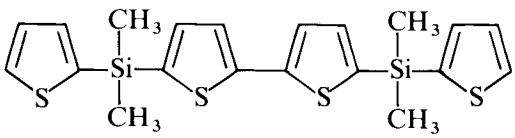
$n = 2, 6, 9$

18

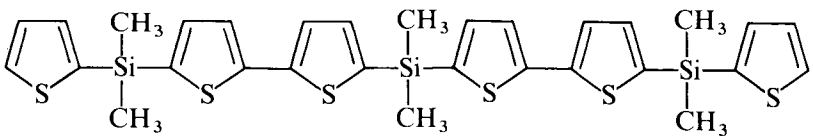


19 R = Cl

20 R = 



21



22

Scheme 5

TABLE 1. Preparations of the 2,2′-Bithienyl Framework

Compound Name or Formula No.	Method[a]	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
2,2′-Bithienyl[b]	A	33; 125–128/12	44	9
	A	31–32; 141–142/24	54	2
	B	31–33	67	25
	C	33; 125/12	90	45
	C	32; 128–132/15	—	85
	C	32	80	48
	E	—	82	59
	E	—	81	60
–, ^{3}H-labeled	B	115/0.01	59	26
–, 5,5′-diacetyl	C	233–234	18	51, 52
–, –, 3,3′-dinitro	B	128.5	39	35
–, 3,3′-diamino-4,4′-diethoxycarbonyl-5,5′-dimethyl	G	144–145	41	78
–, 5-benzoyl	H	75	58	82
–, –, 3′,4,5′-triphenyl	H	168–169	—	84
–, –, 4-phenyl-3′,5′-di-*p*-tolyl	H	—	—	84
–, 5-*p*-bromobenzoyl	H	139–142	40	92
–, 5,-*p*-methylbenzoyl-4-*p*-tolyl-3′,5′-diphenyl	H	—	—	84
–, 5-benzyl	B	—	—	1, 21
–, 5,5′-dibenzyl	B	96.5–97.5	14	1, 21, 71
–, 3-bromo	C	86–87/0.02	82	46
–, 3,3′-dibromo	A	102–104	61	11
–, –, 4,4′5,5′-tetramethyl	—[c]	181–182	9	14
–, 4-bromo	C	Oil	88	47
–, 5-bromo	C	32–33; 89–91/0.04	53	46
–, –, 5′-formyl	F	Dec.	99	63
–, 5,5′-dibromo	E	—	77	59
–, 5-*n*-butyl	B	128–130/0.5	7	36
–, 5,5′-di-*t*-butyl	B	89; 200/13	80	31
–, 3-chloro	E	—	47	59

–, 5-chloro	D	100–110/4	—	56, 57
–, –, derivative **54**	D	51.5–52.5	—	56
–, 5,5′-dichloro	B, D	108–108.5	60	29
–, 3,5,5′-trichloro	D	102–103	—	29
–, 3,3′-5,5′-tetrachloro	D	127–128	—	29
–, hexachloro	B	187–189	75	27
–, 5,5′-diethyl	C	—	—	53
–, 3- or 5-ethoxycarbonyl-4-hydroxy	H	—	—	83
–, 5-formyl	C	—	71	48
–, –, 5′-methyl	F	98–99	69	63
–, 5,5′-diformyl	C	215–218	—	51, 52
–, –, 4,4′-dimethyl	C	217–219	—	52
–, 5-hydroxymethyl	C	50–51	79	48
–, –, acetate	C	—	63	48
–, –, isovalerate	C	—	58	48
–, –, tetrahydropyranyl ether		—	—	—
–, –, –, 5′-(C≡CCH$_2$CH$_2$OCOCH$_2$CH(CH$_2$)$_2$	C	—	62	48
–, 3,3′-diiodo	A	149.5–151	25	12
–, –, 4,4′,5,5′-tetramethyl	A	179–180, dec.[a]	44	14
–, 3,3′,5,5′-tetraiodo	A	190.5–192	8	12
–, 4,4′-diisopropenyl (**69**)	F	—	—	69
–, 3,3′-dimethoxycarbonyl	B	145–147	24	34
–, 5,5′-dimethoxycarbonyl	—	—	—	—
–, –, 3,3′-dinitro	B	168–169.5	53	35
–, 3,3′-dimethyl	A	131/11	84	15
	B	160–162/25	26	32
–, 4-methyl	E	—	46	58
–, 4,4′-dimethyl	—	—	—	—
–, –, 5,5′-dinitro	C	262–264	—	52
–, 5-methyl	B	145–146/17	—	1, 21
–, 5,5′-dimethyl	B	67	80	1, 28
	C	64–65	—	85
–, 3,3′,4,4′-tetramethyl	B	87	23	32
–, 4,4′,5,5′-tetramethyl	A	123.5–124.5	68	14
–, 3,3′-dinitro	B	186–187	74	33

TABLE 1. (*Continued*)

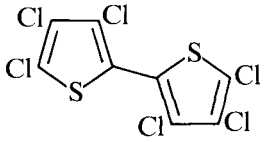
Compound Name or Formula No.	Method[a]	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
–, 3,5′-dinitro	B	132–133	39	33
–, 5,5′-dinitro	B	251–252	80	10
	B	255–257	70	33
	C	259–262	—	52
–, 3,3′,5,5′-tetranitro	B	194.5–196	43	35
	B	193–194	78	33
–, 5-phenyl	B	122–123	30	32
		119	—	21
	H	121	66	79
–, 5,5′-diphenyl	A	246–247	—	86
	B	237	37	32
		247	—	21
	H	245–247	24	79
–, 5,5′-triphenylmethyl	B	277	—	37
–, 5-(1-methyl-2-pyrrolyl)	B	47–49	—	41
14	A	84–85	24	16
15	A	77	66	16
16	A	216–217	28	17
17, $n = 2$	A	108–109	32	17
$n = 6$	A	68–70	40	17
$n = 9$	A	47–48	33	17
18, $n = 2$	A	145–146	7	17
$n = 6$	A	107–109	7	17
$n = 9$	A	77	6	17
19	A	235–237	82	18
20	A	270–273	25	18
21	A	91	29	19
22	A	102	4.5	19

[a] Refers to Section II.1, where the method is described.
[b] Selected examples.
[c] See Section II.2.A.
[d] Decomposition.

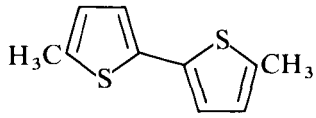
In a series of papers dealing with protophanes and polyarenes, Kauffmann and coworkers have shown that the coupling reaction of a 2-thienyllithium derivative with cupric chloride is very little affected by long alkyl chains or other bulky groups at the 5-position. Thus they have prepared compounds **14**, **15**,[16] **16–18**,[17] **19**,[18] **21**, and **22**[19] (Scheme 5) in relatively good yields (Table 1). (Compound **20** was prepared from **19** and imidazole.) Previously, a similar bulky compound, 5,5′-dibenzyl-2,2′-bithienyl, was prepared by Steinkopf et al.[20]

B. Ullmann-Type Coupling

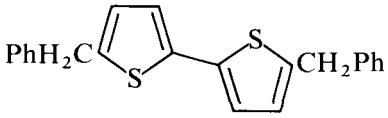
In the conventional Ullmann reaction an iodoarene is heated with copper powder without solvent until an exothermic reaction starts at relatively high temperatures, often above 200°C, to produce a biarene. In this manner, 2,2′-bithienyl may be obtained in relatively low yields from 2-iodothiophene, together with thiophene oligomers.[21–23] By performing the reaction in dimethyl formamide[24] (DMF) Wynberg and Logothetis[25] raised the yield to 67% and avoided the formation of polythienyls. In a similar manner, Jente et al.[26] obtained 59% of ^{3}H-labeled 2,2′-bithienyl by coupling 2-iodothiophene, labeled in one of the β-positions with tritium. Trichloro-2-iodothiophene with copper–bronze in DMF gave 75% of the theoretical amount of hexachloro-2,2′-bithienyl[27] (**23**, Scheme 6). In DMF 2,2′-bithienyl may also be prepared from 2-bromothiophene.[5]



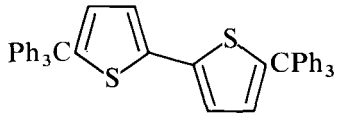
23



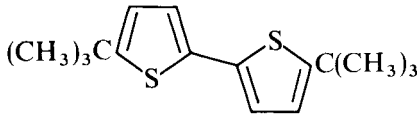
24



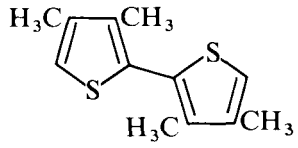
25



26



27

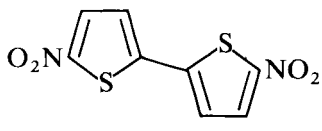


28

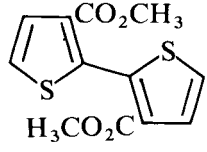
Scheme 6

Homologs of 2,2′-dithienyl may, at least in some cases, be prepared by the conventional Ullmann reaction in relatively good yields. 5,5′-Dimethyl-2,2-bithienyl (**24**), in which the positions for further reactions to polythienyls are blocked, was obtained from 2-iodo-5-methylthiophene in about 80% yield.[28] 2-Chloro-5-iodothiophene gave 60% of 5,5′-dichloro-3,3′-bithienyl.[29] Other similarly substituted bithienyls are 5,5′-dibenzyl-2,2′-bithienyl[21] (**25**), 5,5′-di(triphenylmethyl)-2,2′-bithienyl[30] (**26**), and 5,5′-di-*tert*-butyl-2,2′-bithienyl[31] (**27**) (Scheme 6). Coupling of 3-methyl-2-iodothiophene and 3,4-dimethyl-2-iodothiophene gave considerably lower yields (~ 25%) of 3,3′-dimethyl-2,2′-bithienyl (**13**, Scheme 4) and 3,3′-,4,4′-tetramethyl-2,2′-bithienyl (**28**, Scheme 6), respectively.[32]

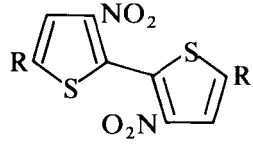
It is well known that *-I,-M*-substituents such as nitro groups and ester groups, especially if situated ortho to the halogen, may facilitate the coupling reaction. 2-Bromo-5-nitrothiophene readily gave 5,5′-dinitro-2,2′-bithienyl (**29**, Scheme 7) in good yields,[10,33] and the same is true for the preparation of 3,3′-dinitro-2,2′-bithienyl from 2-bromo-3-nitrothiophene.[33] However, the yield of 3,3′-dicarbomethoxy-2,2′-bithienyl (**30**) was relatively low (24%), even though the 2-bromo instead of the 2-iodo derivative of methyl 3-thenoate was used for the coupling.[34]



29



30



31 R = NO_2
32 R = $COCH_3$
33 R = CO_2CH_3

Scheme 7

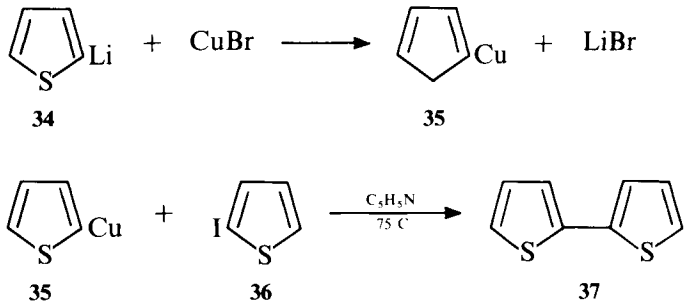
Chloroarenes are usually considered as still less suitable than bromo compounds for the solvent-free Ullmann reaction, but Jean and Nord[35] used 3,5-dinitro-2-chlorothiophene, 5-acetyl-3-nitro-2-chlorothiophene, and 5-carbomethoxy-3-nitro-2-chlorothiophene in this connection and obtained acceptable yields of the corresponding 2,2′-bithienyls; 3,3′,5,5′-tetranitro-2,2′-bithienyl (**31**) (43%), 5,5′-diacetyl-3,3′-dinitro-2,2′-bithienyl (**32**) (39%), and 5,5′-dicarbomethoxy-3,3′-dinitro-2,2′-bithienyl (**33**) (53%), respectively.

For the preparation of unsymmetrically substituted bithienyls by the Ullman reaction a mixture of two different halothiophenes may be used, but this necessarily leads to the risk of the formation of symmetric by-products, and an accompanying decrease in the yield of the desired substance. Mixing copper–bronze and 2-iodothiophene with 5-methyl-2-iodothiophene or 5-benzyl-2-iodothiophene gave small amounts of 5-methyl-2,2′-bithienyl[21,22] (**24**) and 5-benzyl-2,2′-bithienyl[21] (**25**), respectively, together with the symmetrical biaryls (**24** and **25**).

Uhlenbroek and Bijloo[36] isolated only about 7% of crude 5-butyl-2,2'-bithienyl from the Ullmann reaction of 2-iodothiophene with 5-butyl-2-iodothiophene. Reacting 2-iodothiophene with 5-phenyl-2-iodothiophene gave a higher yield (30%) of 5-phenyl-2,2'-bithienyl together with 37% of 5,5'-diphenyl-2,2'-bithienyl.[32] A considerably lower yield was obtained in the same reaction by Steinkopf et al.[21]

Nilsson[37] and coworkers made a careful investigation of the connection between the Ullmann biaryl synthesis and copper-catalyzed decarboxylation. Through their work unsymmetric biaryls have become available in reasonable yields. This has been demonstrated primarily by the preparation of mixed biaryls, such as various phenylthiophenes,[38,39] but might be valuable for the preparation of unsymmetrically substituted bithienyls as well.

The key step in their reaction is the coupling of an organocopper arene with an iodoarene. 2-Thienylcopper (**35**), for example, is prepared from 2-thienyllithium (**34**) or the corresponding Grignard reagent and copper(I)iodide or copper(I)bromide (Scheme 8).



Scheme 8

Reaction with an iodo- or bromoarene in pyridine or quinoline at temperatures between 0 and 115°C yields the corresponding 2-arylthiophene without halogen–metal exchange or dimerization of the 2-thienylcopper to 2,2'-bithienyl.[39] Reaction with 2-iodothiophene yields 42% of 2,2'-bithienyl.[39] However, on reaction of 2-furylcopper with 2-iodothiophene only 16% of the expected 2-(2-furyl)thiophene was obtained, whereas 2,2'-bithienyl was formed in 27% yield.[40] A similar observation was made by Gjøs and Gronowitz[41] in the reaction of 1-methyl-2-pyrrolylcopper with 2-iodothiophene, which gave a mixture of 7% of 2,2'-bithienyl and 14% of 5-(1-methyl-2-pyrrolyl)-2,2'-bithienyl, in addition to 1,1-dimethyl-2,2'-bipyrrole (24%) and 1-methyl-2-(2-thienyl)-pyrrol (53%). In the reaction with 3-iodothiophene minor amounts of 3,3'-bithienyl and 2,3'-bithienyl were formed, which indicates that some rearrangement had occurred.

C. Coupling Catalyzed by Co, Ni, Pd, Rh, and Te

Morizur[42] and Morizur and Pallaud[43] reacted aromatic organomagnesium and organolithium compounds with bromoarenes in the presence of 0.1 eq of anhydrous cobalt chloride. Biaryls were obtained in 50–65% yield, except for 2,2′-bithienyl, which was isolated in 25–30% yield. It was proposed that the coupling proceeds from a $CoAr_2$ complex and that a cobalt salt regenerates as $CoBr_2$ via a free-radical mechanism.[42]

Zerovalent nickel in the form of bis(1,5-cyclooctadiene)nickel(0) catalyzes the coupling of a variety of aryl halides to biaryls, including 2-bromothiophene to 2,2′-bithienyl in 30% yield [determined by gas–liquid chromatography (GLC)].[44] A considerably higher (and isolated) yield (90%) was obtained by Rossi and coworkers[45] in their coupling of 2-thienylmagnesium iodide with 2-iodothiophene on a 0.1-mol scale by the aid of a catalytic amount of $NiCl_2$(dppe) [dppe = ethylenebis(diphenylphosphine), Ph_2P–CH_2–CH_2–PPh_2]. This seems to be the highest yield reported for any practicable method for the preparation of 2,2′-bithienyl on a laboratory scale.

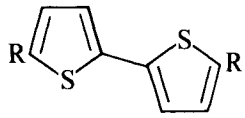
Palladium-catalyzed couplings of halothiophenes with Grignard reagents have been reported by Rossi and Carpita.[46] On reaction of various dibromothiophenes with 1 eq of 2- or 3-thienylmagnesium bromide in the presence of $PdCl_2$(dppf) [dppf = 1,1′-bis(diphenylphosphino)ferrocene] they obtained monobromo-2,2′-, 3,3′-, or 2,3′-bithienyls, such as 3-bromo-2,2′-bithienyl and 5-bromo-2,2′-bithienyl. Jayasuriya and Kagan[47] used the same method for the preparation of 4-bromo-2,2′-bithienyl.

However, the synthetic routes just described are limited to compounds whose functional groups do not interfere with Grignard reagents. Crisp[48] worked out a dichlorobis(triphenylphosphine)palladium-catalyzed coupling reaction between 2-iodothiophenes and 2-tributylstannylthiophenes, which permits groups such as formyl, hydroxymethyl, and ester to be present in the molecules. Yields in the range 60–80% were obtained.

Blum and coworkers[49] found that 2,2-bithienyl and 2,3′-bithienyl were formed in small amounts ($< 10\%$) on catalytic treatment of 2-thenoic anhydride with chlorotris(triphenylphosphine)rhodium(I), $RhCl(PPh_3)_3$, at 285°C.

The same bithienyls were formed on attempted acetoxylation of thiophene in acetic acid with $PdCl_2$ and $Pd(OAc)_2$ catalysts[50] and on attempted oxidative cross-coupling of thiophene and benzene with $Pd(OAc)_2$ in acetic acid.[51] Under similar conditions, 2-formylthiophene gave as main products 2-formyl-4-phenylthiophene (30%) and 5,5′-diformyl-2,2′-bithienyl (**38**, Scheme 9) (16%), and the corresponding acetyl derivatives (cf. **39**) were formed in about the same yields from 2-acetylthiophene. Treatment of 2-formylthiophene, 2-nitrothiophene, 2-formyl-3-methylthiophene, and 2-nitro-3-methylthiophene with palladium acetate in acetic acid gave the corresponding 2,2′-bithienyls, whereas the reaction of 2-methylthiophene gave a mixture of 2,2′- and 2,3′-bithienyls.[52]

Bergman and Engman[53] investigated the acetoxymethylation of alkylarenes in catalytic systems containing TeO_2, LiBr, and HOAc. Among the compounds



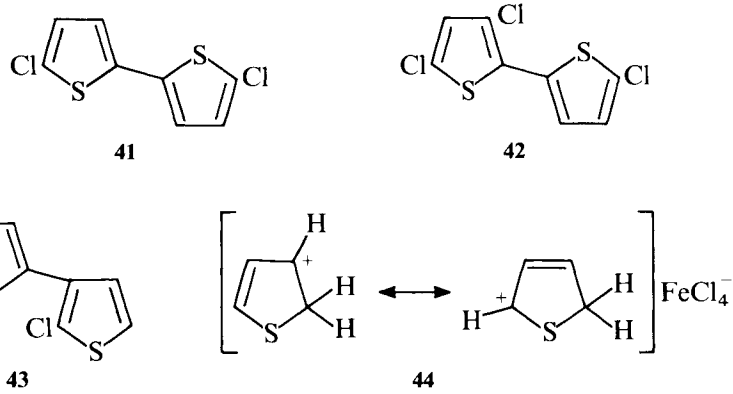
38 R = CHO
39 R = $COCH_3$
40 R = CH_2CH_3

Scheme 9

reacted was 2-ethylthiophene, which yielded 5,5′-diethyl-2,2′-bithienyl (**40**) together with 5,5′-diethyl-2,2′-dithienylmethane in unspecified amounts. A mechanism for the alkylation process, but not for the coupling, was suggested.

D. Coupling under Friedel–Crafts Conditions

As early as 1893, Töhl and Eberhard[54] noticed that the reaction of thiophene, sulfuryl chloride, and aluminum chloride gave a mixture of dichloro- and trichlorobithienyls. Sy et al.[31] found that one product of the stannic chloride-catalyzed alkylation of thiophene with *tert*-butyl chloride is 5,5′-di-*tert*-butyl-2,2′-bithienyl (**27**, Scheme 6). Sone and coworkers[29,55] investigated the former type of reaction further and found that in the presence of iron powder, as well as of Friedel–Crafts-type catalysts, thiophene and sulfuryl chloride react to afford a mixture of chlorinated bithienyls. No coupling was observed without the catalysts.[29] For example, in one experiment, catalyzed by iron powder (viz., $FeCl_3$ from Fe and SO_2Cl_2), the main products were 5,5′-dichloro-2,2′-bithienyl (**41**, Scheme 10) (10%) and 3,5,5′-trichloro-2,2′-bithienyl (**42**) (16%), but some 2′,5-dichloro-2,3′-bithienyl (**43**) (7%) was obtained as well.[55] The coupling efficiency of the Friedel–Crafts-type catalysts investigated was found to decrease in the order $AlCl_3 > FeCl_3 > SnCl_4 > ZnCl_2$.[29]

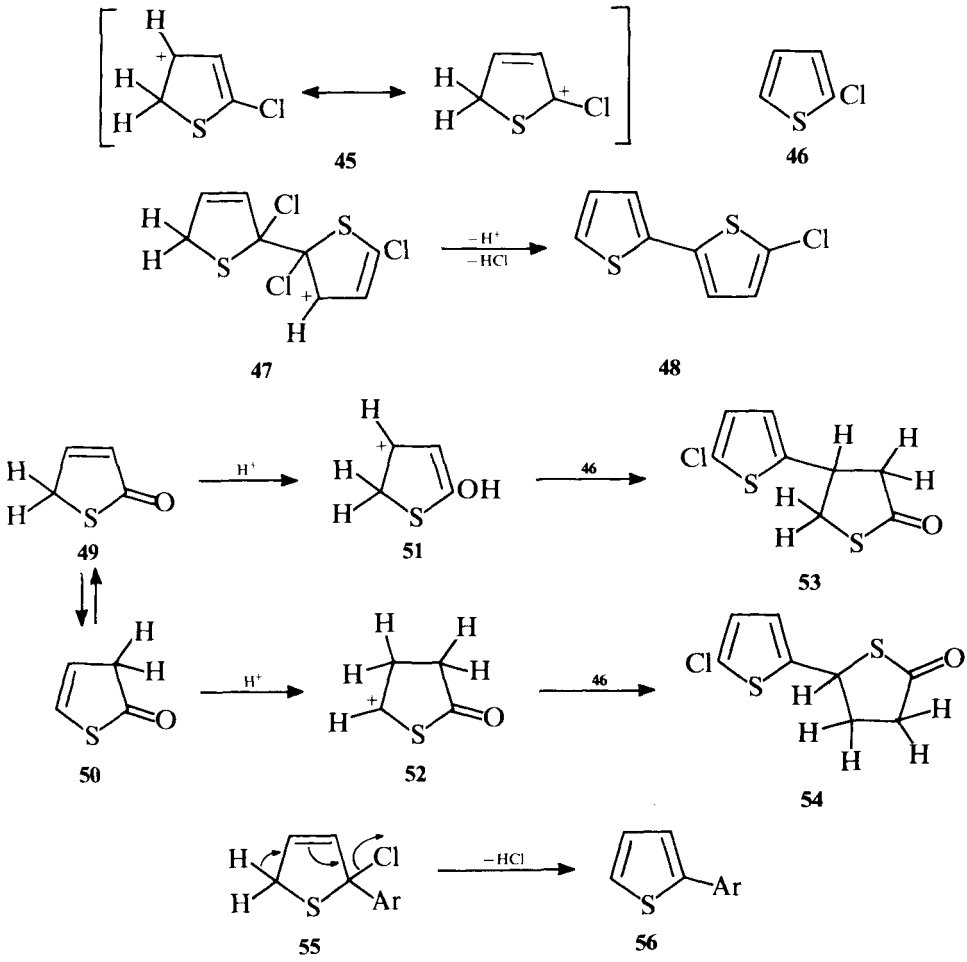


41 **42** **43** **44**

Scheme 10

The coupling was suggested to proceed via an ionic mechanism involving the cation described by the mesomeric structures **44** (Scheme 10). Attack of this bidentate cation at the 2-position of thiophene with the loss of one proton from each ring, and subsequent chlorination of the bithienyl, might explain the observed products.

On treatment of 2-chlorothiophene with a cation-exchange resin (Amberlyst 15) or 100% orthophosphoric acid, a mixture of compounds (**48**, **53**, and **54**; Scheme 11) was formed.[56] A mechanism similar to that above was proposed, with the protonation of 2-chlorothiophene to **45** as the initiating step. Attack of **45** at the 5-position of 2-chlorothiophene with the loss of H^+ and HCl yields **48** via **47**. Compound **45** might also be hydrolytically transformed to the thiolenones **49** and **50**, which after protonation to give **51** and **52**, respectively, and reaction with 2-chlorothiophene, afford compounds **53** and **54** (Scheme 11).



Scheme 11

When a mixture of 2-chlorothiophene and an aromatic compound (benzene, toluene, naphthalene, and their methoxy derivatives) was treated with $AlCl_3$ under mild conditions, a mixture of the corresponding 2-arylthiophene and 5-chloro-2,2′-bithienyl was obtained as the main product.[57] The yield of the bithienyl varied from traces (activated arenes) to 42% (benzene) and that of the 2-arylthiophene varied from traces (benzene) to 83% (1-methoxynaphthalene).

Even this reaction was considered to involve the bidentate cation **45**, which attacks the chlorothiophene and/or the activated arene, yielding the biaryl via the intermediate **55** (Scheme 11).

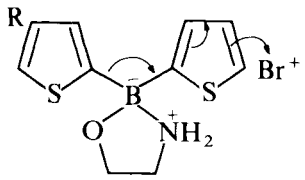
For the action of $AlCl_3$–$CuCl_2$ on 2,5-dichlorothiophene, see Section II.3.D.

E. Coupling of Organoboron Reagents

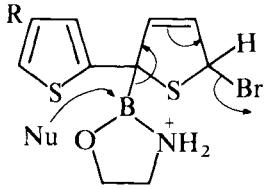
Davies and coworkers[58] found that ethanolamine salts of borinic acids (boroxazolidines) gave biaryls on treatment with bromine or N-bromosuccinimide. They proposed a mechanism for the reaction, which is shown in Scheme 12, illustrating the formation of 2,2′-bithienyls.

2-Aminoethyl dithien-2-ylborinate (**57**) gave 2,2′-bithienyl in 50% yield, and 4-methyl-2-2′-bithienyl was obtained in 46% yield from 2-aminoethyl(4-methyl-2-thienyl)-2-thienylborinate (**58**). The reaction is highly stereospecific and thus well suited for the preparation of unsymmetric biaryls. However, it is dependent on the susceptibility of the borinate to electrophilic attack. For example, 2-aminoethyl bis(5-methyl-2-thienyl)borinate (**60**) gave only 2-bromo-5-methylthiophene.

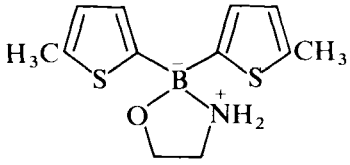
The reaction shown in Scheme 12 was further investigated in a subsequent paper.[59] By a modification the yield of 2,2′-bithienyl was increased to 82% (90%



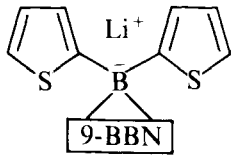
57 R = H
58 R = CH_3



R = H, CH_3
59



60



61

Scheme 12

by GLC). Treating **57** with 3 eq of bromine in sodium methoxide gave a 77% yield of 5,5′-dibromo-2,2′-bithienyl. (The text states 4,4′-dibromo-2,2′-bithienyl, which is probably a printing error.)

Kagan and Arora[60] used a similar approach for the preparation of 2,2′-bithienyl in 81% yield as a first step in their syntheses of thiophene oligomers (see Section III.1.A). The boroxazolidine system in **57** was replaced by 9-borabicyclo[3.3.1]nonane (9-BBN), and the oxidation was performed with iodine. The reagent (**61**) was prepared from the B-methoxy derivative of 9-BBN and 2-thienyllithium.

F. Coupling Initiated by Free Radicals

Free radicals are probably involved in some of the reactions mentioned above, such as in the pyrolysis of thiophene. However, this section treats the coupling of thiophenes under conditions that are known to produce free radicals (decomposition of peroxides, irradiation, etc.).

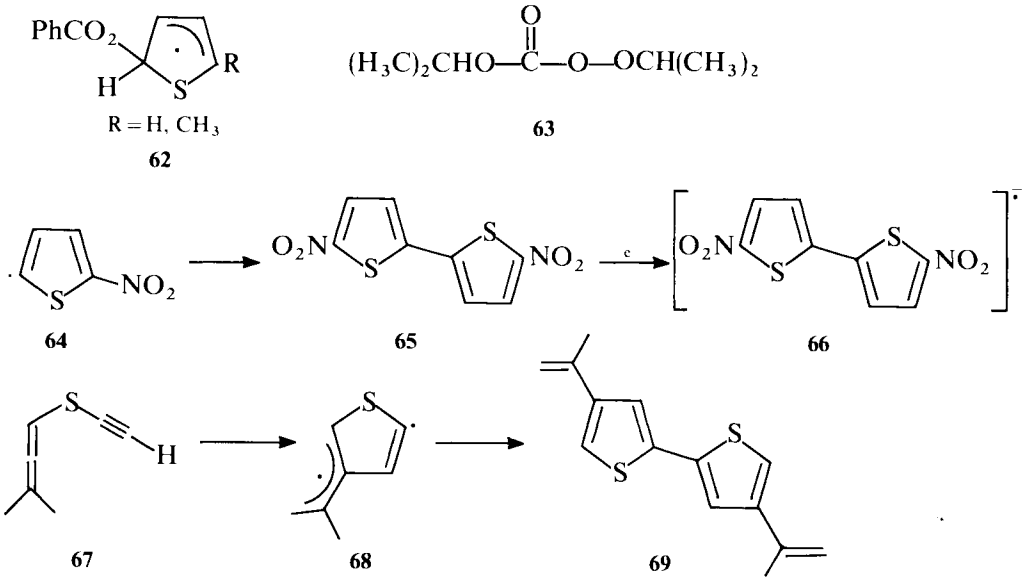
Griffin and Martin[61] studied the decomposition of a 0.01 M solution of dibenzoyl peroxide in thiophene at 80°C. Besides benzoic acid and benzene, they isolated a biaryl fraction containing 2-phenylthiophene (22.8 mol%), 2,2-bithienyl (58.8 mol%), and 2,3′-bithienyl (18.3 mol%). UV irradiation of iodobenzene in thiophene in the presence of metallic silver gave the same biaryls (63.1, 24.5, and 6.8 mol%, respectively) and in addition 3-phenylthiophene (5.5 mol%).

However, Camaggi and coworkers[62] found no bithienyls on photolysis of iodobenzene in thiophene, in 2-methylthiophene, or in some other 2-substituted thiophene, but irradiation of 2-bromothiophene in thiophene gave 2,2′- and 2,3′-bithienyl via thienyl radicals from fission of the aryl–Br bond.

D'Auria et al.[63] obtained 99% yield of 5-bromo-5′-formyl-2,2′-bithienyl on irradiation of a mixture of 5-iodo-2-formylthiophene and 2-bromothiophene in acetonitrile. With 2-methylthiophene instead of 2-bromothiophene the yield of the coupling product was 69%.

The decomposition of benzoyl peroxide in thiophene was assumed to yield 2-thienyl radicals.[61] This reaction was examined also by Camaggi et al.,[64] who found no free thienyl radicals involved. They identified 3,3′-bithienyl as well among the products, which was not consistent with the mechanism due to Griffin and Martin. It was therefore suggested that the bithienyls are formed by dimerization of a benzoyloxythiophene radical σ-complex (**62**, R = H, Scheme 13), with subsequent loss of benzoic acid. An alternative reaction involves homolytic substitution on the thiophene ring by the complex **62**, which might better explain the formation of 5,5′-dimethyl-2,3′-bithienyl, when the decomposition of benzoylperoxide was carried out in 2-methylthiophene.

Decomposition of diisopropyl peroxydicarbonate (**63**) in thiophene and acetonitrile gave the three isomeric bithienyls in yields from 0.7% to 9%[65] (see also Vol. 44, Part 3, Chapter I, Section II.3.F).



Scheme 13

Dell'Erba and coworkers[66] studied the reactivity of nitrothiophenes with some nucleophiles and found that N-lithiumpiperidine gave coupling products with 2-nitrothiophene (see Section II.2.D) and 3-nitrothiophene. The latter compound gave 3,3′-dinitro-2,2′-bithienyl (~ 10%, based on unrecovered 2-nitrothiophene), in addition to 2-N-piperidyl-3-nitrothiophene, via a suggested radical anion.

Sosonkin and coworkers[67] found that mixing solutions of 2-bromo- or 2-iodo-5-nitro-thiophene and tetrabutylammonium hydroxide in dimethylformamide under argon gave the radical anion of 5,5′-dinitro-2,2′-bithienyl (**66**, Scheme 13) in amounts of up to 10% of the original compound, as determined by ESR. For comparison, the same anion was prepared by applying a strong base to 5,5′-dinitro-2,2′-bithienyl, in which case the yield reached 14% of the original concentration.

It was proposed that an electron is transferred from a hydroxide ion to the halonitrothiophene. Loss of a bromide or iodide ion yields the nitrodithienyl radical **64**, which dimerizes to the bithienyl **65**. Further reduction by the base affords the radical anion **66**, detectable by ESR.

In a subsequent paper[68] the reduction of 2-bromo- and 2-iodothiophene was studied by various electrochemical methods. Radical anion **66** was formed in these reactions as well, and the results did not contradict those for the same mechanism as in Scheme 13.

On preparation of γ,γ-dimethylallenyl ethynyl sulfide (**67**), a variety of by-products were obtained, including 3-isopropenylthiophene (**68**) and 4,4′-diisopropenyl-2,2′-bithienyl (**69**). These by-products were best explained by

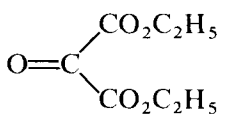
assuming the diradical intermediate **68**, since all possible dimeric combinations of **68** were observed in the product mixture.[69]

Irradiation syntheses of 2,2′-bithienyl, 2,3′-bithienyl, and 3,3′-bithienyl from thiophene with the aid of high-energy irradiation sources have been described in a patent by Berk.[70]

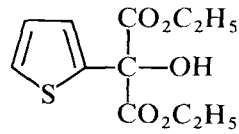
G. Miscellaneous Types of Coupling

Steinkopf and Hanske[71] reacted 2-thienylmagnesium bromide with diethyl mesoxalate (**70**, Scheme 14), and on treatment of the resulting alcohol (**71**) with zinc in acetic acid, the malonic ester derivatives **72** and **73** were obtained. Hydrolysis and decarboxylation gave **74**.

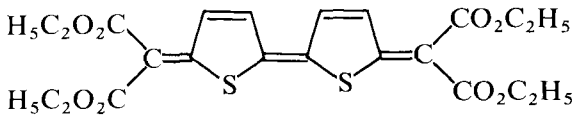
Compound **72** is reminiscent of the pigments obtained by the reaction of thiophene under acid catalysis with dicarbonyl reagents, such as benzil (**75**, Scheme 15) and isatin (**76**) and assigned structures **77** and **78**, respectively.[71] The blue color of **78** has been used as a sensitive test for thiophene (the indophenine test), but its insolubility and involatility has made a closer investigation of its structure by NMR, mass spectrometry, and other methods difficult. However,



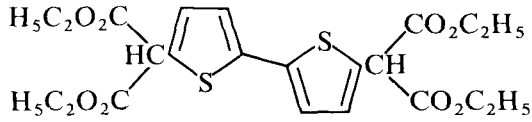
70



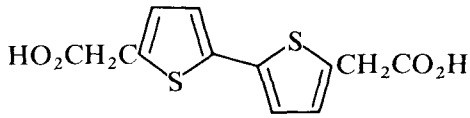
71



72

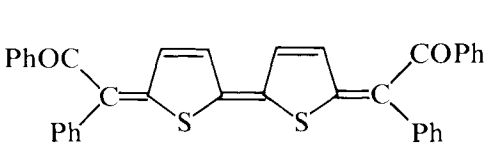


73

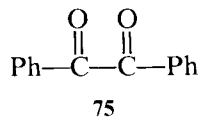


74

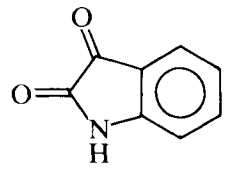
Scheme 14



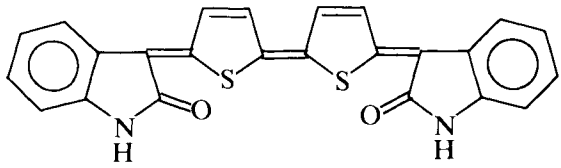
77



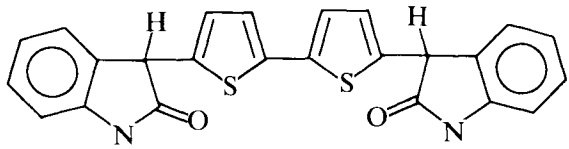
75



76



78

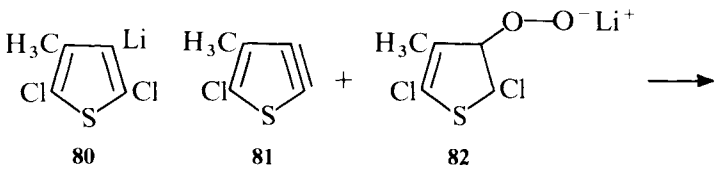


79

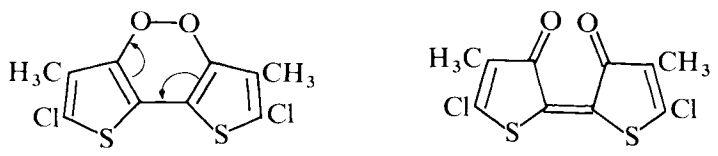
Scheme 15

Ballantine and Fenwich[72] reduced **78** to the leuko compound **79**, which did not have these disadvantages. Its ^{1}H NMR and mass spectra were consistent with those of structure **79**, and the 2,2′-connection of the rings was confirmed by desulfuration. It should be pointed out, however, that the *cis–trans*-isomerism of **78** (or **77** or **72**) is not elucidated by such methods.

When 2,5-dichloro-3,4-dilithiothiophene was reacted with dimethyl sulfate and the mixture was left overnight open to the atmosphere, 0.17% of the *cis*-isomer (UV, IR)[73] of bisthiopheneindigo **84** (Scheme 16) was obtained, in



80 81 82



83 84

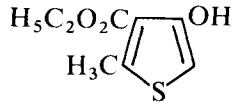
Scheme 16

addition to the desired 2,5-dichloro-3,4-dimethylthiophene.[74] It was proposed that **82**, formed by air oxidation of some **80**, reacted with the thiophyne **81**, generated from **80** as well, to yield **83**. Subsequent rearrangement of electrons might give the *cis* compound **84**.

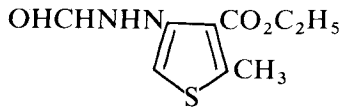
Indigoid derivatives of type **84** are also formed by oxidative coupling of hydroxythiophenes, which has been surveyed by Gronowitz and Hörnfeldt (see Vol. 44, Part 3, Chapter I, Section V.7).

Attempts to prepare 2-hydroxythiophene by oxidation of 2-thienylmagnesium bromide with oxygen resulted in the simultaneous formation of up to 29% of 2,2′-bithienyl.[75] Analogously, the formation of minor amounts of 5,5′-diphenyl-2,2′-bithienyl was reported on oxidation of the Grignard reagent of 2-bromo-5-phenylthiophene with oxygen.[76]

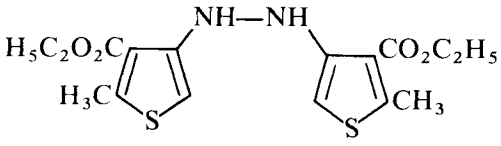
Shvedov and coworkers[77,78] found that bithienyl **88** (Scheme 17) could be isolated in 15% yield on preparation of **86** from **85**. Reaction of **85** with **86** afforded **88** in 41% yield, and it was suggested that **88** was formed by a benzidine type of rearrangement of the intermediate **87**.[78]



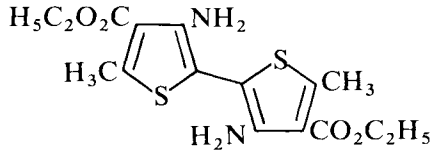
85



86



87



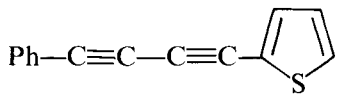
88

Scheme 17

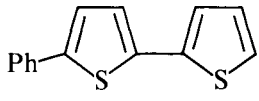
H. Ring-Closure Methods

Schulte and coworkers[79,80] prepared 2,5-disubstituted thiophenes by treating 1,4-disubstituted diacetylenes with H_2S at room temperature or at 50–60°C. In this way 5-phenyl-2,2′-bithienyl (**90**, Scheme 18) was obtained from 1-(2-thienyl)-4-phenylbutadiyn (**89**). Attempts to obtain the bithienyl system in a similar way directly from diphenyloctatetrayn **91** failed, and resulted in **92**.[81] However, on reaction of **92** and H_2S in ethanol at about 90°C, 5,5′-diphenyl-2,2′-bithienyl (**93**) was obtained in 24% yield. Thus, in the case of **93**, both thiophene rings were formed by a ring-closure reaction, although not simultaneously.

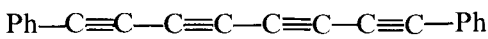
2-Aminovinyl thioketone **94** (Scheme 19) reacts with α-bromoketone **95** to give the 5-acyl-2,2′-bithienyl **97** (R = *p*-BrC_6H_4) in 65% yield.[82] Compound **96** is a probable intermediate.



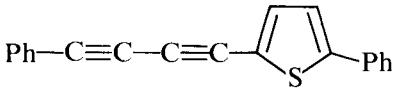
89



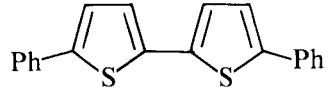
90



91

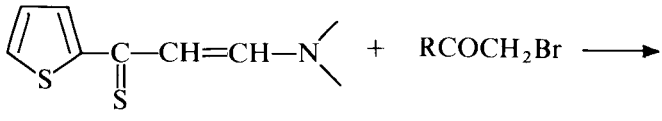


92

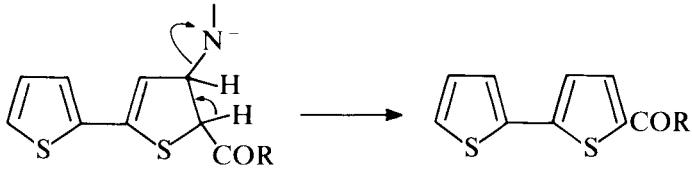


93

Scheme 18



94 95

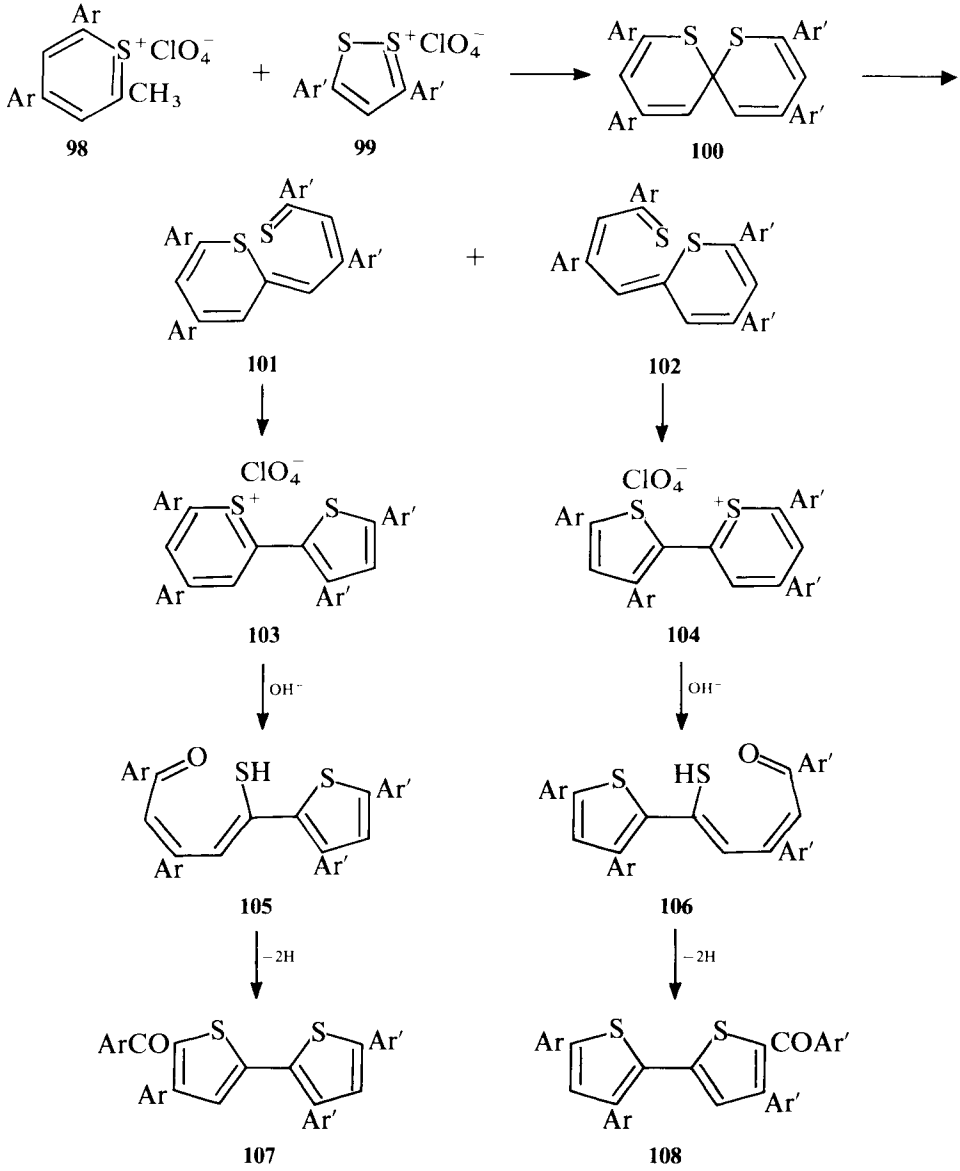


96 97

Scheme 19

Brelivet et al.[83] reacted methyl and ethyl esters of thioglycolic acid with esters of 2-thienylpropiolic acid, which gave a mixture of 4-hydroxy-2,2′-bithienyls with ester groups at the 3- or 5-positions.

Brown and coworkers[84] studied the condensations of 4,6-diaryl-2-methylthiopyrylium salts (**98**, Scheme 20) with 3,5-diaryl-1,2-dithiolylium salts (**99**). When the reaction was performed in boiling acetic acid–pyridine a uniform purple crystalline product (29%) of **103** = **104** was obtained for Ar = Ar′ = phenyl. For Ar = phenyl and Ar′ = *p*-tolyl, or Ar = *p*-tolyl and Ar′ = phenyl in the starting material, the same mixture of **103** and **104** was formed in both cases. This was consistent with the unsymmetrically substituted spiro compound **100** as an intermediate (symmetric for Ar = Ar′ = phenyl). To avoid the assumed oxidation of **100**, the reaction was performed in pyridine at room temperature. This resulted in a complex mixture of colored products, from which a yellow solid, 5′-benzoyl-3,4′,5-triphenyl-2,2′-bithienyl, could be isolated when Ar = Ar′ = phenyl. Combinations Ar = phenyl, Ar′ = *p*-tolyl or Ar = *p*-tolyl, Ar′ = phenyl again yielded a mixture assigned to **107** + **108**. The proposed mechanism is given in Scheme 20.



Scheme 20

2. Preparation of 3,3′-Bithienyls

Since the α-positions of thiophene are more reactive than the β-positions, the 3,3′-bithienyl system is not as easily attainable as the 2,2′-system. Indeed, besides the parent compound, only five derivatives had been reported at the time of

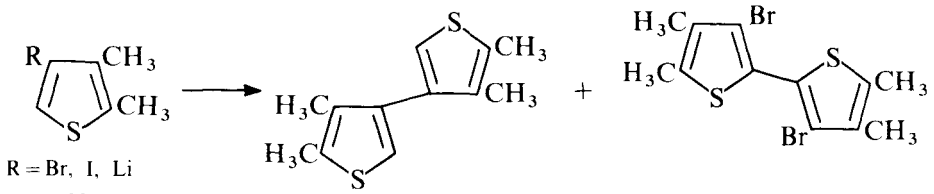
Hartough's survey,[1] and no good method for the preparation of 3,3′-bithienyl existed. It was known to be present in the pyrolysis products of thiophene, and it had been prepared in yields around 10% by ring-closing the tetrasodium salt of 1,2,3,4-butanetetracarboxylic acid with phosphorus trisulfide.[20]

The formation of 3,3′-bithienyl on pyrolysis of thiophene,[3-6] decomposition of benzoyl peroxide in thiophene,[64] and irradiation of thiophene[70] was mentioned in Section II.1 and will not be further commented on here.

A. Coupling of 3-ThLi Derivatives with $CuCl_2$

The first preparation of 3,3′-bithienyl, which made the compound easily available, was reported by Gronowitz and Karlsson[2] in 1960. They reacted 3-thienyllithium, readily prepared at $-70°C$ from 3-bromothiophene and *n*-butyllithium, with $CuCl_2$ and attained a yield of 49% of the desired product. In a similar way, 4,4′-dibromo-3,3′-bithienyl was obtained[11] in 52% yield from 3,4-dibromothiophene via 4-bromo-3-thienyllithium. The somewhat simpler procedure described for the latter bithienyl may be followed for the preparation of 3,3′-bithienyl as well, without influencing the yield.[87]

In Table 2 other derivatives of 3,3′-bithienyl, obtained by the same method, are collected. Usually good yields are attained without complications. However, on preparation of 4,4′,5,5′-tetramethyl-3,3′-bithienyl (**110**, Scheme 21) from $CuCl_2$ and 2,3-dimethyl-4-thienyllithium (**109**, R = Li), prepared at $-70°C$ from 2,3-dimethyl-4-bromothiophene (**109**, R = Br) and ethyllithium, only 21% of **110**, accompanied by 9% of 3,3′-dibromo-4,4′,5,5′-tetramethyl-2,2′-bithienyl (**111**), was obtained.[14] Starting with the iodo derivative, **109** (R = I) gave, in the normal way, 47% of **110**. The unexpected result was explained in terms of a slow halogen–metal exchange reaction of the bromo derivative and a metalation of unreacted **109**, R = Br, by **109**, R = Li (Scheme 21).



Scheme 21

B. Ullmann-Type Coupling

Attempts to prepare 3,3′-bithienyl by the Ullmann reaction with 3-iodothiophene gave very poor yields (~ 1%).[2,88] 2,2′,5,5′-Tetramethyl-3,3′-bithienyl was

TABLE 2. Preparations of the 3,3′-Bithienyl Framework

Compound Name or Formula No.	Method[a]	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
3,3′-Bithienyl[b]	A	132–134	49	2
	C	130	70	97
	C	133–134	88.3	100
–, 2-bromo	C	124–130/11	57	97
–, 4-bromo	D	40–41; 127–130/0.9	47	101
	C	88/0.05	16	46
–, 4,4′-dibromo	A	127–129	52	11
		195–200/15	62	103
–, –, 2,2′-dimethoxycarbonyl	B	158–160	12	87
–, 4,4′-dichloro	A	107–109	55	104
–, 5,5′-dichloro	A	116–118	36	104
–, 2,2′,5,5′-tetrachloro	A	122–123	41	74
–, –, 4,4′-diiodo	A	126	28	74
	B	126	7	74
–, 2,2′,5,5′-tetraethyl	A	143–146/0.03	77	105
–, 2-formyl	C	142–144/0.4	67	97, 98
–, –, 2′-methylthio	C	174/1.5	60	98
–, –, 2′-nitro	C	123–125	60	98
–, 4-formyl	C	166–168/4.5	57	98
–, –, 2′-methylthio	C	160–162/1	60	98
–, –, 2′-nitro	C	171–173	60	98
–, 2,4′-diformyl	C	108	70	98

–, 2,2′-dimethoxycarbonyl-4,4′-dinitro	B	164–165	73	93
–, 4,4′-dimethoxycarbonyl-2,2′,5,5′-tetramethyl	B	50.5–51.5	35	35
–, 2,2′,4,4′-tetramethoxycarbonyl	B	159–160	53	94
–, 2,2′-dimethyl	A	141–144/17	39	106
		135.5–137.5/11	—	15
–, 2,4-dimethyl[c]	C	115–117/1	72	97
–, 4,4′-dimethyl	A	133–134/10	49	106
–, 5,5′-dimethyl	A	135–136	27	107, 108
			34	109
–, –, 2,2′,4,4′-tetranitro	B	185–186	29	35
–, 2,2′,4,4′-tetramethyl	A	52–52.5; 90–100/0.1	64	110
–, 2,2′-5,5′-tetramethyl	A	132–135/1.5	58	111
	B	148–152/12	—	89
–, 4,4′,5,5′-tetramethyl	A	71–72	47	14
–, 2-methylthio	C	128–130/1	60	97, 98
–, 2-nitro	C	90–91	70	97, 98
–, 2,2′-dinitro	B	215	—	92
–, 2,2′,4,4′-tetranitro	B	210	—	92
–, 2,2′,5,5′-tetranitro	B	260	—	92
–, 4,4′-dinitro	B	224–225	86	95
	B	208	1	112
–, 5,5,′-diphenyl	A	168–169	—	86

[a] Refers to Section II.2, where the method is described.

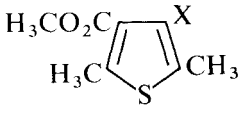
[b] Selected examples.

[c] Erroneously reported as 2,4-dimethyl-2,3′-bithienyl. The correct structure is evident from the mode of preparation and from NMR data.

prepared in an unspecified yield from 2,5-dimethyl-3-iodothiophene and copper bronze at 250°C.[89] However, 2,5-dimethyl- and 2,5-dichloro-3,4-diiodothiophene sublimed unchanged when heated with copper bronze.[74] The latter thiophene gave 7% of 2,2′,5,5′-tetrachloro-4,4′-diiodo-3,3′-bithienyl when the reaction was performed in DMF, but the former thiophene gave no isolable yield under these conditions either.[74]

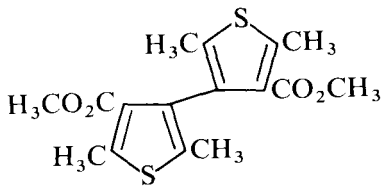
Better results are obtained when electron-withdrawing groups are present at the 2- and/or 4-position. Jean and Nord[35] isolated 35% of 2,2′,5,5′-tetramethyl-4,4′-dicarbomethoxy-3,3′-bithienyl (**113**, Scheme 22) from methyl 2,5-dimethyl-4-iodo-3-thiophenecarboxylate (**112**, X = I) at 230°C, whereas the corresponding 4-bromothiophene **112** (X = Br) gave only a 7.4% yield.[35,90] Coupling of 4-iodo-3,5-dinitro-2-methylthiophene (**114**) at 155°C gave a 29% yield of 5,5′-dimethyl-2,2′,4,4′-tetranitro-3,3′-bithienyl (**115**).[35,91] Dell'Erba et al.[92] also prepared some di- and tetranitro derivatives of 3,3′-bithienyl by Ullmann coupling in xylene, but they report no yields.

Attempts to apply the Ullmann coupling to **116** (R = CHO) met with difficulties.[93] The conventional Ullmann reaction of **116** ($R = CO_2CH_3$) led to decomposition. Performing the coupling with xylene as solvent[33] gave erratic

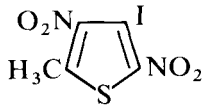


X = Br, I

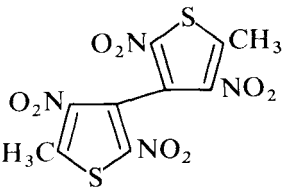
112



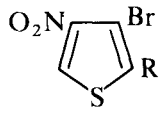
113



114

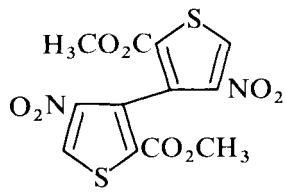


115

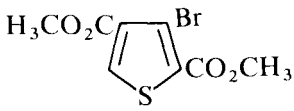


R = CHO, CO_2CH_3

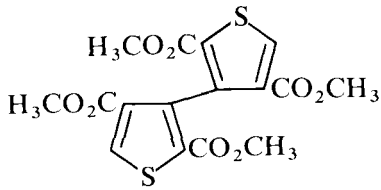
116



117



118



119

Scheme 22

and unreproducible results, involving reduction to methyl 4-nitro-2-thiophenecarboxylate, whereas in DMF a yield of 73% of **117** could be obtained, using electrolytically prepared copper powder.

However, even with DMF as solvent and with the same kind of copper powder, up to 50% reduction to the dimethyl ester of 2,4-thiophenedicarboxylic acid was observed on attempts to Ullmann-couple compound **118**. Yet, in one experiment, 53% of pure **119** could be isolated.[94]

A conventional Ullmann coupling of 3-iodo-4-nitrothiophene proved unsuccessful.[95] However, under very mild conditions an 86% yield of 4,4′-dinitro-3,3′-bithienyl was obtained.[96] This method implies the addition of the iodonitro compound and aqueous ammonia to a mixture of cupric sulfate and copper powder in acetone–acetonitrile at room temperature, with subsequent gentle heating.

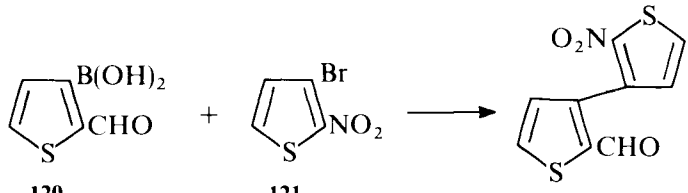
C. Coupling Catalyzed by Pd and Ni

Relatively recently Gronowitz and coworkers[97,98] presented a new synthetic path to 3,3′- and 2,3′-bithienyls especially useful for the preparation of unsymmetrically substituted bithienyls. They followed a procedure developed by Suzuki et al.[99] involving cross-coupling of 3-thiophene boronic acid with a halothiophene, using 3% of $Pd[P(Ph)_3]_4$ in a solvent mixture of aqueous sodium carbonate and toluene or glycol dimethyl ether. One example of the reaction is shown in Scheme 23, and other compounds prepared in a similar way are listed in Table 2.

One advantage of this method, compared to those involving organolithium or organocopper reagents, is that certain functional groups such as the formyl group may be present. Indeed, such electron-withdrawing groups facilitate the reaction, while it is retarded by electron-donating groups.[98]

4-Bromo-3,3′-bithienyl (16% yield) was obtained together with 3,3′ : 4′,3″-terthienyl (50% yield) on reaction of 3-thienylmagnesium bromide with 3,4-dibromothiophene in the presence of $PdCl_2(dppf)$[46] (see Section II.1.C).

A high yield (88.3%) of 3,3′-bithienyl was obtained on coupling of 3-thienylmagnesium bromide with 3-bromothiophene in the presence of



120 **121** **122**

Scheme 23

$NiCl_2(dppp)$ [dppp = $Ph_2P(CH_2)_3PPh_2$].[100] This method of coupling, and that catalyzed by $PdCl_2(dppf)$,[46] have been worked out for the preparation of terthienyls (Section III.1.B).

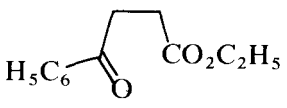
D. Various Preparations of the 3,3′-Bithienyl System

It was mentioned in Section II.1.F that Dell'Erba and coworkers[66] studied the reactivity of nitrothiophenes with N-lithiumpiperidine. In this reaction 2-nitrothiophene forms 2,2′-dinitro-3,3′-bithienyl in addition to 3-N-piperidyl-2-nitrothiophene.

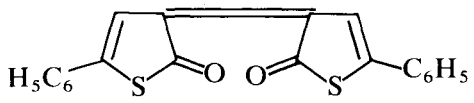
Using a method originally worked out for the preparation of 2,3′-bithienyl (Section II.3.A), 3,3′-bithienyl has also been prepared[2] in 17% yield by the reaction of 3-thienyllithium with 3-ketotetrahydrothiophene at $-70°C$ and subsequent aromatization of the resulting alcohol with chloranil.

Wynberg et al.[101] used the same method in their preparation of 4-bromo-3,3′-bithienyl from 4-bromo-3-thienyllithium and 3-ketotetrahydrothiophene.

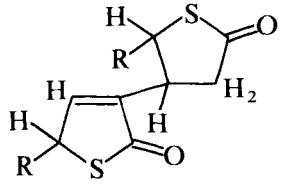
The 3,3′-bithienyl system may also be recognized in compounds **124** and **125** (Scheme 24). Compound **124** was formed on oxidation of 5-phenyl-2-thiophenol[76] and obtained in 10% yield on treatment of γ-oxoester **123** with hydrogen sulfide in the presence of hydrogen chloride.[102]



123



124



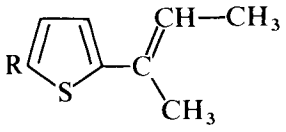
125

Scheme 24

Compounds of type **125** are dimerization products of the Michael reaction of 5-alkyl-substituted thiolene-2-ones (2-hydroxythiophenes). For further comments on these adducts and on compounds of type **124**, see the survey of Gronowitz and Hörnfeldt in Vol. 44, Part 3, Chapter I, Sections V.6 and V.7, respectively.

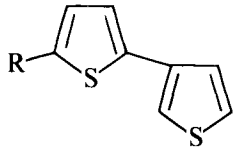
3. Preparation of 2,3′-Bithienyls

Although some complex derivatives had been prepared previously,[1] unsubstituted 2,3′-bithienyl was unknown until 1954, when Teste and Lozac'h[113]



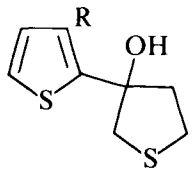
R = H, CH_3

126



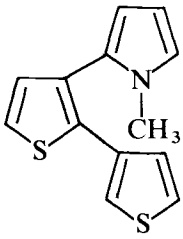
R = H, CH_3

127

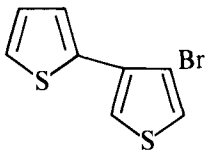


R = H, Br

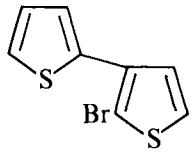
128



129



130



131

Scheme 25

obtained this compound and its 5-methyl derivative (**127**, Scheme 25) as by-products in unspecified amounts on treatment of alkenylthiophene **126** with sulfur. Later it was found[5] that 2,3′-bithienyl is one product of thiophene pyrolysis, as mentioned previously.

A. Reaction of 2-ThLi Derivatives with 3-Ketotetrahydrothiophene

The first useful method for the preparation of 2,3′-bithienyl was developed in 1957 by Wynberg and coworkers.[114] They reacted 2-thienyllithium with 3-ketotetrahydrothiophene, and the resulting tertiary alcohol, **128** (R = H), was dehydrated and aromatized to **127** (R = H) on treatment with chloranil. 3-Bromo-2,3′-bithienyl has been prepared in an analogous way via **128** (R = Br),[101] and 5,5′-diphenyl-2,3′-bithienyl was obtained from 5-phenyl-2-thienyllithium and 2-phenyl-4-ketotetrahydrothiophene.[86] As mentioned in Section II.2.D, the method has been utilized for the preparation of some 3,3′-bithienyls as well.

B. Coupling of 2-ThCu with 3-Halothiophenes

The conventional Ullmann reaction is less suited for the preparation of unsymmetric biaryls on the whole, and especially when 3-halothiophenes are involved.

Reaction of 2-thienylcopper with 3-iodothiophene by the method of Nilsson and Ullenius[39] gave a low yield of less pure 2,3′-bithienyl (Table 3). This compound and probably 1-methyl-2-[3-(2,3′-bithienyl)]pyrrole (**129**) were

TABLE 3. Preparations of the 2,3′-Bithienyl Framework

Compound Name or Formula No.	Method[a]	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
2,3′-Bithienyl	B	53–59	14	39
	C	67–68	72	97
	C	66–67	77	100
	E	65	—	113
	A	68.0–68.4	55	114
–, 5′-amino-4′-ethoxycarbonyl	E	77–78	33	118
–, 2′-benzoyloxy	D	129–131	—	64
–, 2′-bromo	B	110–112/0.5	53	115
–, 3-bromo	A	117–118/0.5	50	101
	C	Oil	45	46
–, 4-bromo	C	70–72	64	46
–, –, 3,4′-dinitro	B	350 dec.	8	112
–, 4′-bromo	B	98–100/0.5	55	115
–, 5,5′-di(4-bromophenyl)	D	208–210	50	86
–, 2′,5-dichloro	D	53–54	—	55
–, 2′,5,5′-trichloro	D	—	—	117
–, 5-ethyl	A	21–23.9; 99/0.28		114
–, 2′-formyl	C	151–152/2	50	98
–, 5,5′-di(4-methoxyphenyl)	D	240–242	51	86
–, 3-methyl	C	135–137/11	60	97
–, 5-methyl	E	68	—	113
–, 5,5′-dimethyl	E	73–75	15	64
–, 5,5′-di(4-methylphenyl)	D	189–190	44	86
–, 5,5′-di(2,4-dimethylphenyl)	D	64–65	19	86
–, 3-(1-methyl-2-pyrrolyl)	B	—	—	41
–, 2′-nitro	C	49–50	50	98
–, 5,5′-diphenyl	A,D	168–169	38	86
53 (Scheme 11)		$85–87/5 \times 10^{-4}$	—	56
53,3′4′-dehydro		165–166	—	56

[a] Refers to Section II.3, where the method is described.

formed as by-products on reaction of 1-methyl-2-pyrrolylcopper with 3-iodothiophene.[41]

Relatively good yields of 4′-bromo-2,3′-bithienyl (**130**) (55%) and 2′-bromo-2,3′-bithienyl (**131**) (53%) were obtained when 2-thienylcopper was reacted with 3-bromo-4-iodothiophene and 2-bromo-3-iodothiophene, respectively.[115]

C. Coupling Catalyzed by Pd and Ni

The Pd-catalyzed coupling of thiopheneboronic acids with halothiophenes was presented in Section II.2.C and in Scheme 23 in connection with synthetic paths to 3,3′-bithienyls. It offers an excellent alternative to the preparation of unsymmetric bithienyls of various kinds. Besides the parent compound, three 2,3′-bithienyls have been prepared[97,98] in good yields in this way. (See Table 3 and footnote *c* of Table 2.)

The Pd- and Ni-catalyzed couplings of Grignard reagents with bromo- and dibromothiophenes, mentioned in Sections II.1.C and II.2.C, have been used for the preparation of 2,3′-bithienyl (77% yield)[100] and 3-bromo- and 4-bromo-2,3′-bithienyl[46] (Table 3). In all three cases 3-thienylmagnesium bromide was the Grignard reagent and was reacted with 2-bromo-, 2,3-dibromo-, and 3,4-dibromothiophene, respectively.

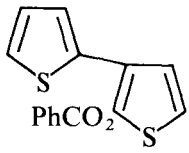
D. Miscellaneous Types of Coupling

2′-Nitro-2,3′-bithienyl is one of the compounds prepared by the method including the thiopheneboronic acids, mentioned in the previous section (Table 3). It has also been obtained in an unspecified yield by Dell'Erba et al.[116] by reaction of diazotized 2-nitro-3-aminothiophene with thiophene.

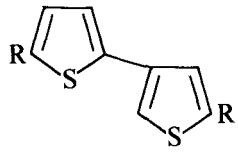
2,5,5′-Trichloro-2,3′-bithienyl was believed to be one of the products formed on polymerization of 2,5-dichlorothiophene with $AlCl_3$–$CuCl_2$.[117]

The formation of 2′,5-dichloro-2,3′-bithienyl (**43**, Scheme 10) in the reaction of thiophene with sulfuryl chloride and iron powder[55] was described in Section II.1.D. It was also mentioned previously that 2,3′-bithienyl is formed on irradiation of 2-bromothiophene,[62] in the decomposition of diisopropyl peroxydicarbonate in thiophene,[65] and in the decomposition of benzoyl peroxide in thiophene.[64] Another product, "formed in considerable amounts" in the latter case, was assigned as 2′-benzoyloxy-2,3′-bithienyl (**132**, Scheme 26). Further examples of the formation of 2,3′-bithienyls were given in Section II.1.C.

Sone and coworkers[86] found that the acid-catalyzed reaction of 2-arylthiophenes with a cation-exchange resin (Amberlite CG-120) gave good yields of 5,5′-diaryl-2-3′-bithienyls as unsymmetric coupling products (**133**, Ar = phenyl and substituted phenyl, see Table 3). The reaction was proposed to proceed via the bidentate cation **134**, reacting as if it were represented solely by the mesomeric structure **134a** (see Section II.1.D and Scheme 11). The 2,3′-coupling

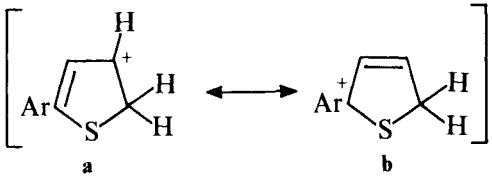


132



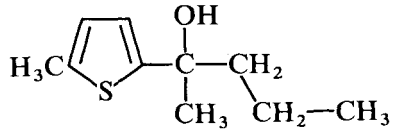
R = CH_3, Ar

133

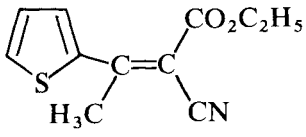


a b

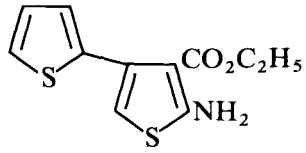
134



135



136



137

Scheme 26

of the thiophene rings was considered to be unique, since coupling of 2-arylthiophenes with a $AlCl_3$–$CuCl_2$ system was reported to yield primarily 5,5′-diaryl-2,2′-bithienyl.[86]

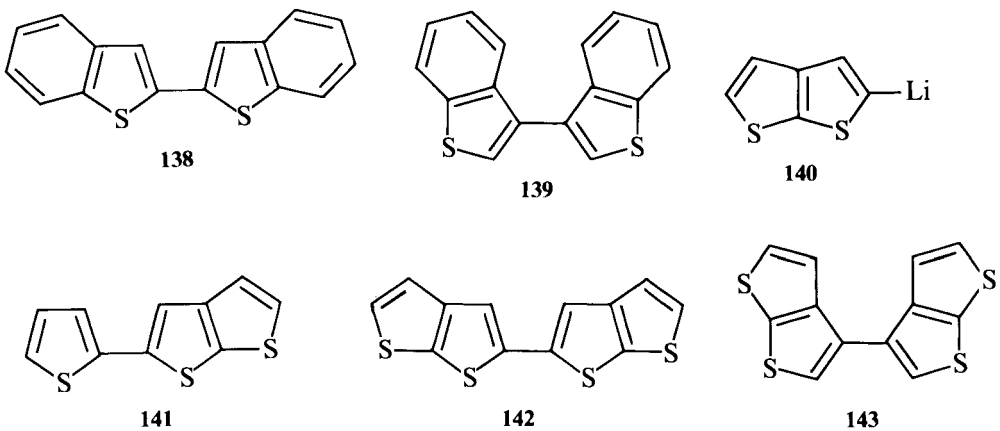
E. Ring-Closure Methods

The formation of 2,3′-bithienyl on treatment of compound **126** (Scheme 25) with sulfur[113] means a ring-closure reaction of the alkenyl group to yield the 3′-connected ring of **127**. Camaggi and coworkers[64] prepared 5,5′-dimethyl-2,3′-bithienyl (**133**, R = CH_3) in about 15% yield in a similar way from the tertiary alcohol **135**, which was treated with sulfur at 200–220°C. (Compound **135** was obtained by reacting the Grignard reagent of 2-bromo-5-methylthiophene with methylpropyl ketone.) Dehydration of **135** would yield an alkenylthiophene, homologous to **126** (R = H).

Shvedov and Grinev[118] obtained 5′-amino-4′-ethoxycarbonyl-2,3′-bithienyl (**137**) in 33% yield after reaction of compound **136** with sulfur in ethanol–diethylamine.

4. Preparation of Some Bithienyls with Annelated Rings

Both compounds **138** and **139**, as well as **142** and **143** (Scheme 27), and corresponding 2,3′-connected biaryls, might be considered as thiophene analogs of binaphthyl. In addition, in the case of the 2,2′-connected compounds **138** and **142**, the possibility of annelation over the 3,4- and 3′,4′-positions exists, and in, for example, **142** and **143** the annelated thiophene rings may be oriented in different ways ([3,4-*b*] and [3,4-*c*]). This offers many symmetric and unsymmetric isomers, of which only a few will be mentioned here (see also Table 4).



138 **139** **140**

141 **142** **143**

Scheme 27

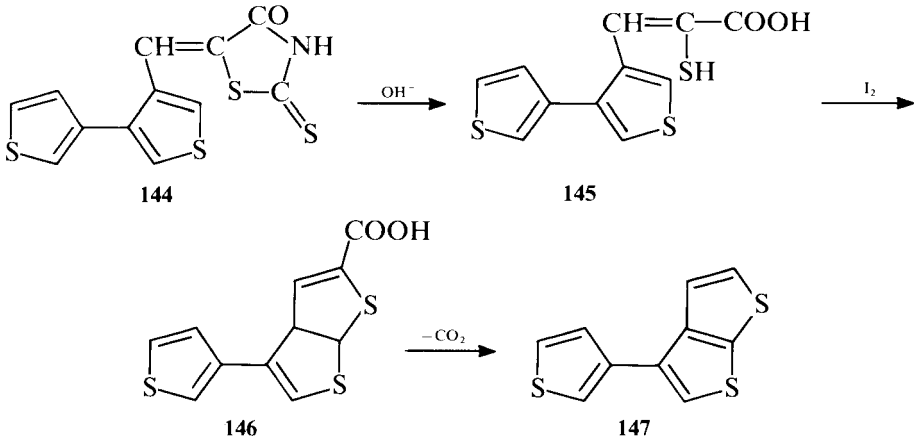
TABLE 4. Some Annelated Bithienyls

Compound	m.p. (°C)	Yield (%)	Ref.
2,2′-Biacenaphtho[1,2-*b*]thienyl	220–221	53	121
3,3′-Bithianaphthenyl	82.7–83	72	120
–, 2,2′-diformyl	171–172	66	120
2,2′-Bithieno[2,3-*b*]thienyl	247	63	13
–, 3,3′-dibromo	170	72	13
3,3′-Bithieno[2,3-*b*]thienyl	145	55	13
–, 2,2′-dibromo	150	73	13
2,2′-Thienylthieno[2,3-*b*]thienyl	105	32	13
–, 3,3′-dibromo	70–72	—	13
3,3′-Thienylthieno[2,3-*b*]thienyl	76–78	32	13
–, 2,2′-dibromo	Unstable	—	13
3,3′-Thienylthieno[2,3-*b*]thienyl-5-carboxy	300 (dec.)	48	13

3,3′-Bithianaphthenyl or 3,3′-bibenzo[*b*]thienyl **139** was prepared in 11% yield by Pandya et al.[119] Wynberg and Cabell[120] obtained 72% of **139** by coupling 3-benzo[*b*]thienyllithium with $CuCl_2$ at $-70°C$.

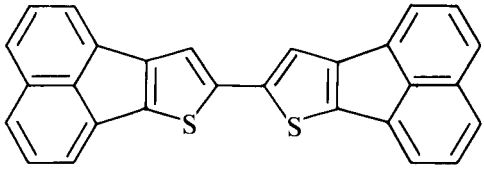
Compounds of types **141** and **142** were mentioned in Section II.1.A and shown in Scheme 3; **141** was prepared from **140** after transformation to the 2-Cu derivative with CuI and subsequent reaction with 2-iodothiophene.[13] 2,2′-Bithieno[2,3-*b*]thienyl (**142**) was obtained after treatment of **140** with $CuCl_2$, and the 3,3′-isomer **143** was prepared in a similar way from the 3-lithium derivative of thieno[2,3-*b*]thiophene.

To get 3-(3′-thienylthieno[2,3-*b*]thienyl (**147**)), a somewhat more laborious method was used, as shown in Scheme 28. Compound **144** was prepared by condensing 4-formyl-3,3′-bithienyl with rhodanine. After ring opening and cyclization of the resulting mercaptoacrylic acid **145**, carboxylic acid **146** was obtained and decarboxylated with copper in quinoline.



Scheme 28

When the ethyl ester of 2-acenaphtho[1,2-*b*]thiophenecarboxylic acid was treated with lithium aluminum hydride in THF at room temperature (5 h), a 95% yield of the expected 2-hydroxymethyl derivative was obtained.[121] However, when the same reaction was performed in boiling THF (1 h), 53% of 2,2′-biacenaphtho[1,2-*b*]thienyl was isolated (**148**, Scheme 29).



148

Scheme 29

III. PREPARATION OF POLYTHIENYLS

Poor yields of α-thiophene oligomers with two to seven thiophene units were obtained by Ullmann coupling of 2-iodothiophene[21] or copper-catalyzed coupling of 2-iodothiophene with 2-iodo-2,2′-bithienyl or 2,5′-diiodo-2,2′-bithienyl.[20] In laborious and tedious operations these complex mixtures could be separated by extensive chromatography[22] or by repeated sublimations and crystallizations.[21] Some methyl, phenyl, and halogen derivatives were also prepared by Steinkopf et al.[1,21]

In the mid-1940s α-terthienyl (**149**, Scheme 30) was discovered in the African variety of the common Marigold (*Tagetes erecta* L.).[122,123] Later it was found that this substance exhibits photoenhanced toxic activity against nematodes, microorganisms, algae, human erythrocytes, and insect larvae and eggs. It also acts as a herbicide and seed germination inhibitor, and it generates skin pigmentation. (For references see, for example, Kagan and Arora[124] and D'Auria et al.[63]) Therefore, more attention has been given to methods for the preparation of terthienyls than of higher thiophene oligomers, and these are presented separately in the next section.

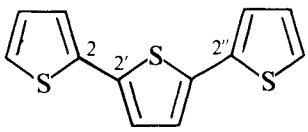
1. Preparation of Terthienyls

There are 14 different isomers of terthienyl, which are shown in Scheme 30. They have all been prepared by various methods, of which those involving the Pd- or Ni-catalyzed coupling of Grignard reagents with the appropriate monobromobithienyls or dibromothiophenes have been found to be particularly valuable (See Sections II.1.C, II.2.C, and II.3.C).

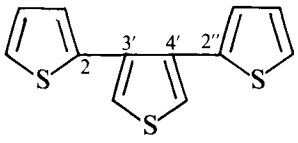
A. Preparation of α-Terthienyls

Uhlenbroek and Bijloo[32] used the conventional Ullmann reaction for the preparation of α-terthienyl and α-quaterthienyl from 2-iodothiophene. From 2-iodo-3,4-dimethylthiophene 3,4,3′,4′,3″,4″-hexamethyl-2,2′ : 5′2″-terthienyl was obtained as a by-product. Mixed coupling of 2-iodothiophene and 2,5-diiodo-3,4-dimethylthiophene gave 3,4′-dimethyl-2,2′ : 5′2″-terthienyl, and from the mixture of 2,5-diiodothiophene and 2-iodo-3,4-dimethylthiophene 3,4,3″,4″-tetramethyl-2,2′ : 5′,2″-terthienyl was obtained. 3,3′,3″-Trimethyl-2,2′ : 5′,2″ terthienyl was isolated from the product mixture after Ullmann coupling of 2-iodo-3-methylthiophene. In all cases the yields were very poor.

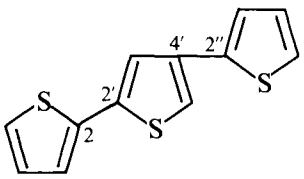
Schulte et al. prepared α-terthienyl[80,81] and its 5,5″-diphenyl derivative[79] in 40–50% yield from 1,4-diaryl-substituted butadiyns (Ar—C≡C—C≡C—Ar) and hydrogen sulfide. A similar method has also been used by Carpita et al.[125] and Kagan and coworkers. For example, Beny and Kagan[126] prepared



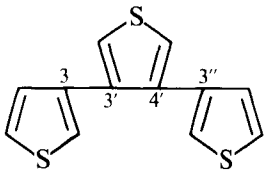
149



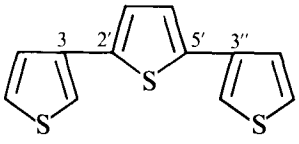
150



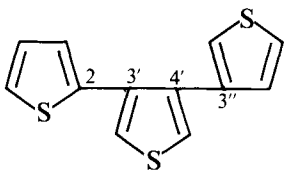
151



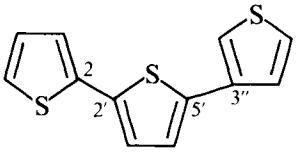
152



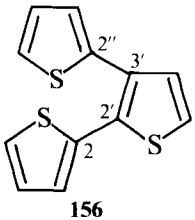
153



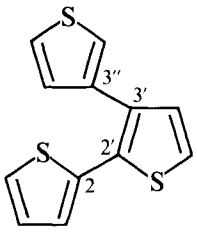
154



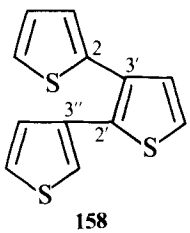
155



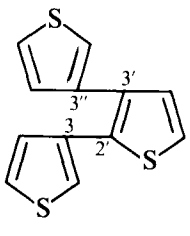
156



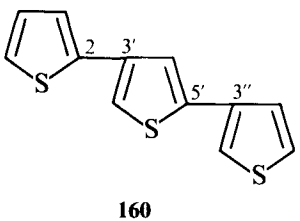
157



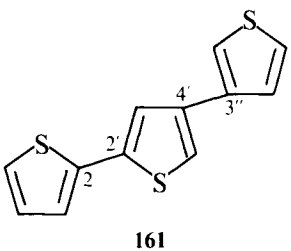
158



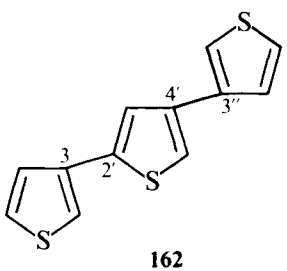
159



160



161



162

Scheme 30

2′,5′-$^{14}C_2$-labeled α-terthienyl in about 50% yield from 1,4-bis(2-thienyl) [1,4-$^{14}C_2$] butadiyne and sodium sulfide in methanol. The unlabeled compound was prepared in 84% yield, and good yields were also obtained for the 3,3″-dimethyl, 5,5″-dimethyl, and 5,5″-dibutyl derivatives[127,128] (Table 5).

TABLE 5. Preparations of Polythienyls

Compound	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
2,2′ : 5′,2″-Terthienyl	94	50	81
	93–94	84	127
	94–94.5	70	129
	92–93	66	130
	93.5–95	85	131
	96–97	35	132
	95–95.5	37	60
	93–94	86	125
	92–94	61	48
–, 2′,5′-^{14}C	93.5–94.5	48	126
–, 5,5″-diacetyl	249–250	61	195
–, 3′-bromo	40.5– 41.5	88.7	46
–, 5-bromo	135–136	85	143
–, 5,5″-dibromo	—	—	21, 32
	155–157	—	143
–, 5-(2,2-dibromoethenyl)	158–160	96	124
–, 5,5″-dibutyl	76–77	82	128
–, 5,5″-di-*t*-butyl	116; 275–285/13	—	31
–, 5-carboxy	239–240	68.5	196
–, –, methyl ester	180–182	95	196
–, 5,5″-dicarboxy	> 330	90	196
–, –, dimethyl ester	220	90	196
–, 5-chloro	129–130	55	129
–, 5,5″-dichloro	134–134.5	90	129
–, –, 3′-dimethylamino	102–103	55	129
–, 5-ethynyl	118–119	96	124
–, 5-formyl	140–141	75	132
–, 5-hydroxymethyl	151–152	Quantitative	132
–, –, ester 5-CH_2OCOR			
R = CH_3	113–114	Quantitative	132
R = $CH(CH_3)_2$	65.5–66.5	Quantitative	132
R = $CH{=}C(CH_3)_2$	79–82	Quantitative	132
R = *cis*-$C(CH_3){=}CH(CH_3)$	72.5–73.5	96	132
R = *trans*-$C(CH_3){=}CH(CH_3)$	82.5–83	—	132
–, 3,3′-dimethyl	55–56	95	127
–, 3′,4′-dimethyl	128	—	32
–, 5,5″-dimethyl	—	—	21, 32
	100.5–101	60	127
–, 3,3′,3″-trimethyl	Oil	—	32
–, 3,4,3″,4″-tetramethyl	80	—	32
–, 3,4,3′,4′,3″,4″-hexamethyl	Oil	—	32
–, 5,5″-diphenyl	276	40	79
2,3′ : 4′,2″-Terthienyl (**150**)	64; 217/17	76	32
	64–65	—	132
	64–66	50–85	133
–, 2′,5′-dicarboxy	340 dec.	73	32
–, –, diethyl ester	—	—	32
–, 5-chloroacetyl	68.5–69	79	133
–, 5,5″-bis(chloroacetyl)	122–122.5	6	133
–, 5,5′,5″-tris(chloroacetyl)	214	13	133

TABLE 5. (*Continued*)

Compound	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
2,2′ : 4′,2″-Terthienyl (**151**)	53–54	20	114
	53	95	136
3,3′ : 4′,3″-Terthienyl (**152**)	—	—	137
	83.5–84.5	50	46
	81–82	85	100
3,2′ : 5′,3″-Terthienyl (**153**)	193	100	127
	192–193	75	138
–, 5,5″-dichloro	178–179	21	129
2,3′ : 4′,3″-Terthienyl (**154**)	68–69	83	47
–, 2′,5′-dicarboxy-5-chloro-2″,5″-dimethyl	273–274	77	129
2,2′ : 5′,3″-Terthienyl (**155**)	158–160	87	139
	—	84	131
2,2′ : 3′,2″-Terthienyl (**156**)	60–61	85	46
	59–60	83	100
–, 5′-methyl	—	—	131
2,2′ : 3′,3″-Terthienyl (**157**)	38–39	93	100
–, 5′-methyl	—	—	131
2,3′ : 2′,3″-Terthienyl (**158**)	39–40	95	47
3,2′ : 3′,3″-Terthienyl (**159**)	49–50	77	100
2,3′ : 5′,3″-Terthienyl (**160**)	103–104	94	47
2,2′ : 4′,3″-Terthienyl (**161**)	101–102	72	47
3,2′ : 4′,3″-Terthienyl (**162**)	156–158	48	46
	157.5–158.5	61	100
α-Quaterthienyl	210–212	—	1, 21
	215–216	—	1, 22
	211–212	100	124
	211–212	50	60
	—	85	140
	215–216	66	143
–, 5-bromo	226–227	51	143
–, 5,5‴-dibromo	251	—	1, 22
	255–256	15	143
–, 5,5‴-dimethyl	184–185	—	1, 21
	172–173.5	—	1, 22
–, 5,5‴-diphenyl	317	—	1, 21
3,3′ : 2′,2″ : 3″,3‴-quaterthienyl	169.5–171.5	84	141
α-Quinquethienyl	256–257		1, 21
	256–258	73.5	124
	257–258	55	60
	—	—	142
α-Sexithienyl	304	—	1, 21
	303–305	59	60
	304–305	73	140
	301–302	58	143
α-Septithienyl	326–328	—	1, 21
	327–328	97.5	124
2,3′ : 4′,2″ : 5″,3‴ : 4‴,2⁗ : 5⁗,3⁗⁗ : 4⁗⁗,	—	—	142
2⁗⁗⁗-Septithienyl	126–127	66–79	133
α-Octithienyl	364	18	143

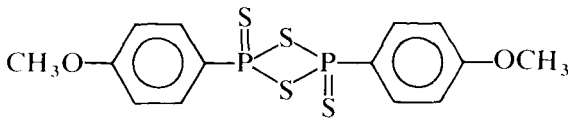
TABLE 5. (*Continued*)

Compound	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
"Pentadecathiophene"	Glassy		133
(All-α*S*)-cyclotetrathiophene (**180**)	255–266	24	148
–, 2-trimethylsilyl	148	79	149
–, 2-nitro	264	4	197
–, "dinitro"	304–306	7.1	197
–, "dinitro"	317	3.9	197
–, 2,7,12-trinitro	336	- -	197
–, 2-(4-pyrimidinyl)	248	44	149
–, 2-(2-quinolinyl)	244	15	149
–, 2-(2-quinoxalinyl)	319	14	149
(All-β*S*)-cyclotetrathiophene (**181**)	300–301	26	148
(All-α*S*)-cyclohexathiophene	—	4	148
(All-α*S*)-tetrathionaphthalene	410, dec.	10	148
2,2′-Bi-(all-α*S*)cyclotetrathiophene (**182**)	355, dec.	28	149

Carpita et al.[125] achieved a 86% yield of α-terthienyl from 1,4-bis(2-thienyl)-1,3-butadiyn and Na_2S. The same terthienyl was also prepared in 70% yield by reacting 2-thienylmagnesium bromide with 2,5-dibromothiophene in the presence of $NiCl_2$(dppe).[125]

Another synthetic pathway proceeds via 1,4-diaryl-substituted 1,4-diketones (Ar—CO—CH_2— CH_2—CO—Ar), which are cyclized to a thiophene ring by treatment with hydrogen chloride and hydrogen sulfide. By this method, α-terthienyl and some chloro derivatives were prepared by Kooreman and Wynberg.[129] Asano et al.[130] utilized the same procedure, whereas Wynberg and Metselaar[131] used P_4S_{10} for the cyclization. Otherwise, the synthetic differences in these examples consist in the preparations of the diketone.

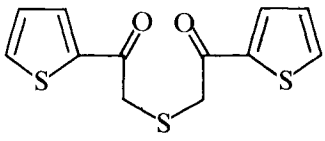
Wynberg and Metselaar[131] also used another method for the cyclization of the diketone, namely, treatment with Lawesson's reagent (**163**, Scheme 31), which gave good yields of α-terthienyl (85%) and other terthienyls (see below). This procedure is better suited for large-scale syntheses than those mentioned previously.



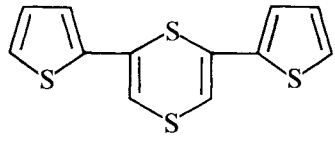
163

Scheme 31

Nakayama et al.[132] used Lawesson's reagent for the preparation of 2,6-di-(2-thienyl)-1,4-dithiin (**165**, Scheme 32) from diketosulfide **164**. On refluxing **165** in *o*-dichlorobenzene, a 13 : 1 mixture of terthienyls **149** and **150** was obtained



164



165

Scheme 32

in up to 85% yield on a 10-mmol scale. On a 0.2-mol scale 35% of purified **149** was isolated.

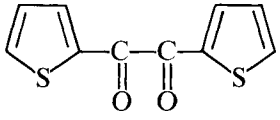
The preparation of 2,2′-bithienyl by Kagan and Arora[60] from reagent **61** (Scheme 12) was mentioned in Section II.1.E. A similar ate complex was prepared from lithiated 2,2′-bithienyl, 9-BBN, and 2-thienyllithium, from which α-terthienyl was obtained in 37% yield.

α-Terthienyl is also commercially available.

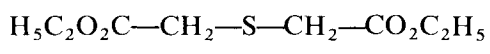
B. Preparation of α-Terthienyl Isomers

The formation of **150** as a minor constituent in the product mixture of Nakayama et al. was mentioned above. However, an overall yield of about 80% of **150** was obtained in a recently presented method, which involves reductive coupling of **164** with $TiCl_4/Zn$ to a *cis*-3,4-hydroxythiolane, followed by acid-catalyzed dehydration.[133]

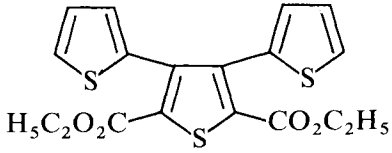
Uhlenbroek and Bijloo[32] prepared the same compound by reacting 2,2′-thenil (**166**, Scheme 33) with sulfide **167** in a Hinsberg thiophene ring-closure reaction. The resulting ester **168** was hydrolyzed and decarboxylated to **150** in an overall yield of 55%.



166



167



168

Scheme 33

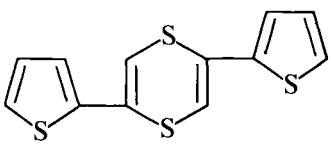
For the preparation of 2,2′ : 4′,2″-terthienyl (**151**), three alternatives are given.[114] One utilizes the thermal desulfuration of the dithiin **169** (Scheme 34; cf. **165**), which gives only a 12% yield. The second method involves the coupling

of 2-thienylmagnesium bromide with ketone **170** and subsequent dehydration and aromatization of the resulting tertiary alcohol (cf. the preparation of 2,3′-bithienyl via **128**). The third path is the dehydrogenation of tetrahydroterthienyl **171**, formed together with a thiophene pentamer on treatment of thiophene with orthophosphoric acid.[134] Its structure has been investigated by Curtis et al.,[135,136] who also dehydrogenated the *trans* form of **171** to **151** with chloranil in xylene almost quantitatively.

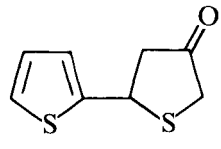
Compound **152** was first reported in a thesis by Dodson.[137] It was later prepared by Carpita and Rossi[46] from 3-thienylmagnesium bromide and 3,4-dibromothiophene in the presence of $PdCl_2$(dppf) and in a similar way by Jayasuriya and Kagan,[100] who used $NiCl_2$(dppp) [dppp = 1,3-bis(diphenylphosphino)propane] as a catalyst.

3,2′ : 5′,3″-Terthienyl (**153**) was prepared by treatment of 1,4-di(3-thienyl)-1,3-butadiyne with sodium sulfide in methanol, in analogy with one of the methods for the preparation of α-terthienyl from the 2-thienyl isomer.[127] The diketone variant has also been utilized. Moriarty et al.[138] reacted 1,4-di(3-thienyl)-1,4-butanedione with P_4S_{10}, which yielded 75% of **153**. 5,5″-Dichloro-substituted **153** was obtained by Kooreman and Wynberg[129] from the reaction of 1,4-di(2-chloro-4-thienyl)-1,4-butanedione and HCl/H_2S.

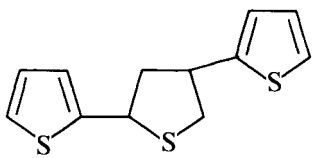
The same authors prepared a derivative of compound **154** as well, using the Hinsberg thiophene ring synthesis (cf. Scheme 33). They reacted 2,3′-thenil **172** (Scheme 34) with sulfide **167**, which gave 2′,5′-dicarboxy-5-chloro-2″,5″-dimethyl-2,3′ : 4′,3″-terthienyl in 77% yield. The unsubstituted compound **154** was obtained by Jayasuriya and Kagan,[47] who coupled 2-thienylmagnesium bromide with 4-bromo-3,3′-bithienyl in the presence of $NiCl_2$(dppp).



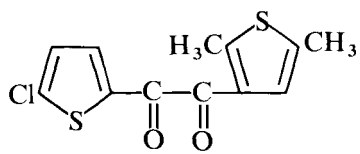
169



170



171

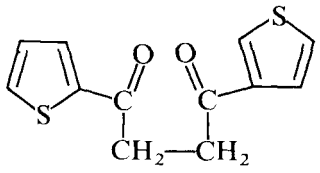


172

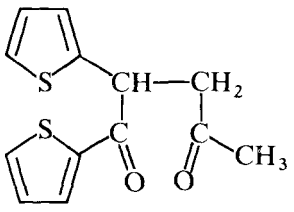
Scheme 34

2,2′ : 5′,3″-Terthienyl (**155**) has been prepared by at least three methods, two of which were developed by Kagan and coworkers.[139] One involves the treatment of 1(2-thienyl)-4-(3-thienyl)-1,3-butadiyne with sodium sulfide in methanol, which yields 87% of **155**. The second method is modeled on the

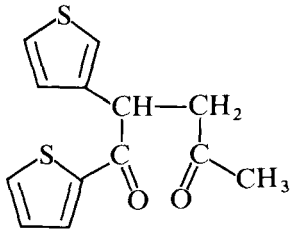
preparation of 2,3′-bithienyl by Wynberg et al.[114] Reaction of the Grignard reagent of 2-iodo-2,2′-bithienyl with 3-ketotetrahydrothiophene gave the tertiary alcohol (**128**, Scheme 25) in about 80% yield, but the subsequent aromatization gave only 18% of the desired product. The third synthetic path to **155** follows the method of Wynberg and Metselaar,[131] previously mentioned, namely, treatment of 1,4-diketone **173** (Scheme 35) with P_4S_{10} or Lawesson's reagent. The yield was 84%.



173



174



175

Scheme 35

When diketone **174** was reacted in the same way, a 1 : 1 mixture (yield 92%) of the 5′-methyl derivative of terthienyl **156** and 2,4-di(2-thienyl)-5-methylfuran was obtained, and diketone **175** gave a 7 : 3 mixture (yield 90%) of the 5′-methyl derivative of terthienyl **157** and 2-(2-thienyl)-3-(3-thienyl)-5-methylfuran. The mixtures could be separated by preparative GLC, but no physical data were given.[131]

The unsubstituted terthienyl **157** was obtained by Jayasuriya and Kagan,[100] who coupled 2-thienylmagnesium bromide with 2-bromo-3,3′-bithienyl in the presence of $NiCl_2$(dppp). With the same catalyst compound **158** was prepared from 2-thienylmagnesium bromide and 3-bromo-2,3′-bithienyl,[47] compound **159** from 3-thienylmagnesium bromide and 2,3-dibromothiophene,[100] compound **160** from 2-thienylmagnesium bromide and 4-bromo-2,3′-bithienyl,[47] compound **161** from 3-thienylmagnesium bromide and 4-bromo-2,2′-bithienyl,[47] and compound **162** from 3-thienylmagnesium bromide and 2,4-dibromothiophene.[100] The latter terthienyl has been prepared from the same reagents in the presence of $PdCl_2$(dppf)[46] as well, and with this catalyst Rossi and Carpita[46] obtained compound **156** from 2-thienylmagnesium bromide and 2,3-dibromothiophene.

2. Preparation of Polythienyls with Four or More Units

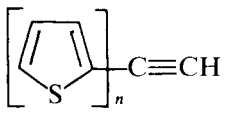
Lately, macromolecular polythienyls received growing attention, but comparatively little interest has been devoted to higher thiophene oligomers after the early work mentioned at the beginning of Section III. Although some attempts have been described, such as the preparation of α-quaterthienyl in 30% yield from 5-iodo-2,2′-bithienyl and cuprous acetate by Atkinsson et al.,[85] the main recent work in this field has been done by Kagan and coworkers[60,124,140,141] and Nakayama et al.[133,142,143] They have adapted some of the methods mentioned previously to the preparation of polythienyls.

Almost exclusively α-thiophene oligomers have been prepared. However, by coupling the 2-lithio derivative of 3,3′-bithienyl with $CuCl_2$ a low yield of a mixed α,β-terthienyl, 3,3′ : 2′,2″ : 3″,3‴-terthienyl, was obtained.[141] A better yield (84%) was achieved when the corresponding Grignard reagent (prepared from 2-bromo-3,3′-bithienyl) was coupled with 2-bromo-3,3′-bithienyl in the presence of $NiCl_2$(dppp). The structure and the conformation in the crystal of the terthienyl was obtained from X-ray data.

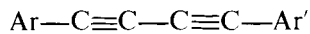
Various α-thiophene oligomers have been prepared from suitably chosen 1,3-butadiynes and sodium sulfide. Although it is beyond the scope of this chapter to treat the preparation of such compounds, some comments may be made, since they are key substances in this connection.

The synthesis starts with thiophene, 2,2′-bithienyl, α-terthienyl, or similar, which is formylated in one of the outer α-positions. The aldehyde group is converted to an ethynyl group via a Wittig reaction. This aryl-substituted acetylene **176** (Scheme 36) is coupled to a symmetric, 2,4-disubstituted 1,3-butadiyne **177** [Ar′ = Ar = 2-thienyl, 5-(2,2′-bithienyl), etc.], with Cu_2Cl_2 (Glaser coupling[144]). On treatment with sodium sulfide a polythienyl with an *odd* number of thiophene rings is obtained. As examples, α-quinquethienyl and α-septithienyl were prepared in good overall yields.[124]

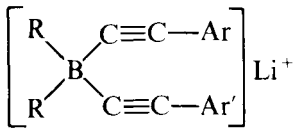
The preparation in a similar way of thiophene oligomers with an *even* number of thiophene rings implies unsymmetric diarylbutadiynes (**177**) as



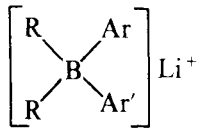
176



177



178



179

Scheme 36

precursors. These may be obtained by coupling odd-membered with even-membered arylacetylenes by Cadiot–Chodkiewitz coupling.[145] In this case, one of the acetylenic units is converted to a bromoacetylene with sodium hypobromite and then coupled to the second unit with Cu_2Cl_2.

An alternative way of coupling the two acetylenes to a butadiyne is via an organoborane intermediate (**178**), which is treated with iodine. Intermediate **178** may, for example, be prepared from 9-BBN and the lithium acetylides, which are introduced one at a time.

α-Quaterthienyl was prepared as an illustration of this synthetic path.[124]

It is stated that the generality of the preparation of thiophene oligomers via butadiynes as described above is severely limited by their solubilities, which decreases rapidly with increasing molecular weight of the oligomers.

Organoboranes of type **179** were mentioned previously in connection with the preparation of 2,2′-bithienyl and α-terthienyl and have been utilized for the preparation of higher thiophene oligomers as well.[60] Thus, α-quaterthienyl was formed in 48% yield by coupling of bithienyl with itself and in 50% yield from thiophene and α-terthienyl.

α-Quinquethienyl was prepared in 55% yield by coupling 2,2′-bithienyl with α-terthienyl and in 53% yield from thiophene and α-quaterthienyl.

Similarly, α-sexithienyl was obtained by two alternative routes: from **179**, Ar = Ar′ = α-terthienyl (45%); and from **179**, Ar = 2,2′-bithienyl, Ar′ = α-quaterthienyl (59% yield).

The organoboranes were prepared by metalation of suitable thiophene compounds with lithium diisopropylamide and stepwise reaction of the lithium derivatives with B-methoxy-9-BBN. Even-numbered oligomers, however, may be obtained directly from the lithium compounds on coupling with $CuCl_2$. In this way, 2,2-bithienyl, α-quaterthienyl, and α-sexithienyl were synthesized in 83, 85, and 73% yields from thiophene, 2,2′-bithienyl, and α-terthienyl, respectively.[140]

Nakayama et al. have expanded their method, involving the preparation of α-terthienyl via compounds **164** and **165** (Scheme 32), to the preparation of higher thiophene oligomers. Exchanging the thienyl groups in the two compounds mentioned for 2,2′-bithienyl or α-terthienyl (connected to an α-position) yields α-quinquethienyl and α-septithienyl, respectively.[142]

However, as was the case with the diarylbutadienes, obtained by the Glaser coupling mentioned above, this method is best suited for the preparation of thiophene oligomers with an odd number of thiophene rings. Therefore, a method was worked out for the preparation of even-membered polythienyls, which appears relatively simple. The 5-bromo derivative of 2,2′-bithienyl, α-terthienyl, or α-quaterthienyl, readily obtained in good yields with NBS, was coupled with a Ni(0) reagent, $Ni(PPh_3)_3$ (prepared *in situ* from $NiCl_2$, zinc powder, and triphenylphosphine) to yield α-quaterthienyl, α-sexithienyl, and α-octithienyl, respectively.[143]

The latter compound turned out to be the highest member of an α -oligothienyl ever synthesized. It is practically insoluble in all solvents, which prevents

closer examination, e.g., of its UV spectrum. In the series the visual color changes from pale yellow over chrome yellow and orange to red, on going from α-terthienyl to α-sexithienyl. The bathochromic shift on going further to α-septithienyl is only about 2 nm (from 438 nm to ~ 440 nm; the value is somewhat inaccurate because of poor solubility). α-Octithienyl is red as well, as are the de-doped polythienyls, prepared by electrochemical polymerization (see below), although they may consist of hundreds of thiophene units. Therefore, it appears that a limit of conjugation exists between thiophene rings, situated at about six or seven units.[143]

An α,β-type septithienyl was prepared from diketosulfide **164**, in which the 2-thienyl groups were exchanged for the 5-terthienyl system, derived from **150**. On reductive coupling of the carbonyl groups with $TiCl_4/Zn$ and subsequent dehydration of the resulting *cis*-dihydroxythiolane (see the preparation of **150** from **164** by Nakanishi et al.) a septithienyl was obtained in about 80% yield, in which the thiophene rings are connected with alternating α,β and β,α bonds.[133] (For the complete name, see Table 5.) Repeating this synthetic sequence with the obtained α,β-septithienyl as substitute for the thienyl groups in **164** yielded a product $C_{60}H_{32}S_{15}$, which might be a similar α,β-polythienyl with 15 thiophene units.[133]

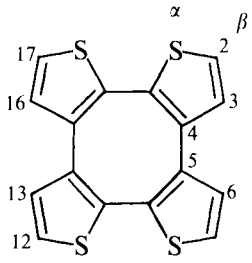
The α,β-septithienyl is a white crystalline solid, easily soluble in organic solvents, and thus quite different from the α-septithienyl isomer.

Kauffmann and coworkers[146–149] have prepared some interesting cyclic thiophene oligomers, such as cycloocta[1,2-*b* : 4,3-*b*′ : 5,6-*b*″ : 8,7-*b*‴]-tetrathiophene (**180**, Scheme 37) and cycloocta[1,2-*c* : 3,4-*c*′ : 5,6-*c*″ : 7,8-*c*‴]-tetrathiophene (**181**), called (all-α*S*)- and (all-β*S*)-cyclotetrathiophene, respectively. Compound **180** was obtained from either 2,2′-dibromo-3,3′-bithienyl (23% yield) or 3,3′-dibromo-2,2′-bithienyl (24% yield) after halogen–metal exchange and coupling of the dilithium derivative with $FeCl_3$ or $CuCl_2$. In the coupling of the 2,2′-bithienyl with $CuCl_2$ a by-product assigned as cyclohexathiophene was isolated. Similarly, **181** was prepared in about 25% yield from 4,4′-dibromo-3,3′-bithienyl.

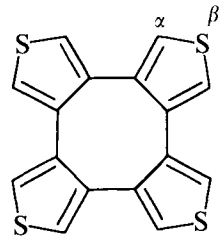
A thionaphthene analogue of **180**, cycloocta[1,2-*b* : 4,3-*b*′ : 5,6-*b*″ : 8,7-*b*‴]tetrathionaphthene was also prepared from 3,3′-bibenzo[*b*]thiophene (**139**, Scheme 27) by lithiation at the 2,2′-positions and subsequent coupling with $CuCl_2$.[147,148]

Compound **180** is easily monolithiated at the 2-position with *n*-butyllithium in THF.[149] The dimer **182** could be obtained on coupling of this lithium derivative with $CuCl_2$. By reaction of the same lithium compound with pyrimidine, quinoline, or quinoxaline, the derivatives given in Table 5 were prepared. In addition, some more complex compounds with two units of **180** coupled to the nitrogen heterocycles were isolated in about 7% yield.

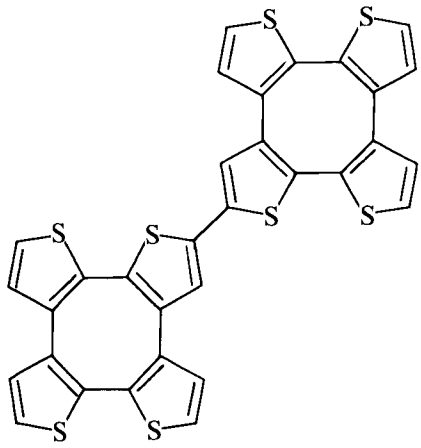
By treatment of 2,5-dichlorothiophene with $AlCl_3$–$CuCl_2$ in carbon disulfide, a 93% yield of poly-5-chloro-2,3-thienylene was obtained, and a similar polymer was formed from 2,3,5-trichlorothiophene.[117] Yamamoto et al. have developed a general method for the preparation of polymers by the dehalogenation method



180



181



182

Scheme 37

with Ni or Pd complexes as catalysts. (See Ref. 150 and references therein). Thus a 78% yield of poly-2,5-thienylene was obtained from a mixture of 2,5-dibromothiophene, zinc powder, and $NiCl_2$(dpe) in hexamethyl phosphonic triamide at 150°C.[150]

Such polymers are electrically conducting, and during the last decade it has been an increasing interest in this field. A considerable amount of papers dealing with conducting polymers have appeared during the 1980s, and a great many of these treat polythienyls or other macromolecules containing thiophenes. Some references are given below, and further references may be found therein.

Of the methods of preparation, which have been worked out, may be mentioned, in addition to the dehalogenating method,[150] the coupling of dilithiated monomers with $CuCl_2$,[151–153] coupling of Grignard reagents with $NiCl_2$(dppp),[154–158] and electrochemical polymerization.[156,159–168]

Some of the references given do not deal with pure polythienyls, but with copolymers of 3-methylthiophene and methyl methacrylate,[158] and with mixed polyaryls containing thiophene and selenophene rings.[157] Other related poly-

mers are poly(2,5-thienylene vinylenes)[169-172] or consist of alternating phenyl and thienyl units.[173]

The electrically conducting polymers are used, for example, in the fabrication of molecular electronic devices and as chemically modified electrodes, for example, in $Li|LiI|I_2$ and $Zn|ZnI_2|I_2$ galvanic cells[174] and for the ferri/ferrocyanide couple.[153] Recently chiral conducting polymers have been prepared electrochemically from (*S*)-(+)-3-(2-methylbutyl)thiophene[156] and from the ether obtained on reacting (*S*)-(+)- or (*R*)-(−)-2-phenylbutanol with 3-(3-thienyl)propyltosylate.[168] The latter polymer could stereoselectively recognize chiral anions used as doping agents.

Other modified types of polymers have been investigated as well. Lemaire et al.[165] studied the effect of branching by polymerizing various 3-alkylthiophenes. From other types of 3-substituted thiophenes conducting polymers have been obtained, which are soluble in organic solvents[153, 163, 164] and even in water.[162]

The conducting polymers are doped with various agents, such as iodine, AsF_5, and KPF_6 to increase the conductivity. The affinity of polythienyl toward electron acceptors (iodine and SO_3) was investigated by Yamamoto et al.[175] Cao et al.[159] have studied the reoxidation to the metallic state of neutral electrochemically prepared polythienyl film, obtained by NH_4OH compensation.

Guenther et al.[176] found that the conductivity of I_2-doped poly(2,5-thienylene) was higher than that of the similarly doped poly(2,5-selenienylene) by a factor of 10^3.

When prepared electrochemically the polymer is obtained as a film on the anode surface, which may be of various kind, for example, a platinum disk for electrochemical characterization or a transparent indium–tin oxide electrode for spectroscopic investigations.

The conducting polymers have been investigated by various physical methods including IR, FTIR, and Raman spectroscopy,[152, 154, 159, 177-184] UV spectroscopy,[152, 155, 185] ESR spectroscopy,[154, 184, 186-190] Carbon-13 NMR investigations,[152, 191] X-ray scattering,[192] and X-ray photoelectron spectroscopy (XPS) technique.[193, 194]

IV. REACTIONS OF BI- AND POLYTHIENYLS

The reactions of bi- and polythienyls closely resemble those of simple thiophenes. This means, among other things, that the α-positions are more reactive than the β-positions, which should lead to substitution preferably at the 5- and 5′-positions of 2,2′-bithienyl. In 3,3′-bithienyl there are two "inner" (2,2′-) and two "outer" (5,5′-) α-positions, and 2,3′-bithienyl has three different reactive α sites.

However, in bithienyls one thiophene ring may be considered as a substituent on the other ring, with an accompanying directing effect, which at least partly

determines the composition of the substitution products. This effect is obvious, such as in the bromination of 3,3′-bithienyl, but it is perhaps most pronounced in the nitration reactions.

The activating effect of a thienyl group as substituent is demonstrated under Section IV.1.B.

Only a few investigations of the reactions of higher thiophene oligomers have been performed. In α-terthienyl, α-quaterthienyl, etc. the substitution first takes place at the 5-position.

Some reactions of 3,3′-bithienyls are also discussed in Section VI.

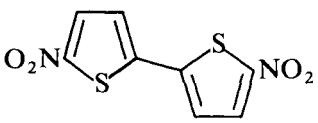
1. Electrophilic Substitution

A. Nitration

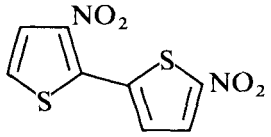
a. 2,2′-Bithienyl

Steinkopf et al. prepared two nitro derivatives of 2,2′-bithienyl, namely, 5-nitro-2,2′-bithienyl[198] and its 3,3′,5′-triiodo derivative.[199]

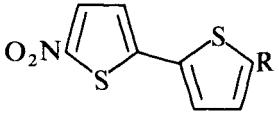
Later, the nitration of bithienyls was investigated by Russian and Italian researchers. Lipkin[10] found that nitration of 2,2′-bithienyl with copper nitrate in acetic anhydride (yielding diacetylorthonitric acid) gave a mixture of 5,5′-dinitro-2,2′-bithienyl (**183**, Scheme 38) (25% yield) and 3,5′-dinitro-2,2′-bithienyl (**184**) (41% yield). The structure of the latter dinitro compound was assumed from the fact that it could be oxidized to 3-nitro-2-thiophenecarboxylic acid.



183

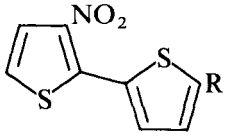


184

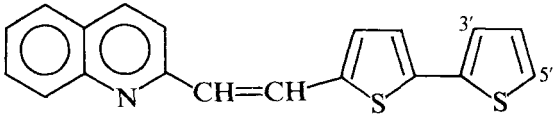


R = $COCH_3$, CHO, CH_3

185



186



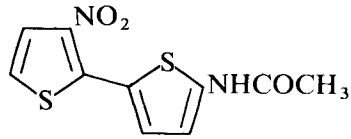
187

Scheme 38

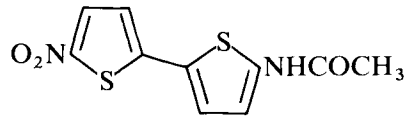
In a similar way, 5-acetyl-2,2′-bithienyl[200] and 5-formyl-2,2′-bithienyl[201] were nitrated. In both cases, a mixture of 5′-nitrated (**185**) and 3′-nitrated (**186**) products was obtained. In the former case, the 3′-substituted product dominated ($3'\text{-}NO_2/5'\text{-}NO_2 = 2.0$). In the formyl case, the situation was reversed ($3'\text{-}NO_2/5'\text{-}NO_2 = 0.63$).

Nitration of 5-[2-(2-quinolyl)vinyl]-2,2′-bithienyl (**187**) with nitric acid in acetic anhydride also gave 3′- as well as 5′-nitrated products ($3'\text{-}NO_2/5'\text{-}NO_2 = 0.4$),[202] and so did the nitration of 5-methyl-2,2′-bithienyl (**185**, **186**; $3'\text{-}NO_2/5'\text{-}NO_2 = 0.4$).[203]

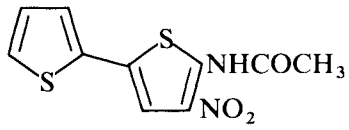
5-Acetamido-2,2′-bithienyl gave a three-component mixture of 5-acetamido-3′-nitro-2,2′-bithienyl (**188**, Scheme 39), 5-acetamido-5′-nitro-2,2′-bithienyl (**189**), and 5-acetamido-4-nitro-2,2′-bithienyl (**190**) in the proportions 1 : 2 : 2 at 0°C and 1 : 1 : 1 at −20°C.



188



189



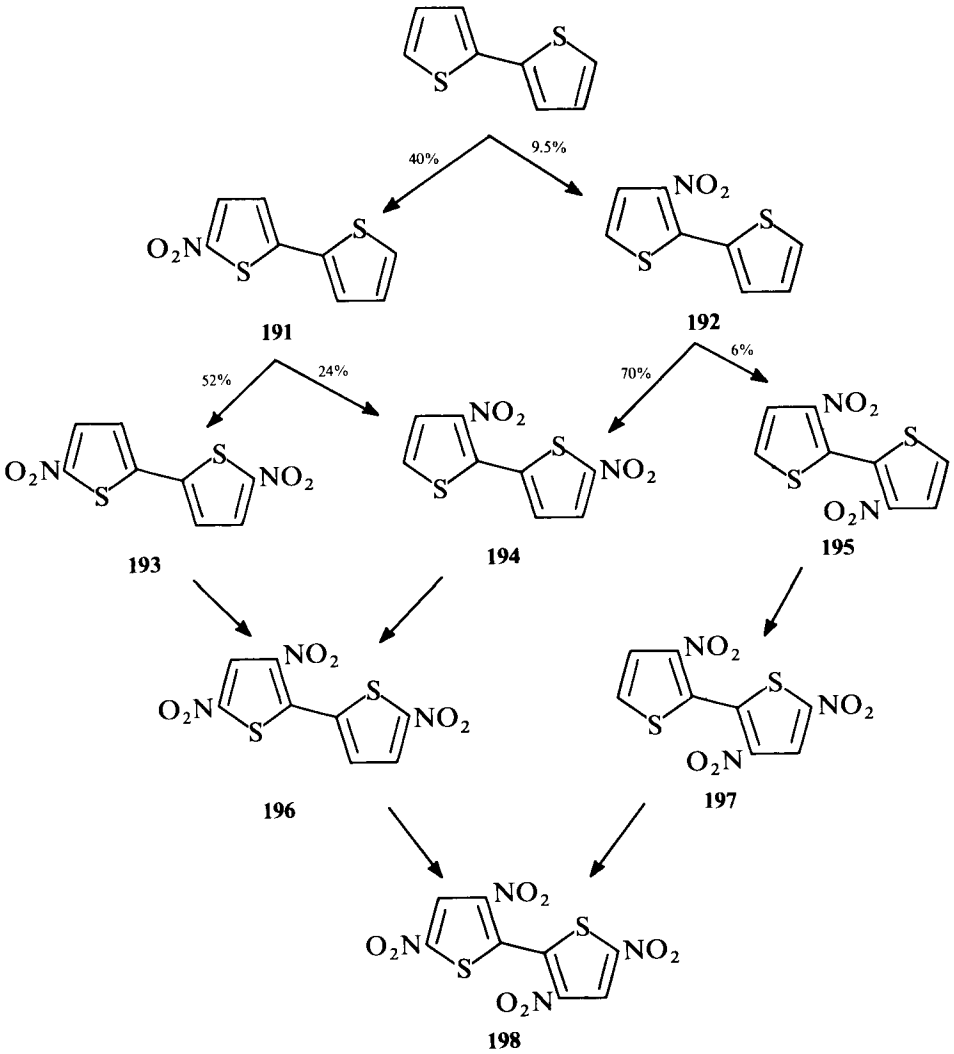
190

Scheme 39

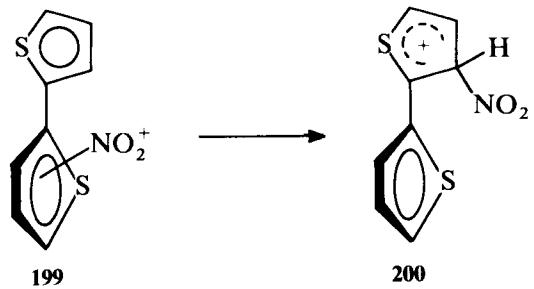
The above results indicate an ortho-directing effect of the thienyl ring. This may also be concluded from the work of Carpanelli and Leandri,[33] who made successive mononitrations of 2,2′-bithienyl, the outcome of which is summarized in Scheme 40. The percentages given are isolated yields. Dell'Erba et al.[204] investigated the temperature dependence of the mononitration of 2,2′-bithienyl with nitric acid in acetic acid and in acetic anhydride. In acetic acid, a 5/3 ratio of 3.25 at 10°C and 3.07 at 20°C was found, whereas in acetic anhydride the 5/3 ratio decreased from 1.46 at 20°C to 0.89 at −40°C. The greater amount of 3-nitration with nitric acid in acetic anhydride was explained in terms of an alternative mode of nitration, involving a π-complex between the nitronium ion and the π-electrons of the thiophene ring. Subsequent rearrangement of the nitronium ion to the second ring would, because of the noncoplanarity of the system, result in substitution at the nearby 3-position (**199**, **200**, Scheme 41). 2,2′-Bithienyls are listed in Table 6.

b. 3,3′-Bithienyl

The mononitration of 3,3′-bithienyl with fuming nitric acid in acetic anhydride yields 2-nitro-3,3′-bithienyl (**201**, Scheme 42) almost quantitatively.[92] Further



Scheme 40



Scheme 41

TABLE 6. 2,2′-Bithienyls[a]

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
3-Acetamido	—	—	—
–, 3′-nitro	170	34	240
5-Acetamido	152–153	70	203
–, 4-nitro	198–199	19	203
–, 3′-nitro	215–216	10	203
–, 5′-nitro	247–248	20	203
3,5′-Diacetamido	219–220	43	10
5,5′-Diacetamido	Infusible	70	10
5-Acetic acid; 5-(—CH_2—COOH)	117–118	—	209
–, amid	181.2–182	63.5	209
–, thiomorpholide	200	75.7	209
–, amino derivative; 5-[—CH(NH_2)–COOH]	229, dec.	28	209
3-Acetyl	—	—	—
–, 5,5′-dimethyl	49	—	23
3,3′-Diacetyl	93	—	241
–, 5,5′-dimethyl	109–111	—	207
	111	—	23
5-Acetyl	114–115	—	200
	114.5–115.5	—	207
	113–114	—	209
	108–111	—	218
–, 3′-amino, hydrochloride, tin salt	—	—	200
–, 5′-amino, hydrochloride, tin salt	—	—	200
–, 5′-bromo	170–172	—	218
	174–175	90	221
	170–172	—	218
–, 5′-[2-(6-chloropyridyl)]	169–170	62	213
–, 5′-ethyl	106–107	65	211
–, 3,3′-diiodo	152–159	95	212
–, 5′-[2-(4-methoxycarbonylquinolyl)]	210	50	242, 243
–, 3′-nitro	139–140	53	200
–, 5′-nitro	190–191	27	200
–, oxime	204–205	—	209
–, 5′-(2-pyridyl)	178–179	60	213
5,5′-Diacetyl	231–232	—	207
	233.5–234	—	25
5-(β-Acrylic acid); 5(—CH=CH—COOH)	177		23
	171	73	209
–, ethyl ester	66; 240/16	—	23
–, bromo derivative; 5-(—CH=CBr—COOH)	> 250	82	209
3-Amino	150–152/0.5	92	115
–, 3′-nitro	90	13	240
–, –, hydrochloride	170, dec.	—	240
–, N-phenyl	84–86	90	244
3,5′-Diamino, HCl, tin salt	153–155, dec.	61	10
5,5′-Diamino, HCl, tin salt	252, dec.	70	10
3-Azido	110–112	72	115
3-(2-Benzimidazolyl)	—	—	—
–, 5,5′-dimethyl	220–222	22	245

TABLE 6. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
5-(2-Benzimidazolyl)	245–246	62	245
5-(2-Benzothiazolyl)	167–170	—	245
–, 5′-formyl	207–209	32	245
–, 5′-methyl	136–137	—	245
3-(2-Benzoxazolyl)	125–126	—	245
–, 5′-methyl	136	—	245
3-Benzoyl	Oil	22	231
–, tosylhydrazon	106–108	68	231
5-Benzoyl	– –	—	—
–, 5′-(2-pyridyl)	177–179	68	213
–, 5′-[2-(6-chloropyridyl)]	204–206	62	213
5,5′-Dibenzoyl	250–252	—	71
–, 3,3′-dibromo	195–197	—	71
5,5′-Dibenzoyl	250–252	—	71
–, 3,3′-dibromo	195–197	—	71
3-Bromo	154–161/10	51	226
–,4,4′,5,5′-tetramethyl			
–, –, tricarbonylchrom complex	133	5	233
3,3′-Dibromo			
–, 4,4′,5,5′-tetramethyl			
–, –, tricarbonylchrom complex	133	4	233
5-Bromo	30–33; 50/0.006	—	219
	30–33		219
	28.5–30	61	143
	—	—	229
–, tricarbonylchrom complex	80, dec.	2	233
–, 5′-(2-bromoacetyl)	128–129	—	218
–, 5′-carboxy	261–262	—	219
–, –, methyl ester	125–126	—	219
–, 5′-ethenyl	—	80	63
–, 5′-hydroxymethyl	—	91	63
–, 5′-phenylethynyl	114.5–115.5	2.5	220
–, 5′-(CO—CH_2NHCO—$CHCl_2$)	188–190	—	218
–, 5′-[CO—CH(CH_2OH)NHCO—$CHCl_2$]	168–169	—	218
–, 5′-[CH(OH)—CH(CH_2OH)NHCO—$CHCl_2$]	113–114	—	218
5,5′-Dibromo	149–151	96	216
	145–146	—	143
	146.0–146.5	—	5
3,3′,4,4′-Tetrabromo	—	—	—
–, 5,5′-diglycolic acid	—	—	—
–, –, diethyl ester	176–178	70	232
–, 5,5′-diglyoxalic acid	180, dec.	—	232
–, –, diethyl ester	199–200	33	232
–, –, dipropyl ester	156–158	28	232
–, –, diisopropyl ester	179–180	30	232
Hexabromo	257–258	75	232
	257	—	4
5-(2,2′-Dibromoethynyl)	112–112.5	82	246

TABLE 6. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
3,3′-Bis(bromomethyl)	87.5–88	45	15
	85	66	241
5-(1,3-Butadienyl)			
–, ^{3}H-labeled	—	—	26
–, 5′-methyl	—	—	26
	46–47	—	247
	—	61	63
–, –, maleic anhydride adduct	135	—	247
5-Butanoyl	76–77	76	248
5-(3-Buten-1-ynyl)	Oil	35	220
	Oil	93	45
	82–92/0.04	—	85
	Oil	—	249
	Oil	30	246
	Oil	—	36
–, ^{3}H-labeled	—	—	26
–, 5′-hydroxymethyl	95–96	—	85
–, 5′-methoxycarbonyl	111	—	85
–, 5′-methyl	—	—	26
	61.5	—	85
5-*n*-Butyl	109–113/1.5	65.6	248
–, 5′-[(5-methoxycarbonyl-1-oxo)pentyl]	68–69	48	248
–, 5′-(5-carboxypentyl)	60–61	76.6	248
–, tricarbonylchrom complex	115	50	233
3-Carboxy	168–169	62	226
	167–167.5	80–92	250
–, ethyl ester	—	48	46
–, 5,5′-dimethyl	151	—	23
3,3′-Dicarboxy	289–281, dec.	70	11
	278–281	—	226
	276–278	80	250
–, dimethyl ester	150–151	—	11
–, 5,5′-dimethyl	296–298	—	23
5-Carboxy	179–180	—	220
	183–184	74	195
	176–177.5	Quantitative	209
–, ethyl ester	96–97/16	55	46
–, –, 3,3′-diiodo	185–187	90	212
–, methyl ester	74–75	89	195
	71.5–72	—	209
–, 5′-chloro	270–271	—	219
–, –, methyl ester	95	—	219
–, 5′-iodo	256–258	—	219
–, –, ethyl ester	74–75.5	96	46
–, –, methyl ester	161–162	—	219
–, 5′-[2-(4-methoxycarbonylquinolyl)]	250, dec.	—	242
			243
–, –, methyl ester	143–145	30	242

TABLE 6. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
–, 3′-nitro	278–280	—	201, 203
	280	81	251
–, –, ethyl ester	80–82	—	201
	82	96	251
–, 5′-nitro	286–288	—	203
			201
	288	72	251
–, –, ethyl ester	158–160	—	201
	160	95	251
–, 5′-(1-propynyl)	225–227	96	46
–, –, ethyl ester	88.5–90.5	93	46
5,5′-Dicarboxy	371–375	48	195
	> 350	72	12
–, dimethyl ester	211–212	—	195
	208–210	85	12
–, –, 3-iodo	127.5–129	65	12
5-(2-Carboxyethyl)	105–106	Quantitative	209
	97–98	56	237
–, *N*,*N*-dimethylamide	—	53	237
5-[(3-Carboxy-1-oxo)propyl	175–177	—	252
5-[2-(4-Carboxyquinolyl)]			207
–, ethyl ester	96–97	96	243
–, methyl ester	96	97	243
–, 5′-[2-(4-methoxycarbonylquinolyl)]	297–305	73.5	243
–, –, methyl ester	369–271	10	243
–, 3′-nitro	249	18.8	243
–, –, ethyl ester	159–160	75	243
–, 5′-nitro	278	16.3	243
–, –, ethyl ester	187	80	243
–, 5′-formyl	302–304	50	253[b]
	302	50	243
–, –, methyl ester	187–188	92	243
5-Chloro	55/0.05	—	219
	—	24	229
5-(4-Chloro-3-hydroxybut-1-ynyl)	48.5–49	7	254
5,5′-Dichloro	109	69	32
5-(1,1-Dichloroethyl)	50–53	—	249
5-Chloromercury	235	46	220
5-Dichloromethyl	97–98	—	249
	—	—	255
3,3′-Bis(chloromethyl)	57–58	74	241
5-[2-(6-Chloropyridyl)]	121	44	213
5-(*E*)-(1,2-Dichlorovinyl)	98	—	255
3,3′,5-Trichloro	56–57	—	29
5-Cyano	76–77	—	85
–, 5′-(2-quinolyl)	Oil	20	245
3,3′-Bis(cyanomethyl)	125.5	72	15
5-(3-Cyanopropanoyl)	158.5–159	75.7	209
2,2′-Dideuterio	—	—	256

TABLE 6. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
5,5′-Dideuterio	—	67	216
	—	—	229
5-Ethenyl	—	—	—
–, 5′-(1-propynyl)	—	85	63
5-[2-(4-Ethoxycarbonyl-2-quinolyl)vinyl]	131	52	202
–, 5′-formyl	172	62	202
–, 5′-methyl	94–96	82	202
5-Ethyl	95–99/0.5	80	211
–, 5′-(2-quinolyl)	69–70	—	245
5,5′-Diethyl	140–143/0.5	68	211
5-(3-Diethylaminopropyl)	—	90	237
5-(3-Ethylthiopropyl)	—	92	237
5-Ethynyl	Oil	65	45
	—	91	235
	Oil	—	249
	Oil	100	246
–, 5′-(1-propynyl)	Oil	—	63
5-Fluoro	—	15	229
3-Formyl	120/0.7	35	257
–, tosylhydrazon	152–156	95	257
–, azine	202–204	16	257
–, 5,5′-dimethyl	65	—	23
3,3′-Diformyl	155–157	50	226
	160.5–162	—	258
	154	—	241
5-Formyl	59; 210/18	—	23
	58–59	—	214
	56	98	32
	61	73	209
	54.5–55.5	85	246
–, thiosemicarbazon	197	—	23
–, 4-oxo-2-thiazolin-2-yl-hydrazon	269	—	23
–, 5′-(4-hydroxybut-1-ynyl)	—	76	63
–, 5′-iodo	186	—	214
–, 5′-methyl	98; 208/18	—	23
	98–99	—	247
–, 5′-(1-propynyl)	93–95	83	63
–, 5′-(2-quinolyl)[b]	152–153	60	253
–, 3′-nitro[b]	154	85	251
–, 5′-nitro[b]	193	98	251
5-(2-Formylethyl)	—	37	237
–, ethylene acetale	61–61.5	40	237
5-(2-Formylethynyl)	—	74	235
5-(3-Formylprop-1-ynyl)	65–66	—	85
5,5′-Diformyl	217–218	—	214
5-Furyl	83–85	87	125
5-Hydantoin	246–247	97.2	209
5-(3-Hydroxybut-1-ynyl)	58–59	—	254
cis-5-(4-Hydroxybut-1-enyl)	57–58	—	249

TABLE 6. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
trans-5-(4-Hydroxybut-1-enyl)	80	—	249
5-(4-Hydroxybut-1-ynyl)	71–72	—	45
	67–68	—	85
	66	—	249
–, tosylate	Oil	—	249
–, 5′-hydroxymethyl	Oil	97	63
–, –, diisovalerate	Oil	71	63
5-Hydroxymethyl	52–52.5	52.5	209
–, phenylurethan	119	—	209
–, 5′-(1-propynyl)	87–88	95	63
3,3′-Bis(hydroxymethyl)	168	96	241
5-(3-Hydroxypropyl)	45–46.5	80	237
–, tosylate	75–76.5	90	237
5-(3-Hydroxyprop-1-ynyl)	130–140/0.2	—	254
	63	—	85
3-(2-Indolyl)	—	—	—
–, 5,5′-dimethyl	180/0.1	—	245
5-(2-Indolyl)	207–209	28	245
–, 5′-methyl	145	—	245
5-Iodo	32; 95–97/0.12	80	220
	75/0.007, 150/3.5	—	219
	32; 108–109/0.03	85	45
	—	—	229
5,5′-Diiodo	167–168	93	220
	164	—	219
Iron carbonyl derivative	133–134	—	259
5-Lithio	—	—	229
5-(4-Methoxycarbonyl-2-quinolyl)	96	97	242
5-[3-(*N*,*N*-Dimethylamino)propanoyl]			
–, hydroklorid	213–215	67.5	209
–, 5′-(4-methoxycarbonyl-2-quinolyl)	187–188	92	242
–, 3′-nitro	152–154	—	201
	156	—	202
–, –, diacetate	124–126	—	201
–, –, semikarbazone	235–236	—	201
–, 5′-nitro	193	—	201
	196	—	202
–, –, diacetate	150–152	—	201
–, –, semikarbazone	318–320	—	201
–, 5′-(2-thienylmethyl)	109; 265–268/17	—	23
–, 5′-(2-quinolyl)	—	—	245
–, 5′-[2-(2-quinolyl)vinyl]	180	61	202
5-Methyl	147/15	—	23
	142/14	—	203
	50/0.006	83	214
	139–140/14	75	32
	—	—	229
–, 5′-[2-(4-hydrazinocarbonyl-2-quinolyl)vinyl]	206–208	42	202
–, 5′-[2-(6-methylquinolyl)]	161	—	245

TABLE 6. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
–, 3′-nitro	214–216/10	14	203
–, 5′-nitro	137–138	34	203
–, 5′-styryl	125–126	—	23
–, 5′-(2-thienylmethyl)	42	—	23
–, 5′-(2-quinolyl)	128–130	—	245
–, 5′-[2-(2-quinolyl)vinyl]	118–119	43	202
–, 5′-[CH=C(CN)-(4-Cl—C_6H_5)]	189	—	23
5,5′-Dimethyl	68	—	23
–, tricarbonylchrom complex	119, dec.	60	233
–, 3-[CH=CH–CO–2-(5-Cl–C_4H_2S)]	136	—	23
4,4′,5,5′-Tetramethyl			
–, tricarbonylchrom complex	115, dec.	95	233
Hexamethyl	163–165	77	233
–, tricarbonylchrom complex	130	95	233
3,3′-Bis(1,1-dimethylhydroxymethyl)	90	67	241
5-(5-Methyl-2-thenoyl)	103; 289–290/18	—	23
5-(5-Methyl-2-thienylmethyl)	44; 243–245/15		23
3-Nitro	38–39	—	203
	38–39; 153–155/3	9.5	33
	39	—	251
–, 3′-diazonium fluoborate	170–172	76	240
–, 3′(5″-nitro-2″-thenylidenamino)	162–163	30	240
–, 5′-[2-(2-quinolyl)vinyl]	180	48	202
5-Nitro	109	—	198
	108–109	—	203
	105–107	40	33
	109	52	251
–, 5′-(2-quinolyl)	219	88	245
–, 5′-[2-(2-quinolyl)vinyl]	218	82	202
3,3′-Dinitro	185–186	6	33
3,5′-Dinitro	130–131	41	10
	132–133	70	33
5,5′-Dinitro	251–252	25	10
	260	52	33
3,5,3′-Trinitro	157–158	—	33
3,5,5′-Trinitro	160–161	85	33
3,3′,5,5′-Tetranitro	193–194	85	33
5-Octanoyl	82.5–83	79	211
–, 5′-*n*-octyl	95.5–96	57.5	211
5-*n*-Octyl	28.0–29.0	78	211
5,5′-Di-*n*-octyl	42.0–42.5	74.5	211
5-(3-Oxobut-1-ynyl)	77–79	—	85
5-(3-Ar-3-oxoprop-1-enyl)			
Ar = 4-biphenylyl	166–168	41.1	260
Ar = 2-thienyl	105–108	27.2	260
Ar = 2-naphthyl	109–110	34.1	260
Ar = 2-(5-phenyl)thienyl	161–163	26.6	260
Ar = 2-[5-(2-napthyl)]thienyl	88–92	25.3	260
5-[2-(4-Oxo-1,3-thiazolidinyl)]	—	—	—

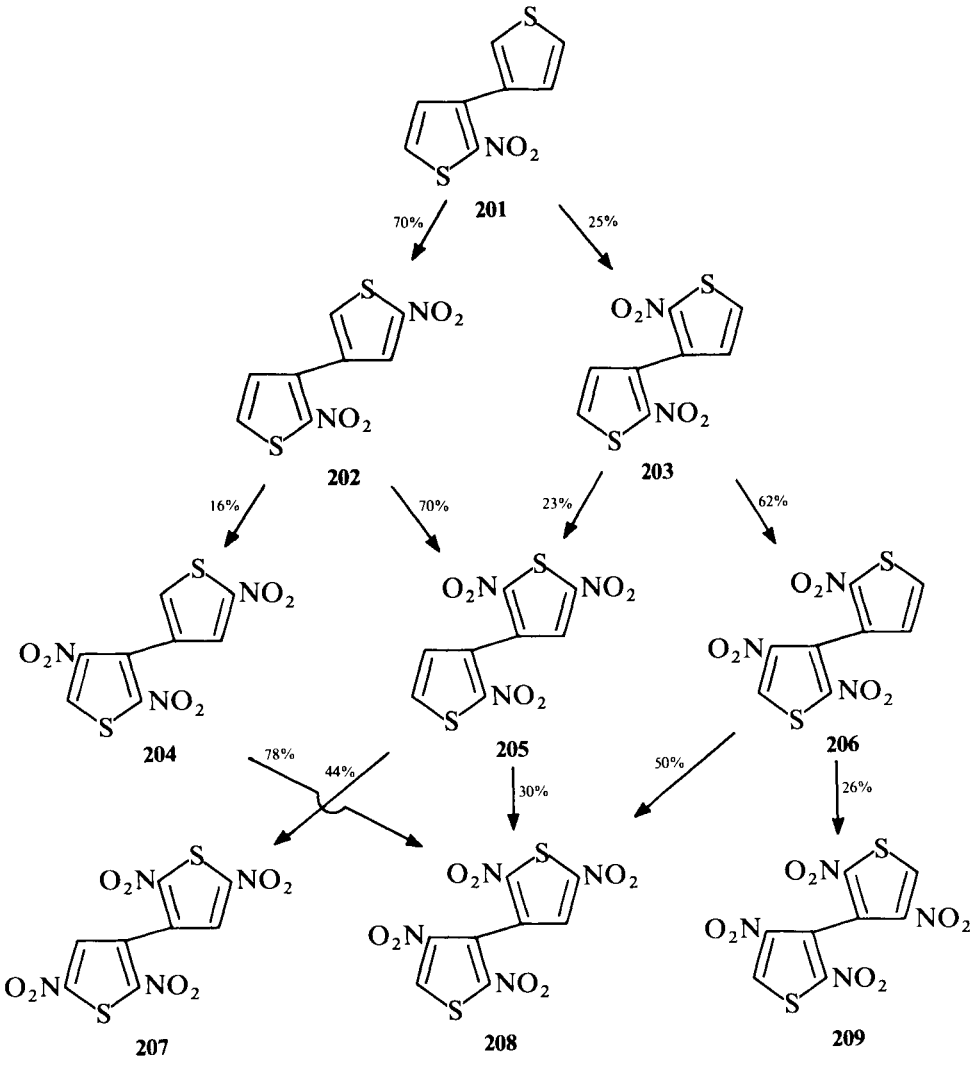
TABLE 6. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
–, *N*-phenyl	179	60	261
–, *N*-(4-methylphenyl)	158	75	261
–, *N*-(4-hydroxyphenyl)	246	70	261
–, *N*-(4-carboxyphenyl)	257	68	261
5-(4-Penten-1-ynyl)	Oil	—	246
3-Phenyldiazomethane (—C(Ph)=N_2)	25	85	231
5-Phenylethynyl	89–90	51	220
	90–91	—	45
5-Propanoyl	90	—	32
	87–90	—	252
5, 5′-Dipropanoyl	180	—	32
	117–180	—	252
5-(Prop-1-ynyl)	49	—	85
5-(2-Pyridyl)	118–120	49	213
5-(2-Quinolyl)	142	—	253
–, 5′-formyl	152–153	60	253
5-[2-(R-quinolyl)]			
R = 3-bromo	149–150	—	245
R = 6-bromo	140	—	245
R = 6-chloro	136	—	245
R = 6-methoxy	177	—	245
R = 4-methyl	145–148	—	245
R = 6-methyl	173	—	245
R = 7-methyl	112–114	—	245
R = 8-methyl	115	—	245
5-Styryl	115; 220–240/0.3	—	23
5-(2-Thenoyl)	104; 265–270/18	—	23
5-(2-Thienylmethyl)	46; 225–228/15	—	23
5-CH=CH—CO—2-(5-Cl—C_4H_2S)	120	—	23
5-CH=C(CN)—C_6H_5	147	—	23
5-CH=C(CN)—(4-Cl—C_6H_4)	204	—	23
5-CH=C(CN)—(3,4-Cl_2—C_6H_3)	223	—	23
5-CO—CH_2—$CH(CH_3)$—CH_2—$COOCH_3$	99–99.5	—	210
5-CH_2—CH_2—$CH(CH_3)$—CH_2—$COOCH_3$	163–164/0.18	—	210
–, 5′-CH_2—$CH(CH_3)$—$(CH_2)_6$—CH_3	Liquid	—	210
5-CH(S—CH_2—$COOH)_2$	130	95	261
–, 5′-Nitro	170	50	261

[a] See also Table 1,

[b] Several derivatives of the imine type are presented as well.

nitration results in a mixture of 2,5′- and 2,2′-dinitro-3,3′-bithienyl (**202**, **203**), and continued reaction results in substitution at β-positions. In Scheme 42 the investigation of Dell'Erba et al.[92] on the successive nitration of 3,3′-bithienyl is summarized, and again the percentages given are isolated yields. Nitration of 4,4′-dicarboxy-3,3′-bithienyl gave 4,4′-dicarboxy-5,5′-dinitro-3,3′-bithienyl in 63% yield.[103]

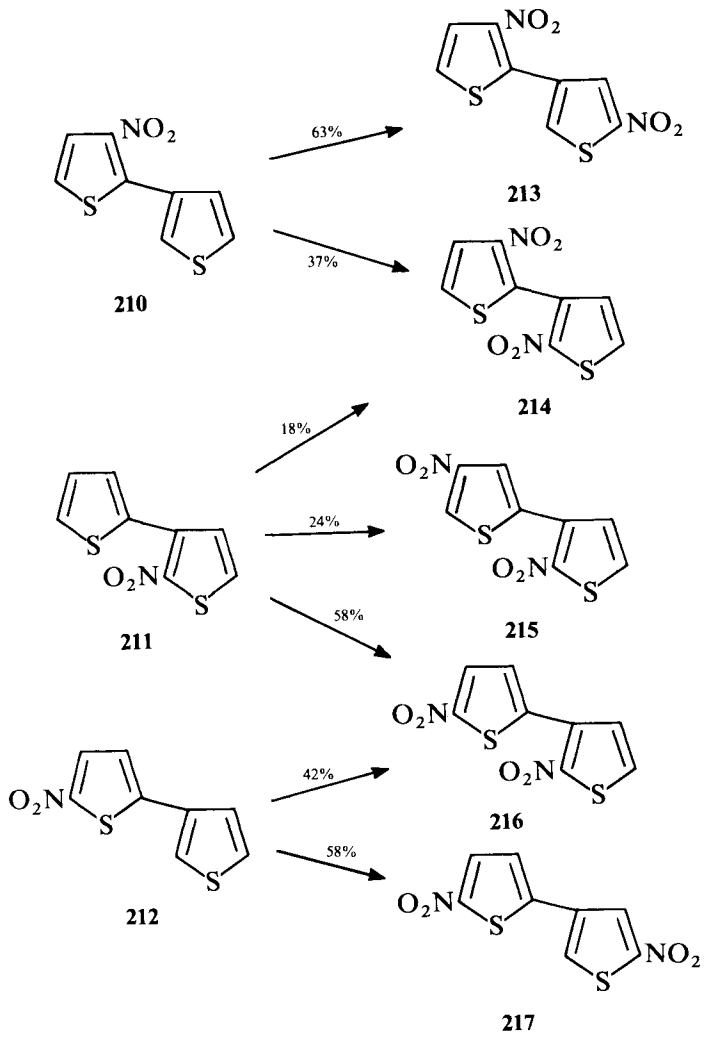


Scheme 42

c. 2,3′-Bithienyl

Dell'Erba et al.[116] also investigated the nitration of 2,3′-bithienyl, which is illustrated in Scheme 43. This time the percentages given are relative, as determined by VPC analysis. Mononitration of 2,3′-bithienyl with fuming nitric acid in acetic anhydride yielded a mixture of **210**, **211**, and **212** in relative percentages 38.7, 34.8, and 26.5, respectively. With fuming nitric acid in acetic acid the figures were somewhat different: 20.4, 26.5, and 43.1, respectively.

Further nitration of the 3-NO_2 substituted compound **210** gave **213** and **214**, and corresponding α-positions were attacked to about the same extent on



Scheme 43

nitration of **212**, yielding **216** and **217**. Compound **211** was nitrated mainly to **216**, but considerable amounts of **214** and **215** were formed as well. Of these the formation of **215** in 24% relative yield is particularly noteworthy. Here, the nitro group is introduced not only at the β-position of the thiophene ring but also in a *meta*-position with respect to the pivot bond. Such behavior is not known from the nitration of 2,2'- or 3,3'-bithienyl, nor in any other electrophilic substitution reaction of bithienyls.

d. Polythienyls

Kauffmann et al.[197] investigated the bromination, acylation, and nitration of (all-αS)cyclotetrathiophene (**180**). Nitration with nitric acid in acetic anhydride

gave low yields of 2-nitro (4%) and 2,7,12-trinitro (8%) derivatives, together with two dinitro compounds of unknown structure (3.9 and 7.1%).

B. Acylation

Competition reactions with thiophene, 2,2′- and 3,3′-bithienyl, α-terthienyl, and α-quaterthienyl involved have been carried out.[205] Various combinations were treated with $CH_3COCl/SnCl_4$ 1 : 1 in benzene at 22°C. When a mixture of thiophene and 2,2′-bithienyl was acylated, 1% of 2-acetylthiophene and 53% of 5-acetyl-2,2′-bithienyl was obtained, indicating an activating effect of the other thiophene ring. The mode of coupling appeared to be of minor importance, since 2,2′- and 3,3′-bithienyl were acylated to an equal degree in a subsequent experiment, and so were combinations of bi- and polythienyls.

The much stronger activating effect of a thienyl group compared to a phenyl group was pointed out in connection with detritiation experiments.[206]

a. 2,2′-Bithienyl

Steinkopf and Petersdorff[207] acetylated 2,2′-bithienyl with acetyl chloride and $TiCl_4$ in benzene and obtained a mixture of 5-acetyl-2,2′-bithienyl and 5,5′-diacetyl-2,2′-bithienyl.[1] 5,5′-Dibenzoyl-2,2′-bithienyl was prepared in a similar way.[1,71] When the 5,5′-positions are blocked, as in 5,5′-dimethyl-2,2′-bithienyl, the acetylation takes place at the 3- and 3′-positions.[207,208]

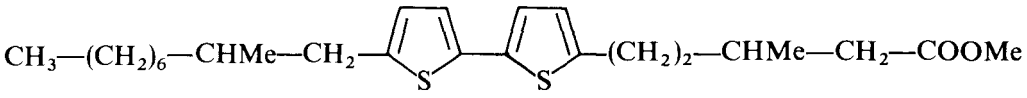
5-Acetyl-2,2′-bithienyl was synthesized in 79% yield by Matsuki and Miyake with $SnCl_4$ as a catalyst.[209] Wynberg and Logothetis[25] used 85% phosphoric acid in an excess of acetic anhydride for the preparation of 5,5′-diacetyl-2,2′-bithienyl in 83% yield.

Analogous methods were chosen by Uhlenbroek and Bijloo[32] for the propionylation of 2,2′-bithienyl : propionyl chloride and $TiCl_4$ gave 5-propionyl-2,2′-bithienyl, and propionic anhydride with phosphoric acid gave 5,5′-dipropionyl-2,2′-bithienyl.

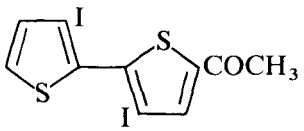
Thiophene and 2,2′-bithienyl have been used as chain extenders.[25,210,211] In this connection, 2,2′-bithienyl is acylated stepwise at the 5- and 5′-positions in a suitable way and the carbonyl functions are reduced to methylene groups after each step, whereupon the bithienyl is desulfurated with Raney nickel. For example, methyl 3,15-dimethyldocosanate was prepared in this way from **218** (Scheme 44).[210] The side chains were introduced by acylation, first with the acid chloride obtained from the methyl half-ester of β-methylglutaric acid, and second with the acid chloride of 2-methylnonanoic acid with $SnCl_4$ as catalyst.

Rather unexpected difficulties appeared on acylation of some substituted bithienyls. Diacetylation of 3,3′-diiodo-2,2′-bithienyl with acetyl chloride and $SnCl_4$ could not be achieved (except for traces), and although a 95% yield of 5-acetyl-3,3′-diiodo-2,2′-bithienyl (**219**) was obtained after 15 h of refluxing, the reaction was described as sluggish by Gronowitz and Karlsson.[212]

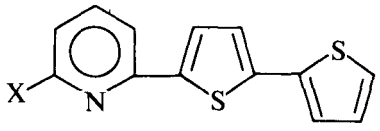
Kauffmann and coworkers[213] found that acylation of **220** (X = H) with 1 eq of acetyl chloride or benzoyl chloride failed, whereas 35 and 24% yields of



218

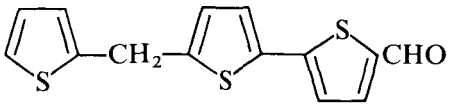


219

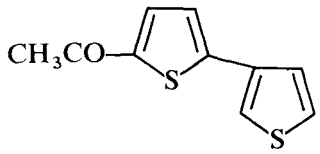


X = H, Cl

220



221



222

Scheme 44

5-acylated product could be obtained in the case of **220** (X = Cl). With 2 eq of acylating reagent acceptable yields were isolated from both compounds, but still the enhancing effect of chlorine was evident in the acetylation. The reason for this was discussed.

The formylation of 2,2′-bithienyl was first investigated by Lescot et al.,[23] who found that the reaction with dimethyl formamide in the presence of phosphorus oxychloride gave 5-formyl-2,2′-bithienyl. 5-Methyl-2,2′-bithienyl reacted in the 5′-position and 5,5′-dimethyl-2,2′-bithienyl in the 3-position. It is interesting to note that under the same conditions 5-(2-thienylmethyl)-2,2′-bithienyl was formylated at the 5′-position to yield **221**, which shows that the reactivity of the α-positions of 2,2′-bithienyl is greater than that of the 5-position in a 2-alkylthiophene.

5,5′-Diformylation seems to be more difficult to achieve. Curtis and Phillips[214] reported on the second observation of such a reaction in connection with their isolation of a small but significant yield of 5,5′-diformyl-2,2′-bithienyl (1.0 g) together with 5-formyl-2,2′-bithienyl (25.7 g) on formylation of 2,2-bithienyl. The first observation was made by Grundmann and Dean.[215]

b. 3,3′-Bithienyl

4,4′-Diacetyl-2,2′,5,5′-tetramethyl-3,3′-bithienyl was prepared by Steinkopf and Petersdorff,[207] and 4,4′-diacetyl-2,2′,5,5′-tetraethyl-3,3′-bithienyl has been obtained by Gronowitz and Skramstad.[105]

c. 2,3′-Bithienyl

The acylation of 2,3′-bithienyl with acetic anhydride and phosphoric acid at room temperature was investigated by Wynberg et al.[114,195] The reaction took place at the 5-position to yield 39% of 5-acetyl-2,3′-bithienyl (**222**). Its structure was confirmed by oxidation to the corresponding acid and subsequent desulfuration to 6-methyloctanoic acid.[195] Attempts to bring about a diacetylation by using more drastic conditions resulted in tars.[114]

d. Polythienyls

Wynberg and Bantjes[195] easily obtained the 5,5″-diacetyl derivative of α-terthienyl in 61% yield with acetic anhydride and 85% phosphoric acid. Desulfuration and transformation to 2,15-hexadecanedione confirmed its structure.

The acylation of (all-α*S*)cyclotetrathiophene takes place at the same positions as the nitration.[197] The better yield (46%) of monosubstitution in the former reaction than in the latter was explained in terms of higher solubility of the thiophene compound in the reaction medium.

C. Halogenation

Several halogen derivatives of 2,2′-bithienyl and some of polythienyls as well were prepared by pioneer researchers in this field.[1] 2,3′-Bithienyl was not known until late, and 3,3′-bithienyl was for a long time not easily accessible. Therefore only two derivatives of the latter compound were mentioned by Hartough:[1] 2,2′5,5′-tetrabromo-3,3′-bithienyl and hexabromo-3,3′-bithienyl.

Kellogg et al.[216] have reported the complete analyses of the kinetically controlled products of the electrophilic bromination and deuteration of the three isomeric bithienyls. Molecular-orbital calculations have been carried out,[217] which are in agreement with the experimental data.

a. 2,2′-Bithienyl

In contrast to the behavior of 2,2′-bithienyl in the nitration and acylation reactions, attempts to stop the direct halogenation at the monohalogen stage are complicated. This was pointed out originally by Steinkopf,[218] and it was later confirmed by Uhlenbroek and Bijloo[32] and by Curtis and Phillips.[219] Accordingly, the latter authors prepared 5-iodo-2,2′-bithienyl by treating the methyl ester of 2,2′-bithienyl-5-carboxylic acid with iodine and mercuric oxide to obtain the 5′-iodo derivative. Subsequent hydrolysis and decarboxylation gave the desired product. The 5-bromo and 5-chloro compound were similarly prepared. The brominating agent was bromine in chloroform, and the chlorination was performed with sulfuryl chloride in chloroform.

Rossi et al.[45] and Brown et al.,[220] however, prepared 5-iodo-2,2′-bithienyl in rather good yields by iodination of 2,2′-bithienyl via the mercury derivative.

2,2′-Bithienyl is conveniently brominated to 5,5′-dibromo-2,2′-bithienyl in 96% yield with NBS in a 1 : 1 mixture of chloroform and acetic acid.[216] The acetic acid seems to have a catalytic effect on the reaction. The product exhibits a notable insolubility in other organic solvents than CS_2.[216]

A good yield (90%) of 5-acetyl-5′-bromo-2,2′-bithienyl could be obtained on bromination of 5-acetyl-2,2′-bithienyl with NBS in acetic acid.[221]

Sone and Abe[55] chlorinated 2,2′-bithienyl with 1–10 eq (moles) of sulfuryl chloride in carbon tetrachloride. It was found that the chlorine atoms entered first the 5- and 5′-positions, as expected, then the 3-position, and to a minor extent the 3′-position as well. For example, a mole ratio of 1 : 10 gave a mixture of 69 mol% of 5,5′-dichloro-2,2′-bithienyl, 22 mol% of 3,5,5′-trichloro-2,2′-bithienyl, and only about 1.5 mol% of 3,3′,5,5′-tetrachloro-2,2′-bithienyl, as determined by VPC.

Difficulties to achieve 3,3′-dihalogenation of a 5,5′-disubstituted 2,2′-bithienyl were also observed by Gronowitz and Vilks[12] on attempts to prepare 3,3′-diiodo-5,5′-dicarbomethoxy-2,2′-bithienyl with iodine–iodic acid[222] or via the mercury derivative. The former reagent, which worked well in the thiophene series,[12] reacted very sluggishly on the whole. With the mercuration method the reaction stopped after monoiodination.

However, hexaiodo-, hexabromo-, and hexachloro-2,2′-bithienyl as well as several other highly halogenated 2,2′-bithienyls have been prepared.[1]

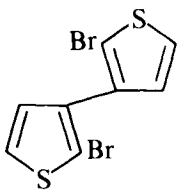
b. 3,3′-Bithienyl

Bromination of 3-aryl-substituted thiophenes with bromine is complicated because of rearrangements induced by the hydrogen bromide evolved.[216,223] This problem can be avoided by using NBS in chloroform–acetic acid.[216] 3,3′-Bithienyl gave 2,2′-dibromo-3,3′-bithienyl (**223**, Scheme 45) quantitatively with 2 eq of NBS. Further bromination of this compound with NBS in CCl_4 during 152 h afforded 34% of 2,2′,5,5′-tetrabromo-3,3′-bithienyl (**224**).[216] However, bromination of 4,4′-dicarboxy-3,3′-bithienyl with bromine in acetic acid, as well as with NBS in acetic acid, resulted in a mixture of acids containing bromine at various α-positions.[224] On the other hand, bromination (Br_2) of 4,4′-diformyl-3,3′-bithienyl in methylene chloride in the presence of $AlCl_3$ gave the 2,2′-dibromo derivative in 76% yield.[224]

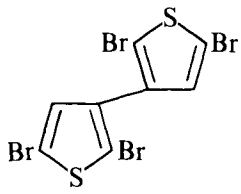
2-Bromo-3,3′-bithienyl was obtained as a liquid in about 90% yield on reaction of 1 eq of NBS with 3,3′-bithienyl in CCl_4 in the presence of benzoyl peroxide.[101] Since this bromo compound is very unstable it was not characterized further, but transformed via the 2-lithium derivative to the corresponding carboxylic acid.

Even 2,2′-dibromo-3,3′-bithienyl and 2,2′,5,5′-tetrabromo-3,3′-bithienyl are unstable at room temperature, where they decompose under evolution of hydrogen bromide. They can, however, be stored at $-20°C$.[216]

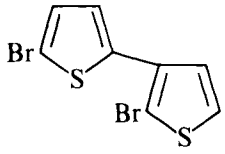
The tendency for decomposition seems to be characteristic for 2,2′-dibromo-3,3′-bithienyls without deactivating substituents in at least one ring.[225] For



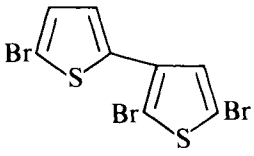
223



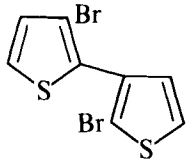
224



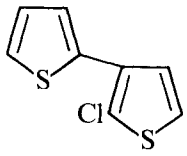
225



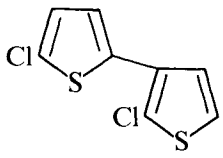
226



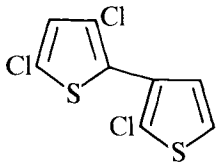
227



228



229



230

Scheme 45

example, 2-bromo-2′-carboxy-3,3′-bithienyl is stable, as are aldehyde and carboxy derivatives of 2,2′-dibromo-3,3′-bithienyl.

In contrast to 2,2′-dibromo-3,3′-bithienyl, 2,2′-dichloro-3,3′-bithienyl is completely stable and can be stored at room temperature without decomposition.[104] No rearrangement was observed after refluxing this compound for 3 h in acetic acid containing 10% hydrochloric acid.

Several other chloro and mixed bromochloro derivatives of 3,3′-bithienyl have also been prepared (Table 7). Steinkopf[218] found that when molecular chlorine is used as chlorinating agent for the preparation of thiophenes containing other halogens as well, bromine is easily exchanged for chlorine. On contrast, chlorine substituents are inert during bromination.

Direct chlorination of 3,3′-bithienyl with gaseous Cl_2 or N-chlorosuccinimide (NCS) gave 2,2′,5,5′-tetrachloro-3,3′-bithienyl in about 70% yield. Chlorination of 2,2′,4,4′-tetrabromo-3,3′-bithienyl with gaseous Cl_2 yielded hexachloro-3,3′-bithienyl in 81% yield. This halogen-exchange reaction was found to be the most convenient way to prepare hexachloro-3,3′-bithienyl.[104] Via the 5,5′-dilithium derivative, 2,2′,4,4′-tetrabromo-3,3′-bithienyl is easily accessible from hexabromo-3,3′-bithienyl, which is formed quantitatively on dissolving 3,3′-bithienyl in bromine. Attempts to chlorinate hexabromo-3,3′-bithienyl directly in a similar way resulted in a complex mixture of products.

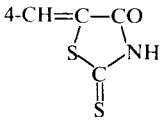
TABLE 7. 3,3′-Bithienyls[a]

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
2,2′-Diacetyl	132	—	241
4,4′-Diacetyl	208	—	241
–, 2,2′,5,5′-tetraethyl	69.5–71	46	105
–, 2,2′,5,5′-tetramethyl	90–91	—	207
2-Acetylamino	113–115	85	115
2-Amino	120–122/0.5	87	115
–, 2′-nitro	112	2.5	240
4-Amino	36–38	91	115
2-Azido	Oil, unstable	41	115
4-Azido	56–57	77	115
2-Bromo	—	90	101
–, 2′-carboxy	177–179	—	225
–, –, methyl ester	76–78	—	225
–, –, 5,5′-dimethyl	175, dec.	—	225
–, –, –, methyl ester	54–56	—	225
–, –, 4,4′,5,5′-tetramethyl	230, dec.	—	225
–, –, –, methyl ester	Oil	—	225
4-Bromo-4′-carboxy	—	—	—
–, 2,2′,5,5′-tetramethyl	203–205	—	225
–, –, methyl ester	Oil	—	225
2,2′-Dibromo[b]	78–79	100	216
–, 4,4′-dichloro	152–154	70	104
–, 4,4′,5,5′-tetrachloro	129–132	99	104
–, 4,4′-diformyl	155–155.5	76	224
–, –, bis(ethylenacetal)	Oil	—	262
–, –, bis(dimetylacetal)	118–119.5	73	262
–, 5,5′-dimethyl[b]	90–91	97	225
–, 4,4′,5,5′-tetramethyl[b]	160–161	90	225
4,4′-Dibromo			Table 2
–, 5-carboxy	224–226	—	225
–, 5,5′-dicarboxy	305, dec.	91	225
–, –, dimethyl ester	222–223	—	225
–, 2,2′-dichloro	132–134	63	104
–, 2,2′,5,5′-tetrachloro	151–152	98	104
–, 2,2′-diformyl	167–168.5	86	263
–, –, bis(ethylenacetal)	150–151	30	262
–, –, bis(dimethylacetal)	140–141	81	262
–, 5,5′-diiodo	165–167	53	225
–, 2,2′-dimethyl	76–78	86	262
–, 5,5′-dimethyl	74–75	73	225
–, 2,2′,5,5′-tetramethyl	89–91	90	225
5,5′-Dibromo-2,2′,4,4′-tetrachloro	143–145	79	104
2,4,4′-Tribromo-2′-carboxy	246–248	—	225
–, methyl ester	90–91	—	225
4,4′,5-Tribromo-5′-carboxy	242–245	22	225
2,2′,4,4′-Tetrabromo	162–163	75	263
–, 5,5′-dichloro	155–156	73	104
2,2′,5,5′-Tetrabromo	133–136	34	216
–, 4,4′-dichloro	155–157	89	104

TABLE 7. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
4,4',5,5'-Tetrabromo	156–158	35	225
–, 2,2'-dichloro	172–174	90	104
4,4'-Bis(bromoacetyl)-2,2',5,5'-tetramethyl	105–106	80	264
2,2'-Bis(bromomethyl)	80–82	79	265
	—	—	15
	80–82	69	241
4,4'-Bis(bromomethyl)	61.0–62.0	55	266
	75	72	241
2-Carboxy	156.5–157	60	101
	156.5–157	90–92	250
	166–167	75	267
–, methyl ester	74–75	—	267
4-Carboxy	161–162	68	250
–, 2,2',5,5'-tetraethyl	170/0.01	71	226
–, 2,2',5,5'-tetramethyl	143.5–144.5	84	14
2,2'-Dicarboxy	295, dec.	88	225
	254–256	94	250
–, dimethyl ester	198–199	—	225
–, 5,5'-dimethyl	254–257, dec.	45	108
	258–260, dec.	83	109
–, –, dimethyl ester	134–136	—	225
4,4'-Dicarboxy	275–280	80	11
–, dimethyl ester	147–148	—	11
–, 2,2'-diiodo	237–239	51	94
–, –, dimethyl ester	156–159	—	94
2,2'-Dichloro	52–54	78	104
2,2',4,4'-Tetrachloro	119–121	39	104
2,2',5,5'-Tetrachloro	126–127	70	104
	122–123	—	74
4,4',5,5'-Tetrachloro	143–145	50	104
Hexachloro	130–132	81	104
2,2'-Bis(chloromethyl)	53	63	241
4,4'-Bis(chloromethyl)	76–77	72	241
2,2'-Dideuterio	—	91	216
2,2',5,5'-Tetradeuterio	—	73	216
4-Formyl	Oil	38	13
2,2'-Diformyl	137–138	—	258
			265
	139	—	241
–, 4,4'-dimethyl	134.5–135.5	93	262
2,4'-Diformyl	110	14	13
4,4'-Diformyl	169.5–170	58	224
	167–168	53	268
	166–171	—	258
	168	—	241
–, 2,2'-dimethyl	108–110	72	262
2,2'-Bis(hydroxymethyl)	122–124	75	265
	124	92	241
4,4'-Bis(hydroxymethyl)	136–137	90	268

TABLE 7. (*Continued*)

Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
	137	89	241
4-Iodo	—	—	—
–, 2,2',5,5'-tetraethyl	—	85	226
–, 2,2',5,5'-tetramethyl	117–119.5	81	14
4,4'-Diiodo	—	—	—
–, 2,2',5,5'-tetraethyl	Oil	70	105
–, 2,2'-dimethyl	65–68	43	106
–, 2,2',5,5'-tetramethyl	104–106	83	111
5,5'-Diiodo-2,2'-dimethyl	128–129	—	106
2,2',4,4'-Tetraiodo	138–139.5	29	227
2,2',5,5'-Tetraiodo	162.5–164	75	227
4,4',5,5'-Tetraiodo	—	—	—
–, 2,2'-dimethyl	135–136.5	64	106
Hexaiodo	230–231.5	95	227
2,2'-Bis(1,1-dimethylhydroxymethyl)	118	43	241
4,4'-Bis(1,1-dimethylhydroxymethyl)	156	47	241
2-Nitro (**201**)	90–91	98	92
2,2'-Dinitro (**203**)	215	25	92
2,5'-Dinitro (**202**)	143–144	70	92
2,2',4-Trinitro (**206**)	201	62	92
2,2',5-Trinitro (**205**)	173	70	92
2,4,5'-Trinitro (**204**)	160	16	92
2,2',4,4'-Tetranitro (**209**)	210	26	92
2,2',4,5'-Tetranitro (**208**)	205–207	30–78	92
2,2',5,5'-Tetranitro (**207**)	260	44	92
4-CH=C(SH)–COOH	108–110	90	13
	228	78	13

[a] See also Table 2. For optically active 3,3'-bithienyls, see Table 9.
[b] Unstable.

2,2',5,5'-Tetramethyl-3,3'-bithienyl on iodination with iodine–iodic acid[222] gave 81% of 4-iodo-2,2',5,5'-tetramethyl-3,3'-bithienyl.[14,226]

Iodination of 3,3'-bithienyl with an excess of iodine–iodic acid stopped after the formation of 2,2',5,5'-tetraiodo-3,3'-bithienyl.[227] Hexaiodo-3,3'-bithienyl could be obtained via the mercury derivative (0.05 mol of 3,3'-bithienyl and 0.3 mol of $HgAc_2$ in 500 ml of HOAc; 0.5 mol of iodine was added in portions during 4 h. The HgI_2 formed was dissolved in KCl solution).[227]

c. 2,3'-Bithienyl

The bromination of 2,3'-bithienyl with 2 eq of NBS in chloroform–acetic acid yielded 2',5-dibromo-2,3'-bithienyl (**225**) essentially quantitatively.[216] Further

bromination gave 2′,5,5′-tribromo-3,3′-bithienyl (**226**). Compounds **225** and **226**, which are stable at − 20°C, decompose at room temperature. In the case of **225** this has occurred with near-explosive violence.[216]

3-Bromo-2,3′-bithienyl[101] is brominated with NBS in chloroform–acetic acid at the 2′-position to yield 2′,3-dibromo-2,3′-bithienyl (**227**).[228]

Chlorination of 2,3′-bithienyl with 2 molar eq of sulfuryl chloride yields a mixture containing 53 mol% of 2′-chloro-2,3′-bithienyl (**228**) and 41 mol% of 2′,5-dichloro-2,3′-bithienyl (**229**), which could be separated.[55] Further chlorination of the mixture with a large excess of sulfuryl chloride was reported to give 2′,3,5-trichloro-2,3′-bithienyl (**230**).[55] This is interesting to note, since bromination of **225**, the bromine analog of **229**, gave **226**.[216]

2. Reactions via Organometallic Compounds

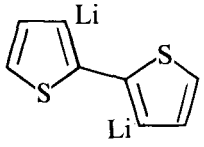
Bithienyls can be mercurated with mercuric chloride, mercuric oxide, or mercuric acetate,[1] and, as mentioned above, some iodinated bithienyls may be prepared by the reaction of these derivatives with iodine.

A highly useful synthetic method for the preparation of various substituted thiophenes and bithienyls involves intermediate lithium or Grignard derivatives, obtained by direct metalation or from bromo or iodo compounds after halogen–metal exchange or Grignard entrainment reactions. As is evident from Section II, the bithienyl frameworks themselves may be formed in this way. Substituents, which can be introduced via the derivatives mentioned, are, for example, fluoro, chloro, iodo, azido, cyano, thiocyanato, mercapto, methyl, formyl, and carboxy. By hydrolysis the metal atom can be replaced by a hydrogen (or deuterium). This offers a possibility to obtain certain desired derivatives (e.g., 2,2′4,4′-tetrabromo-3,3′-bithienyl; see below) by utilizing the blocking and/or directing effect of a halogen, which can subsequently be removed via the organometallic derivative.

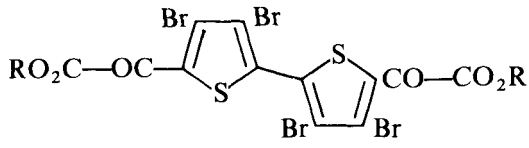
A. 2,2′-Bithienyl

As expected, 2,2′-bithienyl is metalated with *n*-butyllithium or phenyllithium at the 5- and 5′-positions.[216] Monolithiation can be achieved, and via the 5-lithium derivative the 5-carboxy-,[195] 5-fluoro-, 5-chloro-, 5-iodo-, and 5-methyl-2,2′-bithienyls were prepared.[229]

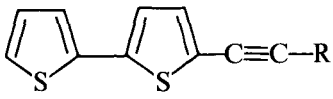
Introduction of lithium atoms at the β-positions cannot be made by direct metalation. 3,3′-Dilithio-2,2′-bithienyl (**231**, Scheme 46) was obtained from 3,3′-dibromo-2,2′-bithienyl[11] by reaction with *n*-butyllithium at − 70°C. At higher temperatures, rearrangements may occur.[230] Reaction of the lithium compound with CO_2 yielded 3,3′-dicarboxy-2,2′-bithienyl.[11] Ethyl formate gave 3,3′-diformyl-2,2′-bithienyl,[226] but with benzaldehyde and subsequent oxidation, 3-benzoyl-2,2′-bithienyl was obtained.[231]



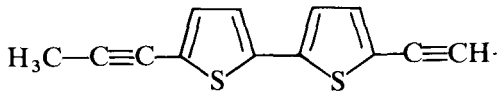
231



232



233



234

Scheme 46

Attempts to prepare the 3-monolithium derivative from 3,3′-dibromo-2,2′-bithienyl with *n*-butyllium at − 70°C gave dilithiation to a large extent. Therefore, the entrainment Grignard reaction followed by hydrolysis was used to prepare the desired 3-bromo-2,2′-bithienyl.[226] This reaction involves the addition of ethylene bromide to a mixture of the bromo compound and magnesium in dry ether. The same method was subsequently used for the preparation of 3-carboxy-2,2′-bithienyl from the 3-bromo-2,2′-bithienyl via carbonation of the Grignard reagent.[226]

The 5,5′-diorganomagnesium derivative, obtained from hexabromo-2,2′-bithienyl in a similar way, was used for the preparation of 3,3′,4,4′-tetrabromo-5,5′-bithienyldiglyoxalic acid esters (**232**).[232]

The previously (1986) unknown hexamethyl-2,2′-bithienyl was prepared from 3,3′-dibromo-4,4′,5,5′-tetramethyl-2,2′-bithienyl[14] via the 3,3′-dilithium derivative, which was allowed to react with dimethyl sulfate at − 30°C.[233] At this temperature the reaction may be kept under control by observing the increase in temperature on addition. The reaction of the very toxic dimethyl sulfate with thienyllithium at lower temperatures is slow, and the addition of excessive quantities of reagent at once may result in a sudden violent exothermic reaction, when the temperature is raised.[234] The authors used the hexamethyl compound and some other 2,2′-bithienyls for the preparation and investigation of tricarbonylchromium complexes.[233]

Brown et al.[220] prepared acetylenic 2,2′-bithienyls (**233**, Scheme 46) from 5-iodo-2,2′-bithienyl and acetylenic Grignard reagents in the presence of cuprous chloride. The reverse procedure, reaction between bromoacetylenes and arylmagnesium iodide, also gave the desired product, but in lower yields.

Atkinson et al.[85,235] reacted 5-iodo-2,2′-bithienyl with cuprous acetylides for the preparation of various 2,2′-bithienyl acetylenes. Attempts to react 5-bromo-2,2′-bithienyl in the same way were unsuccessful. Reaction of 5-iodo-2,2′-bithienyl with cuprous cyanide or cuprous thiocyanate gave 5-cyano-2,2′-bithienyl, whereas cuprous acetate gave α-quaterthienyl.[85]

Unfortunately, the ethynyl group cannot be introduced directly in this way, since monocuprous acetylide is unknown.[235] However, by using a substituted cuprous acetylide with a readily removable group such as formyl (protected as acetal) or ester, this difficulty can be overcome.[235,236] Compounds of this type are of interest for preparations in connection with the study of naturally occurring 2,2′-bithienyls, such as **234**.[236]

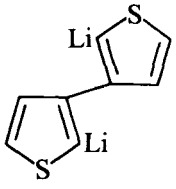
5-Carboxy-5′-(1-propynyl)-2,2′-bithienyl (arctic acid, isolated from the roots of *Arctium lappa*) was prepared by Carpita and Rossi.[46] The relatively short and high-yielding synthesis included the coupling of 5-ethoxycarbonyl-5′-iodo-2,2′-bithienyl with propyne in the presence of CuI and triethylamine with $Pd(PPh_3)_4$ as catalyst (93% yield). In a preceding step, 5-ethoxycarbonyl-2,2′-bithienyl was obtained in 93% yield by reaction of 5-bromo-2,2′-bithienyl at 100°C and 294-psi CO pressure in ethanol and triethylamine in the presence of $PdCl_2(PPh_3)_2$. 3-Ethoxycarbonyl-2,2′-bithienyl and 4-ethoxycarbonyl-2,3′-bithienyl were prepared from the corresponding bromobithienyls by similar ethoxycarbonations.

Recently, Kao and Hwang[237] reacted 5-lithio-2,2′-bithienyl with 2-(2-iodoethyl)-1,3-dioxolane, which, after hydrolysis of the acetal, gave 3-[5-(2,2′-bithienyl)propanal].

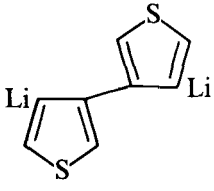
B. 3,3′-Bithienyl

Metalation of 3,3′-bithienyl takes place at both the 2,2′- and 5,5′-positions.[216] Carbonation of the product obtained on reaction of 3,3′-bithienyl with *n*-butyllithium yields about equal amounts of the 2,2′- and 5,5′-dicarboxylic acids.[107,108] Therefore, in order to obtain a uniform product on metalation, either of these positions must be blocked in a suitable way.

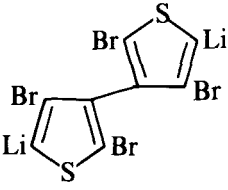
2,2′-Dilithio-3,3′-bithienyl[224] (**235**, Scheme 47) and 4,4′-dilithio-3,3′-bithienyl[11] (**236**) are easily prepared by the reaction of 2,2′-dibromo-3,3′-bithienyl and 4,4′-dibromo-3,3′-bithienyl, respectively, with *n*-butyllithium at − 70°C. Isomer-free 5,5′-dilithio-3,3′-bithienyl is more difficult to obtain. Since the corresponding 5,5′-dibromo- and 5,5′-diiodo derivatives are unknown, this organometallic compound cannot be prepared by halogen–metal exchange, and, as mentioned previously, direct metalation yields 2,2′-dilithiation as well.



235



236



237

Scheme 47

However, 4,4′-dibromo-5,5′-dilithio-3,3′-bithienyl is available from 4,4′,5,5′-tetrabromo-3,3′-bithienyl,[224] and when hexabromo-3,3′-bithienyl is treated with *n*-butyllithium at $-70°C$, the 5,5′-dilithium derivative **237** is formed.[87]

Hydrolysis of **237** yields 2,2′4,4′-tetrabromo-3,3′-bithienyl, which proved to be a highly useful starting material for the preparation of optically active 3,3′-bithienyls (Section VI). By a series of reactions involving first the 2,2′-dilithium derivative and in subsequent steps a 4,4′-dilithium compound, various substituents were introduced at the positions mentioned.

Attempts have been made to prepare monolithium derivatives from some dibromo-3,3′-bithienyls through halogen–metal exchange.[224] It was found that ethyllithium and *n*-butyllithium reacted differently in these cases. For example, after carbonation 2,2′-dibromo-3,3′-bithienyls gave mainly monocarboxylic acids in reaction with *n*-butyllithium (1 eq), but ethyllithium yielded mixtures of about 60% dicarboxylic acid and 40% monocarboxylic acid. 4,4′-Dibromo-3,3′-bithienyl was metalated at one of the 5-positions, blocking of which resulted in a mixture of a 4-monocarboxylic acid and a 2,4′-dicarboxylic acid with both lithium reagents.

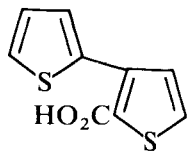
C. 2,3′-Bithienyl

Metalation of 2,3′-bithienyl (Table 8) with *n*-butyllithium may take place at all three α-positions.[216]

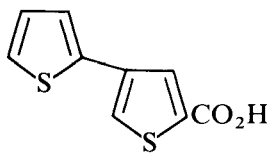
With phenyllithium and subsequent carbonation a 52% yield of 2′-carboxy-2,3′-bithienyl (**238**, Scheme 48) and a 38% yield of 5′-carboxy-2,3′-bithienyl (**239**) was obtained.[195] Possible reasons for the electrophilic attack at the 5-position on acylation (Section IV.1.B.c), and the nucleophilic attack mainly at the 2′- and 5′-positions on metalation, were discussed.[195]

Through halogen–metal exchange in various monobromo-2,3′-bithienyls at low temperature, and subsequent reaction with *p*-toluenesulfonyl azide, some monoazido-2,3′-bithienyls were prepared.[115] The azido groups were then transformed to amino groups by reduction with hydrogen sulfide.

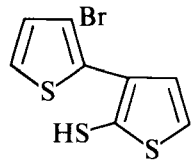
This synthetic path was found to be a very convenient route for the preparation of all six possible *o*-azidobithienyls and *o*-aminobithienyls, which, in turn, have been utilized for the syntheses of various nitrogen-containing bridged bithienyls (Section V).



238



239



240

Scheme 48

TABLE 8. 2,3′-Bithienyls[a]

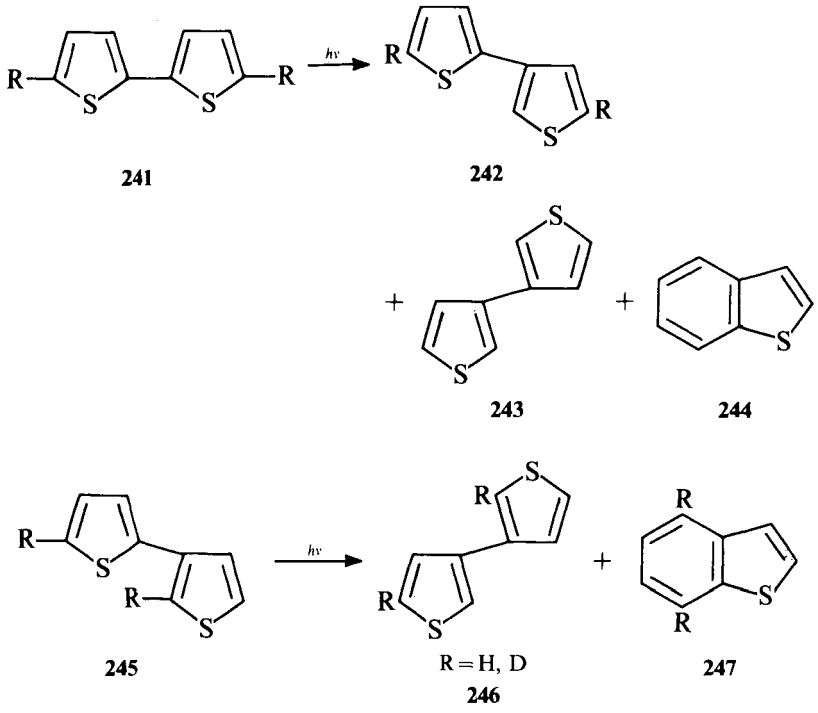
Substituents	m.p. (°C) b.p. (°C/mmHg)	Yield (%)	Ref.
5-Acetyl	121.5–122.5	39	114
2′-Acetylamino	104–106	83	115
5′-Acetylamino	—	—	—
–, 4′-ethoxycarbonyl	54–55	90	118
–, –, oxazine derivative	149–150	61	118
2′-Amino	Oil, unstable	71	115
3-Amino	108–110/0.5	93	115
4′-Amino	97–98/0.01	95	115
2′-Azido	Oil, unstable	33	115
3-Azido	92–95/0.5	73	115
4′-Azido	118–120/0.5	75	115
3-Bromo-2′-mercapto	Oil, unstable	88	228
2′,3-Dibromo	54–55	83	228
2′,5-Dibromo	46–47	94	216
2′,5,5′-Tribromo	54.0–55.3	40	216
2′-Carboxy	107–109	52	195
3-Carboxy	187–188	86	250
4-Carboxy	—	—	—
–, ethyl ester	—	87	46
5-Carboxy	203–205	91	195
5′-Carboxy	173–175	38	195
2′-Chloro	103–104/4	—	55
2′,5-Dichloro	53–54	—	55
2′,3,5-Trichloro	77–78	—	55
2′,5-Dideutero	—	65	216
2′,5,5′-Trideutero	—	79	216
5-Ethyl	21.7–23.7	—	114
2′-Nitro (**211**)	50	—	116
3-Nitro (**210**)	77–78	—	116
5-Nitro (**212**)	92–93	—	116
2′,3-Dinitro (**214**)	194–195	—	116
2′,4-Dinitro (**215**)	135–136	—	116
2′,5-Dinitro (**216**)	163–164	—	116
3,5′-Dinitro (**213**)	132–133	—	116
5,5′-Dinitro (**217**)	238–239	—	116

[a] See also Table 3.

Via the 2′-lithio-3-bromo-2,3′-bithienyl, available from 2′,3-dibromo-2,3′-bithienyl and *n*-butyllithium at −70°C, 2′-mercapto-3-bromo-2,3′-bithienyl (**240**) was obtained after reaction of the lithium compound with sulfur.[228]

3. Photochemical Rearrangements

Wynberg and coworkers discovered that arylthiophenes undergo photochemically induced valence bond isomerization on irradiation.[238] For 2-arylthio-



Scheme 49

phenes this means an irreversible interchange of the 2- and 3-carbon atoms of the thiophene ring. Thus irradiation of 2,2′-bithienyl (0.60 g) yielded 2,3′-bithienyl (100 mg) as the main product and minor amounts of 3,3′-bithienyl (10–15 mg) and benzo[*b*]thiophene (5 mg)[239] (Scheme 49). When the experiment was repeated with 5,5′-dideuterio-2,2′-bithienyl, the product **242** was identified as 5,5′-dideuterio-2,3′-bithienyl.

Irradiation of 2,3′-bithienyl and its 2′,5-dideuterio derivative gave 3,3′-bithienyl (2,5-dideuterio) (**246**) and benzo[*b*]thiophene (4,7-dideuterio) (**247**) in low yields and trace quantities of 2,2′-bithienyl.

3,3′-Bithienyl gave no rearrangements under the same conditions.

Possible mechanisms for the formation of the various products were discussed.[239]

V. BRIDGED BITHIENYLS

The importance of bridged and doubly bridged bithienyls might necessitate a separate chapter. A detailed presentation of their chemistry would lead beyond the limits of this survey, and therefore only a brief summary and some references

will be given here. In the tables only some bridged bithienyls, related to optically active 3,3′-bithienyls, have been included (Section VI).

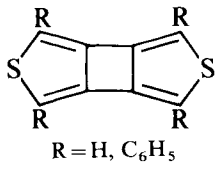
As mentioned previously, the systematic names of the bridged bithienyls seldom include the term *bithienyl*, and therefore they may not be recognized in the literature. The reason for including them in this chapter is their relationship to bithienyls. They are in some cases prepared from such compounds, and they may be compared with bithienyls with respect to certain properties, for example, UV spectra, since they possess a locked conformation and similar.

In principle, the bridging may be performed in two ways. The thiophene rings may be attached to the ends of the prospective bridge, whereupon they are connected by the methods presented in Section II. Alternatively, the bridge may be formed by some side-chain reaction of a suitably substituted bithienyl.

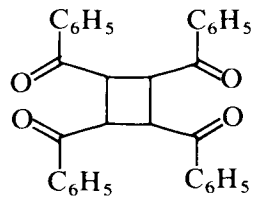
In the following paragraphs the number and kinds of atoms in the bridge will be the basis for the account.

1. Zero-Atom Bridge

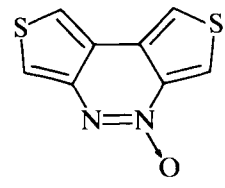
The situation implies the cyclobutadithiophene system, the dithiophene analog of biphenylene, of which there are four possible isomers. Cyclobuta[1,2-*c*; 3,4-*c*′] dithiophene (**248**, Scheme 50) is predicted to be the most stable of these. Several attempts to synthesize this compound were made without success[74] before the preparation by Garratt and Soon Bin Neoh[269] of **248** (R = C_6H_5) in 3% yield by treatment of **249** with P_2S_5. Later the unsubstituted system **248** (R = H) was obtained by Shepherd[95] in 4% yield by flash-vacuum thermolysis of the N-oxide **250**.



248



249



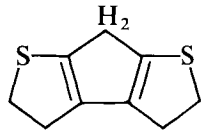
250

Scheme 50

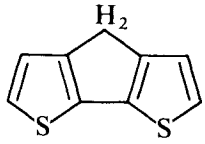
2. One-Atom Bridge

A. Cyclopentadithiophenes

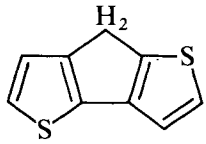
There are six possible isomers of this system (Scheme 51), which have all been synthesized by Wynberg and coworkers from various dithienylmethanes.[270,271]



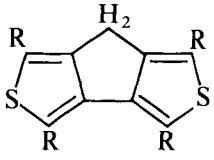
251



252

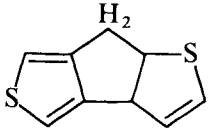


253

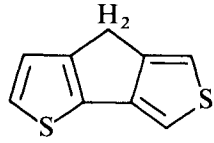


R = H, CH_3, C_2H_5

254



255

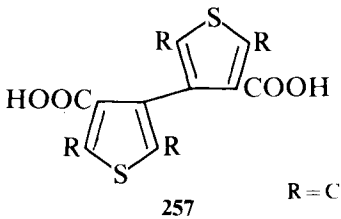


256

Scheme 51

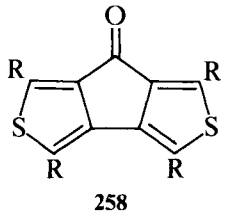
The last synthetic step involves the coupling of the thiophene rings to a bithienyl system by reaction of the appropriate dilithio intermediate with $CuCl_2$.

Gronowitz et al.[226] prepared **254** (R = CH_3, C_2H_5) by another approach. Treatment of **257** (Scheme 52) with polyphosphoric acid easily yielded the cyclopentadithiophenones **258**. The tetraethyl compound was also obtained from the 4-monoacid analog of **257** on reaction with acetyl chloride and $SnCl_4$. Reduction of **258** with $LiAlH_4/AlCl_3$ yielded **254**. (Wolff–Kishner and Clemmensen reductions were unsuccessful.)



257

R = CH_3, C_2H_5



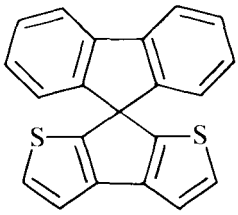
258

Scheme 52

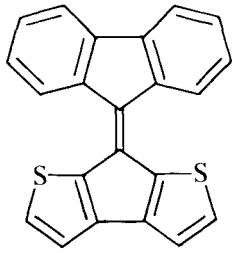
The compounds in Scheme 51 are dithiophene analogs of fluorene. The six corresponding fluorenones (cf. **258**) have also been prepared.[272]

The metalations[226,273,274] and oxidations[275] of cyclopentadithiophenes, the pinacol reductions of cyclopentadithiophenones,[276] and the reactions of cyclopentadithiophenones with dienophiles[277,278] have been investigated.

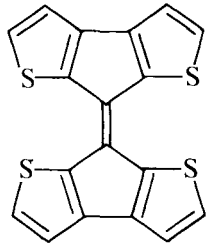
Spiro compounds of type **259**[101] and heterofulvalenes of types **260** and **261** (Scheme 53) have been prepared by Wynberg et al.[279]



259



260

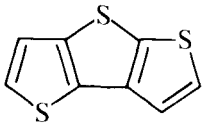


261

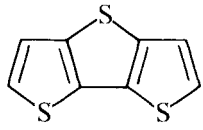
Scheme 53

B. Dithienothiophenes

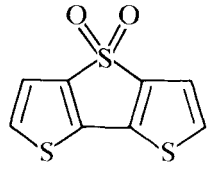
Exchanging the methylene groups in **251–256** for sulfur would yield the six isomeric dithienothiophenes. They have all been prepared by de Jong and Janssen[228,280] by various methods, one of which is the coupling of the appropriate dilithio derivative of a dithienyl sulfide with $CuCl_2$. Compound **262** (Scheme 54) was obtained by reacting **240** (Scheme 48) with Cu_2O in DMF.[228] The bridge sulfur is easily oxidized to the corresponding sulfone by peracids. Dithienothiophene **263** and the corresponding sulfone **264** were previously prepared by Stoyanowich and Fedorov.[281]



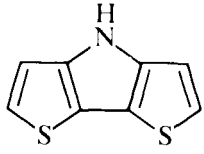
262



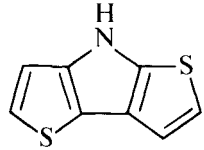
263



264



265



266

Scheme 54

C. Dithienopyrroles

This system also has six possible isomers. Zanirato et al.[282] tried to obtain them by the thermal decomposition of various *o*-azidobithienyls[115] (Section IV.2.C) in chlorobenzene or refluxing *o*-dichlorobenzene. This was successful only with

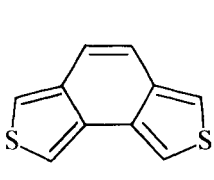
3-azido-2,2′-bithienyl and 3-azido-2,3′-bithienyl, which gave **265** and **266**, respectively (Scheme 54). 4-Azido-3,3′-bithienyl and 4′-azido-2,3′-bithienyl yielded polymers, and 2′-azido-2,3′-bithienyl gave intractable nitrile-containing materials. 2-Azido-3,3′-bithienyl, probably in some ring-opening and cyclodimerization reaction, gave rise to two *m*-dithiin isomers.

3. Two-Atom Bridge

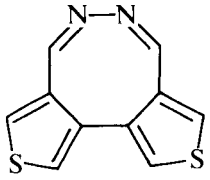
A. Benzodithiophenes

Connection of a bithienyl with a two-carbon bridge leads to the six thiophene analogs of phenanthrene or 9,10-dihydrophenanthrene. Work in this field was performed in the 1950s by Rao and Tilak,[283–285] who reacted benzodithiols with the dimethyl acetate of bromoacetaldehyde and ring-closed the product to benzodithiophenes with phosphoric acid.

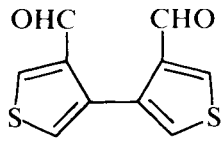
Wynberg et al.[286] irradiated some dithienylethenes in the presence of iodine, which gave benzodithiophenes, and the same compounds were in some cases obtained on reaction of cyclopentadithienones with dienophiles.[277,278]



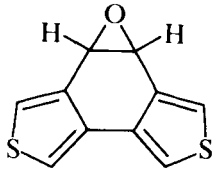
267



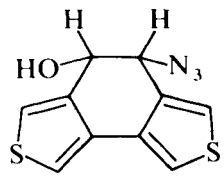
268



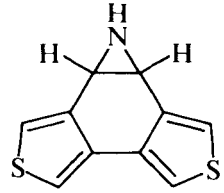
269



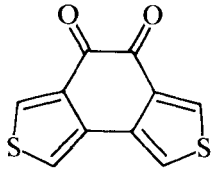
270



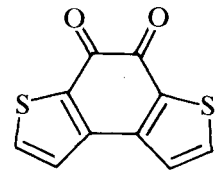
271



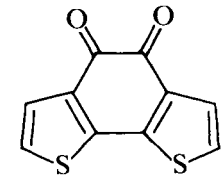
272



273



274



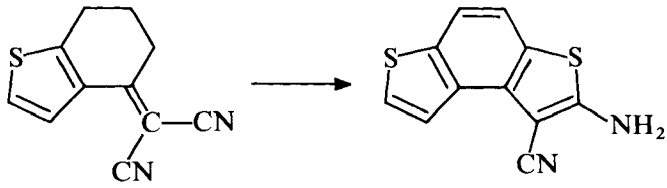
275

Scheme 55

MacDowell and Maxwell[268] prepared benzo[1,2-*c* : 3,4-*c'*]dithiophene (**267**, Scheme 55) via the intermediate **268**, obtained by treatment of 4,4'-diformyl-3,3'-bithienyl (**269**) with hydrazine. Reaction of **269** with hexamethylphosphorous triamide gave 7,8-epoxy-7,8-dihydrobenzo[1,2-*c* : 3,4-*c'*]-dithiophene (**270**). Compound **270** has been treated with sodium azide by Weitzberg et al.[287] to yield **271**, which with an excess of triethyl phosphite gave the imine **272**.

When dialdehyde **269** was heated in refluxing ethanolic sodium cyanide solution, quinone **273** was formed in an intramolecular benzoin condensation. The corresponding products **274** and **275** were obtained from 2,2'-diformyl-3,3'-bithienyl and 3,3'-diformyl-2,2'-bithienyl, respectively.[258]

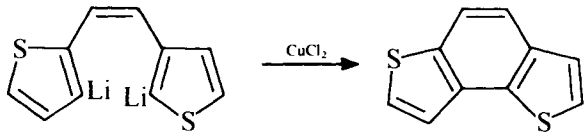
The benzodithiophene system has also been prepared in a Gewald type of ring-closure reaction by treatment of **276** (Scheme 56) with sulfur and aromatization of the initially isolated product to **277**.[288]



276 **277**

Scheme 56

The most extensive investigation of the chemical and physical properties of the benzodithiophene system was made by Gronowitz and Dahlgren.[289] They prepared all six isomers from suitable dibromodithienylethenes by coupling the appropriate dilithio derivative with $CuCl_2$, as illustrated for benzo-[1,2-*b* : 3,4-*b'*]dithiophene (**279**) in Scheme 57.

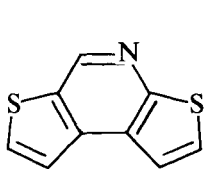


278 **279**

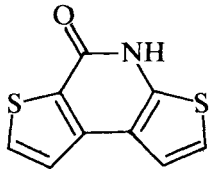
Scheme 57

B. Dithienopyridines

These compounds are dithiophene analogs of phenanthridine. Some dithienopyridines, for example, **280** (Scheme 58), have been prepared by reduction of the corresponding dithienopyridones (**281**) with $LiAlH_4/AlCl_3$.[290] The pyridones were obtained by the cyclization of the appropriate dithienylazides.[291]



280



281

Scheme 58

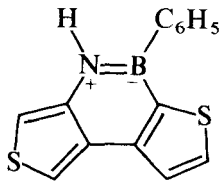
All nine isomeric dithienopyridines have recently been synthesized by Gronowitz et al. through the Pd(0)-catalyzed coupling reactions between *ortho*-formylthiopheneboronic acids[292] or *ortho*-formylthienyltin derivatives[293,294] and *t*-butyl-N-(*ortho*-halothienyl)carbamates.

C. Dithienopyridazines

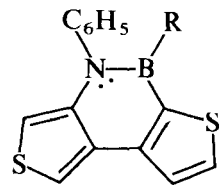
Dithieno[3,4-*c* : 3′,4′-*e*]pyridazine and the corresponding N-oxide **250** (Scheme 50) have been reported by Shepherd[95] in connection with the preparation of **248** (see above). Compound **250** was prepared by cyclization of 4,4′-dinitro-3,3′-bithienyl. In a similar way, some isomers of **250** and the corresponding dithienopyridazines have been prepared from 3,3′-dinitro-2,2′-bithienyl and 2,2′-dinitro-3,3′-bithienyl.[112]

D. Borazarobenzodithiophenes or Dithienoazaborines

There is some controversy about the nomenclature of these compounds, which are isoelectronic with the thiophene analogs of phenanthrene. They have also been represented by different mesomeric structures, as illustrated in Scheme 59. Compound **282** and some of its isomers were obtained by Gronowitz et al.[295,296] on reaction of suitable *o*-aminobithienyls with dichlorophenylborane. Their ^{1}H- and ^{13}C-NMR, UV, and mass spectra are discussed.



282



R = Cl, OCH_3

283

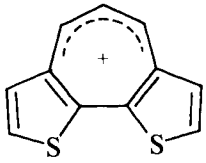
Scheme 59

Zanirato[244] reacted *o*-azidobithienyls (precursors of the *o*-aminobithienyls; see Section IV.2.C) with dichlorophenylborane to yield labile and moisture-sensitive B-chloro derivatives such as **283** (R = Cl; Scheme 59). In the case of the latter compound, obtained from 4-azido-3,3′-bithienyl, treatment with boiling methanol gave **283** (R = OCH_3). Hydrolysis of the chloro derivatives generally gave bis[1,2]azaborine ethers with the ether bridge between the borine atoms.

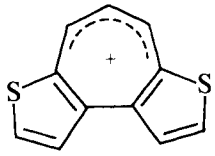
4. Three-Atom Bridge

A. Cycloheptadithiophenes

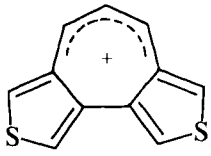
Gronowitz and Pedaja prepared some cycloheptadithiophenes by ring closure of bis(bromomethyl)-2,2′- and 3,3′-bithienyls with diethyl malonate.[15,266] A cycloheptatriene system was subsequently formed on oxidative decarboxylation of the resulting monocarboxylic acid,[266] or after Hofmann elimination of the quaternary ammonium salt, which could be obtained after a multistep conversion of the carboxylic group[15] (involving a Curtius rearrangement to form the carbon–nitrogen bond). Good yields (76–83%) of the stable tropylium ions **284** and **285** (Scheme 60) as fluoborate salts were obtained on treatment of the corresponding cycloheptatrienes with triphenylmethyl fluoborate.[15] The isomeric thieno[*c*]-annelated tropylium ion **286** could not be identified on attempts to prepare it in a similar way, however.[266]



284



285



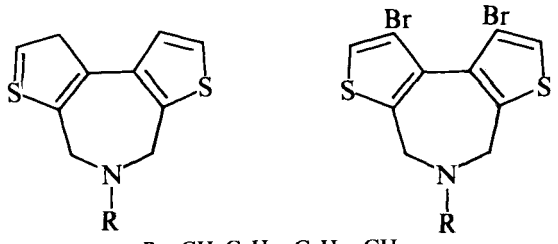
286

Scheme 60

B. Dithienazepines

Wynberg and Cabell[120] prepared N-benzyl-5,6-dihydro-4*H*-dithien[2,3-*c* : 3′,2′-e]-azepine (**287**, R = —$CH_2C_6H_5$; Scheme 61) in 94% yield by simultaneous treatment of 2,2′-diformyl-3,3′-bithienyl with sodium dithionite and benzylamine. The corresponding N-phenyl derivative **287** (R = —C_6H_5) was obtained in a similar way. The same authors also prepared an analogous azepine system from 2,2′-diformyl-3,3′-bithianaphthenyl (cf. **139**, Scheme 27) and benzylamine.

Almqvist and Håkansson[265] used the same method for the preparation of **287** (R = —CH_3) from 2,2′-diformyl-3,3′-bithienyl and methylamine, and the corres-



287 288

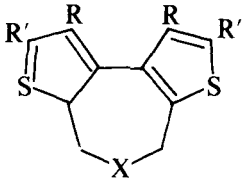
Scheme 61

ponding 4,4′-dibromo aldehyde gave **288** (R = —$CH_2C_6H_5$, —CH_3) in a similar way. The latter two compounds were obtained from 4,4′-dibromo-2,2′-bis(bromomethyl)-3,3′-bithienyl and the appropriate amine as well.[297]

Meunier[241] has prepared some N-ethyl and N-phenyl-substituted dithienoazepines, starting from 3,3′-diformyl-2,2′-bithienyl and 2,2′- and 4,4′-diformyl-3,3′-bithienyl. The formyl groups were transformed to chloromethyl or bromomethyl groups, and the ring closure was performed with ethylamine or aniline.

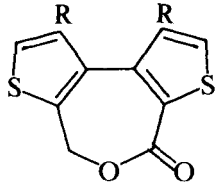
C. Dithienoxepines and Dithienothiepines

In connection with an investigation of the chiroptical properties of 3,3′-bithienyls, some dithienoxepines and dithienothiepines of the type shown



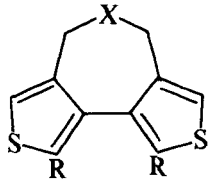
X = O, S; R = H, Cl, Br, CH_3, COOH; R′ = H, CH_3

289



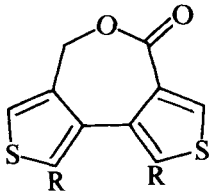
R = Br, CH_3

290



X = O, S; R = Br, CH_3

291



R = Br, CH_3

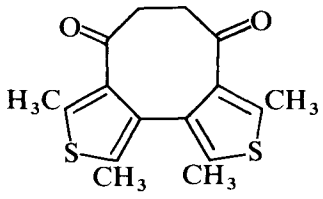
292

Scheme 62

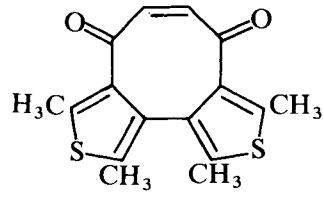
in Scheme 62 were prepared. The oxepines were obtained by ring closure of bis(hydroxymethyl)-3,3′-bithienyls with *p*-TSA, and the thiepines were formed from bis(bromomethyl) derivatives and Na_2S. By the same methods, Meunier[241] prepared dithienoxepines and dithienothiepines, starting from the three dialdehydes mentioned above in connection with the preparation of dithienazepines. 2,2′- and 4,4′-Diformyl-3,3′-bithienyls were found to undergo intramolecular Cannizzaro reactions, yielding *o*-carboxy-*o*′-hydroxymethyl-3,3′-bithienyls,[298] from which lactones **290** and **292** were prepared. Some of the compounds in Scheme 62 are further presented in the next section, where references are given.

5. Four-Atom Bridge

Ghera et al.[264] prepared the dithienocyclooctene **293** (Scheme 63) by the use of a zinc-induced cyclization of 4,4′-bis(bromoacetyl)-2,2′,5,5′-tetramethyl-3,3′-bithienyl. The conversion of **293** into **294** was achieved by bromination and subsequent dehydrobromination.



293

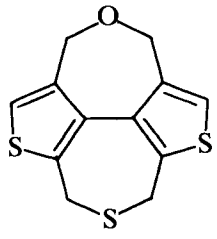


294

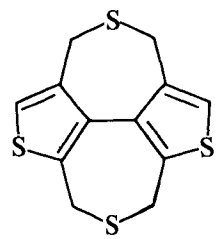
Scheme 63

6. Doubly Bridged Bithienyls

Two doubly bridged bithienyls, shown in Scheme 64, were prepared from **289** (X = S, R = COOH, R′ = H) after conversion of the carboxylic groups to hy-



295



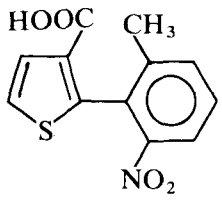
296

Scheme 64

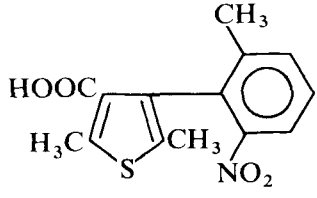
droxymethyl groups (yielding **295** with *p*-TSA) or bromomethyl groups (yielding **296** with Na_2S).[299]

VI. OPTICAL ACTIVITY OF 3,3′-BITHIENYLS

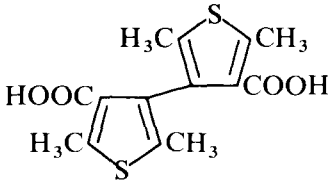
Atropisomerism in thiophene compounds was first demonstrated by Owen and Nord.[34] They resolved compound **297** (Scheme 65), which is optically unstable at room temperature. The β-phenylthiophene **298**[35,300] was resolved by Jean.[301] It racemizes with a half-life of about 3 min in refluxing acetic acid. Jean et al.[35,90] also prepared minor amounts of bithienyl **299**, which they predicted to be resolvable on basis of its UV spectrum. Gronowitz and Beselin[111] later performed the resolution.



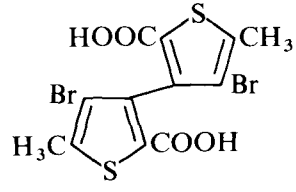
297



298



299



300

Scheme 65

The first example of atropisomerism in the bithienyl series was demonstrated by Gronowitz and Frostling[107,108] on compound **300** in 1961. This was the beginning of an extensive study of the stereochemistry of 3,3′-bithienyls, initiated by Gronowitz and subsequently continued in his laboratories by Håkansson and coworkers. The compounds investigated are collected in Tables 9–11.

So far, optical activity has been observed only in derivatives of 3,3′-bithienyl. Attempts to resolve 5-carboxy-3,3′-diiodo-2,2′-bithienyl[212] and 5,5′-dicarboxy-3,3′,4,4′-tetraiodo-2,2′-bithienyl[302] failed, probably because of a low steric barrier in these compounds. 2,3′-Bithienyls have not been investigated in this respect.

A special kind of optically active compounds, in which a bithienyl, terthienyl, or quaterthienyl system might be recognized, has been investigated by Wynberg and Groen. These compounds, called *heterohelicenes*, are related to hexahelicene, the archetypical molecule of this kind, in which some benzene rings

TABLE 9. Optically Active 3,3′-Bithienyls[a]

Substituents	(R,S) m.p. (°C)	(R) m.p. (°C)	(R) $[a]_D^{25}$ (deg)	Ref.
2-Carboxy				
–, 2′,4,4′-tribromo[c]	—	236–240	+ 15.6	304
–, 2′-hydroxymethyl				
–, –, 4,4′-dibromo	161–162	155–157	+ 9.8	263
–, –, –, methyl ester	91.5–92	106.5–107	+ 30	263
–, –, 4,4′-dimethyl	143–145	138–142	– 41	262
–, –, –, methyl ester	Oil	—	—	262
2,2′-Dicarboxy				
–, 4,4′-dibromo	295[d]	—	—	87
	—	255–258	+ 44	304
				263
–, –, dimethyl ester	160–162	—	—	87
	—	138.5–139	+ 59	263
–, –, 5,5′-dimethyl	311–313[d]	302–305[d]	+ 55	108
			+ 60	109
–, –, –, dimethyl ester	154–156	—	—	108
	—	178–180	+ 61[b]	109
–, 4,4′-dichloro	280–283[d]	280[d]	+ 50	316
–, 4,4′-dimethyl	280–285	—	—	106
	285–290[d]	250 (rac.)	+ 27	262
–, –, dimethyl ester	165	—	—	106
	—	119.5–120.5	– 7	262
–, –, 5,5′-dibromo	295–300[d]	255 (rac.)	+ 94	262
–, –, –, dimethyl ester	98.5–99	—	—	262
–, 4,4′,5,5′-tetramethyl	286–287[d]	—	—	14
	—	270–273[d]	+ 79	314
–, –, acid dichloride	—	129–131	+ 103[b]	314
–, –, dimethyl ester	92–93	—	—	225
	—	89–90	+ 56[b]	314

TABLE 9. (*Continued*)

Substituents	(*R*,*S*) m.p. (°C)	(*R*) m.p. (°C)	(*R*) $[a]_D^{25}$ (deg)	Ref.
–, –, diamide	249–250	215–223	– 21	314
–, 4,4′-dinitro	283–285	—	—	93
	—	225–287	+ 225[b]	313
–, –, dimethyl ester	164–165	—	—	93
	—	157.5–159	+ 81	313
4-Carboxy				
–, 4′-bromo-2,2′,5,5′-tetramethyl[c]	—	260–265[d]	– 18[b]	109
–, 4′-hydroxymethyl				
–, –, 2,2′-dibromo	153–153.5	Glassy	– 65[e]	224
–, –, –, methyl ester	81.5–83.5	88–88.5	– 42[e]	224
–, –, 2,2′-dimethyl	141.5–142.5	162–163	– 29	262
–, –, –, methyl ester	Oil	Oil	– 23[e]	262
4,4′-Dicarboxy				
–, 2,2′-dibromo	265[d]	205–206	– 104	224
–, –, dimethyl ester	110–111.5	105–106.5	– 101	224
–, 5,5′-dibromo				
–, –, 2,2′-dimethyl	280–285[d]	117–119	– 60	262
–, –, –, dimethyl ester	Oil	—	—	262
–, 2,2′,5,5′-tetrabromo	320–325[d]	240 (rac.)	– 59	224
–, –, dimethyl ester	121–122	126–126.5	– 62	224
–, 2,2′,5,5′-tetraethyl	183–186	70–80	– 281[f]	105
–, –, diamide	—	221–223	—	315
–, 2,2′-diformyl	225–229	225–229	– 87	94
–, –, dimethyl ester	164–167	112–113	– 110	94
–, 2,2′-dimethyl	308–311[d]	—	—	106
	284–285[d]	210 (rac.)	– 49	262
–, –, dimethyl ester	89–90	Oil	– 78	262
–, 2,2′,5,5′-tetramethyl	295–305[d]	295–305[d]	– 53	111

–, –, diamide	—	236–238	– 7.5	315
–, –, dimethyl ester	—	Oil	—	315
–, 2,2′-dinitro	285–287	289–293[d]	+ 98	103
–, –, dimethyl ester	154	150–152	+ 98	103
5,5′-Dicarboxy				
–, 2,2′,4,4′-tetrabromo	275[d]	248–250[g]	– 7.9	87 304
–, –, dimethyl ester	167–168	181–83	– 9.3[f]	87
–, 2,2′,4,4′-tetramethyl	270[d]	214–216	– 5.5	110
–, –, dimethyl ester	Oil	95–96	– 7.4	110
2,4,4′-Tricarboxy				
–, 2-hydroxymethyl	—	215–216	– 24	94
2,2′,4,4′-Tetracarboxy	310–315[d]	310[d]	– 12	94
2,2-Bis(bromomethyl)				
–, 4,4′-dibromo	99.5–100.5	53–55	+ 24[b]	263
–, –, 5,5′-dimethyl	116–118	114–116	+ 32[b]	109
–, 4,4′-dichloro	83–84	Oil	+ 5.5[h]	316
–, 4,4′-dimethyl	108–109	104.5–106	– 90[b]	262
–, 4,4′,5,5′-tetramethyl	—	—	– 5.7[b]	314
–, –, (*S*)-form	—	149–151	+ 11[b]	314
4,4′-Bis(bromomethyl)				
–, 2,2′-dibromo	110–111	59–60.5	+ 17[b]	224
–, 2,2′-dimethyl	100–101	42–48	– 61[b,e]	262
–, 2,2′,5,5′-tetramethyl	—	201–203	+ 13[b,e]	315
2,2′-Bis(chloromethyl)				
–, 4,4′-dimethyl	"Solid"	Oil	– 45[b,e]	262
–, 4,4′,5,5′-tetramethyl	—	143–145	+ 3.3[b]	314
2,2′-Bis(hydroxymethyl)				
–, 4,4′-dibromo	146–147	111–112	+ 58	263
–, –, 5,5′-dimethyl	90–92	128–130	+ 37	109
–, 4,4′-dichloro	155–157	181–183	+ 35	316
–, 4,4′-dimethyl	101–101.5	71–73	+ 24	262
–, 4,4′,5,5′-tetramethyl	137–139	118–120	+ 37[i]	314

TABLE 9. (*Continued*)

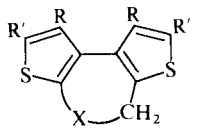
Substituents	(*R*,*S*) m.p. (°C)	(*R*) m.p. (°C)	(*R*) $[a]_D^{25}$ (deg)	Ref.
4,4′-Bis(hydroxymethyl)				
–, 2,2′-dibromo	134–136	Oil	+ 28	224
–, 2,2′-dimethyl	127–128	Oil	+ 29[e]	262
–, 2,2′,5,5′-tetramethyl	—	—	+ 23[e]	315
5,5′-Diacetoxymercury				
–, 2,2′,4,4′-tetrabromo	—	> 350	− 23.8[e]	304
2,2′-Dibromo				
–, 4,4′-dimethyl	—	79–82	− 10	224
4,4′-Dibromo				
–, 2,2′-dimethyl	—	75–83	+ 39	263
–, 2,2′,5,5′-tetramethyl	93–94	97–99	+ 18[b]	109
5,5′-Dibromo				
–, 2,2′,4,4′-tetramethyl	107–108.5	140–141.5	− 1	110
2,2′,4,4′-Tetrabromo	162–163	—	—	263
	—	163–164	− 20	304
–, 5,5′-dimethyl	146–148	160–162	− 15[b]	109
Hexabromo	181–182	—	—	87
	—	142–142.5	− 12.2	304
2,2′,4,4′-Tetramethyl	51–52	50–52	− 6.7	110

Hexamethyl	92.5–93	65.5–66.5	+ 9.1	110
2,2′(—CH_2—S—CH_2—) (cf. **289**)				
–, 4,4′-dibromo	155–156	137–148	– 68[b]	263
–, –, 5,5′-dimethyl	—	100–125	– 137	109
–, 4,4′-dicarboxy	304–307	310–313	– 113[e]	299
–, 4,4′-dichloro	151–153	—	– 35[b]	316
–, 4,4′-bis(hydroxymethyl)	176–180	129–133	+ 8.8[e]	299
–, 4,4′-dimethyl	95.5–96	76–79	+ 44[b]	262
–, 4,4′,5,5′-tetramethyl	—	Oil	CD[k]	314
4,4′(—CH_2—S—CH_2—) (cf. **291**)				
–, 2,2′-dibromo	116–116.5	135–136	– 121[b,e]	262
–, 2,2′-dimethyl	181–183	142–144	– 290[b]	224

Acid groups and derived forms have been given preference.

[a] Rotational values of the (*R*)-forms in ethanol if not otherwise stated.
[b] In dioxane.
[c] (*R′*)-form.
[d] Decomposition.
[e] Estimated from the (*S*)-form.
[f] In bensen.
[g] See the text.
[h] In ethanol.
[i] Erroneously reported as – 37 in Ref. 314.
[k] CD data are given for the (*S*)-form.

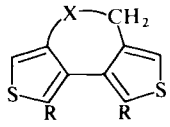
TABLE 10. Inactive 2,2′-Bridged 3,3′-Bithienyls[a]



X	R	R′	m.p. (°C)	Yield (%)	Ref.
—CH_2—N(R″)—					
R″ = —CH_3	H	H	101–103	77	265
	Br	H	113–115	69	297
R″ = —CH_2CH_3	H	H	63	48–63	241
R″ = —$CH_2C_6H_5$	Br	H	136–137	72	297
R″ = —C_6H_5	H	H	141	83	241
—CH_2—O—	H	H	58–60	82	265
			62	72	241
	Br	H	202–203	90	263
	Br	CH_3	169–171	90	109
	Cl	H	190–192	75	316
	CH_3	H	125.5–126.5	75	262
	CH_3	CH_3	Oil	—	314
—CO—O—	Br	H	215–217	47	263
	CH_3	H	128.5–130	61	262
—CH_2—S—	H	H	86–88	89	265
			91	61–69	241
	Br	H	155–156	67	263
	Cl	H	151–153	93	316
	CH_3	H	95.5–96	91	262
	CH_2OH	H	176–180	27	299
	COOH	H	304–307	73	299
	COOH	CH_3	300, dec.	60	314
	—CH_2—O—CH_2—	H (**295**)	71–74	76	299
	—CH_2—S—CH_2—	H (**296**)	180–185	—	299

[a] For optically active thiepines, see Table 9.

TABLE 11. Inactive 4,4′-Bridged 3,3′-Bithienyls[a]



X	R	m.p. (°C)	Yield (%)	Ref.
—CH_2—N(R′)—				
R′ = —CH_2CH_3	H	Oil	57–66	241
R′ = —C_6H_5	H	167	71	241
—CH_2—O—	H	111	68	241
	Br	159–160	84	224
	CH_3	107.5–109	89	262
—CO—O—	Br	192–192.5	77	224
	CH_3	154.4–155.5	64	262
—CH_2—S—	H	160	49–73	241
	Br	181–183	67	224
	CH_3	116–116.5	80	262

[a] For optically active thiepines, see Table 9.

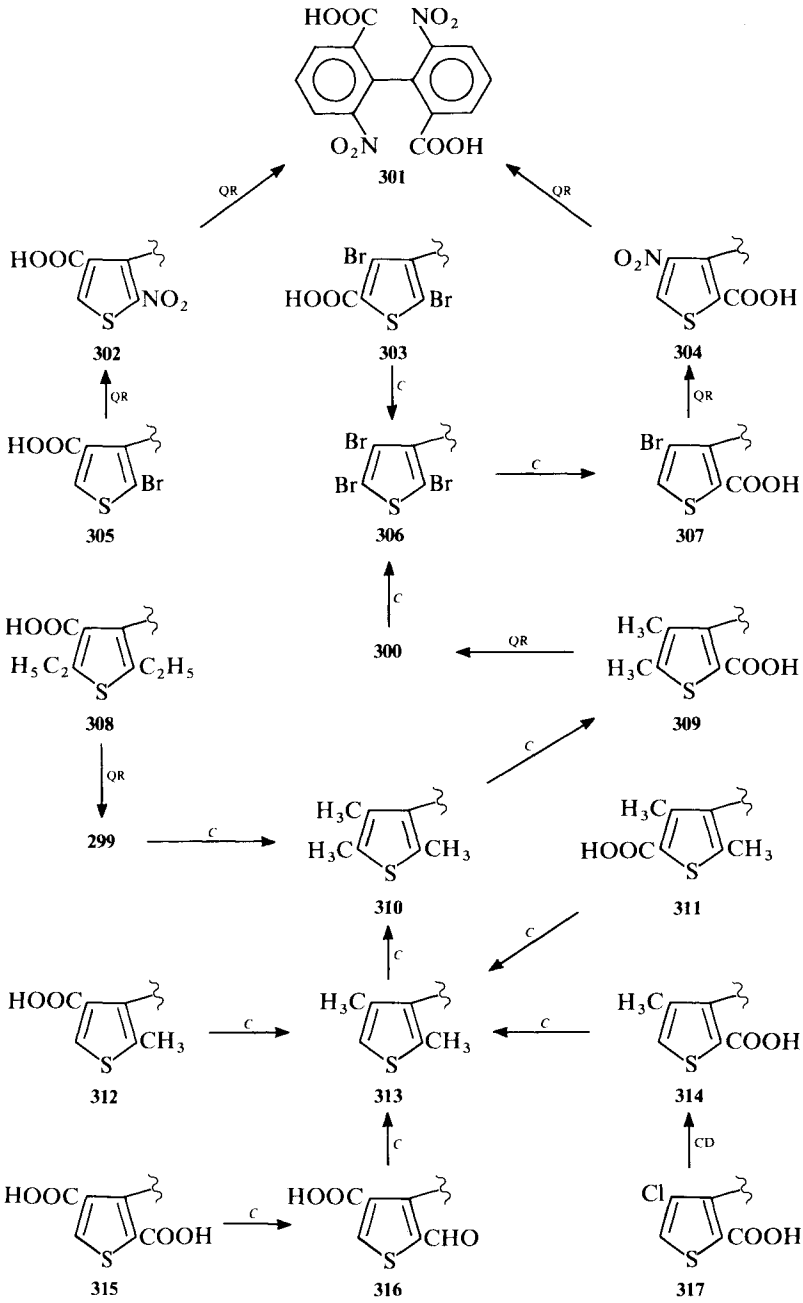
have been exchanged for thiophene rings. The optical rotations are usually very high, due to the presence of an inherently chiral chromophore. In a paper by Groen and Wynberg[303] in which references to syntheses and resolutions are given, the optical properties (ORD and CD spectra) of some heterohelicenes are presented and discussed.

1. Preparations and Absolute Configurations

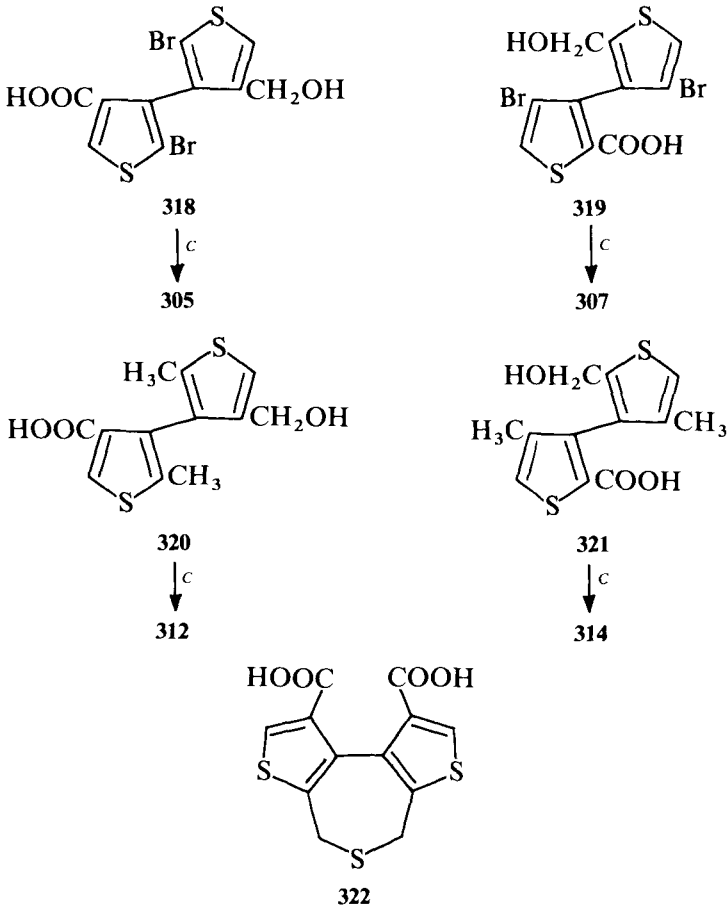
Optically active 3,3′-bithienyls were obtained on resolution of racemic mono- or dicarboxylic acids. Subsequent transformations of the carboxylic groups and/or substitution at accessible positions yielded various other optically active compounds.

The resolved acids are collected in Schemes 65–67. Schemes 66 and 67 also show the course of the determinations of the steric relationships of the active 3,3′-bithienyls. To make this possible in a limited space, only half of the symmetrically substituted 3,3′-bithienyls are shown in Scheme 66. This scheme also includes the key substances hexabromo-3,3′-bithienyl (**306**), hexamethyl-3,3′-bithienyl (**310**), and 2,2,4,4′-tetramethyl-3,3′-bithienyl (**313**).

The latter compound, as well as the corresponding 2,2′,4,4′-tetrabromo-3,3′-bithienyl (**323**, Scheme 68) and tetracarboxylic acid **315**, exhibit atropisomerism, in contrast to the similarly tetrasubstituted biphenyls. This is due to the sulfur atoms of the rings, and on assignment of the chirality symbols these atoms give precedence to C-2 and C-2′ over C-4 and C-4′. This results in the relationship


HOOC NO2
O2N COOH
301
QR
QR
HOOC NO2
S
302
Br HOOC Br
S
303
O2N COOH
S
304
QR
C
QR
HOOC Br
S
305
Br Br Br
S
306
Br COOH
S
307
C
HOOC H5C2 C2H5
S
308
300
QR
H3C H3C COOH
S
309
QR
C
299
C
H3C H3C CH3
S
310
H3C HOOC CH3
S
311
C
C
HOOC CH3
S
312
C
H3C CH3
S
313
C
H3C COOH
S
314
C
CD
HOOC COOH
S
315
C
HOOC CHO
S
316
Cl COOH
S
317

Scheme 66

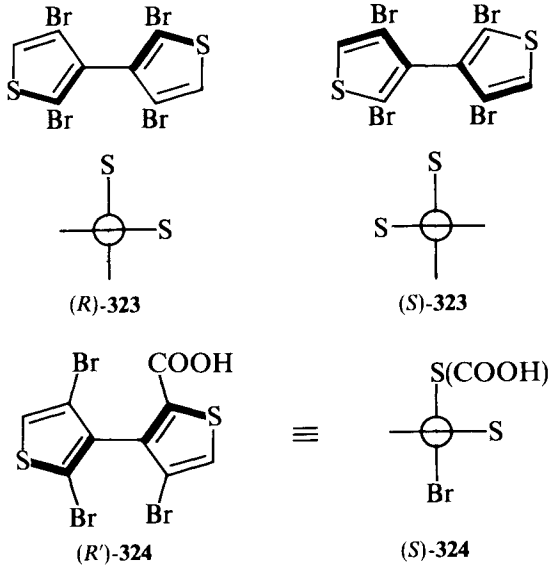


Scheme 67

between the twist of the bithienyl skeleton and the chirality symbols shown in Scheme 68.

In general, symmetrically substituted 3,3′-bithienyls such as those shown in Scheme 66 exhibit the corresponding connections; that is, the (*R*)-forms are twisted in a similar way as shown for (*R*)-**323**. However, in the case of 2,4,4′-tribromo-2′-carboxy-3,3′-bithienyl (**324**), for example, which has been obtained in optically active form from (*R*)-**323**,[304] the chirality symbol should be altered to (*S*) despite the "(*R*)-configuration" of the 3,3′-bithienyl skeleton. This is because in the unsymmetrically substituted ring the heavy bromine atom gives precedence to C-4′ over C-2′, whereas in the other ring C-2 still takes precedence over C-4.

For the sake of convenience, as in comparisons of CD spectra of sterically related compounds and for discussions in general, the following rule was suggested:[304]



Scheme 68

A 3,3'-bithienyl will be assigned the chirality symbol *R* (or *S*) if the unsubstituted compound with unchanged chirality of the bithienyl skeleton would be assigned the chirality symbol *R* (or *S*). If the symbol should be altered, using the general rules, this is indicated with *R'* (or *S'*).

In the following presentation, the description will be connected to the course of the determination of the steric relationships, as shown in Schemes 66 and 67, rather than to the chronological order of preparation or any other order.

Nitro compound **302** was prepared by Gronowitz and Gustafson[103] in 63% yield by nitration of 4,4'-dicarboxy-3,3'-bithienyl, obtained on carbonation of **236** (Scheme 47). It was resolved via the brucine and quinine salts, giving the dextrorotatory and levorotatory forms, respectively.

The absolute configuration of **302** was deduced by the quasi-racemate method[305,306] (indicated by QR in Scheme 66), using the methyl esters of **302** and **301**. The absolute configuration of **301** had previously been determined by Mislow and coworkers,[307] and their conclusions from chemical methods were later confirmed unequivocally by Bijvoet X-ray analyses.[308–311]

The criteria for the application of the quasi-racemate method, which was developed by Fredga and coworkers, are generally the formation of a molecular compound in the ratio 1 : 1 (a quasi-racemate) on mixing the two components to be related that have opposite configurations, while those with the same configuration form a solid solution or a eutectic mixture, as judged from melting-point diagrams. Alternatively, one combination may give a solid solution (same configuration) and the other a eutectic type of diagram (opposite

configurations). The two compounds should not differ too much structurally, since preferably they might replace each other in the crystal lattice.

However, in the present case, the mixture of the methyl esters of **301** and **302** with the same direction of rotation, as well as that of those with opposite directions of rotation gave melting point diagrams of the eutectic type. In the latter system the eutectic temperature was about 10° lower. Since it is considered [305,312] that in such cases the lower eutectic temperature is observed when the components have opposite configurations, it was concluded that dextrorotatory **302** has the (*R*)-configuration. [Levorotatory **301** has the (*S*)-configuration,[307] and the esters exhibit the same mode of rotation as their acids.]

Nitro compound **304** was prepared by Gronowitz and Dahlgren[93] via an Ullmann coupling of methyl 3-bromo-4-nitro-2-thiophenecarboxylate to the corresponding methyl ester **117** (Scheme 22, Section II.2.B). The resolution and evaluation of the absolute configuration was performed by Gronowitz.[313] The levorotatory form was obtained via the quinine salt and the dextrorotatory form via the cinchonidine salt.

The mixtures of the methyl esters of these forms with the levorotatory methyl ester of **301** gave melting-point diagrams of a similar type as those obtained in the case of **302**. The eutectic temperature of the combination of the esters with opposite direction of rotation was about 15° lower than that of the alternative combination, indicating the (*R*)-configuration for dextrorotatory **304** and its methyl ester.

Compounds **302** and **304** were also interrelated by the same method. In both cases, the inactive methyl esters were true racemates. On mixing the esters of **302** and **304** with opposite modes of rotation a quasi-racemate was formed, while those of the same sign formed a solid solution. This was consistent with the previous results. The study of X-ray powder photographs derived from mixtures of the optically active acids **302** and **304** gave additional evidence for the steric relationships, as did a comparison of the effect of solvents on the rotational values of the two compounds.[313]

As mentioned previously (Sections IV.1.C.b and IV.2.B), a 5,5′-dilithio derivative can be obtained[263] from hexabromo-3,3′-bithienyl and alkyllithium. Carbonation of this intermediate gave carboxylic acid **303** in 60% yield,[87] while hydrolysis afforded 2,2′,4,4′-tetrabromo-3,3′-bithienyl **323** in 61% yield.[87,263] From the latter compound, dicarboxylic acid **307** could be prepared in 59% yield on halogen–metal exchange at the 2,2′-positions and subsequent carbonation.

The dimethyl ester of **307** was also formed in 12% yield from 3,4-dibromo-2-carbomethoxythiophene in an Ullmann reaction, which confirmed the structures of **307**, **323**, and **303**.

The 5,5′-dicarboxylic acid **303** was resolved via its monbrucine salt.[87,304] The pure optically active forms did not crystallize, but they could be obtained in a crystalline state by distilling off the ether from an ether–carbon tetrachloride solution. In the crystals 1 mol of carbon tetrachloride was associated with 2 mol

of acid. The solvent of crystallization was not removed on drying at 95°C/10 mmHg for 5 h. On melting-point determination, a solid foam was obtained at about 120°C, which gave a transparent liquid at 248–250°C, reported as the melting point in Table 9.[87]

Dicarboxylic acid **303** was decarboxylated with mercuric acetate. Levorotatory (ethanol) **303** gave levorotatory (benzene) tetrabromo compound **323**, from which levorotatory (benzene) hexabromo-3,3′-bithienyl (**306**) was obtained on bromination.

Attempts to prepare optically active dicarboxylic acid **307** from optically active **323** via the 2,2′-dilithio derivative failed, since complete racemization occurred during the reaction. (This behavior will be further treated in Section VI.2.) However, by using less than 1 eq of butyllithium, dextrorotatory monocarboxylic acid **324** was obtained from levorotatory **323**.[87]

Dicarboxylic acid **307** was resolved into optically active forms via its brucine salt.[304] Its absolute configuration was deduced by the quasi-racemate method, using the methyl esters of **304** and **307**. The forms with the same mode of rotation gave a melting-point diagram of the eutectic type, while those with opposite modes of rotation exhibited a weakly pronounced quasi-racemate. From this it could be concluded that dextrorotatory **307** has the (*R*)-configuration.

In order to effect a steric connection to **323**, **306**, and **303**, dextrorotatory 2,2′-dicarboxylic acid (*R*)-**307** was decarboxylated with mercuric acetate in boiling acetic acid, and the intermediate 2,2′,5,5′-tetraacetoxymercuri derivative (the free 5,5′-positions were also mercurated) treated with an aqueous bromine–potassium bromide solution to yield levorotatory hexabromo-3,3-bithienyl **306**, about 25% optically pure.[304] Accordingly, the levorotatory forms of **306**, **303**, and **323** also have the (*R*)-configuration, whereas dextrorotatory **324** may be represented as (*R*′).

(In Schemes 66 and 67 the letter *C* on the arrow means that the two compounds have been sterically related by chemical methods in some way or another. The arrow points toward the compound of previously known configuration, regardless of the direction of the chemical transformations).

As mentioned above, dicarboxylic acid **300** was prepared and resolved by Gronowitz and Frostling.[107,108] 5,5′-Dimethyl-3,3′bithienyl (Table 2) was metalated at the 2,2′-positions. Carbonation yielded 2,2′-dicarboxy-5,5′-dimethyl-3,3′-bithienyl (45% yield), which was brominated at the 4,4′-positions in 78% yield. The resolution of **300** was performed by fractional crystallization of the cinchonine salts.

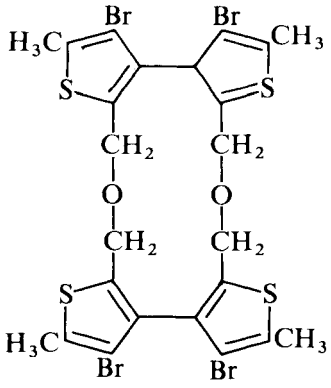
Even dicarboxylic acid **300** could be sterically related to hexabromo-3-3′-bithienyl, as both compounds could be transformed to optically active 2,2′4,4′-tetrabromo-5,5′-dimethyl-3,3′-bithienyl.[109] The levorotatory form of this compound was prepared from the 5,5′-dilithio derivative of levorotatory (*R*)-**306** and dimethyl sulfate, whereas the dextrorotatory form was obtained from levorotatory **300**. Accordingly, the two latter compounds have the (*S*)-configuration.

The transformation of **300** involved decarboxylation with mercuric acetate in

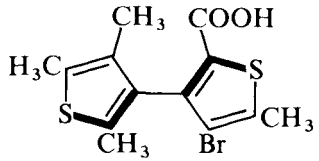
a way similar to that used for acid **307**, but it resulted in racemization to a still greater extent. This was explained in terms of a larger buttressing effect of the acetoxymercury groups at the 5,5′-positions in the case of **307**, compared to that of the methyl groups in the 2,2′-diacetoxymercury derivative of **300**.

Some other optically active compounds were prepared from active **300**.[109] The carboxylic groups were reduced to hydroxymethyl groups with $LiAlH_4$–$AlCl_3$ 1 : 1 and to methyl groups with $LiAlH_4$–$AlCl_3$ 1 : 4. It was found that the bromine atoms, even if situated at the 2,2′-positions of a 3,3′-bithienyl (as in the case of **305**; see below), are not removed on using equimolar mixtures of the reagents mentioned, whereas they may disappear with $LiAlH_4$ alone.

Treatment of the optically active bis(hydroxymethyl) compound with *p*-toluenesulfonic acid gave inactive oxepine **289** (X = O, R = Br, R′ = CH_3). A by-product assigned the structure (*S*,*S*)-**325** (Scheme 69) ($[a]_D^{25} = -56°$, dioxane, m.p. 205–220°C) was also obtained from the levorotatory dialcohol.



325



(*R*′)-**326**

Scheme 69

Reaction of the active bis(hydroxymethyl) compound with phosphorus tribromide yielded an active bis(bromomethyl) derivative, from which optically active thiepine **289** (X = S, R = Br, R′ = CH_3) was prepared with sodium sulfide.

Attempts to prepare optically active dicarboxylic acid **299** from active 4,4′-dibromo-2,2′5,5′-tetramethyl-3,3′-bithienyl (obtained by reduction of **300**) via the 4,4′-dilithio derivative gave a racemic product, as was the case in a similar attempt with the 2,2′-dilithio derivative of **323**. An optically active monocarboxylic acid (**326**) could be isolated in a low yield after reaction of the active 4,4′-dibromo compound with 1 eq of butyllithium and subsequent carbonation.

2,2′-Dibromo-4,4′-dicarboxy-3,3′-bithienyl (**305**) was investigated by Wiklund and Håkansson.[224] It was prepared by the oxidation of 2,2′-dibromo-4-4′-diformyl-3,3′-bithienyl (see Section IV.1.C.b for the bromination of 4,4′-dicarboxy and 4,4′-diformyl-3,3′-bithienyl). The resolution was performed with brucine as resolving base. The salt of the levorotatory form is less soluble in ethanol than that of the dextrorotatory form.

The crystals of the optically active forms of **305** turned glassy at about 115–118°C, whereupon new crystals melting at 205–206°C formed. (The racemic form melted with decomposition at 265°C.)

For the evaluation of the absolute configuration, an attempt was made to relate acid **305** to the isomeric acid **307** by the quasi-racemate method, using the active methyl esters. However, both combinations of the active esters gave eutectic phase diagrams of almost identical shapes, and thus no safe conclusions about the configurational relationships could be drawn.

Better results were obtained on applying the same method to the steric correlation of dicarboxylic acids **305** and **302**. The corresponding methyl esters with the same mode of rotation gave a quasi-racemate, indicating opposite configurations, whereas those with the same rotational sign gave a eutectic diagram. Since the esters exhibit the same sign as the acids, this means that levorotatory **305** has the (*R*)-configuration.

Active **305** has been brominated at the 5,5′-positions, and the carboxylic groups of the enantiomers of **305** have been transformed to methyl groups via the bis(hydroxymethyl) and bis(bromomethyl) derivatives. From the latter two an inactive oxepine (**291**, X = O, R = Br) and an active thiepine (**291**, X = S, R = Br), respectively, could be obtained. The reduction to the dialcohol was performed with $LiAlH_4$–$AlCl_3$ 1 : 1, leaving the 2,2′-bromines intact.

The synthetic path to 2,2′-dicarboxylic acid **309** was described by Wiersema and Gronowitz[14] in connection with their studies of the thiophene analogus of fluorene. It involved the coupling step to compound **110**, described in Scheme 21 and commented on in Section II.2.A. Metalation of **110** and subsequent carbonation gave **309** in 84% yield.[14]

The resolution of the acid was performed with quinine and cinchonine as resolving bases.[314] The levorotatory form was obtained optically pure after one recrystallization of the quinine salt.

The active acids crystallized from ethanol–water 1 : 2 with 1 mol of water per mole of acid. The values given in Table 9 are valid for the anhydrous form, obtained after evaporation of an acetone solution.

The absolute configuration of **309** was determined by relating the active dimethyl esters of **309** to the active dimethyl esters of **300** by the quasi-racemate method. Both racemic esters are true racemates, but the racemate-forming tendency of the dimethyl ester of **300** is very low. The components with opposite modes of rotation gave a melting-point diagram of the eutectic type, while those with the same direction of rotation formed a solid solution, indicating the same configuration. Accordingly, dextrorotatory **309** has the (*R*)-configuration.

Opticlly active dicarboxylic acid **309** has been transformed into various derivatives, as described for acids **300** and **305** above. In addition, the active acid dichloride and diamide were prepared. Some racemization occurred during these preparations, probably on treatment of the acid with thionyl chloride.[314]

A 2,2′-bis(hydroxymethyl) compound was prepared from dicarboxylic acid **309** with $LiAlH_4$ alone, since in this case the mixture $LiAlH_4$–$AlCl_3$ 1 : 1 gave hexamethyl-3,3′-bithienyl as the main product.

Attempts to prepare thiepine **289** (X = S, R = R' = CH_3) from Na_2S and the 2,2'-bis(bromomethyl) compound derived from (*S*)-**309** in ethanol resulted in solvolysis to (*S*)-2,2'-bis(ethoxymethyl)-4,4'5,5'-tetramethyl-3,3'-bithienyl ($[a]_D^{25} = +1°$, dioxane). The active thiepine was instead prepared from the corresponding 2,2'-bis(chloromethyl) compound in acetonitrile. This thiepine, as well as the corresponding oxepine (inactive), was isolated as a noncrystallizable oil.[314]

5,5'-Dicarboxylic acid **311** was obtained in 77% yield[110] on metalation and subsequent carbonation of 2,2'4,4'-tetramethyl-3,3'-bithienyl (Table 2). Levorotatory **311** was isolated via the monobrucine salt and dextrorotatory **311** via the dibrucine salt.

The absolute configuration was deduced by transformation of the two optically active dicarboxylic acids **311** and **309** to optically active hexamethyl-3,3'-bithienyl **310**. Decarboxylation of levorotatory **311** yielded levorotatory 2,2'4,4'-tetramethyl-3,3'-bithienyl (**313**). Metalation of this product and reaction of the intermediate 5,5'-dilithio derivative with dimethyl sulfate yielded dextrorotatory hexamethyl-3,3'-bithienyl.

Reduction of active 2,2'-bis(bromomethyl)-4,4'5,5'-tetramethyl-3,3'-bithienyl of known absolute configuration with sodium borohydride to active **310** revealed that dextrorotatory **310**, levorotatory **313**, and levorotatory **311** have the (*R*)-configuration.

The decarboxylation of **311** to **313** was performed with copper in quinoline. The tested mercuric acetate method obviously resulted in some redox reaction, since metallic mercury appeared in the reaction vessel during the reaction.

As mentioned above, 4,4'-dicarboxylic acid **299** was first prepared in low yield by Jean et al.,[35,90] and later the acid was resolved by Gronowitz and Beselin.[111] The preparation by Jean et al. involved an Ullmann coupling of **112** to compound **113** (Scheme 22).

Gronowitz and Beselin used another approach. 3-Iodo-2,5-dimethylthiophene was coupled via the 3-lithio derivative with $CuCl_2$ to 2,2',5,5'-tetramethyl-3,3'-bithienyl (Table 2). This compound was iodinated at the 4,4'-positions, and after halogen–metal exchange with butyllithium, followed by carbonation, dicarboxylic acid **299** was obtained in 78% yield.

The levorotatory form of **299** was prepared from the brucine salt and the dextrorotatory acid from the quinine salt.

The absolute configuration of **299** was deduced by reduction of the active acid to active hexamethyl-3,3-bithienyl **310** via the corresponding 4,4'-bis(hydroxymethyl) and 4,4'bis(bromomethyl) compounds.[315] From this it was evident that levorotatory **299** has the (*R*)-configuration.

Compound **308** was prepared by Gronowitz and Skramstad,[105] following a route similar to that used for the preparation of **299**. 2,2',5,5'-Tetraethyl-3,3-bithienyl (from the coupling of 2,5-diethyl-3-iodothiophene; Table 2) was iodinated at the 4,4'-positions, yielding 70% of a colored viscous liquid, which decomposed on attempted distillation at 0.01 mm Hg. After purification by passing through an alumina column, it was transformed to dicarboxylic acid **308** in 60% yield on carbonation of the derived 4,4'-dilithio compound.

An alternative route involving diacetylation of 2,2′,5,5′-tetraethyl-3,3′-bithienyl (46% yield) and subsequent oxidation with sodium hypobromite (haloform reaction) gave the same product (40% yield).

Quinine formed a salt with the levorotatory acid, whereas the dextrorotatory form was obtained via the cinchonidine salt.

In most cases, an active acid of 3,3′-bithienyl exhibits the same sign in various organic solvents, whereas it may be altered in 0.1 M sodium hydroxide. However, for dicarboxylic acid **308**, assigned as dextrorotatory, the following specific rotations were observed:[105] − 75° (0.1 M sodium hydroxide), − 3° (ethanol), + 3° (methanol), + 16° (dioxane), + 138° (methylene chloride), + 218° (carbon tetrachloride, + 284° (benzene). In chloroform containing 1% ethanol, concentration dependence was found in connection with the resolution. Ethanol or methylene chloride added to carbon tetrachloride had a similar effect. It was also found that the rotation of dicarboxylic acid **299** exhibited concentration dependence in solutions of chloroform–ethanol mixtures. This phenomenon was explained in terms of conformational changes, associated with different hydrogen bonding possibilities in the various cases.

For the evaluation of the absolute configuration of **308** the amides of optically active **299** and **308** were related by the quasi-racemate method.[315] Both amides form true racemates; that of the enantiomeric amides of **299** is especially pronounced. The melting point of the racemic form is more than 40° higher than that of the pure enantiomers.

The amides of the acids with opposite modes of rotation formed a quasi-racemate, indicating opposite configurations, and the alternative combination yielded a eutectic mixture. This implies that levorotatory dicarboxylic acid **308** has the (*R*)-configuration.

The isomeric dicarboxylic acids **312** and **314** were originally prepared by Gronowitz and Hagen.[106] The bithienyl system of **314** was obtained on coupling 3-bromo-4-methylthiophen to 4,4′-dimethyl-3,3′-bithienyl. Metalation and subsequent carbonation gave a complex mixture of acids, which was esterified with methanol via the acid chlorides. Through fractional crystallization, a 30% yield of the dimethyl ester of **314** was isolated, which was hydrolyzed to the desired compound.

Coupling of 3-iodo-2-methylthiophene by the $CuCl_2$ method yielded 2,2′-dimethyl-3,3′-bithienyl (Table 2). Iodination with iodine–iodic acid gave 2,2′-dimethyl-4,4′5,5′-tetraiodo-3,3′-bithienyl (64%), the α-halogens of which were removed via hydrolysis of the 5,5′-dilithio derivative (43%). Renewed halogen–metal exchange and subsequent carbonation afforded **312** in 45% yield.

Having 2,2′4,4′-tetrabromo-3,3′-bithienyl (**323**) readily available, Wiklund and Håkansson chose an alternative synthetic route.[262] Halogen–metal exchange and reaction of the resulting 4,4′-dibromo-2,2′-dilithio compound with dimethyl sulfate gave 4,4′-dibromo-2,2′-dimethyl-3,3′-bithienyl in 86% yield. Repeated reaction with alkyllithium followed by carbonation gave an 88% yield of dicarboxylic acid **312**.

Reaction of the latter 4,4′-dilithio intermediate with *N*,*N*-dimethylformamide instead resulted in 4,4′-diformyl-2,2′-dimethyl-3,3′-bithienyl (72%), used for the preparation of hydroxy acid **320** (Scheme 67).

For the preparation of **314**, 4,4′-dibromo-2,2′-dilithio-3,3′-bithienyl was reacted with *N*,*N*-dimethylformamide. The resulting dialdehyde[263] (86%) (cf. the preparation of **319** below) was protected as the dimethyl acetal, while the methyl groups were introduced at the 4,4′-positions with the aid of alkyllithium and dimethyl sulfate (93%). The resulting 2,2′-diformyl-4,4′-dimethyl-3,3′-bithienyl was oxidized ($KMnO_4$) to dicarboxylic acid **314** in 68% yield and was also used for the preparation of hydroxy acid **321**.

The enantiomers of dicarboxylic acid **312** were easily separated on fractional crystallization of the quinine and brucine salts, yielding the dextrorotatory and levorotatory forms, respectively.

In the case of **314**, dehydroabietylamine was the only base that permitted resolution, yielding the mono salt of the dextrorotatory acid. The levorotatory form could be obtained after treatment of the acid enriched in this form (from the mother liquor of the salt crystllization) with ethyl acetate.

As indicated in Scheme 66, the absolute configurations of dicarboxylic acids **312** and **314** were determined by reduction of the carboxyl groups to methyl groups, that is, to active 2,2′,4,4′-tetramethyl-3,3′-bithienyl (**313**). Levorotatory **312** gave (*R*)-(−)**313**, and levorotatory **314** gave (*S*)-(+)-**313**. Accordingly, the symbols should be (*R*)-(−)-**312** and (*R*)-(+)-**314**.

Dicarboxylic acids **312** and **314** were transformed to various derivatives as described previously for **300**, **305**, **309**, and **299**. Previous findings were confirmed, specifically, that with $LiAlH_4/AlCl_3$ carboxylic groups at the 2,2′-positions are much more easily reduced to methyl groups than are those at the 4,4′-positions, and that these reactions are enhanced by other methyl groups on the rings.

Bromination of **312** and **314** at the 5,5′-positions with elementary bromine resulted in some side-chain bromination, which could be avoided by using dibromoisocyanuric acid instead.

To avoid extensive racemization and ethanolysis, active thiepins **289** (X = S, R = CH_3, R′ = H) and **291** (X = S, R = CH_3) were prepared from the corresponding bromomethyl or chloromethyl compounds and sodium sulfide in acetonitrile at room temperature, instead of the usual solvent boiling ethanol.

Compound **316** was also prepared from tetrabromobithienyl **323**.[94] 4,4′-Dibromo-2,2′-diformyl-3,3′-bithienyl and its dimethyl diacetal were intermediate products in the synthesis of **314**. The 4,4′-dilithio derivative obtained on reaction of this diacetal with alkyllithium yielded compound **316** in 91% yield, after carbonation, and hydrolysis to recover the aldehyde groups.

Compound **316** was converted to an optically active form in a way that probably involved a second-order asymmetric transformation. This means that as a result of a low barrier to racemization all molecules of the compound may be converted to one enantiomer in connection with salt formation. In this case, it was the cinchonidine salt of dextrorotatory **316**.

For the evaluation of the absolute configuration this dextrorotatory form was treated for a couple of days with $LiAlH_4/AlCl_3$, giving a low yield (6.5%) of (*S*)-(+)-**313**.

From active **316**, active 2,4,4′-tricarboxy-2′-hydroxymethyl-3,3′-bithienyl was formed in an intramolecular Cannizzaro reaction.[94]

The tetramethyl ester of tetracarboxylic acid **315** was prepared in an Ullmann reaction (Table 2 and Section II.2.B), and after hydrolysis compound **315** was obtained.[94] The dextrorotatory form was prepared from the brucine salt, and even in this case a second-order asymmetric transformation was probably involved.

A more convenient synthetic pathway to **315** might seem to be that starting with tetrabromobithienyl **323**, with oxidation of dialdehyde **316** in the last step, but **315** was prepared for the first time much earlier.[94] However, the reaction mentioned was used for the determination of the absolute configuration, revealing that the dextrorotatory form of **315** has the (*S*)-configuration. [In cases like this, when only the (*S*)-form has been investigated, the values in Table 9, valid for the (*R*)-forms for the sake of simplicity and uniformity, have been estimated and/or recalculated.]

The last compound in Scheme 66, chloro acid **317**, was prepared from 4,4′-dichloro-3,3′-bithienyl (Table 2). After bromination of the free positions, and removal of the 5,5′-bromines on reaction with alkyllithium and subsequent hydrolysis, 2,2′-dibromo-4,4′-dichloro-3,3′-bithienyl was obtained. Renewed halogen–metal exchange reaction, followed by carbonation, gave **317** in 84% yield.[316]

The resolution was performed with the aid of dehydroabietylamine, affording the salt of the dextrorotatory form, and brucine, yielding the levorotatory form.

On the basis of the great similarities of the CD spectra of dextrorotatory **317** and (*R*)-(+)-**314** and (R)-(+)-**307** (see Section VI.3), the configurational connection (*R*)-(+)-**317** was established.

The hydroxy acids of Scheme 67 were all obtained through intramolecular Cannizzaro reactions of the corresponding dialdehydes. These dialdehydes and their preparations were mentioned in the foregoing; those yielding **320** and **321**, respectively, in connection with the acids **312** and **314**,[262] and that giving **318** in connection with acid **305**.[224] The precursor of **319**, 4,4′-dibromo-2,2′-diformyl-3,3′-bithienyl, conveniently prepared from tetrabromo compound **323**, has also been indicated in connection with the preparation of **314**.[263]

Hydroxy acids **318**,[224] **319**,[263] and **320**[262] were resolved into optically active forms via the brucine salts, whereas dehydroabietylamine was used in the case of **321**.[262]

Oxidation to the corresponding dicarboxylic acids of known absolute configurations (Scheme 67) revealed that levorotatory **318**, dextrorotatory **319**, levorotatory **320**, and levorotatory **321** possess the (*R*)-configuration.

The racemic bridged 4,4′-dicarboxylic acid **322** was prepared from thiepine **289** (R = Br, R′ = H) on treatment with alkyllithium and subsequent car-

bonation.[299] The thiepine was obtained from dicarboxylic acid **307** or hydroxy acid **319** via the bis(hydroxymethyl) and bis(bromomethyl) derivatives.[263]

By salt formation with quinine, the dextrorotatory form of **322** was obtained in a process involving a second-order asymmetric transformation. This form was suggested to have the (*S*)-configuration on the basis of its CD spectrum.

The carboxylic groups of **322** were converted to bis(hydroxymethyl) and bis(bromomethyl) groups by methods mentioned previously. From the bis(hydroxymethyl) derivative the doubly bridged bithienyl **295** (Scheme 64) was prepared, and the bis(bromomethyl) derivative gave the dithiepine **296** with Na_2S. Both **295** and **296** were racemic.

2. Optical Stabilities

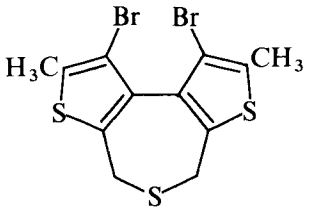
The rotational barriers and thus the optical stabilities of 3,3'-bithienyls are lower than those of the corresponding biphenyls, which is an expected consequence of the different ring sizes in the two systems. The barriers to internal rotation have been determined in racemization experiments with optically active 2,2'- and 4,4'-dicarboxylic acids and by dynamic NMR investigations of some inactive bridged compounds.

A surprisingly facile racemization took place on treatment of optically active tetrabromo compound **323** with alkyllithium, as mentioned previously, and this gave rise to a closer scrutiny of possible structures and bondings in organic lithium compounds.[317]

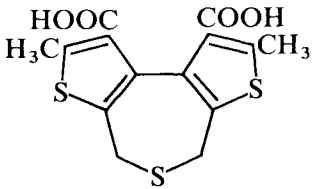
A. Racemization on Halogen–Metal Exchange; Structures of 2,2'- and 4,4'-Dilithio-3,3'-bithienyls

When optically active 2,2',4,4'-tetrabromo-3,3'-bithienyl (**323**) or 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithienyl was treated with 2 eq of alkyllithium at $-70°C$ for < 2 min, followed by carbonation, the products **307** and **299**, respectively, were completely racemic.[317] However, optically active monocarboxylic acids could be isolated, using 1 eq of alkyllithium. Since the two dicarboxylic acids **307** and **299** are optically stable at room temperature, the conclusion was that racemization must have taken place during the reaction, probably in the intermediate dilithium compounds. This implies an achiral conformation at some point with at least nearly coplanar rings.

Two possibilities, which may be described as cis and trans, or by some authors syn and anti, were considered. At first sight the latter conformation seemed most probable, an imagined "small" lithium atom passing a more bulky bromine atom. However, even the optically active bridged compound **327** (Scheme 70) exhibited a racemization process on treatment with alkyllithium at $-70°C$ for a few minutes followed by carbonation. The product **328**



327



328

Scheme 70

was completely inactive,[317] and in this case an trans conformation could be excluded.

Available data on C—Li distances in the literature indicated that a lithium atom might be at least as bulky as a bromine atom, provided that the types of bonding in the two cases are comparable. However, this seemed inconsistent with the facile racemization of the compounds mentioned above, especially considering the low temperatures and the short reaction times.

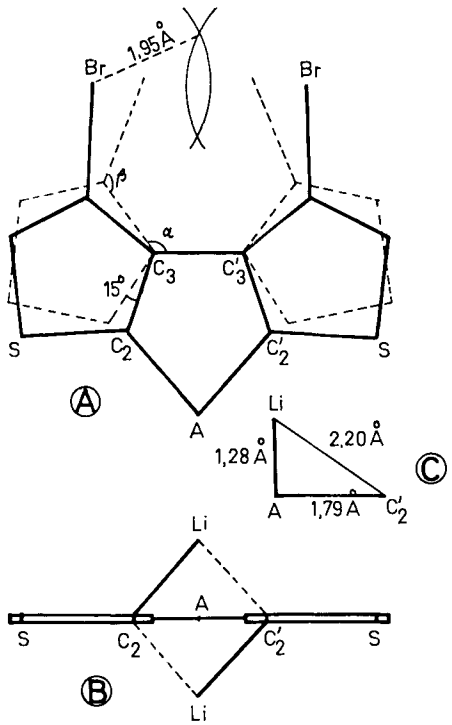


Figure 1. Proposed geometry of 4,4′-dibromo-2,2′-dilithio-3,3′-bithienyl: (*a*) model viewed perpendicular to the ring plane; (*b*) model viewed in the ring plane; (*c*) model viewed perpendicular to the plane containing C′-2 and the lithium atoms.

On the basis of what was known about structure and bonding in various organic lithium compounds, and otherwise taking normal interatomic distances and van der Waals radii into consideration, a structure for 2,2′- and 4,4′-dilithio-3,3′-bithienyls was proposed.[317] This is illustrated for 4,4′-dibromo-2,2′-dilithio-3,3′-bithienyl in Figure 1. In the model the rings are coplanar in a cis conformation. The two lithium atoms are situated 1.28 Å above and below the ring plane, and each is equally bonded to both the C_2- and C'_2-position by means of electron-deficient bonds.

About 10 years later X-ray crystallography of 2,2′-di(lithium–tmeda)biphenyl (tmeda = $Me_2NCH_2CH_2NMe_2$) by Schleyer and coworkers[318] confirmed unequivocally the existence of structures similar to that proposed for the dilithiobithienyls. For the biphenyl a structure analogous to that in Figure 1 was found. The average C—Li distance was 2.13 Å (2.20 Å proposed), and the Li—Li separation was 2.55 Å (2.56 Å in Figure 1). Each lithium atom, although coordinated by tmeda, interacts with C-2 and C-2′ in the same way as described in Figure 1.

The X-ray investigation confirmed previous theoretical predictions of the structure, based on molecular-orbital calculations. Similar calculations on dilithio-3,3′-bithienyls with the semiempirical MNDO method were performed by Kos,[319] and these were in full accordance with the structure given in Figure 1.

B. Racemization of Carboxylic Acids

The lower optical stabilities of 3,3′-bithienyls compared to those of the corresponding biphenyls was demonstrated by Gronowitz and Skramstad,[105] who compared the racemization of 4,4′-dicarboxy-2,2′,5,5′-tetramethyl-3,3′-bithienyl (**299**) with that of 3,3′,6,6′-tetramethyldiphenic acid in 0.1 M sodium hydroxide, although no quantitative difference was obtained. In the case of the biphenyl no racemization was observed even after 4 h at 150°C, whereas the racemization of optically active **299** could be conveniently followed at temperatures of 90–100°C.

In Tables 12 and 13 the activation parameters for the racemization of **299** and some other 2,2′- and 4,4′-dicarboxy 3,3′-bithienyls have been collected. The activation parameters were obtained by plotting ln (k/T) versus $1/T$ according to the Eyring equation[320] in the form

$$\ln\left(\frac{k}{T}\right) = -\frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R} + \ln\left(\frac{\kappa k_b}{h}\right)$$

where k is the rate constant at temperature T(kelvin), R is the gas constant, k_b is Boltzmann's constant, h is Planck's constant, and $\kappa = 1$ (the transmission coefficient). The value of k was obtained by following the change in rotation with time at a particular temperature and plotting $\ln(\alpha_0/\alpha)$ versus time, where α_0 is the rotation at the beginning of the experiment.

TABLE 12. Activation Parameters for the Racemization of Optically Active Dianions of 2,2′-Dicarboxy-3,3′-bithienyls in 0.1 M Sodium Hydroxide[a]

Substituent	$\Delta H^{\dagger}$ (kcal/mol)	$\Delta S^{\dagger}$ (cal/deg·mol)	$t_{1/2}$ (min)[b]	Ref.
4,4′-Dibromo	28.8 ± 1.6	− 12.6 ± 3.5	8000[c]	321
4,4′-Dicarboxy	24.4 ± 0.1[d]	− 7.4 ± 0.4	—	94
4,4′-Dichloro	25.2 ± 1.1	− 11.9 ± 2.8	88	316
4,4′-Dimethyl	25.6 ± 0.4	− 14.4 ± 1.3	330[c]	321
4,4′,5,5′-Tetramethyl	26.9 ± 0.4	− 13.6 ± 0.9	1200[c]	321

[a] The limits of error in this table are standard deviations obtained from least-squares treatment of the corresponding data.
[b] At 120°C.
[c] Estimated by extrapolation.
[d] Racemization of the tetrasodium salt at 75–85°C.

TABLE 13. Activation Parameters for the Racemization of Optically Active Dianions of 4,4′-Dicarboxy-3,3′-bithienyls in 0.1 M Sodium Hydroxide[a]

Substituent	$\Delta H^{\dagger}$ (kcal/mol)	$\Delta S^{\dagger}$ (cal/deg·mol)	$t_{1/2}$ (min)[b]	Ref.
2,2′-Dibromo	24.7 ± 0.2	− 14.7 ± 0.3	125	321
2,2′,5,5′-Tetraethyl	25.3	− 16	—	105
	26.3 ± 0.2	− 13.3 ± 0.4	500[c]	321
2,2′-Diformyl[d]	21.5 ± 0.1	− 9.4 ± 3.2	—	94
2,2′-Dimethyl	22.6 ± 0.3	− 13.0 ± 0.7	4[c]	321
2,2′,5,5′-Tetramethyl	22.1	− 15	—	105
	22.8 ± 0.8	− 13.1 ± 2.2	5[c]	321
2,2′(—CH_2—S—CH_2—), **322**	22.7 ± 0.8[d]	− 1.7 ± 2.8[e]	—	299
	22.5 ± 1.1[e]	− 5.8 ± 3.5[f]	—	299

[a] The limits of error in this table are standard deviations obtained from least-squares treatment of the corresponding data.
[b] At 120°C.
[c] Estimated by extrapolation.
[d] Racemization in diglyme at 45–50°C.
[e] Racemization in 0.1 M sodium hydroxide at 30–40°C.
[f] Racemization in ethanol at 45–55°C.

One aim of the racemization experiments was to investigate the effect of interchanging the 2,2′- and the 4,4′-substituents on the optical stability. From Tables 12 and 13 it is obvious that the 2,2′-dicarboxylic acids are more stable than the coresponding 4,4′-dicarboxylic acids, the difference amounting to 3–4 kcal/mol. The buttressing effect of a 5-(5′-) methyl group appears to be negligible or relatively small, and simple calculations were in agreement with these results.[321]

The racemization of dialdehyde **316** was investigated in diglyme, since in 0.1 M sodium hydroxide an intramolecular Cannizzaro reaction took place simultaneously with racemization.[94]

The facile racemization of the 2,2′-bridged compound **322** at 30–55°C has been investigated (Table 13). In this case, a considerably less negative value of $\Delta S^{\dagger}$ was observed, compared to those of the open structures, which was ascribed to a smaller change in the degree of ordering on-going from the ground state to the transition state. The $\Delta H^{\ddagger}$ values both for the salt and the free acid were found to be of the same magnitude as those for the open compounds.

The racemizations of **316** and **322**, taking place at relatively low temperatures, are in accordance with the second-order transformations observed in connection with their resolutions.

C. Barriers to Inversion of Bridged Compounds

As mentioned previously, oxygen- and nitrogen-bridged 3,3′-bithienyls (oxepines and azepines) have too low barriers to rotation to permit optically stable forms at room temperature, in contrast to similar cases in the biphenyl series.[322] However, some optically active sulfur-bridged 3,3′-bithienyls (thiepines) have been prepared (Section VI.1, Tables 10, 11).

In the bridged systems the two diastereotopic methylene protons of the bridge in most cases exhibit magnetic nonequivalence in deuterated dimethyl sulfoxide (DMSO-d_6), giving rise to an AB pattern in the ^{1}H NMR spectrum due to geminal coupling. On inversion, the two protons exchange magnetic environments, and when the inversion rate is sufficiently high on the NMR time scale only a single sharp methylene proton signal is observed.

The free energy of activation ($\Delta G_c^{\dagger}$) at the coalescence temperature T_c has been determined for the compounds collected in Tables 14 and 15 using the expression

$$\Delta G_c^{\dagger} = 4.57\, T_c \left[9.97 + \log \frac{T_c}{(\Delta\nu^2 + 6J_{AB}^2)^{1/2}} \right]$$

obtained by combining an approximate expression for the exchange rate constant[323,324]

$$k_c = \pi(\Delta\nu^2 + 6J_{AB}^2)^{1/2}/2^{1/2}$$

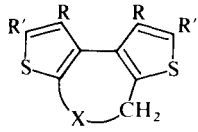
and the Eyring equation (above)

$$k_c = (\kappa k_b T_c/h)\exp(-\Delta G_c^{\ddagger}/RT_c)$$

$\Delta\nu$ is the difference in chemical shift for protons A and B and J_{AB} is the coupling constant for the protons

The interchange of 2,2′- and 4,4′-substituents in the oxepines and lactones investigated does not appear to influence the inversion barriers to any great extent, or in any definite direction (Tables 14 and 15). The buttressing effect of a

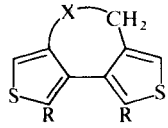
TABLE 14. Coalescence Temperatures (T_c) and Free Energies of Activation ($\Delta G_c^{\ddagger}$) for Inversion of Some 2,2′-Bridged 3,3′-Bithienyls in Deuterated Dimethyl Sulfoxide



X	R	R′	J_{AB} (Hz)	T_c (K)	$\Delta G_c^{\ddagger}$ (kcal/mol)	Ref.
—CH_2—O—	CH_3	H	12.4	349	17.3	321
	CH_3	CH_3	12.7	412	20.6	314
	Cl	H	10.7	360	17.8	316
	Br	H	12.8	424	21.1	321
						263
	Br	CH_3	12.5	450	22.5[a]	109
—CO—O	CH_3	H	13.6	363	18.2	321
	Br	H	14.0	407	20.5	321
						263
—CH_2—N(R″)—						
R″=—CH_3	Br	H	13.5	455	22.4	297
R″=$CH_2C_6H_5$	Br	H	14.3	443	21.8	297

[a] In hexamethyl phosphoramid.

TABLE 15. Coalescence Temperatures (T_c) and Free Energies of Activation ($\Delta G_c^{\ddagger}$) for Inversion of Some 4,4′-Bridged 3,3′-Bithienyls in Deuterated Dimethyl Sulfoxide



X	R	J_{AB} (Hz)	T_c (K)	$\Delta G_c^{\ddagger}$ (kcal/mol)	Ref.
—CH_2—O—	CH_3	11.7	347	17.3	321
	Br	12.0	400	20.0	321
—CO—O—	CH_3	12.8	374	18.8	321
	Br	13.0	404	20.4	321

5-(5′-)methyl group is greater in the bridged compounds than in the open ones. This was explained[321] in terms of a necessary cis coplanar activated state in the bridged 3,3′-bithienyls, in which two buttressed 4,4′-groups have to pass each other, whereas in a trans coplanar activated state, possible in open compounds, one buttressed 4-substituent may pass a nonbuttressed 2′-substituent.

From the few examples investigated, it appears that an azepine is slightly more stable toward inversion than the corresponding oxepine (Table 14). It may

also be concluded that the presence of an N-benzyl group instead of an N-methyl group decreases rather than increases the stability.[297]

The barriers to inversion of the inactive doubly bridged compounds **295** and **296** (Scheme 64) have not been determined, but it may be mentioned that compound **295** was dissolved in CS_2 and the temperature of the solution lowered to $-95°C$ without any change of the proton NMR spectrum (i.e., splitting of the sharp methylene signals).[299] This might be due to a low barrier to inversion, but other explanations may also be found (e.g., active **322** exhibits a methylene singlet at room temperature). For comparison it may be mentioned that Mislow et al.[325] have reported $E_{rac} = 30.6$ kcal/mol (in *o*-xylene, half-life $t_{1/2} = 181$ min at 104.9°C) for the biphenyl analog of **295** and $E_{rac} = 35.0$ kcal/mol (in *o*-xylene, $t_{1/2} = 34$ min at 215.0°C) for the biphenyl analog of **296**.

3. Circular Dichroism Spectra

The CD and UV spectra of the optically active 3,3′-bithienyls are presented mainly in Refs. 315 and 326–328. The investigations have extended over several types of compounds: 2,2′-dicarboxylic acids and derived dimethyl esters,[326,328] acid chlorides and amides,[326] as well as bis(hydroxymethyl) and bis(bromomethyl) compounds,[328] 4,4′-dicarboxylic acids and derivatives of the kind mentioned above,[315,328] 2- and 4-monocarboxylic acids,[328] 5,5′-dicarboxylic acids,[327] and noncarboxylic open and bridged compounds.[327] The CD spectra of **315** and **316** (Scheme 66) have been presented elsewhere,[94] as have those of **322**,[299] **317**, and some derived compounds.[316] The CD spectra of the 3,3′-bithienyl analogs **302** and **304** and of 2,2′-dinitro-6,6′-diphenic acid (**301**) (Scheme 66) were first published by Gronowitz.[313]

In Figures 2–20 some CD spectra of various types of optically active 3,3′-bithienyls are shown. The spectra represent (*R*)-forms, with the exception of those of the bridged dicarboxylic acid in Figure 13, and of the diphenic acid in Figures 18–20, which were recorded on (*S*)-forms.

A typical feature for a 2,2′-dicarboxylic acid of (*R*)-configuration in most solvents is a positive CD band of relatively high intensity near 250 nm, combined with a negative band at higher wavelengths, as observed in Figures 2–4. A similar feature is preserved in 0.1 M sodium hydroxide solution, although the relative intensities of the two bands are altered, as the long-wavelength band is diminished. The same effect on this band has been observed on substitution at the 5,5′-positions, with bromines in particular, and a combination of the two effects may result in the disappearance of the band, as seen in Figure 3.[326] In 2,2′-dicarboxy-4,4′-dinitro-3,3′-bithienyl, on the other hand, the negative CD band is dominant and the positive one supressed (see Figure 17).

Noncarboxylic bromo and methyl derivatives of 3,3′-bithienyl exhibit the same negative–positive combination bands near 250 nm as demonstrated for the 2,2′-dicarboxylic acids (Figures 5, 6), and even the bridged compounds with a

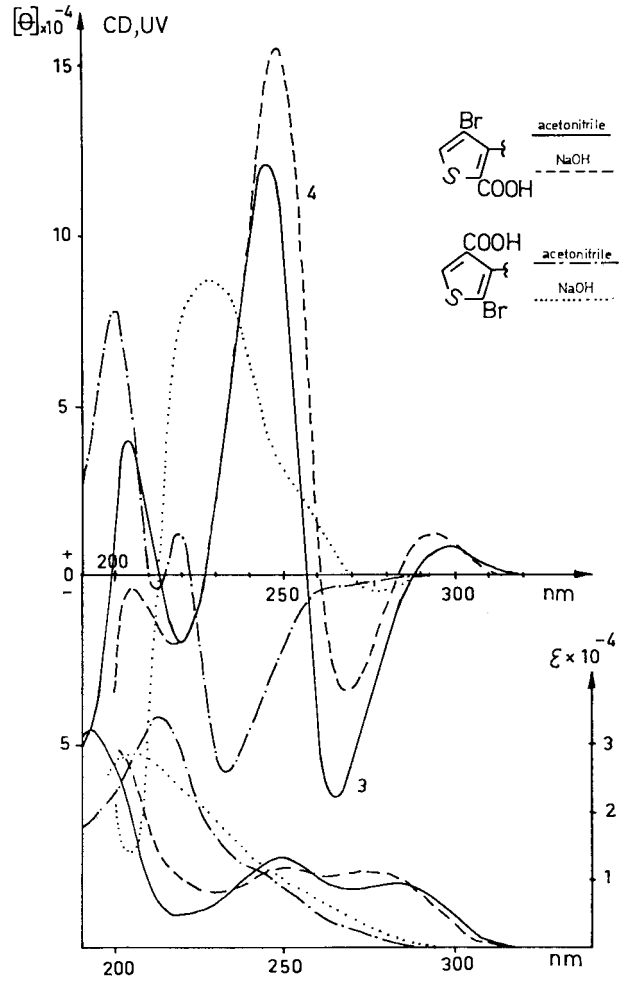


Figure 2. CD and UV spectra of (*R*)-(+)-4,4′-dibromo-2,2′-dicarboxy-3,3′-bithienyl and (*R*)-(−)-2,2′-dibromo-4,4′-dicarboxy-3,3′-bithienyl in acetonitrile and in 0.01 M sodium hydroxide.

fixed cis–skew conformation have similar CD spectra (Figures 7, 8). Again, 5,5′-bromines have a pronounced effect on the appearance of the spectra (Figure 6).

Inspection of the minor variations of several CD spectra, recorded on the same or on a closely related compound under different conditions, revealed that at least eight individual CD bands were probably involved in some cases, and it was demonstrated, for example, that a theoretical CD spectrum composed of the sum of eight Gaussian partial bands could be fitted to the experimental CD spectrum of the acid chloride of (*R*)-2,2′-dicarboxy-4,4′5,5′-tetramethyl-3,3′-bithienyl (**309**)[326] (Figure 9). Each partial band *k* was described by the

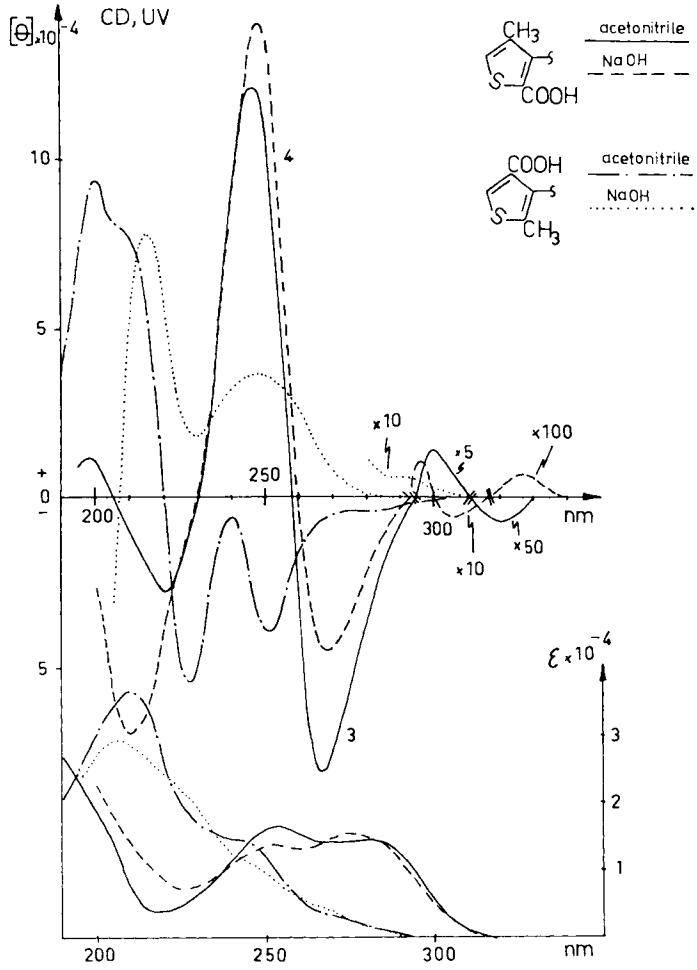


Figure 3. CD and UV spectra of (*R*)-(+)-2,2′-dicarboxy-4,4′-dimethyl-3,3′-bithienyl and (*R*)-(−)-4,4′-dicarboxy-2,2′-dimethyl-3,3′-bithienyl in acetonitrile and in 0.01 M sodium hydroxide.

expression

$$[\theta_k] = [\theta_k^\circ] \exp\left[\frac{-(\lambda - \lambda_k^\circ)^2}{(\Delta_k^\circ)^2}\right]$$

where $[\theta_k^\circ]$ is the maximum ellipticity value of band k reached at wavelength λ_k° and Δ_k° is the half-width of band k at the height $[\theta_k^\circ]/e = 0.368\,[\theta_k^\circ]$, as shown for band $k = 1$ in Figure 9. Probable starting values were chosen and varied to fit the theoretical curve to the experimental.

In a similar way, it was demonstrated that the spectrum of 5,5′-dibromo-2,2′,4,4′-tetramethyl-3,3′-bithienyl in Figure 6 might be the result of a similar set

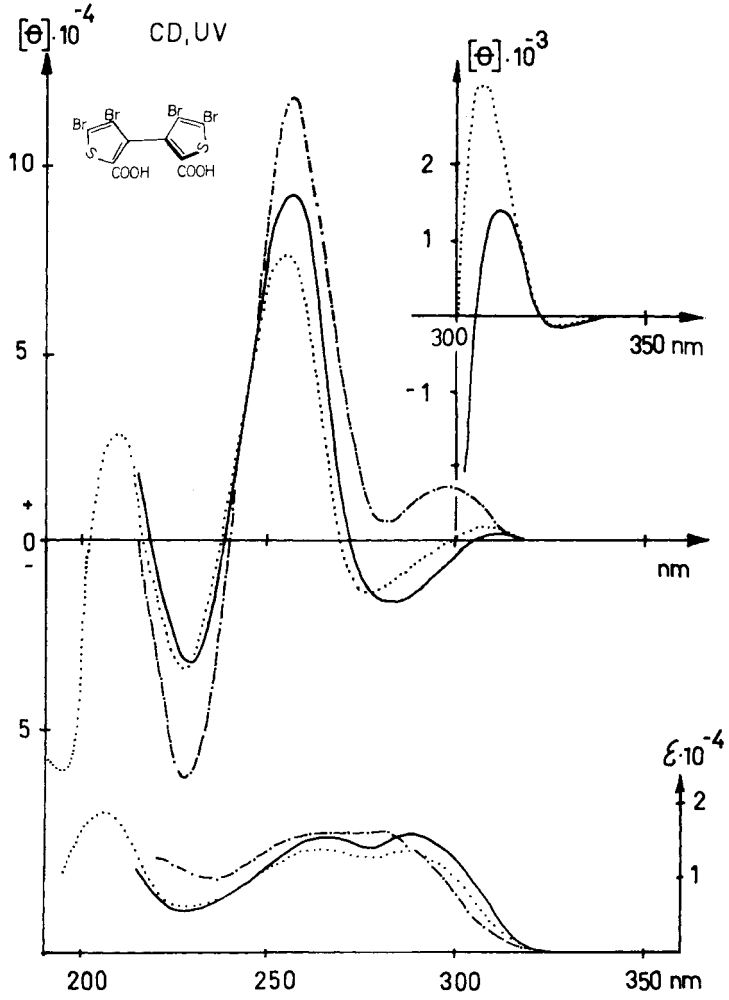


Figure 4. CD and UV spectra of (*R*)-(+)-4,4',5,5'-tetrabromo-2,2'-dicarboxy-3,3'-bithienyl; (——) in dioxane; (. . . .) in acetonitrile; (–.–.–.–.) in 0.1 M sodium hydroxide.

of Gaussian bands (Figure 10). It should be strongly emphasized that there are certainly several other solutions. The aim was to show that the appearance of the spectrum does not exclude the presence of a relatively strong negative band (3) near 250 nm, and that the curve shape is very sensitive to small shifts of the various bands, to a great extent evident for the operator during the calculation work. Such shifts may be the simple explanation of the various substitution effects instead of the more drastic inversion of the sign of a band.

In the case of a 4,4'-dicarboxylic acid, however, the situation is different (Figures 2, 3). To explain the large changes in the CD spectra observed in some

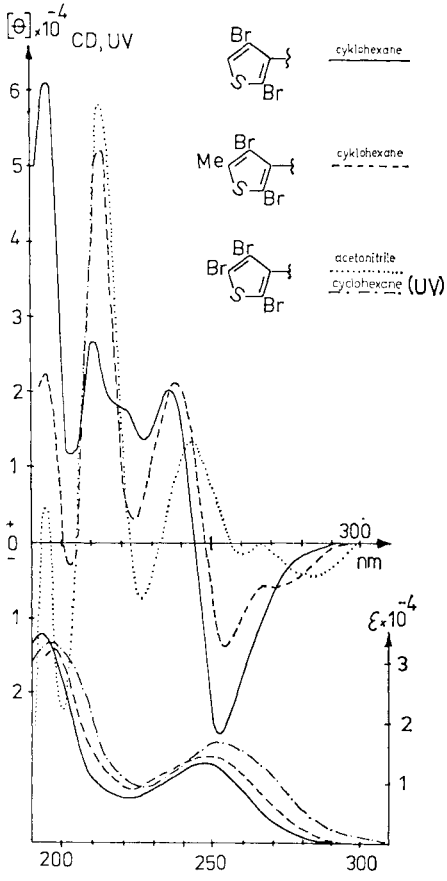


Figure 5. CD and UV spectra of (*R*)-(−)-2,2',4,4'-tetrabromo-3,3'-bithienyl and (*R*)-(−)-2,2',4,4'-tetrabromo-5,5'-dimethyl-3,3'-bithienyl and UV spectrum of (*R*)-(−)-hexabromo-3,3'-bithienyl in cyclohexane. CD spectrum of (*R*)-(−)-hexabromo-3,3'-bithienyl in acetonitrile.

cases on going from an acidic to an ionic form, for example, inversions of the signs of bands must be taken into consideration.

Compared to that of a 2,2'-dicarboxylic acid, the UV spectrum of a 4,4'-dicarboxylic acid appears more compressed from both the long-wavelength and short-wavelength sides. The intensities of the long-wavelength bands are lower, which, combined with the shift in positions, indicates greater conjugation in the 2,2'-dicarboxylic acids.

Corresponding shifts for the various CD bands are expected, and consequently the first long-wavelength CD band of a 4,4'-dicarboxy-3,3'-bithienyl is observed near 250 nm. A characteristic feature for the (*R*)-form in a neutral solvent is a negative CD band near and often below this wavelength, as can be seen in Figures 2 and 3. It might be that this band corresponds to the typical

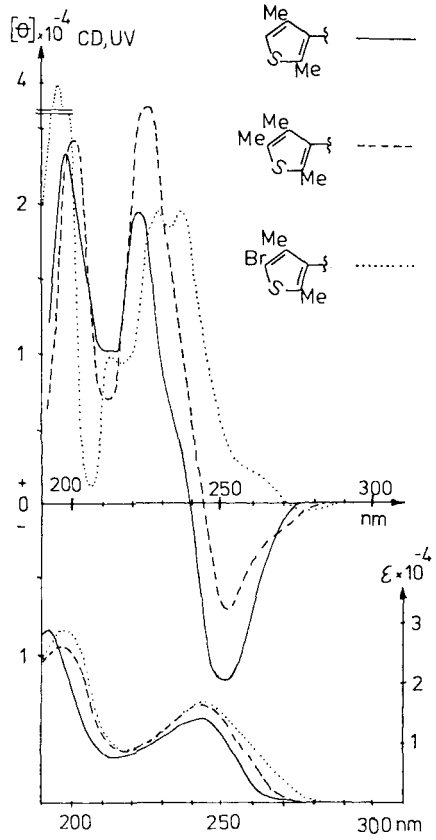


Figure 6. CD and UV spectra of (*R*)-(−)-2,2′,4,4′-tetramethyl-3,3′-bithienyl, (*R*)-(+)-hexamethyl-3,3′-bithienyl, and (*R*)-(−)-5,5′-dibromo-2,2′,4,4′-tetramethyl-3,3′-bithienyl in cyclohexane.

negative band at somewhat higher wavelength, previously pointed out for the 2,2′-dicarboxylic acids. A completely different spectrum is observed for the dianionic form recorded in 0.1 M sodium hydroxide, hardly interpretable solely in terms of wavelength shifts.

The ionization constants at 20°C and 0.002 M in 50% w/w methanol–water for some 2,2′- and 4,4′-dicarboxy-3,3′-bithienyls and a related biselenienyl and biphenyl have been determined by potentiometric titration.[315] Some titration curves are shown in Figure 11, and the differences are obvious. A large separation of pK_1 and pK_2 was explained by a suitable geometry for a strong internal hydrogen bond between the carboxylic groups in the monoanionic form. This would, for example, imply a cis–skew conformation for the monoanionic form of the tetramethyl compound **299**. Thus, provided that the above assumption is correct, the conformation as well as the configuration, i.e., the absolute twist P_x (right-handed helicity) or M_x (left-handed helicity; see

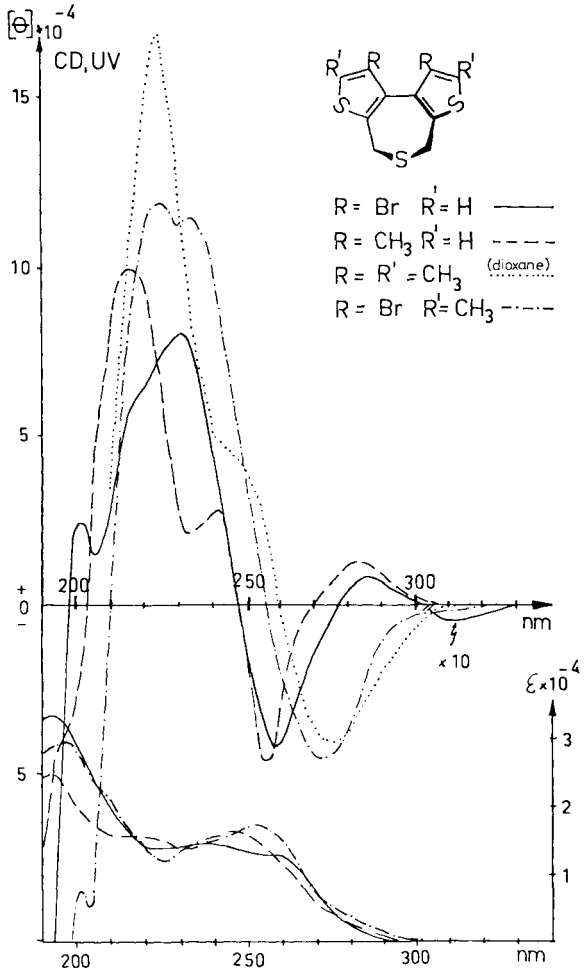


Figure 7. CD and UV spectra of (*R*)-(−)-1,9-dibromo-4,6-dihydrodithieno[2,3-*c* : 3',2'-*e*]thiepine, (*R*)-(+)-1,9-dimethyl-4,6-dihyrodithieno[2,3-*c* : 3',2'-*e*]thiepine, and (*R*)-(−)-1,9-dibromo-2,8-dimethyl-4,6-dihydrodithieno[2,3-*c* : 3',2'-*e*]thiepine in cyclohexane. CD spectrum of (*R*)-1,2,8,9-tetramethyl-4,6-dihydrodithieno[2,3-*c* : 3',2'-*e*]thiepine in dioxane [recorded on the (*S*)-form; see Table 9].

Figure 12) of the bithienyl skeleton is known (*x* means that the molecule is viewed along the pivot bond, by definition directed along the *x*-axis).

The large separation between the pK_a values of **299** permitted the recording of the CD spectrum even of the monoanionic form, as shown in Figure 12. It may be seen that this spectrum is virtually the mirror image of that of the di-acidic form. Its shape is reminiscent of that of the CD curve of a 2,2'-dicarboxylic acid, for example, the tetrabromo compound in Figure 4.

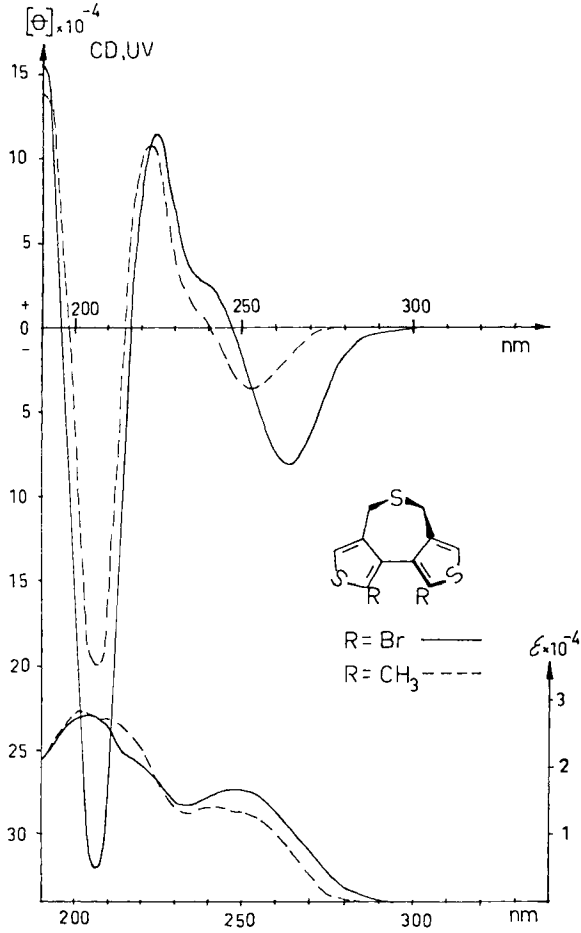


Figure 8. CD and UV spectra of (*R*)-(−)-1,9-dibromo-4,6-dihydrodithieno[3,4-*c* : 3′,4′-*e*]thiepine and (*R*)-(−)-1,9-dimethyl-4,6-dihydrodithieno[3,4-*c* : 3′,4′-*e*]thiepine in cyclohexane.

Going further to the dianionic form results in the apparent change in sign of some band(s).

The explanation nearest to hand might be that the CD spectra reflect a change from a trans–skew (P_x) conformation in the diacidic form to a cis–skew (M_x) conformation in the monoanionic hydrogen bonded form. However, certain experimental facts contradict such a statement. For example, the CD spectrum of the dextrorotatory form of the bridged 4,4′-dicarboxylic acid **322** in dioxane (not easily soluble in acetonitrile) has been recorded[299] (Figure 13). The long-wavelength bands in this case appear to retain their signs in sodium hydroxide solution. On the basis of a comparison with the CD spectrum of a bridged diphenic acid and, perhaps more reliably, a comparison of the CD

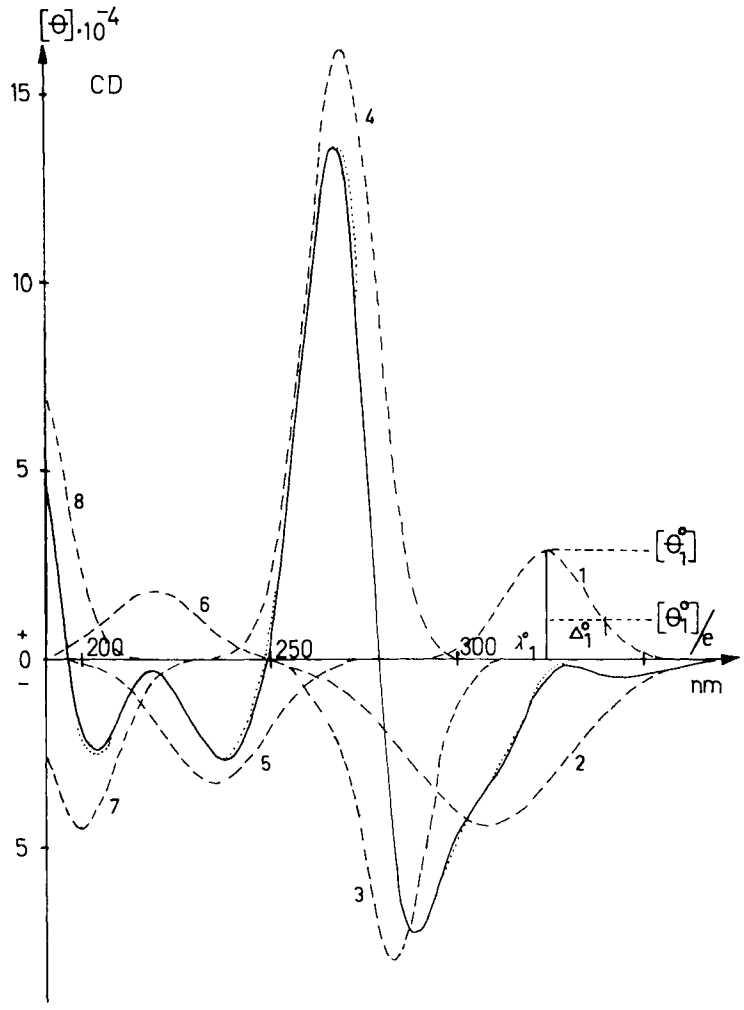


Figure 9. Theoretical CD spectrum (——) composed of eight Gaussian partial bands (– – –) compared with the CD spectrum of the acid chloride of (*R*)-2,2'-dicarboxy-4,4',5,5'-tetramethyl-3,3'-bithienyl in acetonitrile (. . . .).

spectrum of the 4,4'-bis(hydroxymethyl) derivative of **322** with the spectra of other bridged noncarboxylic compounds (Figure 7), it was concluded that the published spectrum represents an (*S*)-form. [Attempts to reduce the carboxylic groups to methyl groups, yielding a product with known absolute configuration (Figure 7), resulted in a complex mixture of products.] Since compound **322** necessarily has a cis–skew conformation and possesses (*S*)-configuration, leading to P_x helicity, the molecule should be approximately the mirror image of the proposed structure of the monoanionic form of (*R*)-**299** as far as the bithienyl

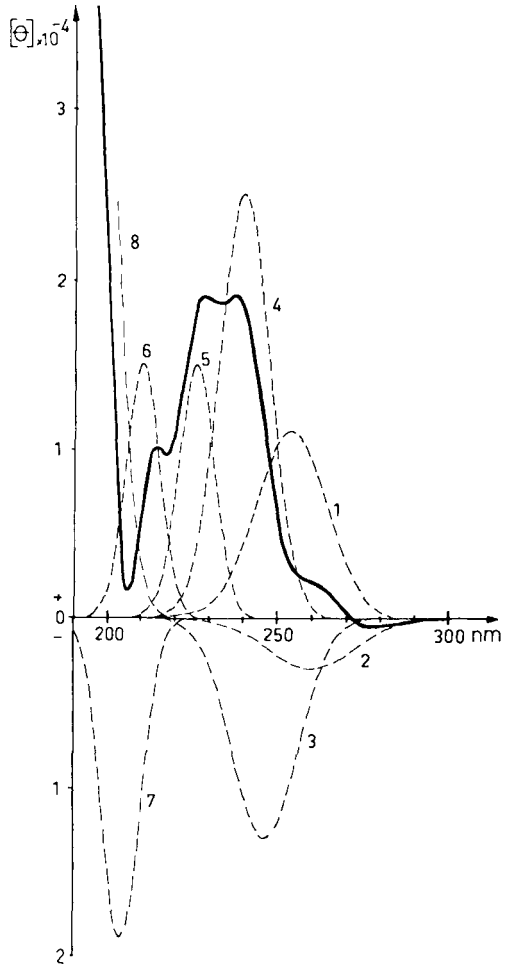


Figure 10. Theoretical CD spectrum of eight Gaussian partial bands fitted to the CD spectrum of (*R*)-5,5′-dibromo-2,2,4,4′-tetramethyl-3,3′-bithienyl.

skeleton is concerned (M_x helicity), which is far from reflected by the CD spectra. Instead, the (*S*)-form of this bridged 4,4′-dicarboxy-3,3′-bithienyl has a CD spectrum of the same type as those of the (*R*)-forms of the unbridged 2,2′-dicarboxy-3,3′-bithienyls (Figure 13) and the monoanionic form of (*R*)-**299** (Figure 12).

It should be pointed out that the reduction of the carboxylic groups of **322** to hydroxymethyl groups alters the signs of the CD bands. The reduced compound exhibits a spectrum with a positive CD band above 250 nm, followed by a negative band below this wavelength, i.e., the reverse spectrum of those in Figure 7, as expected for a noncarboxylic (*S*)-form.

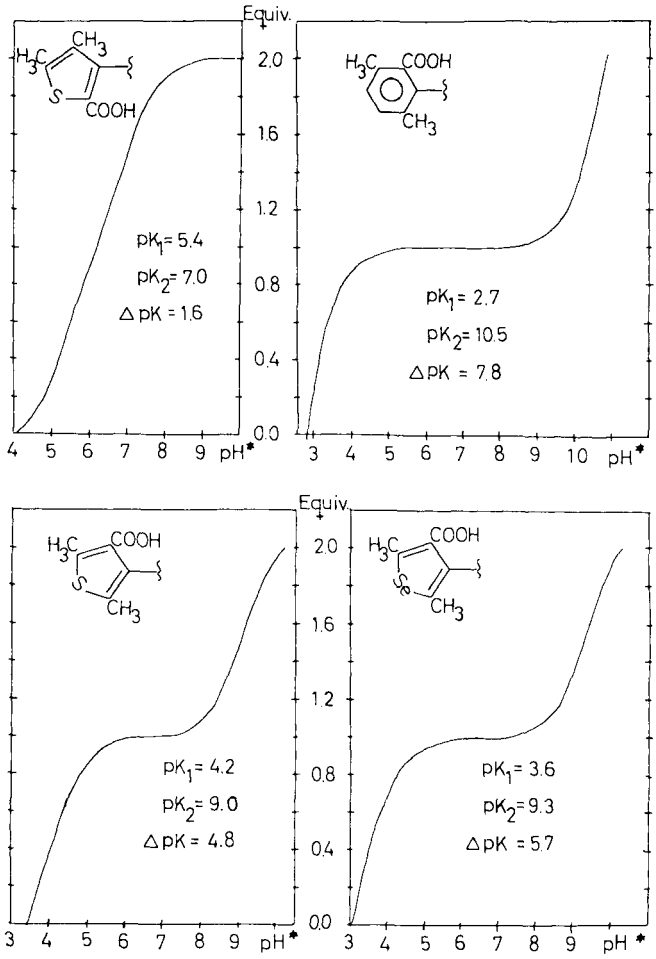


Figure 11. Titration curves for 2,2'-dicarboxy-4,4',5,5'-tetramethyl-3,3'-bithienyl, 3,3',6,6'-tetramethyl-2,2'-diphenic acid, 4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl, and 4,4'-dicarboxy-2,2,5,5'-tetramethyl-3,3'-biselenienyl.

Furthermore, the CD spectra of the crystalline states of 4,4'-dibromo-2,2'-dicarbomethoxy-3,3'-bithienyl (cf. **307**) and 2,2'-dibromo-4,4'-dicarbomethoxy-3,3'-bithienyl (cf. **305**) have been recorded[329] (Figure 14). In both cases the solution spectrum of the ester is virtually the same as that of the corresponding acid;[328] thus Figure 2 might represent the CD spectra of the methyl esters as well, in terms of the main features. A comparison with Figure 14 reveals that the spectra for solution and for the solid state agree well, from which it might be concluded that the molecules retain their crystal shapes in solution.

The stereochemistry of the two esters in the crystals are known in detail from X-ray diffraction data obtained by Aurivillius and coworkers.[330,331] A stereo-

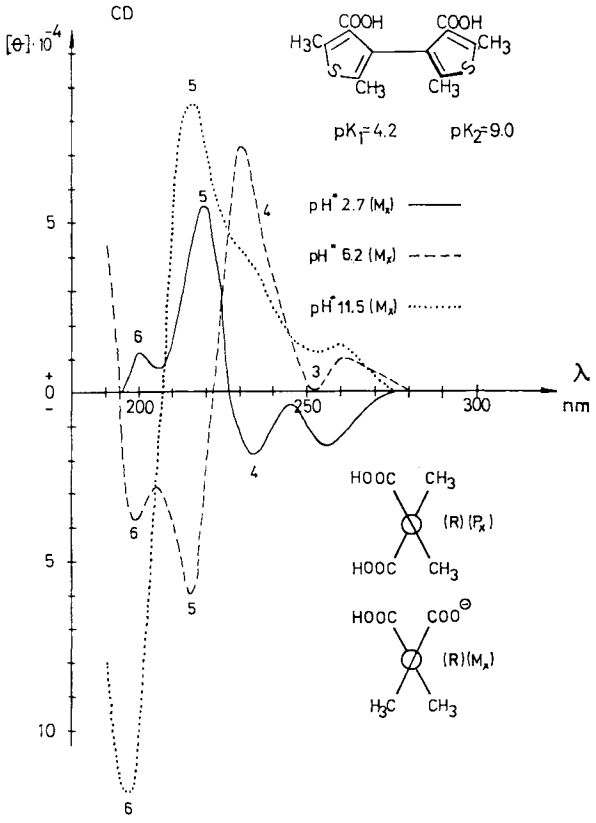


Figure 12. CD spectra of the diacidic, monoanionic, and dianionic forms of (*R*)-4,4′-dicarboxy-2,2′,5,5′-tetramethyl-3,3′-bithienyl in 50% aqueous methanol.

scopic view of 4,4′-dibromo-2,2′-dicarbomethoxy-3,3′-bithienyl based on these data[330] is shown in Figure 15, and a similar view of 2,2′-dibromo-4,4′-dicarbomethoxy-3,3′-bithienyl[331] can be seen in Figure 16.

Indeed, investigation of the 2,2′-dicarboxylic ester revealed three only slightly different conformations, which were difficult to distinguish on comparison of the corresponding stereoscopic views, and thus the one selected in Figure 15 may be considered as representative. In addition to the confirmation of the proposed absolute configuration, it can be seen that the molecule has a cis–skew conformation, that the two halves of the molecule are symmetric even with respect to the twist of the ester groups (the carbonyl oxygens point toward each other), and that each ester group is nearly coplanar with the ring to which it is attached.

In the case of the 4,4′-dimethyl ester in Figure 16 one single conformation was observed,[331] and it can be seen that the two halves of the molecule are not symmetric with respect to the ester groups. In both groups, the carbonyl oxygen is directed to the right, as the model is oriented, and the left group seems to be

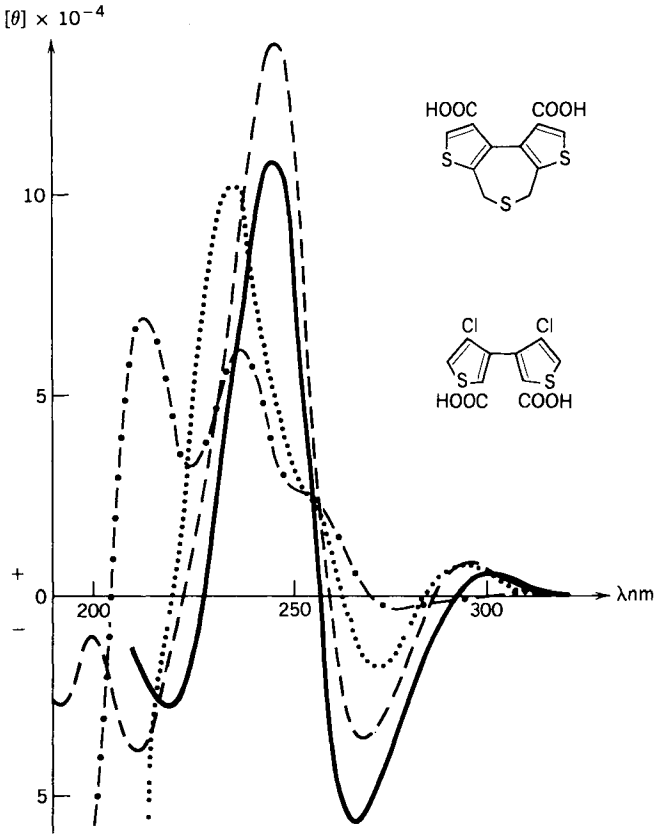


Figure 13. CD spectra of (*S*)-1,9-dicarboxy-4,6-dihydrodithieno[2,3-*c* : 3′,2′-*e*]thiepine (- - - -) in dioxane and (·—·—·—·) in 0.01 M sodium hydroxide and (*R*)-2,2′-dicarboxy-4,4′-dichloro-3,3′-bithienyl (———) in dioxane and (– – – – –) in 0.01 M sodium hydroxide.

more twisted out of the plane of its thiophene ring with *M* helicity as viewed along the bond between the ring and the carbonyl carbon. The twist of the bithienyl skeleton is cis–skew, which means M_x helicity for the (*R*)-form.

In consequence, the reversal of the CD spectrum of **299** on going from the diacidic form to the monoanionic form does *not* reflect the alteration of the bithienyl skeleton from a trans–skew to a cis–skew conformation, since the latter is obviously already present in the diacidic form.

It is evident from the spectra of the bridged 4,4′-dicarboxylic acid **322** and its reduced form that the signs of the bands around 250 nm do not reflect the twist of the bithienyl skeleton. A similar conclusion was previously drawn by Mislow et al.[325] on work with a corresponding bridged diphenic acid, which initiated the investigation of **322**. In the biphenyl as well as the bithienyl case, reduction of the carboxylic groups reverses the signs of bands around 250 nm. Mislow and

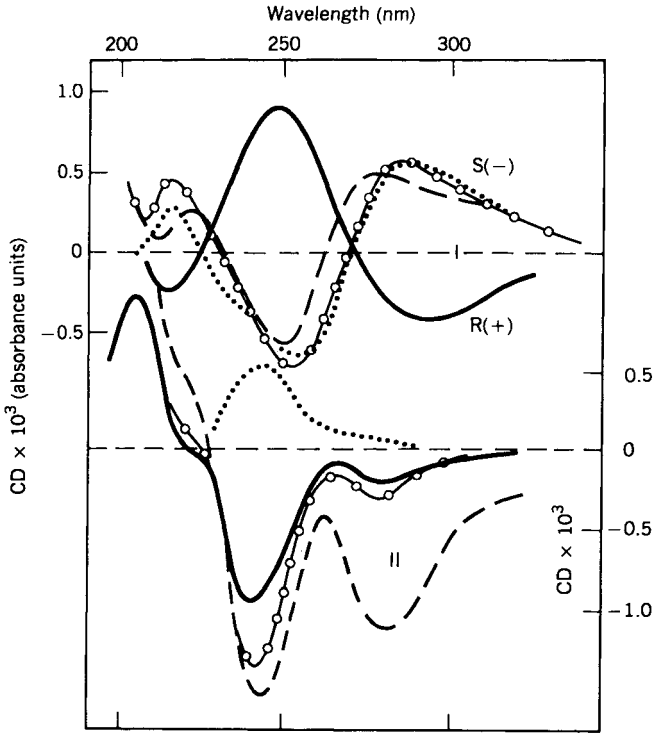


Figure 14. Top: CD spectra of (*R*)-(+)-4,4′-dibromo-2,2′-dicarbomethoxy-3,3′-bithienyl, (——) 3.0×10^{-3}% in KCl, and (*S*)-(−)-4,4′-dibromo-2,2′-dicarbomethoxy-3,3′-bithienyl, (. . . .) 2.0×10^{-3}% in KCl, (–○–○–) 1.5×10^{-3}% in KCl, (– – –) 0.5×10^{-3}% in KCl. Bottom: CD spectra of (*R*)-(−)-2,2′-dibromo-4,4′-dicarbomethoxy-3,3′-bithienyl, (– – –) 3.7×10^{-3}% in KBr, (–○–○–) 0.7×10^{-3}% in KBr, (——) 0.5×10^{-3}% in KCl, and (*S*)-(+)-2,2′-dibromo-4,4′-dicarbomethoxy-3,3′-bithienyl, (. . . .) 0.3×10^{-3}% in KBr.

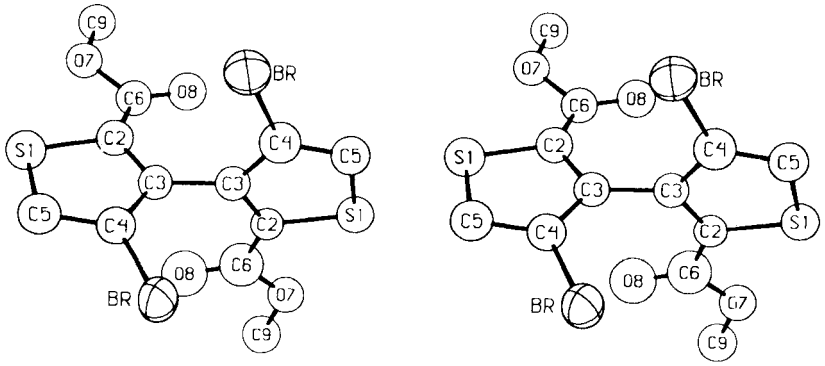


Figure 15. Stereoscopic view of (*R*)-(+)-4,4′-dibromo-2,2′-dicarbomethoxy-3,3′-bithienyl, based on X-ray diffraction data.

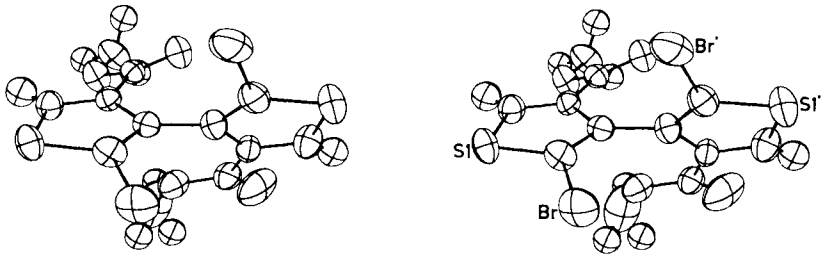


Figure 16. Stereoscopic view of (*R*)-(−)-2,2'-dibromo-4,4'-dicarbomethoxy-3,3'-bithienyl, based on X-ray diffraction data.

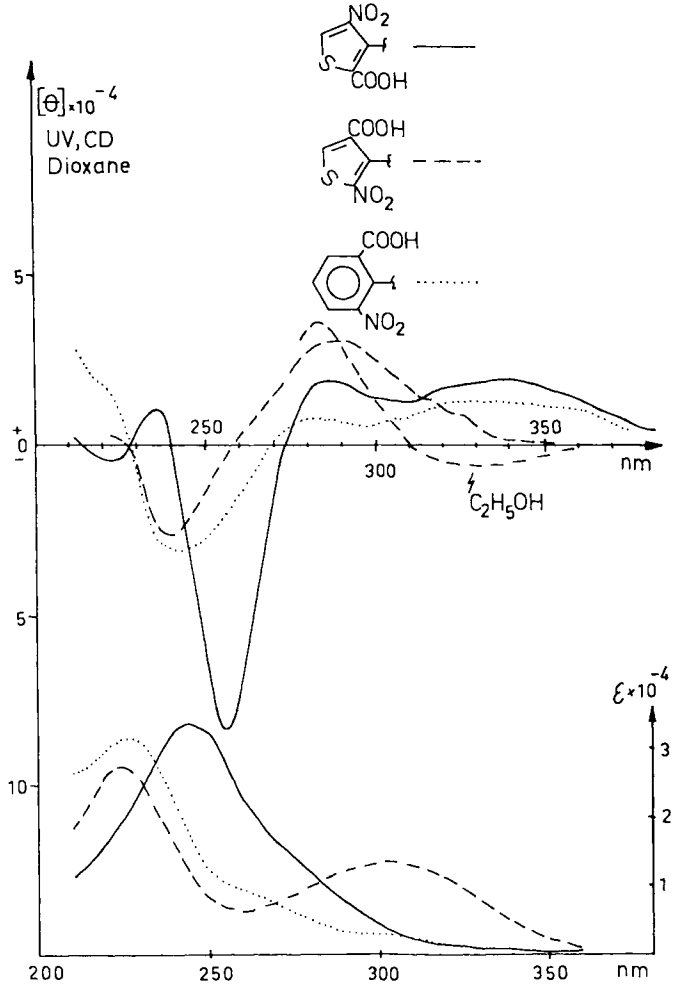


Figure 17. CD and UV spectra of 2,2'-dicarboxy-4,4'-dinitro-3,3-bithienyl, 4,4'-dicarboxy-2,2'-dinitro-3,3'-bithienyl, and 6,6'-dinitro-2,2'-diphenic acid in dioxane.

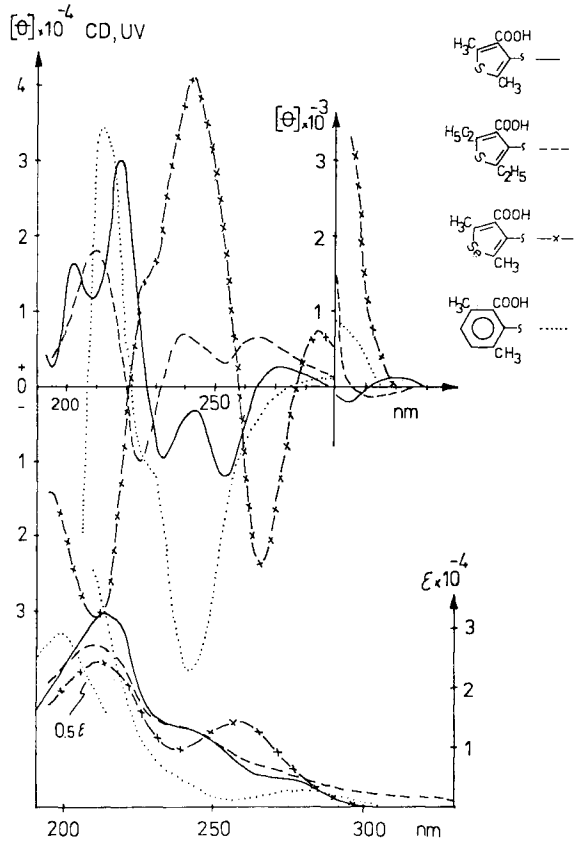


Figure 18. CD and UV spectra of (*R*)-(−)-4,4′-dicarboxy-2,2′,5,5′-tetramethyl-3,3′-bithienyl, (*R*)-(−)-4,4′-dicarboxy-2,2′,5,5′-tetramethyl-3,3′-biselenienyl, and (*S*)-(−)-3,3′,6,6′-tetramethyl-2,2′-diphenic acid in acetonitrile.

coworkers arrived at the conclusion that the 250-nm CD band of the biphenyl discussed instead reflected the twist of the carboxylic groups relative to the aromatic rings. A similar explanation seemed the only alternative in the case of compound **322** as well.[299]

Thus it is reasonable to conclude that even in the case of the unbridged 4,4′-dicarboxylic acids, the signs of the bands around 250 nm are associated with the twists of the carboxylic groups rather than that of the bithienyl skeleton.

Only two optically active 5,5′-dicarboxy-3,3′-bithienyls have been investigated in this connection (Figure 17). Their UV spectra exhibit bands at 250–300 nm of somewhat higher intensities than do those of the 2,2′-dicarboxylic acids. The corresponding CD bands, on the contrary, are of considerably lower intensities, the differences amounting to a factor of 10. The shapes of the CD spectra are of the same type as for the 2,2′-dicarboxylic acids, which is valid

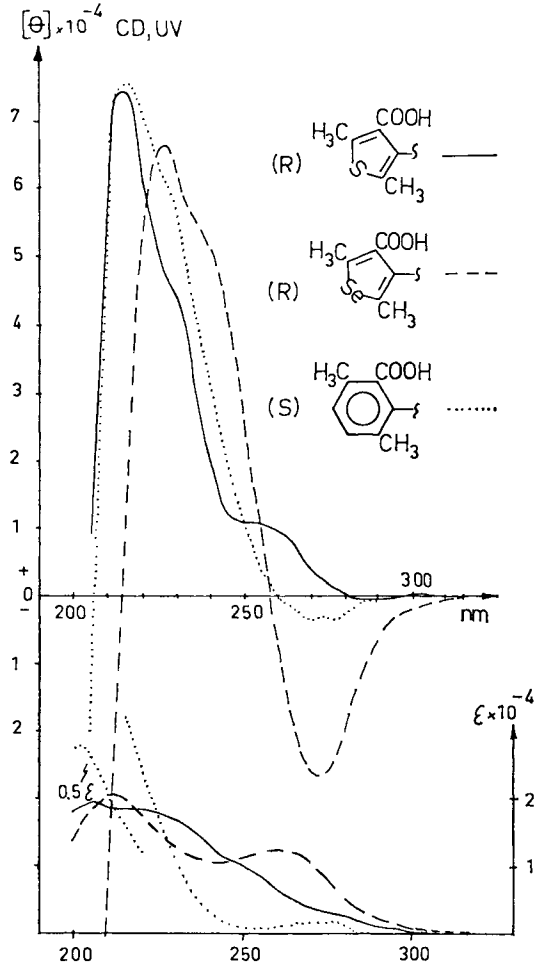


Figure 19. CD and UV spectra of (*R*)-(−)-4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl, (*R*)-(−)-4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-biselenienyl, and (*S*)-(−)-3,3',6,6'-tetramethyl-2,2'-diphenic acid in 0.01 M sodium hydroxide.

for the bromo compound in particular. The spectrum of the methyl compound in sodium hydroxide is dominated by the long-wavelength positive band and the medium-wavelength negative band. The latter is also observable in the dioxane solution spectrum. These spectra as well may be influenced by the twist of the carboxylic groups.

The CD spectra of the 2-monocarboxylic acids can be compared with those of the 2,2'-dicarboxylic acids, exhibiting the typical negative–positive double band at about 250 nm.[328]

In the same way, the CD spectra of the 4-monocarboxylic acids investigated are of the same type as that of 2,2'-dibromo-4,4'-dicarboxy-3,3'-bithienyl in

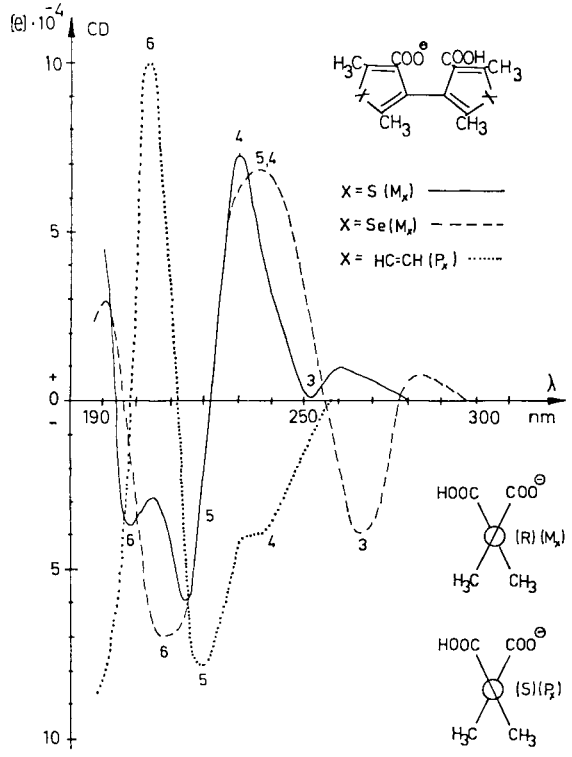


Figure 20. CD spectra of monoanionic forms of (*R*)-(−)-4,4′-dicarboxy-2,2′,5,5′-tetramethyl-3,3′-bithienyl, (*R*)-(−)-4,4′-dicarboxy-2,2′,5,5′-tetramethyl-3,3′-biselenienyl, and (*S*)-(−)-3,3′,6,6′-tetramethyl-2,2′-diphenic acid in 50% aqueous methanol.

Figure 2. However, the spectra of the monocarboxylic acids retain their shapes on recording sodium hydroxide solutions.[328]

The CD spectra of 3,3′-bithienyls have also been compared with those of other biaryl systems, such as biphenyl and 3,3′-biselenienyl[315] (Figures 17–20). In the case of the dinitro compounds shown in Figure 17, the spectra of 2,2′-dicarboxy-4,4′-dinitro-3,3′-bithienyl and 2,2′-dinitro-6,6′-diphenic acid are similar at longer wavelengths, whereas those of the 4,4′-dicarboxy-3,3′-bithienyl and the diphenic acid are comparable at shorter wavelengths. This is valid for both UV and CD spectra. It should be noted that (*R*)-forms are compared in Figure 17.

The similarities of the CD spectra of a 4,4′-dicarboxy-3,3′-bithienyl and a corresponding 2,2′-diphenic acid are also obvious from Figure 18, but in this case an (*R*)-form is compared with an (*S*)-form. The CD spectrum of the biselenienyl analogue of the 4,4′-dicarboxylic acid **299** is comparable to the spectra of 2,2′-dicarboxy-3,3′-bithienyls. However, in sodium hydroxide solution the three systems exhibit rather similar CD spectra, at least at shorter wave-

lengths (Figure 19), but again it should be remembered that the biphenyl spectrum represents an (*S*)-form.

It is evident from Figure 11 that the biselenienyl and the biphenyl under consideration also exhibit well-separated ionization constants, permitting the study of the CD spectra of their monoanionic forms at an intermediate pH. It was found that the biselenienyl retained the main shape of its CD spectrum at various pH levels. The diphenic acid exhibited enhanced CD bands with retained signs on going from the diacidic form to the monoanion (Figure 20). Going further to the dianion resulted in a virtually reversed CD spectrum.

If we still take the well-separated pK_1 and pK_2 values of the three compounds represented in Figures 18 and 19 as evidence for strong internal hydrogen bonds between the carboxylic groups in the monoanion, we arrive at the conclusion that in these species the twists of the biaryl skeletons, *as well as those of the carboxylic groups*, are the same with respect to helicities for the bithienyl and the biselenienyl and reversed for the biphenyl, which is quasi-enantiomeric in all respects with the other two.

In Figure 20 the CD spectra of the three monoanions are shown, and it may be seen that finally, having full control of the detailed stereochemistry, including that of the carboxylic groups, it is possible to establish the fact that the absolute geometries of the molecules are reflected in their CD spectra. Those of the sterically related bithienyl and biselenienyl coincide satisfactorily, whereas that of the biphenyl is reversed.

VII. PHYSICAL PROPERTIES OF BI- AND POLYTHIENYLS

Some physical properties of interest in connection with the optical activity of certain 3,3′-bithienyls were treated in the previous section (viz., UV and CD spectra, rotational barriers, dissociation constants, and conformations). At the end of Section III.2, several references were given to papers dealing with investigations of conducting polymers by physical methods.

In this section, a more general treatment of the physical properties of bi- and polythienyls will be presented. However, with the exception of conducting polymers, relatively little work on polythienyls, limited mainly to the study of absorbance and fluorescence, has been reported.

The question of the preferred conformations of the three isomeric bithienyls has received a great deal of attention, and UV spectroscopy and molecular-orbital calculations have often been utilized in this connection. These three subjects appear to have been woven together in various patterns with wefts of dipole-moment data, NMR and ESR measurements, electron diffraction studies, photoelectron spectra, and so on. Below an effort has been made to make some separation, at least between conformational analyses and more "pure" UV spectroscopy, but because of the close connection it was not possible to perform this separation strictly and entirely.

Several physical data of various kinds may be found in connection with the description of the syntheses of the compounds. With the exception of melting and boiling points, these data have not been generally collected in tables. Those given here were easily available from other tables or especially pointed out or discussed by the authors of the original papers.

1. Conformational Analyses

The most reliable information about molecular structure and stereochemistry is usually obtained by X-ray methods. In Section VI.3 it was pointed out that X-ray investigations of two optically active 3,3′-bithienyl dicarboxylic acids (as dimethyl esters) were valuable for the interpretation of their CD spectra. The crystal structures of the three isomeric unsubstituted bithienyls have been examined by Visser et al.[332] However, 2,2′-bithienyl appeared to decompose during the X-ray exposure, and 2,3′-bithienyl and 3,3′-bithienyl showed disorder in the crytals. Because of these difficulties, no accurate values for bond distances and angles were obtained, but in all cases the molecules were found to be planar in the crystals. 2,2′-Bithienyl was assigned an anti conformation. For 2,3′-bithienyl no information on the conformation could be obtained because of the high degree of disorder in the crystals. In the case of 3,3′-bithienyl, it was impossible to decide whether all molecules preserved the anti conformation, ascribed to the "average" molecules lying at inversion centers in the unit cell; 0–30% might have a syn conformation.

The conformations of 2,2′-bithienyl[333] and 3,3′-bithienyl[334] in the gas phase were studied by electron diffraction.[333,334] 2,2′-Bithienyl seemed to have a trans–skew conformation with a torsion angle of about 35°, but an essentially free rotation within values from about 35° to about 85° was not excluded.[333]

The investigation of 3,3′- bithienyl[334,335] revealed two preferred conformations with torsion angles of 30° and 150°, respectively, corresponding to about 40% of the cis–skew form and 60% of the trans–skew form.

Skanke[335,336] made a molecular-orbital study [Pariser–Parr–Pople (PPP)] of the brrier to internal rotation in 3,3′-bithienyl and 2,2′-bithienyl, and her results for 3,3′-bithienyl were in excellent agreement with the preceding experimental results. Energy minima were found at about 30° and 150° from the coplanar form. No distinct minima were found for 2,2′-bithienyl, however.

Galasso and Trinajstić[337] as well made a quantum-mechanical study on the stereochemistry of the three isomeric bithienyls and other biaryls, such as bipyrroles, bifurans, biselenienyls, and furylthiophenes. Of the bithienyls only the 3,3′-isomer displayed a slight tendency to assume a nonplanar conformation. Two flat minima were found at around 25° and 150° from the planar cis conformation (extended Hückel energy vs. angle of twist). According to these calculations, the energy difference between the cis and trans forms was relatively small for all three isomers.

Some conclusions about the conformations in solution have been drawn by Wynberg from dipole-moment measurements.[338] The results were as follows: 0.77 D for 2,2′-bithienyl, 1.07 D for 2,3′-bithienyl, and 0.75 D for 3,3′-bithienyl in benzene solutions. This indicates a predominantly coplanar structure for 2,3′-bithienyl, whereas the other two might be somewhat twisted.

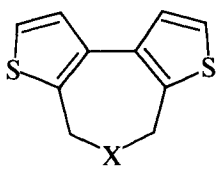
Lumbroso and Carpanelli[339] found the value 0.66 D for 2,2′-bithienyl and 5.55 D for 3,3′-dinitro-2,2′-bithienyl in the same solvent (benzene at 25°C). From these results a trans–skew conformation with a torsion angle of 30–40° was proposed for 2,2′-bithienyl, and a nearly orthogonal conformation was suggested for the dinitro derivative.

Negative attempts to demonstrate a 2,2′-bithienyl-Cu^{2+} complex were explained by Kahman et al.[340] with the assumption that the molecule might attain a nonplanar trans–skew conformation.

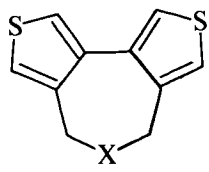
Veracini and coworkers[341] tested the liquid crystal NMR approach to conformational analyses of 5,5′-dichloro-, 5,5′-dibromo-, and 5,5′-dinitro-2,2′-bithienyls, from which it was concluded that these compounds consist of an equilibrium between a trans rotamer (77–84%) and a cis rotamer.

Electron-spin resonance analysis[256,342] (at −80°C) of the unsubstituted 2,2′-bithienyl radical anion revealed the presence of two very similar radicals with an intensity ratio 4 : 1. This was ascribed to two rotamers with planar or nearly planar conformations, held in a position with the sulfur atoms cis and trans, respectively, for a sufficient time for each rotamer to give an individual spectrum. However, the data did not allow the rotamer in excess to be identified.

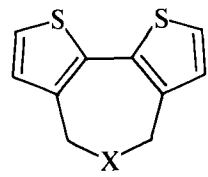
Photoelectron spectroscopy of 2,2′- and 3,3′-bithienyl and some of their dibromo derivatives,[343] and of bridged 3,3′-bithenyls[344] of the type shown in Scheme 71 (**329** and **330**), gave results that were reasonably consistent with a twisted conformation (in the vapor phase).



329



330



331

X = N–R, O, S

Scheme 71

Several authors have recorded the UV spectra of bithienyls (see next section) and made correlations with various theoretical calculations to obtain information about preferred conformations, but in most cases a coplanar cis or trans conformation has been assumed in the calculations. However, Meunier et al.[345,346] are among those who have even considered twisted forms. They have treated 2,2′- and 3,3′-bithienyl and some dibromo derivatives[345] as well as

TABLE 16. UV Spectra of Some Selected Bi- and Polythienyls[a]

Compound Name or Formula No.	λ_{max} (ε or log ε)			Solvent[b]	Ref.
2,2'-Bithienyl			301 (1.23)	x	114
		246 (6.000)	301 (13.000)	e	5
	206 (4.200)	246 (6.400)	301 (12.800)	e	214
		245 (2.150)	301 (3.800)	h	345
		245 (5.850)	301 (11.800)	h	346
		245 (5.850)	302 (12.300)	a	346
	192 (16.000)	247 (7.100)	302 (12.300)	c	353
		246 (6.400)	301 (12.800)	i	32
–, 5-acetoxymethyl-5'-(but-3-en-1-ynyl)	208 (16.700)	252 (9.700)	348 (28.200)	e	214
–, 5-acetyl	207 (9.730)	245 (8.710)	348 (21.900)	e	214
		245 (3.90)			
		264 (3.72)[c]	352 (4.38)	b	348
–, –, 3'-nitro		240 (3.83)			
		279 (4.00)	376 (4.20)	b	348
–, –, 5'-nitro		276 (3.80)	385 (4.34)	b	348
–, -5,5'-diacetyl	208 (12.800)	260 (7.410)	357 (29.500)	e	214
–, 3,3'-dibromo	220 (5.550)	255 (10.250)	294 (4.100)	h	345
–, 5-bromo	209 (5.590)	249 (5.400)	311 (13.660)	e	214
–, –, 5'-methoxycarbonyl	210 (8.490)	245 (5.950)	339 (22.230)	e	214
–, 5,5'-dibromo		247 (5.750)	318 (16.800)	h	345
	208 (6.320)	255 (6.910)	318 (15.210)	e	214
–, 5-(3-buten-1-ynyl)	210 (12.645)	249 (8.820)	341 (22.930)	e	214
–, –, 5'-hydroxymethyl	207 (12.100)	252 (5.220)	348 (24.400)	e	214
–, –, 5'-methoxycarbonyl	207 (15.600)	263 (9.010)	358 (23.730)	e	214
–, –, 5'-methyl	207 (14.710)	252 (9.210)	350 (27.300)	e	214
–, 2-carboxy		237, 257 (3.7)	328 (4.3)	e	195
–, 5-chloro	207 (7.210)	247 (5.880)	311 (13.800)	e	214
–, –, 5'-methoxycarbonyl	207 (11.780)	245 (7.774)	339 (18.820)	e	214
–, 5,5'-dichloro	206 (5.060)	250 (6.300)	318 (16.500)	e	214
–, 5-(4-chloro-3-hydroxy-but-1-ynyl)	214 (9.540)	245 (9.120)	331 (25.120)	e	214
–, 5-dichloromethyl	210 (10.100)	248.5 (8.150)	342 (20.560)	e	214

–, 5-formyl	207 (7.960)	244 (7.240)	350, 5 (22.400)	e	214
–, –, 5′-iodo	210 (11.950)	258 (11.222)	357 (25.120)	e	214
–, 5,5′-diformyl	207 (11.100)	260 (6.310)	336 (25.570)		
			358 (24.000)	e	214
–, *trans*-5-(4-hydroxy-but-1-enyl)	210 (9.860)	245 (8.630)	339–341 (20.300)	e	214
–, *cis*-5-(4-hydroxy-but-1-enyl)	207 (12.700)	243 (9.330)	333–337 (20.900)	e	214
–, 5-(4-hydroxy-but-1-ynyl)	207 (8.270)	242 (6.580)	328 (22.060)		
			334 (22.280)	e	214
–, 5-iodo	210 (6.570)	248 (5.640)	314 (15.700)	e	214
–, –, 5′-methoxycarbonyl	210 (10.380)	251 (6.750)	344 (23.090)	e	214
–, –, 5′-methyl	204 (9.370)	239.5 (6.770)	320 (17.070)	e	214
–, 5,5′-diiodo	209 (9.650)	246 (6.740)	324 (19.880)	e	214
–, 5-methoxycarbonyl	206 (8.720)	257 (5.610)	332 (19.700)	e	214
–, 3,3′-dimethyl		247 (10.800)		i	32
–, 3,3′,4,4′-tetramethyl		251 (12.900)		i	32
–, 5-methyl	210 (5.570)	245 (5.820)	308 (13.230)	e	214
		245 (6.150)	307 (13.500)	i	32
–, -5,5′-dimethyl		245 (6.700)	311 (15.200)	i	32
–, 3,5′-dinitro		244 (4.41)			
		282 (4.33)	379 (4.29)	b	348
–, 5,5′-dinitro		244 (3.91)			
		285 (3.70)	392 (4.45)	b	348
–, 5-phenyl		245 (9.450)	337 (26.000)	i	32
–, 5,5′-diphenyl		231 (18.300)	367 (33.000)	i	32
3,3′-Bithienyl		230 (9.500)	260 (11.300)	e	5
	210 (4.3)	230 (4.0)[c]	260 (4.1)	c	270
	211 (25.100)		261 (13.300)	c	353
	213 (25.950)		259 (14.200)	h	345
	213 (25.950)	230 (10.650)[c]	259 (14.200)	h	346
	210 (26.000)	232 (10.700)[c]	260 (13.900)	a	346
–, 2,2′-dibromo	211 (14.450)		246 (14.400)	h	345
–, 4,4′-dibromo	211 (15.100)		250 (10.150)	h	345
–, 5,5′-dimethyl	220 (25.000)		265 (12.400)	c	353
–, hexamethyl	195 (27.300)		244 (16.300)	c	353

TABLE 16. (*Continued*)

Compound Name or Formula No.	λ_{max} (ε or log ε)			Solvent[b]	Ref.
2,3′-Bithienyl		235 (8.400)	283 (11.900)	e	5
		234 (9.250)	281 (12.600)	i	32
			283 (1.19)	e	114
–, 2′-carboxy		248 (4.1)	285 (4.0)	e	195
–, 5-carboxy		238 (3.8)	311 (4.3)	e	195
–, 5′-carboxy		247 (4.1)	305 (4.1)	e	195
329, X = NC_2H_5	226 (24.600)		290 (6.000)	h	346
	227 (25.800)		290 (6.300)	a	346
X = O	229 (21.500)		278 (6.000)	h	346
	228 (22.050)		283 (6.300)	a	346
X = S	215 (21.000)	237 (16.000)	290 (2.700)	h	346
	212 (19.300)	237 (16.900)	289 (3.900)	a	346
330, X = NC_2H_5	206 (20.500)	225 (14.200)[c]	264 (7.200)	a	346
X = O	208 (22.200)	230 (13.600)[c]	265 (7.900)	h	346
	209 (19.000)	229 (12.500)[c]	267 (6.000)	a	346
X = S	210 (25.400)		255 (10.150)	a	346
331, X = NC_2H_5	216 (8.500)	249, 258 (6.050)	320 (12.800)	h	346
	217 (7.400)	249, 258 (5.800)	321 (12.400)	a	346
X = O	216 (6.500)	251 (5.700)	315 (12.900)	h	346
	218 (6.850)	250 (6.150)	317 (13.600)	a	346
X = S	218 (9.200)[c]	254 (6.200)	308 (7.800)	h	346
	217 (9.250)[c]	255 (5.750)	318 (8.650)	a	346

2,2′ : 5′,2″-Terthienyl (**149**)	210 (12.420)	252 (9.220)	350 (22.650)	e	214
		251 (9.200)	350 (24.000)	i	32
			350 (2.31)	x	114
–, 3′,4′-dimethyl		255 (10.200)	326 (17.500)	i	32
–, 5,5″-dimethyl		251 (9.400)	350 (24.000)	i	32
–, 3,3′,3″-trimethyl		250 (10.600)	318 (17.000)	i	32
–, 3,4,3″,4″-tetramethyl		253 (10.300)	334 (19.800)	i	32
–, 3,4,3′,4′,3″,4″-hexamethyl		250 (17.800)	290 (13.900)	i	32
2,3′ : 4′,2″-Terthienyl (**150**)		245 (22.100)	272 (16.700)	e	32
2,2′ ; 4′,2″-Terthienyl (**151**)			282 (24.800)	i	32
			283 (2.98)	e	114
3,3′ : 4′,3″-Terthienyl (**152**)	210 (32.400)	250 (15.900)		m	100
2,3′ : 4′,3″-Terthienyl (**154**)	210 (17.300)	242 (14.900)		m	47
2,2′ : 3′,2″-Terthienyl (**156**)	205 (18.600)	254 (13.400)	296 (9.400)	m	100
2,2′ : 3′,3″-Terthienyl (**157**)	203 (18.600)	250 (12.500)	295 (7.900)	m	100
2,3′ : 2′,3″-Terthienyl (**158**)	207 (14.400)	244 (14.800)	292 (10.900)	m	47
3,2′ : 3′,3″-Terthienyl (**159**)	210 (20.400)	255 (11.300)	275 (10.700)	m	100
2,3′ : 5′,3″-Terthienyl (**160**)	205 (9.700)		272 (14.700)	m	47
2,2′ : 4′,3″-Terthienyl (**161**)	210 (29.000)	263 (23.600)	310 (9.800)	m	47
3,2′ : 4′,3″-Terthienyl (**162**)	222 (24.000)	262 (22.400)		m	100
2,2′ : 5′,2″ : 5″,2‴-Quaterthienyl		251 (12.700)	385 (32.000)	i	32
3,3′ : 2′,2″ : 3″,3‴-Quaterthienyl		262 (20.200)		e	141

[a] UV spectra of optically active 3,3′-bithienyls are not included.

[b] Solvents: a = acetonitrile, b = butanol, c = cyclohexane, e = ethanol, i = *iso*-octane, h = heptane, m = methanol, x = hexane.

[c] Shoulder or inflex.

dithienoazepines, -oxepines, and -thiepines[346] (Scheme 71), in which the conformation is more or less known, at least with respect to the cis–trans isomerism. The bridged compounds were found to be twisted, in agreement with the findings from photoelectron spectroscopy, with the torsion angle dependent on the heteroatom in the seven-membered ring (30–40° for azepines and oxepines, 50–60° for thiepines). In the case of the unbridged biaryls, 2,2′-bithienyl and its 5,5′-dibromo derivative, as well as 3,3′-bithienyl, were proposed to prefer a trans–skew conformation with a torsion angle of 30–40° (in *n*-heptane), whereas the 3,3′-dibromo derivative of 2,2′-bithienyl and 2,2′- and 4,4′-dibromo-3,3′-bithienyl were more twisted. (The UV data for the compounds mentioned are given in Table 16.)

Kraak and Wynberg[347] carried out charge-transfer measurements on the three isomeric dithienyls, the corresponding flat cyclopentadithiophenes **251–253** (Scheme 51), and some other thiophenes with 1,3,5-trinitrobenzene as the electron acceptor in cyclohexane. The ionization potentials of the donors were derived from the energies of electron transfer, and thermodynamic data for complex formation were obtained from measurements at three different temperatures: 15, 30, and 45°C. Differences in preferred conformations of the bithienyls might expectedly be reflected in the stabilities of the CT complexes. However, the CT studies did not allow for any decisions about the energies hindering free rotation. The relative stabilities and the thermodynamic properties suggested almost free rotation around the pivot bonds of the bithienyls.

2. UV Spectroscopy

Ultraviolet spectra of bithienyls were briefly mentioned in the preceding sections. Several spectra of optically active 3,3′-bithienyls were presented in Section VI.3, and UV spectroscopy has been utilized for conformational analyses in some cases.

An early investigation of the UV absorption between 300 and 220 nm of 2,2′- and 3,3′-bithienyls in ethanol was performed by Jean and Nord.[208] They made a comparison of the spectra of *ortho*-substituted bithienyls with those of similarly substituted "uncoupled" thiophenes in order to trace the absence of a conjugation band associated with coplanarity of the molecules. This, in turn, might permit conclusions about restricted rotation and possibilities of resolution to be drawn. The bithienyls studied were 4,4′-dicarboxy-2,2′,5,5′-tetramethyl-3,3′-bithienyl (**299**, Scheme 65), 5,5′-dimethyl-2,2′,4,4′-tetranitro-3,3′-bithienyl, 3,3′,5,5′-tetranitro-2,2′-bithenyl, 5,5′-diacetyl-3,3′-dinitro-2,2′-bithienyl, and 5,5′-dicarbomethoxy-3,3′-dinitro-2,2′-bithienyl.

In summary, the 3,3′-bithienyls exhibited spectra of approximately the same type as those of the uncoupled parts, indicating deviations from coplanarity. (As mentioned in Section VI, **299** has been resolved.) The spectra of the 2,2′-bithienyls showed increased intensities and shifts toward longer wavelengths, interpreted as conjugation effects due to the possibilities to attain coplanar conformations.

A similar comparison between the UV spectra of coupled and uncoupled parts was made by Gronowitz and Frostling[108] in connection with their synthesis of the first optically active 3,3′-bithienyl, and they observed the same close resemblances.

In view of these facts, the spectra of the optically active 3,3′-bithienyls have been considered of minor interest in this section and are not further analyzed here.

The UV absorption of the three isomeric unsubstituted bithienyls in ethanol was first determined by Wynberg and Bantjes,[5] and the results are given in Table 16 together with some of later date.

It has been proposed[108] that the 301-nm band of 2,2′-bithienyl, the 284-nm band of 2,3′-bithienyl, and the 260-nm band of 3,3′-bithienyl correspond to the conjugation band at 249 nm in biphenyl and should thus be sensitive to conformational changes.

The 5- and 5,5′-substituted 2,2′-bithienyls have been investigated by Lipkin[348] and Curtis and Phillips.[214] The latter authors observed three bands; one short-wavelength band at 207 ± 3 nm of varying intensity (ε_{max} = 4000–17,000), assigned to an $n \rightarrow \sigma^*$ transition of the nonbonding electrons of the heteroatom to the antibonding σ-orbital, one band at medium wavelengths (240–250 nm) of moderate intensity (ε_{max} = 5000–9000) assigned to the $\pi \rightarrow \pi^*$ local excitation transition of the heteroaromatic nucleus, and finally one broad band at 300–360 nm of relatively high intensity (ε_{max} = 12,000–30,000) characteristic of an electron-transfer transition. The latter was subdivided into two types, one of which involves an electron transition from the π-orbital of the aromatic ring to the π^*-orbital of a chromophoric group (e.g., an acyl group or an alkenyl group; Table 16). The bathochromic shift relative to the local $\pi \rightarrow \pi^*$ excitation of the parent 2,2′-bithienyl is of the order of 50 nm. The second type involves transitions between the *p*-orbital of an auxochrome (e.g. a halogen atom) and the antibonding π^*-orbital of the thiophene rings, with bathochromic shifts of the order of 10 nm. The effects of auxochromes and chromophores appear to be additive, and the correlations were considered useful for the determinations of the substitution pattern in naturally occurring 2,2′-bithienyl derivatives.

The UV spectra of some terthienyls and α-quaterthienyl have been determined by Uhlenbroek and Bijloo[32] (see Table 16).

As mentioned in Section VI, similar systems may be recognized in some heterohelicenes. Their UV spectra, often extending into the visible, exhibit resolved bands and vibrational structure in marked contrast to the blurred spectra of hexahelicene and its benzologs.[303]

Bridged bithienyls of the type shown in Scheme 71 were investigated with respect to UV absorption by Meunier and Arriau,[346] and the observed values were compared with those obtained on theoretical calculations (CNDO/S). Bridging 2,2′-bithienyl to give **331** resulted in a bathochromic shift and increased intensity of the long-wavelength band for X = NC_2H_5 and O but decreased intensity for X = S. Compared to 3,3′-bithienyl, **329** and **330** exhibit a bathochromic shift but decreased intensity of the long-wavelength band. In the case of

329, the short-wavelength band as well is shifted to longer wavelengths with a slightly decreased intensity (Table 16). Corresponding wavelength shifts on bridging may be observed in the spectrum of the more or less related cyclopentadithiophene **251**[270,271] (Scheme 51) of known coplanar but strained geometry.[349]

The UV spectra of all six isomeric cyclopentadithiophenes in Scheme 51 have been recorded and compared with those of the corresponding unbridged bithienyls.[271] Except for the 2,2′-bridged 3,3′-bithienyl **251**, just mentioned above, the largest differences are observed on comparison of the parent compound and the 4,4′-bridged 3,3′-bithienyl **254** (R = H). Both bands are shifted toward longer wavelengths, and in this case there is a relatively large increase in the intensity of the long wavelength band (ε_{max} = 27,000 at 295 nm) with a pronounced fine structure.

The UV absorption data of some tetramethyl-substituted cyclopentadithiophenes and cyclopentadithiophenones have been given by Wiersema.[350]

Calculations of the UV spectra of the three isomeric bithienyls by the self-consistent MO method by Wachters and Davies[351] gave less satisfactory agreement with experiment, whereas Trinajstic' and Hinchliffe[352] reported good agreement with observed values for the first $\pi \rightarrow \pi^*$ electron transition in 2,2′- and 3,3′-bithienyl by calculations within the framework of the PPP approximation.

Molecular-orbital calculations combined with polarized spectroscopy on substances in stretched films (linear dichroism) have been performed on 2,2′-bithienyl, 3,3′-bithienyl, 5,5′-dimethyl-3,3′-bithienyl, and hexamethyl-3,3′-bithienyl in order to evaluate directions of moments and make assignments of $\pi \rightarrow \pi^*$ transitions.[353] Judging from the spectra, the 210-nm band of 3,3′-bithienyl was assigned a perfect long-axis polarization (parallel to the pivot bond, $\alpha = 0$), whereas there might be a departure for the 260-nm band. For the 5,5′-dimethyl derivative, adopting $\alpha = 0$ for the 220-nm transition, a value of $\alpha = 40°$ was obtained for the long-wavelength band. Hexamethyl-3,3′-bithienyl, which is more spherical, exhibited the same spectrum regardless of the orientation of the stretched film (random directions of the molecules in the film). In the case of 2,2′-bithienyl, the long-wavelength transition was found to be perfectly long-axis-polarized, but for the 247-nm transition a value of $\alpha = 46°$ was determined.

The linear dichroism of thiophene, 2,5-dimethylthiophene, and some substituted open and bridged 3,3′-bithienyls was further investigated by Nordén[354] to determine the polarizations of the various transitions and to derive relationships that give the observed CD pattern. It was suggested that the two lowest $\pi \rightarrow \pi^*$ transitions with mutual orthogonal polarization in thiophene may be recognized at longer wavelengths in the UV spectra of the bithienyls and that the polarizations as obtained in 2,5-dimethyl thiophene may be uitilized to predict the optical activities in the bithienyls.

Determinations of the directions of the moments of the transitions associated with the UV absorption bands of α-terthienyl and α-quaterthienyl in stretched

oriented films using polarized light, as well as measurements of the polarization of the fluorescence, have been made by Eckert and Kuhn.[355] The long-wavelength band at 350–400 nm is long-axis-polarized. The 250 nm band of α-terthienyl appears to be short-axis-polarized, whereas in the case of α-quaterthienyl the dichroism of this band is virtually zero. Some conclusons about preferred conformations were drawn.

The absorption and emission spectra of some 2,2′-bithienyls substituted at the 5-position with 2-quinolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidiazolyl, and 2-indolyl substituents have been examined, and the influence of solvent was also investigated.[245]

3. IR Spectroscopy

Infrared absorption bands for the three isomeric bithienyls have been presented (relative intensities are not given) by Wynberg and Bantjes,[5] and the complete spectra of 2,2′- and 3,3′-bithienyl in KBr have been reported by Gronowitz and Karlsson.[2] With a scale linear in wavelengths, the spectrum of 2,2′-bithienyl is dominated by two broad strong bands at 12.2 μm (820 cm^{-1}) and 14.5 μm (690 cm^{-1}), whereas that of 3,3′-bithienyl has a strong band at 13.1 μm (765 cm^{-1}), observed in the spectra of other 2-substituted[356] and 3-substituted[357] thiophenes.

Complete spectra have also been published for some racemic and optically active 3,3′-bithienyls[103,93,111,105] (**302**, **304** and dimethyl esters, Scheme 66, **299**, Scheme 65, and 4,4′-diiodo-2,2′,5,5′-tetraethyl-3,3′-bithienyl), and for 5-carboxy-3,3′-diiodo-2,2′-bithienyl.[212]

The IR absorption spectra of some nitrated 2,2′-bithienyls and 5-acetyl-2,2′-bithienyls have been reported by Lipkin et al.[348] All compounds investigated exhibit an intense absorption band in the 720–728 cm^{-1} region. Other bands discussed are associated with the nitro or acyl group vibrations.

Curtis and Phillips[214,219] have investigated a series of 5- and 5,5′-substituted 2,2′-bithienyls. They found[214] that 2,2′-bithienyl exhibits maxima at 835 and 690 cm^{-1}, 5-substituted derivatives at 840, 800, and 690 cm^{-1}, and 5,5′-disubstituted derivatives at 800 cm^{-1}. The vibrational origins of these and some other bands were discussed, and the usefulness of IR spectroscopy in investigations of the substitution patterns of naturally occurring bithienyls was pointed out.

Similar systematic studies of the IR absorption of 2,3′- and 3,3′-bithienyls apparently were not carried out.

4. NMR Spectroscopy

Frequently, ^1H NMR data of bithienyls can be found in the experimental parts of most papers after 1960, which deal with the preparation of such compounds. In this section, only a few more detailed investigations will be mentioned.

The strongly coupled (40 MHz) ^{1}H NMR spectrum of 2,2′-bithienyl was interpreted by Hoffman and Gronowitz,[88,358] who found the following concentration-dependent chemical shifts in parts per million for the ring protons, extrapolated to infinite dilution in cyclohexane: 5.60 (3-*H*), 5.42 (4-*H*), and 5.56 (5-*H*), with $J_{34} = 3.4$ Hz, $J_{35} = 1.6$ Hz, and $J_{45} = 5.0$ Hz.

The NMR spectra of all three isomeric bithienyls in deuterated acetone were analyzed by Kellogg et al.[216] The ABC spectrum of 2,2′-bithienyl was solved by substitution of approximate values (obtained from an ABX approximation with parameters from 5,5′-dideuterio-3,3′-bithienyl) in an ABC matrix equation and fitting the calculated to the observed spectrum by minor changes of the spectral parameters. The following final values were found: $\nu_3 - \nu_5 = 7.1$ Hz and $\nu_4 - \nu_5 = 18.8$ Hz, with $J_{34} = 3.4$ Hz, $J_{35} = 1.2$ Hz, and $J_{45} = 5.0$ Hz.

For 5,5′-dideuterio-2,2′-bithienyl the resonance signals were observed at 7.00 ppm (4-*H*) and 7.20 ppm (3-*H*).

The spectrum of 3,3′-bithienyl was also solved, yielding the parameters $\nu_5 - \nu_2 = \nu_4 - \nu_2 = 11.2$ Hz, with $J_{25} + J_{24} = 4.3$ Hz. The coupling value of J_{45} was not measurable, and only the combined value $J_{25} + J_{24}$ was obtained. However, in 2.5′-dideuterio-3,3′-bithienyl, J_{25} was measured as 1.2 Hz, from which a value of $J_{24} = 3.1$ Hz may be estimated. In 2,2′-dibromo-3,3′-bithienyl, J_{45} was found to be 5.7 Hz. In carbon tetrachloride the spectrum of 3,3′-bithienyl collapses to a singlet.

The spectrum of 2,3′-bithienyl, exhibiting two overlapping ABC spectra, could be only partially solved. Even this spectrum is solvent-sensitive. The signals from 4′-*H* and 5′-*H* in 2,3′-bithienyl and deuterated derivatives were resolved in acetone-d_6 but collapsd to a singlet in carbon tetrachloride, which facilitated the analysis. The available parameters were $\nu_{4'} - \nu_{5'} = 8.2$ Hz and $\nu_4 - \nu_3 = 3.6$ Hz, with $J_{4'5'} = 5.0$ Hz and $J_{34} = 3.6$ Hz.

In the spectrum of 2′,5-dideuterio-2,3′-bithienyl, the following resonances were observed (ppm): 7.04 (4-*H*), 7.70 (3-*H*, $J_{34} = 3.5$ Hz), 7.35 (4′-*H*), and 7.49 (5′-*H*, $J_{4'5'} = 5.0$ Hz).

Nuclear magnetic resonance data for eight mono- and dinitro-2,3′-bithienyls have been tabulated by Dell'Erba et al.[116]

Complete analyses of the proton NMR spectra of 5-(but-3-en-1-ynyl)-2,2′-bithienyl and α-terthienyl[359] have been carried out[360] with the aid of an iterative program, and the values obtained were compared with the parameters for 2,2′-bithienyl.

In connection with work on optically active 3,3′-bithienyls, it was found that the structures of 3,3′-bithienyl methyl esters[267,361] and those of methyl-substituted 3,3′-bithienyls[362] could be deduced from their NMR spectra. The OCH_3 resonance (CS_2) in 2- and 3-carbomethoxythiophenes and in 5,5′-dicarbomethoxy-3,3′-bithienyls occurred within the small interval of 3.80–3.90 ppm but was shifted 0.2–0.3 ppm upfield in 2,2′- and 4,4′-dicarbomethoxy-3,3′-bithienyls.[361] Even for 3,3′-bithienyls with only one carbomethoxy group at the 2-(2′-) or 4-(4′-) position, the same values of the resonances were observed.[267]

In the NMR spectra of 62 methyl-substituted 3,3′-bithienyls,[362] the methyl resonances of unbridged 3,3′-bithienyls without substituents such as carboxyl or formyl groups were found in the following intervals: 4,4′-CH_3 at 1.69–2.07 ppm, 2,2′-CH_3 at 2.05–2.36 ppm, and 5,5′-CH_3 at 2.28–2.43 ppm. Carboxylic groups caused upfield or downfield shifts, depending on positions, and bridging also affected the resonance of the 2,2′- and 4,4′-methyl groups, resulting in downfield shifts.

The proton NMR technique has been used for the study of the protonation of cyclopentadithiophenes and cyclopentadithiophenones.[363] Protonation may occur on the carbonyl oxygen or on the aromatic ring, and UV spectroscopy was also utilized in the investigation. (An interesting observation might be that the protonated carbonyl group appears to retain the structure $C{=}OH^+$ rather than the mesomeric $+\ C{-}OH$.)

5. Miscellaneous Investigations

It was mentioned above that ESR spectroscopy has been used for conformational analyses of 2,2′-bithienyl. ESR spectroscopy has also been used for tracing the formation of the radical anion of 5,5′-dinitro-2,2′-bithienyl on alkaline hydrolysis[67] and electrochemical reduction[68] of 2-halogen-5-nitrothiophenes. Splitting constants in the ESR spectrum of the dinitrobithienyl are given.

The relative stabilities toward electron impact (70 eV) as evaluated from their mass spectra has been determined for the three isomeric bithienyls and two terthienyls.[364]

In the mass spectra (70 eV) of 2,2′- and 3,3-bithienyl disubstituted with 2-pyridyl, 4-pyrimidinyl, 2-pyrazinyl, 2-quinoxalyl, and 2-quinolyl groups, fragment ions were observed that indicated the elimination of a heteroaromatic nucleus in the *o,o′*-substituted molecules. The subsequent formation of a cationic condensed aromatic system by cyclization of the remaining substituent to the vacant *o*-position was proposed.[365]

Ionization constants for some optically active biaryl dicarboxylic acids were given in Section VI.3. Dell'Erba et al.[366] have measured the ionization constants of some 5′-substituted 2,2′-bithienyl-5-carboxylic acids and correlated the results by means of the Hammett equation.

Forsyth and Vogel[229] studied the effects of substituents on the rotational barrier of protonated 2,2′-bithienyls and correlated the rate of rotation with the Hammett σ^+ constants. Protonation of 2,2′-bithienyl in superacid media gave the stable 2-(2′-thienyl)-5-thiophenium ion, and by dynamic NMR methods, the energy barrier to rotation in this ion was found to be $\Delta G^{\dagger} = 11.4$ kcal/mol.

Thin-layer chromatography (Alumina G) of some bi- and polythienyls has been performed by Curtis and Phillips,[367] and gas-chromatographic separation of the isomeric bithienyls and α-terthienyl has been worked out by Berk[368] (15% Carbowax 2M on 80–100-mesh Chromosorb W at 220°C).

See also the introduction to Section III concerning chromatographic separation of bi- and polythienyls.

REFERENCES

1. H. D. Hartough, *Thiophene and its Derivatives*, in *The Chemistry of Heterocyclic Compounds*, A. Weissberger, ed., Interscience, New York, 1952, Vol. 3, p. 459.
2. S. Gronowitz and H.-O. Karlsson, *Arkiv Kemi*, **17**, 89 (1960).
3. R. Nahnsen, *Berichte*, **17**, 789 (1884).
4. K. Auwers and T. V. Bredt, *Berichte*, **27**, 1741 (1894).
5. H. Wynberg and A. Bantjes, *J. Am. Chem. Soc.*, **84**, 1421 (1959).
6. E. K. Fields and S. Meyerson, *Chem. Commun.*, **20**, 708 (1966).
7. A. Töhl, *Berichte*, **27**, 665 (1894).
8. O. Eberhard, *Berichte*, **27**, 2919 (1894).
9. W. Steinkopf and J. Roch, *Liebigs Ann. Chem.*, **482**, 251 (1930).
10. A. E. Lipkin, *Zh. Obshch. Khim.*, **33**, 196 (1963); *J. Gen. Chem. USSR*, **33**, 188 (1963).
11. S. Gronowitz, *Acta Chem. Scand.*, **15**, 1393 (1961).
12. S. Gronowitz and V. Vilks, *Arkiv Kemi*, **21**, 191 (1963).
13. P. Meunier, *Bull. Soc. Chim. Belg.*, **88**, 325 (1979).
14. A. Wiersema and S. Gronowitz, *Acta Chem. Scand.*, **24**, 2593 (1970).
15. S. Gronowitz and P. Pedaja, *Tetrahedron*, **34**, 587 (1978).
16. T. Kauffmann and A. Woltermann, *Angew. Chem.*, **84**, 824 (1972).
17. T. Kauffmann, J. Jackisch, A. Woltermann, and P. Röwemeier, *Angew. Chem.*, **84**, 826 (1972).
18. T. Kauffmann, J. Legler, E. Ludorff, and H. Fischer, *Angew. Chem.*, **84**, 828 (1972).
19. T. Kauffmann and H.-H. Kniese, *Tetrahedron Lett.*, 4043 (1973).
20. W. Steinkopf, H. J. v. Petersdorff, and R. Gording, *Liebigs. Ann. Chem.*, **527**, 272 (1923).
21. W. Steinkopf, R. Leitsmann, and K. H. Hoffmann, *Liebigs Ann. Chem.*, **546**, 180 (1941).
22. J. W. Sease and L. Zechmeister, *J. Am. Chem. Soc.*, **69**, 270 (1947).
23. E. Lescot, Ng. Ph. Buu-Hoï, and Ng. D. Xuong, *J. Chem. Soc.*, 3234 (1959).
24. N. Kornblum and D. L. Kendall, *J. Am. Chem. Soc.*, **74**, 5782 (1952).
25. H. Wynberg and A. Logothetis, *J. Am. Chem. Soc.*, **78**, 1958 (1956).
26. R. Jente, G. A. Olatunji, and F. Bosold, *Phytochemistry*, **20**, 2169 (1981).
27. A. G. Mack, H. Suschitzky, and B. J. Wakefield, *J. Chem. Soc. Perkin I*, 1682 (1980).
28. W. Steinkopf, R. Leitsmann, A. H. Müller, and H. Wilhelm, *Liebigs Ann. Chem.*, **541**, 271 (1939).
29. T. Sone, K. Sakai, and K. Kuroda, *Bull. Chem. Soc. Jpn.*, **43**, 1411 (1970).
30. W. Minnis, *J. Am. Chem. Soc.*, **51**, 2143 (1939).
31. M. Sy, Ng. Ph. Buu-Hoï, and Ng. D. Xuong, *J. Chem. Soc.*, 1975 (1954).
32. J. H. Uhlenbroek and J. D. Bijloo, *Rec. Trav. Chim.*, **79**, 1181 (1960).
33. C. Carpanelli and G. Leandri, *Ann. Chim. (Rome)*, **51**, 181 (1961).
34. L. J. Owen and F. F. Nord, *Nature*, **167**, 1035 (1951); *J. Org. Chem.*, **16**, 1864 (1951).
35. G. N. Jean and F. F. Nord, *J. Org. Chem.*, **20**, 1363 (1955).
36. J. H. Uhlenbroek and J. D. Bijloo, *Rec. Trav. Chim.*, **78**, 382 (1959).
37. M. Nilsson, *Acta Chem. Scand.*, **20**, 423 (1966).
38. M. Nilsson, *Tetrahedron Lett.*, 679 (1966).

39. M. Nilsson and Ch. Ullenius, *Acta Chem. Scand.*, **24**, 2379 (1970).
40. Ch. Ullenius, *Acta Chem. Scand.*, **26**, 3383 (1972).
41. N. Gjøs and S. Gronowitz, *Acta Chem. Scand.*, **25**, 2596 (1971).
42. J. P. Morizur, *Bull. Soc. Chim. Fr.*, 1331 (1964).
43. J. P. Morizur and R. Pallaud, *Compt. Rend. Acad. Sci. (Paris)*, **254**, 1093 (1962); **255**, 711 (1962).
44. M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.*, **93**, 5908 (1971).
45. R. Rossi, A. Carpita, and A. Lezzi, *Tetrahedron*, **40**, 2773 (1984).
46. R. Rossi and A. Carpita, *Gazz. Chim. Ital.*, **115**, 575 (1985).
47. N. Jayasuriya and J. Kagan, *Heterocycles*, **24**, 2901 (1986).
48. G. T. Crisp, *Synth. Commun.*, **19**, 307 (1989).
49. J. Blum, D. Milstein, and Y. Sasson, *J. Org. Chem.*, **35**, 3233 (1970).
50. L. Eberson and L. Gomez-Gonzalez, *Acta Chem. Scand.*, **27**, 1249 (1973).
51. T. Itahara, *J. Org. Chem.*, **50**, 5272 (1985).
52. T. Itahara, M. Hashimoto, and H. Yumisashi, *Synthesis*, 255 (1984).
53. J. Bergman and L. Engman, *Tetrahedron Lett.*, 3279 (1978).
54. A. Töhl and O. Eberhard, *Berichte*, **26**, 2940 (1893).
55. T. Sone and Y. Abe, *Bull. Chem. Soc. Jpn.*, **46**, 3603 (1973).
56. T. Sone, O. Shiromaru, S.-I. Igarashi, E. Kato, and M. Sawara, *Bull. Chem. Soc. Jpn.*, **52**, 1126 (1979).
57. T. Sone, R. Yokoyama, Y. Okuyama, and K. Sato, *Bull. Chem. Soc. Jpn.*, **59**, 83 (1986).
58. G. M. Davies, P. S. Davies, W. E. Paget, and J. M. Wardeworth, *Tetrahedron Lett.*, 795 (1976).
59. A. Pelter, H. Williamson, and G. M. Davies, *Tetrahedron Lett.*, **25**, 453 (1984).
60. J. Kagan and S. K. Arora, *Tetrahedron Lett.*, **24**, 4043 (1983).
61. C. E. Griffin and K. R. Martin, *Chem. Commun.*, 154 (1965).
62. C. M. Camaggi, G. De Luca, and A. Tundo, *J. Chem. Soc. Perkin II*, 412 (1972).
63. M. D'Auria, A. De Mico, F. D'Onofrio, and G. Piancatelli, *J. Org. Chem.*, **52**, 5243 (1987).
64. C. M. Camaggi, R. Leardini, A. Tundo, and M. Tiecco, *J. Chem. Soc. Perkin I*, 271 (1974).
65. A. P. Manzara and P. Kovacic, *J. Org. Chem.*, **39**, 594 (1974).
66. C. Dell'Erba, M. Novi, G. Guanti, and D. Spinelli, *J. Heterocycl. Chem.*, **12**, 327 (1975).
67. I. M. Sosonkin, G. N. Strogov, and N. V. Fedyainov, *Dokl. Akad. Nauk SSSR*, **253**, 365 (1980); *Proc. Acad. Sci. USSR*, 349 (1981).
68. I. M. Sosonkin, G. N. Strogov, T. K. Ponomareva, A. N. Domarev, A. A. Glushkova, and G. N. Freidlin, *Khim Geterotsikl. Soedin*, 195 (1981); *Chem. Heterocycl. Comp.*, 137 (1981).
69. S. Braverman, Y. Duar, and M. Freund, *Isr. J. Chem.*, **26**, 108 (1985).
70. S. Berk, U.S. Patent 3,454,480; *Chem. Abstr.*, **71**, 306 (1969).
71. W. Steinkopf and W. Hanske, *Liebigs Ann. Chem.*, **541**, 238 (1939).
72. J. A. Ballantine and R. G. Fenwich, *J. Chem. Soc. C*, 2264 (1970).
73. H. Hermann and W. Lüttke, *Chem. Ber.*, **101**, 1715 (1968).
74. B. E. Ayres, S. W. Longworth, and J. F. W. McOmie, *Tetrahedron*, **31**, 1755 (1975).
75. Ch. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **72**, 5543 (1950).
76. A. I. Kosak, R. J. F. Palchak, W. A. Steele, and Ch. M. Selwitz, *J. Am. Chem. Soc.*, **76**, 4450 (1954).
77. V. I. Shvedov, Yu. I. Trofimkin, V. K. Vasil'eva, T. F. Vlasova, and A. N. Grinev, *Khim. Geterotsikl. Soedin*, 914 (1975); *Chem. Heterocycl. Comp.*, 802 (1976).
78. V. I. Shvedov, Yu. I. Trofimkin, V. K. Vasil'eva, and A. N. Grinev, *Khim. Geterotsikl. Soedin*, 1324 (1975); *Chem. Heterocycl. Comp.*, 1133 (1976).

79. K. E. Schulte, J. Reisch, W. Hermann, and G. Bohn, *Arch. Pharm.*, **296**, 456 (1963).
80. K. E. Schulte and J. Reisch, Ger. Patent 1,202,796; *Chem. Abstr.*, **64**, 6619 (1966).
81. K. E. Schulte, J. Reisch, and L. Hörner, *Chem. Ber.*, **95**, 1943 (1962).
82. J. C. Meslin, Y. T. N'Guessan, and H. Quiniou, *Tetrahedron*, **31**, 2679 (1975).
83. J. Brelivet, P. Appriou, and J. Teste, *Compt. Rend. Acad. Sci., Ser. C*, **269**, 398 (1969).
84. E. I. G. Brown, D. Leaver, and D. M. McKinnon, *J. Chem. Soc. Perkin I*, 1511 (1977).
85. R. E. Atkinsson, R. F. Curtis, and G. T. Phillips, *J. Chem. Soc. C*, 2011 (1967).
86. T. Sone, M. Kubo, and T. Kanno, *Chem. Lett.*, 1195 (1982).
87. R. Håkansson and E. Wiklund, *Arkiv Kemi*, **31**, 101 (1969).
88. R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 515 (1960).
89. W. Steinkopf, Th. Barlag, and H. J. v. Petersdorff, *Liebigs Ann.*, **540**, 7 (1939).
90. G. N. Jean, L. J. Owens, and F. F. Nord, *Nature*, **169**, 585 (1952).
91. F. F. Nord and G. N. Jean, *Naturwissenschaften*, **39**, 480 (1952).
92. C. Dell'Erba, G. Garbarino, and G. Guanti, *Gazz. Chim. Ital.*, **100**, 916 (1970).
93. S. Gronowitz and K. Dahlgren, *Arkiv Kemi*, **21**, 201 (1963).
94. R. Håkansson and A. Svensson, *Chem. Scripta*, **7**, 186 (1975).
95. M. K. Shepherd, *J. Chem. Soc. Chem. Commun.*, 880 (1985).
96. J. Cornforth, D. D. Ridley, A. F. Sierakowski, D. Uguen, and T. W. Wallace, *J. Chem. Soc. Perkin Trans. I*, 2317 (1982).
97. S. Gronowitz and K. Lawitz, *Chem. Scripta*, **22**, 265 (1983).
98. S. Gronowitz, V. Bobosik, and K. Lawitz, *Chem. Scripta*, **23**, 120 (1984).
99. N. Miyama, T. Yanagi, and A. Zuzuki, *Synth. Commun.*, **11**, 513 (1981).
100. N. Jayasuriya and J. Kagan, *Heterocycles*, **24**, 2261 (1986).
101. H. Wynberg, G. J. Heeres, P. Jordens, and H. J. M. Sinnige, *Rec. Trav. Chim. Pays-Bas*, **89**, 545 (1970).
102. J. Brunet, D. Paquer, and Ph. Rioult, *Phosphorus and Sulfur*, **3**, 377 (1977).
103. S. Gronowitz and P. Gustafson, *Arkiv Kemi*, **20**, 289 (1963).
104. A. Almqvist and R. Håkansson, *Chem. Scripta*, **11**, 57 (1977).
105. S. Gronowtiz and J.E. Skramstad, *Arkiv Kemi*, **28**, 115 (1967).
106. S. Gronowitz and S. Hagen, *Arkiv Kemi*, **27**, 153 (1967).
107. S. Gronowitz and H. Frostling, *Tetrahedron Lett.*, 604 (1961).
108. S. Gronowitz and H. Frostling, *Acta Chem. Scand.*, **16**, 1127 (1962).
109. R. Håkansson, A. Ask, and A. Almqvist, *Chem. Scripta*, **2**, 72 (1972).
110. E. Wiklund and R. Håkansson, *Chem. Scripta*, **3**, 220 (1973).
111. S. Gronowitz and R. Beselin, *Arkiv Kemi*, **21**, 349 (1963).
112. J. C. Nonciaux, R. Guilard, and È. Laviron, *Bull. Soc. Chim. Fr.*, 3318 (1973).
113. J. Teste and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 492 (1954).
114. H. Wynberg, A. Logothetis, and D. VerPloeg, *J. Am. Chem. Soc.*, **79**, 1972 (1957).
115. P. Spagnolo, P. Zanirato, and S. Gronowitz, *J. Org. Chem.*, **47**, 3177 (1982).
116. C. Dell'Erba, G. Guanti, and G. Garbarino, *J. Heterocycl. Chem.*, **11**, 1017 (1974).
117. J. S. Ramsey and P. Kovacic, *J. Polym. Sci.*, **7**, 127 (1969).
118. V. I. Shvedov and A. N. Grinev, *Khim. Geterotsikl. Soedin*, 515 (1966); *Chem. Hetercycl. Comp.*, 385 (1966).
119. L. J. Pandya, D. S. Rao, and P. D. Tilak, *J. Sci. Ind. Res.*, **18B**, 516 (1959).
120. H. Wynberg and M. Cabell, *J. Org. Chem.*, **38**, 2814 (1973).

121. S. Hauptmann, M. Scholz, H.-J. Köhler, and H.-J. Hofmann, *J. Prakt. Chem.*, **311**, 614 (1969).
122. L. Zechmeister and A. Sandoval, *Ark. Biochem.*, **8**, 425 (1945).
123. L. Zechmeister and J. W. Sease, *J. Am. Chem. Soc.*, **69**, 273 (1947).
124. J. Kagan and S. K. Arora, *J. Org. Chem.*, **48**, 4317 (1983).
125. A. Carpita, R. Rossi, and C. A. Veracini, *Tetrahedron*, **41**, 1919 (1985).
126. J.-P. Beny and J. Kagan, *J. Label. Comp. Radiopharm.*, **XIX**, 313 (1982).
127. J.-P. Beny, S. N. Dahwan, J.Kagan, and S. Sundlass, *J. Org. Chem.*, **47**, 2201 (1982).
128. D. M. Perrine and J. Kagan, *Heterocycles*, **24**, 365 (1986).
129. H. J. Kooreman and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, **86**, 37 (1967).
130. T. Asano, Sh. Ito, N. Saito, and K. Hataheda, *Heterocycles*, **6**, 317 (1977).
131. H. Wynberg and J. Metselaar, *Synth. Commun.*, **14**, 1 (1984).
132. J. Nakayama, Y. Nakamura, T. Tajiri, and M. Hoshino, *Heterocycles*, **24**, 637 (1986).
133. J. Nakayama, S. Murabayashi, and M. Hoshino, *Heterocycles*, **26**, 2599 (1987).
134. S. L. Meisel, G. C. Johnson, and H. D. Hartough, *J. Am. Chem. Soc.*, **72**, 1910 (1950).
135. R. F. Curtis, D. M. Jones, G. Ferguson, D. M. Hawley, J. G. Sinne, K. K. Cheung, and G. German, *Chem. Commun.*, 165 (1969).
136. R. F. Curtis, D. M. Jones, and W. A. Thomas, *J. Chem. Soc. C*, 234 (1971).
137. A. R. Dodson, *Diss. Abstr.*, **22**, 4181 (1962); *Chem. Abstr.*, **57**, 11140f (1962).
138. R. M. Moriarty, O. Prakash, and M. P. Duncan, *Synth. Commun.*, **15**, 789 (1985).
139. J. Kagan, S. K. Arora, I. Prakash, and A. Üstünol, *Heterocycles*, **20**, 1341 (1983).
140. J. Kagan and S. K. Arora, *Heterocycles*, **20**, 1937 (1983).
141. N. Jayasuriya, J. Kagan, D. B. Huang, and B. K. Teo, *Heterocycles*, **27**, 1391 (1988).
142. J. Nakayama, Y. Nakamura, S. Murabayashi, and M. Hoshino, *Heterocycles*, **26**, 939 (1987).
143. J. Nakayama, T. Konishi, S. Murabayashi, and M. Hoshino, *Heterocycles*, **26**, 1793 (1987).
144. C. Glaser, *Liebigs Ann. Chem.*, **154**, 137 (1870).
145. T. Chodkiewicz, *Ann. Chim. (Paris)*, **2**, 819 (1957).
146. B. Greving, A. Woltermann, and Th. Kauffmann, *Angew. Chem.*, **86**, 475 (1974).
147. Th. Kauffmann, B. Greving, J. König, A. Mitschker, and A. Woltermann, *Angew. Chem.*, **87**, 745 (1975).
148. Th. Kauffmann, B. Greving, R. Kriegsmann, A. Mitschker, and A. Woltermann, *Chem. Ber.*, **111**, 1330 (1978).
149. Th. Kauffmann and H. P. Mackowiak, *Chem. Ber.*, **118**, 2343 (1985).
150. T. Yamamoto, K. Osakada, T. Wakabayashi, and A. Yamamoto, *Makromol. Chem. Rapid Commun.*, **6**, 671 (1985).
151. A. Berlin, G. A. Pagini, and F. Sannicolò, *J. Chem. Soc., Chem. Commun.*, 1663 (1986).
152. A. Amer, H. Zimmer, K. J. Mulligan, H. B. Mark, Jr., S. Pons, and J. F. McAleer, *J. Polym. Sci., Polym. Lett. Ed.*, **22**, 77 (1984).
153. A. Czerwinski, H. Zimmer, Ch. V. Pham, A. Amer, J. R. Schrader, and H. B. Mark, Jr., *Anal. Lett.*, **18**, 673 (1985).
154. M. Kobayashi, J. Chen, T.-C. Chung, F. Moraes, A. J. Heeger, and F. Wudl, *Synth. Met.*, **9**, 77 (1984).
155. D. D. Cunningham, L. Laguren-Davidson, H. B. Mark, Jr., Ch. V. Pham, and H. Zimmer, *J. Chem. Soc., Chem. Commun.*, 1021 (1987).
156. D. Kotkar, V. Joshi, and P. K. Ghosh, *J. Chem. Soc. Chem. Commun.*, 917 (1988).
157. R. Shabana, A. Galai, H. B. Mark, Jr., H. Zimmer, S. Gronowitz, and A. B. Hörnfeldt, *J. Chem. Soc., Chem. Commun.*, 988 (1988).

158. W.-S. Huang and J. M. Park, *J. Chem. Soc., Chem. Commun.*, 856 (1987).
159. Y. Cao, P. Wang, and R. Qian, *Macromol. Chem.*, **186**, 1093 (1985).
160. H. Shu, H. Tomiharu, and S. Wataru, *Synth. Met.*, **6**, 319 (1983).
161. M. Sato, S. Tanaka, and K. Kaeriyama, *J. Chem. Soc., Chem. Commun.*, 713 (1985).
162. A. O. Patil, Y. Ikenoue, F. Wudl, and A. J. Heeger, *J. Am. Chem. Soc.*, **109**, 1858 (1987).
163. M. Sato, S. Tanaka, and K. Kaeriyama, *Macromol. Chem.*, **188**, 1763 (1987).
164. M. R. Bryce, A. Chissel. P. Kathirgamanathan, D. Parker, and N. R. M. Smith, *J. Chem. Soc., Chem. Commun.*, 466 (1987).
165. M. Lemaire, R. Garreau, F. Garnier, and J. Roncali, *Nouv. J. Chim.*, **11**, 703 (1987).
166. B. Krische, J. Hellberg, and Ch. Lilja, *J. Chem. Soc., Chem. Commun.*, 1476 (1987).
167. J. Roncali, A. Yassar, and F. Garnier, *J. Chem. Soc., Chem. Commun.*, 581 (1988).
168. M. Lemaire, D. Delabouglise, R. Garreau. A. Guy, and J. Roncali, *J. Chem. Soc., Chem. Commun.*, 658 (1988).
169. K. Y. Jen, M. Maxfield, L. W. Shacklette, and R. L. Elsenbaumer, *J. Chem. Soc., Chem. Commun.*, 309 (1987).
170. S. Yamada, S. Tokito, T. Tsutsui, and S. Saito, *J. Chem. Soc., Chem. Commun.*, 1448 (1987).
171. K. Y. Jen, H. Eckhardt, T. R. Jow, L. W. Shacklette, and R. L. Elsenbaumer, *J. Chem. Soc., Chem. Commun.*, 215 (1988).
172. S. Iwatsuki, M. Kubo, and H. Yamashita, *Chem. Lett.*, 729 (1989).
173. K. L. Pouwer, T. R. Vries, E. E. Havinga, E. W. Meijer, and H. Wynberg, *J. Chem. Soc., Chem. Commun.*, 1432 (1988).
174. T. Yamamoto, M. Zama, and A. Yamamoto, *Chem. Lett.*, 1577 (1984); 563 (1985).
175. T. Yamamoto, K, Saneshika, and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, **56**, 1503 (1983).
176. H. Guenther, M. D. Bezoari, P. Kovacic, S. Gronowitz, and A. B. Hörnfeldt, *J. Polym. Sci., Polym. Lett. Ed.*, **22**, 65 (1984).
177. H. Neugebauer, A. Neckel, G. Nauer, N. Brinda-Konopik, F. Garnier, and G. Tourrillon, *J. Physique*, 517 (1983).
178. H. Neugebauer, G. Nauer, A. Neckel, G. Tourillon, F. Garnier, and Ph. Lang, *J. Phys. Chem.*, **88**, 652 (1984).
179. H. Neugebauer, A. Neckel, and N. Brinda-Konopik, *Springer Ser. Solid-State Sci.*, **63**, 227 (1985). *Chem. Abstr.*, **104**, 20013a (1986).
180. S. Hotta, W. Shimotsuma, and M. Taketani, *Synth. Met.*, **10**, 85 (1984/85).
181. C. Yong and Q. Renyuan, *Solid State Commun.*, **54**, 211 (1985).
182. W. Hayes, F. L. Pratt, K. S. Wong, K. Kaneto, and K. Yoshino, *J. Phys. C: Solid State Phys.*, **18**, L555 (1985).
183. D. Delabouglise, R. Garreau, M. Lemaire, and J. Roncali, *Nouv. J. Chim.*, **12**, 155 (1988).
184. F. Moraes, H. Schaffer, M. Kobayashi, A. J. Heeger, and F. Wudl, *Phys. Rev.*, **30**, 2948 (1984).
185. G. Harbeke, E. Meier, W. Kobel, M. Egli, H. Kiess, and E. Tosatti, *Solid State Commun.*, **55**, 419 (1985).
186. V. I. Krinichnyi, O. Ya. Grinberg, I. B. Nazarova, G. I. Kozub, L. I. Tkachenco, M. L. Khidekel', and Ya. S. Lebedev, *Izv. Acad. Nauk SSSR, Ser. Khim.*, 467 (1985); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 425 (1985).
187. K. Tanaka, T. Shichiri, K. Yoshizawa, T. Yamabe, S. Hotta, W. Shimotsuma, J. Yamauchi, and Y. Deguchi, *Solid State Commun.*, **51**, 565 (1984).
188. G. Tourillon, D. Gourier, P. Garnier, and D. Vivien, *J. Phys. Chem.*, **88**, 1049 (1984).
189. K. Kaneto, S. Hayashi, S. Ura, and K. Yoshino, *J. Phys. Soc. Jpn.*, **54**, 1146 (1985).
190. F. Moraes, D. Davidov, M. Kobayashi, T. C. Chung, J. Chen, A. J. Heeger, and F. Wudl, *Synth. Met.*, **10**, 169 (1985).

191. S. Hotta, T. Hosaka, M. Soga, and W. Shimotsuma, *Synth. Met.*, **9**, 87 (1984).
192. Z. Mo, K.-B. Lee, Y. B. Moon, M. Kobayashi, A. J. Heeger, and F. Wudl, *Macromolecules*, **18**, 1972 (1985).
193. P. Pfluger and G. B. Street, *J. Chem. Phys.*, **80**, 544 (1984).
194. P. Pfluger and G. B. Street, *J. Phys. Colloq.*, 1983; *Chem. Abstr.*, **100**, 112948e (1984).
195. H. Wynberg and A. Bantjes, *J. Am. Chem. Soc.*, **82**, 1447 (1960).
196. J. Kagan, S. K. Arora, and A. Üstünol, *J. Org. Chem.*, **48**, 4076 (1983).
197. Th. Kauffmann and H. P. Mackowiak, *Chem. Ber.*, **118**, 3714 (1985).
198. W. Steinkopf and W. Köhler, *Liebigs Ann. Chem.*, **522**, 17 (1936).
199. W. Steinkopf, *Liebigs Ann. Chem.*, **545**, 38 (1940).
200. A. E. Lipkin, *Zh. Obshch. Khim.*, **33**, 2274 (1963); *J. Gen. Chem. USSR*, **33**, 2216 (1963).
201. K. I. Vakhreeva and A. E. Lipkin, *Khim. Geterotsikl. Soedin*, 918 (1971); *Chem. Heterocycl. Comp.*, 857 (1974).
202. P. L. Trakhtenberg, M. N. Zemtsova, V. F. Sakharov, V. P. Zvolinskii, A. N: Gusarov, and A. E. Lipkin, *Khim. Geterotsikl. Soedin*, 1194 (1979); *Chem. Heterocycl. Comp.*, 970 (1980).
203. A. V. Yudashkin, A. E. Lipkin, V. P. Zvolinskii, V. F. Zakharov, and V. F. Ignatov, *Khim. Geterotsikl. Soedin*, 1057 (1979); *Chem. Heterocycl. Comp.*, 864 (1980).
204. C. Dell'Erba, G. Garbarino, and G. Guanti, *J. Heterocycl. Chem.*, **8**, 849 (1971).
205. Th. Kauffmann, J. König, D. Körber, H. Lexy, H.-J. Streitberger, A. Vahrenhorst, and A. Woltermann, *Tetrahedron Lett.*, 389 (1977).
206. A. R. Butler and C. Eaborn, *J. Chem. Soc. B*, 370 (1968).
207. W. Steinkopf and H. J. v. Petersdorff, *Liebigs Ann. Chem.*, **543**, 119 (1940).
208. G. N. Jean and F. F. Nord, *J. Org. Chem.*, **20**, 1370 (1955).
209. Y. Matsuki and Y. Miyake, *Tohoku Daigaku Hisuiyoeki Kagaku Kenkyusho Hokoku*, **12**, 1 (1963); *Chem. Abstr.*, **63**, 11475b (1965).
210. D. E. Minnikin and N. Polgar, *J. Chem. Soc. C*, 575 (1967).
211. K. E. Miller, *J. Chem. Eng. Data*, **8**, 605 (1963); **10**, 305 (1965).
212. S. Gronowitz and L. Karlsson, *Arkiv Kemi*, **22**, 119 (1964).
213. Th. Kauffmann, A. Mitschker, and H.-J. Streitberger, *Angew. Chem.*, **84**, 829 (1972).
214. R. F. Curtis and G. T. Phillips, *Tetrahedron*, **23**, 4419 (1967).
215. C. Grundmann and J. M. Dean, *Angew. Chem. (Int. Ed.)*, **11**, 955 (1965).
216. R. M. Kellogg, A. P. Schaap, and H. Wynberg, *J. Org. Chem.*, **34**, 343 (1969).
217. L. Klasine and K. Hunski, *Z. Naturforsch.*, **25b**, 324 (1970).
218. W. Steinkopf in *Die Chemie des Thiophene*. Verlag Th. Steinkopf, Dresden und Leipzig, 1941.
219. R. F. Curtis and G. T. Phillips, *J. Chem. Soc.*, 5134 (1965).
220. D. Brown, J. Cymerman Craig, N. H. Dyson, and J. W. Westley, *J. Chem. Soc. C*, 89 (1966).
221. V. A. Smirnov and A. E. Lipkin, *Khim. Geterotsikl. Soedin*, 185 (1973); *Chem. Heterocycl. Comp.*, 170 (1975).
222. H. O. Wirth, O. Königstein, and W. Kern, *Liebigs Ann. Chem.*, **84**, 634 (1960).
223. N. Gjös and S. Gronowitz, *Acta Chem. Scand.*, **21**, 2893 (1967).
224. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 137 (1974).
225. R. Håkansson, *Acta Chem. Scand.*, **25**, 1313 (1971).
226. S. Gronowitz, J. E. Skramstad, and B. Eriksson, *Arkiv Kemi*, **28**, 99 (1967).
227. R. Håkansson and Inga Jakobson, unpublished results.
228. F. de Jong and M. J. Janssen, *J. Org. Chem.*, **36**, 1998 (1971).
229. D. A. Forsyth and D. E. Vogel, *J. Org. Chem.*, **44**, 3917 (1979).
230. P. Moses and S. Gronowitz, *Arkiv Kemi*, **18**, 119 (1961).

231. J. Skramstad and H. Storflor, *Acta Chem. Scand. B.*, **38**, 533 (1984).
232. Yu. V. Shklyaev, Yu. P. Dormidontov, and I. I. Lapkin, *Khim. Geterotsikl. Soedin*, 468 (1981); *Chem. Heterocycl. Comp.*, 332 (1981).
233. W. A. Herrmann and D. Andrejewski, *Chem. Ber.*, **119**, 878 (1986).
234. R. Håkansson, personal observation.
235. R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *Chem. Commun.*, 718 (1967).
236. F. Bohlman and J. Kocur, *Chem. Ber.*, **108**, 2149 (1975).
237. Y. M. Kao and W. S. Hwang, *J. Heterocycl. Chem.*, **26**, 533 (1989).
238. H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beckhuis, *J. Am. Chem. Soc.*, **89**, 3501 (1967).
239. R. M. Kellogg, J. K. Dik, H. van Driel, and H. Wynberg, *J. Org. Chem.*, **35**, 2737 (1970).
240. R. Guilard, J. C. Nonciaux, È. Laviron, and P. Fournai, *J. Heterocycl. Chem.*, **12**, 191 (1975).
241. P. Meunier, *J. Heterocycl. Chem.*, **15**, 593 (1978).
242. P. L. Trakhtenberg, A. E. Lipkin, and Z. I. Nuzhdina, *Khim. Geterotsikl. Soedin*, 773 (1972); *Chem. Heterocycl. Comp.*, 699 (1974).
243. M. N. Zemtsova, P. L. Trakhtenberg, A. E. Lipkin, and T. B. Ryskina, *Khim.-Farm. Zh.*, **7**, 13 (1973).
244. P. Zanirato, *J. Organometal. Chem.*, **293**, 285 (1985).
245. R. E. Atkinson and F. E. Hardy, *J. Chem. Soc., Perkin II*, 27 (1972).
246. T. B. Patrick and J. L. Honegger, *J. Org. Chem.*, **39**, 3791 (1974).
247. L. Skatteböl, *Acta Chem. Scand.*, **15**, 2047 (1961).
248. K. E. Miller, *J. Chem. Eng. Data*, **10**, 305 (1965).
249. R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *J. Chem. Soc.*, 7109 (1965).
250. G. Rawson and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, **90**, 46 (1971).
251. K. I. Vakhreeva, A. E. Lipkin, T. B. Ryskina, and N. I. Skachkova, *Khim.-Farm. Zh.*, **7**, 24 (1973).
252. R. G. Child, A. C. Osterberg, A. E. Sloboda, and A. S. Tomcufcik, *Arzneim.-Forsch./Drug Res.*, **30**, 695 (1980).
253. P. L. Trakhtenberg and A. E. Lipkin, *Khim. Geterotsikl. Soedin*, 61 (1974).
254. R. E. Atkinson, R. F. Curtis, and G. T. Phillips, *J. Chem. Soc. C*, 1101 (1966).
255. J. Kagan, S. K. Arora, M. Bryzgis, S. N. Dhawan, K. Reid, S. P. Singh, and L. Tow, *J. Org. Chem.*, **48**, 703 (1983).
256. P. Cavalieri d'Oro, A. Mangini, G. F. Pedulli, P. Spagnolo, and M. Tiecco, *Tetrahedron Lett.*, 4179 (1969).
257. D. P. Munro and J. T. Sharp, *J. Chem. Soc. Perkin Trans. I*, 571 (1984).
258. H. Wynberg and H. J. M. Sinnige, *Rec. Trav. Chim. Pays-Bas*, **88**, 1244 (1969).
259. T. A. Manuel and T. J. Meyer, *Inorg. Chem.*, **3**, 1049 (1964).
260. A. E. Lipkin and N. I. Putokhin, *Khim. Geterotsikl. Soedin*, **3**, 243 (1967); *Chem. Heterocycl. Comp.*, 181 (1967).
261. A. E. Lipkin, K. I. Vakhreeva, P. I. Buchin, D. A. Kulikova, and E. A. Rudzit, *Khim.-Farm. Zh.*, **11**, 46 (1977).
262. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 174 (1974).
263. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 76 (1974).
264. E. Ghera, Y. Gaoni, and S. Shoua, *J. Am. Chem. Soc.*, **98**, 3627 (1976).
265. A. Almqvist and R. Håkansson, *Chem. Scripta*, **10**, 120 (1976).
266. P. Pedaja and S. Gronowitz, *Chem. Scripta*, **20**, 53 (1982).
267. R. Håkansson and E. Wiklund, *Acta Chem. Scand.*, **24**, 2667 (1970).

268. D. W. H. MacDowell and M. H. Maxwell, *J. Org. Chem.*, **35**, 799 (1970).
269. P. J. Garratt and Soon Bin Neoh, *J. Org. Chem.*, **40**, 970 (1975).
270. H. Wynberg and A. Kraak, *J. Org. Chem.*, **29**, 2455 (1964).
271. A. Kraak, A. K. Wiersema, P. Jordens, and H. Wynberg, *Tetrahedron*, **24**, 3381 (1968).
272. P. Jordens, G. Rawson, and H. Wynberg, *J. Chem. Soc. C*, 273 (1970).
273. A. K. Wiersema and S. Gronowitz, *Acta Chem. Scand.*, **25**, 1195 (1971).
274. J. Skramstad, *Chem. Scripta*, **4**, 81 (1973).
275. G. Rawson and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, **90**, 39 (1971).
276. G. J. Heeres and H. Wynberg, *Synth. Commun.*, **2**, 335 (1972).
277. A. K. Wiersema and S. Gronowitz, *Acta Chem. Scand.*, **23**, 2923 (1969).
278. A. K. Wiersema and S. Gronowitz, *Acta Chem. Scand.*, **24**, 2653 (1970).
279. G. J. Heeres and H. Wynberg, *Tetrahedron*, **28**, 5237 (1972).
280. F. de Jong and M. J. Janssen, *J. Org. Chem.*, **36**, 1645 (1971).
281. F. M. Stoyanowich and B. P. Fedorov, *Zh. Org. Khim.*, **1**, 1282 (1965); *J. Org. Chem. USSR*, 1296 (1965).
282. P. Zanirato, P. Spagnolo, and G. Zanardi, *J. Chem. Soc. Perkin I*, 2551 (1983).
283. D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.*, **13B**, 829 (1954); *Chem. Abstr.*, **50**, 934b (1956).
284. D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.*, **16B**, 65 (1957); *Chem. Abstr.*, **51**, 13841i (1957).
285. D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res.*, **17B**, 260 (1958); *Chem. Abstr.*, **55**, 22282e (1960).
286. R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.*, **32**, 3093 (1967).
287. M. Weitzberg, Z. Aizenshtat, P. Jerushalmy, and J. Blum, *J. Org. Chem.*, **45**, 4252 (1980).
288. A. De, J. S. A. Brunshill, and H. Jeffrey, *Ind. J. Chem.*, **23B**, 918 (1984).
289. S. Gronowitz and T. Dahlgren, *Chem. Scripta*, **12**, 57 (1977); **12**, 97 (1977).
290. G. J. Heeres and H. Wynberg, *Synth. Commun.*, **2**, 365 (1972).
291. H. Wynberg and G. J. Heeres, *Synth. Commun.*, **1**, 29 (1971).
292. Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *Chem. Scripta*, **28**, 275 (1988).
293. S. Gronowitz, A.-B. Hörnfeldt, and Y. Yang, *Chem. Scripta*, **28**, 281 (1988).
294. Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *Synthesis*, 130 (1989).
295. S. Gronowitz and I. Ander, and P. Zanirato, *Chem. Scripta*, **22**, 55 (1983).
296. S. Gronowitz and I. Ander, *Chem. Scripta*, **15**, 23, 135 (1980).
297. A. Almqvist and R. Håkansson, *Chem. Scripta*, **10**, 117 (1976).
298. E. Wiklund and R. Håkansson, *Acta Chem. Scand.*, **24**, 341 (1970).
299. A. Almqvist and R. Håkansson, *Chem. Scripta*, **11**, 180 (1977).
300. G. N. Jean, L. J. Owens, and F. F. Nord, *Nature*, **169**, 585 (1952).
301. G. N. Jean, *J. Org. Chem.*, **21**, 419 (1956).
302. S. Gronowitz, personal communication.
303. M. B. Groen and H. Wynberg, *J. Am. Chem. Soc.*, **93**, 2968 (1971).
304. R. Håkansson and E. Wiklund, *Acta Chem. Scand.*, **25**, 2109 (1971).
305. A. Fredga, *Tetrahedron*, **8**, 126 (1960).
306. A. Fredga, *Bull. Soc. Chim. Fr.*, 1731 (1973).
307. P. Newman, Ph. Rutkin, and K. Mislow, *J. Am. Chem. Soc.*, **80**, 465 (1958).
308. H. Akimoto, T. Shioiri, Y. Iitaka, and S. Yamada, *Tetrahedron Lett.*, 97 (1968).
309. H. Akimoto and S. Yamada, *Tetrahedron Lett.*, 3967 (1968).
310. H. Akimoto and S. Yamada, *Tetrahedron*, 27, 5999 (1971).
311. L. H. Pignolet, R. P. Taylor, and W. deW. Horrocks, Jr., *Chem. Commun.*, 1443 (1968).

312. J. E. Ricci, *Tetrahedron*, **18**, 605 (1962).
313. S. Gronowitz, *Arkiv Kemi*, **23**, 207 (1965).
314. R. Håkansson, *Chem. Scripta*, **3**, 177 (1973).
315. R. Håkansson, S. Gronowitz, J. Skramstad, and T. Frejd, *Chem. Scripta*, **7**, 131 (1975).
316. A. Almqvist and R. Håkansson, *Chem. Scripta*, **11**, 186 (1977).
317. R. Håkansson, *Chem. Scripta*, **2**, 109 (1972).
318. U. Schubert, W. Neugebauer, and P. v. R. Schleyer, *J. Chem. Soc., Chem. Commun.*, 1184 (1982).
319. P. v. R. Schleyer and A. Kos, personal communication.
320. S. Glasstone, K. J. Laidler, and H. Eyring, *Theory of Rate Processes*, McGraw-Hill, New York, 1941, p. 195.
321. E. Wiklund and R. Håkansson, *Chem. Scripta*, **6**, 226 (1974).
322. D. M. Hall, in *Progress in Stereochemistry*, B. J. Aylett and M. M. Harris, eds., Butterworth, London, 1969, Vol. 4, pp. 17, 22.
323. M. Oki, H. Iwamura, and N. Hagakawa, *Bull. Chem. Soc. Jpn.*, **36**, 1542 (1963).
324. R. J. Kurland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, **40**, 2426 (1964).
325. K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Whal, Jr., *J. Am. Chem. Soc.*, **86**, 1710 (1964).
326. R. Håkansson, *Chem. Scripta*, **3**, 212 (1973).
327. R. Håkansson and E. Wiklund, *Chem. Scripta*, **7**, 120 (1975).
328. R. Håkansson and E. Wiklund, *Chem. Scripta*, **7**, 173 (1975).
329. R. Håkansson, B. Nordén, and E. Wiklund, *Acta Chem. Scand. B*, **28**, 695 (1974).
330. B. Aurivillius, C. Svensson, and C. Särnstrand, *Chem. Scripta*, **7**, 204 (1975).
331. F. Hopfgarten, C. Svensson, and C. Särnstrand, *Chem. Scripta*, **9**, 66 (1976).
332. G. J. Visser, G. J. Heeres, J. Wolter, and A. Vos, *Acta Cryst. B*, **24**, 467 (1968).
333. A. Almenningen, O. Bastiansen, and P. Svendsås, *Acta Chem. Scand.*, **12**, 1671 (1958).
334. A. Almenningen, O. Bastiansen, and L. Fernholt, cited in Skanke, Ref. 335.
335. A. Skanke, *Acta Chem. Scand.*, **24**, 1389 (1970).
336. H. H. Jensen and A. Skanke, *Acta Chem. Scand.*, **24**, 3766 (1970).
337. V. Galasso and N. Trinajstic', *Tetrahedron*, **28**, 4419 (1972).
338. H. Wynberg, *Angew. Chem.*, **75**, 453 (1963).
339. H. Lumbroso and C. Carpanelli, *Bull. Soc. Chim. Fr.*, 3198 (1964).
340. K. Kahman, H. Sigel, and H. Erlenmeyer, *Helv. Chim. Acta*, **47**, 1754 (1964).
341. C. A. Veracini, D. Macciantelli, and L. Lunazzi, *J. Chem. Soc. Perkin II*, 751 (1973).
342. L. Lunazzi, A. Mangini, G. F. Pedulli, and M. Tiecco, *Gazz. Chim. Ital.*, **101**, 10 (1971).
343. P. Meunier, M. Coustale, C. Guimon, and G. Pfister-Guillouzo, *J. Mol. Struct.*, **36**, 233 (1977).
344. P. Meunier and G. Pfister-Guillouzo, *Can. J. Chem.*, **55**, 2867 (1977).
345. P. Meunier, M. Coustale, and J. Arriau, *Bull. Soc. Chim. Belg.*, **87**, 27 (1978).
346. P. Meunier and J. Arriau, *J. Heterocycl. Chem.*, **17**, 321 (1980).
347. A. Kraak and H. Wynberg, *Tetrahedron*, **24**, 3881 (1968).
348. A. E. Likpin, N. I. Putokhin, and B. V. Rassadin, *J. Gen. Chem. USSR*, **33**, 2999 (1963).
349. P. B. Koster, F. van Bolhuis, and G. J. Visser, *Acta Cryst. B*, **26**, 1932 (1970).
350. A. K. Wiersema, Dissertation, Groningen, Netherlands, 1970.
351. A. J. H. Wachters and D. W. Davies, *Tetrahedron*, **20**, 2841 (1964).
352. N. Trinajstic' and A. Hinchliffe, *Croatica Chem. Acta*, **40**, 163 (1968).
353. B. Nordén, R. Håkansson, and M. Sundbom, *Acta Chem. Scand.*, **26**, 429 (1972).

354. B. Nordén, *Chem. Scripta*, **7**, 226 (1975).
355. R. Eckert and H. Kuhn, *Z. Electrochemie*, **64**, 356 (1960).
356. A. R. Katritzky and A. J. Boulton, *J. Chem. Soc.*, 3500 (1959).
357. S. Gronowitz, A. R. Katritzky, and R. E. Reavill, *J. Chem. Soc.*, 3881 (1963).
358. S. Gronowitz and R. A. Hoffman, *Arkiv Kemi*, **16**, 539 (1960).
359. D. H. S. Horn and J. A. Lamberton, *Aust. J. Chem.*, **16**, 475 (1963).
360. C. K. Coogan, D. H. S. Horn, and J. A. Lamberton, *Aust. J. Chem.*, **18**, 723 (1965).
361. R. Håkansson, *Acta Chem. Scand.*, **23**, 952 (1969).
362. E. Wiklund and R. Håkansson, *Chem. Scripta*, **3**, 226 (1973).
363. P. B. Koster and M. J. Janssen, *J. Chem. Soc. Perkin II*, 323 (1976).
364. J. E. Collin, *Bull. Soc. Chim. Belg.*, **72**, 38 (1963).
365. Th. Kauffmann and A. Mitschler, *Tetrahedron Lett.*, 393 (1977).
366. C. Dell'Erba, D. Spinelli, and G. Garbarino, *Gazz. Chim. Ital.*, **100**, 777 (1970).
367. R. F. Curtis and G. T. Phillips, *J. Chromatogr.*, **9**, 366 (1962).
368. S. Berk, *J. Chromatogr.*, **15**, 540 (1964).

Chemistry of Heterocyclic Compounds, Volume 44
Edited by Salo Gronowitz
Copyright © 1992 by John Wiley & Sons, Ltd.

Index

5-Acetamido-4-nitro-2,2′-bithienyl, 805
5-Acetamido-5′-nitro-2,2′-bithienyl, 805
5-Acetyl-3,3′-diiodo-2,2′-bithienyl, 816–817
Acetylenic 2,2′-bithienyl, 826
Acetylenic natural products, preparation, 727–728
Acetylides, thienylacetylenes preparation, 139–140
N-Acetyl-3-(2-thienyl)alanyl amino acids, preparation, 92
3-Acetyl-2-thienylboronic acid, preparation, 692
Acidity, thienylic protons, 736
2-Acylacrylic acids and esters, 207
Acylation:
  2,2′-bithienyl, 817–818
  2,3′-bithienyl, 819
  3,3′-bithienyl, 818
  polythienyls, 819
2-Acyl-3-(thienyl)acrylic acids and esters, preparation, 20
Aldol condensations, vinylthiophene preparation, 4–5
Alkylation, α-thienyllithium derivatives, 671–679
2-Alkyl-substituted 3-(thienyl)acrylic acids and esters, 202–204
3-Alkyl-substituted thiophene derivatives, metalation, 709–710
Alkylthiophenes, vinylthiophene preparation, 85–86
3-Alkyl thiophenes, preparation, 692–693
Allenes, 133
Aluminum derivatives, thiophenes, 564
Amination, α-thienyllithium derivatives, 680–681
Annelated bithienyls, preparation, 789–790
Antimony derivatives, thiophenes, 586–587
Arsenic derivatives, thiophenes, 586–587
Arylacetic acids, vinylthiophene preparation, condensation with, 18–19
Arylation, α-thienyllithium derivatives, 671–679
2-Aryl-substituted 3-(thienyl)acrylic acids and esters, 202–204
2-Arylthiophene, preparation, 770–771
Atropisomerism, 3,3′-bithienyls, 840
3-(3-Azido-2-thienyl)acrylic esters, preparation, 19
3-Azido-2-vinylthiophenes, 102–104

Benzo[*b*]thiophene (4,7-dideuterio), 830
Benzodithiophenes, 834-835
2′-Benzoyloxy-2,3′-bithienyl, 787–788
5′-Benzoyl-3,4′,5-triphenyl-2,2′-bithienyl, preparation, 777–778
2,2′-Biacenaphtho[1,2-*b*]thienyl, 790
3,3′-Bibenzo[*b*]thienyl, 789-790
trans,trans-5,5′-Bis(4-butylphenyl)-2,2′-bithienyl, preparation, 47
trans,trans-5,5′-Bis(5-butyl-2-thienylvinyl)-2,2′-bithienyl, preparation, 38
2,5-Bisdiazoacetylthiophene, preparation, 73
Bis-magnesiumhalides of thiophene-derivatives, 708–709
2,5-Bis(methylthio)thiophene, metalation, 684
Bismuth derivatives, thiophenes, 586–587
Bisthiopheneindigo, preparation, 775-776
2,2′-Bithieno[2,3-*b*]thienyl, 789–790
2,2′-Bithienyl, 757
  acylation, 817–818
  conformation, 884–885, 890
  ESR spectroscopy, 895
  halogenation, 819–820
  mass spectra, 895
  nitration, 804–814
  ^{1}H NMR spectrum, 894
  preparation, 758–778
    coupling catalyzed by Co, Ni, Pd, Rh, and Te, 768–769
    coupling initiated by free radicals, 772–774
    coupling of 2-ThMgBr or 2-ThLi derivatives with $CuCl_2$, 759–765
    coupling under Friedel–Crafts conditions, 769–771
    miscellaneous types of coupling, 774–776
    organoboron reagent coupling, 771–772
    ring-closure methods, 776–778

2,2′-Bithienyl, preparation (*Continued*)
Ullmann-type coupling, 765–767
protonation, 895
reactions via organometallic compounds, 825–827
UV spectra, 890–891, 893
2,3′-Bithienyl, 757
acylation, 819
conformation, 884–885, 890
halogenation, 824–825
nitration, 815–816
NMR spectra, 894
preparation, 784–788
coupling catalyzed by Pd and Ni, 787
coupling of 2-thienylcopper with 3-halothiophenes, 785–787
miscellaneous types of coupling, 787–788
ring-closure methods, 788
2-ThLi derivatives reacting with 3-ketotetrahydrothiophene, 785
reactions via organometallic compounds, 828–829
3,3′-Bithienyl, 757
acylation, 818
conformation, 884–885, 890
halogenation, 820–824
inactive 2,2′-bridged, 846
inactive 4,4′-bridged, 847
mass spectra, 895
nitration, 805, 814–815
NMR spectra, 894
optical activity, 840–883
atropisomerism, 840
barriers to inversion of bridged compounds, 863–865
carboxylic acid racemization, 861–863
CD spectra, 865–883
free energy of activation, 863–864
optical stabilities, 859–865
preparation, 778–784, 847–859
coupling catalyzed by Pd and Ni, 783–784
coupling of 3-ThLi derivatives with CuCl, 779–781
dicarboxylic acids, 851–853
quasi-racemate method, 850–851, 854
rule, 850
Ullmann-type coupling, 779, 782–783, 851
racemization on halogen–metal exchange, 859–861
reactions via organometallic compounds, 827–828
Ullmann coupling, 851
UV spectra, 890–892
3,3′-Bithienyl (2,5-dideuterio), 830
Bithienyls, *see also* Bridged bithienyls
with annelated rings, preparation, 789–790
conformational analyses, 884–890
IR spectroscopy, 893
miscellaneous investigations, 895
NMR spectroscopy, 893–895
photochemical rearrangements, 829–830
pivot bond, 758
UV spectra, 886–893
Borazarobenzodithiophenes, 836–837
Boron derivatives, thiophenes, 543–563
Bridged bithienyls, 830–840
doubly bridged, 839–840
four-atom bridge, 839
one-atom bridge, 831–834
three-atom bridge, 837–839
two-atom bridge, 834–837
UV spectra, 891–892
zero-atom bridge, 831
2,2′-Bridged 3,3′-bithienyls, coalescence temperatures and free energies of activation, 864
Bromine, halogen–metal exchange, 690–691
3-Bromo-2,5-bis(trimethylsilyl)thiophene, preparation, 719
4-Bromo-3,3′-bithienyl, 783, 784
3-Bromo-2,5-diformylthiophene, preparation, 707
5-Bromo-5′-formyl-2,2′-bithienyl, preparation, 772
2-Bromo-5-methylthiophene, preparation, 771
3-Bromo-2-methyl-5-thiophene aldehyde, condensation, 43
2-Bromo-4-methylthio-5-thiophene carboxylic acid, preparation, 719
3-[2-(2′-Bromophenyl)ethyl]thiophene, intramolecular metalation, 719–720
3-Bromo-2-thienyllithium, preparation, 697
3-Bromothiophene, metalation, 737
3-Bromo-4-thiophene aldehyde, metalation, 712
3-Bromo-2-thiophenecarboxylic acid, preparation, 718
2-Bromo-5-trimethylsilylthiophene, preparation, 719
3-*t*-Butylthiophene, preparation, 708

Cadmium derivatives, thiophenes, 588–590
Calcium derivatives, thiophenes, 542
2-Carbamido-3-(thienyl)acrylonitriles, preparation, 22
Carbanions, Michael additions to vinylthiophenes, 120–122

Carbonyl compounds, alcohol dehydration, 56–62
2′-Carboxy-2,3′-bithienyl, 828
5′-Carboxy-2,3′-bithienyl, 828
Carboxylic acids, racemization, 861–863
2-Carboxymethyl-5-methyl-3-thiophenecarboxylic acid, preparation, 727
3-Carboxy-5-methyl-2-thienylacetic acid, 684
Catalytic hydrogenation, vinylthiophenes, 112–113
Cesium derivatives, thiophenes, 503–509
^{1}H Chemical shifts, 4*H*-cyclopenta[*c*]thiophene, 732
5-Chloro-2,2′-bithienyl, preparation, 770–771
2-Chloro-5-methylthiophene, chlorine–metal exchange, 711
trans-1-(4′-Chlorophenylthio)-2-(2-thienyl)ethene, preparation, 144
1-Chloro-2-(2-thienyl)acetylene, preparation, 141–142
β-Chloro-β-(2-thienyl)acrolein, preparation, 69–70
Claisen–Schmidt condensations, vinylthiophene preparation, 5
Condensations, with arylacetic acids, 18–19
  condensations with ethyl azidoacetates, 19
  Michael-type addition, 20
  Stobbe condensation, 26–30
  thiopheneacetic acids, 31–32
Conformational analysis, bithienyls and polythienyls, 884–890
Copper derivatives, thiophenes, 604–621
Cupric chloride, coupling with 2-thienylmagnesium bromide or 2-thienyllithium, 759–765
Cuprous acetylides, thienylacetylenes from, 138
2-Cyanoacrylic acids and esters, 207
2-Cyano-3-(thienyl)acrylic esters, preparation, 20
3-Cyano-2-thiophenecarboxylic acid, preparation, 697
Cycloadditions, vinylthiophenes, 122–130
Cycloheptadithiophenes, 837
Cyclohexenylthiophenes, synthesis, 59
^{4}*H*-Cyclopenta[*c*]thiophene, ^{1}H chemical shifts, 732
Cyclopentadithiophenes, 831–832
  UV spectra, 892
Cyclotetrathiophenes, 801

Dean–Stark trap, vinylthiophene preparation, 16, 21
Diactylenic thiophene derivative, preparation, 725–726
2,2′-Diacyl-2-(4,5-dichloro-2-thienyl)ethenes, preparation, 23
5,5′-Dibenzyl-2,2′-bithienyl, 765–766
2,5-Dibromo-3-alkyl-substituted thiophene derivatives, halogen–metal exchange, 710
2,2′-Dibromo-3,3′-bithienyl, 820-821
(*R*)-(−)-2,2′-Dibromo-4,4′-dicarbomethoxy-3,3′-bithienyl, CD spectra, 874, 878
(*S*)-(+)-2,2′-Dibromo-4,4′-dicarbomethoxy-3,3′-bithienyl, CD spectra, 874, 878
(*R*)-(+)-4,4′-Dibromo-2,2′-dicarbomethoxy-3,3′-bithienyl:
  CD spectra, 874, 878
  stereoscopic view, 876, 878
(*S*)-(−)-4,4′-Dibromo-2,2′-dicarbomethoxy-3,3′-bithienyl, CD spectra, 874, 878
(*R*)-(−)-4,4′-Dibromo-4,4′-dicarbomethoxy-3,3′-bithienyl, stereoscopic view, 876, 879
2,2′-Dibromo-4,4′-dicarboxy-3,3′-bithienyl, 848, 853
  CD and UV spectra, 865–866
(*R*)-(+)-4,4′-Dibromo-2,2′-dicarboxy-3,3′-bithienyl, CD and UV spectra, 866
2,2′-Dibromo-4,4′-dichloro-3,3′-bithienyl, 858
4,4′-Dibromo-2,2′-diformyl-3,3′-bithienyl, 857
(*R*)-(−)-1,9-Dibromo-4,6-dihydrodithieno[2,3-*c*:3′,2′-*e*]thiepine, CD and UV spectra, 866, 871
(*R*)-(−)-1,9-Dibromo-4,6-dihydrodithieno[3,4-*c*:3′,4′-*e*]thiepine, CD and UV spectra, 866, 872
4,4′-Dibromo-2,2′-dilithio-3,3′-bithienyl, geometry, 860–861
4,4′-Dibromo-2,2′-dimethyl-3,3′-bithienyl, 856
(*R*)-(−)-1,9-Dibromo-2,8-dimethyl-4,6-dihydrodithieno [2,3-*c*:3′,2′-*e*]thiepine, CD and UV spectra, 866, 871
2,4-Dibromo-5-substituted thiophenes, 685–686
4,4′-Dibromo-2,2′,5,5′-tetramethyl-3,3′-bithienyl, 859
(*R*)-5,5′-Dibromo-2,2,4,4′-tetramethyl-3,3′-bithienyl, CD and UV spectra, 867–868, 870, 874
2,4-Dibromothiophene, synthesis, 689
2,5-Dibromo-3-trimethylsilylthiophene, 685
  preparation, 718
5,5′-Di-*tert*-butyl-2,2′-bithienyl, 765–766
3,3′-Dicarbomethoxy-2,2′-bithienyl, preparation, 766
1,2-Dicarbonyl derivatives, thiophenes, 678

2,2′-Dicarboxy-3,3′-bithienyls, racemization activation parameters, 862
4,4′-Dicarboxy-3,3′-bithienyls, racemization activation parameters, 862–863
2′,5′-Dicarboxy-5-chloro-2″,5″-dimethyl-2,3′ : 4′,3″-terthienyl, 797
(*R*)-2,2′-Dicarboxy-4,4′-dichloro-3,3′-bithienyl, CD spectra, 872, 877
(*S*)-1,9-Dicarboxy-4,6-dihydrodithieno[2,3-*c*:3′,2′-*e*]thiepine, CD spectra, 872, 877
(*R*)-(+)-2,2′-Dicarboxy-4,4′-dimethyl-3,3′-bithienyl, CD and UV spectra, 865, 867
(*R*)-(−)-4,4′-Dicarboxy-2,2′-dimethyl-3,3′-bithienyl, CD and UV spectra, 865, 867
2,2′-Dicarboxy-4,4′-dinitro-3,3′-bithienyl, CD and UV spectra, 879–880, 882
4,4′-Dicarboxy-2,2′-dinitro-3,3′-bithienyl, CD and UV spectra, 879–880, 882
4,4′-Dicarboxy-2,2′,5,5′-tetramethyl-3,3′-biselenienyl:
CD and UV spectra, 880, 882–883
titration curves, 870, 875
(*R*)-2,2′-Dicarboxy-4,4′,5,5′-tetramethyl-3,3′-bithienyl, CD spectra, 866–867, 873
(*R*)-(−)-4,4′-Dicarboxy-2,2′,5,5′-tetramethyl-3,3′-bithienyl, CD and UV spectra, 871, 876, 880–883
2,2′-Dicarboxy-4,4′,5,5′-tetramethyl-3,3′-bithienyl, titration curves, 870, 875
4,4′-Dicarboxy-2,2′,5,5′-tetramethyl-3,3′-bithienyl, racemization, 861
4,4′-Dicarboxy-2,2′,5,5′-tetramethyl-2,2′-diphenic acid, titration curves, 870, 875
2′,5-Dichloro-2,3′-bithienyl, 787
5,5′-Dichloro-2,2′-bithienyl, preparation, 769
3,4-Dichloro-2,5-dimethoxythiophene, preparation, 726
3,4-Dichloro-2,5-dithiophenecarboxylic acid, preparation, 708
1,2-Dichloro-1-(2-thienyl)ethene, preparation, 68
1,1-Dichloro-2-(2-thienyl)ethylene, preparation, 68–69
1-*N*,*N*-Diethylamidothiophene, metalation, 713
5,5′-Diformyl-2,2′-bithienyl, preparation, 768–769
3,3′-Diiodo-2,2′-bithienyl, preparation, 759
3,3′-Diiodo-4,4′,5,5′-tetramethyl-2,2′-bithienyl, preparation, 760–761
Dilithiation, halogen–metal exchange, 707
2,2′-Dilithio-3,3′-bithienyl, 827
structures, 859–861
3,3′-Dilithio-2,2′-bithienyl, 825–826
4,4′-Dilithio-3,3′-bithienyl, 827
structures, 859–861
Dilithium derivatives, reactions, 705–709
Dimerization reactions, vinylthiophenes, 122
γ,γ-Dimethylallenyl ethynyl sulfide, preparation, 773
N,*N*-Dimethylaminoethyl group, attachment to thiophene nucleus, 673
2-(2-Dimethylaminomethyl)thiophene, polymerization, 699
3-(*N*,*N*-Dimethylaminomethyl)thiophene, preparation, 712–713
2,2′-Dimethyl-3,3′-bithienyl, 856
5,5′-Dimethyl-2,2-bithienyl, preparation, 765–766
(*R*)-(+)-1,9-Dimethyl-4,6-dihydrodithieno[2,3-*c*:3′,2′-*e*]thiepine, CD and UV spectra, 866, 871
(*R*)-(−)-1,9-Dimethyl-4,6-dihydrodithieno[3,4-*c*:3′,4′-*e*]thiepine, CD and UV spectra, 866, 872
2-(*N*,*N*-Dimethyl-2-imidazolidinyl)thiophene, metalation, 713
2,2′-Dimethyl-4,4′5,5′-tetraiodo-3,3′-bithienyl, 856
5,5′-Dimethyl-2,2′,4,4′-tetranitro-3,3′-bithienyl, 782
1,3-Dimethyl-2-(2-thienyl)imidazolidine, metalation, 706
2,5-Dimethylthiophene, unselective metalation, 698
3,4-Dimethylthiophene:
metalation, 706
preparation, 707–708
2,5-Dimethyl-3-thiophenecarboxylic acid, 684
preparation, 727
N,*N*-Dimethyl 5-trimethylsilyl-2-thiophenesulfonamide, metalation, 687–688
2,2′-Dinitro-3,3′-bithienyl, 784, 814–815
2,5′-Dinitro-3,3′-bithienyl, 814–815
3,3′-Dinitro-2,2′-bithienyl, preparation, 773
5,5′-Dinitro-2,2′-bithienyl, preparation, 766, 773
2,2′-Dinitro-6,6′-diphenic acid, CD spectra, 865
6,6′-Dinitro-2,2′-diphenic acid, CD and UV spectra, 879–880, 882
Dinitrodistyrylthiophenes, preparation, 34
2,4-Dinitrophenylhydrazones, preparation, 91
5,5′-Diphenyl-2,2′-bithienyl, preparation, 776–777

1,4-Diphenyldiacetylene, preparation, 722
2,5-Diphenyl-3,4-diiodothiophene, ring-opening reaction, 722
2,5-Diphenylthiophene, 675
Dipolylithiated thiophenes, 444–457
Directed metalation, *see also* Lithium derivatives, thiophenes
thiophenes, 458–487, 668–670
2,3-Disubstituted thiophene derivatives, preparation, 711, 715
Dithienazepines, 837–838
Dithienoazaborines, 836–837
Dithienopyridazines, 836
Dithienopyridines, 835–836
Dithienopyrroles, 833–834
Dithienothiepines, 838–839
Dithienothiophenes, 833
Dithienoxepines, 838–839
4-Di(thienyl)diacetylenes, 229
2,6-Di-(2-thienyl)-1,4-dithiin, 795–796
E-1,2-Di(thienyl)ethenes, 154–155
2,2′-Dithienylmethane, metalation, 701, 736
3,3′-Dithienylmethylphosphine oxide, metalation, 717
3,3′-Dithienylsulfide, metalation, 712
2,3-Dithiophencarboxylic acid, preparation, 694–695
5,5′-Di(triphenylmethyl)-2,2′-bithienyl, 765–766
2,5-Divinylthiophenes, symmetric, 216–217
Double bond, conservation, vinylthiophenes reactions, 91–95
Doubly bridged bithienyls, 839–840

Electrically conducting polymers, polythienyls, 803
Electrophilic additions, vinylthiophenes, 115–116
Electrophilic substitution, vinylthiophenes, 95–97
Erlenmeyer azlactone synthesis, vinylthiophene preparation, 8–9
Ethyl azidoacetates, vinylthiophene preparation, condensation with, 19
Ethyl 5-nitro-2-thenylidene pyruvate, preparation, 6
Eyring equation, 861, 863

2-Formyl-4-phenylthiophene, preparation, 768–769
3-Formyl-2-thienylboronic acid, preparation, 692
Free radicals, coupling initiated by, 2,2′-bithienyl preparation, 772–774
Friedel–Crafts conditions, coupling under, 2,2′-bithienyls, 769–771
2-(2′-Furyl)thiophene, metalation, 683

Gallium derivatives, thiophenes, 564
Germanium derivatives, thiophenes, 578–585
Gold derivatives, thiophenes, 604–621
Grignard reagents, thenylic, 703–705

Halogenation:
α-thienyllithium derivatives, 679–680
2,2′-bithienyl, 819–820
2,3′-bithienyl, 824–825
Halogen dance, 718
Halogen–lithium rearrangement, 690
Halogen–metal exchange:
2,5-dibromo-3-alkyl-substituted thiophene derivatives, 710
dilithiation, 707
lithium derivatives, thiophenes, 736–737
racemization, 859–861
α-thienyllithium, 688–691
derivatives, 339-372
β-thienyllithium derivatives, 373–429, 692–697
2,3,5-tribromothiophene, 711
Halogen migration, lithium derivatives, thiophenes, 717–721
Halothiophenes:
halogen–metal exchange, 737
palladium-catalyzed couplings, 768
thienylacetylenes preparation, 139–140
3-Halothiophenes, coupling with 2-thienylcopper, 785–787
Heck reaction, vinylthiophene preparation, 77–78
Heterohelicenes, 840, 847
synthesis, 49
Hexabromo-3,3′-bithienyl, 847–848
CD and UV spectra, 865–866, 869
Hexachloro-2,2′-bithienyl, preparation, 765
Hexamethyl-3,3′-bithienyl, 847–848, 855
CD and UV spectra, 867–868, 870
Hydride reductions, vinylthiophenes, 113–114
Hydroboration, 2-vinylthiophene, 115
3-(3-Hydroxyphenyl)thiophene, preparation, 59
Hydroxythiophene systems, 680–681
preparation, 694

Indium derivatives, thiophenes, 564
1-Iodo-2(2-thienyl)acetylene, preparation, 141–142

Iodothiophenes, thienylacetylenes from, 138
IR spectroscopy, bithienyls and polythienyls, 893
Isomerizations, vinylthiophene preparation, 83–84

Karasch reaction, 675
3-Ketotetrahydrothiophene, reaction with 2-thienyllithium derivatives, 785
Knoevenagel reaction, vinylthiophene preparation, 17

Lead derivatives, thiophenes, 578–585
Lithiation:
  thenyllithium and thenylmagnesium halide derivatives, 697–703
  thiophenes, 669–670
Lithium bridging, 735
Lithium–chlorine exchange, 695–696
Lithium derivatives, thiophenes, 669–737
  directed metalation, 709–717
    α/β-selectivity, 716
    alkoxy group effects, 711–712
    3-alkyl-substituted thiophene derivatives, 709–710
    amino and amido functions, 712–713
    aromatic nitrogen heterocycles, 715–716
    carboxylate group, 714
    2,5-dibromo-3-alkyl-substituted thiophene derivatives, 710
    halogen effect, 710–711
    imidazolidine group, 713
    isoxazolinyl groupings, 715
    3-lithiation, 715
    organoseleno group, 712
    sulfur-containing groups, 712
  halogen–metal exchange, 736–737
  halogen migration and rearrangements, 717–721
  metalation, 729–732
    Morton mechanism, 729–730, 737
    Roberts–Curtin mechanism, 729–730
  NMR data, 732–734
  physical chemistry, 728
  reactions of di- and polylithium derivatives, 705–709
  resonance hybrids, 733–734
  ring-opening reactions, 721–728
    acetylenic natural products, 727–728
    based-induced, 724–725
    electronegative substituents, 725–726
    pseudo-first-order rate constants, 722–723
    steric effects, 722–723
    3-thienyllithium derivatives, 724
  thenyllithium and thenylmagnesium halide derivatives, 697–705
    lithiations, 698–703
    thenylic Grignard reagents, 703–705
  thienylic protons, acidity, 736
  thienyllithium derivatives, constitution, 735–736
  α-thienyllithium derivatives:
    from halogen–metal exchange, 688–691
    from metalation, 670–684
  β-thienyllithium derivatives:
    from halogen–metal exchange, 692–697
    from metalation, 684–688
Lithium 2-thienylsulfinate, 682

3-Mecaptothiophene, metalation, 712
2′-Mercapto-3-bromo-2,3′-bithienyl, 828–829
Mercury derivatives, thiophenes, 591–603
Mesityl 2-thienyl sulfones, rearrangement, 720
Metalation, *see also* Directed metalation
  lithium derivatives, thiophenes, 729–732
  nonthienylic or nonthenylic positions, 683–684
  β-thienyllithium derivatives, 684–688
2-Methoxy-5-methylthiophene, metalation, 685
5-Methoxy-2-thienyllithium, vinylthiophene preparation, 57
5-Methyl-2-aminothiophene, 681
Methylation:
  α-thienyllithium derivatives by, 259–327
  β-thienyllithium derivatives by, 328–338
1-Methylbenzo [*b*]thiophen-6-ol, preparation, 11
4-Methyl-2-2′-bithienyl, preparation, 771
4-Methyl-2-(1-cyclohexenyl)thiophene, preparation, 80
5-Methyl-2-(dimethylaminomethyl)thiophene, metalation, 686–687
Methyl α-methylthio-thienylacetates, preparation, 118
3-Methylselenothiophene, metalation, 712
5-Methylthieno[2,3-*b*]indene, metalation, 701
2-Methylthienothiopyrane derivatives, methylation, 702
Methyl thienyl ketones:
  condensation, 28–29
  preparation, 678
3-Methyl-2-thienyllithium, reaction with carbamate derivatives, 676–677
5-Methyl-2-thienyllithium, selective attack by, 673
3-Methyl-2-thiophenecarboxylic acid, preparation, 704

Methylthiophenes, activated, condensation with aldehydes, 33–34
Meyer–Schuster rearrangement, vinylthiophene preparation, 83, 87
Michael addition:
carbanions to vinylthiophenes, 120–122
vinylthiophene preparation, 20
Mixed Claisen condensation, vinylthiophene preparation, 18
Molecular-orbital calculations, bithienyls, 892
Morton mechanism, 729–730, 737

Nickel, coupling catalyzed by:
2,3′-bithienyl preparation, 787
3,3′-bithienyl preparation, 783
Nitration:
2,2′-bithienyl, 804–814
2,3′-bithienyl, 815–816
3,3′-bithienyl, 805, 814–815
polythienyls, 816–817
2′-Nitro-2,3′-bithienyl, 787
3′-Nitro-2,2′-bithienyl, 805
Nitrogen nucleophiles, addition to vinylthiophenes, 117–119
β-Nitrostyrene, preparation, 7
o-Nitrovinylthiophenes, 105–106
β-(Nitrovinyl)thiophenes, from nitroalkanes and aldehydes, 173–174
NMR spectroscopy:
bithienyls and polythienyls, 893–895
lithium derivatives, thiophenes, 732–734
^{1}H NMR, thienyllithium derivatives, 734

α-Octithienyl, 800–801
Optical activity, 3,3′-bithienyls, *see* 3,3′-Bithienyl
Organoboron reagents, coupling of, 2,2′-bithienyl preparation, 771–772
Organometallic compounds, reactions via, 825
2,2′-bithienyl, 825–827
2,3′-bithienyl, 828–829
3,3′-bithienyl, 827–828
Organometallic reagents, alcohol dehydration, vinylthiophene preparation, 62–65
Oxepine, 833–834
Oxidation, α-thienyllithium derivatives, 680–681

Palladium, coupling catalyzed by:
2,3′-bithienyl preparation, 787
3,3′-bithienyl preparation, 783
Palladium-catalyzed synthesis, thienylacetylenes, 139–140
Perkin reaction, vinylthiophene preparation, 18
Phenanthrene, dithiophene analogs, synthesis, 97
5-Phenyl-2,2′-bithienyl, preparation, 767, 776–777
1-Phenyl-1-(2-pyridyl)-2-(2-thienyl)ethene, preparation, 16
Phenyl 2-thienyl ketone, condensation, 28–29
β-Phenylthiophene, 840
Phosphonate method, vinylthiophene preparation, 42–43
Photochemical rearrangements, bi- and polythienyls, 829–830
Photochromic heterocyclic fulgides, preparation, 29–30
Physical properties, vinylthiophenes, 132–133
Pivot bond, bithienyls, 758
Polyenyl-substituted thiophenes, preparation, 50
Polylithiated thiophenes, 444–457
Polylithium derivatives, reactions, 705–709
Polymerization, vinylthiophenes, 131
Poly-(2,5-thienylene)-1,3-butadienylene, preparation, 40
Polythienyls, *see also* α-Terthienyls
acylation, 819
conformational analyses, 884–890
electrically conducting polymers, 803
with four or more units, preparation, 799–803
IR spectroscopy, 893
miscellaneous investigations, 895
nitration, 816–817
NMR spectroscopy, 893–895
photochemical rearrangements, 829–830
preparation, 793–795
UV spectroscopy, 886–893
Potassium derivatives, thiophenes, 503–509
Pyridines, *c*-fused, synthesis, 101–102
3-(4-Pyrimidinyl)thiophene, preparation, 693
Pyrrolo[3,2-*b*][1]benzopyrans, synthesis, 15

α-Quarterthienyl, preparation, 800
Quarterthienyls, 757–758
α-Quinquethienyl, preparation, 800

Racemization:
carboxylic acids, 861–863
halogen–metal exchange, 859–861
Reactions via organometallic compounds, 825
Rearrangements:
lithium derivatives, thiophenes, 717–721

Rearrangements (*Continued*)
thiophenes, 448–493
vinylthiophene preparation, 83–84
Reformatsky reaction, vinylthiophene preparation, 65–66
Resonance hybrids, lithium derivatives, thiophenes, 733–734
Rhodanine, condensations, vinylthiophene preparation, 9–10
Ring-closure reactions:
2,2′-bithienyl preparation, 776–778
2,3′-bithienyl preparation, 788
thienylacetylenes, 140
vinylthiophenes:
with conservation of double bond, *see* Vinylthiophenes
preparation, 80–82
Ring-opening reactions, 722
lithium derivatives, thiophenes, 721–728
thiophene-fused ring systems, vinylthiophene preparation, 84–85
thiophenes, 494, 502
Roberts–Curtin mechanism, 729–730
Rubidium derivatives, thiophenes, 503–509

α,β-Septithienyl, 801
α-Sexithienyl, preparation, 800
Silicon derivatives, thiophenes, 565–577
Silver derivatives, thiophenes, 604–621
Sodium derivatives, thiophenes, 503–509
Stobbe condensation:
2-(thenal)succinic anhydrides, 214–215
vinylthiophene preparation, 26–30
Strontium derivatives, thiophenes, 542
2,3-Substituted thiophene derivatives, synthesis, 706–707
Sulfur-containing groups, addition to vinylthiophenes, 116–117

Tellurium derivatives, thiophenes, 586–587
2,2′:4′,2″-Terthienyl, 796–797
2,2′:5′,2″-Terthienyl, 757
2,2′:5′,3″-Terthienyl, 797–798
3,2′:4′,3″-Terthienyl, 797
3,3′:4′,3″-Terthienyl, 783
α-Terthienyl isomers, preparation, 796–798
α-Terthienyls, preparation, 791–796
from 1,4-bis(2-thienyl)-1,3-butadiyn, 795
from 1,4-diaryl-substituted butadiyns, 791
treatment with Lawesson's reagent, 795–796
Tetraalkyl 2-thenylidene methanediphosphonates, preparation, 24
2,2′,5,5′-Tetrabromo-3,3′-bithienyl, 820–821
2,2′,4,4′-Tetrabromo-3,3′-bithienyl, 828, 847, 850–851, 859
CD and UV spectra, 865, 869
3,3′,4,4′-Tetrabromo-5,5′-bithienyldiglyoxalic acid esters, 826
(*R*)-(+)-4,4′,5,5′-Tetrabromo-2,2′-dicarboxy-3,3′-bithienyl, CD and UV spectra, 865, 868
(*R*)-(−)-2,2′,4,4′-Tetrabromo-5,5′-dimethyl-3,3′-bithienyl, 865–866, 869
2,2′,4,4′-Tetramethyl-3,3′-bithienyl, 847–848, 855, 857
CD and UV spectra, 867–868, 870
2,2′,5,5′-Tetramethyl-3,3′-bithienyl, 855
3,3′,4,4′-Tetramethyl-2,2′-bithienyl, 765–766
4,4′,5,5′-Tetramethyl-2,2′-bithienyl, preparation, 760–761
2,2′,5,5′-Tetramethyl-4,4′-dicarbomethoxy-3,3′-bithienyl, 782
(*R*)-1,2,8,9-Tetramethyl-4,6-dihydrodithieno[2,3-*c*:3′2′-*e*]thiepine, CD spectrum, 866, 871
3,3′,6,6′-Tetramethyl-2,2′-diphenic acid: CD and UV spectra, 880–883
titration curves, 870, 875
3,3′,5,5′-Tetranitro-2,2′-bithienyl, preparation, 766
Thallium derivatives, thiophenes, 564
Thenal azlactones, from thiophene aldehydes and cyclic active methylene derivatives, 212–213
Thenalmalonic acid and esters, synthesis through Knoevenagel condensations, 210
4-(Thenal)-5-oxazolines, synthesis, 8
Thenalrhodanines, from thiophene aldehydes and cyclic active methylene derivatives, 211
2-(Thenal)succinic anhydrides, from Stobbe condensations, 214–215
Thenyl cyanides, condensation with aromatic aldehydes, 32–33
Thenylic Grignard reagents, 703–705
Thenyllithium derivatives, 430–443
ring-opening reaction, 727
Thenyllithium halide derivatives, 697–705
lithiations, 697–703
thenylic Grignard reagents, 703–705
3-Thenylmagnesium bromide, preparation, 704, 705
Thenylmagnesium halide derivatives, 697–705
lithiations, 697–703
thenylic Grignard reagents, 703–705
Thieno[3,2-*e*]indoles, preparation, 98

Thienopyridines, preparation, 107
Thienothiopyrane derivatives, ring-opening reaction, 725
2-Thienylacetic acid, preparation, 703
3-Thienylacetic acid, preparation, 704
Thienylacetylenes, 133–148, 221–229, 224–227
  naturally occurring, 148
  preparation, 674–675
    from iodothiophenes and cuprous acetylides, 138
    palladium-catalyzed synthesis from halothiophenes and acetylides, 139–140
    from precursors containing triple bonds, 140–144
    ring-closure reactions, 140
    from thiophenecarbonyl derivatives, 135–137
    from vinylthiophenes, 137–138
  reactions, 144–147
β-(3-Thienyl)acrolein, preparation, 4
3-(Thienyl)acryl aldehydes, 178–180
3-(Thienyl)acryl alkylketones, 178–180
3-(Thienyl)acryl aryl ketones, 181–183
2-Thienylacrylates, preparation, 674
3-(Thienyl)acryl heterocyclic ketones, 184–185
2-(Thienyl)acrylic acids, 195
3-(Thienyl)acrylic acids and esters, 196–200
  2,3-disubstituted, 208–209
  2-substituted, 205–206
  3-substituted, 201
3-(Thienyl)acrylonitriles, 194
  preparation, 21
3-(Thienyl)acryl thienyl ketones, 186
2-(2-Thienyl)alkanols, dehydration, 66–67
1-(Thienyl)-1-alkylethenes, 153
1-(Thienyl)-2-alkylethenes, 167
1-(Thienyl)alkyl halides, dehydrohalogenation, 67–68
3-(Thienyl)-2-arylacrylonitriles, 190–192
1-(Thienyl)-1-arylethenes, 153
E-1-(Thienyl)-2-arylethenes, 157–161
Z-1-(Thienyl)-2-arylethenes, 156
1-(Thienyl)-1,2-arylethenes, 168–170
1-(Thienyl)-2,2-arylethenes, 171
Thienylarylonitriles, preparation, 21–22
Thienyl azides, preparation, 681
3-(Thienyl)-2-azidoacrylic acids, 100–101
1-(2-Thienyl)-4-(2,2-bithienyl-5)-diacetylene, synthesis, 143
Thienylboronic acids, synthesis, 694
Thienyl boronic esters, 681
1-(Thienyl)1,3-butadienes, 218–219
1-(Thienyl)carbinols, dehydration, 52–66
  alcohols from:
    thienyl metal derivatives and carbonyl compounds, 56–62
    thiophene carbonyl compounds, Reformatsky reaction, 65–66
    thiophene carbonyl derivatives and organometallic reagents, 62–65
  secondary alcohols from thiophene ketone reduction, 52–56
Thienyl carboxylic acids, metalation, 712
2-Thienylcopper:
  coupling with 3-halothiophenes, 785–787
  preparation, 767
1-(Thienyl)-1-cyano-2,3-dialkyl ethenes, 187–189
1-(Thienyl)-1-cyano-2,3-diaryl ethenes, 187–189
2,5-Thienyl diacetylenes, 228
1-(Thienyl)-1,2-dialkylethenes, 168–170
1-(Thienyl)-2,2-dialkylethenes, 171
Thienylenol ethers, 674
2-(2-Thienyl)ethanol, preparation, 703
1-(Thienyl)ethenes, containing at least one group that is not alkyl or aryl, 175–177
2-Thienylglyoxylamides, 678
Thienyl Grignard reagents, 694
E-1-(Thienyl)-2-hetarylethenes, 162–166
3-(Thienyl)-2-heterocyclic acrylonitriles, 193
Thienylic protons, acidity, 736
2-Thienyllithium, reaction with 3-ketotetrahydrothiophene, 785
3-Thienyllithium, coupling with cupric chloride, 779–781
2-Thienyllithium bromide, coupling with cupric chloride, 759–765
Thienyllithium derivatives:
  constitution, 735–736
  ^{1}H NMR, 734
α-Thienyllithium derivatives:
  from halogen-metal exchange, 339–372, 688–691
  from metalation, 259–327, 670–684
    alkylations, 671–679
    amination, 680–681
    arylations, 671–679
    groups carrying nonoxygen and nonnitrogen heteroatoms, 681–683
    halogenations, 679–680
    nonthienylic or nonthenylic positions, 683–684
    oxidation, 680–681
β-Thienyllithium derivatives:
  from halogen-metal exchange, 373–429, 692–697
  by metalation, 328–338, 684–688

3-Thienyllithium derivatives, ring-opening reaction, 724
2-Thienylmagnesium bromide, coupling with cupric chloride, 759–765
2-Thienylmagnesium halides, reactions, 510–536
3-Thienylmagnesium halides, reactions, 537–541
Thienyl metal derivatives, alcohol dehydration, 56–62
1-(Thienyl)-2-nitroalkenes, preparation, 6–7
2-(2-Thienyl)-1-(5-nitro-2-furyl)ethene, preparation, 74
1-(2-Thienyl)polyenes, 220
3-(3′-Thienyl)thieno[2,3-*b*]thienyl, 790
Thienylthienothiophene, preparation, 760
2-Thienyl 3′-thienylsulfide, 682
1-(Thienyl)-1,2,2-trialkylethenes, 172
1-(Thienyl)-1,2,2-triarylethenes, 172
cis-2-(2-Thienyl)-1-(2,4,5-trichlorophenylthio)ethene, preparation, 144
Thiepine, 853–855, 858–859
Thiethyl phosphonoacetic acid, condensation, 20
Thioenynes, preparation, 724–725
Thiolactone systems, 673
Thiopheneacetic acids, condensation with aromatic aldehydes, 31-32
2-Thiophene aldehyde, condensation, 10
Thiophene aldehydes:
  condensation with:
    acidic methyl groups bound to rings, 11–17
    active methylene derivatives, malonic esters, malonitriles, 17–26
    aldehydes and ketones, 4–6
    arylacetic acids, 18–19
    cyclic active methylene derivatives, 8–11
    dimethyl glutarate, 28
    dimethyl methyl- and phenylsuccinates, 27–28
    ethyl azidoacetates, 19
    2-methylimidazole, 14
    methyl-substituted aromatic carbocyles, 12–13
    methylthiazines, 17
    nitro derivatives, 6–8
    rhodanine, 9–10
    Stobbe condensation, 26–30
    sulfonylacetic acid, 23
  Wittig reaction:
    phosphorates, 49–52
    triphenylalkylphosphonium salts, 43–49
Thiophene carbaldehydes, preparation, 678
Thiophenecarbonyl derivatives:
  alcohol dehydration, vinylthiophene preparation, 62–65
  thienylacetylenes from, 135–137
Thiophene carboxylic acids, 677
  metalation, 686, 714
Thiophene-fused ring systems, ring opening, vinylthiophene preparation, 84–85
Thiophene iodonium compound, 680
Thiophene ketones, reduction, secondary alcohol dehydration, 52–56
Thiophene oligomers, *see* Polythienyls
Thiophenes, *see also*Lithium derivatives, thiopenes
  aluminum derivatives, 564
  antimony derivatives, 586–587
  arsenic derivatives, 586–587
  bismuth derivatives, 586–587
  boron derivatives, 543–563
  cadmium derivatives, 588–590
  calcium derivatives, 542
  cesium derivatives, 503–509
  copper derivatives, 604–621
  with cumulative double bonds, 133–135
  1,2-dicarbonyl derivatives, 678
  directed metalations, 458–487, 669–670
  gallium derivatives, 564
  germanium derivatives, 578–585
  gold derivatives, 604–621
  indium derivatives, 564
  lead derivatives, 578–585
  lithiation of α-position, 669–670
  mercury derivatives, 591–603
  potassium derivatives, 503–509
  rearrangements, 448–493
  ring-opening reactions, 494, 502
  rubidium derivatives, 503–509
  silicon derivatives, 565–577
  silver derivatives, 604–621
  sodium derivatives, 503–509
  strontium derivatives, 542
  tellurium derivatives, 586–587
  thallium derivatives, 564
  tin derivatives, 578–585
  transition-metal derivatives, 622–668
  trisubstituted, metalation, 688
  zinc derivatives, 588–590
Thiopyrane derivatives, metalation, 702
Tin derivatives, thiophenes, 578–585
Transition-metal-catalyzed couplings, vinylthiophene preparation, 76–79
Transition-metal derivatives, thiophenes, 622–668
2,4,4′-Tribromo-2′-carboxy-3,3′-bithienyl, 849–850

2,3,5-Tribromothiophene, halogen–metal exchange, 711
2,4,4′-Tricarboxy-2′-hydroxymethyl-3,3′-bithienyl, 858
3,5,5′-Trichloro-2,2′-bithienyl, preparation, 769
2-Trifluoroacetylthiophene, 677
2,3,5-Triiodothiophene, halogen–metal exchange, 711

Ullmann coupling:
  2,2′-bithienyl, 765–767
  3,3′-bithienyls, 851
    preparation, 779, 782–783
UV spectroscopy, bithienyls and polythienyls, 890–893

Vinylthiophenes, 1–133, 151–220
  addition:
    nitrogen nucleophiles, 117–119
    sulfur-containing groups, 116–117
  catalytic hydrogenation, 112–113
  cycloadditions, 122–130
    azodicarboxylates, 124–125
    isocyanides, 130
    methyl propiolate, 124
    4-phenyl-1,2-triazolo-3,5-dione, 125–126
    trans-1-(2-thienyl)-2-nitroethene, 127–128
  dimerization reactions, 122
  electrophilic additions, 115–116
  electrophilic substitution, 95–97
  hydride reductions, 113–114
  Michael additions of carbanions, 120–122
  physical properties, 132–133
  polymerization, 131
  potential pharmaceutical interest, 131–132
  preparation, 4–91, 152. *See also* Thiophene aldehydes; Wittig reaction
    aldol condensations, 4–5
    from alkylthiophenes, 85–86
    Claisen–Schmidt, condensations, 5
    condensation of activated methylthiophenes with aldehydes, 33–34
    condensation of thiopheneacetic acids and thenyl cyanides with aromatic aldehydes, 31–33
    condensation with nitro derivatives, 6–8
    Erlenmeyer azlactone synthesis, 8–9
    Heck reaction, 77–78
    isomerizations and rearrangements, 83–84
    Koevenagel reaction, 17
    Meyer–Schuster rearrangement, 83, 87
    mixed Claisen condensation, 18
    Perkin reaction, 18
    ring-closure reactions, 80–82
    ring opening of thiophene-fused ring systems, 84–85
    2-(2-thienyl)alkanol dehydration, 66–67
    1-(thienyl)alkyl halide dehydration, 67–68
    1-(thienyl)carbinol dehydration, 52–66
    from thiophene carbonyl compounds, 68–74
    from thiophenes and alkenes, 74–75
    transition-metal-catalyzed couplings, 76–79
  reactions, with conservation of double bond, 91–95
  reductions, 114–115
  ring-closure reactions, 3-azido-2-vinylthiophenes, 102–104
  ring-closure reactions with conservation of double bond, 97–112
    c-fused pyridines, 101–102
    dithiophene analogs of phenanthrene, 97
    Gewald reaction, 109
    o-nitrovinylthiophenes, 105–106
    photocyclization, 97–99
    thieno[3,2-*e*] indoles, 98
    thienopyridines, 107
  thienylacetylenes from, 137–138

Wadworth–Emmons–Horner reaction, vinylthiophene preparation, 42–43
Wittig reaction, vinylthiophene preparation, 34–52
  2,3-diformylthiophene and glides, 45–46
  phosphonate method, 42–43
  polycondensation, 41
  from thenyl triphenylphosphonium halides and aldehydes, 34–42
  from thiophene aldehydes:
    and phosphonates, 49–52
    and triphenylalkylphosphonium salts, 43–49

Zinc derivatives, thiophenes, 588–590