
THE CHEMISTRY OF 1,2,3-THIADIAZOLES

Vasiliy A. Bakulev

Department of Technology for Organic Synthesis
The Urals State Technical University

Wim Dehaen

Department of Chemistry
University of Leuven



AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS, INC.

**THE CHEMISTRY
OF 1,2,3-THIADIAZOLES**

This is the sixty-second volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR AND PETER WIPF, *Editors*

ARNOLD WEISSBERGER, *Founding Editor*

THE CHEMISTRY OF 1,2,3-THIADIAZOLES

Vasiliy A. Bakulev

Department of Technology for Organic Synthesis
The Urals State Technical University

Wim Dehaen

Department of Chemistry
University of Leuven



AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS, INC.

Copyright © 2004 by John Wiley & Sons, Inc. All rights reserved.

Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400, fax 978-646-8600, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services please contact our Customer Care Department within the U.S. at 877-762-2974, outside the U.S. at 317-572-3993 or fax 317-572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print, however, may not be available in electronic format.

Library of Congress Cataloging-in-Publication Data:

Bakulev, Vasily and Dehaen, Wim
The Chemistry of 1,2,3-Thiadiazoles

ISBN 0-471-32662-3

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

The Chemistry of Heterocyclic Compounds

Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

The Chemistry of Heterocyclic Compounds has been published since 1950 under the initial editorship of Arnold Weissberger, and later, until his death in 1984, under the joint editorship of Arnold Weissberger and Edward C. Taylor. In 1997, Peter Wipf joined Prof. Taylor as editor. This series attempts to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally 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 chemistry, medicinal chemistry, and biochemistry, 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 heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

Professors Bakulev and Dehaen have produced an authoritative and thorough review of the synthesis, reactions, properties, and applications of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles. These heterocycles are convenient precursors to thioketenes, thirenes, and alkynes, and they are also used as intermediates and building blocks for pharmaceuticals and new materials. This volume fills what has been a significant gap in our coverage of heterocyclic ring systems, and we express our sincere gratitude to the authors for their most welcome contribution to the literature of heterocyclic chemistry.

EDWARD C. TAYLOR

*Department of Chemistry
Princeton University
Princeton, New Jersey*

PETER WIPF

*Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania*

Preface

1,2,3-Thiadiazoles are heterocycles of great practical and theoretical interest. The first derivatives of 1,2,3-thiadiazole have already been prepared in the late nineteenth century but the interest in this heterocycle has been constant up to this day, and we propose that it will continue in the future. Derivatives of 1,2,3-thiadiazole are important in industry, medicine and agriculture. A lot of attention has been devoted to the thermal and photochemical decomposition reactions of the 1,2,3-thiadiazole ring because this system is the only thiadiazole isomer where loss of a nitrogen molecule can readily occur.

Several reviews on the chemistry of 1,2,3-thiadiazoles have appeared, but we feel that a complete treatment has never been carried out to date. This volume will attempt to do this with emphasis on the syntheses, structural data, properties, reactions and applications of 1,2,3-thiadiazoles. Tables dealing with the synthesis of different classes of 1,2,3-thiadiazoles, with references to the literature, and some spectral and physical data are included at the end of Chapter 2. Representative synthetic procedures that were well tested in our laboratories are added to Chapter 1. Structural data on 1,2,3-thiadiazoles are collected in Chapter 2, and the reactivity of 1,2,3-thiadiazoles is treated in Chapter 3. Fused 1,2,3-thiadiazoles (including benzothiadiazoles) and 1,2,3-selenadiazoles are also discussed in separate chapters (Chapters 4 and 5, respectively). Finally, there is a part (Chapter 6) on the applications of 1,2,3-thiadiazoles. We have attempted to cover all known literature until 2002, making a reasonable effort to include anything significant on the parent 1,2,3-thiadiazole system. Reference to patent literature was included wherever relevant. However, for the extensive literature on benzothiadiazoles, we have limited ourselves to the more interesting or recent articles, or to work in comparison with the parent 1,2,3-thiadiazole or other fused 1,2,3-thiadiazoles.

This book can be seen either as an introductory text for anyone becoming interested in 1,2,3-thiadiazole chemistry or as a reference book for the experienced chemist. We also hope that this work will stimulate further research efforts on this interesting heterocyclic system.

VASILY A. BAKULEV
WIM DEHAEN

Acknowledgments

Many people have contributed to the production of this Volume and we express our thanks to all who have made this possible.

A great deal of thanks is due to our many dedicated collaborators, postdoctoral, graduate, and undergraduate, who worked together with us on the research for this book in both of our laboratories. We very much appreciated all their enthusiasm during the years; without them none of these results would have been produced. Rather than mention all of them by name, we refer to the references from our groups, cited in this book.

We thank the colleagues who sent us reprints of their work, including Profs. D. B. Reddy, P. K. Khanna, P. Steel, O. A. Attanasi, L. Burketova, P. K. Saxena, and many others allowing us a more complete treatment of their work.

Dr. Mario Smet and Dr. Albert Lebedev are thanked for their reading of the manuscript and their valuable criticism, suggestions, and comments.

A special thanks to Dr. Elena Sadchikova and Mousumi Sen, who helped a great deal on arranging all the fine details and problems associated with word processing, table formatting, drawing of figures, etc.

All the people at Wiley, especially Darla Henderson, Amy Romano, and Christine Punzo are thanked for their excellent and speedy treatment of our manuscript.

Several institutions have helped us financially during the years. We like to acknowledge the University of Leuven, the Ministerie Voor Wetenschapsbeleid, the F. W. O. Vlaanderen, INTAS, US Civilian Research and Development Foundation (project CRDF RC1-2393-EK-02), and Russian Foundation for Basic Research for their continuing support.

Finally, we thank our families who always been supportive to us even when we were absent while working on this book.

Vasiliy A. Bakulev
Wim Dehaen

Contents

1	Synthesis of 1,2,3-thiadiazoles	1
1.1	Cyclization of Hydrazones with Thionyl Chloride (Hurd–Mori Synthesis)	1
1.1.1	Scope and Limitations	2
1.1.2	Mechanism of the Hurd–Mori Reaction	4
1.1.3	Application of the Hurd–Mori Reaction in Organic Synthesis	5
1.2	Cycloaddition of Diazoalkanes onto a C=S bond (Pechmann Synthesis)	17
1.3	Heterocyclization of α -diazo Thiocarbonyl Compounds (Wolff Synthesis)	22
1.3.1	Introduction of a Diazo Function into Compounds Containing a C=S Bond	23
1.3.2	Introduction of a C=S Bond in the α -position to a Diazo Group	27
1.3.3	Simultaneous Introduction of Diazo and Thiocarbonyl Functions	29
1.4	Transformations of other Sulfur-containing Heterocyclic Compounds	30
1.5	Elaboration of Preformed 1,2,3-Thiadiazoles	33
1.5.1	Carboxylic Acids	33
1.5.2	Functional Derivatives of Carboxylic Acids	35
1.5.3	Aldehydes	36
1.5.4	Amino-1,2,3-Thiadiazoles	37
1.5.5	Halo Derivatives	39
1.5.6	5-Hydrazino-, 5-Mercapto-1,2,3-Thiadiazoles and 5-Sulfide Derivatives	40
1.5.7	2-(1,2,3-Thiadiazol-5-yl)acetic Acid Derivatives	41
1.5.8	Alkenyl-1,2,3-Thiadiazoles	42
1.5.9	5-Hydroxyiminomethyl- and 5-Diazomethyl-1,2,3-Thiadiazoles	42
1.5.10	4-Hydroxymethyl-1,2,3-Thiadiazoles	43

1.6	Tables	44
1.7	Selected Procedures	79
1.7.1	1,2,3-Thiadiazole-4-Carbaldehyde	79
1.7.2	4-Phenyl-1,2,3-Thiadiazole	80
1.7.3	4-Phenyl-1,2,3-Thiadiazole-5-Carbaldehyde	81
1.7.4	4-Phenyl-5-Oxyiminomethyl-1,2,3-Thiadiazole	82
1.7.5	5-Phenyl-1,2,3-Thiadiazole-4-Carbaldehyde	82
1.7.6	5-Chloro-1,2,3-Thiadiazole-4-Carbaldehyde	83
1.7.7	Ethyl 5-amino-1,2,3-Thiadiazole-4-Carboxylate	84
1.7.7.1	Pechmann Method	84
1.7.7.2	Wolff Method	85
1.7.8	Ethyl 5-chloro-1,2,3-Thiadiazole-4-Carboxylate	86
1.7.9	4-Phenyl-2-(2,4,6-Trichlorophenyl)-1,2,3-Thiadiazolium Chloride	86
1.7.10	5-Amino-4-ethoxycarbonyl-2-phenyl-1,2,3-thiadiazolium bromide	87
	References	88
2	Structure of 1,2,3-Thiadiazoles	93
2.1	Theoretical Methods	93
2.2	Experimental Structural Methods	97
2.2.1	X-ray Analysis	97
2.2.2	Nuclear Magnetic Resonance Spectroscopy	103
2.2.2.1	Proton NMR Spectroscopy	103
2.2.2.2	Carbon-13 NMR Spectroscopy	103
2.2.2.3	Nitrogen-14 NMR Spectroscopy	106
2.2.2.4	Nitrogen-15 NMR Spectroscopy	106
2.2.3	Mass Spectrometry	107
2.2.4	Other Spectroscopic Data	110
	References	110
3	Chemical Properties of 1,2,3-Thiadiazoles	113
3.1	Reactions due to the Reactivity of Ring Atoms	113
3.1.1	Reactions with Electrophiles	113
3.1.1.1	Protonation	113
3.1.1.2	Complexation	114
3.1.1.3	Alkylation	115
3.1.1.4	Acylation	116
3.1.1.5	Oxidation	116
3.1.1.6	Electrophilic Substitution of Hydrogen	117
3.1.2	Reactions with Nucleophiles	117
3.1.2.1	Attack at the Sulfur Atom	117
3.1.2.2	Attack at the C ₅ Atom	118

3.1.2.3	Attacks at H ₄ and H ₅	120
3.1.2.4	Cycloaddition Reactions	121
3.2	Reactions of Substituents	122
3.2.1	5-Alkyl-1,2,3-thiadiazoles	122
3.2.2	1,2,3-Thiadiazole-4-carbaldehyde	123
3.2.3	5-Amino-1,2,3-thiadiazole-4-carbothioamide	124
3.2.4	Mercapto-1,2,3-thiadiazoles	124
3.3	Rearrangements	124
3.3.1	Dimroth-type Rearrangements	125
3.3.2	Cornforth-type Rearrangements	129
3.3.2.1	Rearrangements of 4-(iminomethyl)- substituted-1,2,3-Thiadiazoles	129
3.3.2.2	Degenerate Rearrangements of 4-Thiocarbamoyl-1,2,3-Thiadiazoles	133
3.3.2.3	Rearrangements of 1,2,3-Thiadiazoles Bearing Diazo, Azido and Hydrazono Groups in the 5-Position	133
3.3.2.4	Tandem Rearrangements	136
3.4	Ring Cleavage of 1,2,3-Thiadiazoles	137
3.4.1	Thermal Decomposition	137
3.4.2	Photochemical Decomposition	141
3.4.3	Base-catalyzed Decomposition	143
3.4.4	Oxidative and Reductive Processes	149
3.4.5	Other Processes for Ring Cleavage	151
	References	152
4	Fused 1,2,3-Thiadiazoles	155
4.1	1,2,3-Thiadiazoles Fused with Five-Membered Rings	155
4.1.1	Cyclopenteno-1,2,3-thiadiazoles	155
4.1.2	Pyrrolo[2,3- <i>d</i>][1,2,3]thiadiazoles	158
4.1.3	Pyrrolo[3,2- <i>d</i>][1,2,3]thiadiazoles	158
4.1.4	Pyrrolo[3,4- <i>d</i>][1,2,3]thiadiazoles	158
4.1.5	4,6-Dihydrofuran[3,4- <i>d</i>][1,2,3]thiadiazoles	159
4.1.6	Thieno[2,3- <i>d</i>][1,2,3]thiadiazoles	159
4.1.7	Thieno[3,2- <i>d</i>][1,2,3]thiadiazoles	160
4.1.8	Thieno[3,4- <i>d</i>][1,2,3]thiadiazoles	162
4.1.9	Selenopheno[3,4- <i>d</i>][1,2,3]thiadiazole	162
4.1.10	Benzoselenopheno[3,2- <i>d</i>][1,2,3]thiadiazole	163
4.2	1,2,3-Thiadiazoles Fused with Six-Membered Rings	163
4.2.1	Cyclohexeno-1,2,3-thiadiazoles	163
4.2.2	Benzo-1,2,3-thiadiazoles	166
4.2.3	Piperidino[3,4- <i>d</i>][1,2,3]thiadiazoles	173
4.2.4	1,2,3-Thiadiazolo[4,5- <i>b</i>]pyridines	174
4.2.5	1,2,3-Thiadiazolo[4,5- <i>c</i>]pyridines	174

4.2.6	1,2,3-Thiadiazolo[5,4- <i>c</i>]pyridines	176
4.2.7	1,2,3-Thiadiazolo[5,4- <i>d</i>]pyrimidines	176
4.2.8	1,2,3-Thiadiazolo[4,5- <i>d</i>]pyrimidines	178
4.2.9	Pyrano[3,4- <i>d</i>][1,2,3]thiadiazole	179
4.2.10	Thiopyrano[4,3- <i>d</i>][1,2,3]thiadiazoles	179
4.2.11	Thiopyrano[2,1- <i>d</i>][1,2,3]thiadiazole	180
4.2.12	Selenopyrano[4,3- <i>d</i>][1,2,3]thiadiazoles	181
4.3	1,2,3-Thiadiazoles Fused with Seven-Membered Rings	181
4.3.1	Benzooxepino- and Benzothiepine[3,4- <i>d</i>][1,2,3]thiadiazoles	181
4.3.2	Thiadiazolo[5,4- <i>d</i>]benzazepines	182
4.3.3	1,2,3-Thiadiazolo[5,4- <i>b</i>][1,5]benzodiazepine	182
4.4	Bicyclic 1,2,3-Thiadiazoles of Azathiapentalenic Structure	183
	References	188
5	Synthesis and Properties of 1,2,3-Selenadiazoles	193
5.1	Synthesis of 1,2,3-Selenadiazoles	193
5.1.1	Oxidative Cyclization of Hydrazones by Se-containing Reagents	193
5.1.2	Cycloaddition Reactions of Diazoalkanes with Compounds Containing C=Se Bonds	197
5.1.3	Elaboration of Preformed 1,2,3-Selenadiazoles	197
5.1.4	Miscellaneous Syntheses	201
5.2	Structural Data of 1,2,3-Selenadiazoles	201
5.2.1	Mass Spectrometry	201
5.2.2	Proton NMR Spectroscopy	201
5.2.3	Carbon-13 NMR Spectroscopy	202
5.2.4	Nitrogen-15 NMR Spectroscopy	202
5.2.5	Selenium-77 NMR Spectroscopy	203
5.2.6	X-ray Crystallography	203
5.2.7	Miscellaneous	204
5.3	Reactivity of 1,2,3-Selenadiazoles	204
5.3.1	Ring Cleavage	204
5.3.1.1	Thermal Reactions	204
5.3.1.2	Photochemical Reactions	210
5.3.1.3	Base-catalyzed Reactions	211
5.3.1.4	Radical-catalyzed Reactions	214
5.3.1.5	Reaction with Metal Complexes	215
5.3.1.6	Miscellaneous Ring Cleavage Reactions	217
5.3.2	Formation of Salts and Ylides	218
5.4	Fused 1,2,3-Selenadiazoles	220
5.4.1	Bicyclic 1,2,3-Selenadiazoles	220
5.4.2	Tricyclic 1,2,3-Selenadiazoles	221
5.4.3	Tetra- and Pentacyclic 1,2,3-Selenadiazoles	222

5.5 Applications of 1,2,3-Selenadiazoles	222
References	224
6 1,2,3-Thiadiazoles in Medicine and Agriculture	229
6.1 Medicine	229
6.2 Agriculture	231
6.2.1 Thidiazuron	232
6.2.2 Bion	233
References	236
Index	239

THE CHEMISTRY OF 1,2,3-THIADIAZOLES

This is the sixty-second volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

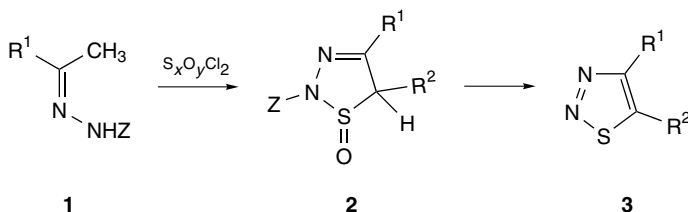
Synthesis of 1,2,3-Thiadiazoles

The known methods leading to 1,2,3-thiadiazoles^{1–10} can be subdivided into five groups:

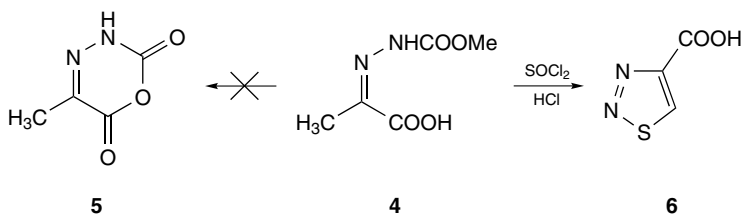
- cyclization of hydrazones with thionyl chloride (Hurd–Mori synthesis),¹⁰
- cycloaddition of diazoalkanes onto a C=S bond (Pechmann synthesis),¹
- heterocyclization of α -diazo thiocarbonyl compounds (Wolff synthesis),²
- ring transformation of other sulfur-containing heterocyclic compounds,³
- elaboration of preformed 1,2,3-thiadiazoles.^{4–6}

1.1. CYCLIZATION OF HYDRAZONES WITH THIONYL CHLORIDE (HURD–MORI SYNTHESIS)

Hydrazone derivatives **1** that are substituted at N₂ with an electron- withdrawing group (Z = CONH₂, COOMe, COR, SO₂R) and are possessing an adjacent methylene group can cyclize in the presence of thionyl chloride with the formation of 1,2,3-thiadiazoles **3**.^{4–10}



This reaction was discovered in 1956 by Hurd and Mori during their unsuccessful attempts to prepare oxadiazinedione **5** from hydrazone **4** by treatment



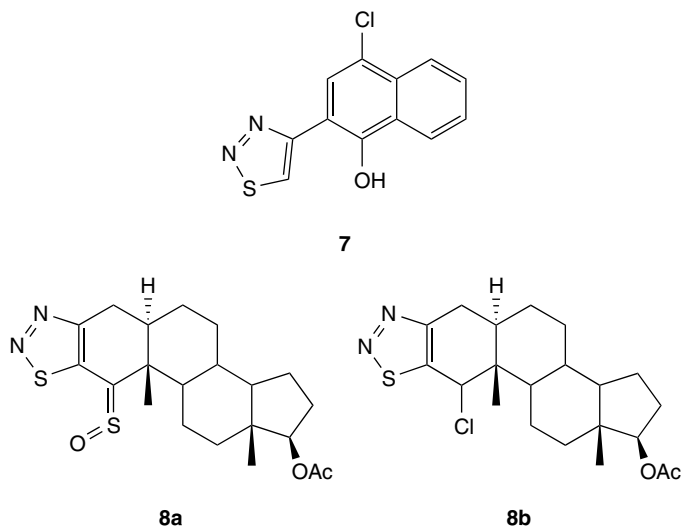
with thionyl chloride. 1,2,3-Thiadiazole-4-carboxylic acid **6** was unexpectedly formed, leading to a new synthetic approach to 1,2,3-thiadiazoles.¹⁰

Since then, more than 100 publications have appeared in the literature on the Hurd–Mori reaction. Most of them were reviewed by Stanetty and colleagues.⁹ Retrosynthetically, the Hurd–Mori synthesis is a [4 + 1] approach using four atoms from the hydrazone and one (the sulfur atom) from the thionating agent.

1.1.1. Scope and Limitations

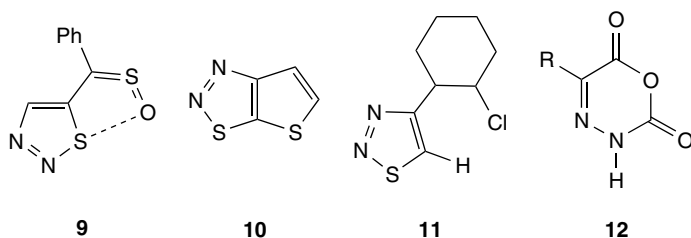
Generally, the hydrazones **1** with $Z = \text{COOR}$ or SO_2R give the best yield in the Hurd–Mori reaction, although in the latter case a chromatographic separation is often necessary to remove the sulfonyl chloride formed. In some cases, sulfur monochloride or dichloride can also be employed as the source of the sulfur atom, although the yields may be substantially reduced because of side reactions.¹¹ Sulfuryl chloride does not form any 1,2,3-thiadiazoles **3** with these hydrazones, instead, chlorinated products are obtained.^{12,13} The Hurd–Mori reaction is by far the most widely used method in the research on 1,2,3-thiadiazoles, and some reactions are carried out on an industrial scale.^{4–7} Obviously, in the case when unprotected amino, hydroxy, or other groups capable of reaction with thionyl chloride are present, the reaction will fail. Furthermore, sterically hindered hydrazone derivatives will generally not yield 1,2,3-thiadiazoles. The reaction is especially suitable for alkyl- and (het)aryl-substituted 1,2,3-thiadiazoles, for which the carbonyl precursors are readily available. Fused 1,2,3-thiadiazoles can be obtained in the same way from cyclic ketones. A number of substituted thiadiazoles, possessing halide,^{14–16} ester,¹⁷ carboxy,¹⁰ aldehyde,¹⁸ sulfide^{19,20} and protected amino groups^{21,22} could be obtained using the Hurd–Mori method. Multiple thiadiazoles of limited solubility were prepared from the corresponding ketones as core reagents for dendrimers^{23,24} and as intermediates in polymer research.²⁵ Some of these reactions that are of significant interest for the synthesis of practically useful compounds will be described in more detail in the second part of this section.

Although the Hurd–Mori reaction is very general in scope, unexpected reactions can occur, mostly involving the rather aggressive thionating agent. 1,2,3-Thiadiazole derivative **7** was obtained after chlorination of the electron-rich naphthalene ring by SOCl_2 under the reaction conditions.²⁶ In steroidal ketones or substituted cyclohexanones, the methylene next to the 5-position of the thiadiazole

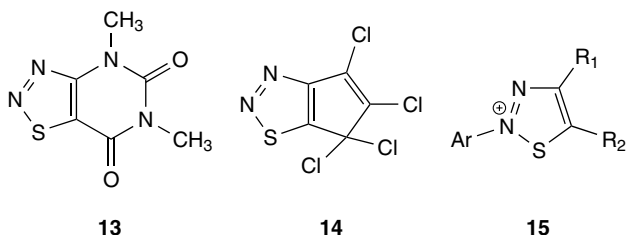


ring can be transformed with thionyl chloride to afford a sulfine derivative such as **8a**. The chlorinated compound **8b** was also formed as a minor product.²⁷

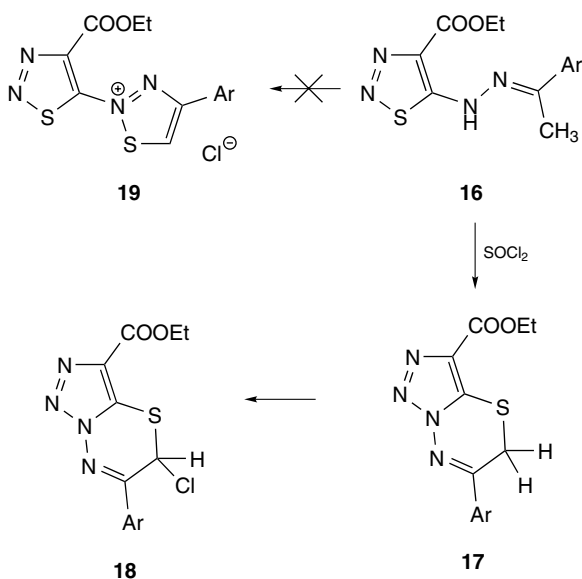
We prepared 5-thiobenzoyl-1,2,3-thiadiazole-S-oxide **9** in 70% yield from the ethoxycarbonylhydrazone of phenylpropionaldehyde and analyzed its structure with X-ray crystallography. The sulfine function of **9** was coplanar with the thiadiazole ring, and a close S...O contact (2.69 Å) was observed.²⁸ During the synthesis of bicyclic 1,2,3-thiadiazoles, aromatization of the other ring can occur, for instance, for the thienothiadiazoles, **10**.²⁹ Cyclohexenyl methyl tosylhydrazone yielded 4-(2-chlorocyclohexyl)-1,2,3-thiadiazole **11**.¹¹ The hydrazones of α -ketoacids were reported to give oxadiazines **12** as side products³⁰ that were the original goal of Hurd and Mori.



There are some reports on related cyclizations using N_2 -unsubstituted hydrazones. 6-Hydrazino-1,3-dimethyluracil and thionyl chloride afforded the fused thiadiazole **13** in good yield.^{31,32} Senning *et al.* described a fused cyclopentadienothiadiazoles **14** from the reaction of the corresponding *N*-unsubstituted hydrazone of tetrachlorocyclopentanone with sulfur mono- or dichloride.³³ *N*-Arylhydrazones yield 2-aryl-1,2,3-thiadiazolium salts **15** on reaction with thionyl chloride.³⁴



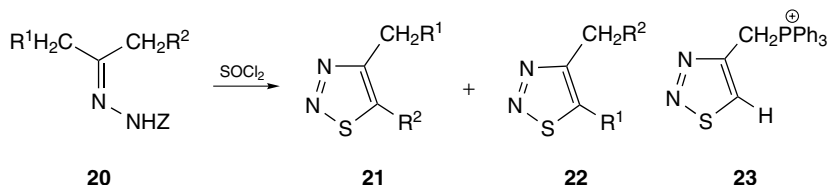
In contrast to the reaction of *N*-arylhyazones³⁴ we have found that 1,2,3-thiadiazoles of type **16**, after treatment with thionyl chloride at room temperature, transform to 1,2,3-triazolo-thiadiazines **18** and not to the expected bithiadiazole **19**. This novel reaction may involve the Dimroth rearrangement of the starting compound to the intermediate 5-mercapto-1,2,3-triazole derivatives. When hydrazone **16** was treated with SOCl₂ at low temperature, the nonchlorinated product **17** was isolated in good yield.³⁵



1.1.2. Mechanism of the Hurd–Mori Reaction

The mechanism of the Hurd–Mori reaction has been investigated in detail,^{36,37} and has been discussed in previous reviews.^{6,7} We can summarize that an intermediate thiadiazoline-1-one **2** is formed first, which readily aromatizes to form the 1,2,3-thiadiazoles **3**. The latter process probably involves a Pummerer-type rearrangement of the sulfoxide **2** with the participation of the excess thionyl chloride. The group Z is then easily cleaved from the resulting salt. The sulfoxide intermediate **2** was isolated and characterized in a number of cases.^{27,38–40}

When two different methylene groups are present adjacent to the hydrazone **20**, the question of selectivity is raised as two thiadiazoles **21** and **22** are possible. Also, a number of studies were carried out on this topic.^{29,41,42} From the results of Fujita, it follows that there is a relation between the rate of enolization of the two methylenes of the corresponding ketone, and the selectivity of the ring closure. Thus, methylenes will be involved in cyclization rather than methyls, and more acidic methylenes will cyclize with higher regioselectivity.⁴² However, bulky groups will direct the cyclization to the other side, even when these groups are electron-withdrawing. Thus, the phosphonium-salt **23** was obtained from **20** ($R^1 = \text{H}$, $R = \text{PPh}_3$) in 100% selectivity.^{34,43}

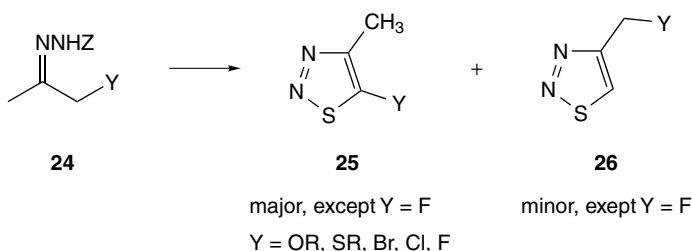


As mentioned above, the Hurd–Mori reaction is often accompanied by side reactions such as chlorination, aromatization and sulfonylation. A variety of mechanisms are possible to explain the formation of the by-products. They were summarized in the review of Stanetty⁷ and will not be described here.

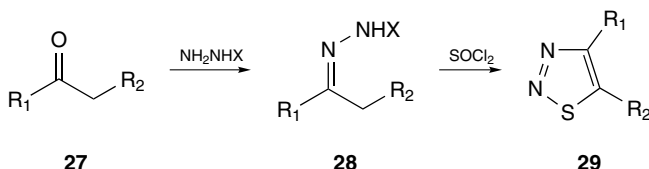
1.1.3. Application of the Hurd–Mori Reaction in Organic Synthesis

In this section, many reactions are summarized that are used or may be used in the synthesis of biologically active compounds and of compounds with other practically useful properties.

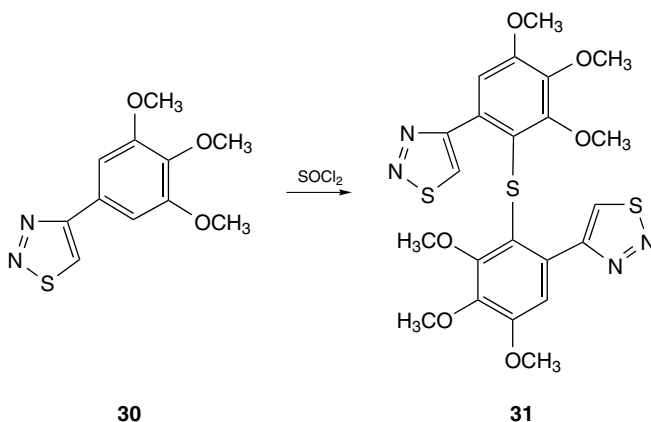
1,2,3-Thiadiazoles **25** bearing ether, sulfide as well as halogen groups were prepared in high to moderate yield when acetone hydrazones **24** with the same substituents were subjected to the Hurd–Mori reaction in 1,2-dichloroethane at room temperature for 1 day. Compounds **25** could be useful synthons to prepare new derivatives of 1,2,3-thiadiazole.⁴²



To search for compounds with antithrombotic activity, Thomas *et al.* prepared a series of 4,5-diaryl- and 4-aryl-substituted 1,2,3-thiadiazoles using the Hurd–Mori reaction. Aldehydes and ketones **27** were treated with (*p*-tolylsulfonyl)hydrazide or ethylcarbazate to form hydrazones **28**. The latter, in most experiments, were treated with neat thionyl chloride to produce the corresponding 1,2,3-thiadiazoles **29**.⁴⁴



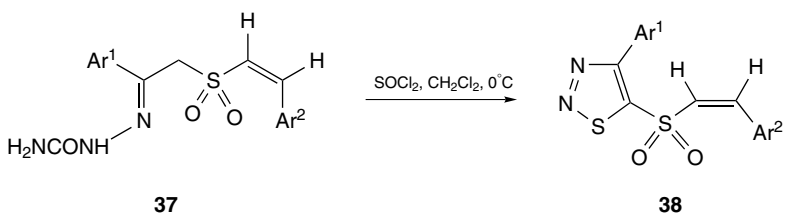
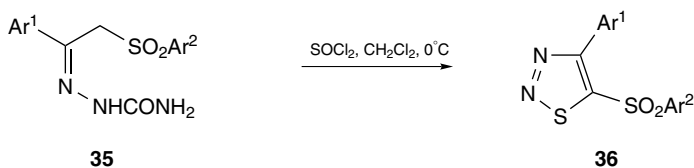
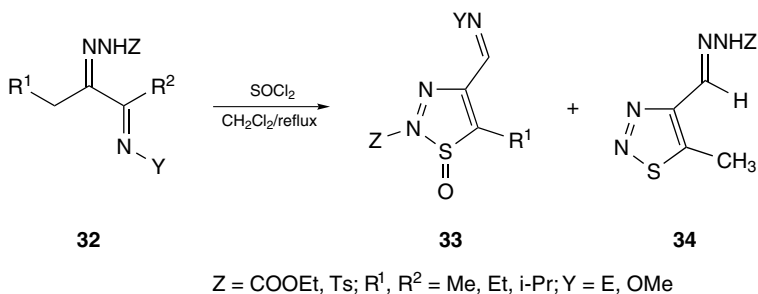
Interestingly, compound **30**, bearing an electron-rich aryl group, can be transformed under the conditions of the Hurd–Mori reaction to sulfide **31**.



1,2,3-Thiadiazoline-1-ones of type **33** are the key intermediates in the Hurd–Mori reaction. One can consider these compounds as cyclic sulfonamides that are potential antibacterial drugs. Fujita *et al.* managed to prepare a series of 1,2,3-thiadiazolin-1-ones **33** under the conditions of the Hurd–Mori reaction (3 mol of thionyl chloride, CH_2Cl_2 , reflux) as the major product in 44% yield from hydrazone **32** ($\text{R}^1 = \text{Me}$), together with a small amount of 1,2,3-thiadiazole **34**. Similar reactions of other derivatives **32** afforded thiadiazolin-1-ones **33** in moderate yield as the only products.^{38,42}

1,2,3-Thiadiazoles containing aryl- (**36**) and alkenylsulfonyl (**38**) groups were recently prepared by the group of D.B. Reddy using the Hurd–Mori reaction.^{45,46} Compounds **36** and **38** have been shown to be very useful starting reagents in the synthesis of polyfunctional alkynes.

β -Adrenergic blocking agents in the 1,2,3-thiadiazole series of type **42** and **46** were prepared by the Hurd–Mori reaction, starting from hydrazones **39** and **43**,



followed by reactions of the initially formed compounds **40** and **44**, containing a phenolic group, with epihalohydrines and subsequent treatment of **41** with aliphatic and aromatic amines.⁴⁷

Tricyclic compounds **48**, that were prepared from hydrazones **47**, contain two hydroxy groups and can be starting materials to prepare structural analogs to compounds **42** and **46**. Interestingly, this reaction is accompanied by demethylation of the two methoxy groups to give the final product **48**.⁴⁸

Very often, the most difficult problem may be preparing the starting hydrazones rather than the synthesis of 1,2,3-thiadiazoles by the Hurd–Mori reaction itself. Thus, to prepare 4-mercapto-1,2,3-thiadiazoles **55** that are intermediates in the synthesis of new cephalosporin antibiotics, Lee *et al.* had to elaborate a four-step synthesis of hydrazones **53** starting from thioamides **49**. In the synthesis of the final compound **55**, the *S*-alkyl unit serves a crucial function as a thiol protecting group. The authors have shown that the best choice of the protecting group is the 3-alkoxycarbonyl ethyl moiety because of its ease of incorporation and eventual smooth removal from alkylthiothiadiazoles **54** via retro Michael addition.²⁰

1,2,3-Thiadiazole-5-thiol **59** is used to prepare Cefuzoname[™], new semisynthetic cephalosporin antibiotic. An approach to this compound was devised where ring construction takes place from sulfide **57**, bearing a hydrazone group, by