HETEROCYCLIC COMPOUNDS

1,2,3-THIADIAZOLES

Volume 62

BAKULEV
DEHAEN

INTERSCIENCE

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

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THE CHEMISTRY OF 1,2,3-THIADIAZOLES

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Acknowledgments

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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.

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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, thiirenes, 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.

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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.

VASILIY A. BAKULEV
WIM DEHAEN

Contents

CHAPTER 1

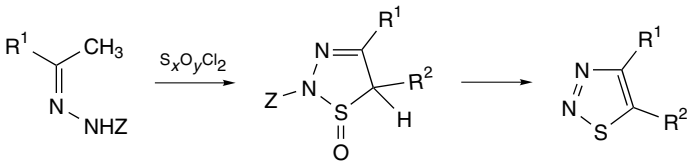
Synthesis of 1,2,3-Thiadiazoles

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 N_2 with an electron- withdrawing group (Z = $CONH_2$, COOMe, COR, SO_2R) 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]



1 **2** **3**

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

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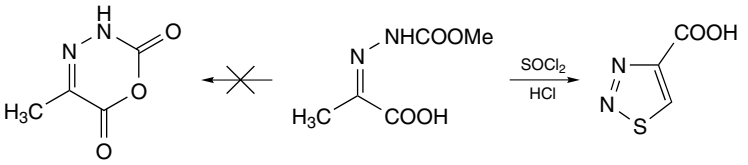


5 **4** **6**

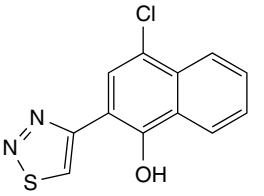
with thionyl chloride. 1,2,3-Thiadiazole-4-carboxylic acid **6** was unexpectedly formed, leading to a new synthetic approach to 1,2,3-thiadiazoles.[10]

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 = 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



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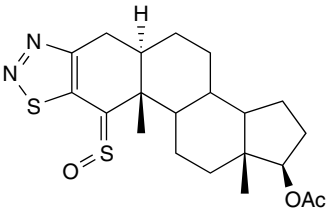

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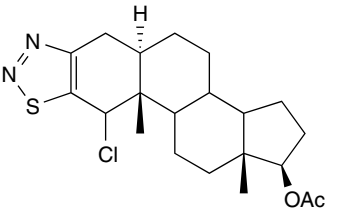
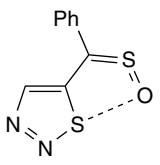


8b

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 thienothiadiazole **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 products[30] that were the original goal of Hurd and Mori.



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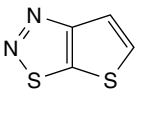

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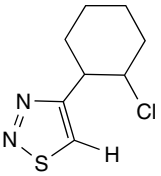

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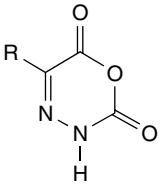
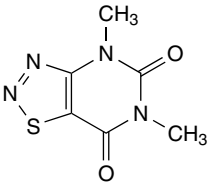


12

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 cyclopentadienothiadiazole **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]



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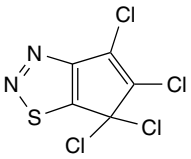

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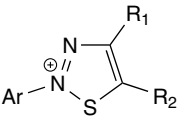
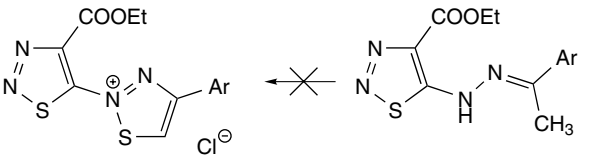
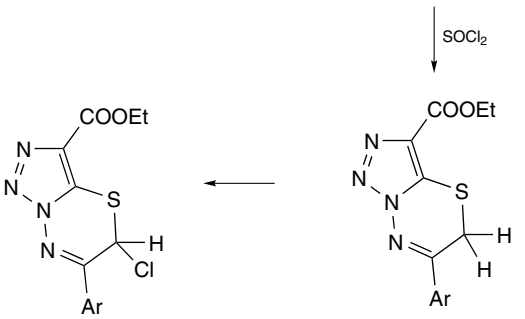


15

In contrast to the reaction of *N*-arylhydrazones[34] 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 bisthiadiazole **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 $SOCl_2$ at low temperature, the nonchlorinated product **17** was isolated in good yield.[35]



19 **16**

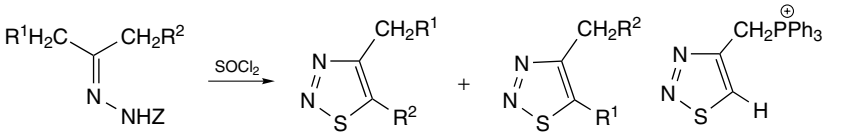


18 **17**

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** ($R^1 = H$, $R = PPh_3$) in 100% selectivity.[34,43]



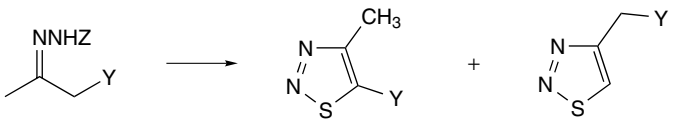
20 **21** **22** **23**

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 Stanetty[7] 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]

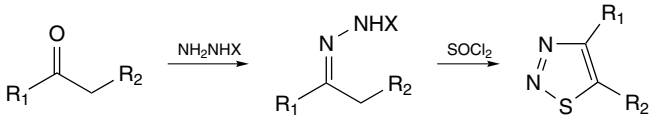


24 **25** **26**

major, except Y = F minor, exept Y = F

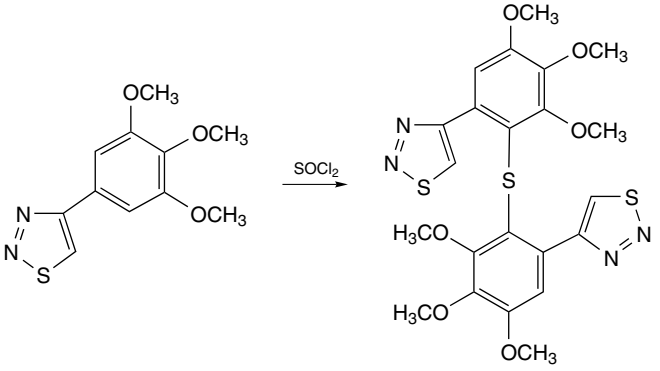
Y = OR, SR, Br, Cl, F

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]



27 **28** **29**

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

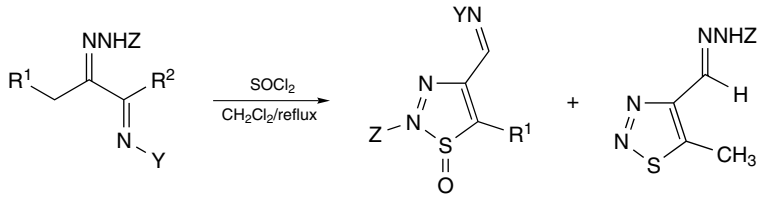


30 **31**

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** (R^1 = 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]

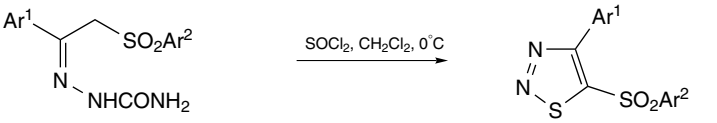
1,2,3-Thiadiazoles containing aryl- (**36**) and alkenylsulfonyl (**38**) groups were recently prepared by the group of D.B. Reddy using the Hurd–Mori reaction.[45,46] Compounds **36** and **38** have been shown to be very useful starting reagents in the synthesis of polyfunctional alkynes.

β-Adrenerging 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**,

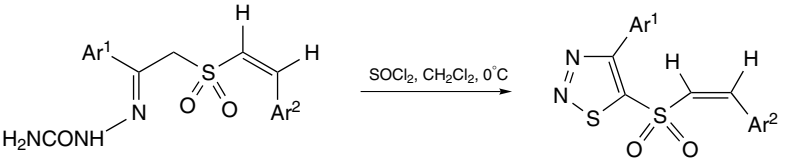


32 **33** **34**

Z = COOEt, Ts; R^1, R^2 = Me, Et, i-Pr; Y = E, OMe



35 **36**



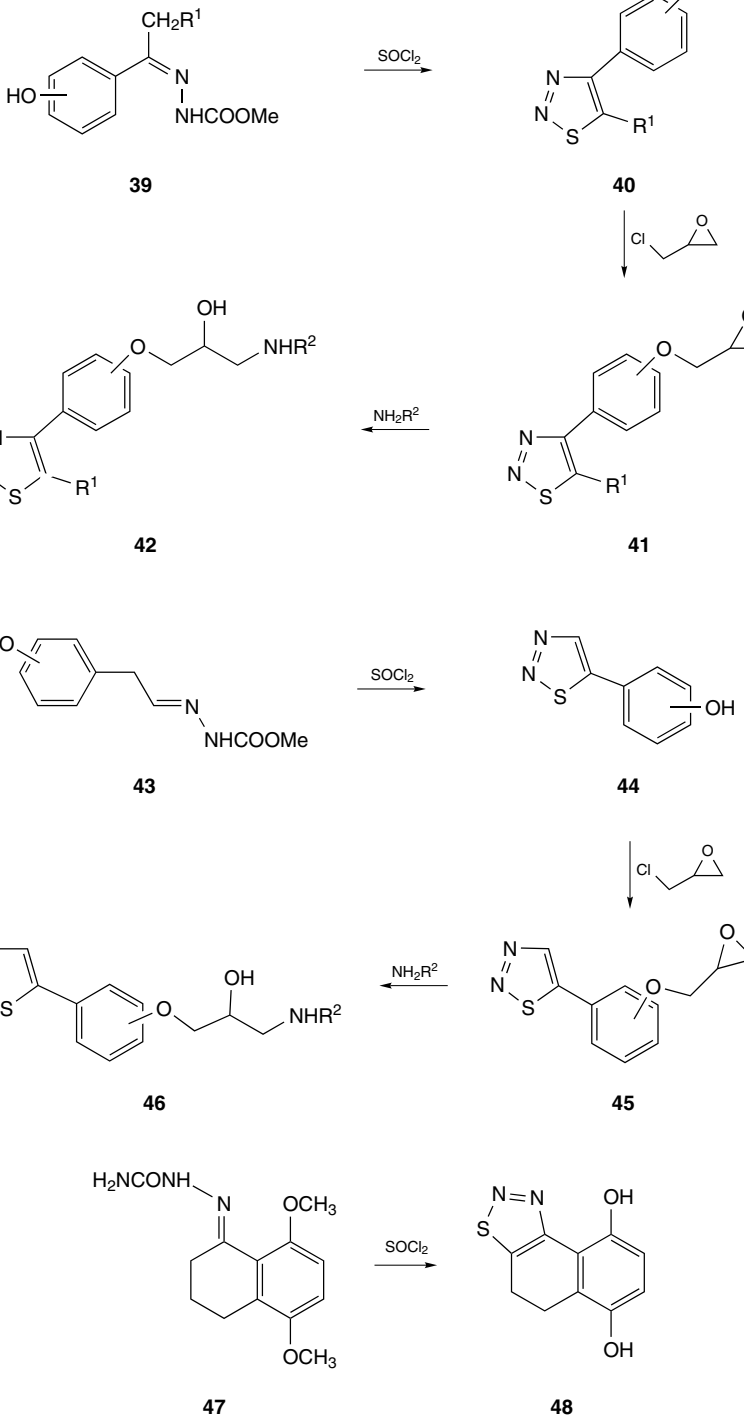
37 **38**

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]

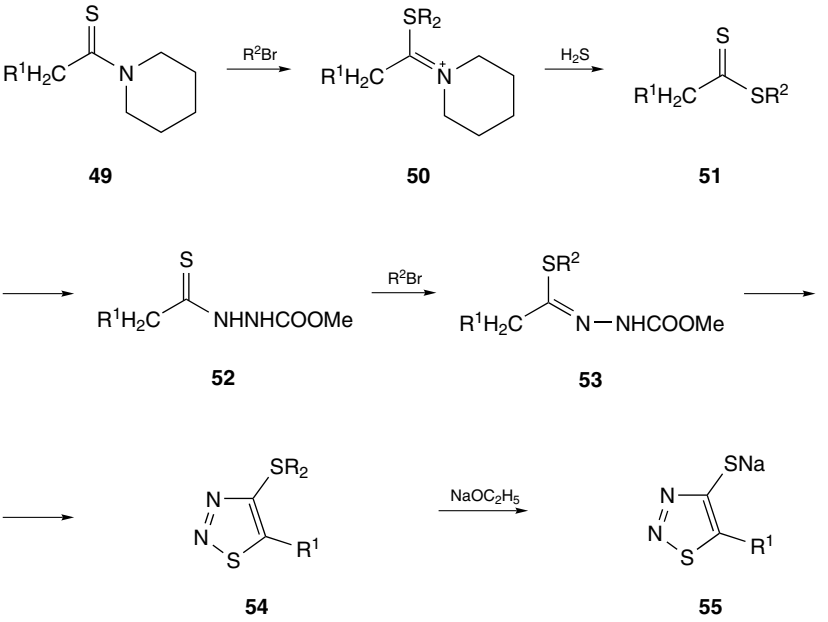
Tricyclic compounds **48**, that were prepared from hydrazones **47**, contain two hydroxy groups and can be starting materials to prepare structural analogs to compounds **42** and **46**. Interestingly, this reaction is accompanied by demethylation of the two methoxy groups to give the final product **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-alkoxycarbonylethyl moiety because of its ease of incorporation and eventual smooth removal from alkylthiothiadiazoles **54** via retro Michael addition.[20]

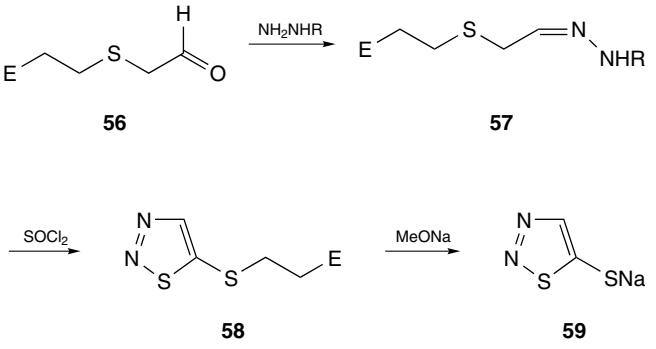
1,2,3-Thiadiazole-5-thiol **59** is used to prepare Cefuzoname™, new semisynthetic cephalosporin antibiotic. An approach to this compound was devised where ring construction takes place from sulfide **57**, bearing a hydrazone group, by



39 **40** **41** **42** **43** **44** **45** **46** **47** **48**

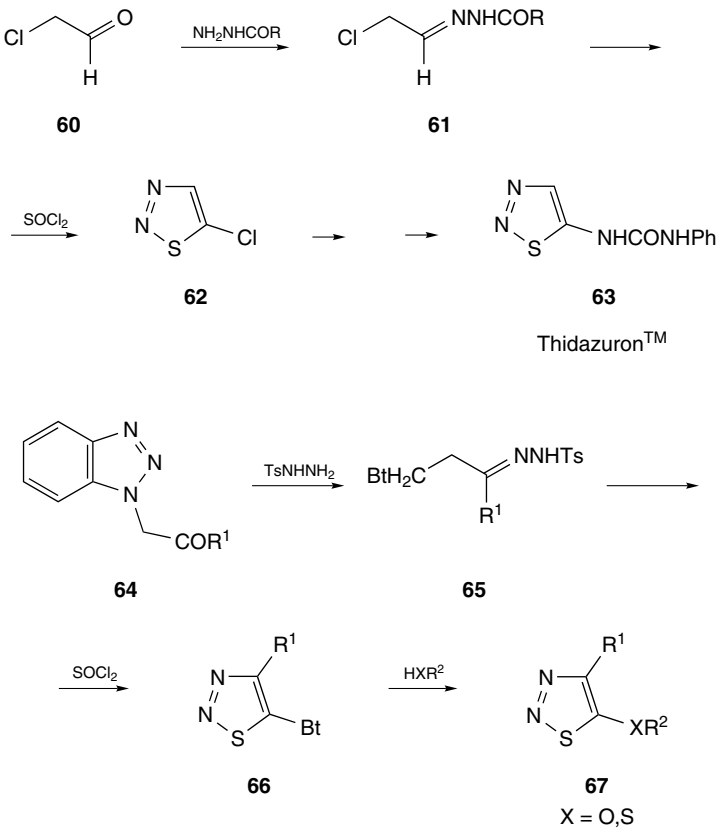


reaction with thionyl chloride. The same thiol protecting group was used in the synthesis of thiadiazoles **59** as in the synthesis of 1,2,3-thiadiazole-4-thiols **55**.[19,49]

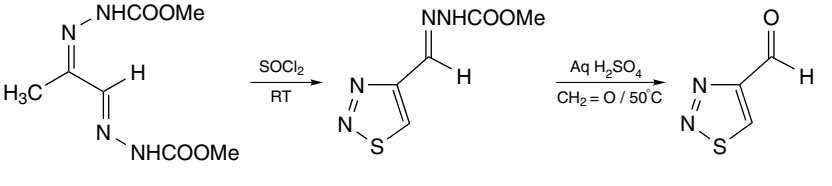


The Hurd–Mori reaction was applied on an industrial scale to prepare 5-chloro-1,2,3-thiadiazole **62**, which is a key intermediate in the synthesis of 5-phenylureido-1,2,3-thiadiazole, a very effective cotton defoliant with the commercial name of thidazuron™.[50]

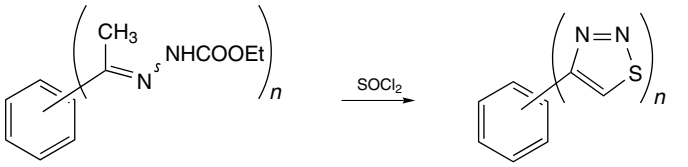
Quite recently, Katritzky and coworkers applied the Hurd–Mori reaction to prepare bicyclic assemblies **66** containing both 1,2,3-thiadiazole and benzotriazole rings[51]. Benzotriazole (Bt) was shown to be a good leaving group, which allowed to prepare 5-aryloxy- and 5-arylthio-1,2,3-thiadiazoles **67** in good yields.



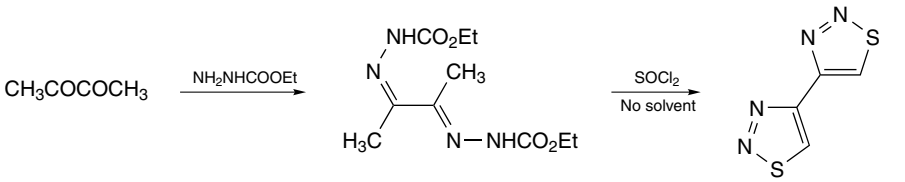
As a part of a program to synthesize new antibacterial cephalosporin analogs, Kobori *et al*. described a two-step synthesis of 4-formyl-1,2,3-thiadiazole **70**. Methylglyoxal was converted with 2 equiv of ethyl carbazate at room temperature into bis(ethoxycarbonylhydrazone) **68**, which was treated with thionyl chloride at room temperature without solvent to give hydrazone **69**. Subsequent acid hydrolysis of the remaining hydrazone moiety gave 1,2,3-thiadiazole-4-carboxaldehyde **70**.[18] It should be noted that the synthesis of aldehyde **70**, directly in one step from the monohydrazone of methylglyoxal, gave only a 4% yield of the desired product.[7]



To prepare multiple 1,2,3-thiadiazoles **72**, which could take part in photo (thermo)crosslinking processes, Meier and coworkers involved polyhydrazones of type **71** to the Hurd–Mori reaction. 2,3-Butanedione bishydrazone **74** gives in analogous conditions, 4,4′-bi(1,2,3-thiadiazolyl) **75** in 85% yield.[24]

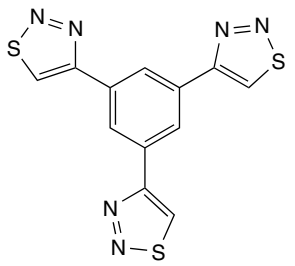


71 **72**



73 **74** **75**

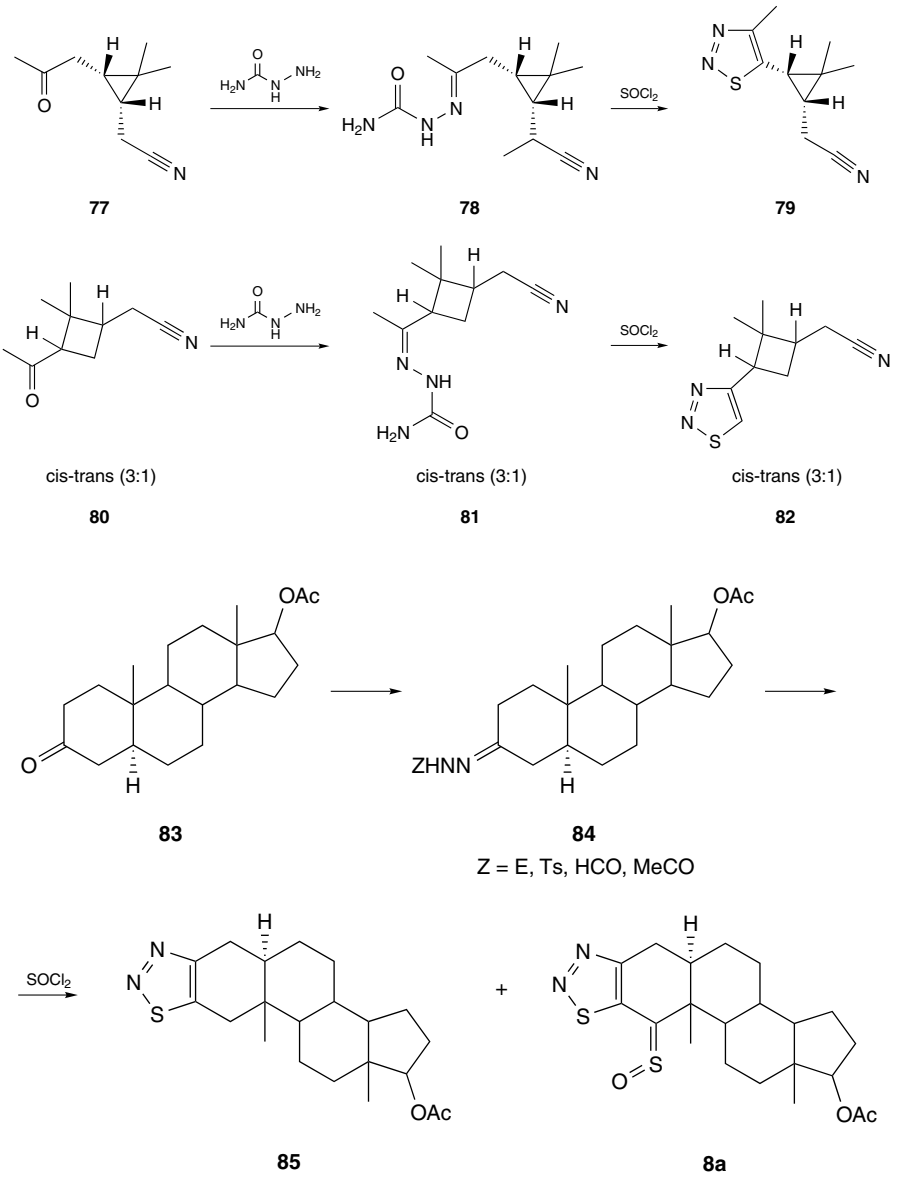
Some years before, we had prepared similar compounds that were used as dendrimer cores and did contain two or three thiadiazole rings (**76**) in one molecule.[23]



76

We reported the use of the Hurd–Mori approach in the synthesis of chiral 1,2,3-thiadiazoles **79** and **82**, bearing either cyclopropyl or cyclobutyl groups, starting from seco-derivatives of (+)-carene **77** and α-pinene **80**. It is worth noting that the first reaction is highly regioselective with participation of the methylene rather than the methyl group.[35]

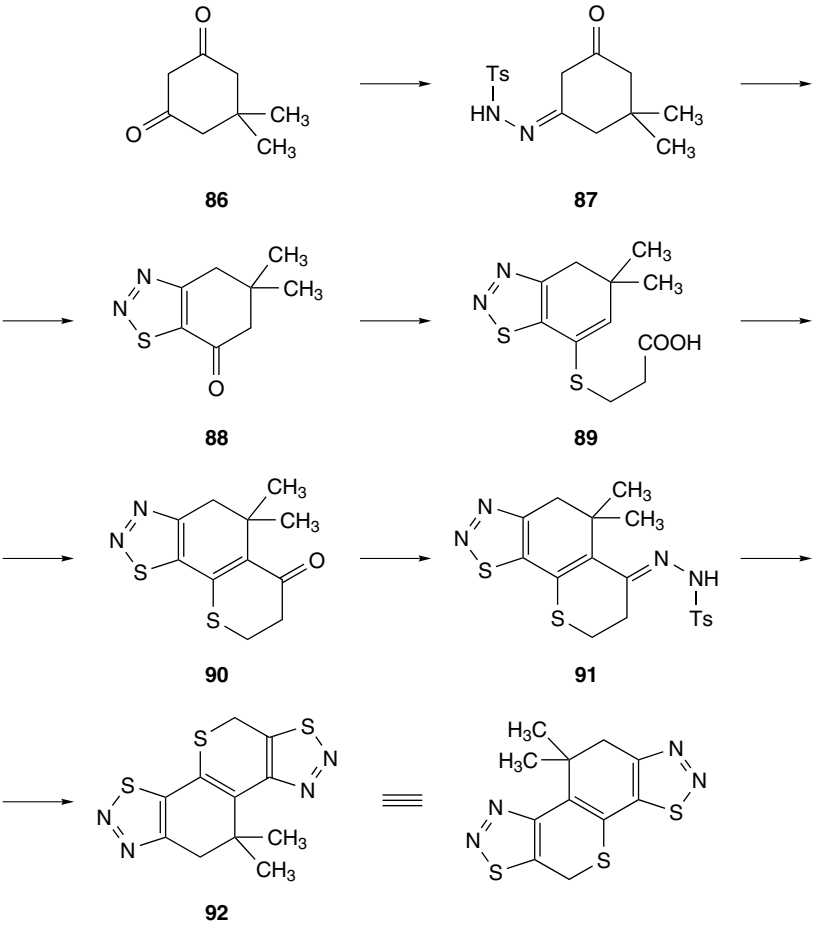
In attempting to prepare novel steroidal [3,2-*d*][1,2,3]-thiadiazoles in support of a program exploring A-ring-fused heterocyclic steroids for use as male contraceptives, Britton *et al.* have found that the reaction of *N*-ethoxycarbonyl hydrazones **84** affords compounds **86** containing a sulfine group instead of thiadiazoles **85**.[27]



Under similar conditions, the corresponding *N*-tosyl and formyl hydrazones afforded thiadiazoles **85** in high yield. At the same time, *N*-acetyl hydrazone **84** gave a mixture of the two products.[27]

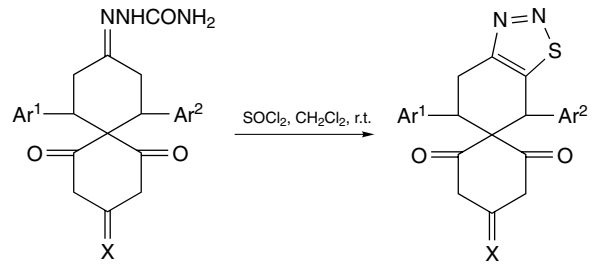
The work of Britton prompted Bakthavatchalam *et al*. to carry out a multi-step synthesis of bisthiadiazolo polycyclic compounds **92**, where both thiadiazole rings were constructed with the Hurd–Mori reaction.[52] The reaction starts from dimedone **86** via the monothiadiazole **88**, which is regioselectively obtained from

monohydrazone **87**. Ring annelation followed by a second Hurd–Mori reaction ultimately gave tetracyclic compound **92**.

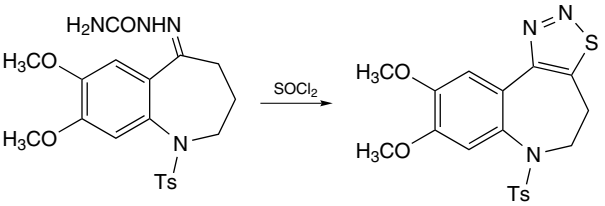


In subsequent work, the same authors prepared compounds, in which one of the thiadiazole rings in **92** was substituted by isoxazole or pyrazole rings.[53] Many other examples of the synthesis of 1,2,3-thiadiazoles fused to other heterocyclic rings by Hurd–Mori reaction were published by Indian chemists.[54–68] D. B. Reddy and colleagues prepared thiadiazoles **94**, which are spiro derivatives of barbituric and thiobarbituric acids and have found that these compounds possess antibacterial and antifungal activities.[62]

An annelation of a 1,2,3-thiadiazole ring to the benzazepine ring system took place when hydrazonobenzazepine **95** was subjected to the Hurd–Mori reaction. In this way, 1,2,3-thiadiazolo[5,4-d]benzazepine **96** was prepared in good yield.[56]



93 X = O, S **94**



95 **96**

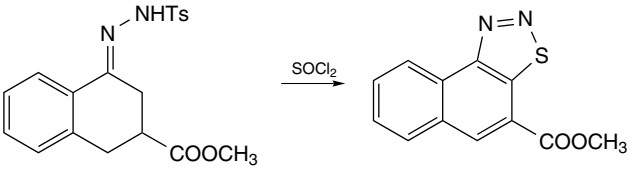
Stanetty and coworkers published data[9,69,70] on the synthesis of structural analogs of Bion™, benzo-[1,2,3]thiadiazole-7-carbothioic acid *S*-methyl ester, the first synthetic chemical, which is recognized as a plant activator.[70]

They prepared tricyclic compounds **98, 100, 102**, in which the thiadiazole ring was fused to either naphthalene or benzothiophene system by the reaction of tosylhydrazones **97, 99, 101** with 20 equiv of thionyl chloride at room temperature. It is worth noting that aromatic compounds were obtained in all reactions without any of the expected dihydrobenzothiadiazoles.

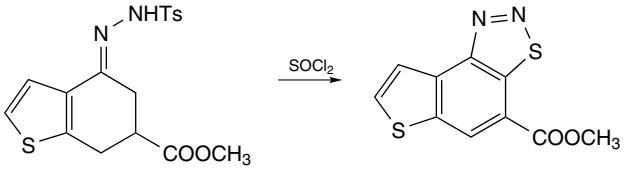
In a related study, the Stanetty group reported an efficient method to prepare thieno[2,3-d][1,2,3]-thiadiazole-6-carboxylic acid derivatives **103**, a new class of compounds biosteric to benzo[1,2,3]thiadiazole-7-carboxylic acid **104**.[69,70]

The synthesis of carbazate **111**, which was used as the starting compound, was a more difficult task than the construction of the thiadiazole ring by the Hurd–Mori reaction. This compound **111** was prepared via a four-step synthetic scheme from methylenebutanedioic acid **105**. Thus, Michael addition of thioacetic acid onto the double bond of **105** followed by hydrolysis of intermediate **106** yielded thiol **107** that was converted further to the thiolactone **108** simply by heating to 140°C. Selective thionation of the methyl ester **109** to dithiolactone by Lawesson's reagent and subsequent condensation with ethylcarbazate led to pure hydrazone **111**.

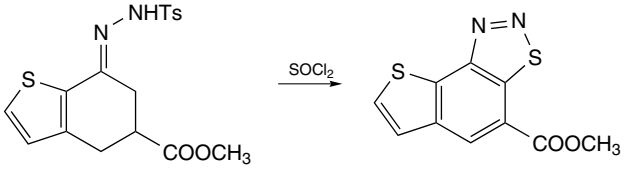
A mixture of the target compound **112** and a by-product, identified as the chlorinated thienothiadiazole **113**, was isolated in a ratio of 8:1 after treatment of the hydrazone **111** with thionyl chloride in dichloromethane at room temperature.



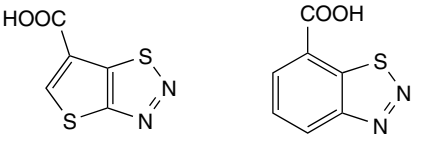
97 **98**



99 **100**



101 **102**



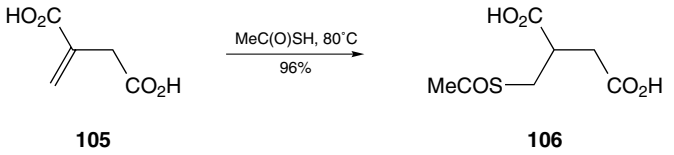
103 **104**

Stanetty has shown that the formation of the by-product can be avoided by raising the temperature of the reaction to 80°C.

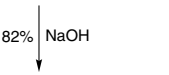
Thienothiadiazole **116**, which is isomeric to **112**, was prepared by Ohno and colleagues from tosylhydrazide **115** by the Hurd–Mori reaction.[71]

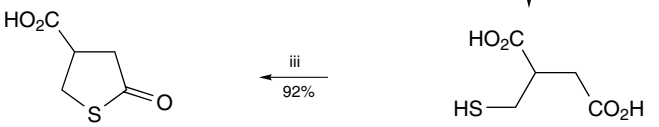
An interesting solid phase synthesis of 1,2,3-thiadiazoles was described. A Merrifield type resin **117**, which was functionalized with sulfonhydrazide groups, was used to "fish out" ketones from a reaction mixture. Subsequent treatment of the isolated resin with thionyl chloride converted the hydrazone functionalities of **118** to 1,2,3-thiadiazoles **119**, disconnecting them from the sulfonyl chloride resin **120** at the same time.[8]

This protocol could be very useful in generating a small library of 1,2,3-thiadiazole derivatives for biological screening.

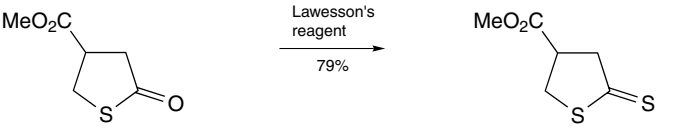


105 **106**

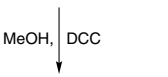


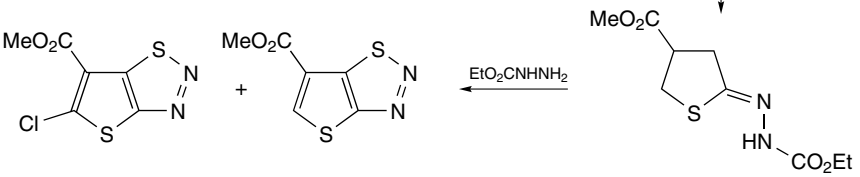


108 **107**



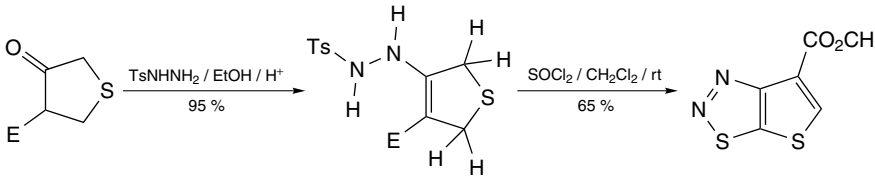
109 **110**



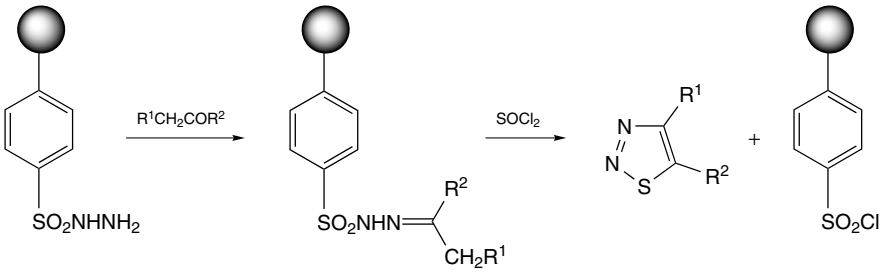


113 **112** **111**

Solvent	Temp. (°C)	Ratio 112:113	Yield of 112 (%)
CH_2Cl_2	25	8:1	60
$C_2H_4Cl_2$	80	1:0	66



114 **115** **116**

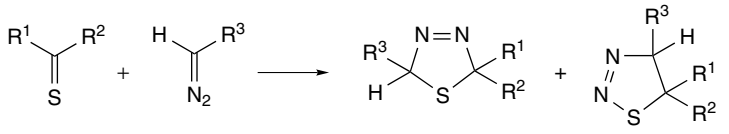


117 **118** **119** **120**

1.2. CYCLOADDITION OF DIAZOALKANES ONTO A C=S BOND (PECHMANN SYNTHESIS)

This synthetic method, leading to 1,2,3-thiadiazoles, includes the reactions of diazo compounds with various thiocarbonyl compounds (thioketones, thioesters, thioamides, carbon disulfide, thioketenes, thiophosgene and isothiocyanates). Various mechanisms are possible for these reactions, including two-step processes.[72] From the retrosynthetic point of view, this is a [3 + 2] method to prepare 1,2,3-thiadiazoles using three atoms of the diazo compound and two atoms of the thiocarbonyl compound.

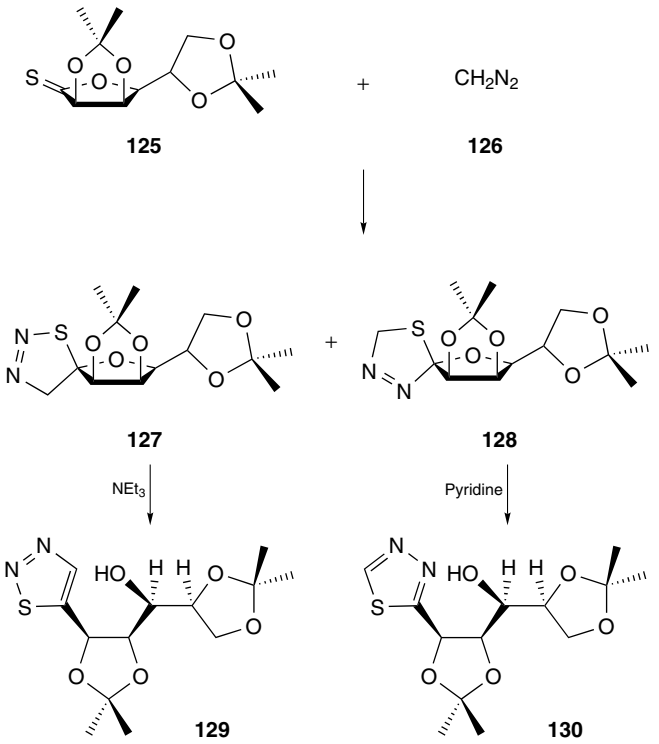
The reaction of diazoalkanes **121** with thioketones **122** gives mixtures of 1,3,4-thiadiazolines **123** and 1,2,3-thiadiazolines **124**. The ratio of the regioisomers depends on the solvent polarity and steric effect. Increasing the solvent polarity and decreasing the steric hindrance favors the formation of the 1,2,3-thiadiazoles.[72,73]



122 **121** **123** **124**

Spirothiadiazolines **127, 128** were obtained from glyconothio-*O*-lactone **125** as the thioketone in this reaction.[74,75] The primary products **127, 128** after treatment with pyridine and triethylamine, respectively, furnish the aromatic 1,2,3-thiadiazoles **129** and 1,3,4-thiadiazoles **130**.

The reaction of lithium(trimethylsilyl)diazomethane **132** with hindered thioketones proceeds in a regioselective manner at a very low temperature to give only one of the possible cycloaddition products. This is either 1,2,3-thiazolines **133, 135**, or aromatic 1,2,3-thiadiazole **137**, depending on the structure of the thioketones as shown below.[76] However, this reaction is very sensitive to the solvent used in the experiments. Thus, replacement of diethyl ether by THF in the reaction



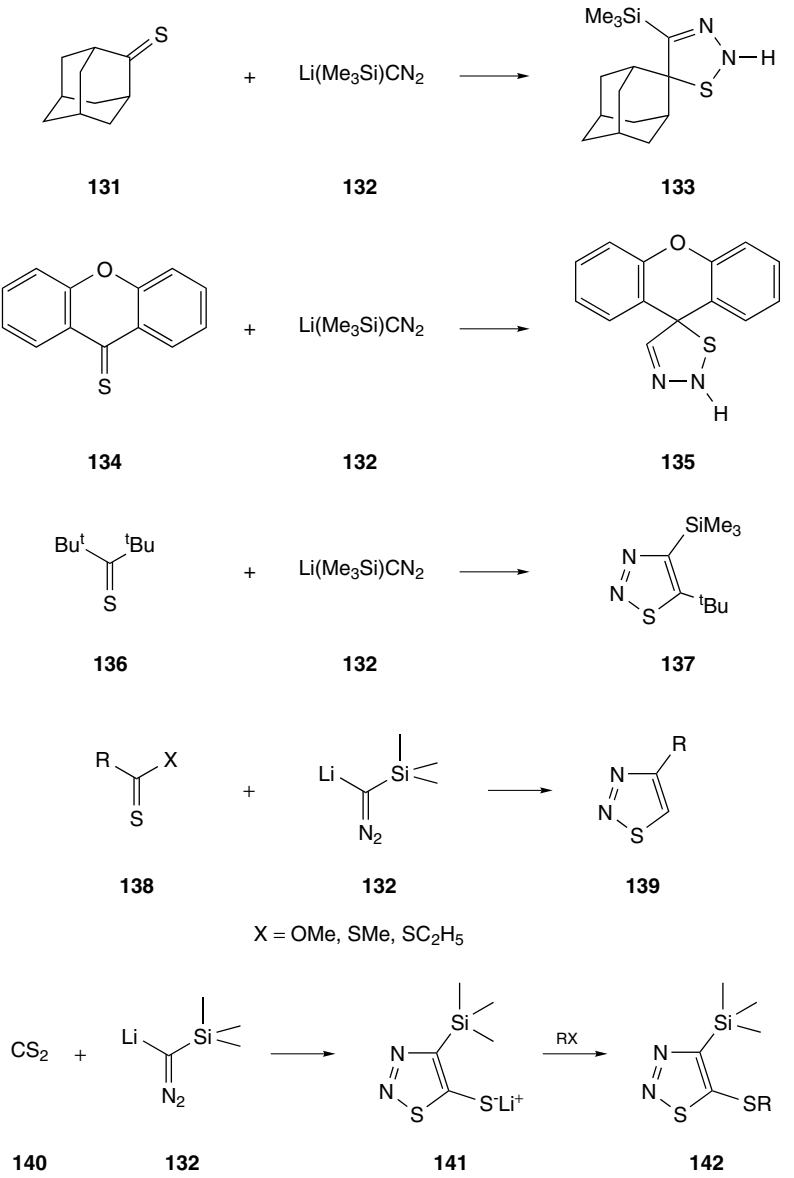
of the adamantyl derivative **131** changes the direction of the reaction drastically to afford the methyleneadamantane, which is a degradation product of the thiadiazoline ring. In the reaction of cyclic ketones, the formation of thiadiazolines **133** and **135** is possible, but in the case of thioketone **136**, the aromatic thiadiazole was obtained in good yield. Most likely, the latter reaction also goes via an intermediate thiadiazoline.

It should also be noted that this reaction is sensitive to the structure of the thioketones. The degradation products of the thiadiazoline ring are obtained in many cases. We can conclude that the scope and limitations of this method for the preparation of 1,2,3-thiadiazolines have so far not been determined.

Lithium(trimethylsilyl)diazomethane **132** also reacted with thioesters, dithioesters and carbon disulfide to give a variety of 5-substituted 1,2,3-thiadiazoles.[77]

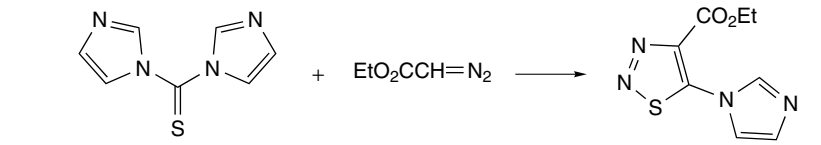
Interestingly, other hindered thiocarbonyl compounds, namely, 1,1′-thiocarbonyl-bis-imidazole **143** and -bis-triazole **145**, reacted with ethyl diazoacetate in a regiospecific manner to give ethyl 5-(imidazol-1-yl)- and 5-(1,2,4-triazol-1-yl)-1,2,3-thiadiazole-4-carboxylates **144** and **146**, respectively, in very high yields.[78]

In the reaction of chlorodithioformates, thiophosgene and isothiocyanates, the aromatization of primary thiadiazolines takes place via elimination of hydrogen

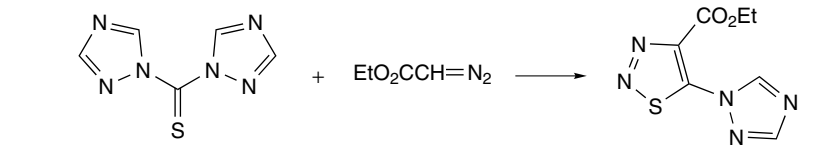


chloride, alcohol or thiol or via a hydrogen shift from the 4-position of the ring to the exocyclic nitrogen atom to form mixtures of aromatic thiadiazoles **149 (153)** and **150 (154)**.[5,79]

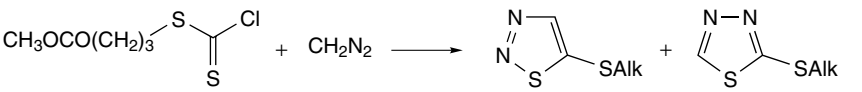
It is interesting to note that ethyl chlorodithioformate **155** preferably affords 1,3,4-thiadiazole **156a** from its reaction with diazoacetic ester in the presence of triethylamine. On the other hand, the isomeric 1,2,3-thiadiazole **156b** was obtained in this reaction when HgO was used instead of triethylamine.[79,80]



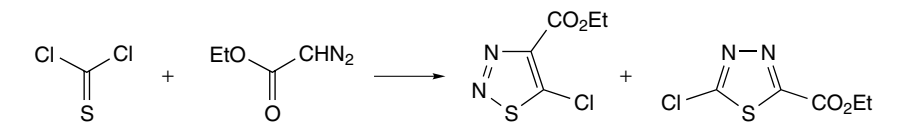
143 **144**



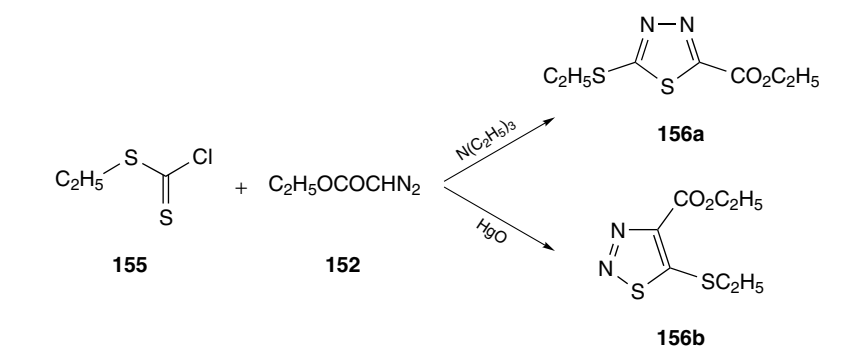
145 **146**



147 **148** **149** **150**



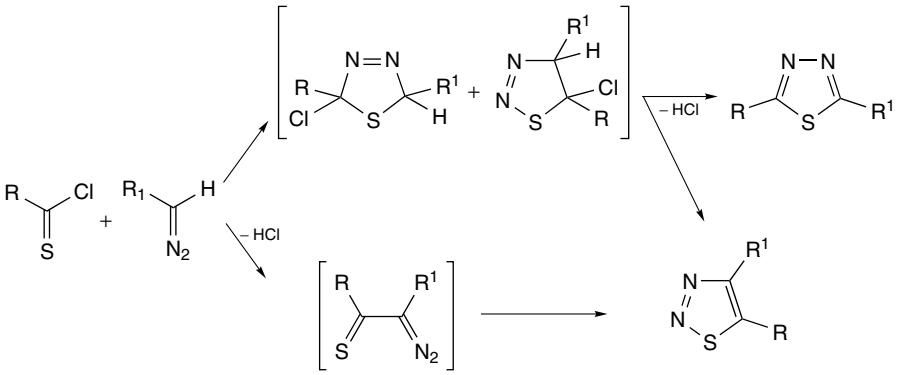
151 **152** **153** **154**



155 **152** **156a** **156b**

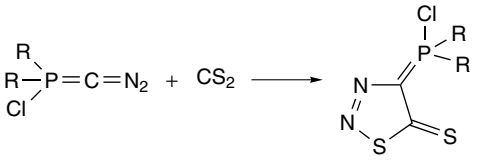
Obviously, the isomeric thiadiazoles are formed *via* different mechanisms. The concerted 1,3-dipolar cycloaddition reaction of diazo compounds onto the C=S double bond takes place regioselectively to give mainly 1,3,4-thiadiazolines, which eliminate hydrogen chloride to afford 1,3,4-thiadiazoles analogous to **156a**.[6]

Acylation of diazo compounds with thiocarbonyl chlorides furnish diazothiocarbonyl compounds. 1,5-Electrocyclic ring closure of the latter affords 1,2,3-thiadiazoles. In fact, this is another method for the synthesis of 1,2,3-thiadiazoles, where the construction of ring takes place by intramolecular cyclization. We refer to this ring-closure reaction by the name of Wolff synthesis, and this process will be considered in Section 1.3 of this chapter.



It should be noted that the reaction of diazoalkanes with thiocarbonyl compounds may be accompanied by reactions of highly reactive carbenes that can readily be obtained from diazoalkanes in these conditions.[4]

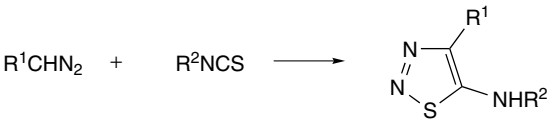
At the same time, only 4-methylene-Δ^2-1,2,3-thiadiazolin-5-thiones **158** were obtained in quantitative yield when diazomethylene phosphoranes **157** were treated with carbon disulfide.[81]



157 **158**

The reaction of isothiocyanates with diazoalkanes is interesting also from a historical point of view. It was the first example of the synthesis of monocyclic 1,2,3-thiadiazoles, described by Pechmann and Nold at the end of the nineteenth century.[1] This reaction was then extensively used for the synthesis of a variety of 5-amino-substituted 1,2,3-thiadiazoles **161**.[4–6] Kinetic studies have shown that the rate of this reaction increases for more electron-releasing R^1 and electron-withdrawing R^2.[6]

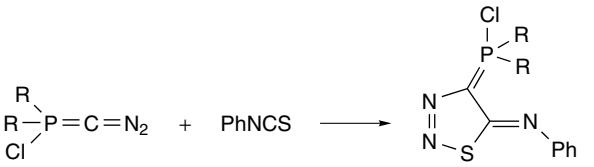
This type of reaction is often accompanied by alkylation of the primary formed 5-amino-1,2,3-thiadiazoles **161** and by the formation of carbene-derived products. Therefore, the yields of the 5-amino-1,2,3-thiadiazoles **161** often are only



159 **160** **161**

moderate.[4–6,82,83] Obviously, upscaling of this procedure is also limited by the explosive nature of the diazo compounds used.

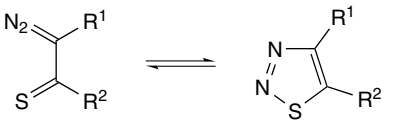
Despite the presence of two cumulated double bonds in the isothiocyanate molecule, the addition of diazo compounds takes place selectively onto the C=S bond to afford only 1,2,3-thiadiazoles. The Pechmann–Nold synthesis of 1,2,3-thiadiazoles is strictly limited to diazomethane or diazo compounds monosubstituted at the α-carbon. The participation of diazomethylene phosphoranes **157**[84,85] and α-trialkylsilyl diazoketones **132**[6] in this reaction could be explained by a mechanism with pseudopericyclic transition states, similar to the reaction of ketoketenes with acetone.[86]



157 **162**

1.3. HETEROCYCLIZATION OF α-DIAZO THIOCARBONYL COMPOUNDS (WOLFF SYNTHESIS)

An efficient method for the preparation of 1,2,3-thiadiazoles **164** involves the generation and subsequent heterocyclization of α-diazothiocarbonyl compounds **163**.[86] At the beginning of the twentieth century, Wolff reported the synthesis of 5-alkyl-1,2,3-thiadiazoles by the reaction of 2-diazo-1,3-dicarbonyl compounds with ammonium sulfide.[2] This method was considerably expanded to prepare a variety of 5-amino- and 5-mercapto-1,2,3-thiadiazoles bearing carbonyl, thiocarbonyl, phosphoryl, cyano, alkyl and aryl groups at the 4-position and also to prepare fused 1,2,3-thiadiazoles.[5,6]



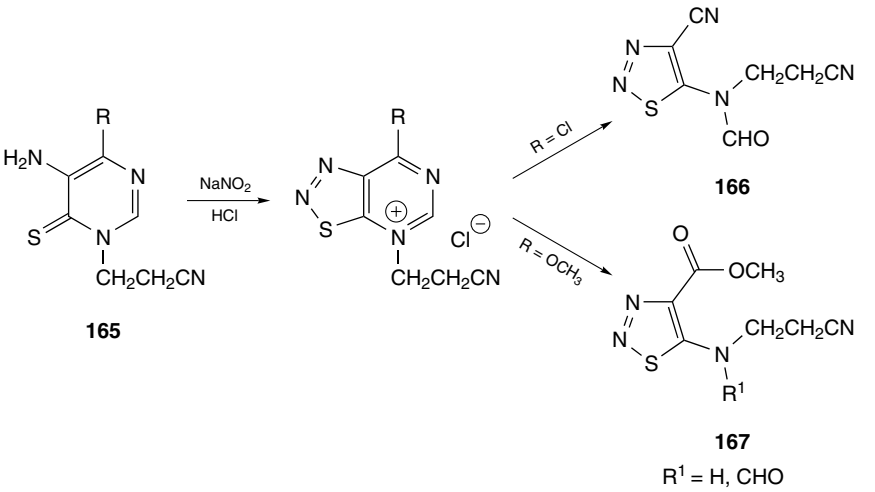
163 **164**

The heteroelectrocyclization reaction of diazothiocarbonyl compounds **163** to 1,2,3-thiadiazoles **164** has a low energy barrier and proceeds under the reaction conditions used to generate the former.[86] Therefore, this synthetic method for 1,2,3-thiadiazoles can be classified according to the different ways to generate diazothiocarbonyl compounds. Thus, diazo thiocarbonyl compounds **163** may be generated (1) by introducing the diazo group into compounds containing a C=S bond, (2) by constructing a C=S group into the α-position of a diazo compound or (3) by simultaneous introduction of both these functions.

1.3.1. Introduction of a Diazo Function into Compounds Containing a C=S Bond

Diazotation of aliphatic α-aminothioacetamides and aromatic (including heteroaromatic) *ortho*-mercaptoamines leads to 5-amino-1,2,3-thiadiazoles or fused 1,2,3-thiadiazoles, respectively, most probably *via* the intermediate diazo thiocarbonyl compounds.[4–6]

The main reaction is often accompanied by the formation of by-products or by the transformation of primary formed compounds.[86–88] Thus, treatment of 5-aminopyrimidine-6-thiones **165** with sodium nitrite in hydrochloric acid leads to 4-cyano-1,2,3-thiadiazoles **166** or 5-ethoxycarbonyl-1,2,3-thiadiazoles **167**, instead of the expected bicyclic compounds.[88]



165

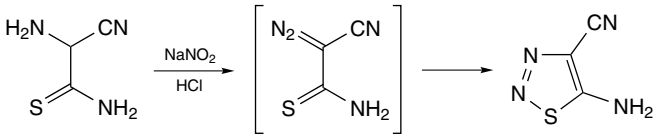
166

167

R^1 = H, CHO

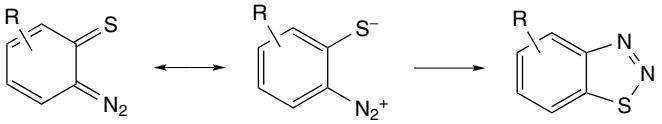
Diazotation of 2-amino-2-cyanothioacetamide **168** under the same conditions proceeds readily to form 5-amino-4-cyano-1,2,3-thiadiazole **170** in good yield.[5,86]

The formation of 1,2,3-thiadiazoles by this method requires the presence of two electron-withdrawing groups at the α-carbon atom of the amino compound. Thus, we did not manage to obtain 5-amino-1,2,3-thiadiazole by diazotation of 2-aminothioacetamide.[6] Obviously, the electron-withdrawing substituents stabilize



168 **169** **170**

the intermediate diazothiocarbonyl compounds and prevent their degradation via carbene formation. The stabilization of diazo compounds can be achieved by including the carbon atom attached to the diazo function onto an aromatic ring. In contrast to aromatic diazooxides, which are relatively stable, diazosulfides **171** undergo rapid cyclization to benzo-1,2,3-thiadiazole **172**.



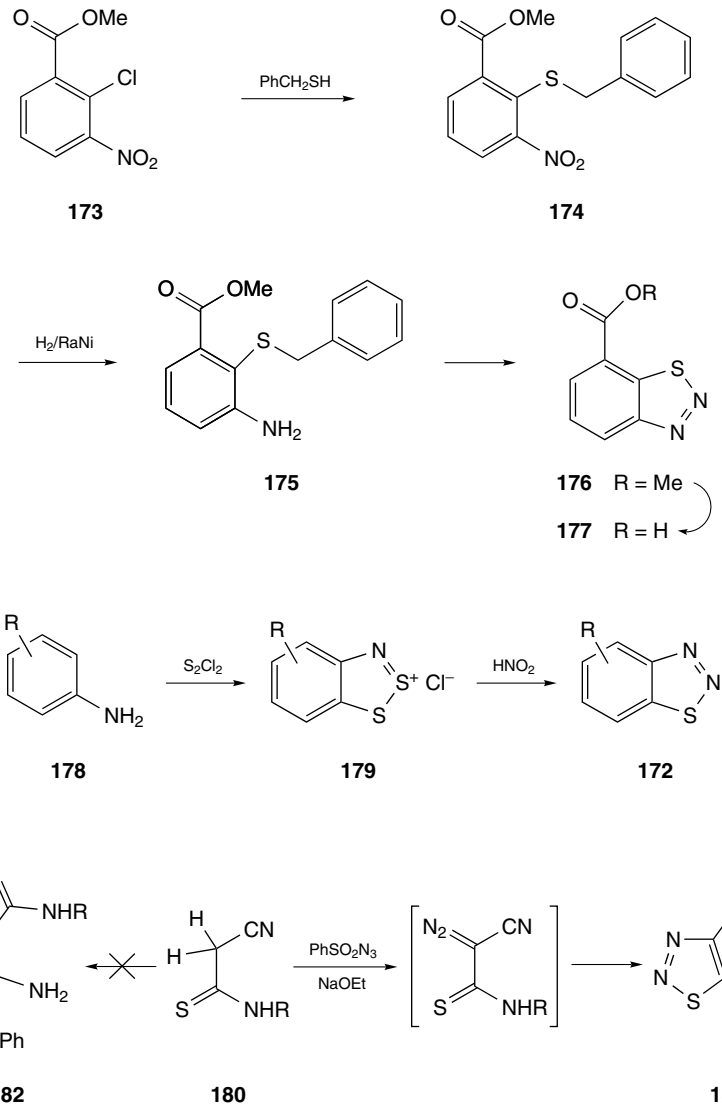
171 **172**

It has been shown that one can obtain better yields of benzothiadiazoles when a protected thiol is used in the diazotation reaction. Benzyl and isopropyl groups have been shown to be the best choice of thiol protecting groups and they are easily cleaved off by S_N1-type solvolysis. This method was used to prepare benzo[1,2,3-]thiadiazole-7-carboxylic acid derivatives, the main intermediate in the synthesis of Bion™.[89,90] Thus, substitution of the chlorine atom in **173** by benzylthiol to the intermediate **174**, followed by reduction in tetrahydrofuran led to methyl-3-amino-2-benzylthiobenzoate **175**, which was cyclized to benzo-[1,2,3]thiadiazole-7-carboxylic acid methyl ester **176**. Hydrolysis yielded the desired carboxylic acid **177**. A few other variants of this approach leading to benzo[1,2,3]thiadiazole-7-carboxylic acid **177** were reviewed by Kunz *et al.*[90]

Benzothiadiazoles **172** can also be obtained by the reaction of aromatic amines **178** with disulfur dichloride and by the treatment of the resulting benzodithiazole salt **179** with nitrous acid.

The so-called diazotation technique was used to prepare a variety of fused 1,2,3-thiadiazoles with other heteroaromatic rings. This will be described in detail in Chapter 4 of this book.

Reactions of thiocarbonyl compounds bearing an active methylene group at the α-position with azides represent an alternative way to generate α-diazothiocarbonyl compounds. Their heterocyclization leads to the formation of 1,2,3-thiadiazoles in very good yield.[4,91] In the reaction of 2-cyanothioacetamides **180**, in principle, both cyano-[92] and thiocarbamoyl[91] groups are able to react with arylsulfonyl azide to form either thiadiazoles **181** or 1-phenylsulfonyl-5-amino-1,2,3-triazole-4-carbothioamides **182**. The latter reaction could occur via a triazene intermediate. However, only 5-amino-substituted-1,2,3-thiadiazoles

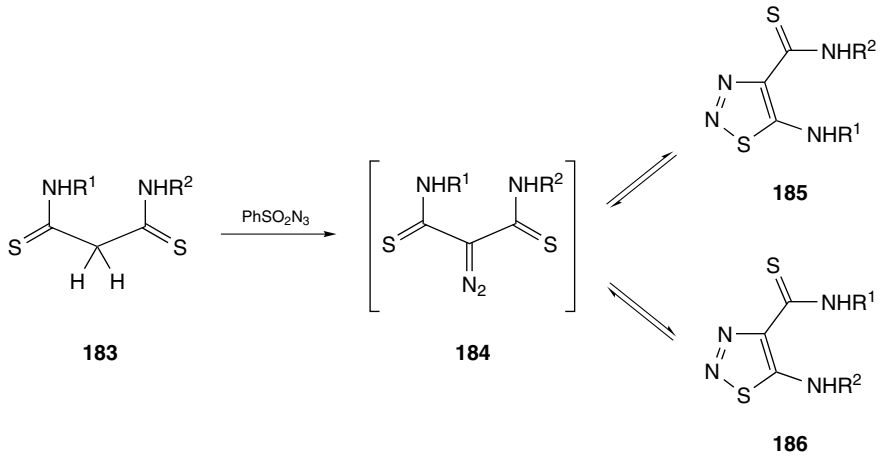


173 **174** **175** **176** **177** **178** **179** **172** **182** **180** **181**

181 were obtained in high yields from the reaction of a number of 2-cyanothioacetamides **180** with phenylsulfonyl azide.[93]

The good yield, smoothness and simplicity of this procedure allows us to recommend this as the method of choice for the preparation of 4-(substituted)carbonyl-5-amino-1,2,3-thiadiazoles **181**.

Reactions of malondithioamides **183** with phenylsulfonyl azide in the presence of a base leads to the generation of 2-diazomalondithioamide intermediates **184** for which cyclization can take place on either one of the thiocarbonyl groups to give isomeric 5-amino-1,2,3-thiadiazole-4-carbothioamides **185** and **186**.[94]



Monoalkyl-substituted malonthioamides **183** (R^1 = Alk, R^2 = H) are transformed under these conditions to form thiadiazoles **186** as the major products; cyclization of aryl derivatives of **183** (R^1 = Ar, R^2 = H) gives a mixture of **185** and **186** (ratio about 1:3). Reaction of dithioamides **183** (R^1 = 2-Py and COR, R^2 = H) with phenylsulfonyl azide leads selectively to 5-amino-substituted 1,2,3-thiadiazole-4-carbothioamides **186** in very good yield. In the case of the reaction of the *N*,*N*′-disubstituted malonthioamides **183**, the formation of an unseparable mixture of isomeric thiadiazoles **185** and **186** takes place. Thiadiazoles **185** and **186** are shown to be in equilibrium (see Chapter 3). Therefore, the ratio of the isomeric products **185** and **186** determined by ^{1}H NMR spectroscopy allows one to determine the equilibrium constants between these compounds. Indeed, the stability of the thiadiazole **185** increases in the following order for substituents R^1:

$$\text{alkyl} < \text{H} < \text{Ar} < \text{2-Py};$$

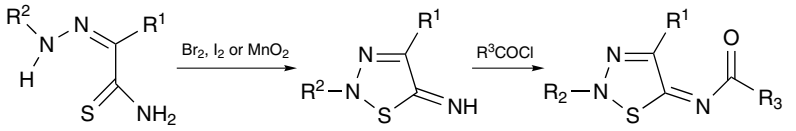
$$\text{Me} < \text{Et} < \text{Bz} < \text{cyclohexyl};$$

$$\text{4-MeO-C}_6\text{H}_4 < \text{4-Me-C}_6\text{H}_4 \sim \text{4-BrC}_6\text{H}_4 < \text{C}_6\text{H}_5.$$

One can use these series to predict the outcome of analogous reactions in which cyclization of diazothiocarbonyl compounds is involved.[93,94]

Treatment of α-thiocarbamoyl *N*-aryl hydrazones **187** (R^1 = CN, COR; R^2 = Ar) with bromine in acetic acid leads to 5-amino-2-aryl-1,2,3-thiadiazolium salts **188** in good yield. To prepare the corresponding 4-aryl derivatives **188** (R^1 = Ar, R^2 = Ar, Me), iodine and MnO_2 were successfully used as oxidizing reagents. However, the yields were lower when these oxidants were used to prepare compounds **188** bearing ester and amide functions at the 4-position of the ring.[95,96]

No diazo intermediate forms in this reaction that most probably occurs via a mechanism involving radical mechanism. The formation of the 1,2,3-thiadiazole



187 **188** **189**

R^1 = CN, COOAlk, COPh, $CONH_2$, Ph; R^2 = Alk, Ar; R^3 = Alk, Ar, NHAlk, NHAr

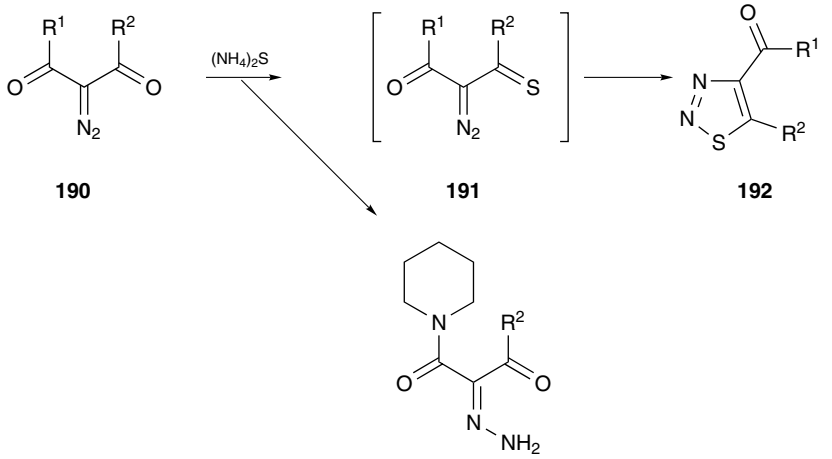
ring takes place here by intermolecular cyclization and, therefore, we can formally classify this approach for the preparation of 2-substituted thiadiazoles **188** as belonging to the Wolff type.

The final compounds **188** bearing amide functions are not particularly stable even as their salts with mineral acids. They can be stabilized by *N*-acylation or carbamoylation reactions with the formation of the carbonyl derivatives **189**.

1.3.2. Introduction of a C=S Bond in the α-position to a Diazo Group

2-Diazo-1,3-dicarbonyl derivatives **190** have been shown to react with various thionating reagents to generate diazocarbonyl intermediates **191** that spontaneously undergo cyclization to form 4-carbonyl-5-alkyl- or 5-aryl-1,2,3-thiadiazoles **192**.[5]

Among carbonyl groups, only the ketone function can react with ammonium sulfide to form a thioketone group. Ester and amide functions are not capable of reacting under these conditions and this allows to obtain thiadiazoles **192**, containing these moieties in the 4-position of the ring.

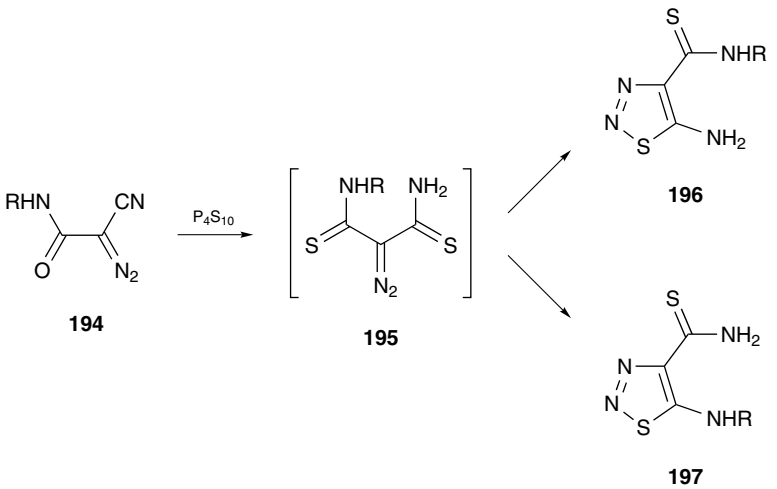


190 **191** **192**

193

The formation of hydrazones **193**, which results from the reduction of the diazo group, has been observed in the reaction of amide **190** (R^1 = piperidinyl).[5] Substituting ammonium sulfide by tetraphosphorous decasulfide or Lawesson's reagent allows one to involve an amide group in this reaction and to expand the scope of the Wolff synthesis. Thus, a variety of fused 1,2,3-thiadiazoles and a number of esters of 5-alkyl-1,2,3-thiadiazole-4-carboxylic acid were prepared in very good yields.[5,97]

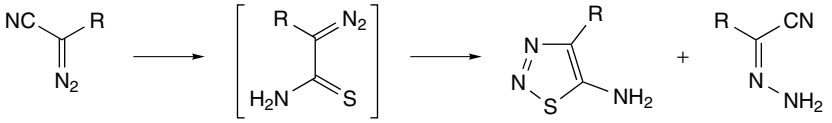
We have found no substantial difference in the results for the reaction of 2-diazo-2-cyanoacetamides **194** with both tetraphosphorous decasulfide and Lawesson's reagent. Both cyano and carboxamide groups of diazo compound **194** take part in the reaction to generate 2-diazomalondithioamide **195**. Again, cyclization can take place involving either thiocarbonyl group to form a mixture of isomeric thiadiazoles **196** and **197**, where the ratio **196:197** depends on the R substituent. Electron-accepting substituents R direct the reaction preferentially to 5-aminosubstituted 1,2,3-thiadiazoles **197**.[93]



194 **195** **196** **197**

The cyano group of α-diazonitriles **198** can also be transformed to an α-thiocarbamoyl moiety by the reaction of the nitrile function with hydrogen sulfide in the presence of a basic catalyst.[98,99] The transient diazothioacetamides **199** spontaneously rearrange to produce 5-amino-1,2,3-thiadiazoles **200**. Hydrazones of type **201** that result from the reduction of the diazo functionality are often isolated as by-products in these reactions, and, therefore, the yield of **200** is moderate in most cases. It is interesting to note that cyano-, carbonyl- and phosphoryl-substituted diazonitriles **198** can react with hydrogen sulfide in the absence of bases at ambient pressure to furnish thiadiazoles **200** exclusively in high yield.[100]

This synthetic method leading to 1,2,3-thiadiazoles is not only of academic interest, because it has been applied on an industrial scale to produce 5-amino-1,2,3-thiadiazole **200** (R = H) as a synthetic intermediate for pharmaceuticals and agrochemicals.[101]

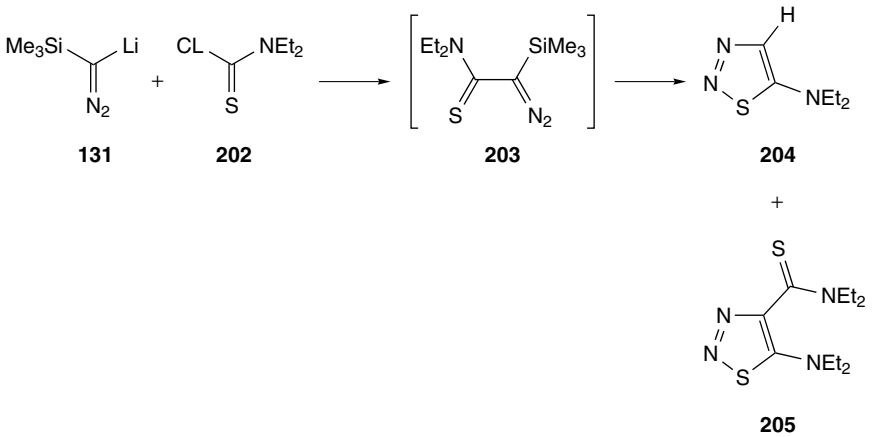


198 **199** **200** **201**

R = COOAlk, CONHR[1], CN, PO(OAlk)$_2$; R[1] = H, Alk, Ar

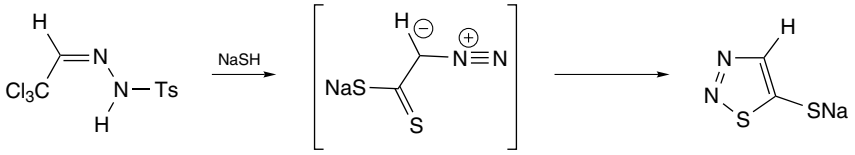
1.3.3. Simultaneous Introduction of Diazo and Thiocarbonyl Functions

The reaction of lithium trimethylsilyldiazomethane **131** with *N*,*N*′-diethylthiocarbamoyl chloride **202** at low temperature leads to a mixture of 5-amino-1,2,3-thiadiazoles **204** and **205** in rather low yields. It is believed that the first step of this synthetic process involves the generation of diazothioacetamide **203** followed by rapid cyclization to thiadiazoles **204**. The authors did not explain the mechanism for the formation of the second product **205**.[102]



131 **202** **203** **204** **205**

Sakai and coworkers proposed that the α-diazo dithioacetate intermediate **207** was generated by treatment of trichloroacetaldehyde tosylhydrazone **206** with sodium hydrosulfide.[103,104] Subsequently, the expected cyclization of diazothioacetate **207** affords sodium 1,2,3-thiadiazole-5-thiolate **59** in 84% yield. This method presents an alternative to the Hurd–Mori approach to 1,2,3-thiadiazol-5-thiol which is one of the intermediates in the synthesis of Cefuzoname™.

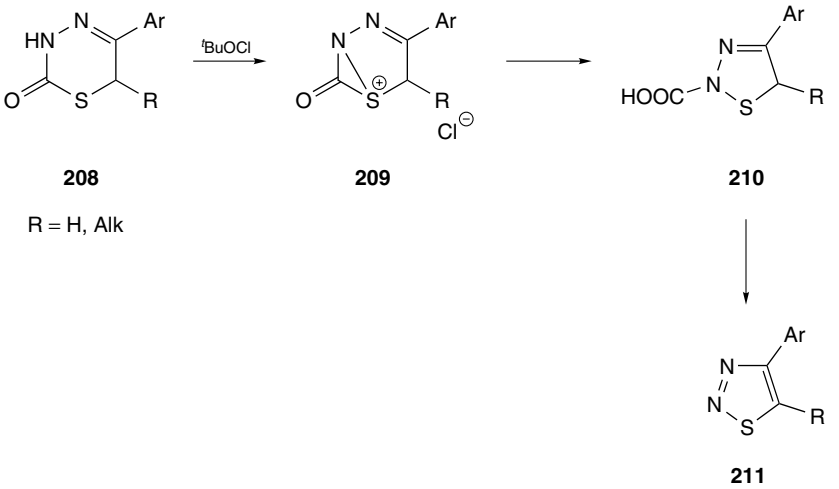


206 **207** **59**

The rearrangement of 5-mercapto-1,2,3-triazoles to 5-amino-1,2,3-thiadiazoles most probably proceeds via diazothioacetamides and can therefore be classified according to the Wolff method for the synthesis of 1,2,3-thiadiazoles. Because the preparation of 5-mercapto-1,2,3-triazoles occurs via the reverse rearrangement of 5-amino-1,2,3-thiadiazoles in basic medium, this method is only of academic interest.[5]

1.4. TRANSFORMATIONS OF OTHER SULFUR-CONTAINING HETEROCYCLIC COMPOUNDS

The 1,2,3-thiadiazole ring can also be obtained by the transformation of other sulfur-containing heterocycles. Thus, the ring contraction of 1,3,4-thiadiazin-2-ones **208** in the presence of *tert*-butyl hypochlorite gives 1,2,3-thiadiazole **211** in 25–85% of yield, probably in accordance with a mechanism involving intermediates **209** and **210**.[5]

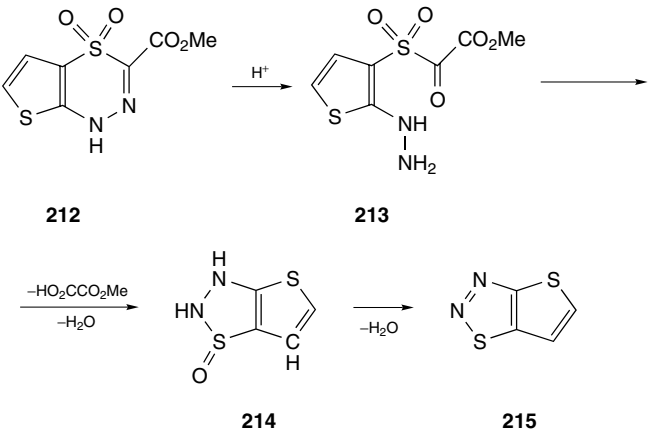


208 **209** **210** **211**

R = H, Alk

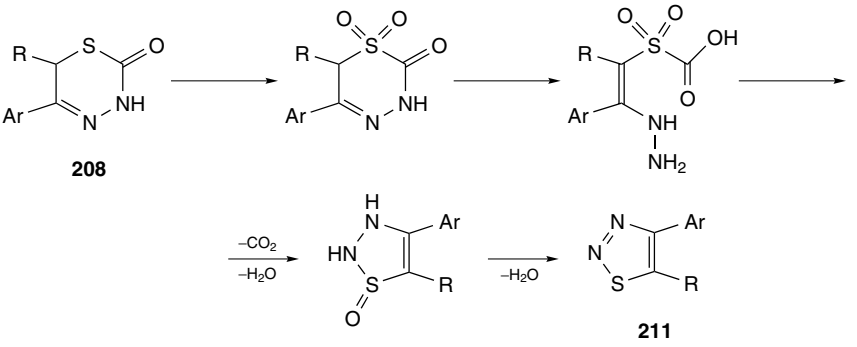
Stephens and Sowell expanded the scope of this reaction to prepare thienothiadiazole **215**.[105] They have found that when a suspension of thienothiadiazine dioxide **212** in a solution of acetic and aqueous sulfuric acid was heated to 100°, thienothiadiazole **215** was obtained in moderate yield.

A plausible mechanism for this reaction begins with the acid-catalyzed hydrolysis of the imine double bond of **212** to give the hydrazino intermediate **213**. Subsequent hydrolytic loss of the oxalate group and condensation of the hydrazine moiety with the resulting sulfinic acid could give the thienothiadiazole derivative **214**. In the presence of mineral acid, this intermediate could then undergo a Pummerer-type dehydration, similar to that found for the Hurd–Mori reaction to give the final product **215**. Though the yield of **215** is only moderate, the method

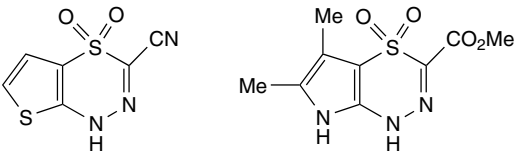


allows to prepare **215** in one pot, instead of the seven-step synthesis based on the Hurd–Mori reaction.[7]

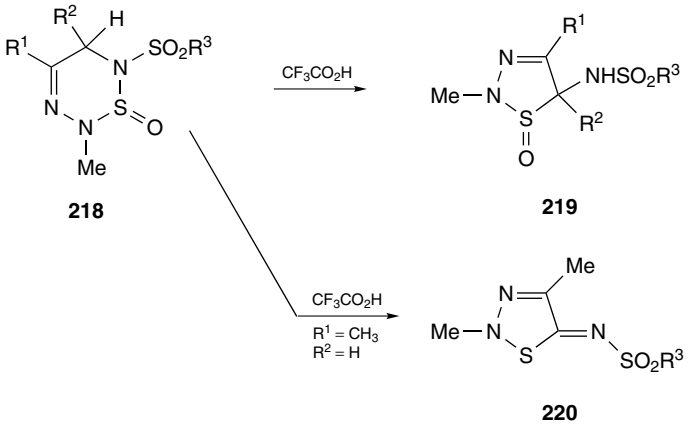
In the light of this work, the mechanism for the transformation of **208** could be reconsidered as including the oxidation of **208** as the first step to afford thiadiazine dioxide **216** which, similar to **213**, undergoes hydrolysis of the imine double bond. Subsequent loss of carbon dioxide and two molecules of water would then give the final product **211**.



Surprisingly, thiadiazine **216**, containing a cyano group instead of an ester function, and pyrrolothiadiazine **217** could not be transformed to the expected bicyclic products. Only degradation products were obtained as dark residues.[105]

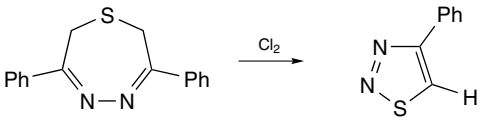


Sommer and Schubert have found that 5,6-dihydro-2H-1,2,3,6-thiatriazine 1-oxides **218** rearrange in the presence of trifluoroacetic acid to give Δ^3-1,2,3-thiadiazoline-1-oxides **219** including fused derivatives in which substituents R^2 and R^3 form a cyclohexyl ring. In a similar reaction of unsubstituted 5,6-dihydro-2H-1,2,3,6-thiatriazine 1-oxides **218** ($R^2 = H$), thiadiazolines **220** are obtained after loss of water. The authors proposed two reaction pathways for the formation of the ring-contraction products, one of them being similar to the transformations of thiadiazines **208** and **212**.[106]



218 **219** **220**

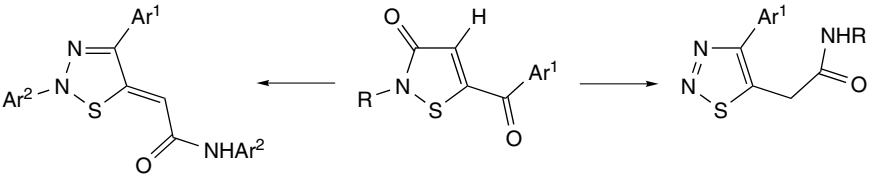
It has been shown that on treatment with chlorine, 2,7-dihydro-3,6-diphenyl-1,4,5-thiadiazepine **221** transforms to 4-phenyl-1,2,3-thiadiazole **222**.[5] The mechanism and scope of this reaction are unclear.



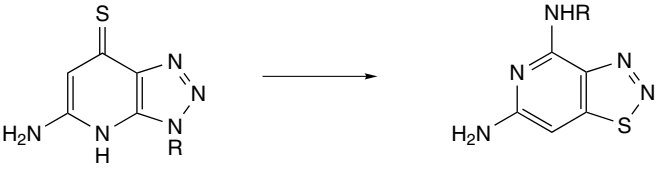
221 **222**

The reaction of 2-substituted-5-aroyl-3(2*H*)-isothiazolones **224** with hydrazines was found to give either 2,4-diaryl-1,2,3-thiadiazolidene **223** or 1,2,3-thiadiazolyl acetamides **225**, depending on the substituent R in the hydrazine molecule. The use of arylhydrazine furnished the compounds of type **223**; on the other hand, semicarbazide and unsubstituted hydrazine led to 1,2,3-thiadiazole **225**.[107] This rearrangement follows the Boulton–Katritzky scheme.[4]

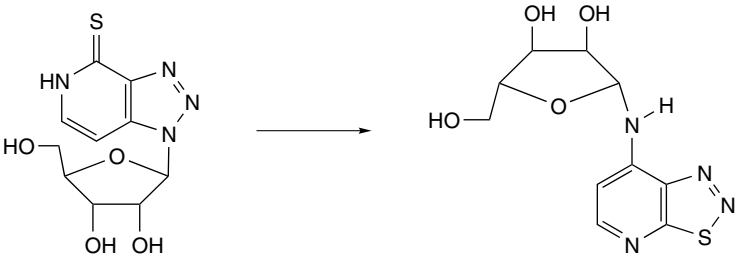
1,2,3-Thiadiazoles can also be prepared by transformation of 1,2,3-triazoles containing a thiocarbonyl group. Thus, in neutral solvents or simply by melting, 1,2,3-triazolo[4,5-*b*]pyridin-4(7*H*)-thiones **226** rearrange to 1,2,3-thiadiazolo[4,5-*c*]pyridines **227**.[5,108–110] It is interesting to note that the rearrangement of the 1-ribosyl derivative **228** proceeds faster than that of thione **226**.



223 **224** **225**



226 **227**



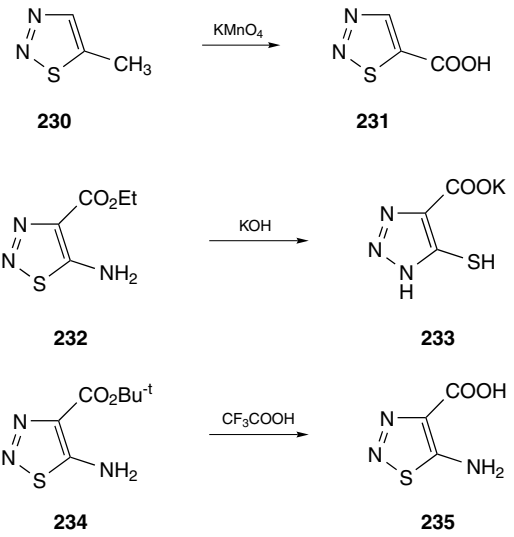
228 **229**

1.5. ELABORATION OF PREFORMED 1,2,3-THIADIAZOLES

A number of 1,2,3-thiadiazole derivatives are best prepared by transformations of the 4- and 5-substituents of a preformed thiadiazole ring. An overview of the methods to prepare various derivatives of 1,2,3-thiadiazole will be given in this section, arranged according to the type of substituents.

1.5.1. Carboxylic Acids

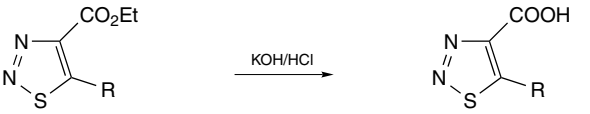
Oxidation of 5-methyl-1,2,3-thiadiazole **230** by potassium permanganate at 100°C in water affords 1,2,3-thiadiazole-5-carboxylic acid **231** in 51% yield.[21] 1,2,3-Thiadiazole-5-carboxylic acid can also be prepared by potassium permanganate oxidation of 5-furyl-1,2,3-thiadiazole-4-carboxylic acid, followed by selective decarboxylation, but here the yield is even lower.[111] The 1,2,3-thiadiazole ring is susceptible to oxidation, explaining the low yields. Therefore, the Hurd–Mori synthesis for the latter compound is preferable.[10]



230 **231** **232** **233** **234** **235**

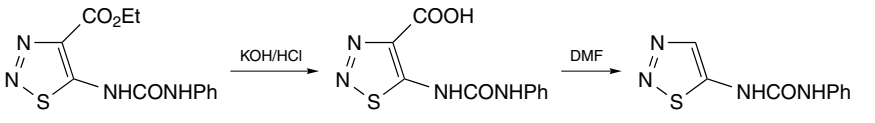
Because of the possibility of a Dimroth rearrangement, the saponification of esters of 5-amino-1,2,3-thiadiazole-4-carboxylic acid in basic solution can be accompanied by the formation of 5-mercapto-1,2,3-triazoles **233**.[112]

5-Amino-1,2,3-thiadiazole-4-carboxylic acid **235**, an intermediate in the latter reaction, was prepared by the same authors when they treated ester **234** with trifluoroacetic acid. Alkaline hydrolysis of ester groups was used without problems to prepare very good yields of 1,2,3-thiadiazole-4-carboxylic acids, bearing acylamino, ureido and mercapto groups at the 5-position of the ring.[112,113] Obviously, the introduction of carbonyl groups on the amino function decreases the lability of aminothiadiazoles towards bases.



236 R = SH, NHAc, NHCONHR[1] **237**

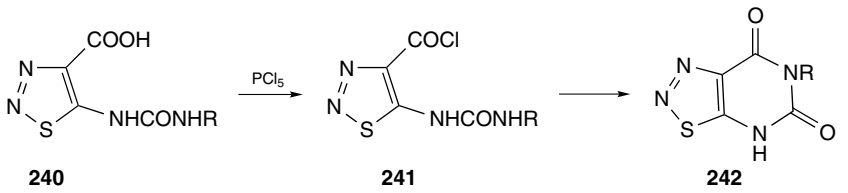
It is interesting to note that saponification of ester **238** with subsequent decarboxylation of primary formed acid **239** was used on an industrial scale to produce urea **63**,[5], which is the main component of the very soft and active cotton defoliant Thidazuron™.



238 **239** **63**

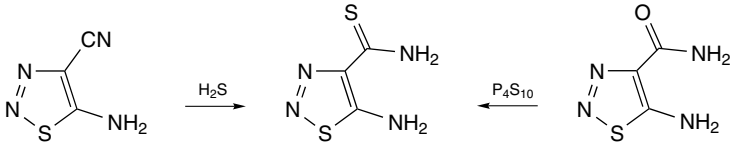
1.5.2. Functional Derivatives of Carboxylic Acids

Already, in earlier works, the esters, acid chlorides, amides, hydrazides, azides, thioamides and 1,2,3-thiadiazole-4-carbonitrile were shown to be formed in good yields by standard procedures starting from both 1,2,3-thiadiazole-4- and 5-carboxylic acids.[19,111] In the case of acid chloride **241**, bearing an urea moiety, subsequent cyclization occurs to afford pyrimido-[5,6-d]thiadiazoles **242**.



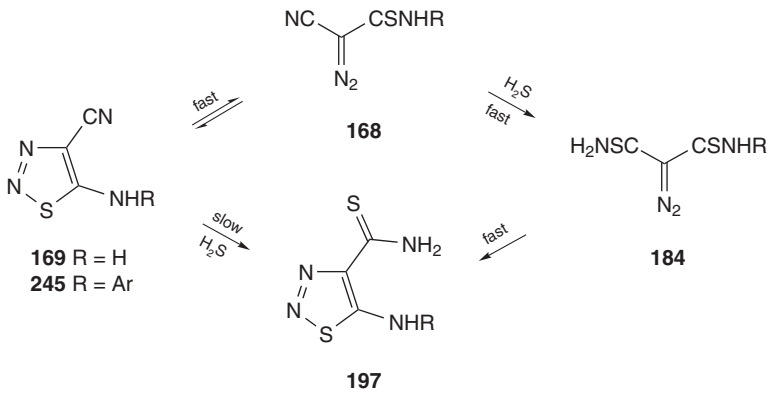
240 **241** **242**

5-Amino-1,2,3-thiadiazole-4-carbonitrile **169** readily reacts with hydrogen sulfide to give 5-amino-1,2,3-thiadiazole-4-carbothioamide **243** in high yield.[114,115] The same product is also prepared by the treatment of the more available 5-amino-1,2,3-thiadiazole-4-carboxamide **244** with tetraphosphorous decasulfide.[115,116]



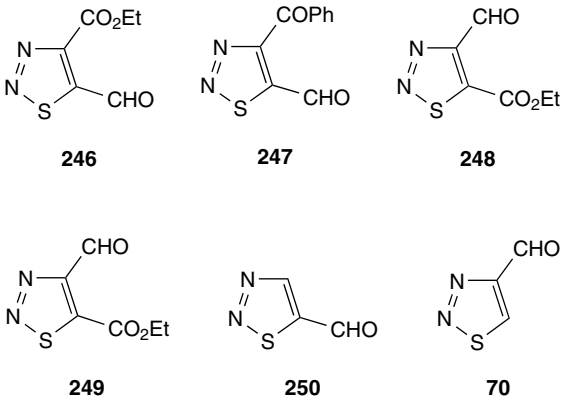
169 **243** **244**

Introduction of aryl substituents at the amino function of 5-amino-1,2,3-thiadiazole-4-carbonitrile has been shown to decrease the rate of the reaction with hydrogen sulfide considerably. If **169** reacts fast at 0°C, then the similar reaction of **245** (R = Ar) can be observed only at 60°C. We can rationalize the higher reactivity of a nonsubstituted compound by the existence of an equilibrium between **169** and the isomeric diazonitrile compound **168**. The latter, by analogy with other diazonitriles **194** (see Wolff method), reacts very fast with hydrogen sulfide. Further cyclization of diazomalonthioamide **184** occurs very fast, according to a heteroelectrocyclic mechanism.[86] In the case of **245** (R = Ar), the cyclic form may be stabilized by conjugation with the aromatic moiety, and this is in accordance with our data on the relative stability of 5-amino-1,2,3-thiadiazoles (see Chapter 3). It should be specially noted that only the reaction of nonsubstituted **169** leads to a single product. On the other hand, the reaction for *N*-substituted 5-amino-1,2,3-thiadiazoles **243** is accompanied by the rearrangement of compounds **197** to their isomers (see details in Chapter 3).



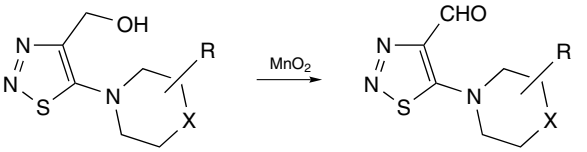
1.5.3. Aldehydes

The oxidation of a hydroxymethyl group to a carbaldehyde function was used by Shafiee to prepare ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate **246**, 5-formyl- 4-benzoyl-1,2,3-thiadiazole **247** and their regioisomers **248** and **249**.[17] 1,2,3-Thiadiazole-4-carbaldehyde **70** and 1,2,3-thiadiazole-5-carbaldehyde **250** were obtained from the corresponding hydrazone and oxime by acid-catalyzed hydrolysis.[18,117,118]

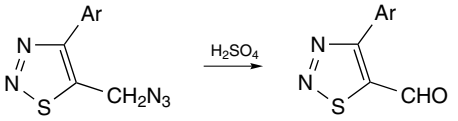


Recently, we prepared a series of 5-cycloalkylamino-1,2,3-thiadiazole-4-carbaldehydes **252** by the smooth oxidation of the corresponding carbinols **251** with active MnO_2. These compounds were shown to be good building blocks to prepare a number of new 1,2,3-thiadiazoles and 1,2,3-triazoles for biological screening.[119]

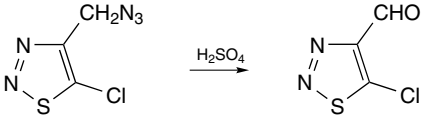
4-Aryl-1,2,3-thiadiazole-5-carbaldehydes **254** and 5-chloro-1,2,3-thiadiazole-4-carbaldehyde **256** were synthesized by the decomposition of the corresponding azidomethyl-1,2,3-thiadiazoles **253** and **255** in concentrated sulfuric acid.[120,121]



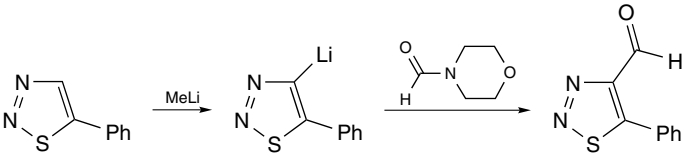
251 **252**



253 **254**



255 **256**



257 **258** **259**

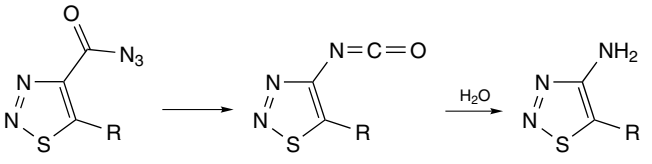
We have found that 5-phenyl-1,2,3-thiadiazole-4-carbaldehyde **259** is formed from 5-phenyl-1,2,3-thiadiazole **257** by the treatment of its 4-lithio derivative **258** with *N*-formylmorpholine in tetrahydrofuran at −70°C.[122]

1.5.4. Amino-1,2,3-Thiadiazoles

5-Amino-1,2,3-thiadiazoles are convenient chemical reagents for the synthesis of 5-ureido-1,2,3-thiadiazoles. Because the latter were found to be very active herbicides, possessing growth-regulating activity, and one of these derivatives was produced in industrial scale to defoliate cotton plants, a number of synthetic procedures for amino-1,2,3-thiadiazoles were described.[4–6]

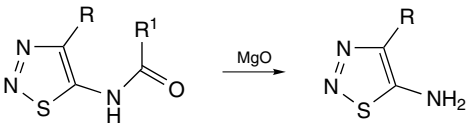
4-Amino-1,2,3-thiadiazole **262** could be prepared by Curtius rearrangement of the corresponding 1,2,3-thiadiazole-4-carbonyl azides **260** followed by the hydrolysis of the intermediate **261**.

Goerdeler and Gnad reported the synthesis of a number of 5-amino-1,2,3-thiadiazoles by the hydrolysis of the corresponding amides with magnesium



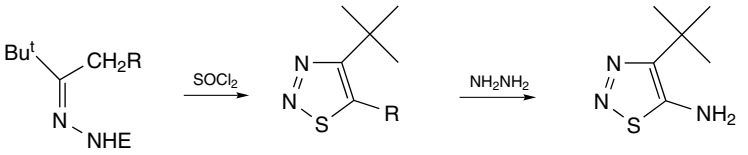
260 **261** **262**

oxide.[112] In contrast to the experiments with alkali, where hydrolysis is accompanied by the Dimroth rearrangement of the intermediate 5-amino-1,2,3-thiadiazoles, the reaction of **263** with the weaker base, MgO, goes cleanly to give only 5-amino-1,2,3-thiadiazole **264**.



263 **264**

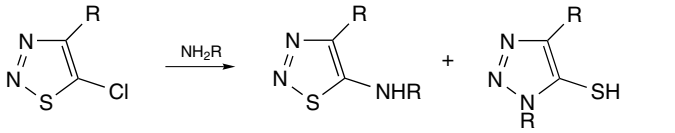
As a part of our program to synthesize thiapentalenes, the 4-*tert*-butyl-5-amino-1,2,3-thiadiazole **267** was obtained, starting from chloropinacolone, which is first converted into hydrazone **265** by successive treatment with potassium phthalimide and then by ethyl carbazate. The latter was transformed to 5-phtalimido-1,2,3-thiadiazole **266** by treatment with thionyl chloride. The phthalimide group is then removed by hydrazinolysis.[123]



265 **266** R = phthalimido **267**

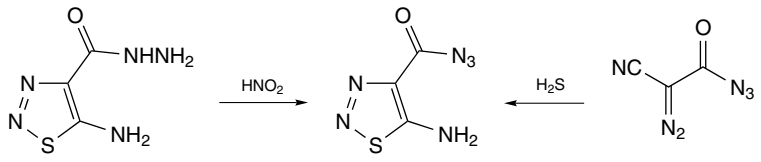
5-Amino-1,2,3-thiadiazole and 5-arylamino-1,2,3-thiadiazoles were prepared in good yield by the nucleophilic substitution of 5-chloro-1,2,3-thiadiazoles by liquid ammonia or anilines, respectively.[101,123] It has been shown that the reaction of the 5-chloro-1,2,3-thiadiazoles with aliphatic amines and hydrazine is accompanied by the formation of the Dimroth-rearrangement products, namely, 5-mercapto-1,2,3-triazoles, and by other by-products.

The ratio of thiadiazole **269:** triazole **270** has been shown to depend on the polarity of the solvent used in this reaction. Thus, triazole **270** was formed when compound **268** was treated with isopropylamine in dimethylformamide DMF. On



the contrary, when the reaction was carried out in chloroform or in hexane, only thiadiazole **269** was obtained.[124]

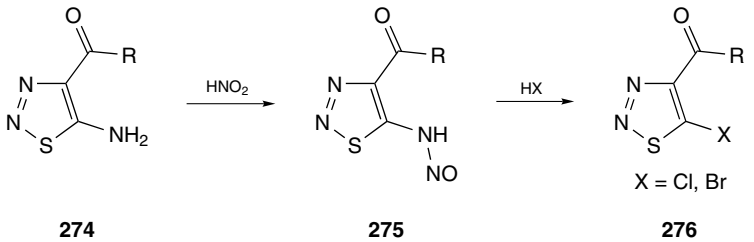
1,2,3-Thiadiazole **272** bearing both an amino and a carboxazide group was prepared by the treatment of 5-amino-1,2,3-thiadiazole-4-carbohydrazide **271** with HNO_2. This compound was also prepared by the reaction of diazonitrile carbonylazide **273** with hydrogen sulfide. We draw attention to the very highly explosive nature of diazo compound **273**.[5]



Together with the modifications of the Wolff synthesis, the methods outlined above provide an efficient approach to various amino-1,2,3-thiadiazoles.

1.5.5. Halo Derivatives

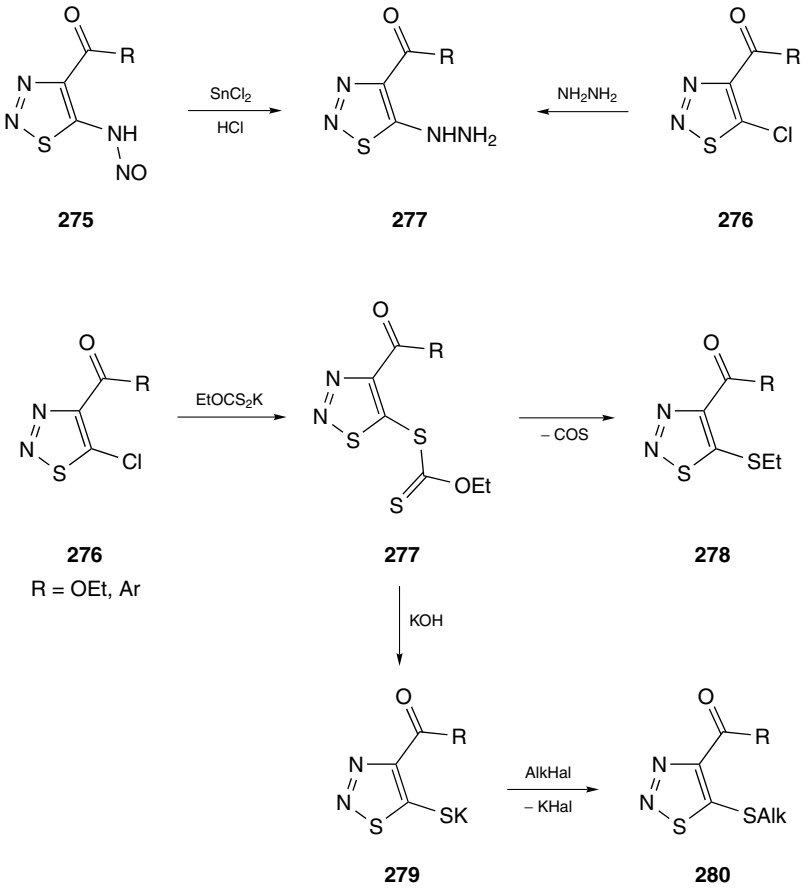
Similar to many other heterocyclic amines, 5-amino-1,2,3-thiadiazoles form isolable 5-nitrosylamino-1,2,3-thiadiazoles **275** by reaction with sodium nitrite in hydrochloric acid. Treatment of the latter with concentrated hydrochloric or hydrobromic acid affords 5-chloro- or 5-bromo-1,2,3-thiadiazoles **276** in high yields.[112]



Alternative ways to obtain 5-halo-1,2,3-thiadiazoles are the Hurd–Mori and Pechmann approaches. However, the latter method leads to the formation of a mixture of 1,2,3-thiadiazoles and 1,3,4-thiadiazoles, limiting its importance.[6]

1.5.6. 5-Hydrazino-, 5-Mercapto-1,2,3-Thiadiazoles and 5-Sulfide Derivatives

The reduction of 5-*N*-nitrosylamino-1,2,3-thiadiazoles **275** with stannous chloride in hydrochloric acid leads to 5-hydrazino-1,2,3-thiadiazoles **277** in moderate yield.[124] The same compounds **277** can also be prepared from 5-chloro-1,2,3-thiadiazoles **276** by treatment with two equivalents of hydrazine hydrate.[125]

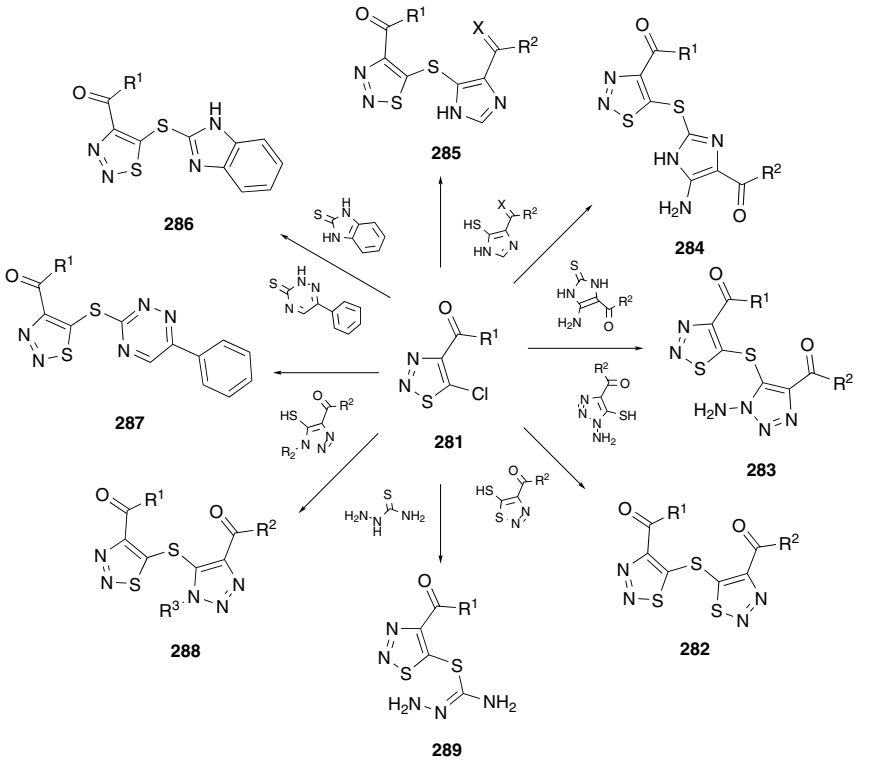


5-Chloro-1,2,3-thiadiazoles **276**, bearing electron withdrawing-acyl and ester groups at the 4-position are also able to react with potassium ethyl xanthate to afford 5 − *S*-dithiocarbonates **277**. These compounds **277** were shown to be very

labile, and they readily lost carboxysulfide to give 5-ethylthio-1,2,3-thiadiazoles **278**. On the other hand, *in situ* treatment of xanthate **277** with an ethanolic solution of potassium hydroxide afforded 1,2,3-thiadiazole-5-thiolates **279** that could be transformed to sulfides **280** by treatment with alkyl halides.[113]

1,2,3-Thiadiazole-4-thiolates were synthesized in good yields by the hydrolysis of the corresponding sulfides prepared by Lee and coworkers using the Hurd–Mori reaction.[20]

We have prepared a large series of bishetaryl sulfides, containing thiadiazole, triazole, imidazole and other heterocyclic systems by the reaction of 5-halo-1,2,3-thiadiazoles with the corresponding thiols.[126]



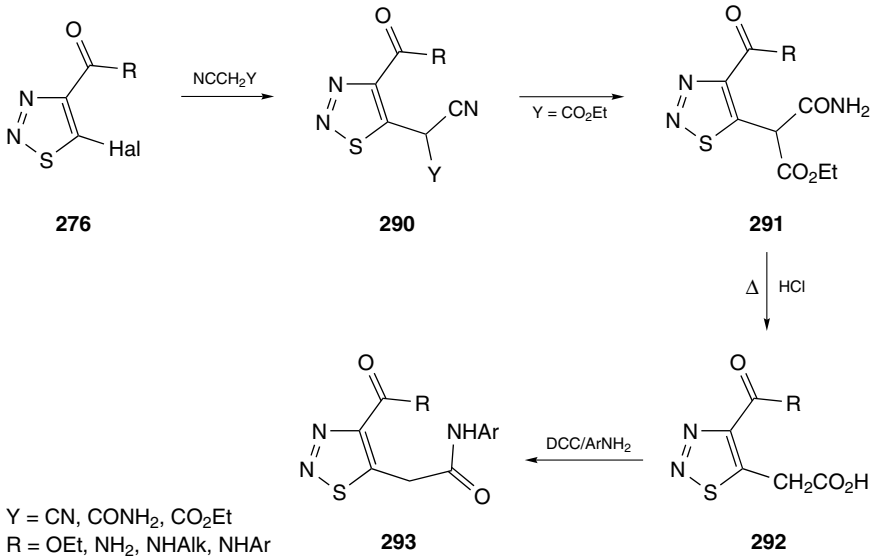
R^1 = OEt , NH_2 , NHMe , NHAr; R^2 = OEt, NH_2, NHMe ; R^3 = H, CH_2Ph ,Me ;
X = O,S

1.5.7. 2-(1,2,3-Thiadiazol-5-yl)acetic Acid Derivatives

The substitution of the chlorine atom in 5-chloro-1,2,3-thiadiazoles by *C*-nucleophiles requires activation either (1) by the introduction of an electron-withdrawing group at the 4-position or (2) by the preliminary transformation of 5-chloro-1,2,3-thiadiazoles to quaternary salts by N-alkylation with Meerwein's

reagent. The latter method is of importance in the synthesis of 1,2,3-thiadiazole ylids and thiazapentalenes (see chapter 4).

5-Halo-1,2,3-thiadiazoles **276** bearing ester or amide functions at the 4-position of the ring have been found to react with activated methylenes to give a number of esters of 2-(1,2,3-thiadiazol-5-yl)acetonitrile **290**, which were isolated as their sodium salts. They were transformed to various derivatives of 2-(1,2,3-thiadiazol-5-yl)acetic acid **291–293** as shown below.[127]



276 **290** **291** **292** **293**

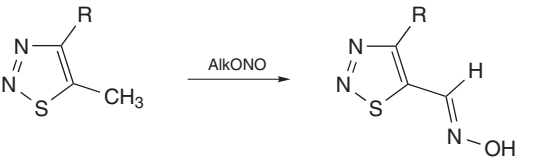
The Pechmann synthesis allows one to prepare ethyl 2-(1,2,3-thiadiazol-5-yl)acetate in 10% yield only.[5]

1.5.8. Alkenyl-1,2,3-Thiadiazoles

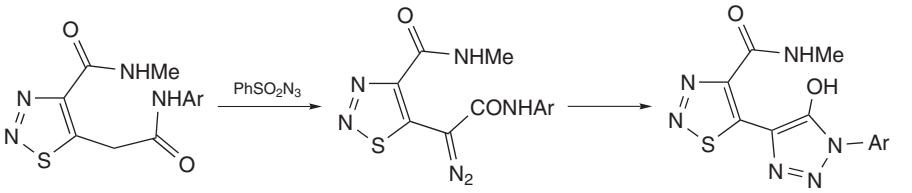
The reaction of either 5-ethyl- or 4-ethyl-1,2,3-thiadiazoles with *N*-bromosuccinimide, followed by treatment with a base, leads to the corresponding alkenyl-1,2,3-thiadiazoles.[128–131] These compounds were subjected to cycloaddition and polymerization reactions.

1.5.9. 5-Hydroxyiminomethyl- and 5-Diazomethyl-1,2,3-Thiadiazoles

The 1,2,3-thiadiazolyl group behaves as an electron acceptor and, in consequence, the 5-methyl- and 5-carbamoylmethyl-substituted derivatives show appreciable CH-acidity. The former compounds **294** can react with alkyl nitrite and a base to form 5-hydroxyiminomethyl-1,2,3-thiadiazoles **295**.[5,132] Compounds **296**,



294 R = H, Ar **295**

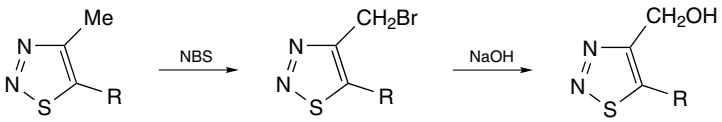


296 **297** **298**

which are even more acidic, undergo the diazo-transfer reaction with phenylsulfonyl azide to give diazo compounds **297**, which spontaneously cyclize to form conjugated 1,2,3-thiadiazoles **298**.[126,133]

1.5.10. 4-Hydroxymethyl-1,2,3-Thiadiazoles

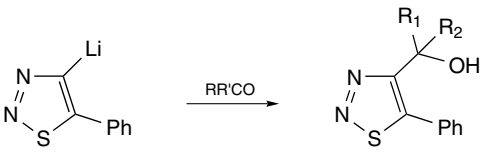
A series of 4-hydroxymethyl-1,2,3-thiadiazoles **301** were obtained by a two-step synthesis from 4-methylthiadiazoles **299** by bromination with *N*-bromosuccinimide, followed by alkaline hydrolysis.[17]



299 **300** **301**

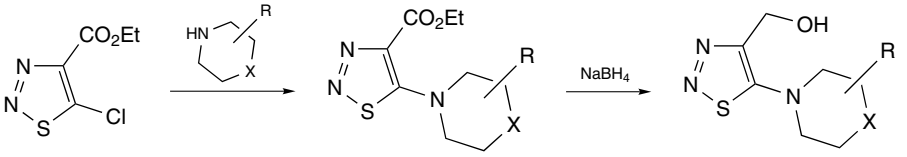
R = CO_2Et

The stable 4-lithio-5-phenyl-1,2,3-thiadiazole salt **258** reacted with aldehydes and ketones to give derivatives of 4-oxymethyl-1,2,3-thiadiazoles **302** in rather good yields.[134]



258 **302**

We have found that the ester group in thiadiazoles **303** could be selectively reduced with sodium borohydride to give oxymethyl derivatives **251**.[132,135] Thus, we have shown that the thiadiazole ring is stable under the conditions of the reduction, in contrast to the work of Pain and Slack,[21] who observed ring degradation in their attempts to reduce 1,2,3-thiadiazole-4-carboxylate in similar conditions.

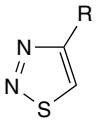


276 **303** **251**

1.6. TABLES

Yields, melting points (boiling points indicated by asterisk), data proving the structure (other data), method of preparation (A—Hurd–Mori reaction, B—Pechmann synthesis, C—cycloaddition of diazocompounds to C=S bond, D—Wolff method, E—elaboration of preformed thiadiazoles) and references for the compounds of the most important classes are included in the following tables.

TABLE 1.1. 4-ALKYL(ARYL)-1,2,3-THIADIAZOLES

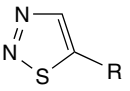


R	Yield (%)	mp (°C)	Other Data	Method	Reference
4-Biphenyl	95	—	NMR, MS	A	8
2-Bromophenyl	100	—	NMR, MS	A	8
3-Bromophenyl	100	—	NMR, MS	A	8
4-Bromophenyl	96	—	NMR, MS	A	8
n-Butyl	20	51–54	—	A	41
Buta-1,3-dien-1-yl	52	—	NMR	A	131
4-Chlorophenyl	91	136–137	NMR, MS	A	44
3-Cyanomethylcyclobutyl	60	Oil	NMR, MS	A	35
Cyclohexyl	27	Oil	NMR, MS	A	44
Dichloromethyl	39	76–80*	NMR, MS	A	22
3,4-Dichlorophenyl	92	87–89	NMR, MS	A	44
3,5-Di(1,2,3-thiadiazol-4-yl)phenyl	91	228	NMR, MS	A	24
Ethyl	4	Oil	NMR, MS	A	44
Ethenyl	69	43–44	NMR	A	131
4-Methoxyphenyl	100	—	NMR, MS	A	8
4-Methoxyphenyl	76	91–93.5	NMR, MS	A	44

TABLE 1.1 (*continued*)

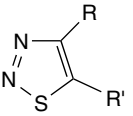
R	Yield (%)	mp (°C)	Other Data	Method	Reference
4-Methylphenyl	51	74–76	NMR, MS	A	44
Penta-1-yn-3-en-1-yl	37	70	NMR	A	131
Phenyl	64	77–78	—	A	10
Phenyl	77	75–77	NMR, MS	A	44
1-Propen-1-yl	8	—	NMR	E	128
n-Propyl	21	30–33	MS	A	41
i-Propyl	87	54–55	NMR	A	16
Triphenylphosphoniummethyl	62	245–250	NMR	A	131
1,2,3-Thiadiazol-4-yl	85	208	NMR, MS	A	24
3-(1,2,3-Thiadiazol-4-yl)phenyl	89	141–142	NMR, MS	A	24
3,4,5-Trimethoxyphenyl	16	91–93	NMR, MS	A	44
4-(1,2,3-Thiadiazol-4-yl)phenyl	95	212	NMR, MS	A	24

TABLE 1.2. 5-ALKYL(ARYL)-1,2,3-THIADIAZOLES



R	Yield (%)	mp (°C)	Other Data	Method	Reference
Benzyl	83	80–85*	NMR	B	78
1-Bromobutyl	79–86	—	NMR	A	130
1-Bromoethyl	79–86	—	NMR	A	130
Bromomethyl	79–86	—	NMR	A	130
1-Buten-4-yl	53	—	NMR, MS	A	130
Butyl	60	52*	NMR	A	130
Cyclohexyl	70	105–110*	NMR	B	78
3,7-Dimethyl-1,6-octadien-3-yl	67	125–135*	NMR	B	78
Ethenyl	55	—	—	A	129
Ethoxyphenyl	67	70–75*	NMR	B	78
Ethyl	59	46*	NMR	A	130
5-Furyl	83	33–35	NMR	B	78
Methyl	50	91	—	E	2
Nonyl	84	65–75*	NMR	B	78
Phenyl	53	—	—	E	2
Phenyl	49	42–46	NMR, MS	A	12
Phenyl	90	50.5–51.0	NMR	B	78
2-Phenylethyl	40	98–100	NMR	B	78
Propyl	48	50*	NMR	A	130
1-Propen-3-yl	78	45–48*	NMR, MS	A	130
6-Pyridyl	69	91–92	NMR	B	78

TABLE 1.3. 4,5-DI(ALKYL, ARYL)SUBSTITUTED-1,2,3-THIADIAZOLES

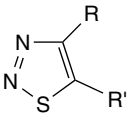


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Aminophenyl	4-Aminophenyl	95	236	NMR, MS	A	44
Benzyl	Phenyl	12	—	NMR, MS	E	134
4-Chlorophenyl	Azidomethyl	67	160	NMR	E	120
4-Chlorophenyl	Bromomethyl	42	140	NMR	E	120
4-Chlorophenyl	Dibromomethyl	21	147	NMR	E	120
4-Chlorophenyl	Methyl	79	—	NMR, MS	A	8
2,4-Dimethoxy-phenyl	4-Methoxy-phenyl	45	90–91.5	NMR, MS	A	44
4-Dimethyl-amino-phenyl	4-Dimethyl-amino-phenyl	72	152.5–154.5	NMR, MS	A	44
Ethenyl	Methyl	67	33	NMR	E	128
Ethenyl	1-Propen-1-yl	—	—	—	A	129
Ethyl	1-Methoxyethyl	70	35*	NMR	E	128
4-Ethylamino-phenyl	4-Ethylamino-phenyl	44	96.5–98	NMR, MS	A	44
4-Fluorophenyl	Phenyl	62	106	NMR	A	12
2-Furyl	4-Methoxyphenyl	31	80.6–82	NMR, MS	A	44
2-Furyl	4-Methoxyphe-nyloxy	76	45–55*	NMR	E	51
H	1-Buten-1-yl	53	45–48*	NMR, MS	E	130
H	1-Propen-1-yl	78	35*	NMR, MS	E	130
4-Methoxyphenyl	2-Methylphenyl	88	93–94	NMR	A	13
4-Methoxyphenyl	4-Methoxyphenyl	60	80–82	NMR, MS	A	44
4-Methoxyphenyl	4-Nitrophenyl	75	136	NMR	A	12
4-Methoxyphenyl	Phenyl	65	81.5–82.5	NMR, MS	A	44
4-Methylthio-phenyl	4-Methoxyphenyl	63	117–118.5	NMR, MS	A	44
Methyl	2-Cyanomethyl-1-cyclopropyl	56	Oil	NMR, MS	A	35
Methyl	Cyclohexyl	36	Oil	NMR, MS	A	44
Methyl	Ethyl	61	35–37	MS	A	41
Methyl	Ethenyl	44	29–32	NMR	E	128
Methyl	Ethenyl	79	—	—	A	129
Methyl	Ethenyl	44	32–35*	NMR, MS	E	130
Methyl	Methyl	38	Oil	NMR, MS	A	44
Methyl	Phenyl	64	100	NMR, MS	E	134
Methyl	Propyl	59	51–54	MS	A	41
4-Nitrophenyl	Bromomethyl	13	184	NMR	E	120
4-Nitrophenyl	Dibromomethyl	15	30	NMR	E	120
4-Nitrophenyl	4-Nitrophenyl	60	185–186.5	NMR, MS	A	44
Phenyl	Azidomethyl	68	114	NMR	E	120
Phenyl	Benzo[1,3]oxol-5-yl	65	107–109	NMR, MS	A	44
Phenyl	Benzotriazol-1-yl	24	—	NMR	E	51

TABLE 1.3 (*continued*)

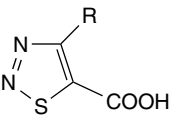
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Phenyl	Bromomethyl	47	101	NMR	E	120
Phenyl	4-Fluorophenyl	87	84	NMR	A	12
Phenyl	2-Methoxyphenyl	89	126	NMR	A	13
Phenyl	4-Methoxyphenyl	82	56.5–58	NMR, MS	A	44
Phenyl	2-Naphthyloxy	11	—	NMR	E	51
Phenyl	Phenoxy	45	101–102	NMR	E	51
Phenyl	Phenyl	69	93–94	—	A	10
Phenyl	Phenyl	72	94	—	A	12
Phenyl	Phenyl	69	93	NMR	A	13
Trimethylsilyl	*t*-Butyl	82	115	—	B	76

TABLE 1.4. 1,2,3-THIADIAZOLE-4-CARBOXYLIC ACIDS



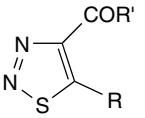
R	Yield (%)	mp (°C)	Other Data	Method	Reference
Amino	—	250	—	E	112
Carboxy	—	98	—	E	2
Carboxymethyl	56	192	NMR	E	133
H	33	227–228	—	A	10
H	—	228	—	E	2
Methyl	—	113	—	E	2
Phenoxymethyl	93	171–172	—	E	110
Phenyl	—	157	—	E	2
Phenyl	45	140–145	NMR, MS	E	134
Phenylcarbonyl	65	248	—	E	112
Phenylsulfonamido	—	260	—	E	112

TABLE 1.5. 1,2,3-THIADIAZOLE-5-CARBOXYLIC ACIDS



R	Yield (%)	mp (°C)	Other Data	Method	Reference
1,3-Butadien-1-yl	90	150–152	NMR	A	131
Ethenyl	70	160–162	NMR	A	131
H	51	104–106	—	E	21

TABLE 1.6. 4-CARBONYL DERIVATIVES OF 1,2,3-THIADIAZOLE: FUNCTIONAL DERIVATIVES OF ACIDS, ALDEHYDES AND KETONES

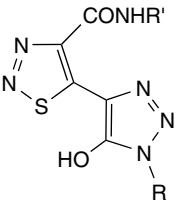


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Amino	*N*-Bromoamino	85	117	NMR, MS	C	94
Amino	Phenylamino	83	124	NMR, MS	C	94
4-Aminophenyl-sulfonamido	Ethoxy	81	—	__	E	112
Benzylamino	Methylamino	98	139	NMR	E	124
Bromo	Amino	—	156	NMR	E	124
Bromo	Methylamino	65	156	NMR	E	124
1-Bromo-1-phenoxymethyl	Ethoxy	92	74.5–76	__	E	110
t-Butyl	Allyl	77	—	NMR, MS	C	97
n-Butylamino	Methylamino	98	114	NMR	E	124
t-Butylamino	Methylamino	94	80	NMR	E	124
Carboxymethyl	Methylamino	60–65	210–212	__	E	133
Chloro	Amino	95	131	NMR	E	124
Chloro	Ethoxy	73	25	__	E	112
Chloro	Methylamino	73	83	NMR	E	124
Cyclohexylamino	Methylamino	99	130	NMR	E	124
Cyclopentyl	Allyl	89	—	NMR, MS	C	97
Dimethylamino	Amino	99	158	NMR	E	124
Dimethylamino	Ethoxy	87	77	NMR	E	124
Diethylamino	Methylamino	99	66	NMR	E	124
Dimethylamino	Methylamino	99	112	NMR	E	124
2,6-Dimethyl-morpholin-4-yl	Ethoxy	85	82–84	__	E	119
2,6-Dimethyl-morpholin-4-yl	H	53	58	NMR, MS	E	119
Ethoxycarbonyl	Ethoxy	—	—	__	C	27
Ethoxycarbonyl	Ethoxy	50	49–51	__	E	21
Ethyl	Allyl	94	—	NMR, MS	C	97
Ethyl	Benzyl	84	—	NMR, MS	C	97
Ethyl	*t*-Butyl	89	—	NMR, MS	C	97
Ethyl	Methyl	95	—	NMR, MS	C	97
Ethyl	2-Trimethylsilylethyl	88	—	NMR, MS	C	97
Formyl	Ethoxy	90	38–40	__	E	110
Formyl	Methoxy	47	45–46	NMR, MS, X-Ray	E	118
H	Amino	71	220–222	__	E	21
H	Amino	95	219–220.5	__	E	111
H	Azido	82	113–114	__	E	110

TABLE 1.6 (*continued*)

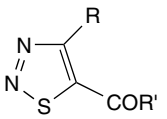
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
H	Chloro	95	52–54	—	E	21
H	Diethylamino	68	85–89	—	E	21
H	Ethoxy	20	86–86.5	—	A	10
H	Ethoxy	48	87–88	—	E	21
H	Ethoxy	59	88–90	—	E	110
H	H	62	86–87	—	A	18
H	Hydrazino	74	214	—	E	21
H	Hydrazino	93	210	—	E	110
H	Methoxy	55	89–90	—	E	21
H	Phenylamino	71	162–163	—	E	21
H	Phenylsulfonyl	—	219–222	—	E	21
H	Thiosemicarbazid-4-yl	—	185–188	NMR, MS	E	21
Hydroxy	Ethoxy	40	64	—	E	112
Hydroxyethylamino	Amino	80	238	NMR	E	124
Hydroxyethylamino	Ethoxy	47	48	NMR	E	124
Hydroxyiminomethyl	Ethoxy	95	192–193	—	E	110
Methoxymethyl	Methoxy	79	48	NMR, MS, X-Ray	E	118
Methyl	Allyl	84		—	C	97
Methyl	Amino	87	118–121	—	E	21
Methyl	Ethoxy	35	—	—	E	2
Methyl	Hydrazino	79	152–153	—	E	21
1-Naphthylazo	Ethoxy	58	230	—	E	112
N-(4-Bromophenyl)-acetamido	Methylamino	67	234–235	—	E	133
N-(3-Chlorophenyl)-acetamido	Methylamino	90	234–235	—	E	133
N-(4-Chlorophenyl)-acetamido	Methylamino	73	245–247	—	E	133
N-(2,6-Dichloro-phenyl)acetamido	Methylamino	16	229–230	—	E	133
N-(2-Methoxy-phenyl)acetamido	Methylamino	70	202–203	—	E	133
N-(4-Methoxy-phenyl)acetamido	Methylamino	75	205–207	—	E	133
N-(4-Methyl-phenyl)acetamido	Methylamino	83	166	—	E	133
N-Phenylacetamido	Methylamino	56	192	—	E	133
Phenoxymethyl	Ethoxy	75	57–58	—	E	110
Phenyl	Ethoxy	42	—	—	C	2
Phenyl	Morpholino	—	80–81	NMR, MS	C	30
Phenyl	Phenyl	10	86.5–87	NMR, MS	E	134
Phenylamino	Methylamino	88	163	NMR, MS	E	94

TABLE 1.7. AMIDES OF 5-(5-HYDROXY-1,2,3-TRIAZOL-4-YL)-1,2,3-THIADIAZOLE-4-CARBOXYLIC ACID



R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Bromophenyl	Methyl	67	205–206	NMR	E	133
3-Chlorophenyl	Methyl	71	180–181	NMR	E	133
4-Chlorophenyl	Methyl	58	200–201	NMR	E	133
2,6-Dichlorophenyl	Methyl	70	166–167	NMR	E	133
2-Methoxyphenyl	Methyl	70	171–173	NMR	E	133
4-Methoxyphenyl	Methyl	73	226–228	NMR	E	133
Methyl	4-Bromophenyl	23	238–240	NMR	D	133
Methyl	3-Chlorophenyl	64	175	NMR	D	133
Methyl	4-Chlorophenyl	60	234–236	NMR	D	133
Methyl	2,6-Dichlorophenyl	62	243–245	NMR	D	133
Methyl	2-Methoxyphenyl	65	230–232	NMR	D	133
Methyl	4-Methoxyphenyl	42	204–205	NMR	D	133
Methyl	4-Methylphenyl	25	205–207	NMR	D	133
Methyl	Phenyl	47	183–185	NMR	D	133
4-Methylphenyl	Methyl	79	208–209	NMR	E	133
Phenyl	Methyl	67	195	NMR	E	133

TABLE 1.8. 5-CARBONYL DERIVATIVES OF 1,2,3-THIADIAZOLE: FUNCTIONAL DERIVATIVES OF ACIDS, ALDEHYDES AND KETONES



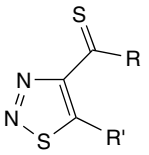
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Amidino	Phenyl	90	222–223	MS	E	136
1,3-Butadien-1-yl	Ethoxy	13	40–47	NMR	A	131

(*continued overleaf*)

TABLE 1.8. (*continued*)

R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Bromomethyl	Ethoxy	80	120–122*	NMR, MS	E	17
Bromomethyl	Phenyl	40	165–170*	NMR, MS	E	17
4-Chlorophenyl	H	57	136	NMR	E	120
Ethenyl	Ethoxy	91	Oil	NMR	A	131
H	H	49	Oil	NMR, MS	E	117
H	Hydrazino	55	151–152	—	E	21
H	Methyl	47	Oil	NMR, MS	E	117
H	Phenyl	67	80	NMR, MS	E	117
Hydroxymethyl	Methoxy	8	118–120*	NMR, MS	E	17
Methyl	Chloro	89	94–96*	NMR, MS	E	17
Methyl	Ethoxy	—	122–124*	NMR, MS	A	17
Methyl	Phenyl	90	140–142*	NMR, MS	E	17
4-Nitrophenyl	H	83	138	NMR	E	120
Phenyl	H	59	69	NMR	E	120
1-Phenyl-1,3-butadien-4-yl	Ethoxy	88	126	NMR	A	131
Triphenyl-phosphoniummethyl	Ethoxy	62	167	NMR	A	131

TABLE 1.9. 1,2,3-THIADIAZOLE-4-CARBOTHIOAMIDES

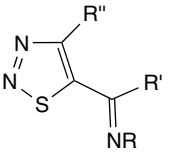


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Amino	Amino	34	171–172	NMR, MS	C	93
Amino	Amino	98	171–172	NMR, MS	E	93
Amino	Acetylamino	77	156	NMR, MS	E	93
Amino	Methylcarbamoyl	77	156	NMR, MS	E	93
Amino	2-Pyridylamino	35	235	NMR, MS	C	93
Methylamino	Amino	65	138–140	NMR, MS	C	93
Methylamino	Amino	98	138–140	NMR, MS	E	93
Methylamino	Methylamino	—	125	NMR, MS	C	94
Phenylamino	Amino	82	120–121	NMR, MS	C	93
Phenylamino	Amino	96	120–121	NMR, MS	E	93
Phenylamino	Phenylamino	80	189	NMR, MS	C	93
Phenylamino	Phenylamino	—	289	NMR, MS	C	94

TABLE 1.10. 4-CARBIMINO-1,2,3-THIADIAZOLES

R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Ethoxyamino	H	Methyl	63	—	NMR	E	38
Phenoxymethyl	Methyl	Methyl	26	—	NMR	E	38

TABLE 1.11. 5-CARBIMINO-1,2,3-THIADIAZOLES

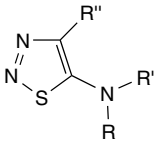


R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Hydroxy	H	Phenyl	49	212	NMR	E	132
Hydroxy	Methyl	H	61	194	NMR, MS	E	117
Hydroxy	Phenyl	H	78	229	NMR, MS	E	117
Methoxy	H	H	58.5	48	NMR	E	132
Phenylamino	H	H	78	184	NMR, MS	E	117
Phenylamino	H	Methoxy	80	141–142	NMR, MS	E	118
Phenylamino	Methyl	H	63	123	NMR, MS	E	117
Phenylamino	Phenyl	H	87	164	NMR, MS	E	117

TABLE 1.12. 4-AMINO-1,2,3-THIADIAZOLES

R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
H	Benzoyl	H	60	258.5–259	—	B	111
H	Benzoyl	Carboxy	63	225–230	—	B	111
H	Benzoyl	Ethoxycarbonyl	63	184.5–185	—	B	111
H	2-Chlorophenyl	H	48	97.5–98.5	—	B	111
H	2-Chlorophenyl	Ethoxycarbonyl	10	142.5144	—	B	111
H	3-Chlorophenyl	Ethoxycarbonyl	23	139–140	—	B	111
H	4-Chlorophenyl	Ethoxycarbonyl	25	149.5–150	—	B	111
H	Ethoxycarbonyl	H	59	216	—	B	111
H	Ethoxycarbonyl	Ethoxycarbonyl	82	42–44	—	B	111
H	Naphthyl	Ethoxycarbonyl	3	112.5–113	—	B	111
H	4-Nitrophenyl	Ethoxycarbonyl	48.5	172–173	—	B	111
H	Phenoxycarbonyl	H	28	237	—	B	111
H	Phenoxycarbonyl	Ethoxycarbonyl	35	155	—	B	111
H	Phenyl	Ethoxycarbonyl	3	91–92	—	B	111
H	Vinyl	Ethoxycarbonyl	26	140–141	—	B	111
Methyl	*N*-Methylthio carbamoyl	H	30	222	—	B	111

TABLE 1.13. 5-AMINO-1,2,3-THIADIAZOLES



R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
2,6-Dimethylmorpholin-1-yl		Hydroxymethyl	55	88–89	NMR, MS	E	[119]
Ethyl	Ethyl	H	22	Oil	NMR	C	102
H	Acetyl	Benzoyl	42	182	NMR	B	82
H	Acetyl	Cyano	77	125	NMR, MS	C	93
H	Acetyl	Dimethoxyphosphoryl	50	64	NMR	B	82
H	Acetyl	Diphenylphosphoryl	26	188	NMR	B	82

(*continued overleaf*)

TABLE 1.13 (*continued*)

R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
H	Acetyl	Ethoxycarbonyl	49	203	NMR	B	82
H	Acetyl	Ethoxycarbonyl	37	—	—	C	112
H	Acetyl	H	27	212	—	C	112
H	4-Anisoyl	Ethoxycarbonyl	27	160	NMR	B	82
H	Benzoyl	Benzoyl	32	181	NMR	B	82
H	Benzoyl	Benzoyl	26	186	—	C	112
H	Benzoyl	Carbamoyl	41	272	—	C	112
H	Benzoyl	Diethoxyphosphoryl	21	97	NMR	B	82
H	Benzoyl	Dimethoxyphenyl-phosphoryl	63	123	NMR	B	82
H	Benzoyl	Dimethoxyphos-phoryl	40	118	NMR	B	82
H	Benzoyl	Diphenylphosphoryl	25	191	NMR	B	82
H	Benzoyl	Ethoxycarbonyl	54	184	NMR	B	82
H	Benzoyl	Ethoxycarbonyl	58	181	—	C	112
H	Benzoyl	H	40	267	—	C	112
H	Benzoyl	Methyl	32	142	—	C	112
H	Benzoyl	Phenyl	35	172	—	C	112
H	Benzyl	H	7.3	93–95	NMR	B	82
H	3-Bromophenyl	H	37	165–166	NMR	B	82
H	4-Bromophenyl	H	13	187–189	NMR	B	82
H	Butanoyl	Ethoxycarbonyl	18	154	—	C	112
H	*t*-Butoxycarbonyl	Phenoxycarbonyl	60	182	—	C	112
H	4-Chlorophenyl	H	10	173–175	NMR	B	82
H	4-Dimethylamino-phenyl	H	23	168–170	NMR	B	82
H	H	H	84	152	—	E	112
H	H	Benzoyl	51	160	—	C	99
H	H	Benzoyl	71	160	—	E	112
H	H	*t*-Butoxycarbonyl	63	142	—	E	112
H	H	Carbamoyl	81	178–179	—	C	99
H	H	Cyano	51	165–166	—	C	99
H	H	Dimethylcarbamoyl	76	135–136	NMR, MS	C	100
H	H	Ethoxycarbonyl	34	125–126	—	C	99
H	H	Methoxycarbonyl	62	170–171	—	B	108
H	H	Methyl	78	102	—	E	112
H	H	*N*-Methylcarba-moyl	30	210–211	—	C	99
H	H	Pyridinylcarbamoyl	90	68	NMR, MS C		93
H	Hexadecanoyl	Ethoxycarbonyl	45	125	—	C	112
H	4-Methoxyphenyl	H	10	155–157	NMR	B	82
H	Methyl	Cyano	64	138	NMR, MS	C	93
H	4-Methylphenyl	H	36	172–174	NMR	B	82
H	Naphthyl	H	20	161–162	NMR	B	82
H	4-Nitrobenzoyl	Ethoxycarbonyl	51	288	—	C	112
H	4-Nitrobenzoyl	Ethoxycarbonyl	50	280	NMR	B	82
H	4-Nitrophenyl	H	20	206–209	NMR	B	82
H	4-Nitrophenoxy-carbonyl	Ethoxycarbonyl	50	231	—	C	112
H	4-Nitrophenyl-sulfonyl	Ethoxycarbonyl	80	171	—	E	112
H	Nitroso	Ethoxycarbonyl	84	127	—	E	112

TABLE 1.13 (*continued*)

R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
H	Phenoxycarbonyl	Benzoyl	35	181	—	C	112
H	Phenoxycarbonyl	Ethoxycarbonyl	—	156	—	C	112
H	Phenoxycarbonyl	H	38	242	—	C	112
H	Phenoxycarbonyl	Methyl	7	193	—	C	112
H	Phenyl	4-Chlorobenzoyl	77	174	—	E	79
H	Phenyl	Cyano	52	165–168	NMR, MS	C	93
H	Phenyl	H	42	180	NMR	B	82
H	Phenyl	H	88	163		E	124
H	Phenyl	Phenyl	53	80–83	NMR	B	82
H	Phenylsulfonyl	Carboxy	—	260	—	E	112
H	Phenylsulfonyl	Ethoxycarbonyl	81	—	—	E	112
H	Phenylsulfonyl	H	63	194	—	E	112
H	4-Toluoyl	Ethoxycarbonyl	34	158	NMR	B	82
Phenyl	Acetyl	H	—	162	—	E	1
Phenyl	Benzoyl	H	—	157	—	E	1
Phenyl	H	H	—	172	—	B	1
Phenyl	Nitroso	H	—	98	—	E	1
Propyl	Formyl	Methoxycarbonyl	79	107–108	NMR	D	88
Propyl	Formyl	Methyl	74	129–131	NMR	D	88
Propyl	H	Methoxycarbonyl	47	160–162	NMR	D	88

TABLE 1.14. 4-CHLORO-5-METHYL-1,2,3-THIADIAZOLES

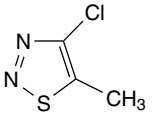
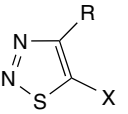
Compound	Yield (%)	mp (°C)	Other Data	Method	Reference
	—	100	—	A	[14]

TABLE 1.15. 5-HALO-1,2,3-THIADIAZOLES



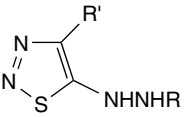
R	X	Yield (%)	Melting Point (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
t-Butyl	Cl	47	62–63	—	A	15
4-Chlorobenzoyl	Cl	35	114	—	B	137
4-Chlorobenzoyl	Cl	13	106–107	—	B	79
H	Cl	—	58–62*	NMR	A	50
H	Br	—	61–64*	—	A	50

(*continued overleaf*)

TABLE 1.15 (*continued*)

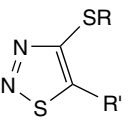
R	X	Yield (%)	Melting Point (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Methyl	Cl	80	182–183	—	A	14
4-Methylbenzoyl	Cl	30	97	—	B	137
4-Methylbenzoyl	Cl	52	56–58	—	B	79
3-Nitrobenzoyl	Cl	35	124	—	B	137
4-Nitrobenzoyl	Cl	60	113	—	B	137

TABLE 1.16. 5-HYDRAZINO-1,2,3-THIADIAZOLES



R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Acetyl	Carbamoyl	92	245	—	E	124
Acetyl	Ethoxycarbonyl	42	175	—	E	124
H	Carbamoyl	87	213	—	E	124
H	Ethoxycarbonyl	21	126	—	E	125
4-Methoxyphenyl	Carbamoyl	88	247	—	E	124
4-Nitrophenyl	Carbamoyl	86	244	NMR	E	124
Phenyl	Carbamoyl	62	199	—	E	124
Phenyl	Ethoxycarbonyl	62	222	—	E	124
Phenyl	Ethoxycarbonyl	32	211	—	E	125
Phenyl	Carbamoyl	80	230	NMR	E	124
Propyl	Carbamoyl	92	246	—	E	124

TABLE 1.17. DERIVATIVES OF 4-MERCAPTO-1,2,3-THIADIAZOLE

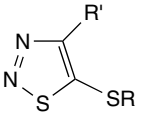


R	R′	Yield (%)	mp (°C)	Other Data	Method	Ref.
1	2	3	4	5	6	7
2-Cyanoethyl	Phenyl	66	—	—	A	20
2-(Ethoxycarbonyl)ethyl	*t*-Butyl	60	Oil	—	A	20
2-(Methoxycarbonyl)ethyl	*t*-Butyl	67	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	4-*t*-Butylphenyl	83	Oil	—	A	20

TABLE 1.17 (*continued*)

R	R′	Yield (%)	mp (°C)	Other Data	Method	Ref.
1	2	3	4	5	6	7
2-(Ethoxycarbonyl)ethyl	4-Chlorophenyl	65	71.5–73.5	—	A	20
2-(Ethoxycarbonyl)ethyl	Ethyl	65	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	4-Fluorophenyl	75	76.5–77.5	—	A	20
2-(Ethoxycarbonyl)ethyl	H	60	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	3-Methoxyphenyl	82	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	4-Methoxyphenyl	60	50.5–51.5	—	A	20
2-(Ethoxycarbonyl)ethyl	Methyl	65	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	4-Methylphenyl	88	68.5–69.5	—	A	20
2-(Ethoxycarbonyl)ethyl	2-Naphthyl	38	46.5–47.5	—	A	20
2-(Ethoxycarbonyl)ethyl	Phenyl	95	57.5–58.5	—	A	20
2-(Ethoxycarbonyl)ethyl	2-Thienyl	45	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	Thiepin-2-yl	65	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	3,4,5-Trimethoxyphenyl	35	27.0–27.5	—	A	20
2-(Ethoxycarbonyl)methyl	4-*t*-Butylphenyl	78	62.5–63.5	—	A	20
2-(Ethoxycarbonyl)methyl	4-*t*-Butylphenyl	92	62.5–63.5	—	E	20
2-(Ethoxycarbonyl)methyl	4-Methylphenyl	75	68.5–69.5	—	A	20
2-(Ethoxycarbonyl)methyl	4-Methylphenyl	85	68.5–69.5	—	E	20
2-(Ethoxycarbonyl)-2-methylethyl	Benzyl	78	—	—	E	20
Ethyl	4-*t*-Butylphenyl	55	Oil	—	A	20
Ethyl	4-*t*-Butylphenyl	85	Oil	—	E	20
2-(Methoxycarbonyl)ethyl	Benzyl	60	Oil	—	A	20
2-(Methoxycarbonyl)ethyl	H	50	Oil	—	A	20
2-(Methoxycarbonyl)ethyl	2-Tetrahydropyranyl	40	Oil	—	A	20
2-(Methoxycarbonyl)ethyl	3-Trifluoro	48	Oil	—	A	20
Methyl	3-Trifluorophenyl	92	Oil	—	E	20
2-Propen-1-yl	4-*t*-Butylphenyl	90	Oil	—	E	20

TABLE 1.18. DERIVATIVES OF 5-MERCAPTO-1,2,3-THIADIAZOLE



R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
2-Amidrazono-*N*-phenyl-*S*-thiosemicarbazido	Phenylcarbamoyl	70	125–126	NMR	E	126
2-Amidrazono-*S*-thiosemicarbazido	Ethoxycarbonyl	62	215–216	NMR	E	126
4-Amino-5-carbamoyl-imidazol-2-yl	4-Chlorobenzoyl	72	285–287	NMR	E	126
4-Amino-5-(*N*-methyl-carbamoyl)imidazol-2-yl	Ethoxycarbonyl	60	>280	NMR	E	126

(*continued overleaf*)

TABLE 1.18 (*continued*)

R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
5-Amino-4-carbamoyl-imidazol-2-yl	Ethoxycarbonyl	68	197–199	NMR	E	126
5-Amino-4-ethoxycarbo-nylimidazol-2-yl	Ethoxycarbonyl	85	246–248	NMR	E	126
Benzimidazol-2-yl	Carbamoyl	67	242	NMR	E	126
Benzimidazol-2-yl	Ethoxycarbonyl	54	121–123	NMR	E	126
Bromo	Carboxy	—	180–182	NMR	E	113
Bromo	H	60	50–51	NMR	E	113
Butyl	H	67	49–51	NMR	E	103
4-Carbamoylimidazol-5-yl	Ethoxycarbonyl	85	281–282	NMR	E	126
4-Thiocarbamoylimidazol-5-yl	Ethoxycarbonyl	25	249–252	NMR	E	[126]
4-Carbamoyl[1,2,3-thiadiazol]-5-yl	Ethoxycarbonyl	72	183	NMR	E	126
4-Carbamoyl-[1,2,3-triazol]-5-yl	Ethoxycarbonyl	89	242–245	NMR	E	126
N,*N*-Diethylthiocarbamoyl	Dimethylamino	22	—	NMR	C	102
4-Ethoxycarbonyl[1,2,3-thiadiazol]-5-yl	Ethoxycarbonyl	85	167	NMR	E	126
4-Ethoxycarbonyl[1,2,3-triazol]-5-yl	Ethoxycarbonyl	80	210	NMR	E	126
Ethyl	Benzoyl	8	93–95	NMR	B	79
Ethyl	Carboxy	84	79–81	—	E	113
Ethyl	4-Chlorobenzoyl	25	110–112	NMR, MS	B	79
Ethyl	4-Chlorobenzoyl	—	106–107	—	E	113
Ethyl	Ethoxycarbonyl	78	50–51	—	E	113
Ethyl	H	60	65	NMR, MS	E	113
Ethyl	1-Hydroxy-1-phenylmethyl	86	63–65	MS	B	79
H	Aminocarbonyl	87	214	NMR	E	124
H	Ethoxycarbonyl	91	65	NMR	E	124
H	H	79	—	—	E	19
H	4-Methylphenyl	42	152–153	NMR	E	51
2-(Methoxycarbonyl)ethyl	H	34	—	—	A	19
Methoxypropionyl	Carboxy	84	112–113	MS	E	113
Methoxypropionyl	Ethoxycarbonyl	42	32–33	MS	E	113
Methoxypropionyl	H	43	100*	NMR, MS	E	113
Methyl	Methyl	87	—	NMR	A	42
4-[*N*-Methylcarbamoyl]-[1,2,3-thiadiazol]-5-yl	Ethoxycarbonyl	55	145	NMR	E	126
4-(*N*-Methylcarbamoyl)[1,2,3-triazol]-5-yl	Ethoxycarbonyl	69	253–255	NMR	E	126
Phenyl	4-Chlorophenyl	57	—	NMR	E	51
Phenyl	Methyl	94	—	NMR	A	42
Phenyl	4-Methylphenyl	68	—	NMR	E	51
Phenyl	2-Naphthyl	30	—	NMR	E	51
6-Phenyl[1,2,4-triazin]-3-yl	Ethoxycarbonyl	86	235–236	NMR	E	126
Potassium	4-Chlorobenzoyl	94	170–171	NMR	E	113
Potassium	Ethoxycarbonyl	83	216	—	E	113
Potassium	H	91	80–82	NMR, MS	E	113
Potassium	Potassium carboxylate	93	204	—	E	113

TABLE 1.18 (*continued*)

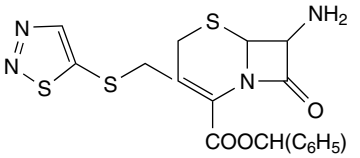
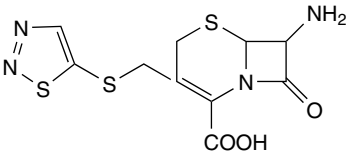
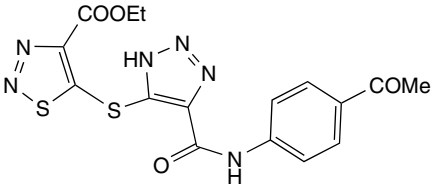
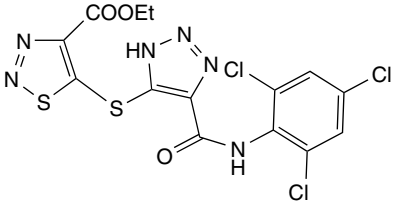
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
Sodium	H	84	—	NMR	C	103
Sodium	H	66	265–267	NMR	C	104
Thienyl	4-Methylphenyl	—	—	NMR	E	51
4-Carbamoylimidazol-5-yl	Carbamoyl	25	285–290	NMR	E	126
4-Thiocarbamoyl-imidazol-5-yl	Carbamoyl	30	250–253	NMR	E	126
		70	—	NMR	E	115
		68	—	NMR	E	115
		72	291–293	NMR	E	127
		91	207–208	NMR	E	127

TABLE 1.19. 1,2-DI(1,2,3-THIADIAZOL-4-YL)ETHENE

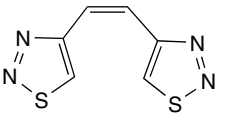
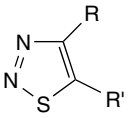
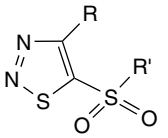
Compound	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6
	32	76	NMR, MS	E	24

TABLE 1.20. 4-HYDROXYALKYL-1,2,3-THIADIAZOLES



R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
1-Hydroxycyclohexan-1-yl	Phenyl	80	70.5–72	NMR, MS	E	134
3-Hydroxycyclohexen-1-yl	Phenyl	62	84–86	NMR, MS	E	134
1-Hydroxycyclopentan-1-yl	Phenyl	83	97–98	NMR, MS	E	134
1-Hydroxybutan-1-yl	Phenyl	85	—	NMR, MS	E	134
1-Hydroxyoctan-1-yl	Phenyl	83	—	NMR, MS	E	134
1-Hydroxypropan-1-yl	Phenyl	72	—	NMR, MS	E	134
2-Hydroxypropan-2-yl	Phenyl	76	87–89	NMR, MS	E	134
1-Phenylhydroxymethyl	Phenyl	90	172–174	NMR, MS	E	134

TABLE 1.21. 5-SULPHONYL-1,2,3-THIADIAZOLES

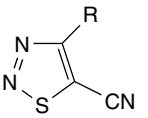


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Bromophenyl	4-Chlorophenyl	77	108–110	—	A	46
4-Bromophenyl	4-Methylphenyl	70	100–102	—	A	46
4-Bromophenyl	2-(4-Methylphenyl)-1-ethen-1-yl	65	110–111	NMR	A	45
4-Bromophenyl	2-(4-Methylphenyl)cyclopropan-1-yl	60	144–145	NMR	E	45
4-Bromophenyl	4-(4-Methylphenyl)pyrazolin-5-yl	62	195–196	NMR	E	45
4-Chlorophenyl	4-Chlorophenyl	76	150–152	—	A	46
4-Chlorophenyl	Phenyl	78	106–108	—	A	46
4-Chlorophenyl	2-Phenylcyclopropan-1-yl	62	155–156	NMR	A	45
4-Chlorophenyl	2-Phenyl-1-ethene-1-yl	72	148–149	NMR	A	45
4-Chlorophenyl	4-Phenylpyrazolin-5-yl	72	212–213	NMR	E	45
4-Ethoxyphenyl	Phenyl	80	154–156	—	A	46
4-Methylphenyl	4-Methylphenyl	72	102–104	—	A	46
4-Methylphenyl	2-(4-Methylphenyl)cyclopropan-1-yl	63	167–168	NMR	E	45
4-Methylphenyl	2-(4-Methylphenyl)-1-ethen-1-yl	68	140–141	NMR	E	45
4-Methylphenyl	4-(4-Methylphenyl)pyrazolin-5-yl	66	202–204	NMR	E	45
4-Methylphenyl	Phenyl	76	96–98	NMR	E	46
4-Methoxyphenyl	2-Phenyl-cyclopropan-1-yl	66	192–193	NMR	E	45
4-Methoxyphenyl	2-Phenyl-1-ethene-1-yl	65	180–181	NMR	A	45
4-Methoxyphenyl	2-Phenylpyrazolin-5-yl	68	274–276	NMR	E	45
4-Nitrophenyl	2-(4-Methylphenyl)cyclopropan-1-yl	64	185–187	NMR	E	45

TABLE 1.21 (*continued*)

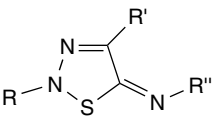
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Nitrophenyl	2-(4-Methylphenyl)-1-ethen-1-yl	70	174–175	NMR	E	45
4-Nitrophenyl	4-(4-Methylphenyl)pyrazolin-5-yl	65	271–273	—	A	45
4-Nitrophenyl	Phenyl	79	102–104	—	A	46
Phenyl	4-Chlorophenyl	76	106–108	—	A	46
Phenyl	4-Methylphenyl	78	106–108	—	A	46
Phenyl	2-(4-Methylphenyl)cyclopropan-1-yl	65	185–187	NMR	E	45
Phenyl	2-(4-Methylphenyl)-1-ethen-1-yl	66	165–166	NMR	A	45
Phenyl	4-(4-Methylphenyl)pyrazolin-5-yl	64	271–273	NMR	E	46
Phenyl	Phenyl	79	110–112	—	A	45
Phenyl	2-Phenylcyclopropan-1-yl	72	165–166	NMR	E	45
Phenyl	2-Phenyl-1-ethen-1-yl	78	170–171	NMR	A	45
Phenyl	4-Phenylpyrazolin-5-yl	65	270–272	NMR	E	45

TABLE 1.22. 5-CYANO-1,2,3-THIADIAZOLES



R	Yield (%)	mp (°C)	Other Data	Method	Reference
t-Butyl	56	59–61	NMR	A	15
Phenyl	59	73–75	NMR	A	15

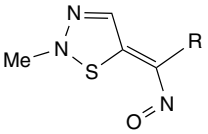
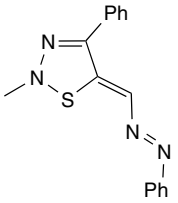
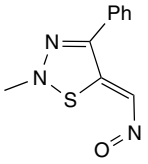
TABLE 1.23. 2-SUBSTITUTED 1,2,3-THIADIAZOLES

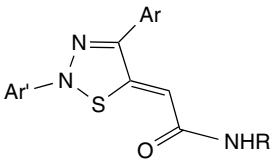


R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Benzoyl	H	Phenoxy-carbonyl	80	193	—	E	112
4-Chlorophenyl	Phenyl	Methyl	86	118	NMR	C	96
H	Benzotriazolyl carbonyl	Acetyl	72	169	—	A	51
Methyl	Phenyl	Methyl	76	—	NMR	C	96
4-Methoxyphenyl	Benzoyl	Acetyl	50–80	119–121	NMR	E	95

(*continued overleaf*)

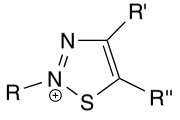
TABLE 1.23 (*continued*)

R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
4-Methylphenyl	Phenyl	Methyl	89	103	NMR	C	96
Phenoxycarbonyl	H	Benzoyl	30	211	—	E	112
Phenyl	Benzoyl	Acetyl	50–80	127–129	NMR	E	95
Phenyl	Carbamoyl	Acetyl	50–80	204–206	NMR	E	95
Phenyl	Ethoxycarbonyl	Acetyl	50–80	112–113	NMR	E	95
Phenyl	Cyano	Acetyl	50–80	125–127	NMR	E	95
Phenyl	Phenyl	Ethyl	70	74	NMR	C	96
Phenyl	Phenyl	Methyl	66	128	NMR	C	96
Phenyl	Phenyl	Propyl	74	107	NMR	C	96
			14	178	NMR, MS	E	117
			86	—	NMR	E	120
			—	117	NMR	E	132



Ar	Ar′	R	Yield (%)	mp (°C)	Other data	Method	Reference
4-Chlorophenyl	2,4-Dinitrophenyl	Bromo	62	185–188	—	D	107
4-Chlorophenyl	2,4-Dinitrophenyl	Phenyl	90	253–255	—	D	107
4-Chlorophenyl	Phenyl	Bromo	75	157–159	—	D	107
Phenyl	Phenyl	Bromo	72	135–136	—	D	107

TABLE 1.24. 4-HYDROXYALKYL-1,2,3-THIADIAZOLES



R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
2,4-Dinitrophenyl	H	Benzyl	75	127	—	A	39
4-Methoxyphenyl	Ethoxy	H	50–80	119–121	—	C	95
4-Methoxyphenyl	Ethoxycarbonyl	Amino	80	90–92	—	C	95
Methyl	*t*-Butyl	Amino	32	186–190	—	E	122
Methyl	H	Diethylamino	—	—	—	E	102
Methyl	Methyl	4-Methylphenyl sulfonylimino	59	148–149	NMR	D	106
Methyl	Methyl	4-Methyl-sulfonylimino	61	139–141	NMR	D	106
Methyl	Phenyl	Olate	60	123–124	NMR, MS	E	22
2-Nitrophenyl	Ethyl	Phenyl	81	204	—	A	39
2-Nitrophenyl	H	Benzyl	93	119	—	A	39
2-Nitrophenyl	H	2,5-Dibromo-phenyl	78	199	—	A	39
4-Nitrophenyl	H	Phenyl	47	215	—	A	39
4-Nitrophenyl	H	Benzyl	74	144	—	A	39
4-Nitrophenyl	H	Ethyl	60	206	—	A	39
4-Nitrophenyl	H	4-Methoxy-phenyl	92	173	—	A	39
4-Nitrophenyl	Methyl	3-Nitrophenyl	82	182	—	A	39
Phenyl	Benzoyl	Amino	66	223–225	—	C	95
Phenyl	Bromoiminium bromide	Amino	75	—	—	C	95
Phenyl	Carbamoyl	Amino	90	240–242	—	C	95
Phenyl	Chloro	Olate	76	116–118	NMR, MS	E	22
Phenyl	Cyano	Amino	57	—	—	C	95

(*continued overleaf*)

TABLE 1.24 (*continued*)

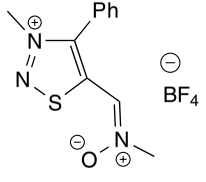
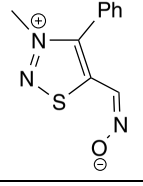
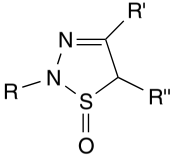
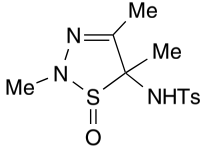
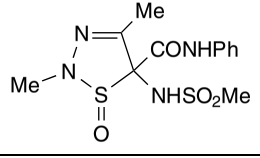
R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Phenyl	Ethoxycarbonyl	Acetylimino	50–80	112–113	—	C	95
Phenyl	Ethoxycarbonyl	Amino	75	227–229	—	C	95
Phenyl	H	Ethoxy	97	71–72	NMR, MS	E	22
Phenyl	H	Dicyanomethide	39	255–258	NMR, MS	E	22
Phenyl	H	Methylamino	57	122–124	NMR, MS	E	22
Phenyl	H	Methylthio	98	146–148	NMR, MS	E	22
Phenyl	H	Olate	85	118–119	NMR, MS	E	22
Phenyl	H	Thiolate	65	170–171	NMR, MS	E	22
Phenyl	Methyl	Ethoxy	100	82–83	NMR, MS	E	22
Phenyl	Methyl	Methylthio	79	120–122	NMR, MS	E	22
Phenyl	Methyl	Olate	74	123–124	NMR, MS	E	22
Phenyl	Methyl	Thiolate	53	144–146	NMR, MS	E	22
Phenyl	Phenyl	Olate	42	142–143	NMR, MS	E	22
			—	238–248	NMR	E	132
			—	156–166	NMR	E	132

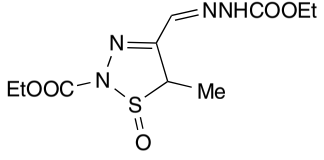
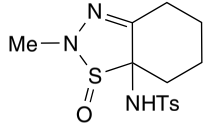
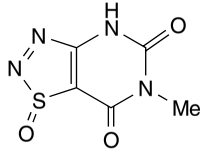
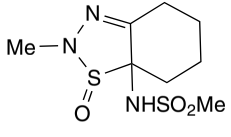
TABLE 1.25. 1,2,3-THIADIAZOLE-1-OXIDES



R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Ethoxycarbonyl	1-Methoxyimino-1-butyl	Propyl	60	—	NMR	A	38
Ethoxycarbonyl	1-Methoxyimino-1-propyl	Ethyl	57	—	NMR, X-ray	A	38
Ethoxycarbonyl	1-Methoxyiminoethyl	Methyl	38	—	NMR	A	38
4-Nitrophenyl	H	4-Nitrophenyl	27	273	—	A	39
4-Nitrophenyl	H	2,5-Dibromo-phenyl	26	197	—	A	39
Phenylsulphonyl	Phenyl	Phenyl	12	154–155	—	A	10
Tosyl	1-Methoxyimino-1-ethyl	Methyl	69	—	—	A	38
			75	172–173	NMR	D	106
			47	180–183	NMR	D	106

(*continued overleaf*)

TABLE 1.25 (*continued*)

R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
			44	—	NMR	A	38
			76	186–187	NMR	D	106
			80	—	MS	A	31
			62	173–174	NMR	D	106

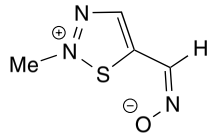
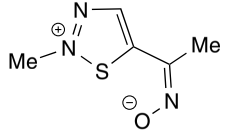
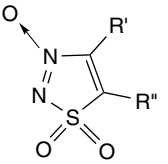
	25	192	NMR, MS	E	117
	41	240	NMR, MS	E	117

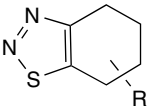
TABLE 1.26. 1,2,3-THIADIAZOLE-1,1,3-TRIOXIDES



R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Methoxyphenyl	2-Methoxyphenyl	36	139	NMR	E	13
4-Methoxyphenyl	2-Methylphenyl	30	134	NMR	E	13
Phenyl	Phenyl	36	146	NMR	E	13

TABLE 1.27. FUSED-1,2,3-THIADIAZOLES

A. Thiadiazoles fused with six-membered carbocycles



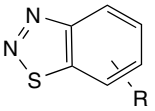
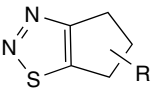
R	Yield (%)	mp (°C)	Other Data	Method	Reference
5,7-Di(4-chlorophenyl)-6,6-diethoxycarbonyl	78	156–157	NMR	A	68
5,7-Di(4-chlorophenyl)-6-oxo	—	169–170	NMR	A	58
5,7-Di(4-methoxyphenyl)-6,6-diethoxycarbonyl	79	168–169	NMR	A	68
5,7-Di(4-methoxyphenyl)-6-oxo	—	174–176	NMR	A	58
6,6-Dimethyl-7-oxo	61	45–46	X-ray	A	52
5,7-Diphenyl	65	93	NMR	A	57
5,7-Diphenyl-6,6-diethoxycarbonyl	73	178–180	NMR	A	68
5,7-Diphenyl-6-oxo	—	168–169	NMR	A	58
5,7-Dithienyl-6-oxo	—	149–150	NMR	A	58
H	92	51–55	NMR, MS	A	12
H	91	70–71	—	A	12
6-Phenyl	94	—	NMR, MS	A	8
5,5,7,7-Tetramethyl	97	44–45	NMR, MS	A	27
	65	96	NMR	A	57

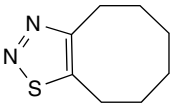
TABLE 1.27 (*continued*)

B. Thiadiazoles fused with five-membered carbocycles

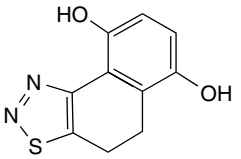
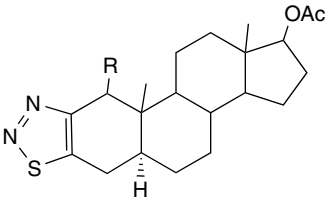


R	Yield (%)	mp (°C)	Other Data	Method	Reference
H	22	42–46	NMR	A	12
H	34	60–62	—	A	12
4,4,5,6-Tetrachloro	—	94–96	NMR, MS, X-ray	A	33

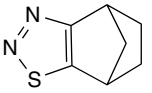
C. Thiadiazoles fused with seven-membered or higher carbocycles

R	Yield (%)	mp (°C)	Other Data	Method	Reference
	98	77–82	NMR, MS	A	12

D. Thiadiazoles fused with bicyclic or higher carbocycles

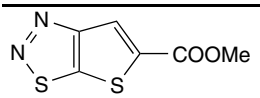
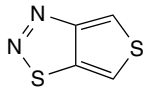
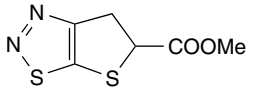
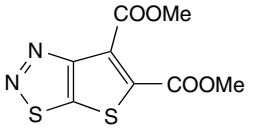
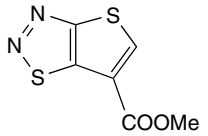
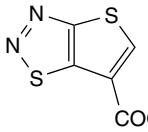
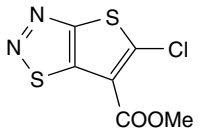
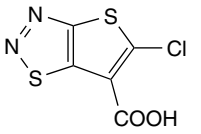
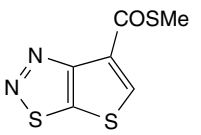
R	Yield (%)	mp (°C)	Other Data	Method	Reference
	47	53–55	NMR, MS	A	48
					
Chloro	5	189–189.5	NMR, MS, X-ray	A	27
H	85	147–149	NMR, MS, X-ray	A	27
Oxo	—	222–224	NMR, MS, X-ray	A	27
Sulfonyl	84	260–262	NMR, MS, X-ray	A	27

E. Thiadiazoles fused with five-membered heterocycles

R	Yield (%)	mp (°C)	Other Data	Method	Reference
	29	75*	NMR, MS, X-ray	A	27

(*continued overleaf*)

TABLE 1.27 (*continued*)

	72	132–133	NMR	A	37
	20	104	NMR	A	37
	50	Oil	NMR	A	37
	17	127–129	NMR	A	37
	66	140–142	NMR	A	69
	98	270–273	NMR	E	69
	78	124–126	NMR	E	69
	99	255–256	NMR	C	70
	—	—	—	C	70

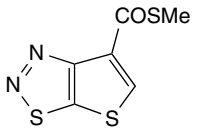
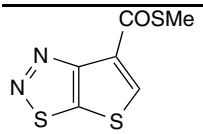
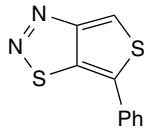
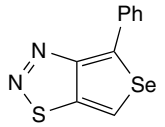
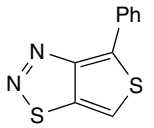
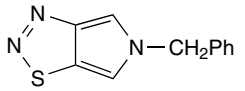
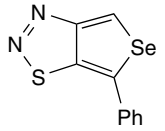
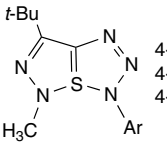
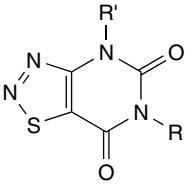
1	2	3	4	5	6
	65	—	NMR	A	71

TABLE 1.27 (*continued*)

	36	77.5–78	—	D	105
	92	115–116	MS	E	136
	90	108–110	NMR, MS	E	136
	50	119–120	NMR, MS	E	136
	95	105–106	NMR, MS	E	136
	10	67–68	NMR, MS	E	136
 4-Bromophenyl	53	125	—	E	122
4-Methoxyphenyl	23	120	—	E	122
4-Nitrophenyl	72	221	—	E	122

F. Thiadiazoles fused with six-membered heterocycles

Compounds	R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
	Ethyl	Ethyl	52–92	81–82	NMR	A	32
	H	Methyl	87	182–185	MS	A	31
	Methyl	H	100	235	MS	A	31
	Methyl	H	49–92	235	NMR	A	32
	Methyl	Methyl	75–83	140–141	MS	A	31
	Methyl	Methyl	63–83	140–141	NMR	A	32
	n-Butyl	H	35–72	179–181	NMR	A	32
	n-Propyl	H	47–51	142–144	NMR	A	32

(*continued overleaf*)

TABLE 1.27 (*continued*)

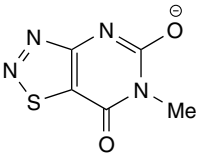
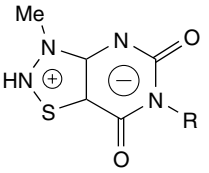
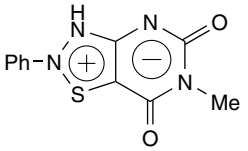
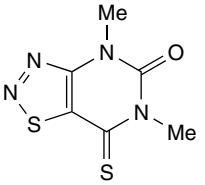
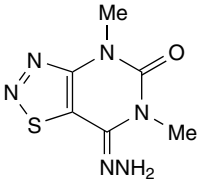
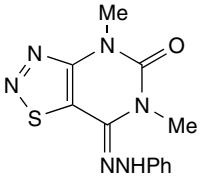
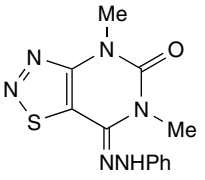
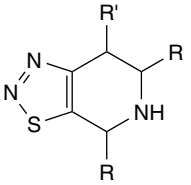
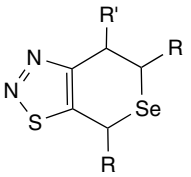
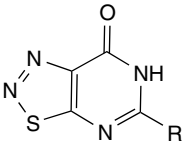
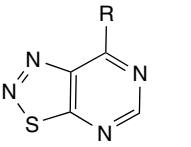
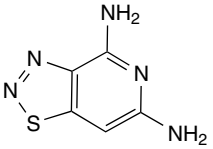
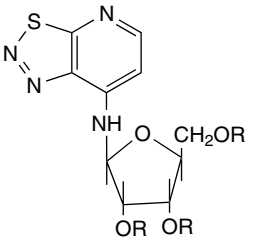
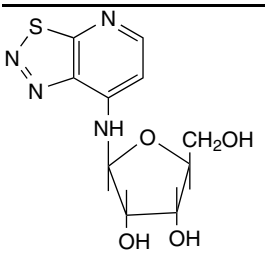
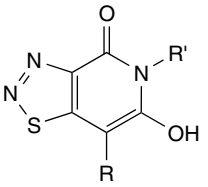
1	2	3	4	5	6	7	8
			70–76	201–203	MS	A	31
	Methyl		67–71	192–193	MS	A	32
	n-Butyl		58	148–149	MS	A	32
	n-Propyl		53	154–155	MS	A	32
			90	294–295	MS	A	32
			85	159–160	MS	E	32
			82	229–230	MS	E	32
			84	135–136	MS	E	32
			81	172–173	MS	E	32

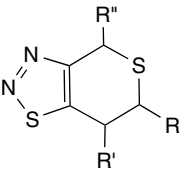
TABLE 1.27 (*continued*)

1	2	3	4	5	6	7	8
	Phenyl	H	44	150–151	NMR	A	55
	Phenyl	Methyl	46	122–123	NMR	A	55
	4-Methylphenyl	Methyl	48	92–93	NMR	A	55
	4-Methoxyphenyl	Methyl	47	86–87	NMR	A	55
	4-Chlorophenyl	Methyl	47	90–91	NMR	A	55
	Phenyl	Ethyl	43	98–99	NMR	A	55
	Phenyl	Propyl	42	82–83	NMR	A	55
	Phenyl	*i*-Propyl	44	85–86	NMR	A	55
	Phenyl	Butyl	46	77–78	NMR	A	55
	Phenyl	Pentyl	43	73–74	NMR	A	55
	Phenyl	Phenyl	43	94–95	NMR	A	55
	Phenyl	H	66	135–136	NMR	A	60
	4-Methylphenyl	H	70	129–130	NMR	A	60
	Phenyl	Methyl	69	118–119	NMR	A	60
	Phenyl	Ethyl	68	126–127	NMR	A	60
	H		66	230–231	—	E	87
	Methyl		33	239–240	—	E	87
	Ethyl		36	213–214	—	C	87
	Propyl		68	145–149	—	C	87
	i-Propyl		59	210–213	—	C	87
	n-Butyl		68	163–165	—	C	87
	s-Butyl		49	149–152	—	C	87
	i-Butyl		56	138–141	—	C	87
	t-Butyl		60	226–229	—	C	87
	n-Pentyl		56	188–191	—	C	87
	Methoxy		67	151–152	—	C	108
	Amino		86	250	—	E	108
	Methylamino		90	219	—	E	108
	Hydrazino		75	208–209	—	E	108
	Piperidino		73	84–85	—	E	108
			—	—	NMR	D	109
			84	—	NMR	D	80

(*continued overleaf*)

TABLE 1.27 (*continued*)

			69	202–204	NMR	E	80
	Ethoxycarbonyl	H	60	—	NMR	E	127
	Ethoxycarbonyl	Methyl	30	—	NMR	E	127
	Ethoxycarbonyl	4-Tolyl	30	—	NMR	E	127
	Ethoxycarbonyl	4-Methoxyphenyl	50	—	NMR	E	127
	Ethoxycarbonyl	4-Chlorophenyl	27	—	NMR	E	127
	Carbamoyl	Methyl	70	—	NMR	E	127
	Cyano	Methyl	78	—	NMR	E	127
	Carbamoyl	Methyl	73	—	NMR	E	127
	Ethoxycarbonyl	Methyl	65	—	NMR	E	127
	Ethoxycarbonyl	Amino	67	—	NMR	E	127



R	R'	R''	Yield (%)	mp (°C)	Other Data	Method	Reference
Phenyl	Phenyl	H	66	99–100	NMR	A	64
4-Methoxyphenyl	4-Methoxyphenyl	H	68	98–100	NMR	A	64
4-Chlorophenyl	4-Chlorophenyl	H	65	81–83	NMR	A	64
2-Thienyl	2-Thienyl	H	68	94–95	NMR	A	64
Phenyl	4-Methoxyphenyl	H	65	114–115	—	A	64
Phenyl	4-Chlorophenyl	H	62	85–86	—	A	64
Phenyl	Phenyl	Methyl	68	102–103	NMR	A	64
Phenyl	4-Methoxyphenyl	Methyl	63	121–122	NMR	A	64
Phenyl	4-Chlorophenyl	Methyl	60	115–116	NMR	A	64
Phenyl	Phenyl	Ethyl	67	124–125	NMR	A	64
Phenyl	4-Methoxyphenyl	Ethyl	66	112–113	NMR	A	64

G. Thiadiazoles fused with bicyclic or higher heterocycles

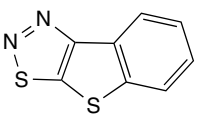
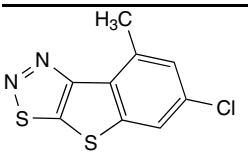
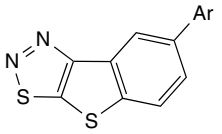
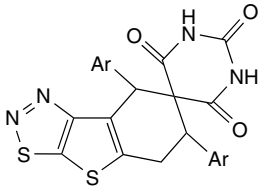
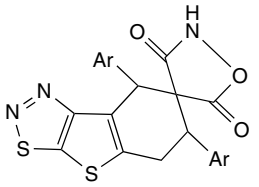
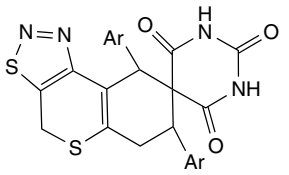
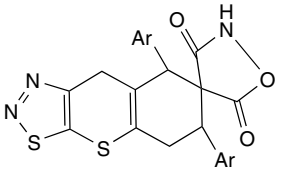
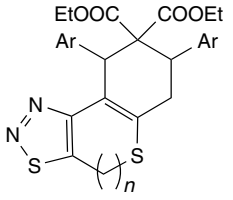
Compounds	R or Ar	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
		51	90	NMR, MS	A	12

TABLE 1.27 (*continued*)

		54	154	NMR, MS	A	12
	H	65	75–76	NMR	A	65
	Methyl	70	79–80	NMR	A	65
	Chloro	68	92–93	NMR	A	65
	Phenyl	62	254–256	NMR	A	66
	4-Methoxyphenyl	63	169–170	NMR	A	66
	Phenyl	55	>300	NMR	A	66
	4-Methoxyphenyl	57	177–178	NMR	A	66
	Phenyl	59	202–203.5	NMR	A	66
	4-Methoxyphenyl	55	212–214	NMR	A	66
	Phenyl	55	>300	NMR	A	66
	4-Methoxyphenyl	57	177–178	NMR	A	66
	4-Chlorophenyl ($n = 0$)	62	202–204	NMR	A	67
	4-Chlorophenyl ($n = 1$)	66	221–223	NMR	A	67
	4-Methoxyphenyl ($n = 0$)	65	194–196	NMR	A	67
	4-Methoxyphenyl ($n = 1$)	68	225–227	NMR	A	67
	Phenyl ($n = 0$)	60	158–159	NMR	A	67
	Phenyl ($n = 1$)	61	175	NMR	A	67

(*continued overleaf*)

TABLE 1.27 (*continued*)

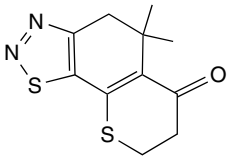
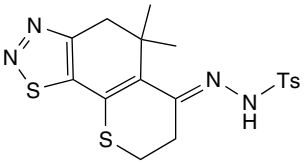
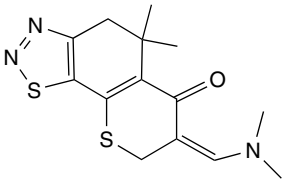
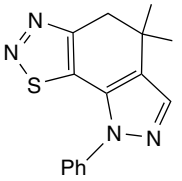
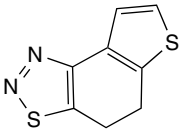
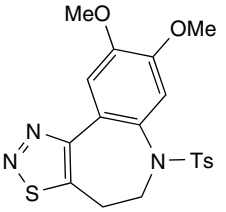
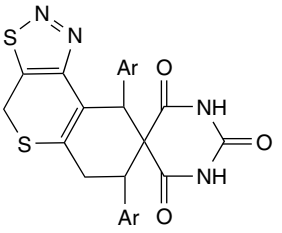
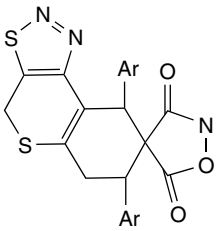
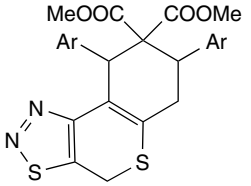
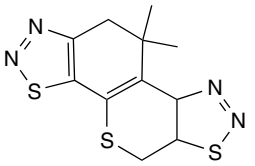
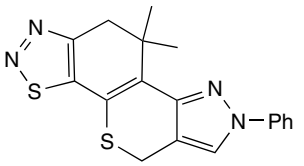
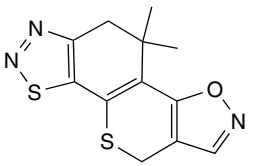
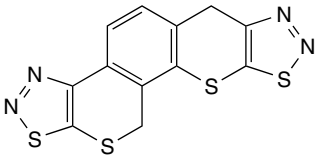
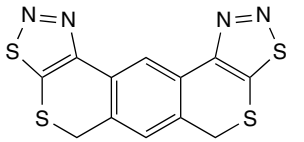
1	2	3	4	5	6	7
		40	148–149	NMR	A	52
		90	181–182	NMR	A	52
		86	163–164	NMR	E	53
		72	179–180	NMR	A	54
		40	98–99	NMR	A	54
		60	134–135	MS	A	56
	Phenyl	59	202–203	NMR	A	66
	4-Methoxyphenyl	55	212–213	NMR	A	66

TABLE 1.27 (*continued*)

	Phenyl	58	275 (d)	NMR	A	66
	4-Methoxyphenyl	59	237–239	NMR	A	66
1	2	3	4	5	6	7
	Phenyl	61	175–176	NMR	A	66
	4-Methoxyphenyl	68	225–227	NMR	A	66
		27	179–180	NMR	A	52
		87	145–146	NMR	E	53
		87	207–208	NMR	E	53
		64	136–137	NMR	A	59
		70	154–155	NMR	A	59

(*continued overleaf*)

TABLE 1.27 (*continued*)

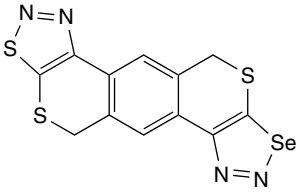
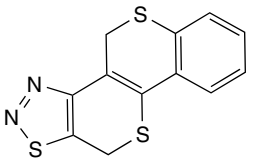
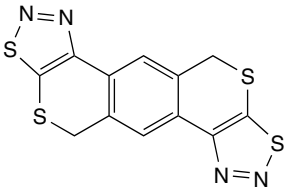
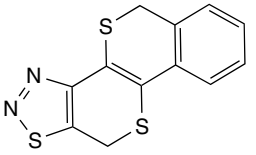
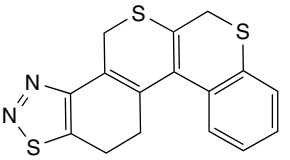
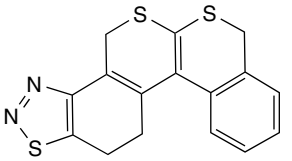
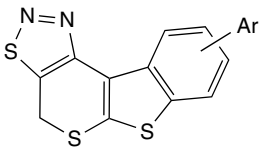
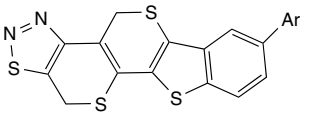
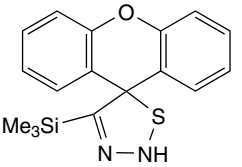
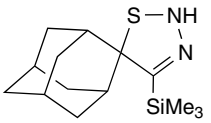
		74	147–149	NMR	A	59
		70	142–144	NMR	A	59
		65	101–102	NMR	A	61
1	2	3	4	5	6	7
		68	114–115	NMR	A	61
		60	112–113	NMR	A	61
		64	107–108	NMR	A	61
	H	59	137–138	NMR	A	65
	Methyl	64	142–143	NMR	A	65
	Chloro	66	140–141	NMR	A	65

TABLE 1.27 (*continued*)

	H	65	133–134	NMR	A	65
	Methyl	62	146–147	NMR	A	65
	Chloro	63	150–151	NMR	A	65

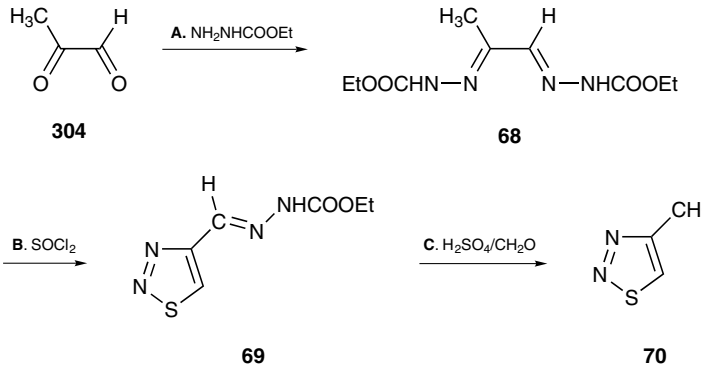
H. Spiro Thiadiazoles

Compound	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6
	74	120–128 (d)	NMR	B	76
	31	24–127	MR	B	76

1.7. SELECTED PROCEDURES

The following procedures are representative of the synthesis of a variety of 1,2,3-thiadiazoles. They are based on data published in the literature and have been tested numerous times in our laboratories over the years. Most of the compounds for which the synthesis is described below have been used extensively as starting materials for our research on rearrangements and ring-cleavage reactions.

1.7.1. 1,2,3-Thiadiazole-4-Carbaldehyde[18,122]



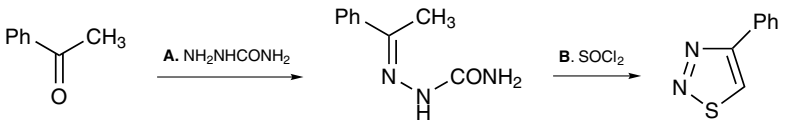
Step A

A solution of methylglyoxal **304** in water (40 wt %, 100 g, 0.51 mol) and ethyl carbazate (115.4 g, 1.10 mol) in ethanol (50 ml) was heated at reflux for 2 h, and the product was allowed to crystallize overnight. The solid was filtered and washed with three portions of 50-ml ice-cold ethanol. The resulting solid of **68** was air-dried overnight on filter paper. Yield 85.0 g, 73%.

Steps B/C

To thionyl chloride (100 ml) at 0°C (ice-salt bath) was added, while stirring, the bishydrazone **68** (51 g, 0.209 mol) in portions. There was a lively HCl evolution. The resulting mixture was stirred for 22 h and then poured into toluene (150 ml). The precipitate of **69** was filtered off and the solid added to a mixture of sulfuric acid/water (1:1 vol, 150 ml) and formaldehyde (60 ml, 37% in water). After 5 h at 50°C, the mixture was cooled to room temperature and extracted with dichloromethane (5 × 50 ml) the organic layers washed with water (2 × 100 ml). After drying on $MgSO_4$, the solvent was stripped off and the residue was chromatographed over silica with dichloromethane. This gave 10.1 g (40%) of **70** as a white–yellow powder. Protect from light by storing in a dark bottle. Mp 87°C.

1.7.2. 4-Phenyl-1,2,3-Thiadiazole[12]



305 **306** **3**

Step A

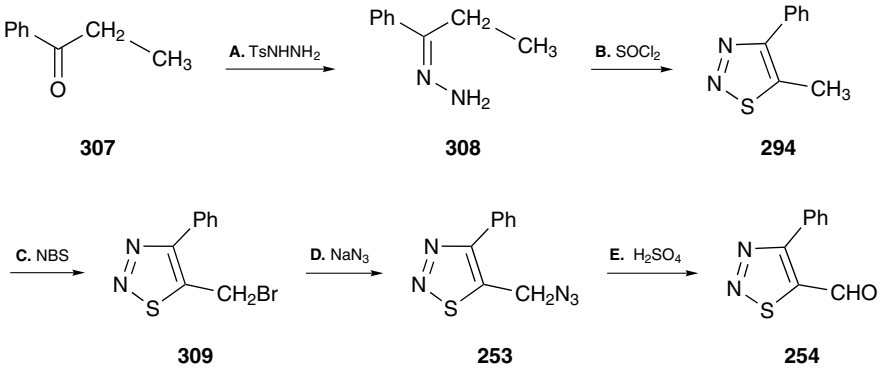
Semicarbazide hydrochloride (67 g, 0.6 mol), together with sodium acetate (67 g, 0.8 mol) in ethanol (500 ml) was heated at reflux. The precipitated sodium chloride was filtered from the hot solution and acetophenone **305** (60 g, 0.5 mol) was added. The mixture was heated at reflux for a further 2 h. Then water was added to the hot solution until precipitation started. After cooling, the crystals of the semicarbazone **306** were collected, washed with water and air-dried. This gave 66.4 g (75%) of product **306**, sufficiently pure for further reaction.

Step B

The dried semicarbazone **306** (53 g, 0.3 mol) was added in small portions with a spatula, while magnetically stirring, to thionyl chloride (250 ml) cooled to 0°C with an ice/salt bath. (*It is best to make preparations (outlet to washing bottle) to capture the HCl gas formed.*) After complete addition, the mixture was allowed to reach room temperature, and the reaction was continued until the gas

evolution ceased (about 2 h). The excess of thionyl chloride was removed *in vacuo* and the residue was crystallized from ethanol. This afforded 25.9 g (72%) of 1,2,3-thiadiazole **3**, mp 78°C.

1.7.3. 4-Phenyl-1,2,3-Thiadiazole-5-Carbaldehyde[12,120]



307 **308** **294**

309 **253** **254**

Step A

Propiophenone **307** (26.8 g) was added over a 30-min period to tosyl hydrazide (37.2 g) in toluene (100 ml), while heating at reflux. After that, the mixture was allowed to reach ambient temperature and then further cooled to −30°C. The precipitated hydrazone **308** was collected and recrystallized from dichloromethane. Yield 52 g (86%).

Step B

Thionyl chloride (25 ml) was added at −30°C to tosyl hydrazone **308** (25 g, 82 mmol). After 1 h at −30°C, the solution was allowed to reach room temperature. After 12 h, the precipitate of **294** was collected, washed with dichloromethane and crystallized from diethyl ether. Yield 10.5 g (72.8%), mp 37°C.

Step C

5-Methyl-4-phenyl-1,2,3-thiadiazole **294** (50 mmol), *N*-bromosuccinimide (1.1 equiv) and benzoyl peroxide (100 mg) in dry tetrachloromethane (800 ml) were heated at reflux during 24 h. The mixture was filtered while hot, and the filtrate was washed with water (3 portions of 300 ml) and then dried over $MgSO_4$. The filtrate was evaporated, and the residue was crystallized from diethyl ether to give the bromide **309**. Yield 47%, mp 115°C

Step D

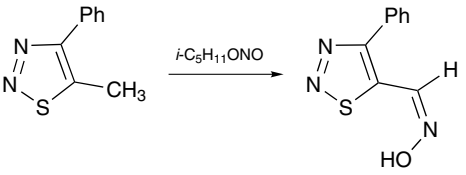
The bromide **309** (10 mmol) was stirred with 4 equiv of sodium azide in a two-phase system of dichloromethane (30 ml) and water (10 ml) at room temperature.

Tetrabutylammonium bromide (0.3 g) was added as a phase-transfer catalyst, as well as a catalytic amount (50 mg) of sodium iodide. After stirring at room temperature for 12 h, the mixture was added to an aqueous solution of sodium thiosulfate (1 g in 50 ml) and the whole was extracted with chloroform. The extracts were dried and evaporated, and the azide **253** crystallized on trituration with diethyl ether. Yield 68%, mp 101°C.

Step E

A solution of the azide **253** (6 mmol) in concentrated sulfuric acid (20 ml) was stirred for 5 days at room temperature. After this, the mixture was carefully poured onto ice/water (50 ml) and extracted with three portions of 10 ml of chloroform. The extracts were combined, dried over $MgSO_4$ and the residue was crystallized from diethyl ether to give the pure aldehyde **254**. Yield 59%, mp 69°C.

1.7.4. 4-Phenyl-5-Oxyiminomethyl-1,2,3-Thiadiazole[12,120]



294 **295**

To a solution of potassium (4 g) in absolute ethanol/diethyl ether (17/25 ml) was added at −5°C isoamyl nitrite (6.5 g, 55 mmol) and 5-methyl-4-phenyl-1,2,3-thiadiazole **294** (9 g, 50 mmol), and the mixture was stirred at room temperature for 24 h. The precipitated yellow potassium salt was dissolved in water and acidified with aqueous hydrochloric acid (2*N*) to pH 3.0. The precipitate of **295** was filtered off, washed with *n*-hexane and crystallized from ethanol/water to give beige needles of the oxime. Yield 49%, mp 212°C.

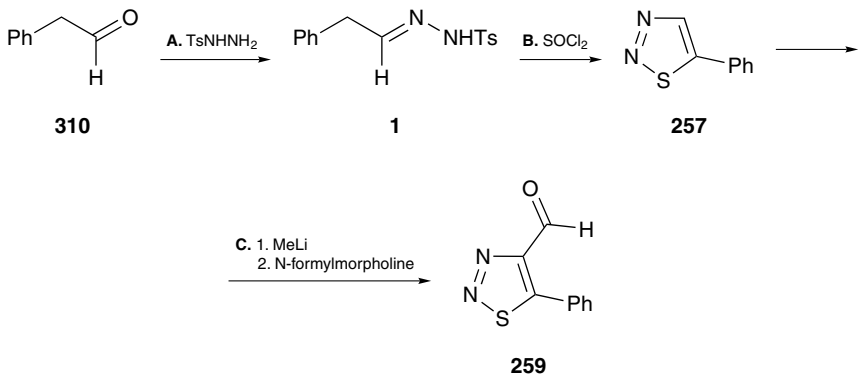
1.7.5. 5-Phenyl-1,2,3-Thiadiazole-4-Carbaldehyde[12,120]

Step A

Equimolar amounts (50 mmol) of tosyl hydrazide and phenylacetaldehyde **310** were added to ethanol (50 ml) and heated at reflux for 3 h. Afterwards the hydrazone crystallizes from the solution, and the crystals were collected and dried. Yield 68%

Step B

The tosylhydrazone **1** (10 mmol) was added while stirring to freshly distilled thionyl chloride (20 ml) while cooling in an ice bath. Afterwards the reaction



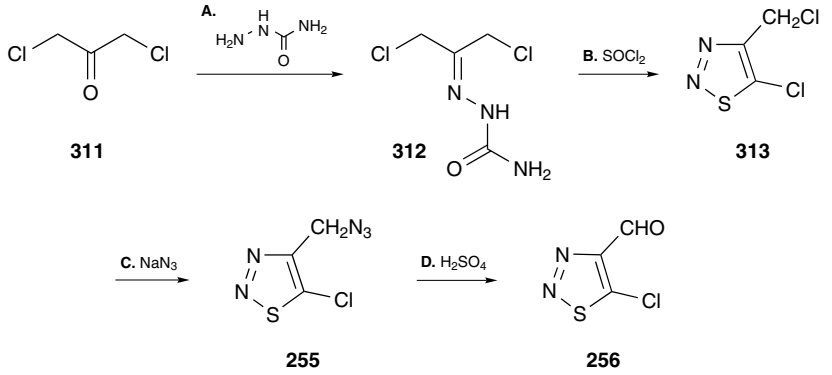
310 **1** **257** **259**

was continued at room temperature until the gas evolution ceases. The excess thionyl chloride was evaporated *in vacuo* and the residue of **257** was purified by chromatography over silica gel with dichloromethane/hexane 1:1 as the eluent. Yield 49%, mp 53°C.

Step C

To a stirred solution of 5-phenyl-1,2,3-thiadiazole **257** (5.0 g, 30.9 mmol) in tetrahydrofuran (75 ml), cooled at −70°C under nitrogen atmosphere, was added slowly a 1.6 M solution of methyllithium in diethyl ether (19.4 ml, 31 mmol). After 1h, *N*-formylmorpholine (3.55 g, 30.9 mmol), dissolved in dry tetrahydrofuran (10 ml) was added and the solution stirred at −70°C for 1 h, then kept at room temperature for another 12 h. The reaction mixture was poured into aq. hydrochloric acid (4M, 50 ml), the aqueous layer extracted with diethyl ether, and the combined organic portions washed with water, dries ($MgSO_4$) and evaporated. The crude product of **259** was purified by column chromatography on silica gel with ethyl acetate-hexane (1:1) as the eluent, and then crystallized from diethyl ether. Yield 4.1 g (70%), mp 54°C.

1.7.6. 5-Chloro-1,2,3-Thiadiazole-4-Carbaldehyde[121]



311 **312** **313** **255** **256**

Step A

To a mixture of semicarbazide hydrochloride (22.3 g, 0.2 mol) and 4.8 g sodium hydroxide in water (100 ml) was added 1,3-dichloroacetone (12.7 g, 0.1 mol) in ethanol (100 ml). After 30 min stirring at room temperature, the precipitate of **312** was filtered off and dried. Yield 49%, mp 114°C.

Step B

The semicarbazone **312** (13.2 g, 72 mmol) was added in portions to thionyl chloride (30 ml) while stirring and cooling in an ice bath. Then the mixture was heated overnight at 65°C, cooled down to room temperature and carefully added to ice-water (100 ml). The product was extracted with chloroform, and after drying of the combined extracts with $MgSO_4$ and evaporation of the solvent an oil of **313** was obtained, of sufficient purity for the next step. The oil might be crystallized from petroleum ether. Yield 67%, mp 34°C.

Step C

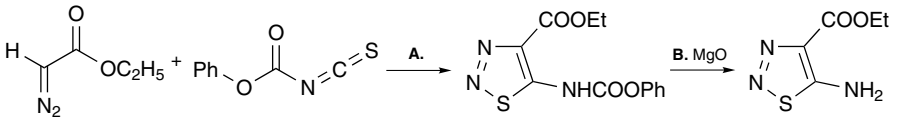
The 4-chloromethyl-5-chloro-1,2,3-thiadiazole **313** (8.2 g, 48.5 mmol) was dissolved in dichloromethane (100 ml) and treated with a solution of sodium azide (11.86 g, 0.182 mol) in water (40 ml), tetrabutylammonium bromide (1.4 g) and sodium iodide (100 mg). The reaction mixture was stirred overnight at room temperature. After addition of sodium thiosulfate to remove any iodine formed, the product was extracted in the usual manner with diethyl ether. The residue after drying of the combined extracts ($MgSO_4$) and evaporation was treated with petroleum ether and the azide product **255** separated as an oil in the refrigerator overnight. Yield 77%.

Step D

The 4-azidomethyl-5-chloro-1,2,3-thiadiazole **255** (1 g, 5.7 mmol) was added at −15°C to concentrated sulfuric acid (10 ml) and the mixture was stirred for 10 days at room temperature, and then added to ice-water (200 ml). The product was extracted with chloroform and obtained as a pure, dark oil, yield 79%. Colorless crystals of **256** might be obtained from chloroform/hexane at −30°C, mp 34°C.

1.7.7. Ethyl 5-amino-1,2,3-Thiadiazole-4-Carboxylate

1.7.7.1. Pechmann Method[112]



152 **160** **263** **274**

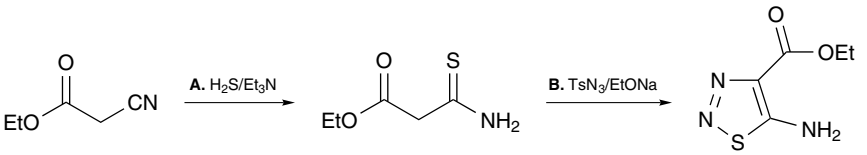
Step A

To a stirred suspension of sodium thiocyanate (0.1 mol) and ethyl diazoacetate **152** (0.1 mol) in dry acetonitrile (40 ml), an equimolar amount of phenyl chloroformate was added in a dropwise manner during 30 min at room temperature. The intermediate isothiocyanate **160** was generated *in situ*. The mixture was stirred for an additional 3 h, and then left for a further 30 h without stirring. Treatment with water (100 ml) gives a precipitate that was collected and recrystallized from ethanol. This gives the carbamate **263** in 48% yield, mp 154–156°C.

Step B

A suspension of the carbamate **263** (10 g) and magnesium oxide (13.6 g) in a mixture of acetone/water (410 ml + 270 ml) was heated at reflux for 1 h. The precipitate was filtered and washed with acetone (100 ml). The filtrates were combined and concentrated, and the residue of **274** was crystallized from tetrachloromethane to give the amine in 54% yield, mp 126°C.

1.7.7.2. Wolff Method



314 **315** **274**

Step A

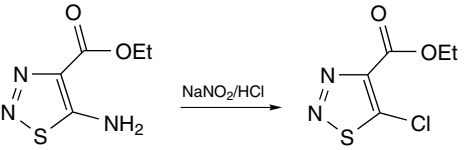
The mixture of anhydrous ethanol (150 ml) and triethylamine (100 ml) was cooled to −15–20°C, and hydrogen sulfide, dried over $CaCl_2$, was bubbled through the solution until the added weight was 15 g. After that, the solution containing triethylammonium hydrogen sulfide was moved into an autoclave, 36 mL (0.34 mol) of ethyl cyanoacetate **314** was added and the reaction mixture was heated at 70°C for 2 h. At the end of this period, the reaction mixture was cooled to room temperature, and the solution was evaporated *in vacuo* to give ethyl(thiocarbamoyl)acetate **315** (49 g, 100%) as a brown oil that was used without further purification. (The product can be crystallized from toluene when cooled down to −30°C).

Step B

Thioamide **315** (49 g, 0.34 mol) was dissolved in 150 ml of ethanol, and a solution of 0.78 (0.034 mol) sodium in 25 ml of ethanol was added. Tosylazide (73 g, 0.37 mol) was added dropwise within half an hour to a stirred and cooled (0–5°C) mixture. The precipitation began after 2/3 of the tosylazide had been added, and

it was important to maintain a vigorous stirring. The reaction mixture was kept stirring for 3 h, then cooled to −15°C, and the precipitate (85 g) containing two products, namely, tosylamine and thiadiazole **274**, was filtered off. The obtained mixture was suspended in 200 ml of cold water (5–10°C), and an aqueous solution of NaOH (20 g in 50 ml) was added. The suspension was stirred vigorously for 2 min and quickly filtered off. The crude product was washed with water and purified by recrystallization from water (2 L per 30 g) to give 25 g (42%) of aminothiadiazole **274**. White crystals, mp 125°C.

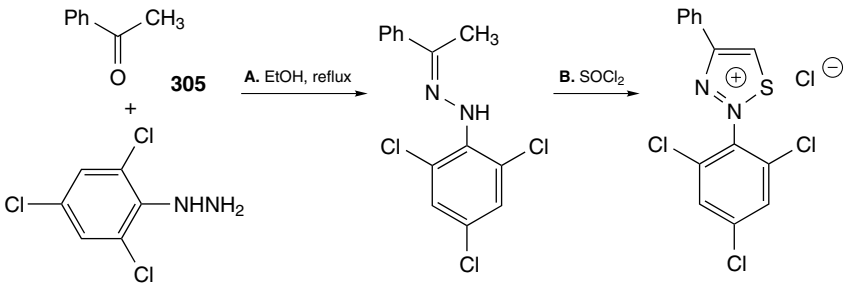
1.7.8. Ethyl 5-chloro-1,2,3-Thiadiazole-4-Carboxylate



274 **276**

The amine **274** (5 g, 28.9 mmol) was suspended upon stirring and cooling in an ice bath in 40 ml of hydrochloric acid. An aqueous solution of sodium nitrite (4 g, 58 mmol in 15 ml) was added in a dropwise manner. The reaction mixture was stirred at 5°C for 2 h, then allowed to warm up to room temperature, diluted with water (100 ml), and extracted with CH_2Cl_2 (3 times 50 ml). Extracts were evaporated to give 5.6 g (100%) of 5-chlorothiadiazole **276** as a dark-red oil, which crystallized upon cooling, mp 25°C.

1.7.9. 4-Phenyl-2-(2,4,6-Trichlorophenyl)-1,2,3-Thiadiazolium Chloride[34]



316 **317** **15**

Step A

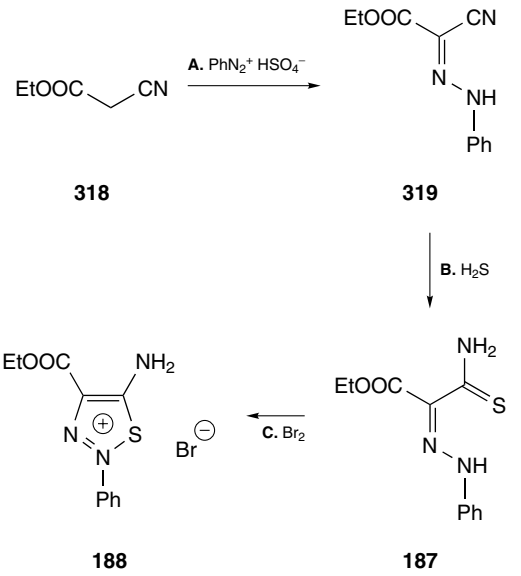
Acetophenone **305** (6 g, 50 mmol) and 2,4,6-trichlorophenylhydrazine **316** (10.5 g, 50 mmol) were dissolved in ethanol (50 ml) and one drop of acetic acid was added.

The mixture was heated at reflux for 10 min and allowed to stand overnight at room temperature. The crystals of **317** were filtered, washed with diethyl ether and recrystallized from ethanol. Yield 12.8 g (82%), mp 66–69°C.

Step B

The hydrazone **317** (3.0 g, 9.6 mmol) was added for 30 min to thionyl chloride (25 ml) while stirring and cooling to 0°C. After this, stirring was continued for 3 h at room temperature, and the excess of thionyl chloride was evaporated *in vacuo*. The orange–yellow residue was washed extensively with diethyl ether and dried. This afforded the pure thiazolium chloride **15**. Yield 3.3 g (91%), mp 163–167°C.

1.7.10. 5-Amino-4-ethoxycarbonyl-2-phenyl-1,2,3-thiadiazolium bromide[95]



Step A

Aniline (9.3 g, 100 mmol) was dissolved under gentle heating in sulfuric acid (2*N*, 100 ml). The solution was cooled to 0°C and sodium nitrite (7.47 g, 110 mmol) dissolved in a minimum amount of water was added at such a rate to keep the temperature below 10°C. The phenyldiazonium solution was then added to a cooled solution of ethyl cyanoacetate (11.3 g, 100 mmol) in ethanol **318** (100 ml) while stirring. Sodium acetate (24 g, 300 mmol) was added as a solid and the resulting mixture was stirred for 5 h at 0°C and overnight at room temperature. The precipitate was filtered, washed with water and crystallized from hot ethanol. Yield 12.6 g (58%), mp 117–121°C.

Step B

To a solution of hydrazone **319** (6 g, 27.6 mmol) in pyridine (30 ml) was added triethylamine (7.5 ml) in a dropwise manner. Hydrogen sulfide was bubbled through during 2 h, and the saturated solution was closed and left to stand for 3 h at room temperature. Water (150 ml) was added and the crystals of **187** were isolated and recrystallized from hot ethanol. Yield 5.0 g (72%).

Step C

The thioamide **187** (5 g, 20 mmol) was directly dissolved in glacial acetic acid (60 ml). At a temperature of 50°C, a solution of bromine (6.4 g, 40 mmol) in acetic acid (40 ml) was added in a dropwise manner while stirring. The solution was cooled, and the resulting precipitate was filtered off and washed with cold ethanol. This afforded the thiadiazolium bromide. Yield 5.03 g (76%), mp 205–209°C.

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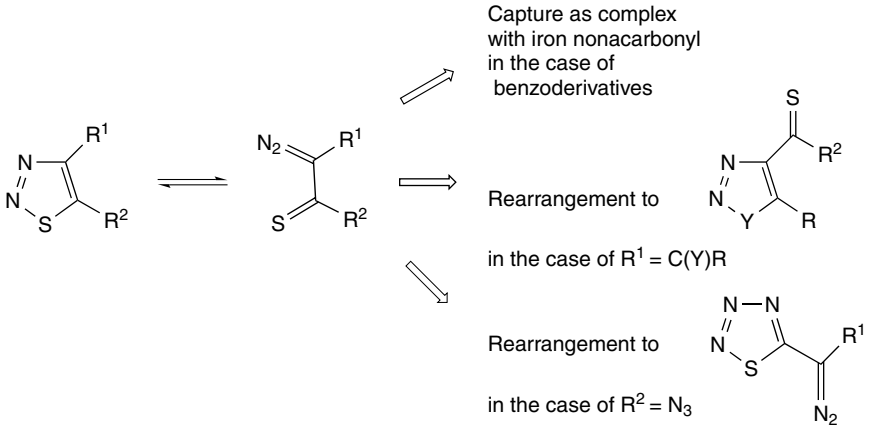
CHAPTER 2

Structure of 1,2,3-Thiadiazoles

Although the 1,2,3-thiadiazole molecule contains three sequential heteroatoms, the derivatives of this heterocycle exhibit remarkable stabilities, including those existing in zwitterionic forms and even those of nonaromatic nature.[1] 1,2,3-Thiadiazole is isomeric to the open-chain diazothioketone. Some of the rearrangements of 1,2,3-thiadiazoles are shown to occur via intermediate diazothioketones.



The existence of these compounds has been proved by isolation of the complex of 2-diazothione with iron nonacarbonyl, obtained by reacting 1,2,3-benzothiadiazole with $Fe_3(CO)_9$,[2] and also by capture with nucleophilic groups attached to the thiadiazole ring.[3] (see Chapter 3).

We subdivided the data on the structural chemistry of 1,2,3-thiadiazoles in two groups, respectively, dealing with theoretical and experimental studies.

2.1. THEORETICAL METHODS

Theoretical studies on the properties of 1,2,3-thiadiazoles or on the mechanisms of their formation are not numerous. Probably the main reason for this is the difficulty associated with calculating sulfur-containing organic compounds.

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The first publication on this topic was reported by Zahradnik and Koutecky, who made simple calculations of the charge density for the parent 1,2,3-thiadiazole by the Linear Combination of Atomic Orbitals (LCAO) method with Huckel approximation.[4] Other research groups have published the results of calculations of UV, Nuclear Quadrupole Resonance (NQR) and MCD spectra for 1,2,3-thiadiazoles.[5–7] It has been shown that the *ab initio* method gives good values for the ionization constants and splitting constants in NQR spectra, and the Pariser-Parr-Pople (PPP) method is suitable for calculations of the transactions in the electronic and MCD spectra.[5–7] A detailed study of isomeric thiadiazoles, thiadiazole mono- and dioxides, thiadiazolines and thiadiazolidines by high-level calculations (local and nonlocal density functional calculations) has been carried out by Glossman and coworkers.[8] The data of the calculated geometry for the parent 1,2,3-thiadiazoles are shown in Table 2.1. The experimental data of the geometry obtained by double resonance–modulated (DRM) microwave spectroscopy[9] are included in the table for the purpose of comparison.

The agreement of both lengths and angles determined from the SVWN functional with the DRM[9] data is better than those obtained with the BLYP functional. The calculated HOMO-LUMO gap was used to determine the total electronegativity and chemical hardness that are presented in Table 2.2, together with similar data for isomeric thiadiazoles.[4]

The authors have presented a distribution of the electronic charge density for the parent 1,2,3-thiadiazole, which shows that the largest negative values are adjacent to the nitrogen atoms. The net charge values on the atoms and

TABLE 2.1. EQUILIBRIUM GEOMETRY PARAMETERS OF THE PARENT 1,2,3-THIADIAZOLE MOLECULE

Bond Length (Å)				Bond Angle (°)			
	SVWN[a]	BLYP[b]	Exp.[9]		SVWN	BLYP	Exp.[9]
S–C	1.6872	1.7186	1.687	C–S–N	92.11	92.87	93.0
S–N	1.7357	1.8257	1.692	S–N–N	110.27	109.51	111.2
N–N	1.2786	1.2874	1.289	N–N–C	115.45	116.21	114.0
C–C	1.3809	1.3928	1.371	C–C–S	106.67	107.55	107.7
C–H	1.0937	1.0922	1.08	S–C–H	124.01	123.26	123.7
				N–C–H	119.93	119.52	119.3

[a]SVWN–Slater and Vosko, Wilk and Nusain[8].
[b]BLYP—Becke and Lee, Yang and Parr[8].

TABLE 2.2. TOTAL ENERGIES E, (IN HARTREE), ELECTRONEGATIVITIES χ (IN eV) AND HARDNESS η (IN eV) FOR THE ISOMERIC THIADIAZOLES

Compound	SVWR			BLYP		
	E	χ	η	E	χ	η
1,2,3-Thiadiazole	−583.02241	4.99	1.79	−585.02499	4.35	1.83
1,2,4-Thiadiazole	−583.05061	5.21	2.21	−585.05097	4.45	2.19
1,2,5-Thiadiazole	−583.04219	5.36	2.19	−585.04370	4.55	2.07
1,3,4-Thiadiazole	−583.02954	4.80	1.94	−585.02983	4.16	2.07

TABLE 2.3. NET CHARGES AND CONDENSED FUKUI FUNCTIONS FOR THE 1,2,3-THIADIAZOLE MOLECULE OBTAINED THROUGH BLYP-DFT CALCULATION

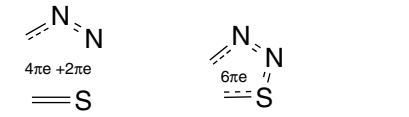
Atom	Net Charge	f^+	f^-	f^0
S	0.2594	0.2705	0.3205	0.2955
C_α	−0.3923	0.1818	0.1054	0.1436
N_α	−0.2109	0.1704	0.1435	0.1570
N_β	0.0081	0.1156	0.1731	0.1444
C_β	−0.1997	0.1215	0.1172	0.1194
H	0.2735	0.0680	0.0682	0.0682

the condensed Fukui functions for 1,2,3-thiadiazole are listed in Table 2.3. The condensed Fukui functions f^+(r), f^-(r), f°(r) predict the reactivity of the atoms to nucleophilic, electrophilic and radical attack, respectively.

The authors outlined the usefulness of the relative densities of the frontier orbitals and Fukui functions as valuable tools to rationalize the chemical reactivity of 1,2,3-thiadiazoles. The relative stabilities of 1,2,3-thiadiazolines and 1,3,4-thiadiazolines that are formed as a mixture of regioisomers in the cycloaddition reaction of aliphatic diazocompounds to thioketones (Pechmann method of the synthesis of 1,2,3-thiadiazoles, see Section 2.2) were determined by semiempirical MNDO-PM3 and AM1 calculations and by *ab initio* Restricted Hartree-Fock (RHF) and Complete Active Space Self-Consistent Field (CASSCF) methods with 3-21G*, 6-31G* and CAS/3-21G* basis sets. According to *ab initio* calculations, 1,2,3-thiadiazoline is 0.9 kcal/mole more stable than 1,3,4-thiadiazoline. The reverse trend was found for alkyl-substituted derivatives; the 2,2-diethyl-1,3,4-thiadiazoline is 4.1 kcal/mole more stable than the corresponding 1,2,3-thiadiazole. According to B3LYP calculations, isomeric 1,2,3- and 1,3,4-thiadiazolines have equal energies.[10]

Within the framework of Frontier Molecular Orbitals (FMO) theory, the MNDO-PM3 energies of the frontier molecular orbitals of diazomethane and thioformaldehyde classify this type of reaction as HOMO-CH_2N_2/LUMO-CH_2S controlled. The structure of the frontier orbitals suggests the formation of a mixture of isomeric thiadiazoles in this reaction (see Fig 2.1).

Extensive *ab initio* calculations on the reaction of diazomethane with thioformaldehyde suggest that both regioisomers should be formed via concerted pathways. In contrast, AM1 and MNDO-PM3 advocate a concerted formation of the 1,3,4-thiadiazoline (A) and a two-step reaction to the 1,2,3-isomer involving the electrocyclic ring closure of an intermediate of the pentadienyl anion type (B).



A. 1,3-Dipolar cycloaddition

B. 1,5-Dipolar electrocyclic cyclization

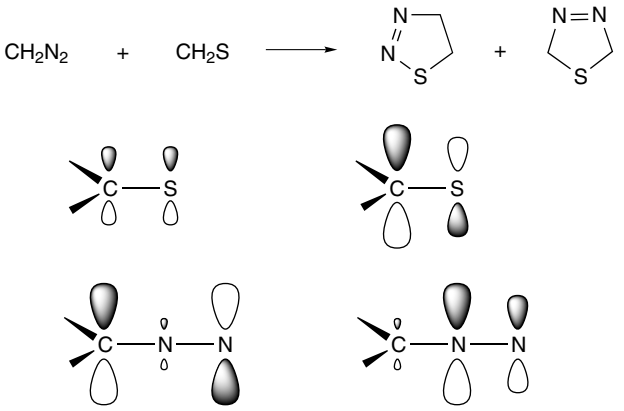
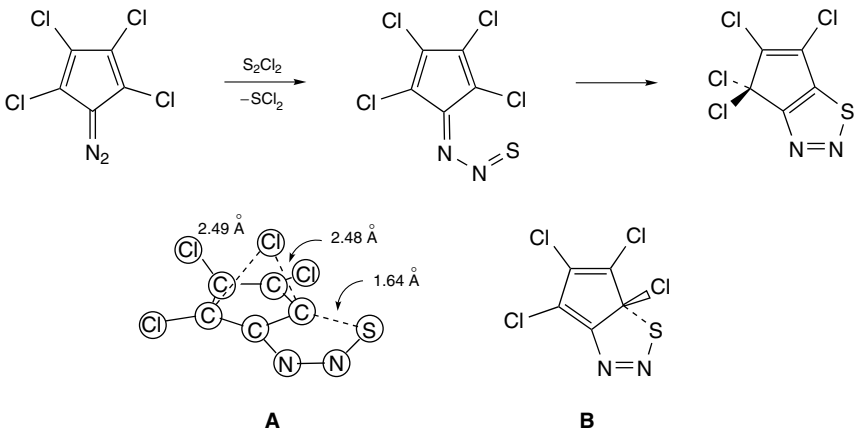


Figure 2.1. Structure of the frontier orbitals of thioformaldehyde and diazomethane that are components in the cycloaddition reaction, leading to isomeric 1,2,3- and 1,3,4-thiadiazolines.

A two-step pathway of this type or other pathways different from a concerted mechanism for the formation of 1,2,3-thiadiazolines can be useful for the rationalization of the known fact of the increase in regioselectivity in the cycloaddition reaction of diazoalkanes to thioketones with an increase in the bulk of the substituents at the thioketone (see Section 2.2).

Christensen *et al*. have shown a good agreement of AM1 geometry calculations for 4,4,5,6-tetrachloro-4*H*-cyclopenta-1,2,3-thiadiazole with the X-ray data for this molecule.[11] Using the AM1 method, they have studied the mechanism of the reaction of 1-diazo-2,3,4,5-tetrachloropentadiene with S_2Cl_2, leading to 4,4,5,6-tetrachloro-4*H*-cyclopenta-1,2,3-thiadiazole. The pathway where a [1,3] sigmatropic chlorine shift and ring closure occur in a concerted manner (A) was found to have 11-kcal/mol less activation energy in comparison to a two-step mechanism (B).



In our opinion, the conclusion of the authors on the mechanism should be checked by a more sophisticated method. To explain the preferred place of the coordination of benzo-1,2,3-thiadiazole with cyclopentadienyldicarbonyl manganese, Mayr and coworkers have calculated 2- and 3-protonated 1,2,3-thiadiazoles.[12] The difference in energy for these structures calculated by the *ab initio* method with a 6-31G basis set with Zero-Point Energy (ZPE) correction was found to be 8.75 kcal/mol in favor of the 2-protonated benzothiadiazole. Indeed, parallels were found in the site of coordination of the thiadiazole ring with both metals and protons.[12]

Friedman and Ferris made a theoretical study of the aromaticity of 1,2,3-thiadiazole-1,1-dioxide using *ab initio* calculations with a 3-21G* split valence basis set level.[13] They have estimated the aromaticity on the basis of the interaction of the lowest π-orbital and indexes, such as N, MDA and $\Delta E_{\pi L}$ (Boys). The heteroaromaticity of 1,2,3-thiadiazole-1,1-dioxide is higher than that for 1,3,4-thiadiazole-1,1-dioxide but less than that for the 1,2,5-isomer.[13] Thiophene is the most aromatic compound in this series, and its 1,1-dioxide has the lowest index of aromaticity.[13] The conclusion was made that the relative aromaticity of thiadiazoledioxides is largely determined by the propensity of the nitrogen atoms to counteract electron withdrawal from the ring by the sulfone oxygens.

2.2. EXPERIMENTAL STRUCTURAL METHODS

2.2.1. X-ray Analysis

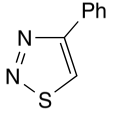
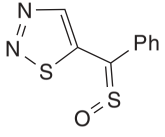
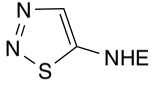
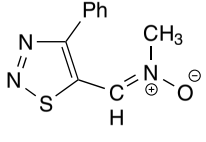
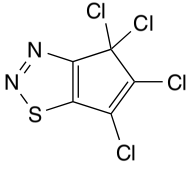
The X-ray diffraction method remains the definitive structural proof, and it has been successfully used for the elucidation of the structures obtained in the methylation reaction of 1,2,3-thiadiazoles[14] and of the place of coordination of this heterocycle with metals.[12,15] It was also used as evidence for the structures of some thiadiazoles existing in the azathiapentalene form.[14,16,17]

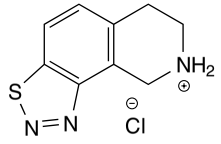
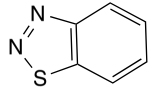
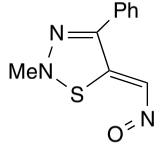
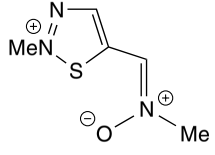
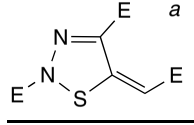
Many papers on crystal structure X-ray analyses of 1,2,3-thiadiazoles have appeared in the literature.[12,14–48] The most important data on the matter are summarized in Table 2.4.

All the 1,2,3-thiadiazoles studied were found to be completely planar; all atoms of the ring lie in the same plane with very slight deviation, less than 0.02° from the plane.[14,18]

Looking at the table, we cannot observe significant changes in the bond lengths, even if we compare nonsubstituted and N-substituted 1,2,3-thiadiazoles. The same trend was observed after complex formation of benzothiadiazoles with metals, independent of where the thiadiazole coordination takes place.[12,15] On the other hand, the bond angles that involve the substituted atoms are more sensitive to the change of the structure. For instance, significant change of the angles C_5SN_2; SN_2N_3 and $N_2N_3C_4$ takes place if one compares the data on rows 1 and 17 (see Table 2.4).

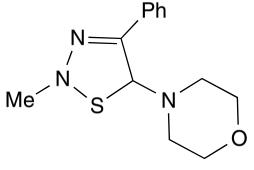
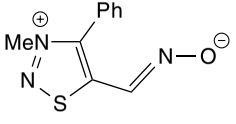
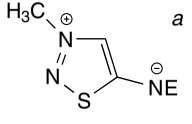
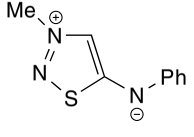
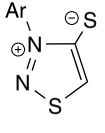
TABLE 2.4. THE DATA OF X-RAY ANALYSIS FOR 1,2,3-THIADIAZOLES: BOND LENGTHS AND BOND ANGLES

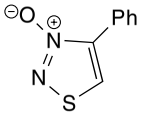
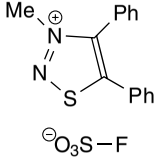
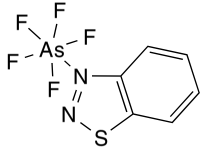
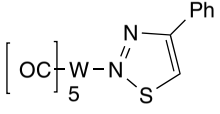
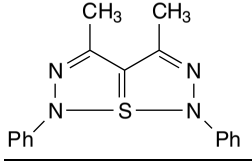
Formula	Bond Length (Å)					Bond Angle (°)					Reference
	S-N_2	N_2-N_3	N_3-C_4	C_4-C_5	C_5-S	C_5SN_2	SN_2N_3	$N_2N_3C_4$	$N_3C_4C_5$	C_4C_5S	
1	2	3	4	5	6	7	8	9	10	11	12
	1.667	1.287	1.378	1.363	1.669	93.2	111.2	114.3	112.1	109.0	12
	1.649	1.296	1.357	1.376	1.706	92.8	112.6	113.5	113.8	107.1	14
a 	1.681	1.297	1.34	1.374	1.691	92.6	110.9	114.7	113.8	107.7	23
	1.706	1.279	1.384	1.397	1.708	92.6	112.7	113.4	114.2	107.1	15
	1.715	1.307	1.346	1.362	1.674	91.9	112.0	111.4	116.7	108.0	11

	1.71	1.281	1.38	1.403	1.706	92.5	112.5	113.6	114.1	107.2	32
	1.705	1.28	1.383	1.397	1.708	92.5	112.6	113.3	114.2	107.1	12
	1.761	1.310	1.350	1.391	1.701	85.8	117.1	109.9	113.8	113.3	15
	1.687	1.322	1.330	1.393	1.695	87.7	117.5	109.3	114.4	111.1	15
 *a*	1.742	1.335	1.302	1.455	1.744	88.1	116.9	109.9	117.2	107.7	30

(*continued overleaf*)

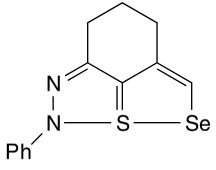
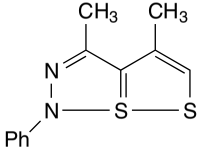
TABLE 2.4 (*continued*)

Formula	Bond Length (Å)					Bond Angle (°)					Reference
	$S\text{-}N_2$	$N_2\text{-}N_3$	$N_3\text{-}C_4$	$C_4\text{-}C_5$	$C_5\text{-}S$	C_5SN_2	SN_2N_3	$N_2N_3C_4$	$N_3C_4C_5$	C_4C_5S	
1	2	3	4	5	6	7	8	9	10	11	12
	1.765	1.376	1.28	1.529	1.838	90.4	110.5	114.3	117.6	101.0	37
	1.657	1.308	1.332	1.389	1.736	94.4	108.5	118.6	112.3	106.0	22
	1.672	1.306	1.366	1.375	1.712	92.0	110.2	117.7	109.4	110.6	15
	1.672	1.313	1.324	1.409	1.77	95.9	106.9	119.8	114.1	103.0	28
	1.623	1.329	1.382	1.392	1.654	95.5	108.3	118.1	107.2	110.8	31

	1.644	1.312	1.401	1.344	1.695	93.9	109.5	116.3	109.7	110.3	43
	1.615	1.336	1.366	1.392	1.698	94.5	111.0	115.0	111.0	108.2	39
	1.63	1.299	1.4	1.423	1.7	94.6	111.7	116.2	109.2	108.1	19
	1.662	1.296	1.377	1.39	1.669	93.8	112.1	113.0	113.1	107.8	45
	1.893	1.338	1.328	1.397	1.734	83.3	115.3	109.6	117.0	114.4	24

(*continued overleaf*)

TABLE 2.4 (*continued*)

Formula	Bond Length (Å)					Bond Angle (°)					Reference
	S-N_2	N_2-N_3	N_3-C_4	C_4-C_5	C_5-S	C_5SN_2	SN_2N_3	$N_2N_3C_4$	$N_3C_4C_5$	C_4C_5S	
1	2	3	4	5	6	7	8	9	10	11	12
	1.811	1.336	1.316	1.399	1.731	85.7	116.2	108.5	118.6	110.7	33
	1.775	1.32	1.318	1.413	1.737	86.5	116.2	110.5	116.3	110.3	39

[a]E = COOMe

Mayr and colleagues proposed that coordination of a metal atom with a lone electron pair of 1,2,3-thiadiazole is the first step in the activation of the heterocyclic ring, which leads to ring opening of 1,2,3-thiadiazoles via elongation of the S−N bond.[12] However, they did not manage to prove their hypothesis analyzing the X-ray data of benzothiadiazole and its manganese complex.[12] The quantum calculation of the N-2 and N-3 protonated forms by the same authors did not shed light on this problem.

Unambiguous structural proof of the methylation products of 4-phenyl-1,2,3-thiadiazole-5-carbaldoxime was given by the study of their structures by X-ray analysis.[14] We have shown the existence of the nitroso compound (entry 8 in Table 2.4) in a bicyclic thiapentalenic form. The alkylation of 8-phenylhydrazono-8*H*-indeno[1,2-*d*]-1,2,3-thiadiazole with Meerwein's reagent furnished 2- and 3-methylated thiadiazoles, respectively, and their structures also were proved by X-ray analysis.[17] Benzo bridging was shown to decrease the extent of the thiapentalenic interaction.

2.2.2. Nuclear Magnetic Resonance Spectroscopy

2.2.2.1. Proton NMR Spectroscopy

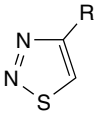
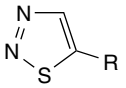
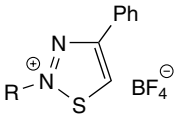
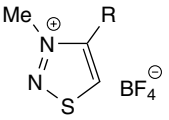
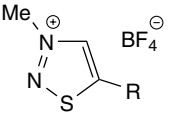
The data of ^{1}H NMR spectroscopy confirmed the aromatic character of the 1,2,3-thiadiazole ring. Proton chemical shifts for 1,2,3-thiadiazole derivatives are found in the region of 7.44–9.37 ppm. *N*-Alkylation of the ring shifts these signals 1.0–1.5 ppm downfield. (see Table 2.5).

2.2.2.2. Carbon-13 NMR Spectroscopy

Carbon-13 NMR spectroscopy is a useful tool for the elucidation of heterocyclic structures that possess few or no ring protons in the molecule. Therefore, this method has been widely used in 1,2,3-thiadiazole chemistry. The first systematic study of the carbon spectra of 4-substituted 1,2,3-thiadiazoles has been made by Looker and coworkers[54] for nine derivatives and for the parent compound. The spectral assignments for the C-4 and C-5 resonances of 1,2,3-thiadiazole derivatives were made from the comparison with data for 1,2,3-triazole and thiophene and also on the base of off-resonance spectrum of 4-methyl-1,2,3-thiadiazole.

To elucidate the effect of the substituents at the 4- and 5-positions on the spectra of 1,2,3-thiadiazoles, we carried out a spectral study for 5-monosubsituted-1,2,3-thiadiazoles and expanded the number of spectra for some new 4-substituted derivatives. The results, together with the literature data, are summarized in Table 2.6, where $Z_{i,j}$ denotes the influence of the substituents in position i on the carbon resonance of position j.[55]

TABLE 2.5. ^{1}H NMR DATA OF 1,2,3-THIADIAZOLES

Structure	R	δ (ppm)	J_{C-H} (Hz)	Solvent	Reference
1	2	3	4	5	6
	Methyl	8.20	—	CCl_4	1
	Ethylthio	8.33		$CDCl_3$	49
	Phenyl	8.60		CCl_4	1
	Formyl	9.37	195	$CDCl_3$	49
	Methyl	8.35	—	CCl_4	1
	Ethylthio	8.30	—	$CDCl_3$	50
	Phenyl	8.70	—	$CDCl_3$	1
	Benzylthio	8.25	—	$CDCl_3$	50
	Acetyl	9.04	192	$CDCl_3$	51
	Formyl	9.20	192	C_6H_6	51
	Diethylamino	7.44	—	$CDCl_3$	52
	Chloro	8.55	—	$CDCl_3$	Unpublished
	Amino	7.80	—	$CDCl_3$	Unpublished
	Azido	8.60	—	$CDCl_3$	Unpublished
1	2	3	4	5	6
	Methyl	10.16	202	DMSO	53
	Aryl	10.40	200	$CDCl_3$	Unpublished
	Phenyl	9.90	205	DMSO	53
	Methoxycarbonyl	10.07	208	DMSO	53
	NPh	8.27	199	DMSO	53
	Methyl	9.93	—	DMSO	1
	Chloro	9.95	208	DMSO	53

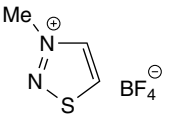
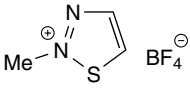
Structure	δ_{H-C_4}	δ_{H-C_5}	J_{C_5-H}(Hz)	J_{C_4-H}(Hz)	Solvent Reference
	9.67	9.86	205	208	DMSO 53
	9.23	9.86	205	206	DMSO 53

TABLE 2.6. INCREMENTAL SUBSTITUENT EFFECTS FOR 4-(OR 5-) SUBSTITUTED 1,2,3-THIADIAZOLES (+DOWNFIELD, −UPFIELD)

R^4/R^5	Solvent	Z_{44}	Z_{45}	Z_{55}	Z_{54}	Reference
1	2	3	4	5	6	7
CH_3	$CDCl_3$	10.5	−2.4	16.7	0.1	54, 55
CH_2CH_3	$CDCl_3$			23.5	−1.5	56
$CH_2CH_2CH_3$	$CDCl_3$			21.8	−0.7	56
$CH(CH_3)_2$	$CDCl_3$			30.3	−3.0	55
$CH_2CH_2CH_2CH_3$	$CDCl_3$			22.0	−0.8	55
$C(CH_3)_3$	$CDCl_3$	26.2	−6.8			55
$CH_2C_6H_5$	$CDCl_3$			21.4	−0.3	55
CH_2Br	$CDCl_3$			17.9	0.3	55
$CHBr_2$	$CDCl_3$			23.5	−1.1	55
1	2	3	4	5	6	7
CBr_3	$CDCl_3$			31.6	−0.7	55
$CH{=}CH_2$	$CDCl_3$	13.9	−5.0	18.4	−1.7	56, 57
C_6H_5	$CDCl_3$	16.6	−4.9	21.3	−3.1	54, 55
CHO	$CDCl_3$			17.5	2.5	55
$COCH_3$	$CDCl_3$			18.9	0.8	55
COC_6H_5	$CDCl_3$			17.3	1.7	55
COOH	DMSO-d_6	8.2	9.1	12.9	3.2	54, 55
$COOCH_3$	$CDCl_3$	7.1	6.7	10.4	2.8	55
COCl	$CDCl_3$	7.3	6.7			54
$CONH_2$	DMSO-d_6	10.4	6.2			54
$CON(C_2H_5)_2$	$CDCl_3$	11.4	4.9	13.8	−0.6	55
CN	$CDCl_3$	−13.7	9.6	−11.7	5.1	54, 55
Cl	$CDCl_3$			9.9	−0.4	55
NH_2	DMSO-d_6			30.3	−16.3	55
NHC_6H_5	DMSO-d_6			24.0	−14.8	55
N_3	$CDCl_3$			10.4	0.0	58
SCH_3	$CDCl_3$			20.1	−3.6	59
$SCH_2COC_6H_5$	$CDCl_3$			15.4	−0.1	55
Sna	D_2O			35.0	2.6	55

Two main observations can be made as follows:

1. In all cases where comparison is possible, the *ipso* effects of the 5-substitutents (Z_{55}) are larger than those of the 4-substituents (Z_{44}) and much larger than those in benzene with one exception for the CN group.
2. The *ortho* effects, on the contrary, are larger for 4-substituents (Z_{45}) than for 5-substituents (Z_{54}).

Witanowski and Biedrzycka reported spin–spin coupling between ^{12}C nuclei in the parent 1,2,3-thiadiazole as 58.9 Hz.[60]

2.2.2.3. *Nitrogen-14 NMR Spectroscopy*

Only one paper appeared in the literature, where solvent effects on ^{14}N NMR spectra are discussed for isomeric thiazoles and thiadiazoles, including 1,2,3-thiadiazole.[61] The results of high precision ^{14}C NMR measurements of the nitrogen shielding for 1,2,3-thiadiazole in a variety of solvents are given in Table 2.7. The choice of the solvents represents a large range of polarity and hydrogen-bonding effects. The data reported in Table 2.7 show that the solvent effect on the nitrogen shieldings of 1,2,3-thiadiazole is significant and ranges from 11 to 30 ppm.

The conclusion was made on the basis of the analysis of the experimental data and molecular orbital studies (INDO/S, TNDO/2 and PM3) that an increase of the solvent polarity favors the delocalization of the lone electron pair from the sulfur atom into the rings and this, in turn, leads to an increase of electronic charge at the nitrogen atoms.[61]

2.2.2.4. *Nitrogen-15 NMR Spectroscopy*

The ^{15}N NMR spectra for 15 monosubstituted 1,2,3-thiadiazoles were recorded, and the assignment of the nitrogen absorptions was based on the multiplicity patterns.[62] The results summarized in Table 2.8 indicate a strong dependence of the N-2 resonance on the R^5 substituent, which could be rationalized by the conjugation effect. It has been shown that substituents at the 4-position have little effect on the nitrogen resonances.

TABLE 2.7. SOLVENT EFFECTS ON THE NITROGEN-14 NMR SHIELDING OF 1,2,3-THIADIAZOLE[a]

Solvent	Measured		Calculated	
	N_3	N_2	N_3	N_2
Cyclohexane	−61.69	−39.19	−61.0	−38.47
Et_2O	−60.56	−35.97	−62.02	−37.80
CCl_4	−59.79	−37.23	−60.39	−37.34
Benzene	−58.95	−35.20	−60.35	−36.56
Dioxane	−59.14	−34.26	−59.26	−34.42
Acetone	−58.50	−32.80	−57.93	−32.42
DMSO	−57.21	−31.26	−58.41	−31.52
CH_2Cl_2	−55.72	−31.45	−54.12	−30.23
$CHCl_3$	−54.94	−31.29	−53.10	−29.67
EtOH	−53.06	−29.89	−52.47	−29.36
MeOH	−51.55	−28.56	−49.73	−27.08
H_2O	−41.10	−17.76	−41.52	−18.74
CF_3CH_2OH	−37.0	−17.5	−38.88	−18.58

[a]All data are corrected for bulk susceptibility effect and related to 0.2 M solutions at $+35.0 \pm 0.2^{\circ}C$.

TABLE 2.8. ^{15}N NMR DATA OF 1,2,3-THIADIAZOLES[a]

R^4	R^5	Solvent	N-2	N-3
H	H	DMSO-d_6	409.9	436
H	Et	$CDCl_3$	403.7	434.5
H	Sme	$CDCl_3$	402	435
H	Cl	DMSO-d_6	414	443.5
H	NH_2[b]	DMSO-d_6	353.6	433.8
H	COPh	$CDCl_3$	421.7	437.6
H	CHO	$CDCl_3$	427.2	438.4
H	CH=NOH (Z)[c]	DMSO-d_6	410.9	430
H	CH=NOMe (Z)[d]	$CDCl_3$	412.6	427.9
H	CH=N(O)Me (Z)[e]	DMSO-d_6	399.9	426.2
H	CH=NNHPh (E)[f]	DMSO-d_6	402.3	438.9
Ph	H	DMSO-d_6	411.2	433.3
t-Bu	H	DMSO-d_6	410.4	439.4
COOMe	H	DMSO-d_6	416.1	438.2
CHO	H	DMSO-d_6	417.0	438.95

[a] δ Values from liquid ammonia quoted, using nitromethane as an external reference. The coupling constants are: $^2J_{N_3-H_4} = 9-11$ Hz, $^3J_{N_2-H_4} = 2-3.5$ Hz, $^3J_{N_2-H_5} \leq 1$ Hz.
[b] NH_2 at δ 58.8.
[c] NOH at δ 378.5.
[d] NOMe at δ 389.
[e] N(O)Me at δ 282.1.
[f] N-NHPh at δ 343.3 and 153.8.

Table 2.9 lists the ^{15}N NMR data of thiadiazolium salts. All nitrogen resonances are shifted when compared to those of the corresponding thiadiazoles. The most dramatic upfield shifts are found for the methyl-substituted nitrogen atoms, ranging from 142 to 145 ppm when the methyl is located at N-2, and from 158 to 167 ppm when N-3 is substituted. The average shielding of the α-nitrogen atom in the two cases is almost the same, that is, 30–40 ppm. For the mesoionic compounds, where a negatively charged 5-substituent displaces electron density towards the positively charged nucleus, the ring nitrogen shielding is even larger.[62] In thiadiazoles existing in a thiapentalenic form, the shielding effect of the 5-substituent on N-2 atom is considerably smaller in comparison to this in mesoionic monocyclic compounds.

2.2.3. Mass Spectrometry

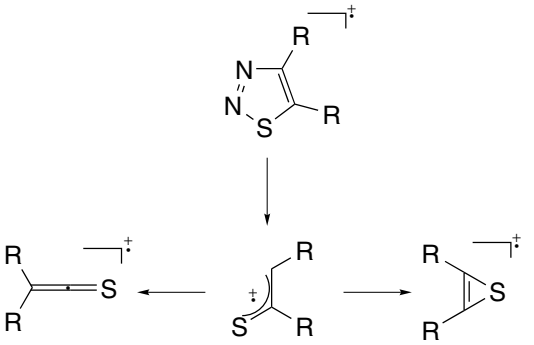
Most of the 1,2,3-thiadiazoles studied exhibit very intense signals for the molecular ions.[63] Predominant fragmentation takes place exclusively with loss of nitrogen, and, therefore, the peak of the $[M\text{-}N_2]^{+\cdot}$ ion is the most intense in the spectrum. It is worth noting that the loss of the nitrogen may also take place in the conditions to form a thioketene.[63] Other types of molecular-ion fragmentations are negligible and happen to be visible only in the study of 1,2,3-thiadiazole

TABLE 2.9. ^{15}NITROGEN NMR DATA OF 1,2,3-THIADIAZOLIUM SALTS[a]

R^4	R^5	A		B	
		N-2	N-3	N-2	N-3
H	H			377.1	278
H	Cl			373.5	276.7
Ph	H	268.9	400.2	376.8	274.1
t-Bu	H	265.7	405.3	381.6	274.8
COOMe	H			387.1	277.7

[a] δ Values from liquid ammonia quoted, using nitromethane as an external reference; solvent: dimethyl sulfoxide. The coupling constants are: for **A**: $^3J_{N_3-H_5} = 2$ Hz, $^3J_{N_2-H_5} = 4$–4.5 Hz, $^2J_{N_2-Me} = {}^3J_{N_3-Me} = 1.5$–2.5 Hz; for **B**: $^2J_{N_3-H_4} = 4$–5 Hz, $^3J_{N_2-H_4} \leq 2$ Hz, $^3J_{N_3-H_5} = 6$ Hz, $^3J_{N_2-H_5} \leq 2$ Hz, $^3J_{N_3-Me} = {}^3J_{N_2-Me} = 1.5$–2.5 Hz.

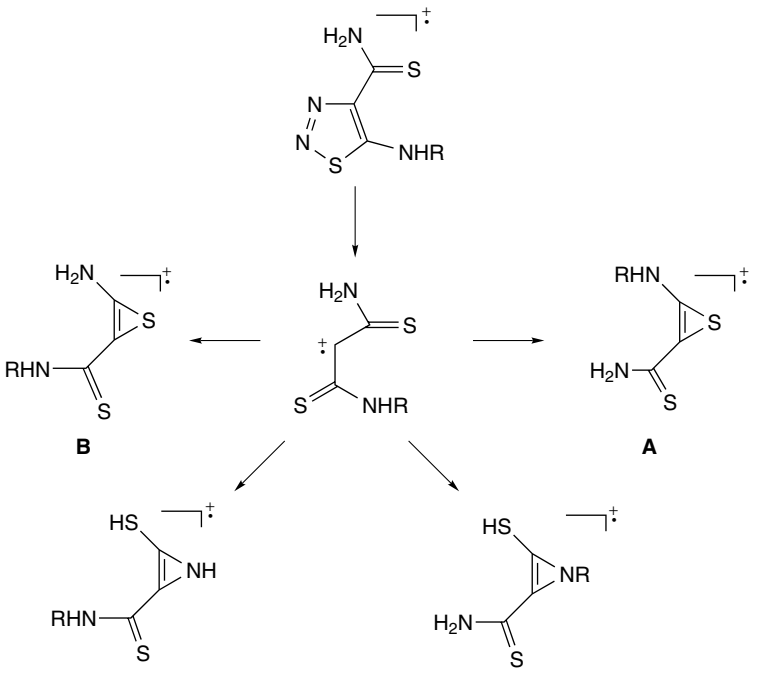
derivatives of complex structures.[64] It should be noted specially that there were no cases of the registration of fragment ions due to the ortho effect of the substituents in the molecular ion in the spectra.[64,65]



The structure of the $[M\text{-}N_2]^{+\cdot}$ fragment has been extensively studied. Depending on the nature of the substituents, it can exist in various isomeric forms. It has been shown to have a thioketene structure and the distonic ion $^{\bullet}CH{=}CH{-}S^+$ for the unsubstituted thiadiazole.[66] In the case of 5-alkyl-substituted 1,2,3-thiadiazoles, the $^{\bullet}CH{=}CH{-}S^+$ ion isomerizes to the thioketene. The $[M\text{-}N_2]^{+\cdot}$ ion for 5-amino-1,2,3-thiadiazoles exists in the thiirene form.[67–69] More complex substituents at the 4- and 5-positions of the ring lead to a $[M\text{-}N_2]^{+\cdot}$ ion of alternative structure.[64,65]

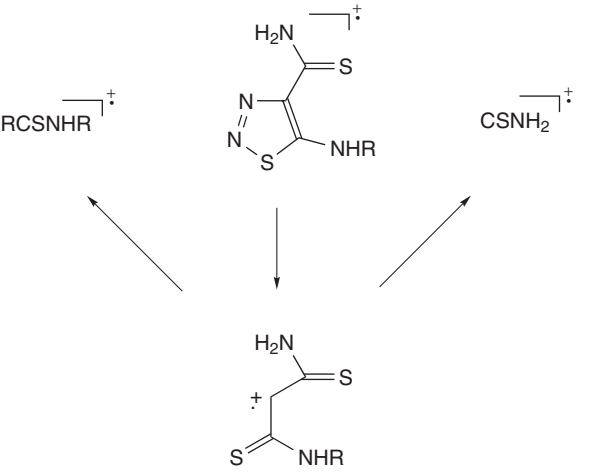
The existence of a thiocarbamoyl group at the 4-position of 5-alkylamino-1,2,3-thiadiazole-4-thiocarboxamides gives two additional centers for the interaction with the cation radical generated. The stabilization of the $[M\text{-}N_2]^{+\cdot}$ ion in

this case is possible due to the cyclization onto one of the four heteroatoms to form a three-membered heterocycle.



An analysis of the spectra for a series of 1,2,3-thiadiazoles allowed us to make a conclusion on the preferential cyclization of the $[M\text{-}N_2]^+$ cation radical onto the substituted thioamide group to form thiirene **A**.[70] Indeed, the main direction of the fragmentation of $[M\text{-}N_2]^+$ of thiirene structure is the loss of RNH_2 due to the ortho effect and RCN. Fragmentation of thiirene **B** should be accompanied by the loss of HCN and RNH_2. In contrast, in the case of thiirene **A**, one can expect the loss of NH_3 and RCN. Because the intensity of the last pair of molecules was shown to be considerably higher, we concluded that the preferential cyclization of the cation radical occurred onto the sulfur of the substituted thioamide group. This process can be rationalized by an increase of electron density on the sulfur of the substituted thioamide group due to the electron-donating properties of the alkyl- and aryl groups that make it a more nucleophilic center in comparison with the sulfur of a nonsubstituted thioamide group. It should be noted that a thiirene of type **A** can also be formed in the fragmentation of 5-amino-1,2,3-thiadiazole-4-*N*-methylcarbothioamide, which is isomeric to 5-methylamino-1,2,3-thiadiazole-4-carbothioamide. Therefore, the analysis of the structure of the a $[M\text{-}N_2]^{+\cdot}$ ion does not allow one to distinguish the isomeric thiadiazoles, the products of the cyclization of diazomalonthioamides and of rearrangements of 1,2,3-thiadiazole- and 1.2.3-triazolecarbothioamides (see Section 4).

We have shown that the intensity of the fragment $RNHCS^+$ that is formed by the cleavage of C_4-C from the molecular ion is higher than that formed from the $[M\text{-}N_2]^{+\cdot}$ ion. This fact gave us the background to distinguish isomeric 5-amino-1,2,3-thiadiazole-4-thiadiazoles by analyzing their mass spectra.



2.2.4. Other Spectroscopic Data

The data on photoelectronic-[5], magnetic circular dichroism-[6], nuclear quadrupole resonance-[7], IR-[41] and UV[42] spectroscopy were published for some 1,2,3-thiadiazole derivatives. They are not considered in detail here because of their limited use for organic chemists working in the area of 1,2,3-thiadiazoles.

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CHAPTER 3

Chemical Properties of 1,2,3-Thiadiazoles

The chemical reactions of 1,2,3-thiadiazoles can be classified according to

— reactions due to the reactivity of ring atoms,
— reactions of substituents,
— rearrangements,
— ring-cleavage reactions.

3.1. REACTIONS DUE TO THE REACTIVITY OF RING ATOMS

Similar to other azoles, 1,2,3-thiadiazoles are capable of reacting with electrophilic and nucleophilic reagents. Moreover, there are examples in the literature on the cycloaddition and electrocyclic reactions of 1,2,3-thiadiazoles where double bonds of the ring take part in a pericyclic process. 1,2,3-Thiadiazoles can also react with strong bases and acids. These reactions often lead to the destruction of the 1,2,3-thiadiazole ring and will be mainly considered in the section on ring-cleavage reactions.

3.1.1. Reactions with Electrophiles

3.1.1.1. Protonation

There are no experimental data on the site of protonation of the 1,2,3-thiadiazole ring. However, Mayr and coworkers have carried out calculations on 2- and 3-protonated 1,2,3-benzothiadiazoles.[1] The difference in energy for these structures calculated by the *ab initio* method with a 6-31-G basis set with zero-point energy (ZPE) correction was found to be 8.75 kcal/mol in favor of the 2-protonated benzothiadiazole.

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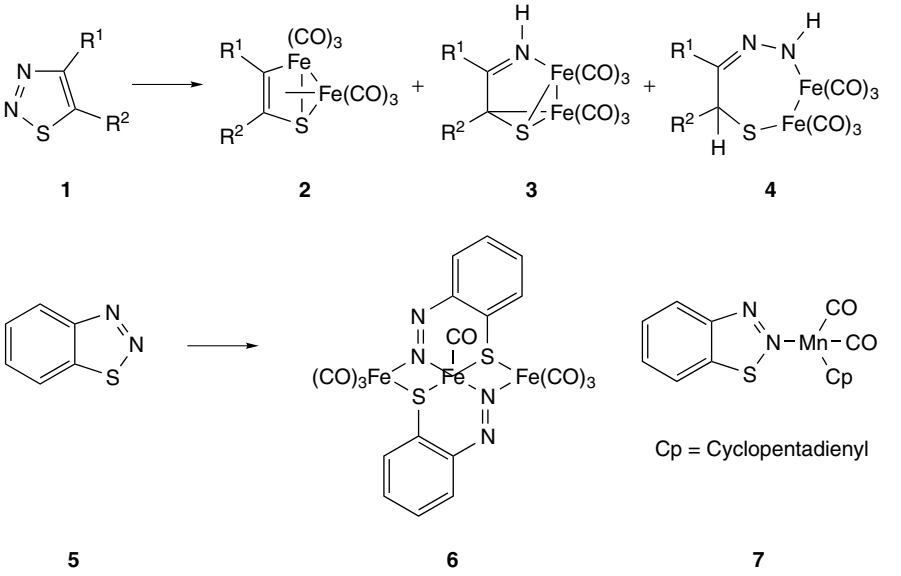
3.1.1.2. Complexation

Reactions of 1,2,3-thiadiazoles with $Fe_2(CO)_9$ were shown to lead to various products depending on the nature of both the thiadiazole and the solvent used.[2] The use of hexane leads to complexes where nitrogen has been either entirely or partially eliminated from the aromatic system to produce carbene and imine diiron hexacarbonyl complexes **2** and **3**. In the case of 1,2,3-benzothiadiazole, a linear triiron complex of α-diazo thioketone **6** was formed.[3] When 1,2,3-thiadiazoles are reacted with $Fe_2(CO)_9$ in the presence of ethyl alcohol, thioketohydrazono complexes **4** are formed. It is interesting to note that the yield of **4** depends on the quantity of alcohol in the solvent mixture: in pure hexane the products are **2** and **3**, whereas in the ethanol complex, **4** is almost exclusively formed. In alcohol/hexane mixtures all three complexes **2**–**4** are produced.



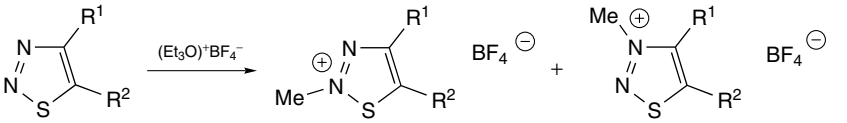
1 **2** **3** **4**

5 **6** **7**

In contrast to the reaction with $Fe_2(CO)_9$, 1,2,3-thiadiazoles are stable in the corresponding complexes of manganese, chromium and tungsten. Relatively stable complexes of simple 1,2,3-thiadiazoles were isolated where the metal is coordinated with the N_2 atom of the thiadiazole ring.[1,4,5] Thus, the complexation reaction of 1,2,3-benzothiaziazole with manganese cyclopentadienyldicarbonyl leads to complex **7.**[1] Indeed, parallels were found in the site of coordination of the thiadiazole ring with either metals or protons.[1] In contrast to the complexation with metals, the reaction of 1,2,3-benzothiadiazole with AsF_5 was directed to position 3 of the thiadiazole ring.[6]

3.1.1.3. Alkylation

The parent 1,2,3-thiadiazole is known to react with Meerwein's reagent to give mainly the product with the methyl group attached to the N_3 ring atom.[7–9] In the case of bulky substituents present at position 4 of the ring, the direction of alkylation changes in favor of the 2-alkyl derivative. Table 3.1 contains a few more examples on this methylation reaction, illustrating the effect of the nature of the substituent at the 4-position on the direction of alkylation.



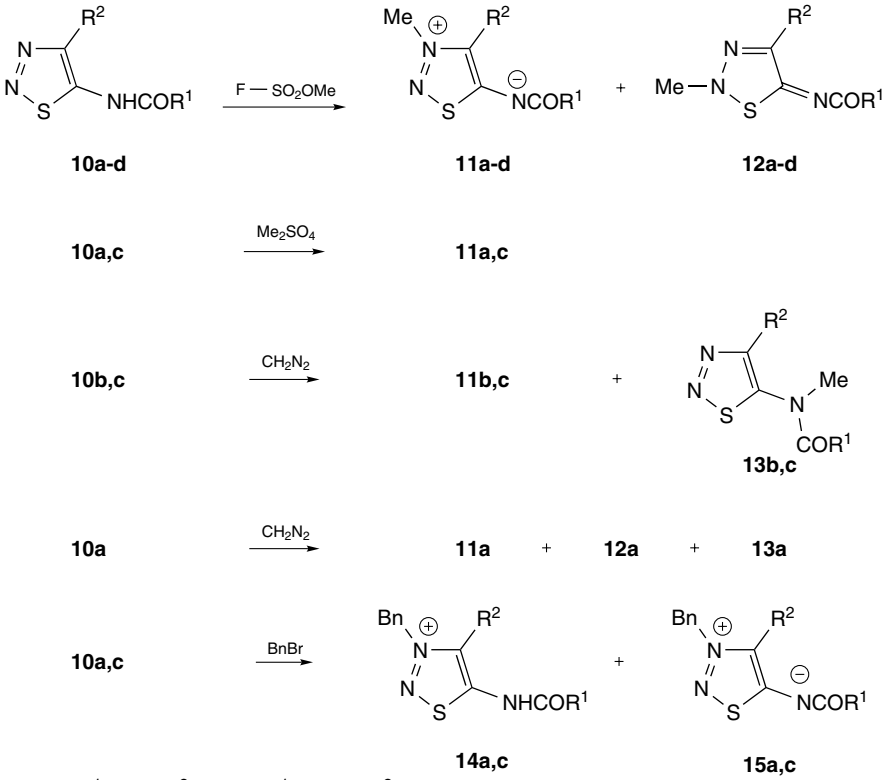
1 **8** **9**

Masuda and coworkers have studied the alkylation of 5-acylamino-1,2,3-thiadiazoles with various alkylating reagents, including dimethyl sulfate, methyl fluorosulfonate, benzyl bromide and diazomethane.[10]

The methylation of compound **10** with methyl fluorosulfonate takes place at the positions 3 and 2 to give a mixture of compounds **11** and **12**. On the other hand, the reactions of compounds **10a** and **10c** with dimethyl sulfate at elevated temperatures, followed by treatment with an alkali gave the monomethyl derivatives **11a** and **11c** respectively, as the sole products. Methylation of **10** with diazomethane has been shown to give products **11**–**13,** depending on the nature of the starting thiadiazole. Whereas the methylation of **10b,c** with diazomethane gave two products, **11b,c/12b,c,** the reaction of **10a** yielded mainly the products of methylation at position 2 and 3 of the ring, compounds **11a** and **12a** with only a trace of **13**. Reactions of **10a** and **10c** with benzyl bromide afforded 3-benzyl-1,2,3-thiadiazolium bromides **14a,c**, which also gave mesoionic compounds **15a,c** by treatment with alkali.[10]

TABLE 3.1. PRODUCT DISTRIBUTION FOR THE METHYLATION OF 1,2,3-THIADIAZOLES WITH MEERWEIN'S REAGENT

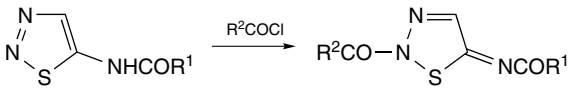
R^1	R^2	**8** (%)	**9** (%)
H	H	4	96
H	Cl	—	100
Bu^t	Cl	100	—
Ph	H	81	19
Bu^t	H	87	13
CO_2Me	H	8	92
Bu^t	NH_2	100	—
Bu^t	NHN=CHAr	100	—



a: R^1 = Ph, R^2 = H; **b**: R^1 = OPh, R^2 = H;
c: R^1 = OEt, R^2 = H; **d**:R^1 = OEt, R^2 = Ph

3.1.1.4. Acylation

The acylation reaction of 5-acylamino-1,2,3-thiadiazoles **10** has been shown by Goerdeler and Gnad to occur at the 2-position of the ring. However, the structural proof is not sufficient to rule out the formation of zwitterionic compounds.[11]



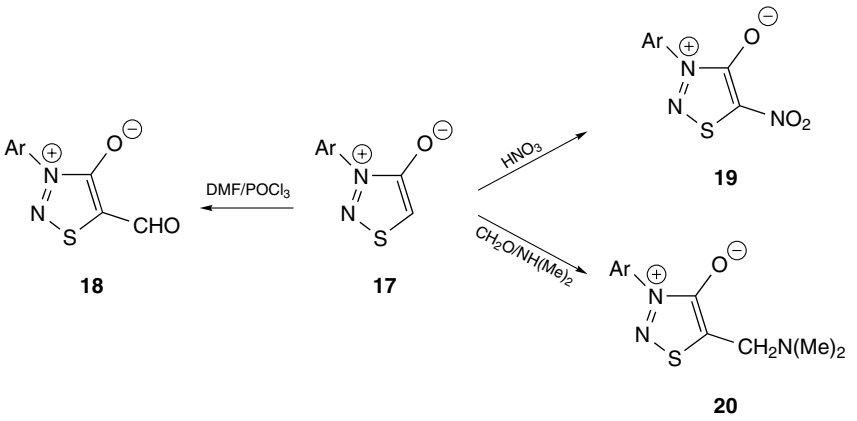
10 **16**

3.1.1.5. Oxidation

It has been shown that the oxidation of 1,2,3-thiadiazoles with peracids takes place at position 3 of the ring, and the use of more than 1 equiv of peracid leads to oxidation of both N_3 and sulfur atoms.[12,13]

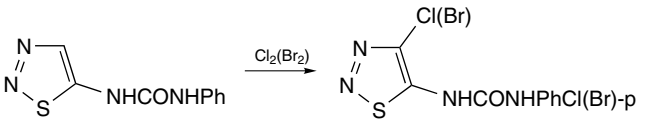
3.1.1.6. Electrophilic Substitution of Hydrogen

The publications on electrophilic substitution of the ring hydrogen are limited to two papers. As a result of the influence of the olate group in the mesoionic 3-phenyl-1,2,3-thiadiazoles **17**, they are capable of reacting with nitric acid and undergoing Mannich aminomethylation and Vilsmeier formylation.[14]



18 **17** **19** **20**

We have also managed to prepare the halogenation products of 1,2,3-thiadiazoles. The compounds **22** were obtained after reaction of 5-phenylureido-1,2,3-thiadiazole **21** with chlorine or bromine. Halogenation occurs on both the phenyl and 1,2,3-thiadiazole rings.[15]



21 **22**

3.1.2. Reactions with Nucleophiles

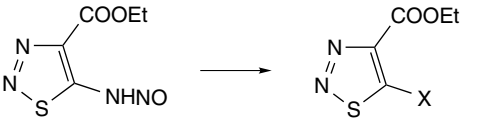
3.1.2.1. Attack at the Sulfur Atom

According to *ab initio* calculations (See Chapter 2), the sulfur atom should be the most electrophilic in the 1,2,3-thiadiazole molecule.[16] The possibility of the existence of some 1,2,3-thiadiazoles in the thiapentalenic form (See Chapter 4) confirms the electrophilic character of the sulfur atom in these compounds. There is also evidence that the fragmentation of 4,5-diphenyl-1,2,3-thiadiazoles[17] and

some of the 5-chloro-1,2,3-thiadiazoles[18] resulting from reactions with butyllithium is initiated by the nucleophilic attack on the sulfur atom.

3.1.2.2. Attack at the C_5 Atom

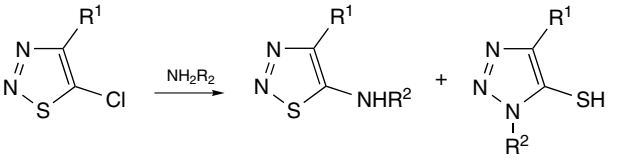
Goerdeler and Gnad have shown that 5-hydroxy-, 5-ethoxy-, 5-chloro- and 5-bromo-1,2,3-thiadiazoles can be easily prepared by treatment of 5-nitrosoamino-1,2,3-thiadiazole **23** with water in the presence of sulfuric acid, with an alcoholic solution of sulfuric acid and with hydrochloric or hydrobromic acids, respectively.[11] The probable mechanism of this reaction involves the nucleophilic substitution of the diazonium group by a nucleophile in the intermediate diazonium salt.



23 **24**

X = OH, OEt,Cl,Br

5-Chloro- and 5-bromo-1,2,3-thiadiazoles in their turn are capable of reacting with O-, N-, S- and C-nucleophilic reagents to form a large variety of 5-substituted 1,2,3-thiadiazole derivatives.[19–21] Thus, 5-amino-1,2,3-thiadiazole and 5-arylamino-1,2,3-thiadiazoles were prepared in good yield by the nucleophilic substitution of 5-chloro-1,2,3-thiadiazoles by liquid ammonia or anilines, respectively.[19,22] It has been shown that the reaction of the 5-chloro-1,2,3-thiadiazoles with aliphatic amines and hydrazine is accompanied by the formation of the Dimroth rearrangement products, namely 5-mercapto-1,2,3-triazoles, and by other by-products.

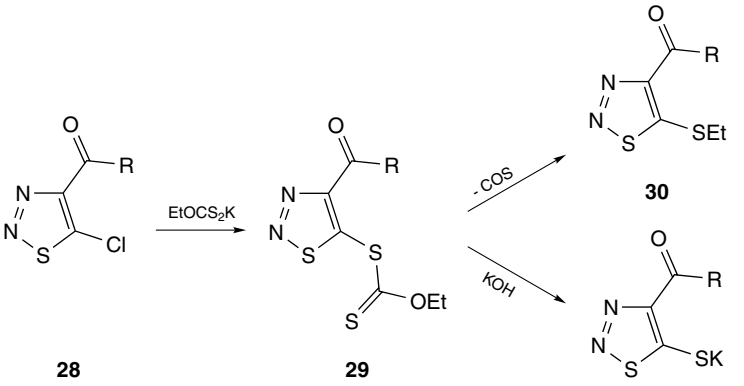


25 **26** **27**

R_1 = Alkyl, R_2 = Alkyl, Aryl, NH_2

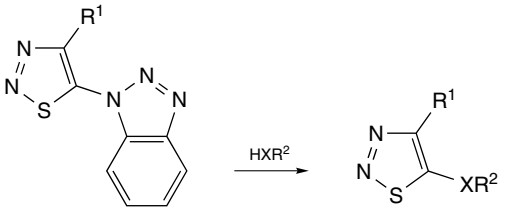
The ratio of thiadiazole **26:**triazole **27** has been shown to depend on the polarity of the solvent used in this reaction. Thus, triazole **27** was formed when compound **25** was treated with isopropylamine in DMF. On the contrary, when the reaction was carried out in chloroform or in hexane, only thiadiazole **26** was obtained.[19]

5-Chloro-1,2,3-thiadiazoles **28**, bearing electron-withdrawing acyl and ester groups at the 4-position are also able to react with potassium ethyl xanthate to afford 5-*S*-dithiocarbonates **29.** These compounds **29** were shown to be very labile, and they readily lost carboxysulfide to give 5-ethylthio-1,2,3-thiadiazoles **30**. On the other hand, *in situ* treatment of xanthate **29** with an ethanolic solution of potassium hydroxide afforded 1,2,3-thiadiazole-5-thiolates **31**.[23]

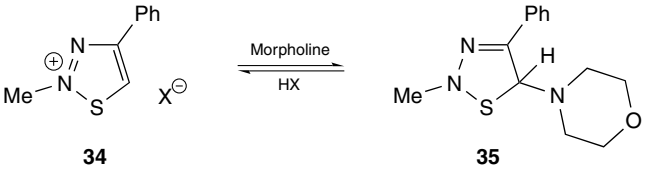


We have prepared a large series of bishetaryl sulfides, containing thiadiazole, triazole, imidazole and other heterocyclic systems by the reaction of 5-halo-1,2,3-thiadiazoles with the corresponding thiols (See Chapter 1).[24] The substitution of the chlorine atom in 5-chloro-1,2,3-thiadiazoles by C-nucleophiles requires activation either (1) by the introduction of an electron-withdrawing group at the 4-position, or (2) by the preliminary transformation of the 5-chloro-1,2,3-thiadiazoles to quaternary salts by N-alkylation with Meerwein's reagent. The latter method is of importance in the synthesis of 1,2,3-thiadiazole ylids and thiazapentalenes.

Katritzky and coworkers have shown that benzotriazole (Bt) is a good leaving group. Compound **32**, containing both 1,2,3-thiadiazole and benzotriazole rings, readily reacts with O- and S-nucleophiles to give 5-aryloxy- and 5-arylthio-1,2,3-thiadiazoles **33** in good yields.[25]

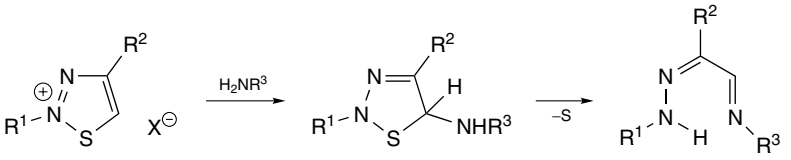


The carbon atom at position 5 of the 1,2,3-thiadiazolium salt **34** should be rather electrophilic according to NMR (Nuclear Magnetic Resonance) spectra.[26] This molecule easily adds morpholine to give the nonaromatic compound **35,** which in turn affords the starting compound in acidic conditions.[27]



34 **35**

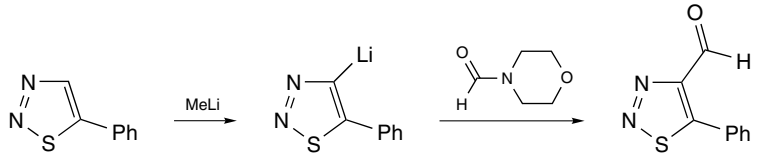
We have found a new reactivity pattern for the reaction of salts **34** with primary amines and hydroxylamines. Thus, the addition of amines to position 5 followed by the elimination of sulfur yields 1-arylamino-1,4-diazadienes **37**.[26]



34 **36** **37**

3.1.2.3. Attacks at H_4 and H_5

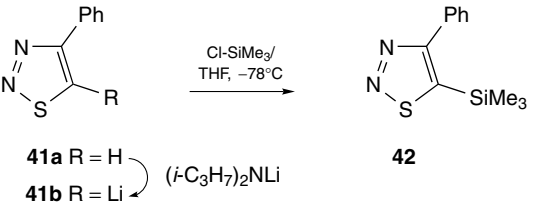
The H_5 proton of 1,2,3-thiadiazole is known to undergo rapid deuterium exchange on heating at reflux with D_2O in the presence of NaOD. Few attempts have been made to metallate this heterocycle.[28] 4-Lithio-1,2,3-thiadiazole and 5-lithio-1,2,3-thiadiazole are found to have different stabilities. The first one is rather stable and can react with electrophilic reagents to give a variety of 4-substituted 1,2,3-thiadiazoles.[28] For example, 5-phenyl-1,2,3-thiadiazole-4-carbaldehyde **40** is formed from 5-phenyl-1,2,3-thiadiazole **38** by treatment of its 4-lithio derivative **39** with *N*-formylmorpholine in tetrahydrofuran at -70°C.[29]



38 **39** **40**

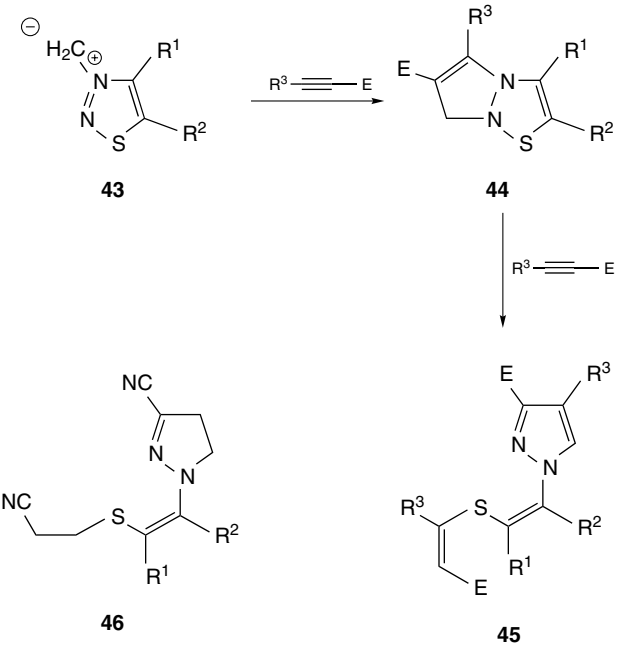
In contrast, 5-lithio-1,2,3-thiadiazole **41b** is extremely unstable and decomposes under the conditions of its preparation leading to various products of the

fragmentation of the ring. Thomas and Zimmerman managed to trap this compound *in situ* with chlorotrimethylsilane, before fragmentation occurred, to give compound **42.**[28]

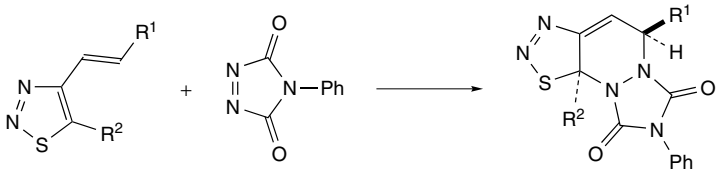


3.1.2.4. Cycloaddition Reactions

Alkylation reactions of 4,5-diaryl-1,2,3-thiadiazoles and 1,2,3-benzothiadiazoles with trimethylsilylmethyl trifluoromethanesulfonate occurred at N-3 to generate after treatment with CsF, 1,2,3-thiadiazol-3-ium-3-methanide 1,3-dipoles **43**. These nonstabilized azomethine ylides react *in situ* with alkynes or alkenes to form a pyrazolo-thiadiazole system **44**. The latter undergoes opening of the 1,2,3-thiadiazole ring followed by reaction with a second molecule of dipolarophile to form substituted 1-(2-vinylthioethenyl)pyrazoles **45** if acetylenes were used, and **46** with acrylonitrile as dipolarophile.[30]



We could find only one example in the literature on cycloaddition reactions where the C_4-C_5 double bond of the 1,2,3-thiadiazole ring takes part in a pericyclic process. Meier and coworkers have prepared 4-alkenyl-1,2,3-thiadiazoles **47** and involved them in a [$4\pi e + 2\pi e$] reaction with 4-phenyl-4H-1,2,4-triazole-3,5-dione **48**. Indeed, tricyclic compounds **49** were prepared in moderate yields.[31]



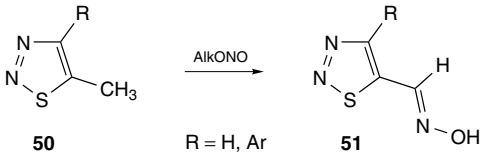
47 **48** **49**

3.2. REACTIONS OF SUBSTITUENTS

Section 1.5 already contains data on the reaction of functional groups attached to the ring. It has been shown there that carboxylic acids, aldehydes, amines, thiols and so on have a similar reactivity when attached to other heterocyclic compounds. Rearrangements and ring-cleavage reactions, however, often accompany the functional group transformations leading to the formation of by-products. Rearrangements and ring-cleavage reactions will be described in the following sections of this chapter. First, we concentrate on the important reactions of 1,2,3-thiadiazole substituents that either were not included in the previous chapter or not dealt with in detail there.

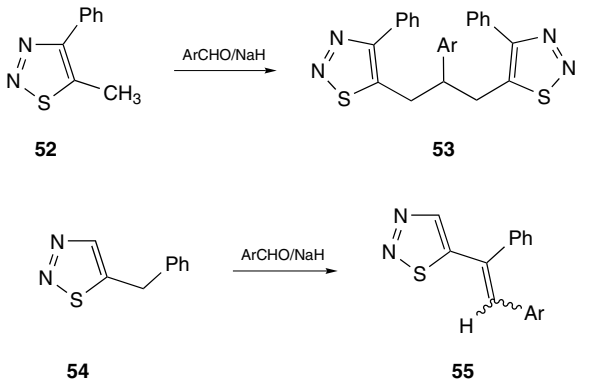
3.2.1. 5-Alkyl-1,2,3-Thiadiazoles

The 1,2,3-thiadiazolyl group behaves as an electron acceptor and, in consequence, 5-methyl-1,2,3-thiadiazoles **50** show appreciable CH-acidity. Compounds **50** can react with alkyl nitrite and base to form 5-hydroxyiminomethyl-1,2,3-thiadiazoles **51**.[32]



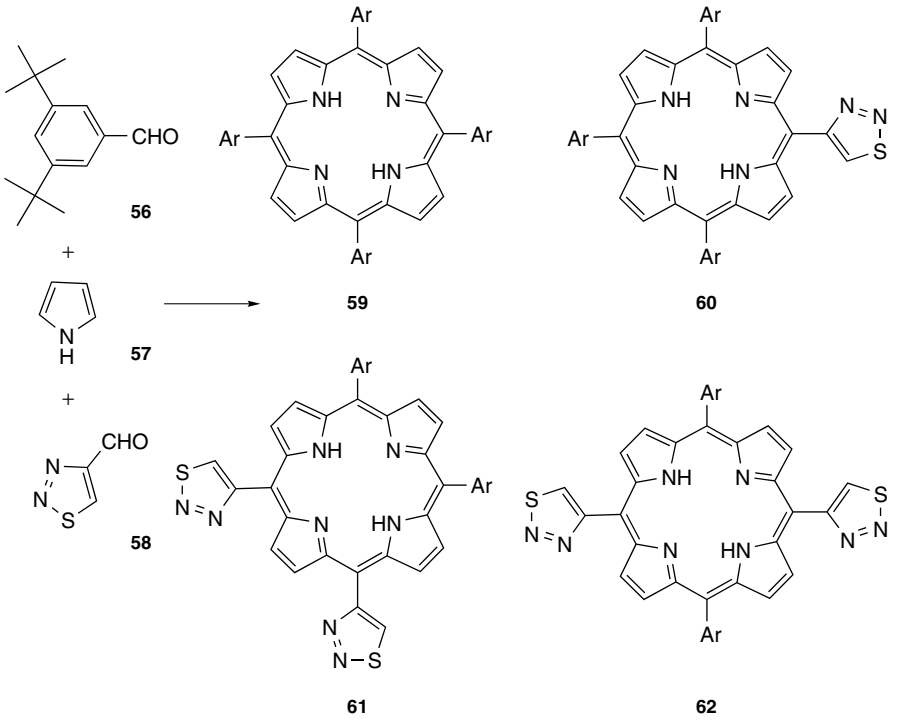
50 R = H, Ar **51**

4-Phenyl-5-methyl-1,2,3-thiadiazole **52** underwent the Knoevenagel reaction, giving bis(1,2,3-thiadiazol-5-yl) alkanes **53** and 5-benzyl-1,2,3-thiadiazole **54** reacts with arylaldehydes to form a mixture of *E*- and *Z*-isomers of the vinyl-substituted 1,2,3-thiadiazoles **55**.[33] Both reactions give additional evidence of the high acidity of 5-alkyl-1,2,3-thiadiazoles.



3.2.2. 1,2,3-Thiadiazole-4-Carbaldehyde

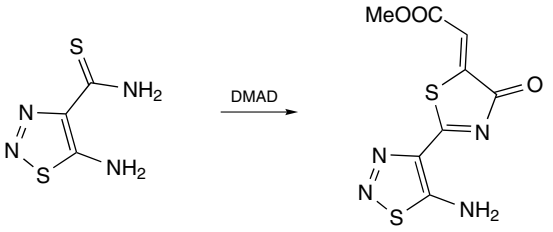
This aldehyde was used to prepare the first mesosubstituted (1,2,3-thiadiazol-4-yl)porphyrin by a mixed Rothemund condensation with 3,5-bis(*tert*-butyl)benzaldehyde **56** (ratio of **56:58** is 1 to 2). This yielded, apart from symmetrical A_4 porphyrin **59** (12%), three 1,2,3-thiadiazole-containing compounds **61** (15%), **62** (11%) and **63** (9%).[34]



Similarly, the phenyl analog of **60** (Ar=Ph) was prepared in 21% yield from benzaldehyde, aldehyde **58** and pyrrole **57**.[35]

3.2.3. 5-Amino-1,2,3-Thiadiazole-4-Carbothioamide

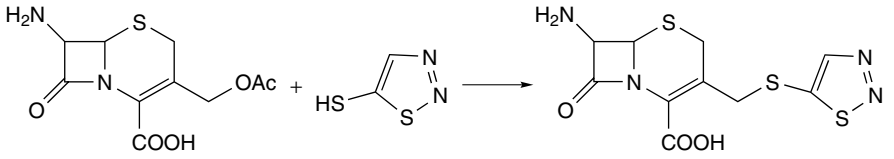
The thioamide group at position 4 of a 1,2,3-thiadiazole is rather susceptible to nucleophilic attack. The alkylation of 5-amino-1,2,3-thiadiazole-4-carbothioamide **63** is directed to the sulfur atom of the thioamide function and accompanied by rearrangement of the thioimidate intermediate to a 5-mercapto-1,2,3-triazole-4-carbothioamide (See details in the next section). In contrast, reaction of **63** with dimethyl acetylenedicarboxylate takes place with participation of both the sulfur and nitrogen atoms of the thioamide group to give thiazolone **64** as the final product.[36]



63 **64**

3.2.4. Mercapto-1,2,3-Thiadiazoles

5-Mercapto-1,2,3-thiadiazole can be alkylated at the sulfur atom to form alkylthio-1,2,3-thiadiazoles.[37] The potassium salt of this compound **66** has been employed to prepare a new cephalosporin antibiotic **67** as depicted below.[38]



65 **66** **67**

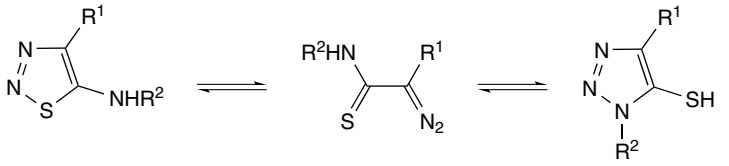
3.3. REARRANGEMENTS

Rearrangements of 1,2,3-thiadiazoles are governed by the following factors: (i) The facile cleavage of the weak N−S bond, (ii) the existence of an equilibrium

between 1,2,3-thiadiazoles and α-diazo thiocarbonyl compounds and (iii) the capacity of both the thiocarbonyl and diazo groups to cyclize onto electrophilic and nucleophilic functionalities.[37] We subdivided the material on the rearrangements of 1,2,3-thiadiazoles into four groups depending on the number of atoms in the chain that take part in the rearrangement process.

3.3.1. Dimroth-type Rearrangements

The base-induced rearrangements of 5-amino-1,2,3-thiadiazoles **68** to 5-mercapto-1,2,3-triazoles **70** result in the exchange of the ring sulfur atom with the exocyclic nitrogen atom and, therefore, can be seen as a part of the family of Dimroth rearrangements.[39] This type of rearrangement includes reactions where one atom of the chain takes part in the rearrangement process. The cyclizations of the diazo group of the intermediate **69** onto either the sulfur or nitrogen atom are a common feature of this type of rearrangement in the 1,2,3-thiadiazole series.

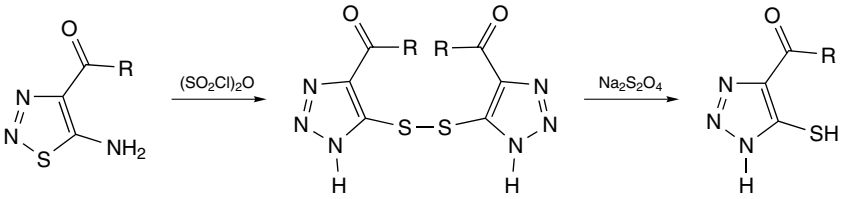


68 **69** **70**

The first examples of this rearrangement were described in the work of Kindt-Larsen and Pedersen in 1962[40] and a few years later by Goerdeler and Gnad.[11] Subsequently, many workers used this reaction to prepare a number of various 5-mercapto-1,2,3-triazoles.[41] The effect of the substituents and the influence of the solvent polarity on the reaction equilibrium and kinetics are in accordance with the mechanism for this reaction outlined in the scheme.[41]

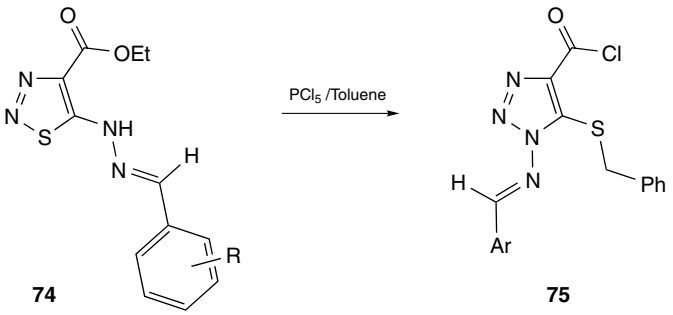
The more acidic 5-mercapto-1,2,3-triazoles **70** can be stabilized as their thiolate salts in basic solution, which is not possible for the isomeric 5-amino-1,2,3-thiadiazoles **68**, and this stabilization is the driving force for the forward process. On the contrary, the reverse process, described only for compounds **70** bearing either strong electron-withdrawing or bulky groups R^2 at the 1,2,3-triazole ring,[40] was observed in acidic or in neutral media.

We have found that esters and amides of 5-amino-1,2,3-thiadiazole-4-carboxylic acid **71** transform to disulfides **72** by treatment either with pyrosulfuryl chloride or with halogens in boiling toluene. 5-Amino-1,2,3-thiadiazoles **68** and 5-mercapto-1,2,3-triazoles **70** do not transform into each other either in toluene or in acetic acid at the same temperature. The conclusion was made that this transformation had a more complex mechanism than the base-induced rearrangement of 5-amino-1,2,3-thiadiazoles to 5-mercapto-1,2,3-triazoles.[15]



71 **72** **73**

The ring transformation of 1,2,3-thiadiazoles to 1,2,3-triazoles was also observed when hydrazones **74** were treated with phosphorus pentachloride in boiling toluene. It was accompanied by the transformation of the ester group to a carbonyl chloride function and "benzylation" at the sulfur atom, leading to the final compounds **75**. The mechanism of this reaction is not completely clear.[42]



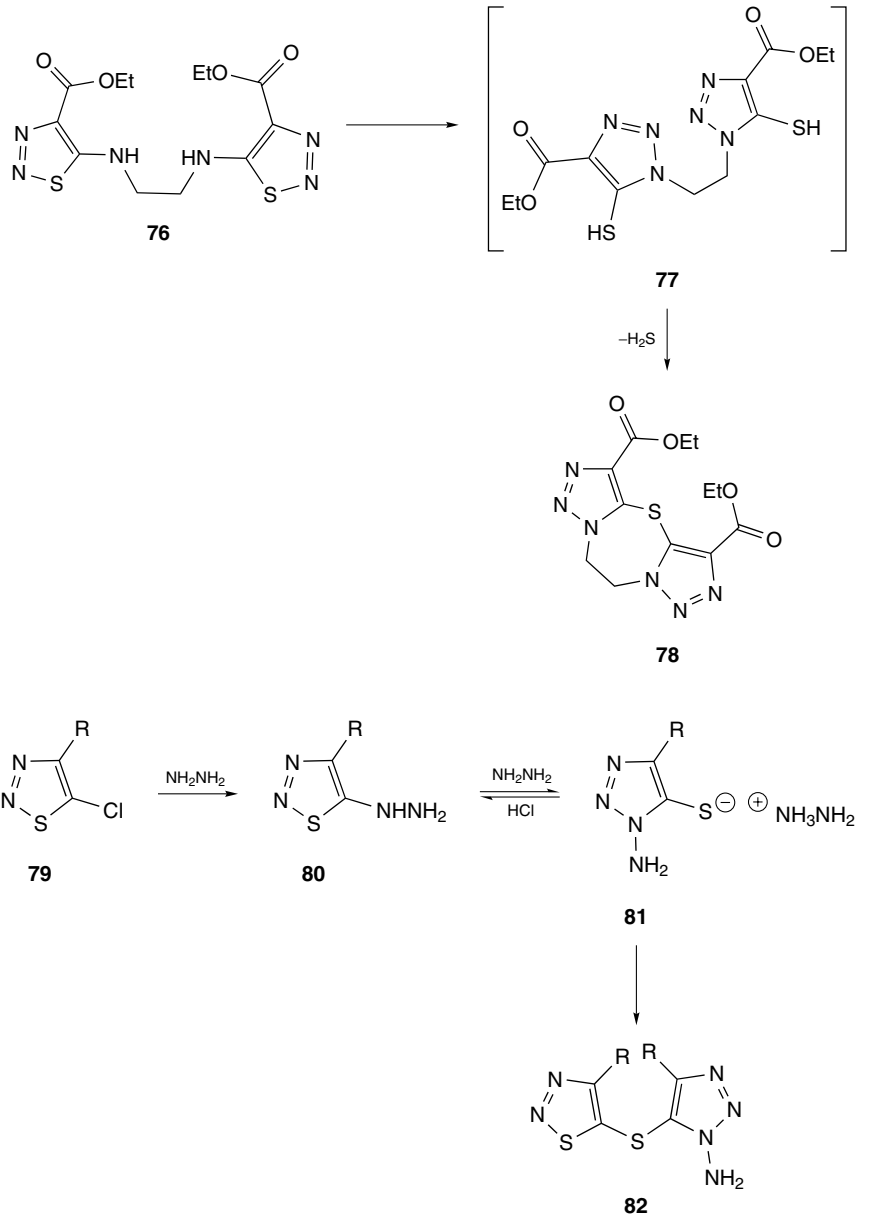
74 **75**

Most probably, a double Dimroth rearrangement occurs in the first step of the novel transformation of bisthiadiazol-5-aminoethane **76** to tricyclic triazole **77**.[43]

The intermediate bisthiol **77** then undergoes an intramolecular nucleophilic substitution reaction, with loss of hydrogen sulfide.

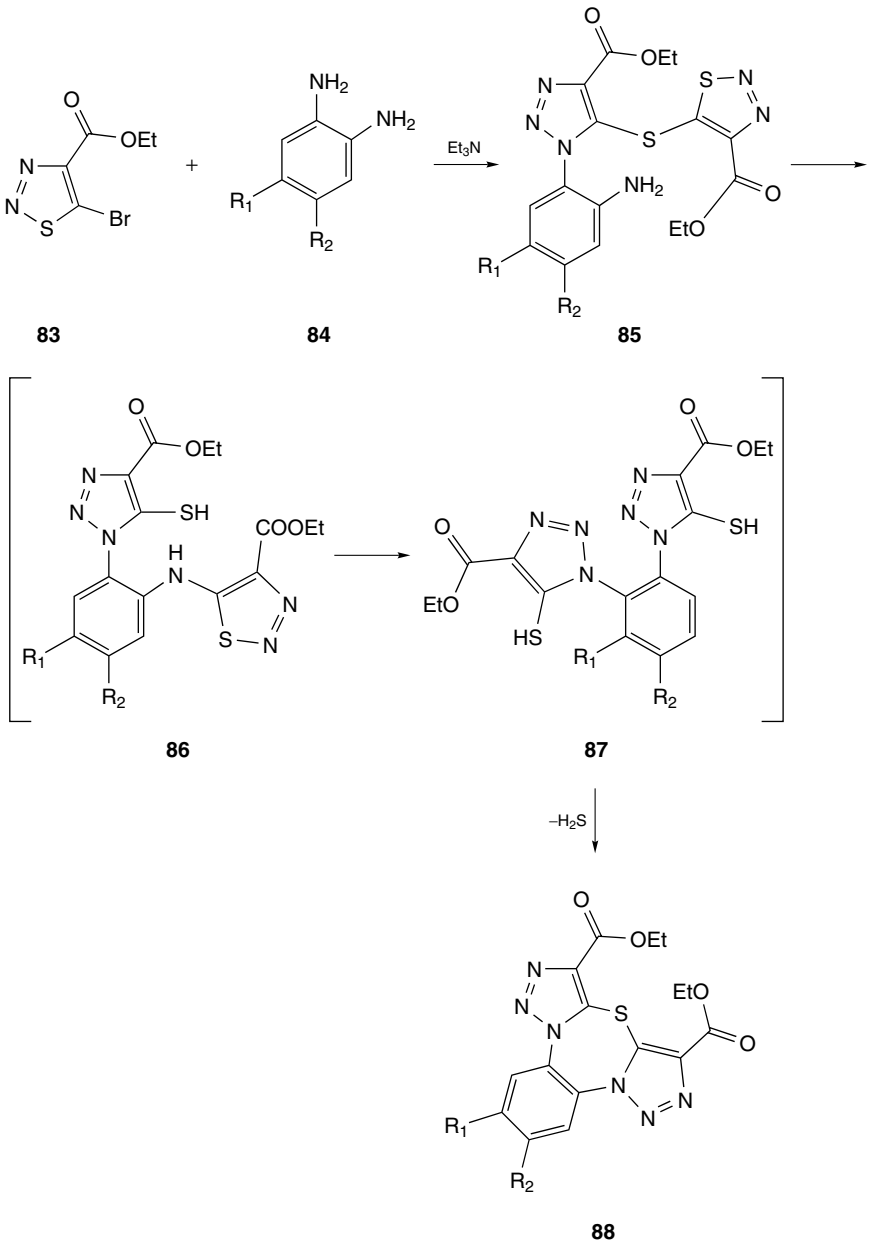
L'abbé and Vanderstede have found that 5-chloro-1,2,3-thiadiazoles **79** on treatment with an excess of hydrazine afford sulfides **82**. This interesting reaction was shown to proceed as a three-step process and includes the rearrangement of 5-hydrazino-1,2,3-thiadiazoles **80** to *N*-amino-1,2,3-triazoles **81**, as shown below. The same workers have isolated the intermediate hydrazine derivative **80** (R = COOEt) and have found that its rearrangement to 5-mercapto-1,2,3-triazole **81** takes place on treatment with hydrazine, whereas acidification of the latter with hydrochloric acid yields **81**, indicating the reversibility of the rearrangement.[20]

Interestingly, the reaction of 5-bromo-1,2,3-thiadiazoles **83** with *ortho*-phenylenediamine **84** leads to thiadiazepine **88**. The intermediate sulfides **85** are more reactive than sulfide **82**. Smiles rearrangement of the intermediate **85** to isomer **86**, followed by Dimroth rearrangement gives bis-triazole **87**.[44] This reaction was expanded to various aromatic phenylenediamines and 1,2-ethanediamines. When

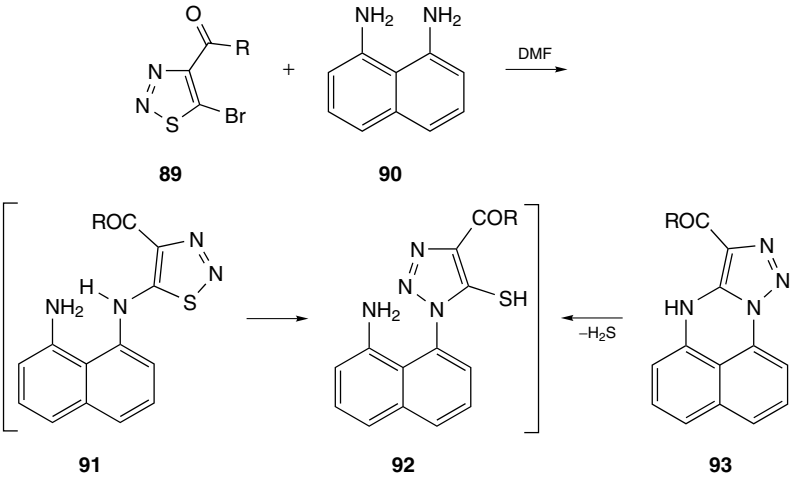


1,3-diaminopropane was used in the reaction with 5-bromo-1,2,3-thiadiazole **83**, a tricyclic compound containing an eight-membered ring was obtained.

On the other hand, the reaction of 5-halo-1,2,3-thiadiazoles with 1,8-diaminonaphthalene occurs in a different fashion to afford pyrimidine **93**. The proposed

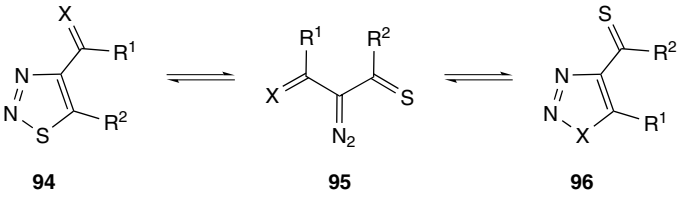


mechanism outlined below includes the nucleophilic substitution of bromine to generate the 5-amino substituted-1,2,3-thiadiazole **91**, which undergoes a Dimroth rearrangement to form 1-aminonaphthyl-5-mercapto-1,2,3-triazole **92**. Intramolecular substitution of the mercapto group of **92** affords the final compound **93**.[42,43]



3.3.2. Cornforth-type Rearrangements

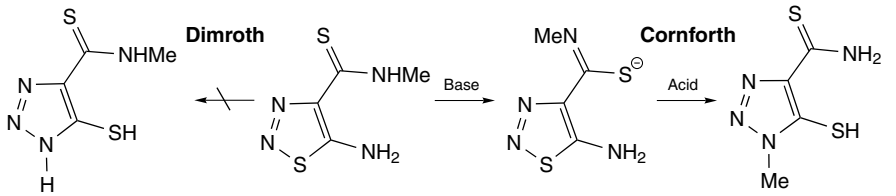
Rearrangements of 1,2,3-thiadiazoles of type **94**, bearing a C=S and C=N function at the 4-position, to isomeric 1,2,3-thiadiazoles **96** (X = S) or 1,2,3-triazoles **96** (X = NR) were found and carefully studied in our laboratories. They involve two atoms of the 4-substituent and are similar in this respect to the interconversion reactions of isomeric 4-acyl-substituted oxazoles via the dicarbonyl nitrile ylides discovered by Cornforth in 1949.[39] These rearrangements proceed via a 1,3-dipolar intermediate diazo compound **95** bearing two nucleophilic groups (two thiocarbonyl functions or a thiocarbonyl and an iminocarbonyl function).



3.3.2.1. Rearrangements of 4-(iminomethyl)-substituted-1,2,3-Thiadiazoles

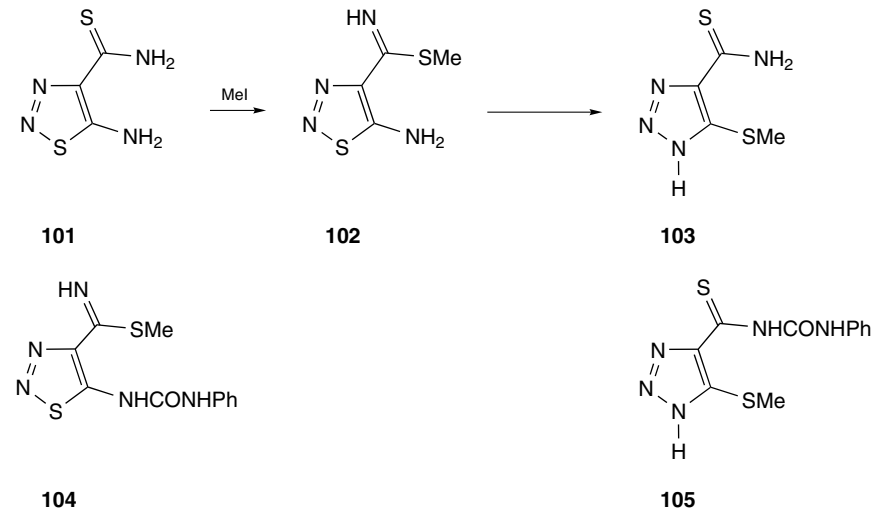
We have found that 5-amino-1,2,3-thiadiazole-4-carbothioamides **97**, similar to thiadiazoles **68,** are capable of rearranging to form 5-mercapto-1,2,3-triazoles **99** by treatment with a base. However, in contrast to the Dimroth type of rearrangement in which one can expect the formation of triazole **100**, this reaction

involves two atoms of the side chain to give 1-alkyl-1,2,3-triazole-5-thiols **99** rather than the isomeric product **100**.[45,46]



100 **97** **98** **99**

It should be noted that the rearrangement of **97** proceeds considerably faster than that of the 5-amino-1,2,3-thiadiazole-4-carboxamides **71,** which proceeds via the Dimroth mechanism. The reason why the Cornforth rearrangement is preferred over the Dimroth rearrangement for 5-amino-1,2,3-thiadiazole-4-carbothioamides is still not rationalized. The transformation of 1,2,3-thiadiazole-4-carbothio-amides **101** to 5-methylthio-1,2,3-triazole **103** by treatment with methyl iodide in the presence of bases proceeds very smoothly even at room temperature. Most probably this reaction involves the rearrangement of the primary formed thioimidate **102**, which is very similar to **98**.[46*a*] In contrast to 5-amino-1,2,3-thiadiazole-4-carbothioimidate **102,** its phenylureido derivative **104** has been shown to be stable and not to rearrange under any conditions studied. This is the result of the weaker thioamide resonance in the rearranged product **105** derived from the urea derivative **104** as compared to product **103**.[47]

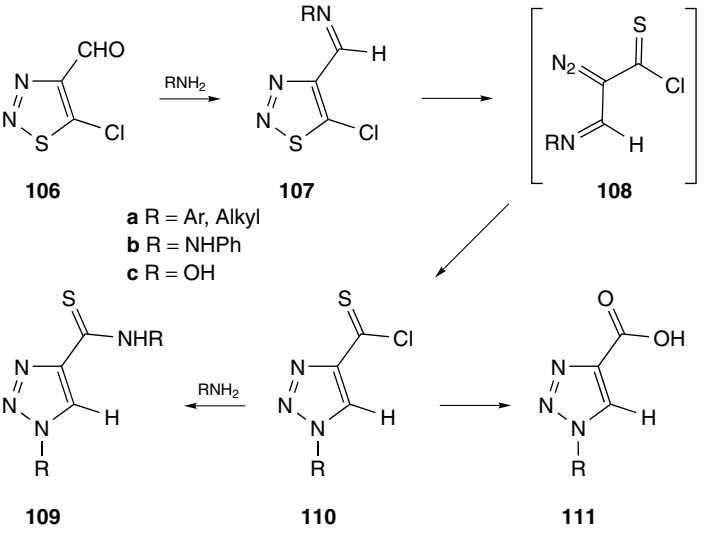


101 **102** **103**

104 **105**

Only the Cornforth type of rearrangement is possible for 4-iminomethyl-1,2,3-thiadiazoles bearing at the 5-position groups such as alkylthio, chloro, phenyl

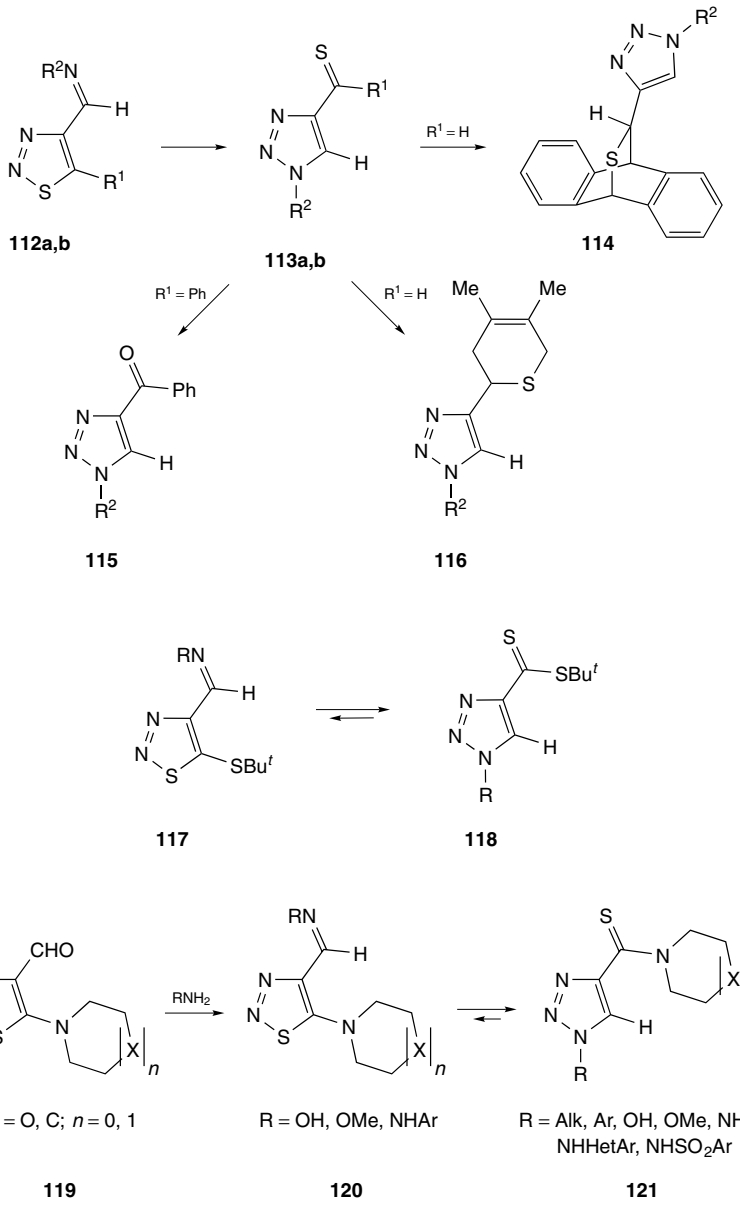
and hydrogen. Thus, 5-chloro-1,2,3-thiadiazole-4-carbaldehyde **106** reacts with alkylamines, arylamines and hydrazines to give 1,2,3-triazole-4-carbothioamides **109** (R = Alk, Ar) and thiohydrazides **109** (R = NHAr), respectively. The reaction mechanism is believed to involve the formation of an intermediate imine derivative **108**, which rearranges to the thioacyl chloride **110.** The latter reacts with a second equivalent of the starting amines to afford the final products **109**. We have managed to isolate the intermediate iminomethyl-1,2,3-thiadiazoles **110** with R = NHPh, OH, which only undergo a similar rearrangement when taken in DMSO solution. The reactive intermediate thioacyl chloride **106** underwent hydrolysis by water to form acids **111** (R = NHPh, OH).[48]



4-Iminomethyl-1,2,3-thiadiazoles **112a** (R^1 = H) and 5-phenyl-4-iminomethyl-1,2,3-thiadiazoles **112b** (R^1 = Ph) rearrange to form unstable 1,2,3-triazoles **113** bearing at the 4-position thioaldehyde and thioketone groups, respectively. They were trapped with anthracene or 2,3-dimethylbutadiene to the adducts **114** and **116** in the case of **113** (R^1 = H) or hydrolyzed to the ketones **115** in the case of thiocarbonyl derivative **113** (R^1 = Ph).[29]

We have found the 5-alkylthio-4-iminomethyl-1,2,3-thiadiazoles **117** to be more reactive than 4-iminomethyl-1,2,3-thiadiazoles **112** (R^1 = H, Ph) in the Cornforth rearrangement.[47]

5-Amino-4-iminomethyl-1,2,3-thiadiazoles have been shown to be even more active than **117**. It allowed us to expand our approach to prepare a large series of 1,2,3-triazole-4-carbothioamides as outlined below. Thus, 1,2,3-thiadiazole-4-carbaldehydes **119** were found to react quickly with aliphatic and aromatic amines, hydrazine and hydroxylamine and their derivatives at room temperature to afford 1,2,3-triazole-4-carbothioamides **121**. The intermediate thiadiazoles **120** were not isolated because of their fast rearrangement to the final compounds.[21]



In the case of 5-alkylthio- **117** and 5-amino-1,2,3-thiadiazoles **120**, we managed to observe the equilibrium between the isomeric heterocyclic compounds **117/118** and **120/121** and to evaluate the effect of the *R*-substituent on its position. As expected, electron-withdrawing groups shift the equilibrium in favor of the thiadiazole structures **117/120**. From the reaction conditions for the rearrangements of **117** and **120**, we conclude that the facility of the rearrangement

of these compounds depends on the nucleophilicity of the imine nitrogen and on the capacity of the 5-substituent to stabilize the thiocarbonyl function formed, which is in the order: NRR > tBuS > Ph > H.

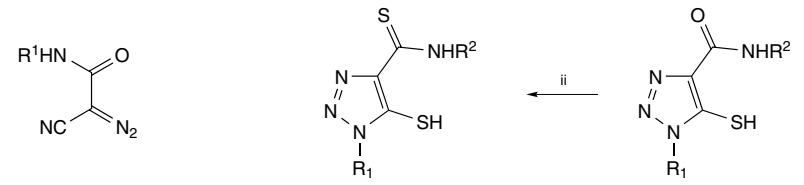
3.3.2.2. Degenerate Rearrangements of 4-Thiocarbamoyl-1,2,3-thiadiazoles

Interconversion between the two isomeric 5-amino-1,2,3-thiadiazole-4-carbothioamides **125** and **127** via a 2-diazomalondithioamide intermediate **126** represents another type of Cornforth rearrangement in the 1,2,3-thiadiazole series. In the case of $R^1 = R^2$, this rearrangement is a degenerate process. Thus, we have found the addition of hydrogen sulfide onto the cyano group of 5-methylamino-1,2,3-thiadiazole-4-carbonitrile **128** to be accompanied by the rearrangement of the initially formed 5-methylamino-1,2,3-thiadiazole-4-carbothioamide **125** (R^1 = Me, R^2 = H) to the isomeric 5-amino-1,2,3-thiadiazole-4-*N*-methylcarbothioamide **127** to form a mixture of "normal" **125** and rearranged products **127** in the ratio 1:19 The reverse rearrangement takes place in the reaction of 5-amino-1,2,3-thiadiazole-4-carboxamides **130** with P_4S_{10}. In the case of R^1 = 2−Py and R^2 = H, this process exclusively leads to 5-(2-pyridyl)amino-1,2,3-thiadiazole-4-carbothioamides **125**. Normally, these reactions afford a mixture of isomeric thiadiazoles **125** and **127**. Electron-withdrawing R^1 and electron-donating substituents R^2 force the reaction in the direction of thiadiazole **125.** The ratio of isomeric thiadiazoles in the mixture is found to be different in various solvents. The individual isomers **125** and **127** (R^1 = Me, R^2 = Bz) were obtained by separation of this mixture with column chromatography. Each isomer was found to transform back to the original mixture in the DMSO solution at room temperature within 4 min.[49,50]

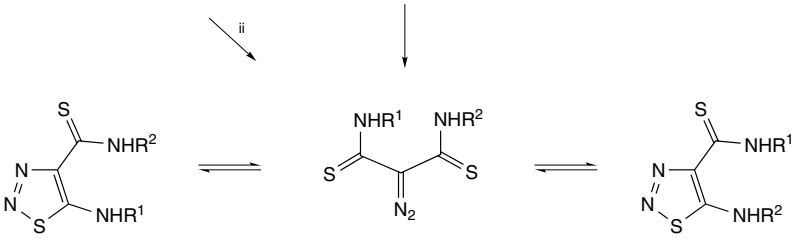
It is interesting to note that the reaction of 5-mercapto-1,2,3-triazole-4-carboxamides **124** with P_4S_{10} leads to a mixture of 5-amino-1,2,3-thiadiazole-4-carbothioamides **125** and **127** in the same ratio that was found from the reaction of nitriles **128** with hydrogen sulfide or thionation of amides **130** with $P_4S_{10.}$ Furthermore, the same ratio of isomeric 5-amino-1,2,3-thiadiazole-4-carbothioamides **125** and **127** was found in the reaction of 2-diazo-2-cyanoacetamides **122** with P_4S_{10} and in the diazo group transfer reaction of malondithioamides **129** with arylsulfonyl azide. These data gave us evidence that the reversible rearrangements of 4-thiocarbamoyl-1,2,3-thiadiazoles occur via a common intermediate diazomalondithioamide of type **126**.[50]

3.3.2.3. Rearrangements of 1,2,3-Thiadiazoles Bearing Diazo, Azido and Hydrazono Groups in the 5-Position

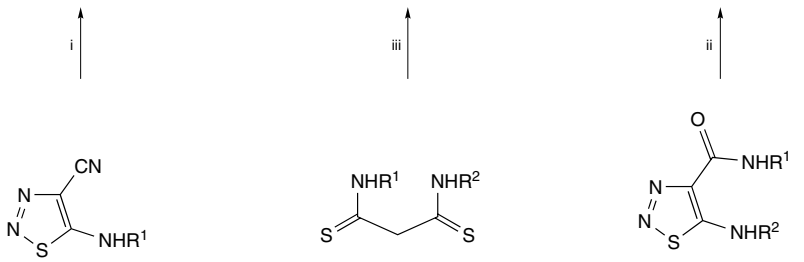
Competitive 1,5-cyclizations of a single thiocarbonyl group onto two 1,3-dipole moieties is another type of rearrangement of 1,2,3-thiadiazoles. Thus, 5-diazomethyl-1,2,3-thiadiazole **132** generated from the tosylhydrazones **131** by



122 **123** **124**

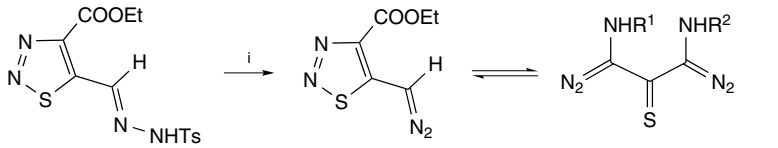


125 **126** **127**



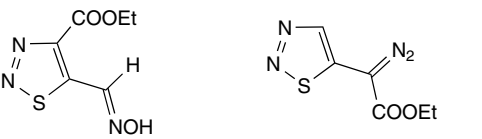
128 **129** **130**

i H_2S, ii P_4S_{10}, iii $ArSO_2N_3$, Base



131 **132** **133**

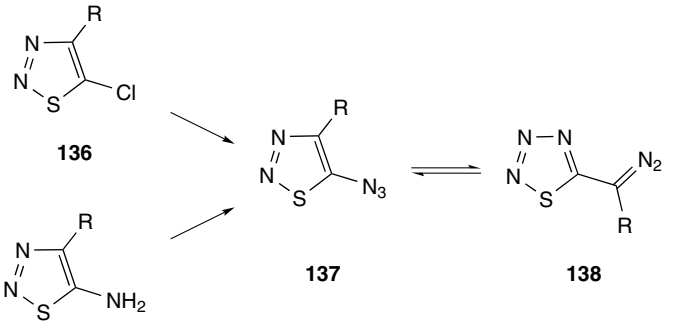
i $NHEt_2$/DMF,
ii NH_2OSO_3, OH



134 **135**

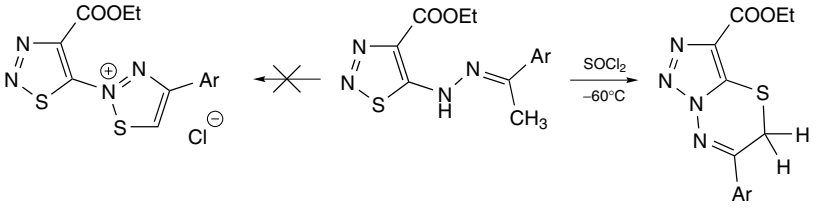
the Bamford–Stevens reaction or from oxime **134** by the Forster reaction was found to undergo a rearrangement to form diazoacetate **135**.[51]

The introduction of the azido function, another 1,3-dipole, at the 5-position of the 1,2,3-thiadiazole ring allows one to observe a 1,2,3-thiadiazole-1,2,3,4-thiatriazole rearrangement. This transformation proceeds spontaneously for compounds **137** with R = ethoxycarbonyl or benzoyl. These products are formed on substitution of the chloride of **136** by azide anion with formation of the diazo compound **138**. The rearrangement does not occur in the case of **138** with R = H.



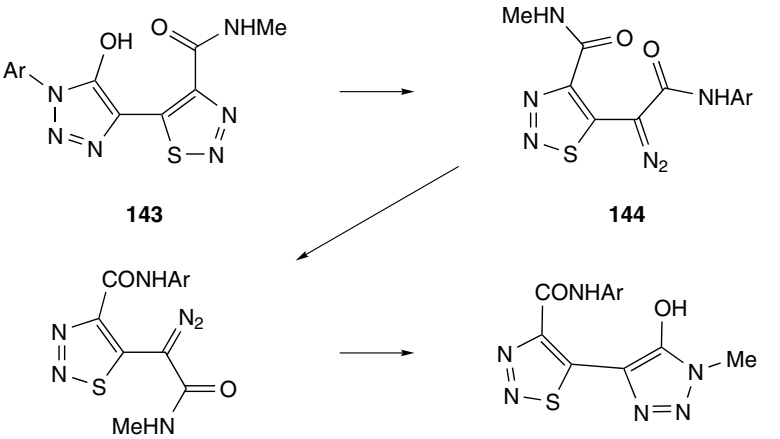
On the other hand, a mixture of thiadiazole **137** and thiatriazole **138** was obtained from the diazotization reaction of 5-amino-4-aryl-1,2,3-thiadiazoles **139**, followed by treatment with azide anion.[52]

L'abbé and coworkers observed a similar rearrangement in the 1,2,3-triazole series.[53] Mechanistically, this type of the rearrangement is quite different from both the Dimroth and Cornforth rearrangements and even from the Boulton–Katritzky rearrangement, which has the same number of participating side-chain atoms. Therefore, we have classified this type of rearrangement as the L'abbé rearrangement.[36] In an attempt to prepare the 2-(1,2,3-thiadiazol-5-yl)thiadiazolium salt **142** from 5-hydrazono-1,2,3-thiadiazole **140** by treatment with thionyl chloride at −60°C (Hurd–Mori approach to 1,2,3-thiadiazole, See Chapter 1), we have prepared triazolo-thiadiazines **141** instead. It is the first example of the rearrangement in the 1,2,3-thiadiazole series where four atoms of the chain take part in the rearrangement. The study of the mechanism of this novel rearrangement is in progress.[54]



3.3.2.4. Tandem Rearrangements

We have found that the heterocyclic ring conjugates **143**, containing 1,2,3-thiadiazole- and 1,2,3-triazole nuclei are capable of undergoing domino-type rearrangements involving both rings to form the isomeric 5-(1,2,3-triazol-4-yl)-[1,2,3]-thiadiazoles **146**. The net result of the process is the interchange of the aryl and methyl groups. This rearrangement is believed to proceed as a three-step process and involves, firstly, ring opening of the hydroxytriazole ring of **143** to form the diazoamides **144**. The acetamides **144** can undergo the L'abbé rearrangement to form the isomeric diazo compounds **145**. Finally, a ring closure occurs to afford the 1,2,3-thiadiazole-4-carboxamides **146**.[55]

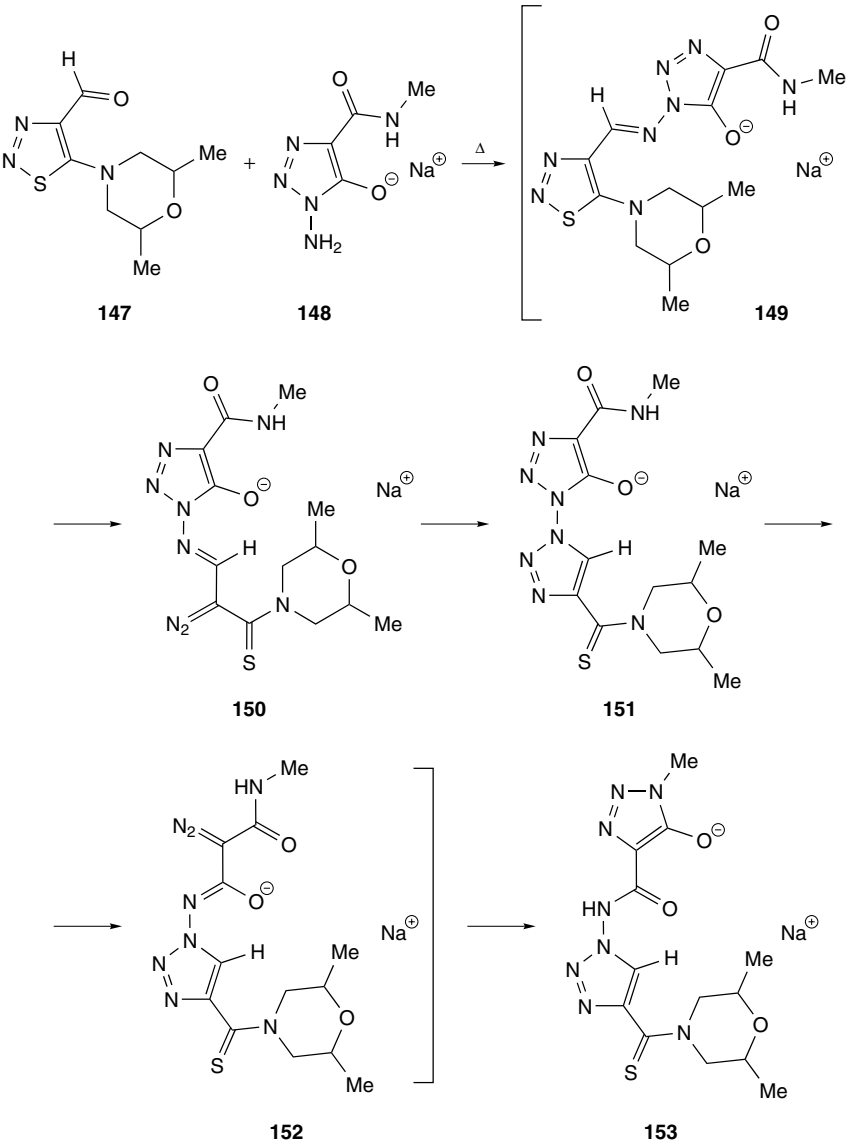


143 **144**

145 **146**

The introduction of electron-withdrawing substituents at the phenyl ring and the increase of the solvent polarity have been shown to accelerate the overall process.[56]

Compound **149**, containing 1,2,3-thiadiazole and 1,2,3-triazole rings, was proposed to be stable because 1,2,3-thiadiazole-5-carbimines containing electron-withdrawing substituents normally do not undergo Cornforth-type rearrangements (See the previous section of this chapter) and 1,2,3-triazolates, in contrast to 5-hydroxy-1,2,3-triazoles, do not undergo ring-opening process to diazo compounds. However, in an attempt to prepare this compound, we have obtained the product of two consecutive Cornforth-type rearrangements, bis-triazole **153**. The proposed mechanism is outlined below. Interestingly, instead of the reverse reaction of bis-triazole **151** to thiadiazole **149,** the ring opening of the 1,2,3-triazole-5-olate ring takes place followed by the cyclization of the diazo group onto the methylamide functionality to form the final product. Again, both 1,2,3-thiadiazole and 1,2,3-triazole underwent ring rearrangement in this reaction.[57]

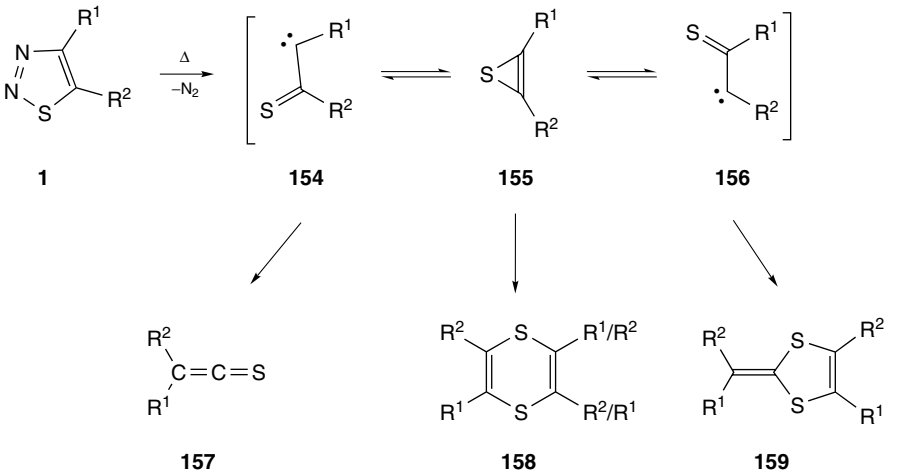


3.4. RING CLEAVAGE OF 1,2,3-THIADIAZOLES

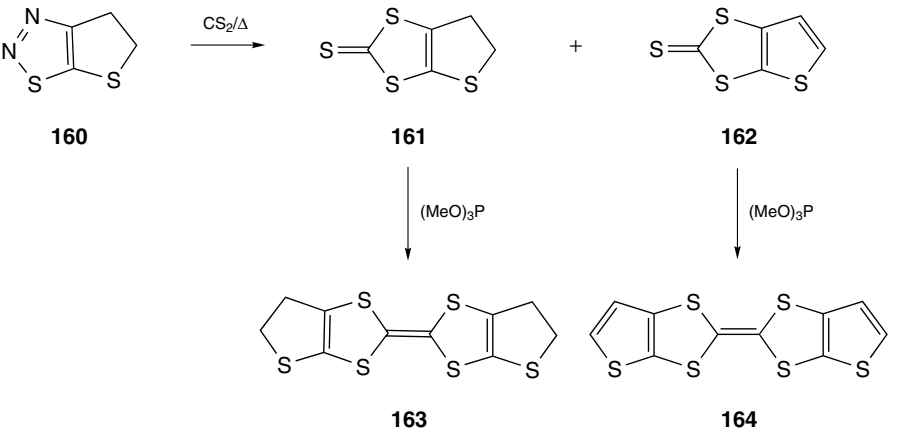
3.4.1. Thermal Decomposition

Thermolysis of 1,2,3-thiadiazoles **1** at 220–230°C leads to nitrogen and primary fragments **154–156**, which are able to react by several routes including (i) rearrangement to thioketenes **157**, (ii) dimerization to 1,4-dithiins **158**

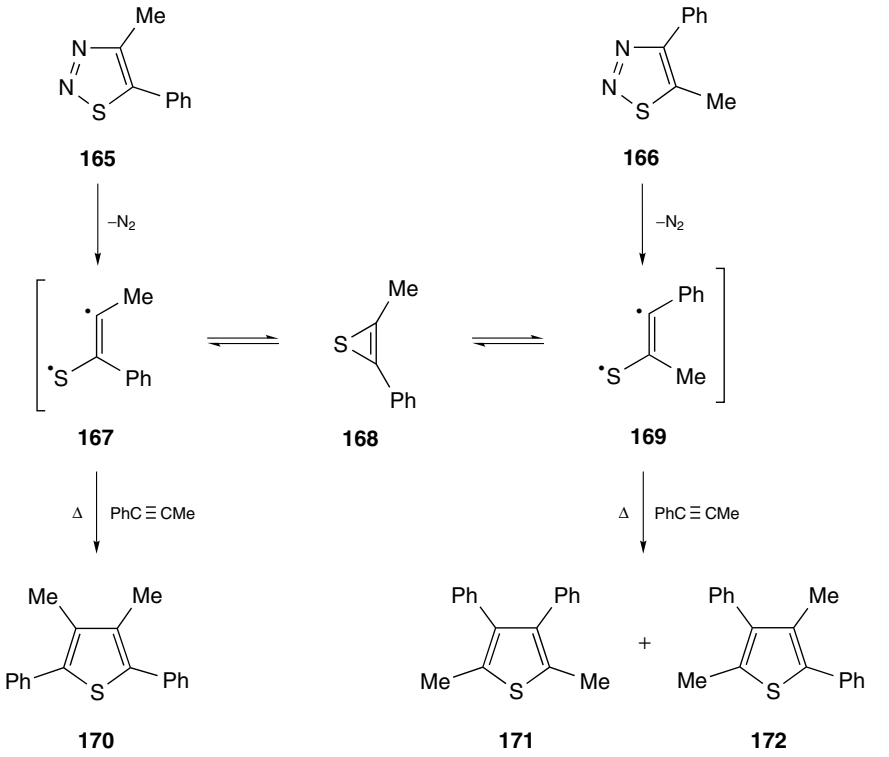
or (iii) cycloaddition of the four electron 1,3-dipole system with a rearranged thioketene to form 1,4-dithiafulvenes **159**.[58–60] Under flash thermolysis conditions (500–600°C) mainly thioketenes **157** are formed. Most of this research has been described in earlier reviews.[28,37,41] It is noteworthy that some of the lower molecular mass 1,2,3-thiadiazoles are reported to be explosive on heating and impact.[61] Therefore, we have to warn against distilling these compounds.



The intermediate four-electron systems resulting from fused thiadiazole **160** could also be trapped by carbon disulfide and provided 1,3-dithiole-2-thiones **161** and **162**. These thiones were coupled to give the corresponding tetrathiafulvalenes **163** and **164**, which are of possible use as π-electron donors.[62,63] This route was used before in the synthesis of tetrathiafulvalenes from other fused 1,2,3-thiadiazoles.[62]



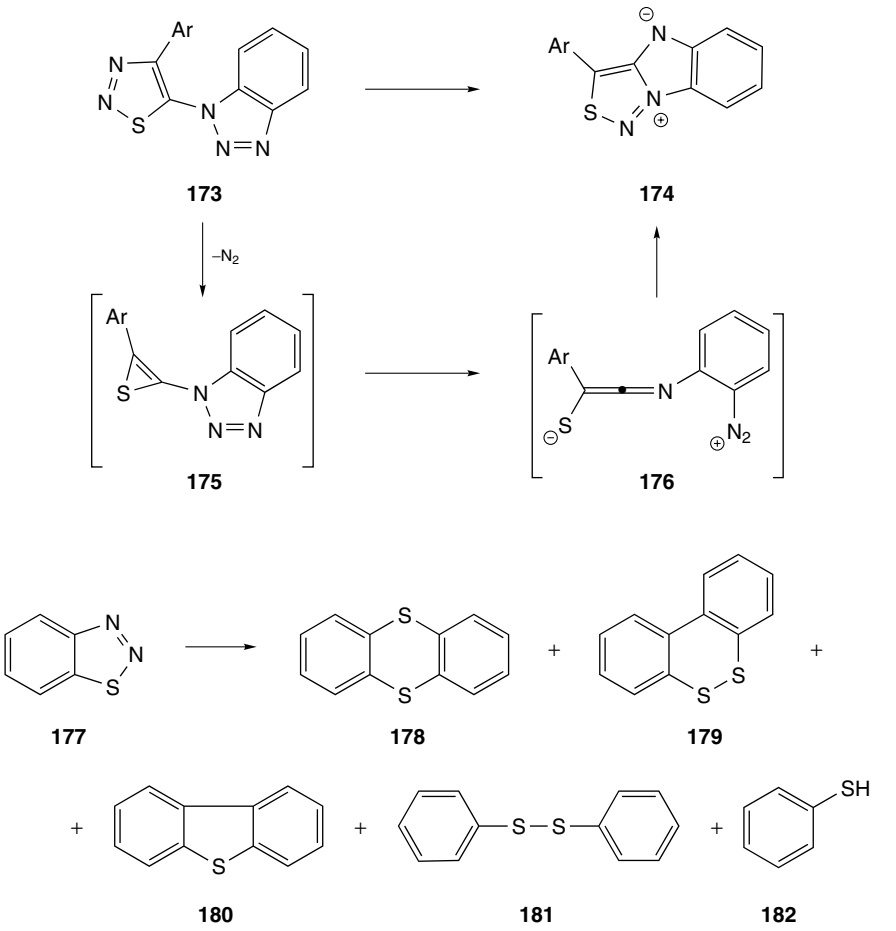
The products of decomposition can also be trapped by adding acetylenes to yield thiophenes.



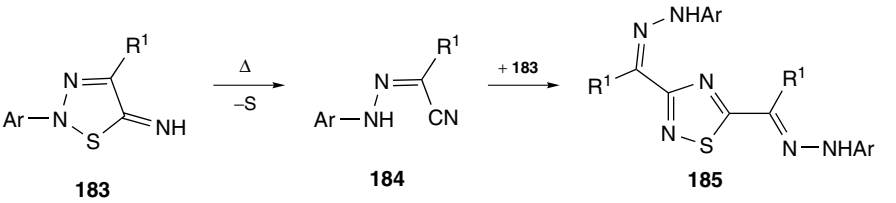
Regioisomeric thiadiazoles **165** and **166** gave the same product distribution **170–172**, proving the equilibrium between the two isomeric 1,3-diradicals **167** and **169** via a thiirene **168**.[64] The capture of the thermal ring-cleavage reaction products can also be done by intramolecular reactions. Thus, Katritzky *et al* have discovered the thermal rearrangement of 5-benzotriazolyl-1,2,3-triazoles **173** to zwitterionic 3-phenyl-4H-[1,2,3]thiadiazolo[3,4-a]benzimidazol-2-ium-4-ides **174**. This reaction proceeds with the evolution of nitrogen and is believed to include the intramolecular heterocyclization of a thiirene intermediate with the 1,2,3-triazole ring.[65]

1,2,3-Benzothiadiazoles **177** do not form thioketenes on thermolysis. Instead, they afford a variety of products **178–182**, depending on the reaction conditions.[58,59]

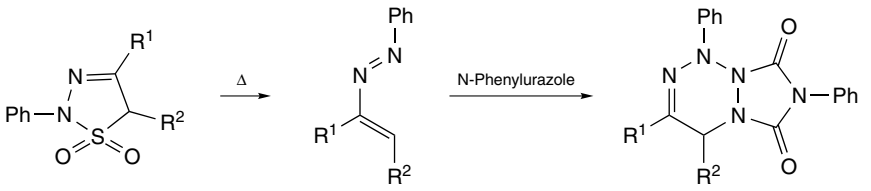
^{13}C-labeling experiments showed that an intermediate benzothiirene was not formed.[66] Similar products were formed on the thermolysis of thiadiazolouracil derivatives.[67] The course for thermal degradation of 2-substituted 1,2,3-thiadiazoles is different from the nonsubstituted derivatives of this heterocycle.



Thus, 2-aryl-1,2,3-thiadiazole-4*H*-5-imines **183** undergo extrusion of sulfur in boiling pyridine to form hydrazones **184**. The latter react with starting thiadiazolin-5-imines to give 1,2,4-thiadiazoles **185**.[68]



2-Phenyl-5-*H*-1,2,3-thiadiazoline-1,1-dioxides **186** underwent extrusion of SO_2 upon heating in toluene to generate very reactive azadienes **187**. The latter

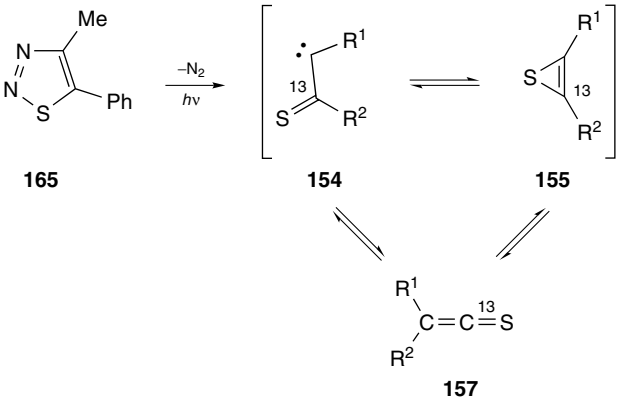


186 **187** **188**

can be trapped with *N*-phenylurazole to afford fused tetrazines **188** in excellent yields.[69]

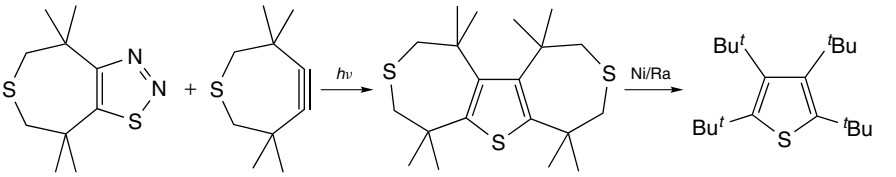
3.4.2. Photochemical Decomposition

1,2,3-Thiadiazoles are to some extent light sensitive and should be treated accordingly. The photochemistry of 1,2,3-thiadiazoles has been reviewed.[70] Similar to the thermolysis reactions, photolysis of 1,2,3-thiadiazoles **165** (at $\lambda \geqslant$ 230 nm) gives extrusion of nitrogen. The resulting 1,3-diradical **154** again leads to the formation of thioketenes **157**, 1,4-dithiins **158** and 1,4-dithiafulvenes **159**.[71] The triplet 1,3-diradical **154** has been characterized by Electron Spin Resonance (ESR) spectroscopy.[72] Another intermediate, the thiirene **155** ($R^1 = H$, $R^2 = Ph$), has been shown by ^{13}C NMR spectroscopy during the photolysis of 5-phenyl-1,2,3-thiadiazole.[60] The lifetime of these thiirenes **155** is short as they rearrange to thioketenes **157**. A more recent study, using trapping of the thioketene with diethylamine, showed that the parent thioketene **157** ($R^1 = R^2 = H$) is formed in solution at room temperature as the primary product without ^{13}C-randomization. However, the thiirene **155** is formed photochemically at 77 K from this thioketene **157** in an EPA glass (diethyl ether-isopentane-ethanol), to which it reverts rapidly. Under these conditions, up to 37% of ^{13}C-randomization was observed.[73]



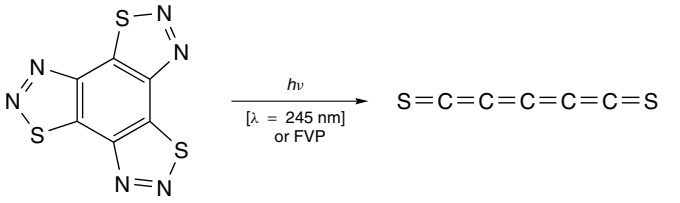
165 **154** **155** **157**

Fused 1,2,3-thiadiazole **189** was irradiated in the presence of the angle-strained acetylene **190**, which gave thiophene **191**, which in turn was selectively desulfurized to yield tetrakis(*t*-butyl)thiophene **192**.[74]

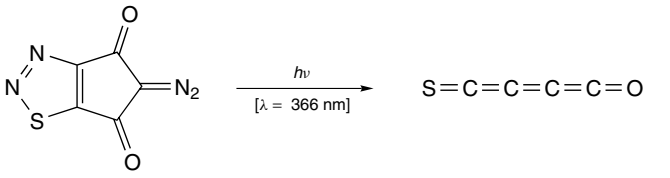


189 **190** **191** **192**

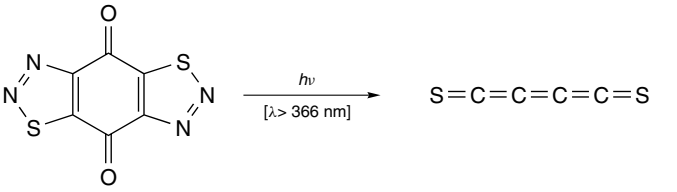
The unusual C_5S_2 (1,2,3,4-pentatetraene-1,5-thione) **194** was formed by photolysis or flash vacuum pyrolysis of the readily available benzotristhiadiazole **193**.[75] Other heterocumulenes obtained in this way are C_4OS **196** and C_4S_2 **198** respectively resulting from the photolysis of indandione **195** and quinone **197**.[76]



193 **194**

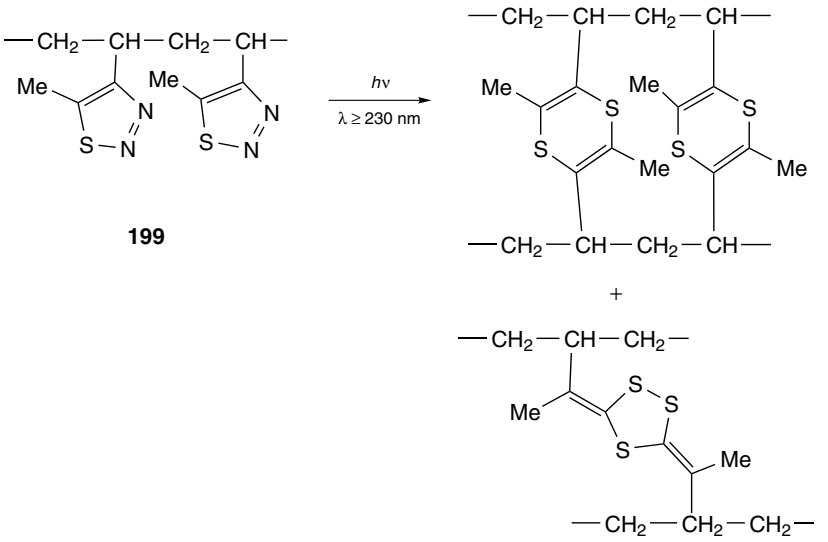


195 **196**



197 **198**

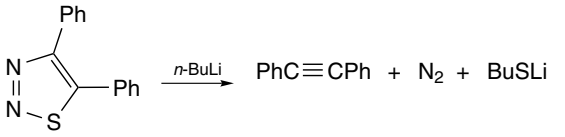
1,2,3-Thiadiazoles with α, β-unsaturated side chains in the 4- or 5-position are suitable starting materials for polymerization reactions. The resulting polymer chains **199** can be photo-cross-linked by photochemical degradation of the thiadiazole rings leading to bridges having sulfur-containing heterocycles.[77,78]



199

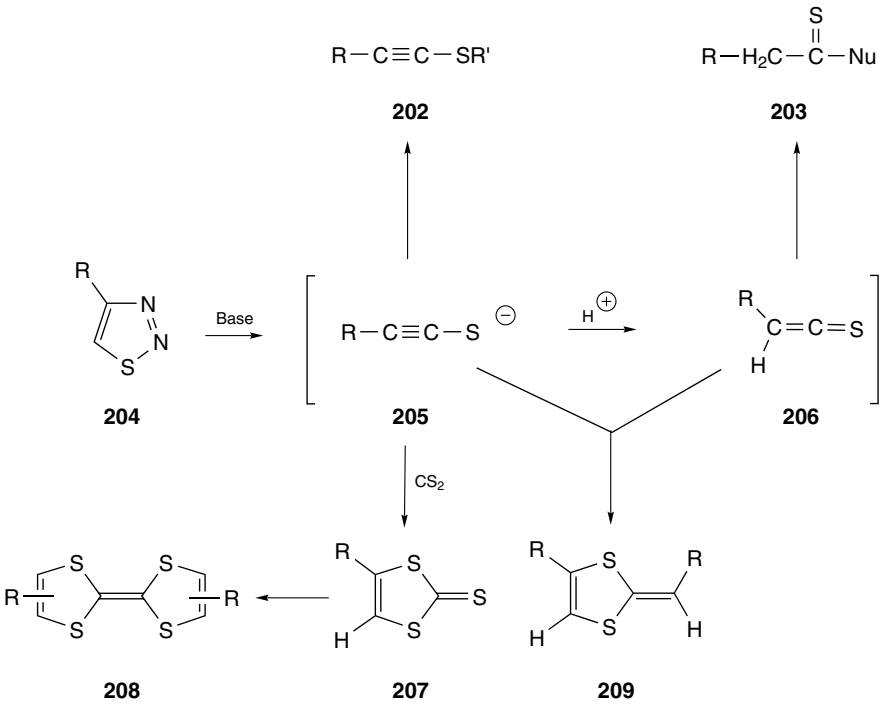
3.4.3. Base-catalyzed Decomposition

4,5-Disubstituted 1,2,3-thiadiazoles are known to undergo ring-cleavage reactions with strong bases. Thus, treatment of 4,5-diphenyl-1,2,3-thiadiazole **200** with *n*-butyllithium at $-60^{\circ}C$ leads to nitrogen gas evolution along with extrusion of sulfur to give 1,2-diphenylacetylene **201**. As far as we know, this reaction represents the most clean method for the preparation of 1,1-diphenylacetylene.[28,41]



200 **201**

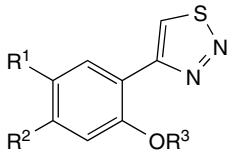
The ring cleavage of 4-monosubstituted 1,2,3-thiadiazoles **204** in the presence of bases such as organolithium reagents, sodamide, sodium hydride and *tert*-butoxide is an effective way of obtaining the reactive alkynethiolates **205**.[79,80]



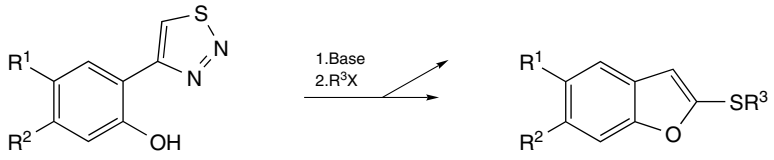
The alkynethiolates can be alkylated or acylated to give alkyne sulfide derivatives **202** or they can cyclize with carbon disulfide to give 1,3-dithiole-2-thiones **207**, which are useful synthetic intermediates toward tetrathiafulvalenes **208**.[81,82]

Protonation of the alkynethiolates **205** gives thioketenes **206**, which on addition of nucleophiles such as amines, thiols or azide anion afford thioamides, dithioesters or 1,2,3,4-thiatriazoles **203** respectively. In the absence of a suitable nucleophile, dimerization of alkynethiolates takes place to give 1,4-dithiafulvenes **209**. Reviews on the chemistry of alkynethiolates and the resulting thioketenes were published.[83] We attempted to alkylate 4-(*o*-hydroxyaryl)-1,2,3-thiadiazoles **210** as a means to attach the 1,2,3-thiadiazole group to other molecules. However, the 1,2,3-thiadiazoles **210** proved to be susceptible to relatively weak bases, such as potassium carbonate, and in the presence of alkylating agents, the unexpected benzofuran-2-sulfides **212** were formed in high yields instead of the O-alkylated 1,2,3-thiadiazoles **211**. Only when the very reactive methyl iodide was added, some O-alkylated product **211** was formed.[84,85]

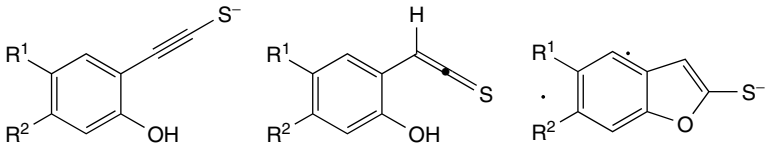
We proved by ^{1}H NMR spectroscopy that benzofuran-2-thiolate **215** is the intermediate in this reaction, and the latter is formed after proton transfer in **213** with subsequent intramolecular addition of the phenolate to the thioketene in the second intermediate product **214**. With this methodology, sulfide thiolates



211

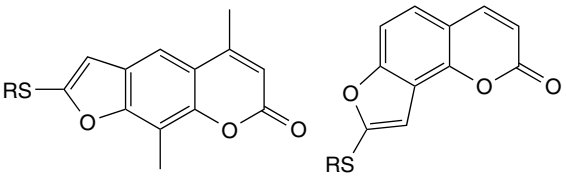


210 **212**

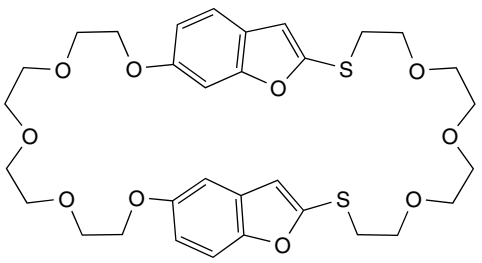


213 **214** **215**

of furocoumarines, including psoralene **216** and angelicin **217** were prepared.[86] Furthermore, starting from 2,5-dihydroxyphenyl-1,2,3-thiadiazole **211** ($R^1 = OH$, $R^2 = H$), we could prepare thiacrown ether **218** by sequential treatment with tetraethylene glycol ditosylate.[85]

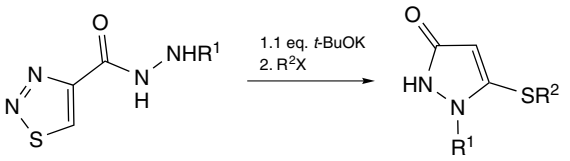


216 **217**



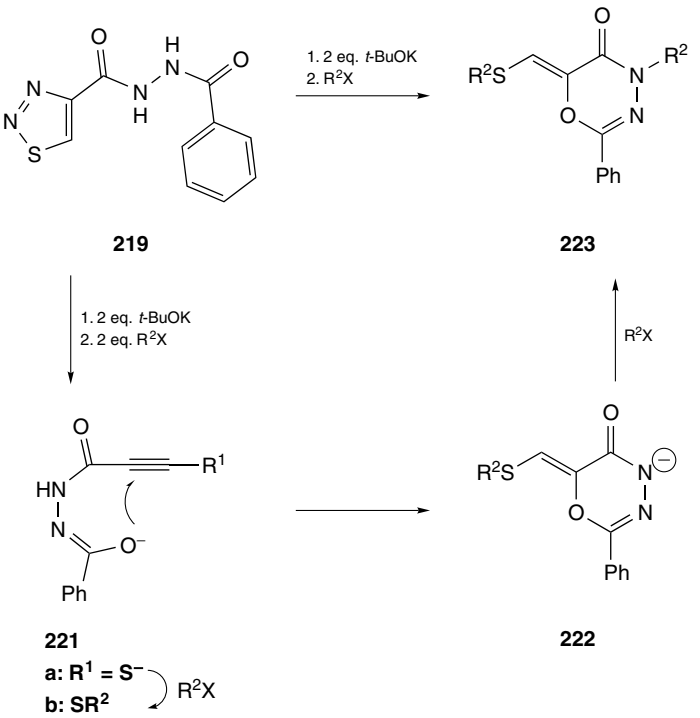
218

To apply this methodology for the formation of nitrogen heterocycles, we have studied the base-catalyzed ring cleavage of 1,2,3-thiadiazole-4-carbonylhydrazide derivatives **219**. Thus, when benzoyl and tosyl derivatives of **219** were treated with 1 equiv of *t*-BuOK followed by alkylation with 1 equiv of alkyl halogenides, the pyrazoles **220** were obtained in moderate yields.[87]



219 **220**

When the ring cleavage of hydrazides **219** was carried out in the presence of 2 equiv or more of *t*-BuOK, the cyclization takes another course. Thus, the decomposition of benzoyl hydrazide **219** followed by alkylation results in 1,3,4-oxadiazine-5-ones **223**. The course of this reaction has been rationalized by the formation of the intermediate alkynethiolate dianion **221a**, which undergoes alkylation to form sulfide **221b**, which in turn undergoes cyclization to a six-membered ring by attack of the imidate anion on the alkyne sulfide. The resulting anion **222** is then alkylated on nitrogen to give the final product.[87]

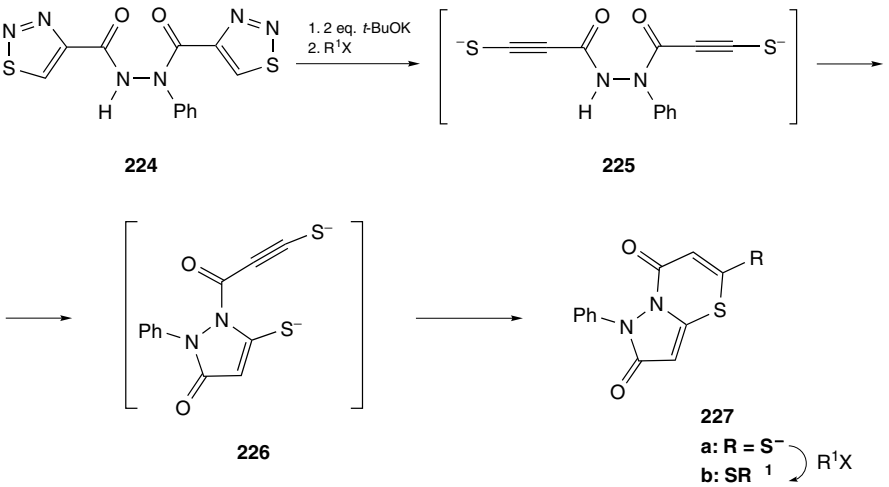


219 **223**

221 **222**

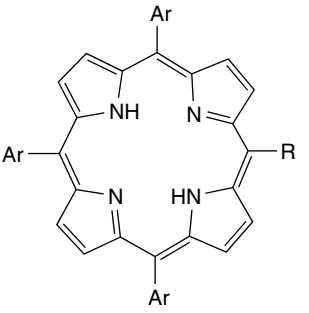
a: $R^1 = S^-$
b: SR^2
R^2X

Bis-1,2-[1,2,3-thiadiazole-4-carbonyl]hydrazine **224**, after cleavage of two thiadiazole rings, recyclization and alkylation, gives fused 7H-pyrazolo[5,1 — *b*][1,3]thiazine-2,7-diones **227**.[87] It was proposed that bis(alkynethiolate) **225** was formed first, which then cyclizes to pyrazole-5-thiolate **226** (somewhat similar to the transformation of **219** to **220**). This can undergo a second cyclization with the formation of a thiazine-6-thiolate **227a**, which finally is alkylated to give the products **227b**.[87]

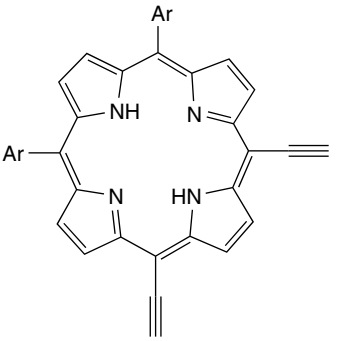


The cleavage of *meso*-(1,2,3-thiadiazol-4-yl)porphyrins **60–62** with potassium *tert*-butoxide as base does not give the expected alkynethiolates. Instead, ethynyl porphyrins **228–230** are isolated.[34] One possible explanation is that the porphyrinyl substituent is releasing electrons into the thiadiazole ring, which drastically lowers the acidity at C-5. An alternative process starting with the attack at sulfur, as we can see in the base-catalyzed decomposition of 4,5-diphenyl-1,2,3-thiadiazole to diphenylacetylene,[88] can be considered. On the other hand, the 1,2,3-thiadiazole ring in the phenyl derivative **60** was found to transform to the dithiolethione system **228b**, which in a subsequent reaction with dithiole-2-one affords the tetrathiafulvalene—porphyrin dyad.[35]

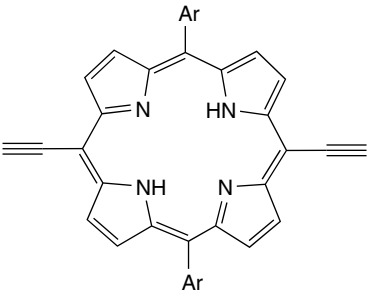
5-Chloro-1,2,3-thiadiazoles **231** remain intact in the presence of weak or moderately strong bases. Reaction of these 1,2,3-thiadiazoles with organometallic reagents gives alkyne sulfides **232** resulting from ring cleavage. The organometallic reagents attack at the sulfur atom of the thiadiazole **231** with cleavage of the N—S bond and subsequent loss of nitrogen. The organometallic reagents used include organolithium and Grignard reagents. Lithium metal could be used to metallate the 5-chloro-1,2,3-thiadiazole ring to give the unstable 1,2,3-thiadiazol-5-yllithium **233**, which immediately lost nitrogen to form the alkynethiolate **234**. The latter was quenched with methyl iodide to give the expected alkyne sulfide **235**.[18]



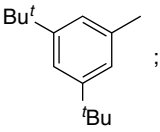
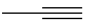
228 a,b

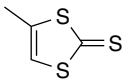


229 a

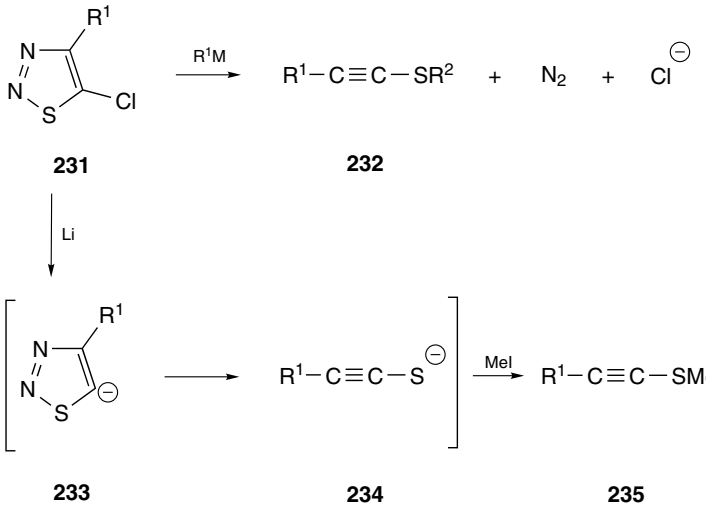


230a

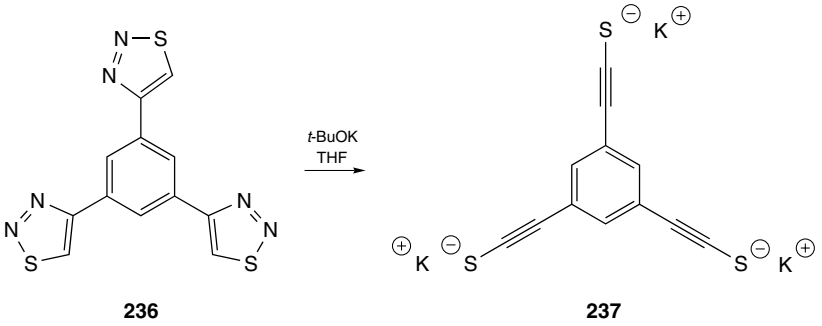
a: Ar =  ; R= 

b: Ar = Ph; R= 

1,2,3-Thiadiazoles have also been used as new core reagents for dendrimer synthesis. 1,3,5-Tris-(1,2,3-thiadiazolyl-4-yl)benzene **236**, prepared from 1,3,5-triacetylbenzene by the Hurd–Mori reaction, was treated with potassium *tert*-butoxide to give the trithiolate **237**. This trithiolate **237** could be coupled, for instance, with Fréchet's G2 dendron **238** to furnish the second-generation dendrimer **239**. The first- and third-generation dendrimers were prepared in the same way. A convergent dendrimer synthesis with a benzyl ether dendron having 1,2,3-thiadiazole, and hence an alkynethiolate at the core, was also reported.[89–92]

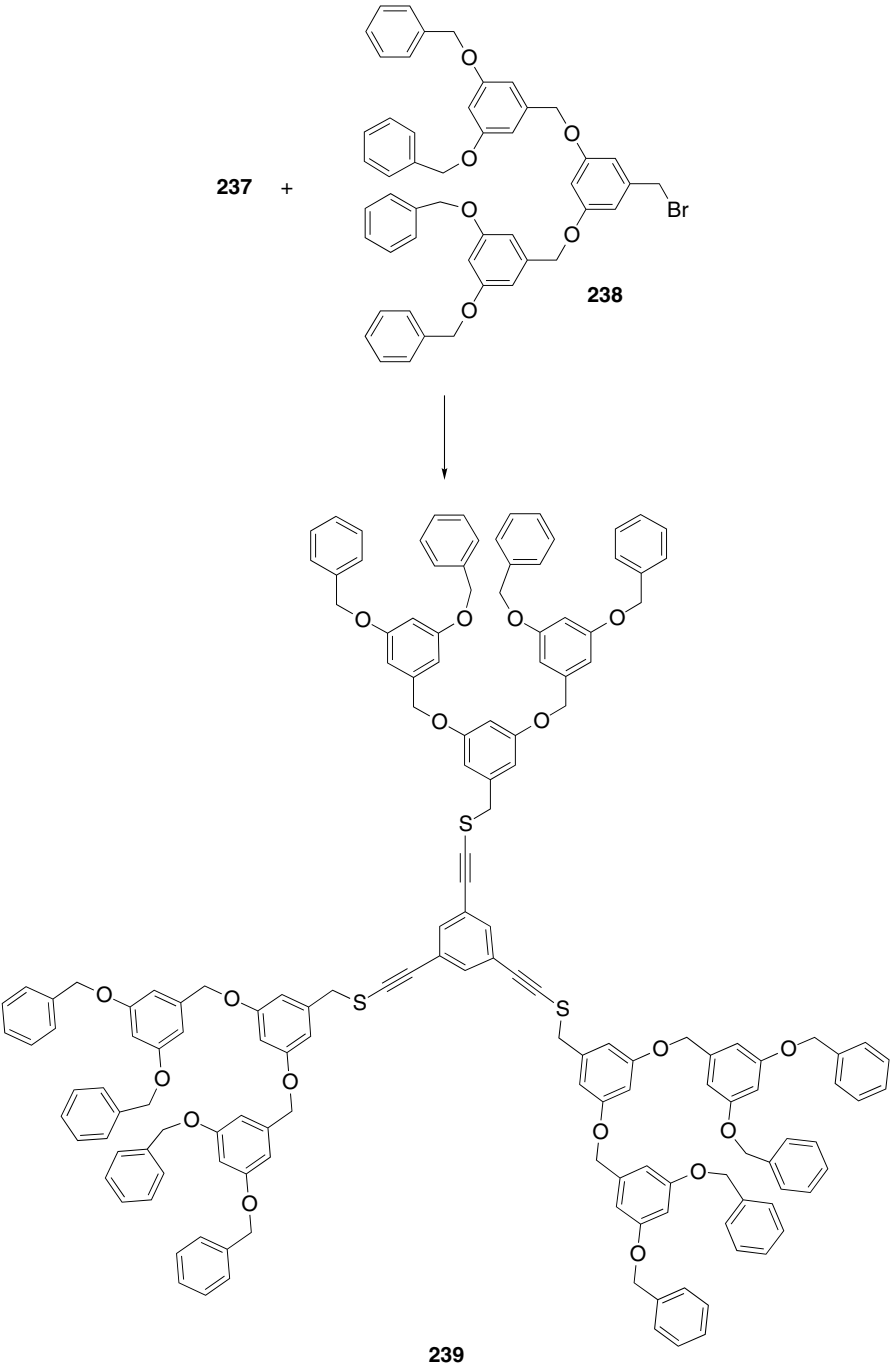


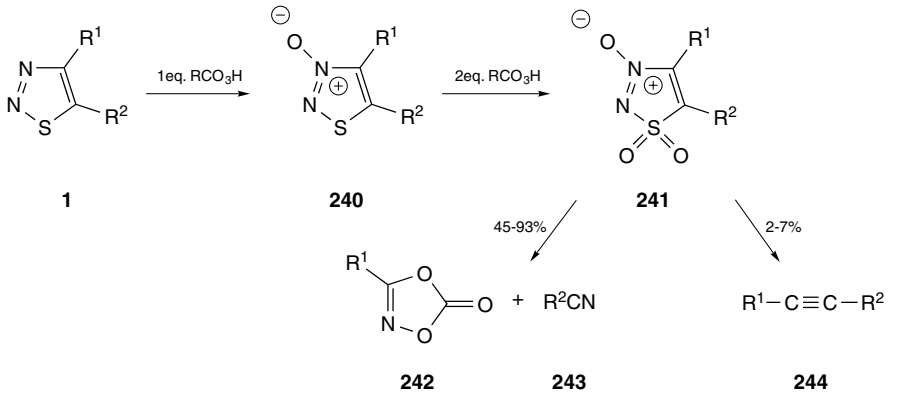
R^1 = Ph, ^{t}Bu
R^2 = Bu, Ph, Et, Me, ^{t}Bu, —C≡C—Ph



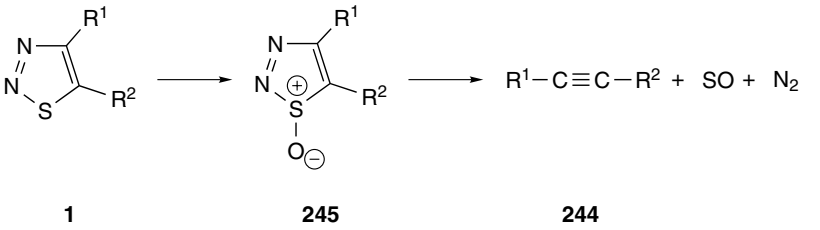
3.4.4. Oxidative and Reductive Processes

Normally, 4,5-disubstituted and 5-monosubstituted thiadiazoles are very stable, even in the presence of strong oxidizing or reducing agents, including chromic acid[93] and $LiAlH_4$.[28,41] However, oxidation of 1,2,3-thiadiazoles **1** with peracetic acid yields 1,2,3-thiadiazole-3-oxides **240**.[13] These products were first erroneously assigned as the 2-oxides.[94,95] With an excess of oxidizing agent, 1,2,3-thiadiazole-1,1,3-trioxides **241** can be formed. The latter products are relatively stable. Photolysis of these trioxides **241** yields several products including dioxazoles **242**, nitriles **243**, (major products) and acetylenes **244** (minor products).[12]


237
+
Br
238
S
S
S
239



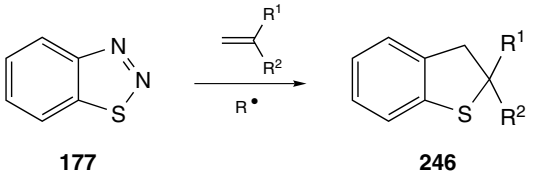
Monocyclic 1,2,3-thiadiazoles **1**, acting as heme ligands are oxidized by cytochrome P450 and oxygen with the formation of an acetylenic product **244**. This was rationalized by the authors to occur via an unstable S-oxide **245**, which loses nitrogen and sulfur monoxide.[96]



Electrochemical reduction of 5-unsubstituted thiadiazoles gives alkynethiolates and can be seen as an alternative to the base-catalyzed decomposition. However, only one report exists in the literature.[97]

3.4.5. Other Processes for Ring Cleavage

Radicals such as *tert*-butoxy initiate the reaction of 1,2,3-benzothiadiazole with radicophilic alkenes to afford benzothiophene cycloadducts **246**.[98]



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CHAPTER 4

Fused 1,2,3-Thiadiazoles

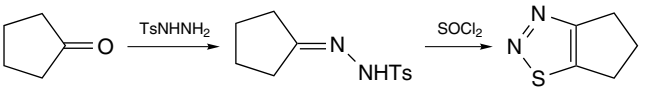
Synthetic methods for the preparation of 1,2,3-thiadiazoles annelated to other ring systems have continued to attract considerable attention because of their importance for medicinal chemistry, and especially because the first chemical plant activator was found recently to be a derivative of benzo-1,2,3-thiadiazole.[1–3] In this chapter, we have collected different types of annelated 1,2,3-thiadiazoles, classified according to both the size and kind of the ring annelated to the 1,2,3-thiadiazole.

4.1. 1,2,3-THIADIAZOLES FUSED WITH FIVE-MEMBERED RINGS

In this section, the literature data on the synthesis of cyclopenteno-1,2,3-thiadiazoles and its heteroanalogs, including pyrrolo-, pyrazolo-, dihydrofurano-, thieno- and benzoselenopheno-1,2,3-thiadiazoles, are summarized.

4.1.1. Cyclopenteno-1,2,3-thiadiazoles

Only very few derivatives of this system are known from the literature. Braun and Meier reported, in 1974, the first synthesis of cyclopenteno-1,2,3-thiadiazole **1** starting from cyclopentanone **2** and tosylhydrazine using the Hurd–Mori approach.[4]

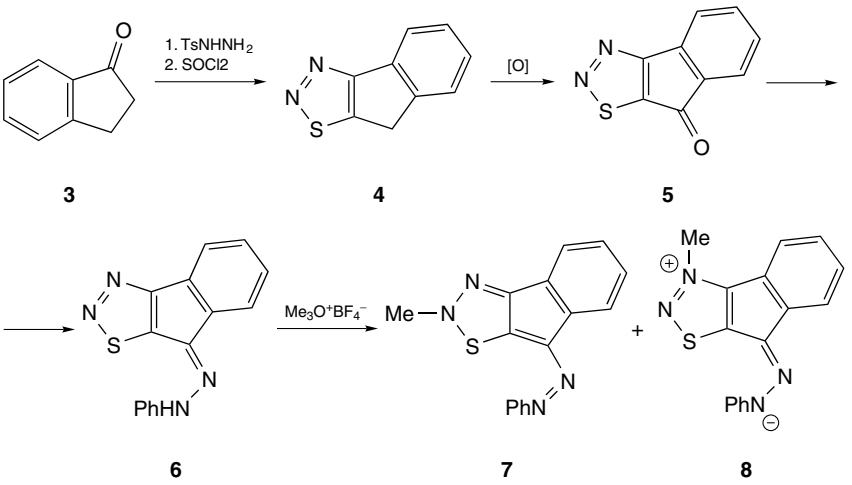


2 **1**

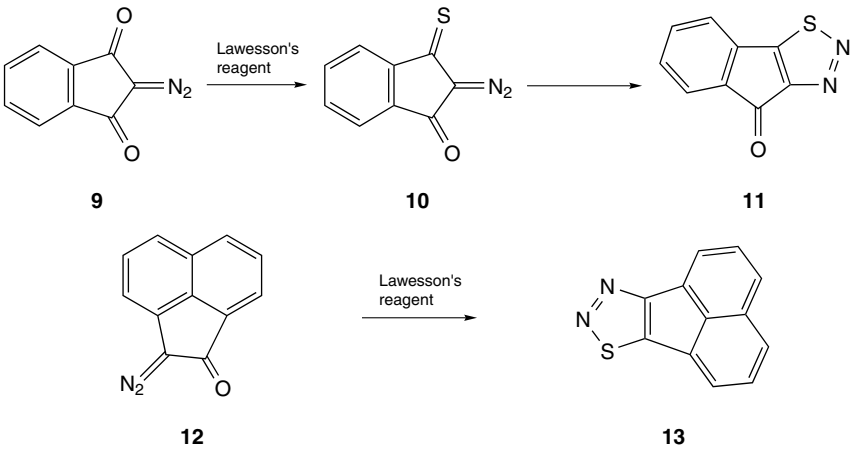
They also managed to prepare indeno-1,2,3-thiadiazole **4**. However, the yield of the final product was only 8%. When the reaction was carried out at −80°C

The Chemistry of 1,2,3-Thiadiazoles, by Vasiliy A. Bakulev and Wim Dehaen
ISBN 0-471-32662-3

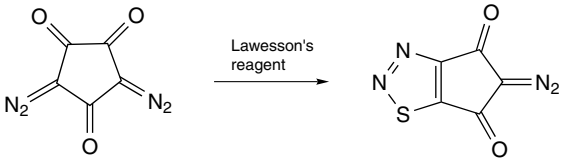
for 2 h, the yield of tricyclic product **4** was considerably higher (46%).[5] We have also noticed that longer reaction times result in a decrease in yield.[6] Oxidation of **3** by potassium dichromate allowed us to prepare ketone **5**, which in subsequent reaction with phenyl hydrazine formed hydrazone **6**. Interestingly, the alkylation of the latter took place at the nitrogen atoms of the thiadiazole ring to give a mixture of compounds **7** and **8** in almost equal amounts. Their structures were unambiguously confirmed by X-ray analysis.[6]



1,2,3-Thiadiazoles fused to cyclopentene rings could also be prepared by the reaction of the appropriate diazoketones with thionating reagents. Thus, treatment of 2-diazoindan-1,3-dione **9** with Lawesson's reagent led to indeno-1,2,3-thiadiazole-4-one **11** in good yield.[7] Tetracyclic thiadiazole **13** was prepared by the analogous reaction of diazoketone **12**.[8]

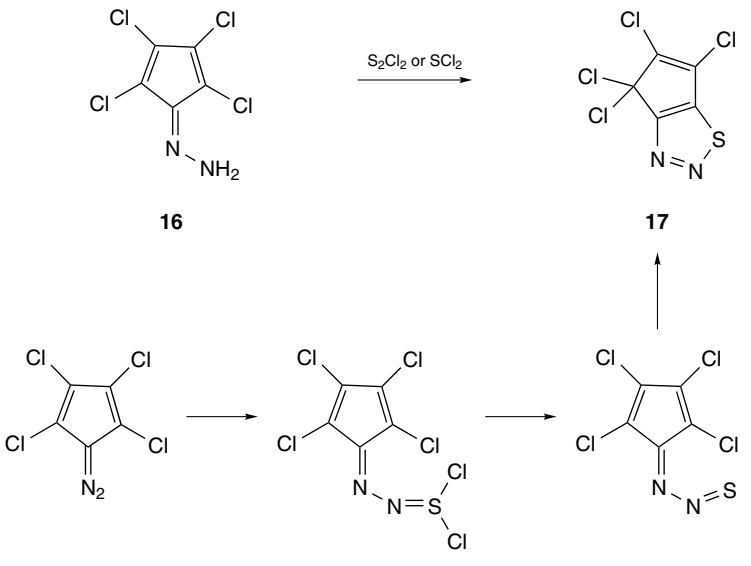


In this respect, it is interesting to note the work of Maier *et al*. on the study reaction of cyclopentane **14** possessing two diazo and three keto groups. One can expect the formation of at least four products in the reaction of this compound with Lawesson's reagent. Surprisingly, 5-diazo-cyclopenteno-1,2,3-thiadiazole-4,6-dione **15** was obtained exclusively in good yield.[9]



14 **15**

Senning and colleagues have discovered that hydrazone **16** on treatment with S_2Cl_2 or SCl_2 affords the 1-diazo-2,3,4,5-tetrachlorocyclopenta-2,4-diene **18** as the minor and the tetrachloro derivative of 4*H*-cyclopenta-1,2,3-thiadiazole **17** as the major product.[10] The diazo compound **18** was also shown to react with S_2Cl_2 and SCl_2 to give product **17**. The same authors, on the basis of AM1 calculations, gave a rationalization for the formation of this product **17**, involving a thionitroso intermediate **20** (see also Chapter 2). The structure of the reaction product **17** was confirmed by X-ray analysis.

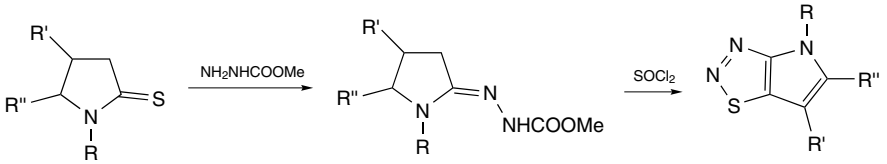


16 **17**

18 **19** **20**

4.1.2. Pyrrolo[2,3-*d*][1,2,3]thiadiazoles

Only one paper has appeared in the literature discussing a synthetic approach to this heterocyclic system. A small series of derivatives was prepared by Stanetty using the Hurd–Mori reaction. This is the first report on an application of this reaction with amidrazones as the starting compounds. Stanetty has shown that pyrrolethiones **21** after treatment with ethylcarbazate, followed by reaction with thionyl chloride, afforded the final pyrrolo[2,3-*d*][1,2,3]thiadiazoles **23**, depending on the substituents at the pyrrole ring, in moderate to high yields.[11] It should be noted that the formation of the 1,2,3-thiadiazole ring in this reaction is accompanied by the aromatization of the dihydropyrrole intermediate.

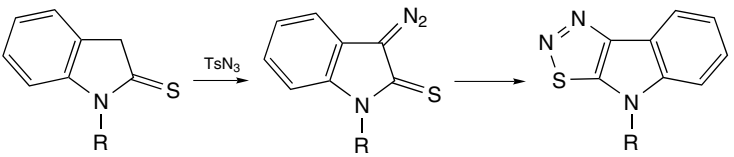


21 **22** **23**

R = H, Me, Bn, COOMe; R', R'' = Y, COOAlk

4.1.3. Pyrrolo[3,2-*d*][1,2,3]thiadiazoles

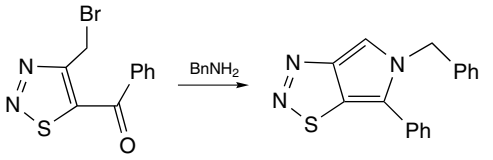
Only two derivatives of this heterocyclic system have been reported in the literature. The diazo group-transfer reaction onto indolinethiones led to the generation of diazothioketone intermediates **24**, which after subsequent cyclization yield 1,2,3-thiadiazolo[5,4-*b*]indoles **25**.[12] In the case of R = H, the minor product, bi-indoline-2,2′-dithione, was isolated additionally after evaporation of the mother liquors. In contrast, the reaction of 1-methylindole-2-thione with tosylazide gave only a small quantity of thiadiazole **25**; bi-indoline-2,2′-dithione was obtained as the major product.



R = H, Me **24** **25**

4.1.4. Pyrrolo[3,4-*d*][1,2,3]thiadiazoles

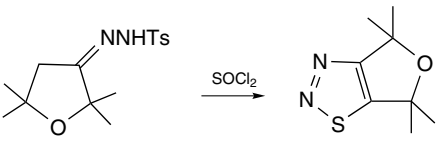
Shafiee has prepared this type of compounds from thiadiazole **26** bearing keto- and bromomethyl groups by reaction with benzylamine.[13]



26 **27**

4.1.5. 4,6-Dihydrofurano[3,4-*d*][1,2,3]thiadiazoles

We could find only one compound of this series in the literature. The sterically protected 4,4,6,6-tetramethyl-4,6-dihydrofurano[3,4-*d*][1,2,3]thiadiazole **28** was prepared by the Hurd–Mori reaction as outlined below.[14]



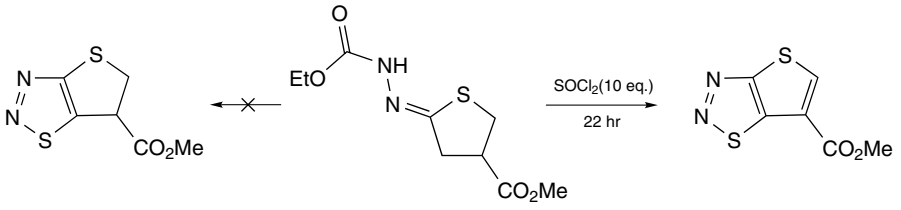
27 **28**

4.1.6. Thieno[2,3-*d*][1,2,3]thiadiazoles

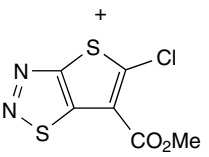
Both the Hurd–Mori and Wolff methods were used to prepare derivatives of this heterocyclic system.[11] Stanetty *et al*. reported in a series of papers, including a review[11] on their systematic work on thienothiadiazoles. They have implemented both the Hurd–Mori reaction and the diazotation of *ortho*-aminothiophenethiols to annelate the thiadiazole cycle to the thiophene ring.

Thus, reaction of hydrazone **29** (prepared by a six-step synthesis) with an excess of thionyl chloride at room temperature is shown to furnish a mixture of an aromatic bicyclic product **30** and its chloro derivative **31**, instead of the expected 5,6-dihydrothieno[2,3-*d*][1,2,3]thiadiazole **32**. Increase of the reaction temperature to 80°C allowed one to avoid the formation of **31**. To account for the facile aromatization in the course of the Hurd–Mori reaction, as well as the formation of the chlorinated by-product **31,** a modified mechanistic model of the Hurd–Mori reaction was proposed by the authors.[15]

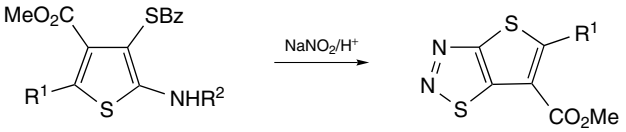
Similar to the behavior of *ortho*-aminobenzenethiols, the reaction of *ortho*-aminothiophene sulfides **33** ($R^1 = H$) under acidic diazotation conditions gives only a very poor yield of thieno[2,3-*d*][1,2,3]thiadiazoles **34**. This was rationalized as a consequence of the many side reactions, such as nitrozation, azo-coupling and polymerization, which can take place under the diazotation conditions. A similar reaction of the methyl derivative **33** ($R^1 = Me$), as proposed by the authors, afforded bicyclic product **34** in a substantially higher yield because of the suppression of the side reactions.[16]



32 **29** **30**



31



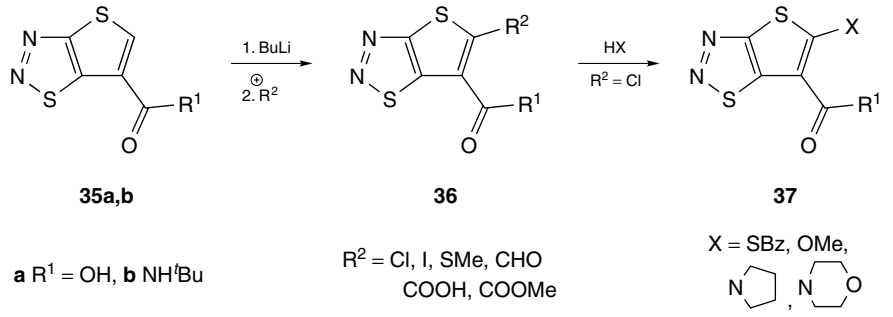
33 **34**

Use of the N-protected derivatives of type **33** (R^2 = Boc) allowed the authors to obtain the desired compounds **34** in higher yield.[17] Stanetty *et al*. explained the improvement by the softer character of the diazotate intermediate formed under the conditions of the Huisgen–White-type reaction in comparison with the diazonium group formed during the diazotation of free amines. A further improvement of the yield of the product **34** was reported for 2-substituted thiophene derivatives.[17] The regioisomers of **34** were obtained by Gewald[18] using a similar pathway.

As an alternative to prepare 5-substituted thieno[2,3-*d*][1,2,3]thiadiazoles, Stanetty *et al*. carried out the metallation of both the free acid **35a** and its *tert*-butyl amide **35b**. The resulting thienyllithium reagents were reacted with a variety of electrophilic reagents to introduce in the 5-position of the products **36** both substituents with electron-donating and electron-withdrawing properties.[15,19] Furthermore, the chloro derivative **36** (R^2 = Cl) that was prepared according to this approach was found to react with S-, O- and N-nucleophiles to give 5-substituted bicyclic compounds **37** in good yield.[19]

4.1.7. Thieno[3,2-*d*][1,2,3]thiadiazoles

All published papers on the synthesis of this heterocyclic system mention the 3,2-annelation of the 1,2,3-thiadiazole ring to the thiophene ring. There are no data on the annelation of a thiophene ring to a 1,2,3-thiadiazole circle.

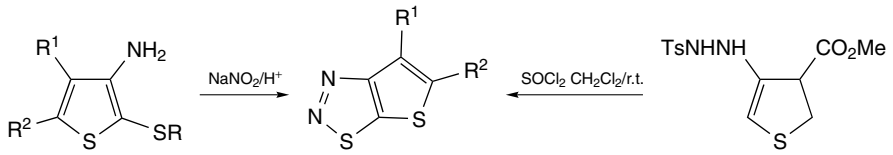


35a,b **36** **37**

a R^1 = OH, **b** NH^{t}Bu

R^2 = Cl, I, SMe, CHO
COOH, COOMe

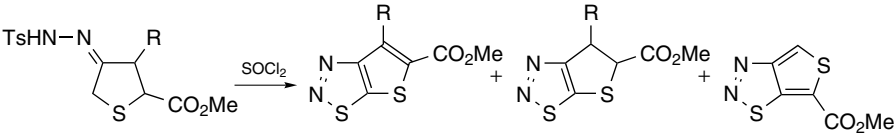
The parent thieno[3,2-*d*][1,2,3]thiadiazole **38** ($R^1 = R^2 = H$) was obtained in 36% yield by diazotation of 3-aminothiopene-2-thiocyanate **39** (R = CN) with sodium nitrite in dilute sulfuric acid.[20] Stanetty and Kremslehner have found that diazotation of amine **39** (R = Bn, $R^1 = H$, $R^2 = CO_2Me$) with sodium nitrite in a mixture of acetic and hydrochloric acids after chromatographic purification affords only 15% of the desired compound **38**.[21]



39 **38** **40**

Ohno *et al*. have prepared the methyl thieno[3,2-*d*][1,2,3]thiadiazoles-6-carboxylate **38** by the Hurd–Mori approach, starting with the tosyl hydrazone of methyl tetrahydro-4-oxothiophene-3-carboxylate **40**.[22] This reaction is shown to be accompanied by the aromatization of thiophene ring during the reaction.[23]

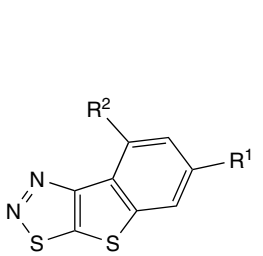
On the other hand, the reaction of hydrazone **41** with $SOCl_2$ leads to a 1:2.6 mixture of thieno[3,4-*d*][1,2,3]thiadiazole **44** and 5,6-dihydrothieno[3,2-*d*][1,2,3]thiadiazole-5-carboxylate **43a** and only traces of the desired [3,2-*d*]annelated compound **42a**.[21] This, together with the experiment of Rovira *et al*. for the reaction of the 4-unsubstituted analog to **41**[24] provides evidence of a preference for [3,2-*d*]- to [3,4-*d*]-annelation.



41 **42** **43** **44**

a R = H	0.15	2.6	1
b R = CO_2Me	3	2	-

Only one possible side of annelation exists for the reaction of hydrazone **41b** substituted by two ester functions in the 2 and 3 positions. However, this reaction gave a 3:2 mixture of aromatic **42b** and *trans*-dihydro products **43b**. The presence of a C_4-C_5 double bound in the hydrazone molecule allows one to avoid side reactions and to selectively prepare thieno[3,2-*d*][1,2,3]thiadiazoles **45–47** in moderate to high yield.[5,25–27]



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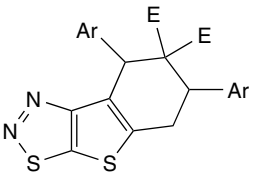

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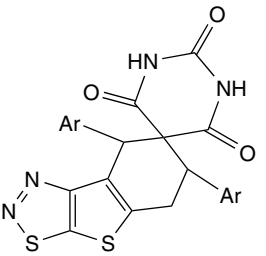
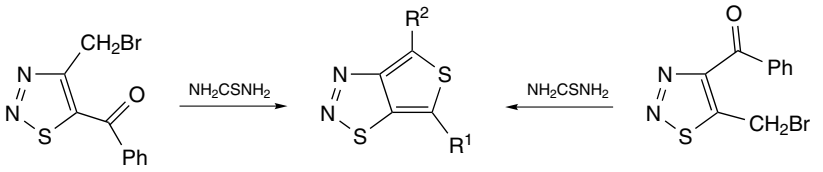


47

It is obvious that the known methods for the preparation of thieno[3,2-*d*][1,2,3]thiadiazoles have serious limitations. It should be noted that an approach to obtain thieno[3,2-*d*][1,2,3]thiadiazoles in which the thiophene ring is formed at a preformed 1,2,3-thiadiazole has so far not been described. This approach might allow one to prepare these compounds in substantial amounts.

4.1.8. Thieno[3,4-*d*][1,2,3]thiadiazoles

Shafiee was the first to show that the reaction of 4-bromomethyl-5-benzoyl-1,2,3-thiadiazole **48** and the isomeric 5-bromomethyl-4-benzoyl-1,2,3-thiadiazole **50** with thiourea gives 5-phenylthieno[3,4-*d*][1,2,3]thiadiazole **49a** and 4-phenylthieno[3,4-*d*][1,2,3]thiadiazoles **49b**, respectively.[13] The same type of compounds are formed as by-products in the reaction of 3-tosylhydrazonothiophene **41** with $SOCl_2$ as already discussed.[19]



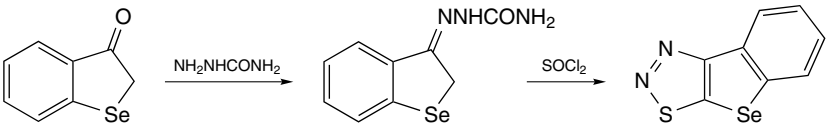
48 **49a,b** **50**

4.1.9. Selenopheno[3,4-*d*][1,2,3]thiadiazole

Shafiee has shown that these compounds can be prepared in the same way as the corresponding thiophenes using the reaction of **49** with selenourea.[13]

4.1.10. Benzoselenopheno[3,2-*d*][1,2,3]thiadiazole

We could find only one example of this type of compounds in the literature. The Litvinov group has prepared benzo[*b*]selenopheno[3,2-*d*][1,2,3]thiadiazole **53** in good yield from benzoselenophenone **51** by the Hurd–Mori reaction.[28]



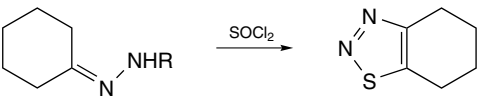
51 **52** **53**

4.2. 1,2,3-THIADIAZOLE FUSED WITH SIX-MEMBERED RINGS

4.2.1. Cyclohexeno-1,2,3-thiadiazoles

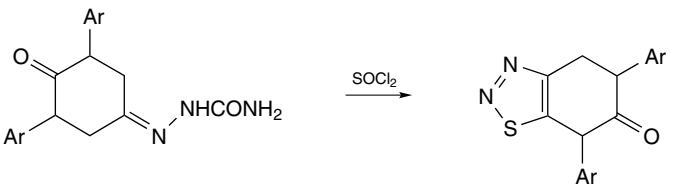
All known methods for the synthesis of tetrahydro- and dihydrobenzothiadiazoles that are discussed in this section are based on the Hurd–Mori reaction.

The parent cyclohexa-1,2,3-thiadiazole **55** was prepared from both cyclohexanone tosyl- (**54a**) and carbamoyl- (**54b**) hydrazones by reaction with thionylchloride.[4] A better yield was achieved when tosylhydrazone **54a** rather than carbamoylhydrazone **54b** was used as the starting compound.[4,5]



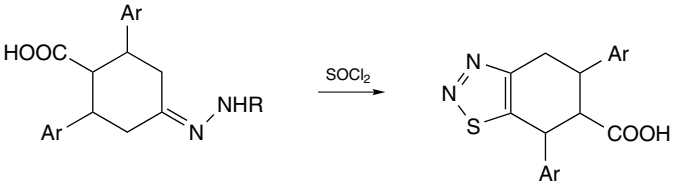
54a R = Ts
54b $CONH_2$ **55**

Reddy *et al*. have shown that 2,6-diarylcyclohexane-1,4-dione reacts selectively at the less-hindered carbonyl group of semicarbazide to form hydrazones **56**. The latter afforded cyclohexeno-1,2,3-thiadiazole-6-ones **57** in moderate yields by treatment with thionyl chloride.[29]

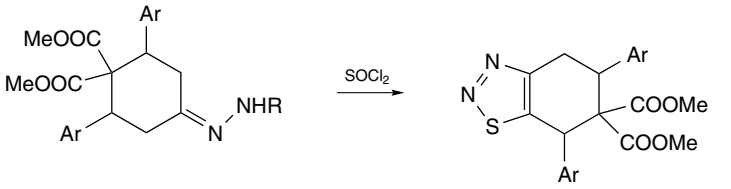


56 **57**

The same authors have prepared cyclohexeno-1,2,3-thiadiazole-6-carboxylic acids **59** and esters of cyclohexa-1,2,3-thiadiazole-6,6-dicarboxylic acids **61** in good yields by a similar reaction.[29,30]



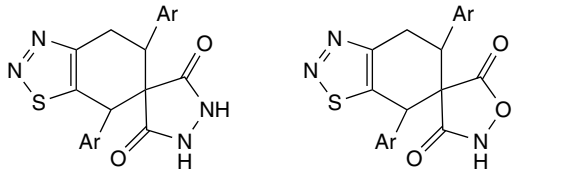
58 **59**



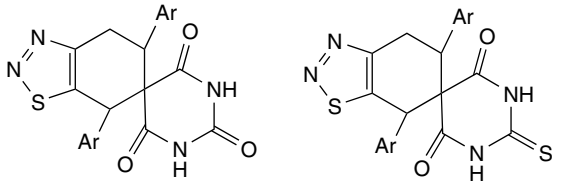
60 **61**

R = Ts, $CONH_2$

Recently, they expanded their approach to prepare spirocyclic cyclohexeno-1,2,3-thiadiazoles **62–65** containing pyrazolidine, oxazolidine and pyrimidine rings.[31,32]



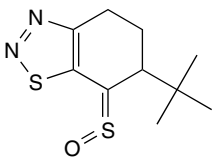
62 **63**



64 **65**

Cyclohexeno-1,2,3-thiadiazoles, containing a sulfine group at position 7, can also be obtained by the Hurd–Mori reaction when cyclohexanone ethoxycarbonylhydrazone is used as the starting reagent.[33]

Britton *et al*. have shown that the Hurd–Mori reaction, depending on the nature of the hydrazone, can lead to either sulfine derivatives or to the "normal" cyclohexeno-1,2,3-thiadiazoles. In the case of cyclohexanone ethoxycarbonylhydrazone having γ-alkyl substituents, the 1,2,3-thiazolylsulfines **66** and **67** are obtained as the exclusive products in moderate to high yield.[33] On the contrary, the 3,3,5,5-tetramethyl- and 2,5-methanocyclohexanone derivatives gave only the corresponding 1,2,3-thiadiazoles **68** and **69**.



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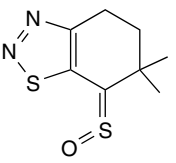

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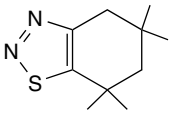
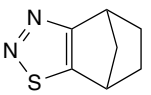
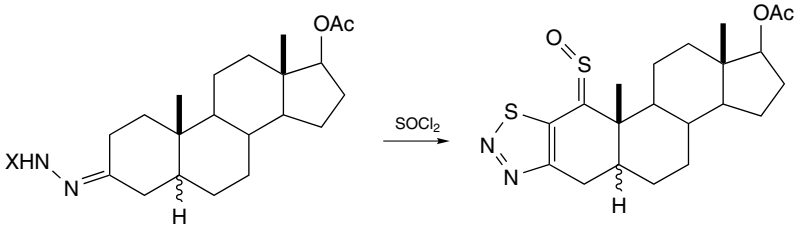


68



69

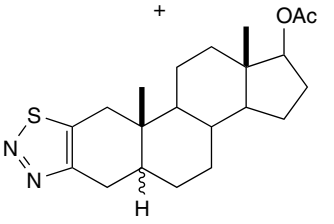
In attempting to prepare novel steroidal [3,2-*d*][1,2,3]thiadiazoles, Britton *et al*. studied the reaction of 17-β-acetoxy-5-α-androstan hydrazones **70a–d** with neat thionyl chloride. They have shown that ethoxycarbonylhydrazone **70a** gave 17-β-acetoxy-5-α-androst-2-eno[2,3-*d*][1,2,3]thiadiazole-1-thione *S*-oxide **71** exclusively in 84% yield. Under similar conditions, the corresponding tosyl- (**70d**) and formyl- (**70c**) hydrazones afforded 17-β-acetoxy-5-α-androst-2-eno[2,3-*d*][1,2,3]thiadiazole **72** in 84% and 85% yields, respectively, while the acetyl hydrazone **70b** gave a mixture of the two products.[33]



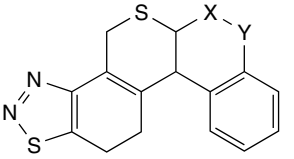
70 a–d

X = CO_2Et (**a**), COMe (**b**), CHO (**c**), Ts (**d**)

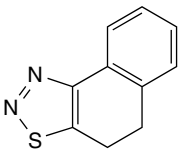
71



72



73
X, Y = CH_2, S



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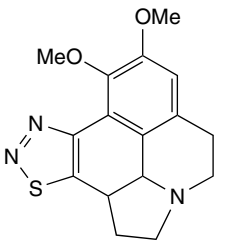

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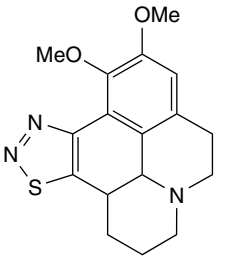
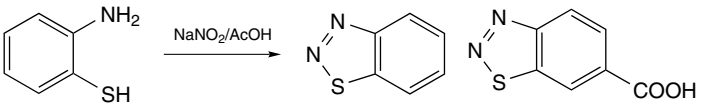


76

Polycyclic compounds containing a 6,7-dihydrobenzo-1,2,3-thiadiazole ring system of type **73, 74, 75** and **76** were prepared by Reddy[34], Meier[5] and Bremner[35], respectively, also using the Hurd–Mori approach.

4.2.2. Benzo-1,2,3-thiadiazoles

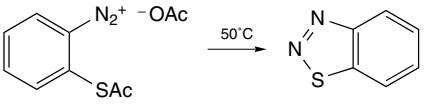
Benzo-1,2,3-thiadiazoles **78** are shown to be mainly prepared by both the Wolff method and the Hurd–Mori reaction. Aromatization of cyclohexa-1,2,3-thiadiazoles, rearrangements of 7-diazobenzothiazoles, isothiazoles and thiophenes and electrophilic substitution reaction in benzene ring are additionally used to prepare derivatives of benzo-1,2,3-thiadiazole.[1–3] The parent benzo-1,2,3-thiadiazole **78** was prepared in 77% yield by reaction of *ortho*-aminothiophenol with sodium nitrite in acetic acid.[36]



77 **78** **79**

Various derivatives of this heterocycle were prepared by this reaction.[37–39] Recently, this approach was used by Chinese scientists in a synthetic program toward plant activators analogous to benzo-1,2,3-thiadiazole-6-carboxylic acid **79**.[40]

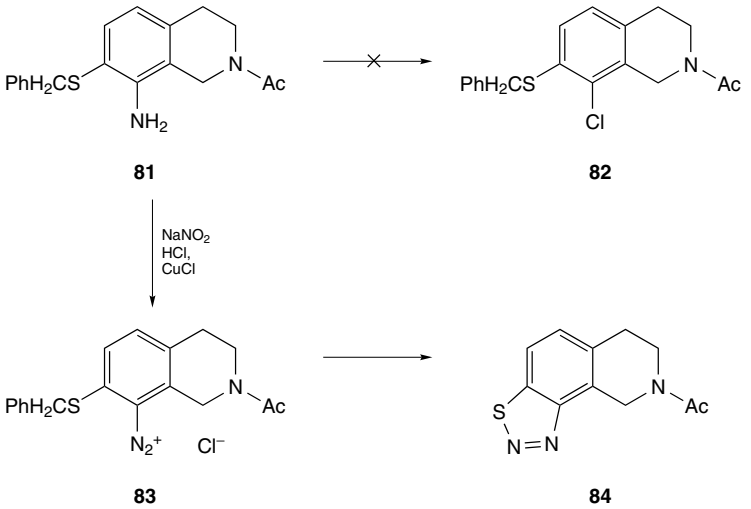
It was reported that the formation of the thiadiazole ring is often accompanied by side reactions of the diazonium salts.[1–3,19] A modification of this method,



80 **78**

the thermal decomposition of diazonium acetate **80** was reported to give a better yield of the target compound **78**.[1]

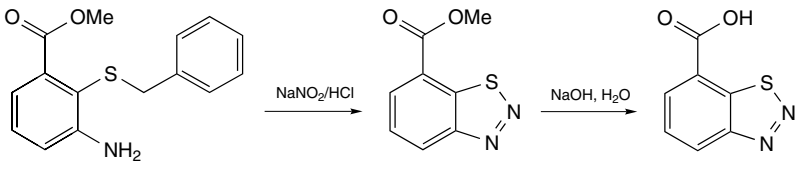
It is interesting to note that diazotation of *ortho*-aminobenzylsulfides also affords benzo-1,2,3-thiadiazoles **78** in good yields.[41,42] Thus, Girard *et al*., in an attempt to prepare 8-chloro-tetrahydroisoquinoline **82** by the diazotization of 8-amino congener **81**, followed by treatment with cuprous chloride in concentrated HCl, have obtained tetrahydrothiadiazoloisoquinoline **84** instead.[41]



81 **82**

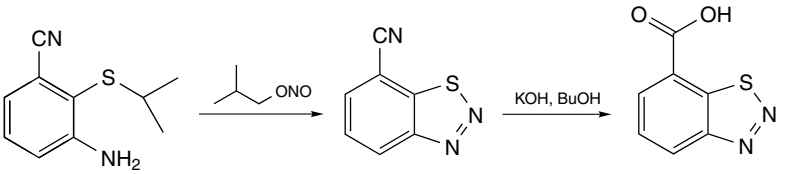
83 **84**

During the preparation of benzo-1,2,3-thiadiazole-7-carboxylic acid **87**, which is a precursor of the plant activator Bion® (see Chapter 6), Kunz and coworkers have shown that the diazotation reaction of the benzylsufide **85** led to benzo-1,2,3-thiadiazole-7-carboxylic methyl ester **86** in 86% yield.[42] Hydrolysis of the latter in aqueous alkali affords the desired carboxylic acid **87** in almost quantitative yield.[42]



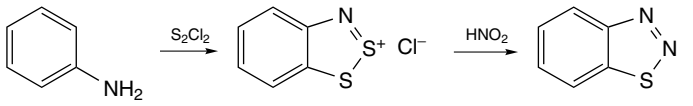
85 **86** **87**

A similar approach was used to prepare benzo-1,2,3-thiadiazole-7-carbonitrile **89** starting from isopropylsulfide **88**. Isobutyl nitrite in the presence of HCl in butanol was used as the source of nitrous acid. The authors have shown that the prepared compound **89** can easily be hydrolyzed to form benzo-1,2,3-thiadiazole-7-carboxylic acid **87**.[12]



88 **89** **87**

Benzothiadiazoles can also be obtained by the reaction of aromatic amines **90** with sulfur monochloride and treatment of the resulting benzodithiazole salt **91** (Herz salts) with nitrous acid. Sometimes, this reaction is accompanied by the chlorination of the aromatic ring.[1–3]

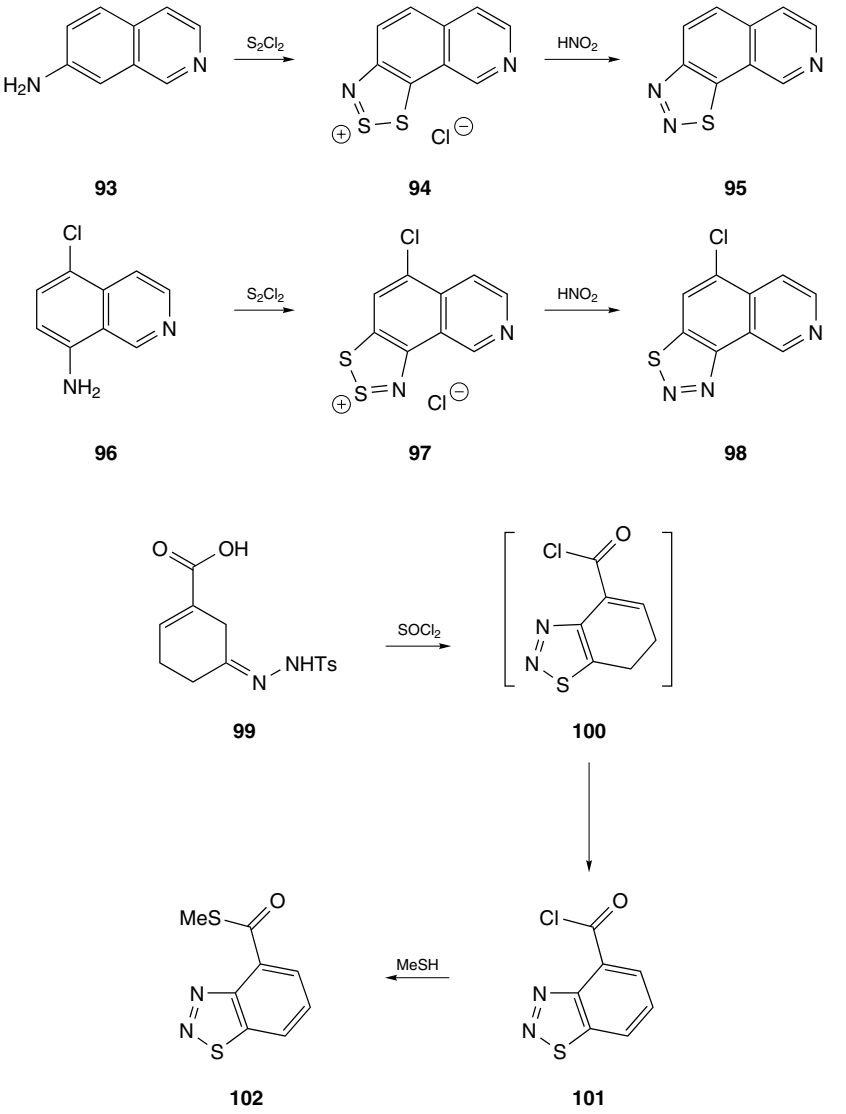


90 **91** **92**

Girard and colleagues have involved 3-amino- and 4-amino isoquinolines **93** and **96** in the Herz reaction to prepare dithiazolium salts **94** and **97**. These compounds, after treatment with sodium nitrite in 50% sulfuric acid, afforded 1,2,3-thiadiazolo[4,5-*h*]- (**95**) and 1,2,3-thiadiazolo[5,4-*h*]- (**98**) isoquinolines in moderate yields.[41]

Reactions of cyclohexenone hydrazones, including those fused to aromatic[42,43] or heteroaromatic[43] rings, with thionyl chloride can be accompanied by the aromatization of cyclohexadiene intermediate to give benzo- and naphtho-1,2,3-thiadiazoles. Thus, Kunz and colleagues reported the synthesis of benzo-1,2,3-thiadiazole-7-carbothioic acid, in which the ring formation by the Hurd–Mori reaction was the key step (see Chapter 1).[42] Tosylhydrazone **99** after treatment with thionyl chloride forms an intermediate thiadiazole **100**, which underwent spontaneous aromatization to the corresponding benzothiadiazole **101**. The latter was quenched with methylthiol to yield the final product **102**.[42]

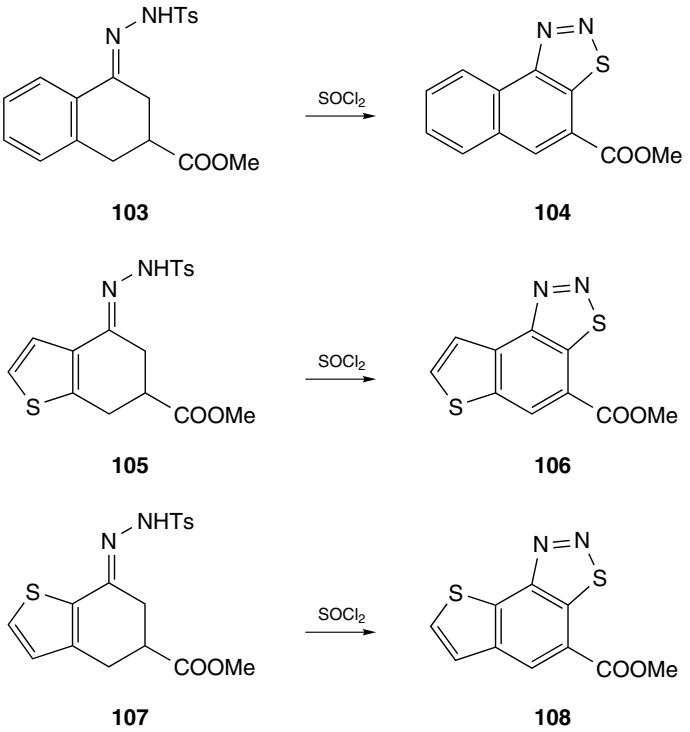
Recently, Naidu *et al*., using a similar approach, obtained a series of derivatives of 8-methoxynaphtho-[1,2-*d*]-1,2,3-thiadiazole-4-carboxylic acid.[44] Stanetty *et al*. found that when the tosylhydrazones **103, 105, 107** were treated with thionyl chloride at room temperature, the fully aromatic thiadiazoles **104, 106, 108**,



respectively, were formed in good yields, instead of the expected dihydrothiadiazoles.[43]

These results are in contrast to the data of Meier *et al.*[5] for the reaction of 1-tetralone(*p*-toluenesulfonyl)hydrazone with thionyl chloride, where the exclusive formation of 4,5-dihydronaphto[1,2-*d*][1,2,3]thiadiazole was registered.

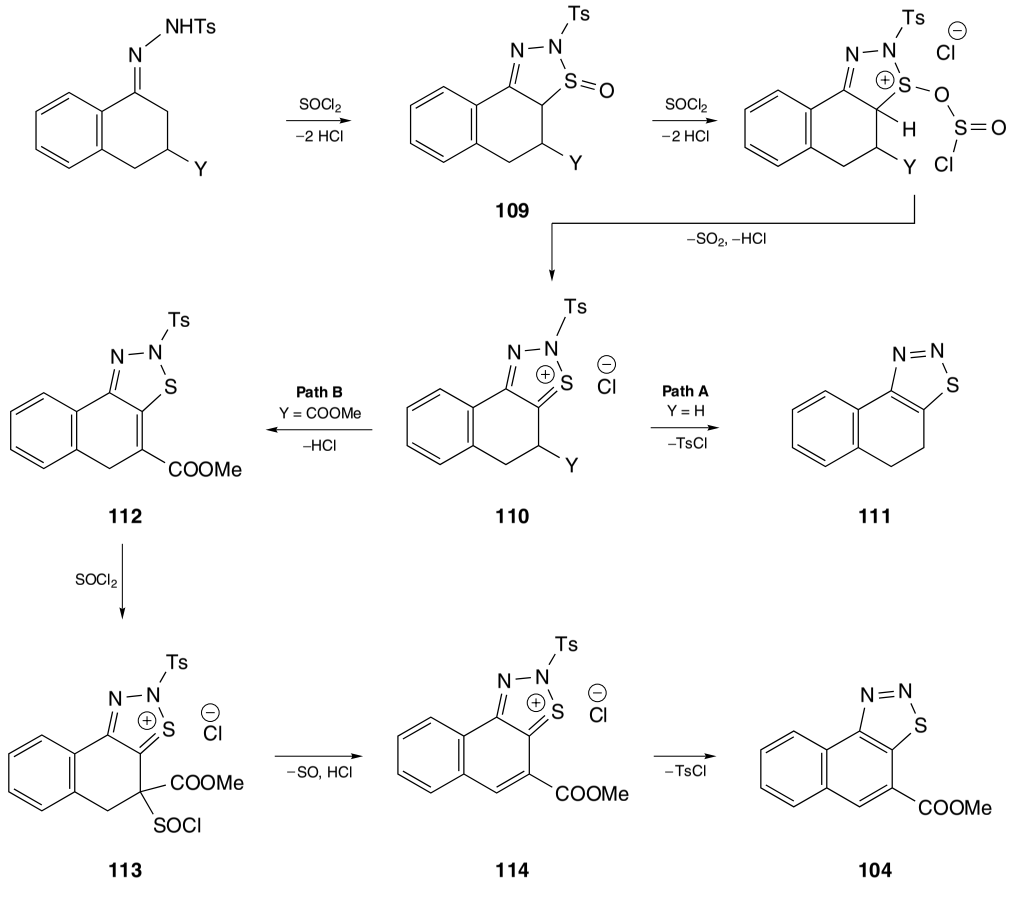
The conclusion was made[43] that the presence of the ester functionality is responsible for the observed aromatization. On the basis of all the reported data on the Hurd–Mori reaction, Stanetty *et al.* proposed a mechanism for the formation of the final products of this reaction as outlined below.



The first intermediate in the proposed mechanism is thiadiazole-1-oxide **109**, which undergoes with thionyl chloride a Pummerer-like rearrangement to *N*-tosyl thiadiazolium chloride **110**. If R = H, then path **A** leads to dihydrothiadiazole **111** via elimination of tosyl chloride. In contrast, when R = ester group, the reaction goes via pathway **B**. Elimination of HCl is favored in this case to yield intermediate product **112**. Then, electrophilic attack of thionyl chloride on the push–pull-substituted double bond in this compound leads to sulfinyl chloride **113** that forms **114** via a syn-elimination. The loss of the tosyl chloride in the last step affords the final aromatic product **104**.[43]

Somewhat in contradiction to the proposed hypothesis is the experiment of Vasumathi and Ramadas, who prepared aromatic thiosulfonate **116** starting from benzofuran-4-one tosylhydrazone **115** without an ester group in the molecule. This should, according the hypothesis of Stanetty, lead to the formation of dihydrobenzothiadiazole. The structure of the final compound was confirmed by X-ray analysis, and the mechanism of the formation of this novel compound had been rationalized.[45]

The Wolff method of the synthesis of 1,2,3-thiadiazoles (see Chapter 1) was also used for the preparation of benzothiadiazoles. Thus, the treatment of diazooxides of type **117** with tetraphosphorus decasulfide leads to the generation of transient diazothioketone, which in spontaneous heteroelectrocyclic reaction yielded naphtho[1,2][1,2,3]thiadiazoles **118**.[1–3]


NHTs
N
Y
SOCl2
−2 HCl
Ts
N–N
S=O
Y
109
SOCl2
−2 HCl
Ts
N–N
Cl
S
O
H
Y
S=O
Cl
−SO2, −HCl
Ts
N–N
S
COOMe
112
Path B
Y = COOMe
−HCl
Ts
N–N
S
Cl
Y
110
Path A
Y = H
−TsCl
N=N
S
111
SOCl2
Ts
N–N
S
Cl
COOMe
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Cl
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114
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N=N
S
COOMe
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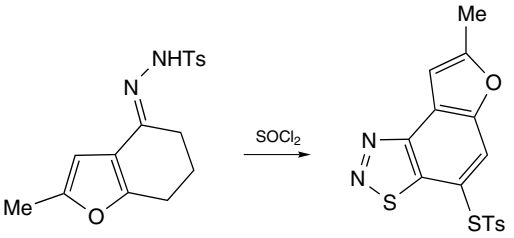
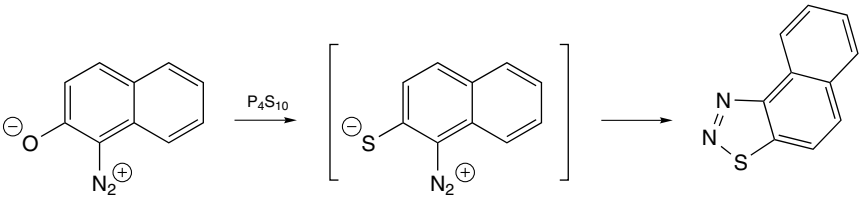
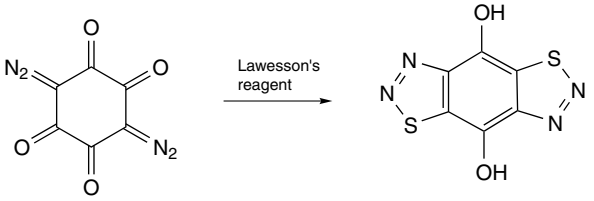


115 **116**

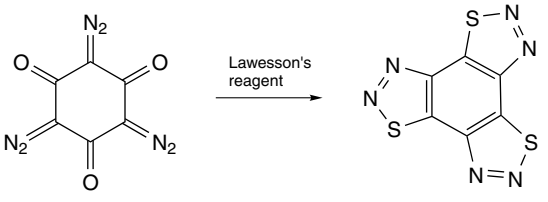


117 **118**



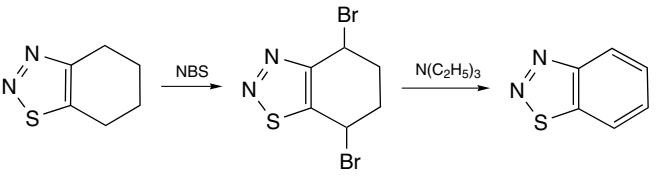
119 **120**

Obviously, the thionation reaction of diazoketones of both aliphatic and aromatic nature with Lawesson's reagent goes well if the diazo function is stabilized by electron-withdrawing substituents. Maier *et al.* have shown that compound **119** bearing two diazo groups and four carbonyl functions in a molecule reacts with Lawesson's reagent to form benzo-bis-thiadiazole **120**.[46] Furthermore, they have prepared by a similar reaction, benzo-*tris*-1,2,3-thiadiazole **122** starting from compound **121** having three diazo and three ketogroups.



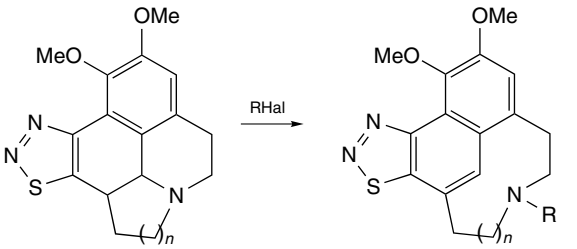
121 **122**

There are only a few examples published in the literature where the transformations of cyclohexeno-1,2,3-thiadiazoles to benzothiadiazoles are described. Meier *et al*. have shown that benzothiadiazole can be prepared by a two-step synthesis from cyclohexeno-1,2,3-thiadiazole **55**.[5] This method was used by the same authors to prepare benzothiadiazole **77** with a ^{13}C label at the position 4 of thiadiazole ring.[47]



55 **123** **77**

Cyclophanes incorporating in benzothiadiazoles could be prepared from 6,7-dihydro-benzo-thiadiazoles **75** by reaction with BrCN or with methyl chloroformate. The electrophilic attack on the nitrogen atom of **75** is accompanied here by the cleavage of the C−N bond and aromatization of the cyclohexadiene ring to give the final product **124**.[35]



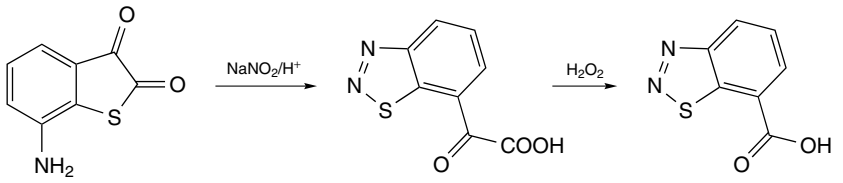
75
n = 1,2

124
n = 1,2; R = CN, COOMe

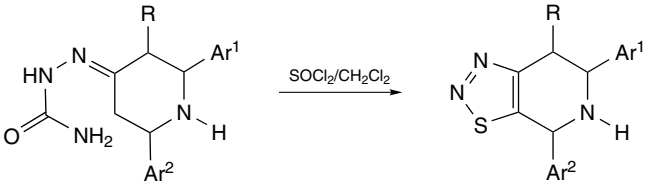
Rearrangements of 5-diazobenzothiazoles and -isothiazoles to benzothiadiazoles are known for many years.[1–3] Although these unusual results are interesting for fundamental heterocyclic chemistry, they were not widely used for the synthesis of benzothiadiazoles. In contrast, a new rearrangement of 7-diazobenzothiophene-2,3-diones to benzothiadiazoles, discovered recently by Goda and coworkers, accompanied by decarbonylation, was used to prepare benzo-1,2,3-thiadiazole-7-carboxylic acid **127**, a precursor of Bion®.[48]

4.2.3. Piperidino[3,4-*d*][1,2,3]thiadiazoles

5,7-Diarylpiperidino[3,4-*d*]thiadiazoles **129** were prepared by Reddy *et al*. from the corresponding semicarbazones **128** by treatment with thionyl chloride



125 **126** **127**



128
R = H, Alk, Ph

129

according to the Hurd–Mori reaction.[49] No aromatization to fused pyridines occurred.

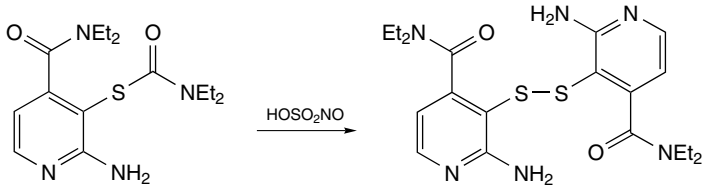
4.2.4. 1,2,3-Thiadiazolo[4,5-*b*]pyridines

1,2,3-Thiadiazolo[4,5-*b*]pyridine-7-carboxylic acid could not be prepared by diazotation of 2-aminopyridine **130** with isoamyl nitrite.[50] On the other hand, treatment of this compound with nitrosyl sulfuric acid afforded the disulfide **131**. The latter happened to be more reactive and was cyclized with isoamyl nitrite to a pyridothiadiazole-*N*-oxide, which was reduced and hydrolyzed to give carboxylic acid **132**.[50]

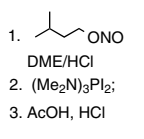
4.2.5. 1,2,3-Thiadiazolo[4,5-*c*]pyridines

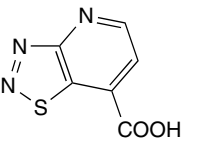
The chemistry of this particular type of the thiadiazolopyridines is most developed as compared to its isomers. Three approaches to 1,2,3-thiadiazolo[4,5-*c*]pyridines are known in the literature including (i) the construction of the thiadiazole ring; (ii) the construction of the pyridine ring and (iii) the rearrangement of anther bicyclic system.

The synthesis of *N*,*N*-diethyl-1,2,3-thiadiazolo[4,5-*c*]pyridine-7-carboxamide **134** was accomplished starting from **133** with isoamyl nitrite under anhydrous conditions. The reaction was carried out in the presence of acetic acid, which is necessary for the nucleophilic cleavage of the thiobenzoate group. Acid-catalyzed hydrolysis of the diethylamide **134** furnished 1,2,3-thiadiazolo[5,4-*c*]pyridine-7-carboxylic acid **135** in high yield.[42]

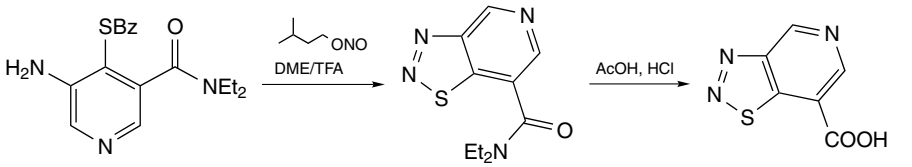


130 **131**



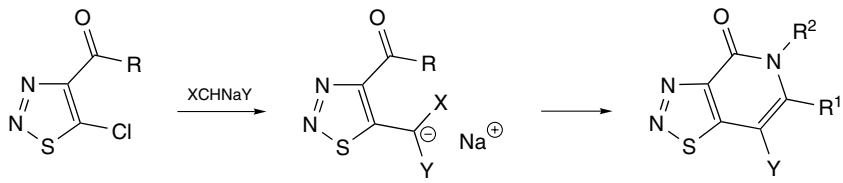


132



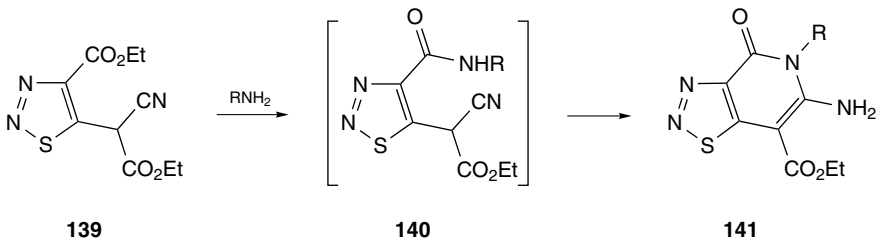
133 **134** **135**

We developed another approach to this heterocycle using the nucleophilic substitution reaction of 5-chloro-1,2,3-thiadiazoles **136** with malonic acid derivatives. Subsequent intramolecular condensation of the initially formed derivatives of 2-(1,2,3-thiadiazol-5-yl) acetic acid **137** was used to prepare a variety of 1,2,3-thiadiazolo[4,5-*c*]pyridin-4(5*H*)-ones **138**.[51,52]

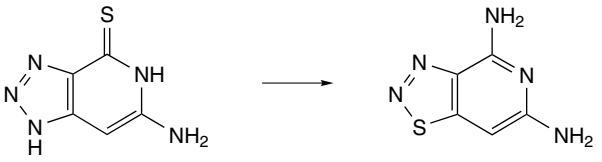


136 **137** **138**

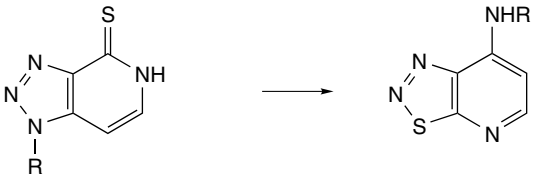
Furthermore, the ester **139**, which could be isolated from the reactions of **136** and ethyl cyanoacetate, was reacted with methylamine and hydrazine to



139 **140** **141**



142 **143**



144 **145**

furnish 6-amino-1,2,3-thiadiazolo[4,5-*c*]pyridin-4(5*H*)-ones **141** via the intermediate amides **140**.[51]

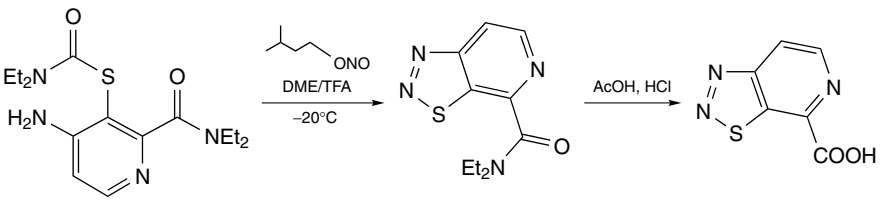
In neutral solvents or simply by melting, 1,2,3-triazolo[4,5-*b*]pyridin-4(7*H*)-thione **142** rearranges to 1,2,3-thiadiazolo[4,5-*c*]pyridine **143**.[1–3] It is interesting to note that the rearrangement of the 1-ribosyl derivative **144** proceeds faster than the analogous reaction of thione **142**.[2]

4.2.6. 1,2,3-Thiadiazolo[5,4-*c*]pyridines

Only one example for the synthesis of this heterocycle was published. Thus, *N*,*N*-diethyl 1,2,3-thiadiazolo[5,4-*c*]pyridine-7-carboxamide **147** was prepared by the diazotation of sulfide **146** with isoamyl nitrite in anhydrous conditions at −20°C by analogy with *N*,*N*-diethyl-1,2,3-thiadiazolo[4,5-*c*]pyridine-7-carboxamide **134**. Similar to **134**, the hydrolysis of this compound in acidic medium affords 1,2,3-thiadiazolo[5,4-*c*]pyridine-7-carboxylic acid **148**.[42]

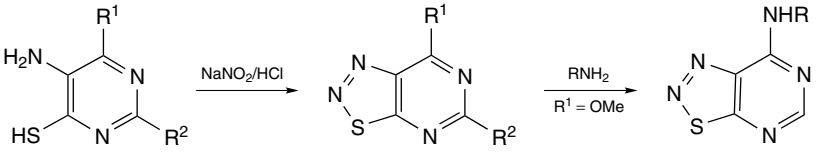
4.2.7. 1,2,3-Thiadiazolo[5,4-*d*]pyrimidines

It is possible to prepare derivatives of this heterocyclic system by (i) 1,2,3-thiadiazole ring synthesis and (ii) pyrimidine ring synthesis. Taylor and Garcia



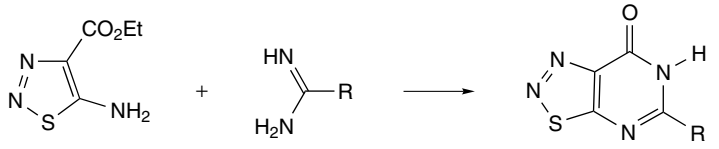
146 **147** **148**

reported that 1,2,3-thiadiazolo[5,4-*d*]pyrimidine **150** could be prepared by the diazotation of *ortho*-aminothiols of type **149** with sodium nitrite in concentrated hydrochloric acid in high yield.[53] The same authors prepared a number of 4-amino-substituted 1,2,3-thiadiazolo[5,4-*d*]pyrimidine **151** by the reaction of **150** ($R^1 = OMe$) with aliphatic amines and hydrazine. Hymans expanded this reaction to prepare the 1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4(5*H*)-ones **150** ($R^1 = OH$, $R^2 = Alkyl$).[54]



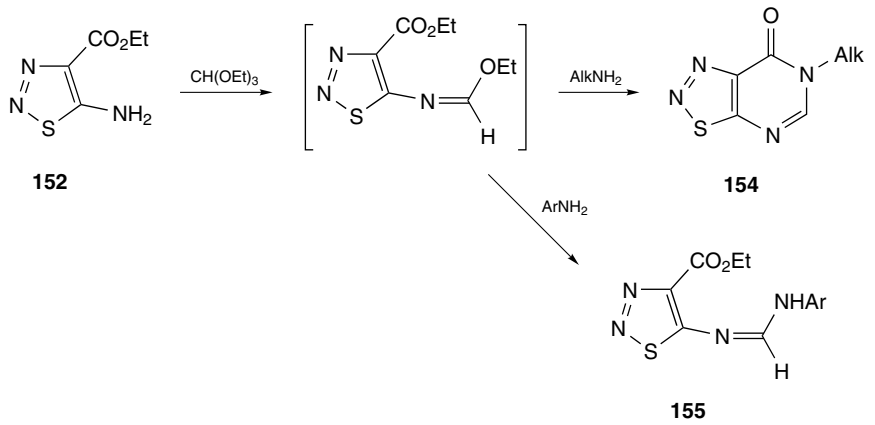
149 **150** **151**

The same type of compounds was prepared by the reaction of ethyl 5-amino-1,2,3-thiadiazole-4-carboxylate **152** with amidine acetate.[2] However, the yields of **153** were lower than those obtained in the former procedure. An additional disadvantage is the fact that the other 2-substituted derivatives of **153** could not be prepared from **152** and the corresponding amidines.[2]



152 **153**

A modification of this method includes treatment of the ester **152** with ortho esters to form intermediate imidates, which in a subsequent reaction with aliphatic amines afford derivatives **154** of the same ring system in a considerably higher yield.[55] The use of anilines in this synthesis instead of aliphatic amines leads to amidines **155**. However, we did not manage to bring these compounds **155** to

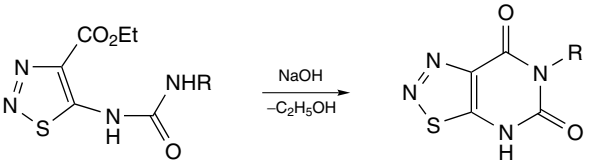


152 **154** **155**

cyclize, most likely because of the low nucleophilicity of the aromatic amidines in comparison with the aliphatic derivatives.

5-Amino-1,2,3-thiadiazole-4-carboxamides are also capable of undergoing cyclization with ortho esters to form 1,2,3-thiadiazolo[5,4-*d*]pyrimidine-4(5*H*)-ones **154** in good yield. So far, the scope and limitations have not been studied for this reaction.[55]

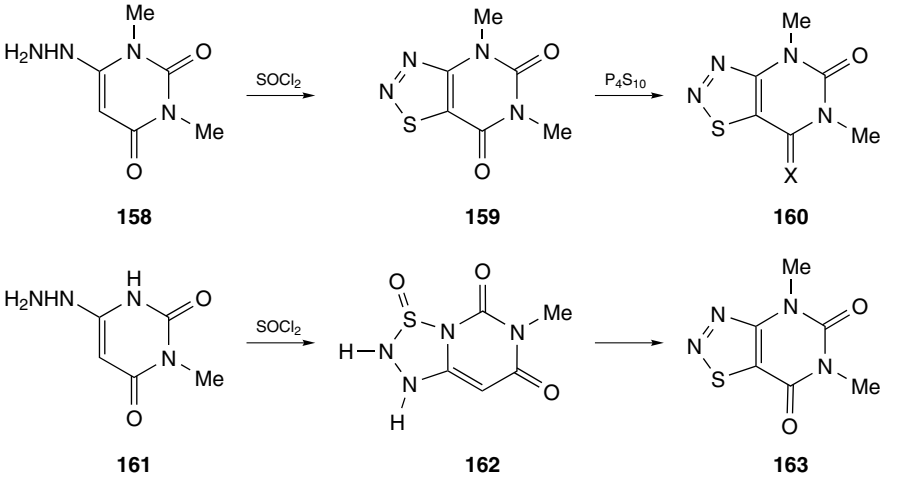
Martin and Mucke elaborated a method for the synthesis of 1,2,3-thiadiazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione **157** by the intramolecular condensation of ureas **156** on treatment with sodium hydroxide.[56]



156 **157**

4.2.8. 1,2,3-Thiadiazolo[4,5-*d*]pyrimidines

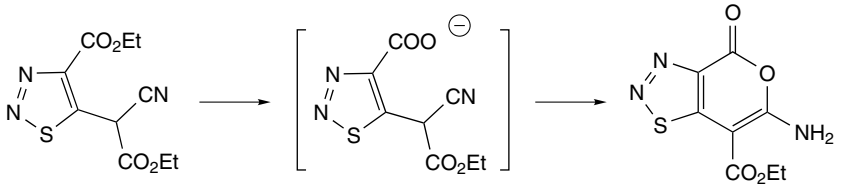
Senga *et al*. have systematically studied the reaction of 6-hydrazinouracils with $SOCl_2$. They have found that treatment of 6-hydrazinouracil **158** with thionyl chloride gave 4,6-dimethyl-1,2,3-thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **159** in good yield. Interestingly, a similar reaction of 6-hydrazino-3-methyluracil **161** afforded thiatriazoline **162**, which was isolated and subsequently converted to **163**. In this way, a variety of 1,2,3-thiadiazolo[4,5-*d*]pyrimidines was prepared, including mesoionic derivatives.[57] The thionation of **159** with P_4S_{10} in pyridine is shown to yield pyrimidinethione **160** (X = S). The



latter was further transformed to hydrazone **160** (X = N-NH_2) by the reaction with hydrazine at 100°C.

4.2.9. Pyrano[3,4-*d*][1,2,3]thiadiazole

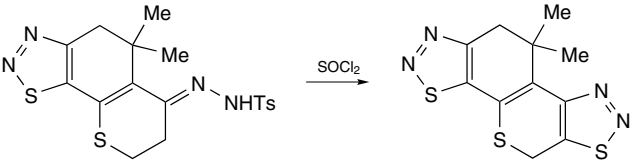
The only representative of this heterocycle, namely, pyrano[3,4-*d*][1,2,3]thiadiazole-4-one **164** was prepared by treatment of thiadiazolylacetate **139** with 2 equiv of alkali in aqueous medium.[51,52]



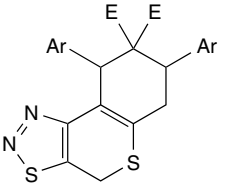
4.2.10. Thiopyrano[4,3-*d*][1,2,3]thiadiazoles

Ramadas *et al*. reported the Hurd–Mori synthesis of tetracyclic bisthiadiazole **166** from a fused thiadiazole derivative **165**, which, in turn, was prepared starting from dimedone. The compound **166** was considered as a steroid analog.[58,59]

A number of other examples **167–172** of polycyclic 1,2,3-thiadiazoles, containing a thiopyran ring, were synthesized by both the Ramadas and Reddy groups using the Hurd–Mori approach.[25–27,34,59–61]



165 **166**



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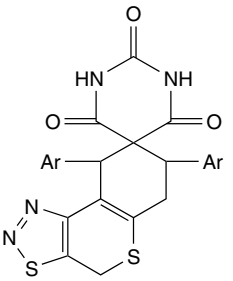

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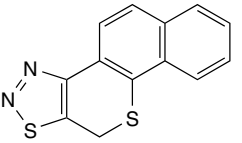

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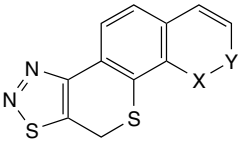

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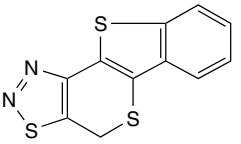

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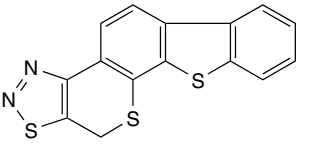

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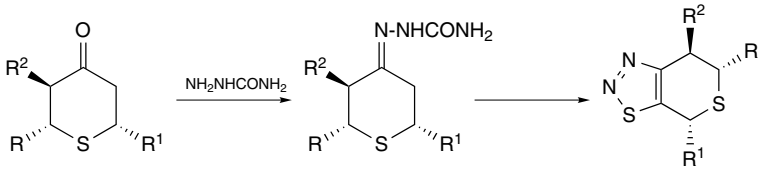


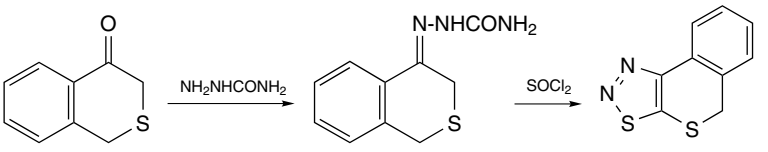
173 **174** **175**

It has been noted that the bicyclic compounds of the parent system 4,5,7-trihydrothiapyrano[3,4-*d*][1,2,3]thiadiazoles were prepared from tetrahydrothiapyranones **173**.[62] The latter were condensed with semicarbazide to form semicarbazones **174** that, in turn, in subsequent oxidative cyclization with thionylchloride afforded 5,7-diaryl-4-alkyl-4,5,7-trihydrothiapyrano-1,2,3-thiadiazoles **175** in good yields.[62]

4.2.11. Thiopyrano[2,1-*d*][1,2,3]thiadiazole

Only one example of such type of compounds has been published in the literature.[34] When the 2-thiachroman-4-one **176** was subjected to treatment with

semicarbazide followed by reaction with thionylchloride in methylene chloride at $-10^{\circ}C$, the 2-thiadihydronaphthalene[3,2-*d*][1,2,3]thiadiazole **178** was obtained in 70% yield.



176 **177** **178**

4.2.12. Selenopyrano[4,3-*d*][1,2,3]thiadiazoles

Reddy *et al*. reported the synthesis of 5,7-diphenyl-4,5,7-trihydroselenopyrano [4,3-*d*][1,2,3]thiadiazole by using a very similar procedure to the one they applied for the synthesis of the sulfur analog compound **175**.[63]

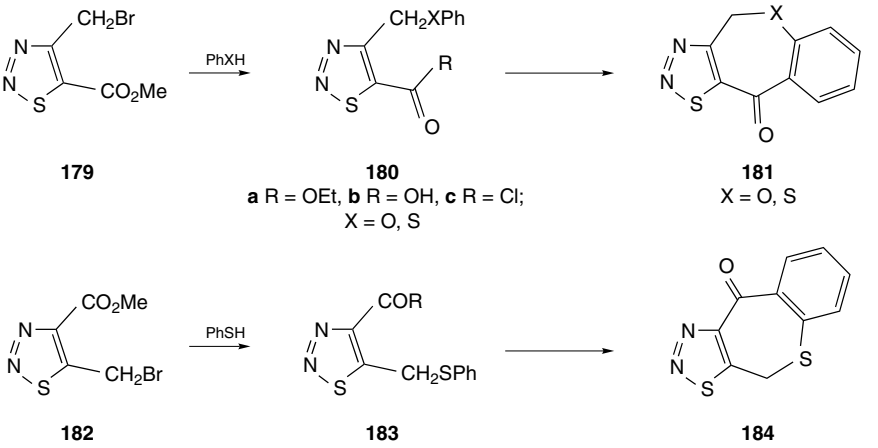
4.3. 1,2,3-THIADIAZOLES FUSED WITH SEVEN-MEMBERED RINGS

The number of this type of bicyclic 1,2,3-thiadiazoles is limited to a few examples. After Meier published, in 1980, the synthesis of benzocyclohepta-1,2,3-thiadiazole[5], only three papers appeared in the literature on the synthesis of 1,2,3-thiadiazoles fused to benzooxepine, thiobenzooxepine, azepine and diazepine rings.[62,64–66]

4.3.1. Benzooxepino- and Benzothiepino[3,4-*d*][1,2,3]thiadiazoles

Starting from methyl 4-bromomethyl-1,2,3-thiadiazole-5-carboxylate **179** and methyl 5-bromomethyl-1,2,3-thiadiazole-4-carboxylate **182**, Shafiee and Kiaeay have prepared 4,10-dihydro-10-oxo[1]benzooxepino[3,4-*d*][1,2,3]thiadiazole **181** (X = O), 4,10-dihydro-10-oxo[1]benzothiepino[3,4-*d*][1,2,3]thiadiazole **181** (X = S) and 4,10-dihydro-4-oxo[1]benzothiepino[3,4-*d*][1,2,3]thiadiazole **184** as shown below.[64]

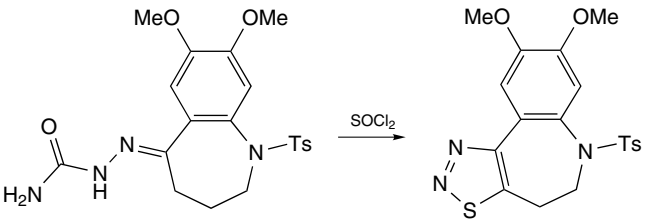
Thus, treatment of methyl 4-bromomethyl-1,2,3-thiadiazole-5-carboxylate **179** with sodium phenoxide in butanone affords methyl 4-phenoxymethyl-1,2,3-thiadiazole-5-carboxylate **180a** (X = O), which was converted to acid **180b** (X = O) by alkaline hydrolysis. Treatment of the latter with thionyl chloride followed by cyclization with stannic chloride provides oxepine **181** (X = O). Reaction of compound **179** with sodium thiophenolate in ethanol afforded phenylthio derivative **180a** (X = S). The latter, via saponification followed by cyclization in polyphosphoric acid yielded thiepine **181** (X = S). Thiepine **184**, which is an isomer



of **181** (X = S), was prepared from methyl 5-bromomethyl-1,2,3-thiadiazole-4-carboxylate **182** in a similar manner.[64]

4.3.2. Thiadiazolo[5,4-*d*]benzazepines

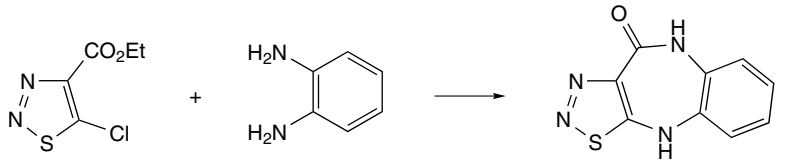
Peesapati *et al*. reported the synthesis of 5,6-dihydro-8,9-dimethoxy-6-tosyl-4*H*-thiadiazolo[5,4-*d*]benzazepine **186** by the reaction of hydrazone **185** with thionyl chloride.[65]



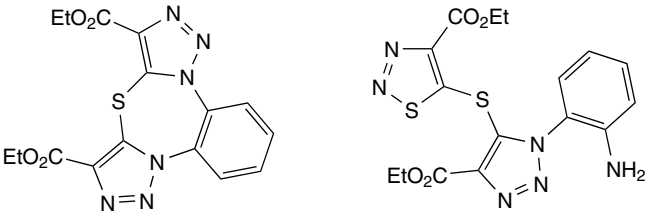
It should be noted that the 5,6-dihydro-6-tosyl-4*H*-thiadiazolo[5,4-*d*]benzazepine was already prepared by Procter *et al*. in 1978 using a similar reaction.[66]

4.3.3. 1,2,3-Thiadiazolo[5,4-*b*][1,5]benzodiazepine

Recently, we have found that 4,5-dihydro-10*H*-[1,2,3]thiadiazolo[5,4-*b*][1,5]-benzodiazepine-10-one **189** can be formed in the reaction of ester **187** with *ortho*-phenylenediamine **188** in DMF. It is interesting to note that, this reaction in



187 188 189

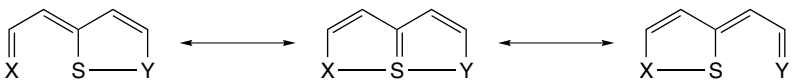


190 191

ethanol in the presence of triethylamine affords another tricyclic product **190** together with the sulfide **191**.[62]

4.4. BICYCLIC 1,2,3-THIADIAZOLES OF AZATHIAPENTALENIC STRUCTURE

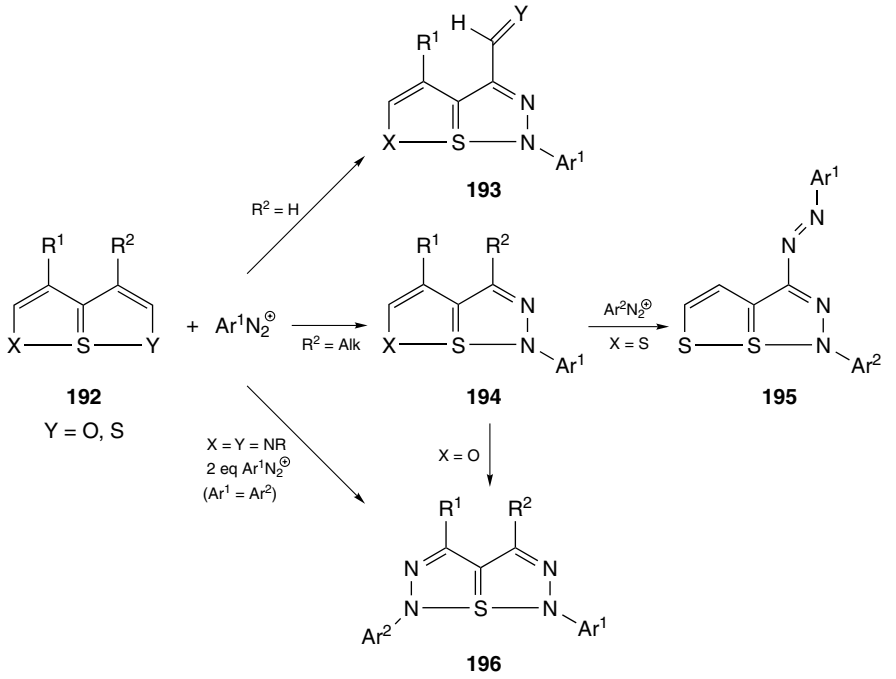
6aλ^4-Thiapentalenes **192** are delocalized 10π-electron systems, which are characterized by single bond/no bond resonance, represented by the canonical structures.[67] The central sulfur atom is hypervalent, and the three heteroatoms X, S and Y are normally collinear. Unsymmetrical structures can be biased to either of the ring-opened resonance forms with only a weak S...X or S...Y bond, which can be named a thiapentalenic interaction.



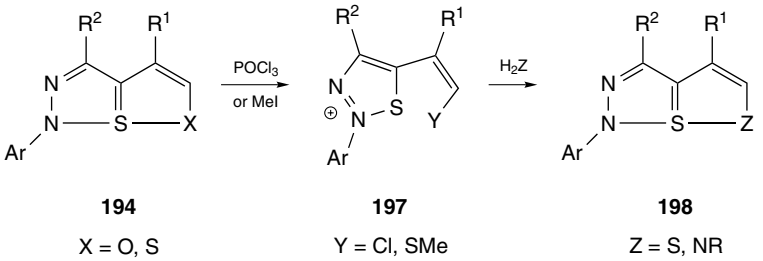
192

A number of 1,2,3-thiadiazole derivatives related to this thiapentalene structure have been investigated. In a series of articles, Reid *et al.* described several ways to obtain these systems. In a first approach, thiapentalene derivatives **192** were reacted with arenediazonium salts depending on the substituent R^2 to afford thiadiazapentalenes **193** with an exocyclic C=Y group in the case of $R^2 = H$ or products of the elimination of the moiety CHY, compounds **194**, when starting compounds **192** (R^2 = Alk) were used.[68–70] Dithiadiazapentalenes **194** (X = S) can react further with arenediazonium salts to give arylazothiapentalenes

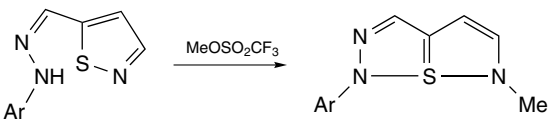
of various structures, including the rearrangement products **195**.[71] Oxathiadiazapentalenes **193** (X = O), however, yielded thiatetraazapentalenes **196**.[72] The latter compounds were also obtained in low yield from thiadiazapentalenes **192** (X = Y = NR) by treatment with 2 equiv of aryldiazonium salt.[73]



Reid investigated another approach to obtain thiapentalenes with a 1,2,3-thiadiazole unit. Firstly, the thiapentalene **193** (X = O, S) was converted with $POCl_3$ or MeI into thiadiazolium salt **197** (Y = Cl, SMe). On treatment of **197** with a nucleophile H_2Z, modified thiapentalenes **198** were obtained.[73,74]

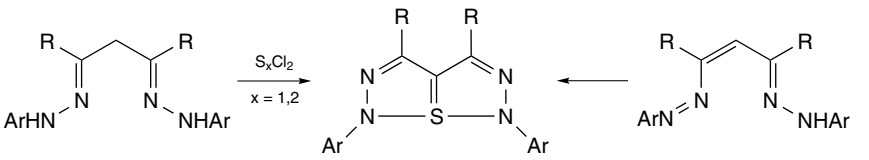


A third approach by Reid starts from isothiazole-5-carbaldehyde hydrazone **199**. Methylation of **199** with methyl fluorosulfonate furnished the thiatriazapentalene **200** in excellent yield.[75] Stable 1:1 complexes between these compounds **200** and 1,3,5-trinitrobenzene were obtained.



199 **200**

1,3-Bis(arylhydrazones) **201** or their oxidized forms **202** were treated with sulfur monochloride or sulfur dichloride to give symmetrical thiatetraazapentalenes **203**. The selenium- and tellurium analogs of **203** were also prepared.[76]

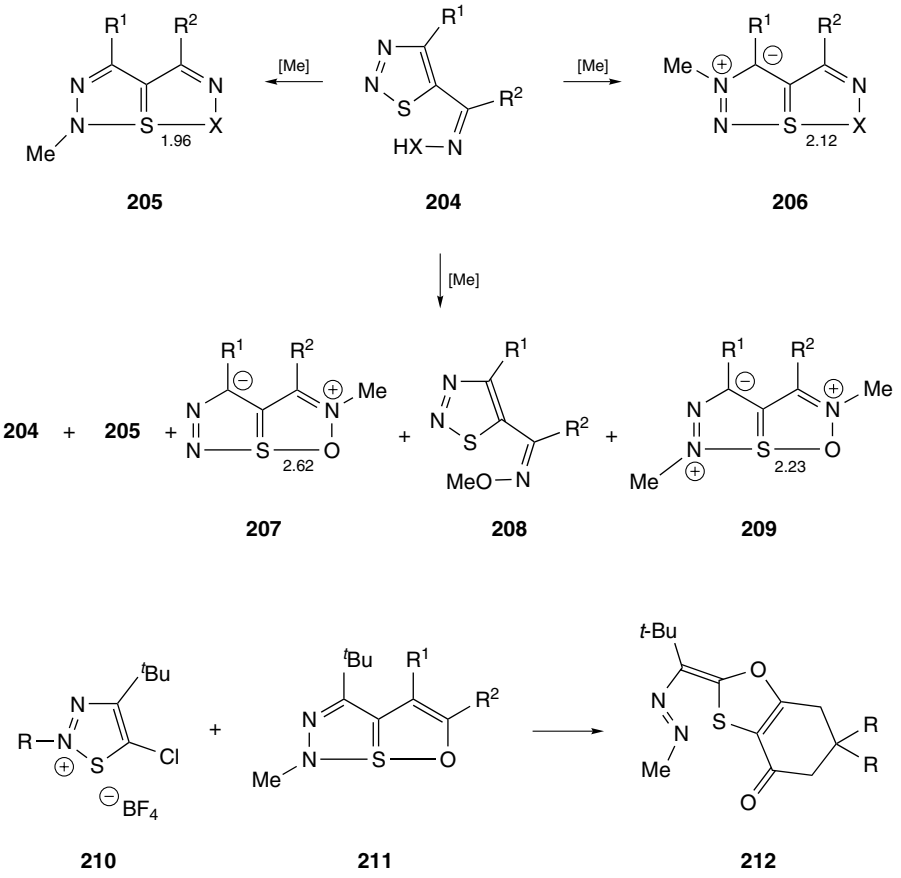


201 **203** **202**

L'abbé *et al*. have carried out the reaction of 1,2,3-thiadiazole-5-carboxaldehyde phenylhydrazones **204** (X = NAr) with several alkylating agents and obtained a mixture of thiatetraazapentalenes **205** and mesoionic compounds **206**. The thiapentalenic character of **205** was confirmed by X-ray crystallography, showing a linear N-S...N arrangement with a short S...N distance (1.97 Å).[77,78] Benzo-bridging was shown to disfavor this S...N contact (2.82 Å) because of increased ring strain.[79] The S...N interaction is also weak for all the mesoionic compounds.[80] Analogously, methylation of 1,2,3-thiadiazole-5-carboxaldehyde oxime with Meerwein's reagent furnished the corresponding oxathiatriazapentalenes **205** (X = O) and mesoionic compounds **206** (X = O). The nitrones **207** and O-methyl oximes **208** were isolated when diazomethane or methyl iodide were used as the alkylating agent.[81,82]

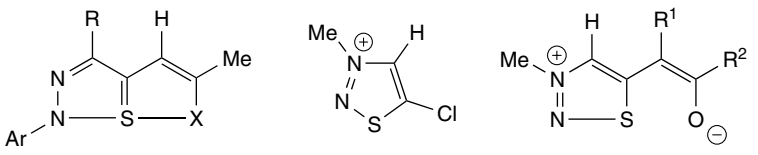
In the case of R^1 = Ph and R^2 = H, an X-ray crystallographic study was undertaken of three methylated products **205, 206, 207**, and also of the dimethylated **209**. The thiapentalenic interaction decreases in the order **205** > **206** > **209** > **207**, with the S...O distances increasing from 1.96 < 2.12 < 2.23 < 2.62 Å.[83]

5-Chloro-1,2,3-thiadiazoles are methylated either in the 2- or 3-position (see Chapter 3), making the heterocycle much more prone to nucleophilic substitution. The reaction of activated methylene compounds with 2-methyl-5-chloro-4-*t*-butyl-1,2,3-thiadiazolium salt **210** in the presence of base afforded oxathiadiazapentalenes **211**. The corresponding adduct with Meldrum's acid existed as two crystallographically independent, almost planar molecules, having an S...O distance of 2.37/2.34 Å, indicating a weak thiapentalene interaction calculated as 2.6–3.0 kcal/mol. Reaction of the salts with α-(azole)acetates gave thiapentalenic compounds **211** (R^1 = azolyl) that existed as two rotamers.[84] Cyclohexanediones reacted differently with this salt, yielding the rearranged oxathioles **212**, in which the thiadiazole ring had opened.[85]



R = H, Me; $R^1 = COR^2$; R^2 = Me, OMe

2-Aryl-1,2,3-thiadiazolium salts **210** (R = Ar), which could be obtained by a Hurd–Mori-type reaction, reacted with acetone under oxidative conditions to give an oxathiadiazapentalene **213** (X = O), which could be transformed to a dithiadiazapentalene **213** (X = S) with P_4S_{10}.[3]

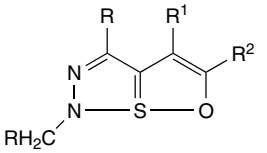


213 **214** **215**

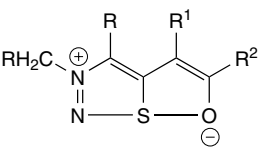
X = O, S

Starting from the 3-methyl thiadiazolium salt **214** and activated methylene compounds, mesoionic compounds **215** were obtained, which showed only very weak thiapentalenic interactions by X-ray crystallographic analysis.[85]

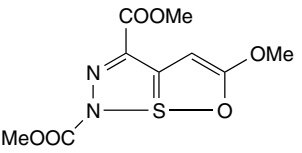
Capuano *et al*. reported the isolation of both thiapentalenes **216** and mesoionic compounds **217** from the reaction between 2 equiv of diazoalkane and 1 equiv of thioketene. As could be expected, the S...O distances are shorter for the former (2.46–2.52 Å) than the latter (2.60 Å).[86] The related 2,4-bis-(methoxycarbonyl)-1,2,3-thiadiazol-5-ylidenemethyl acetate **218** was prepared in one step by a Hurd–Mori reaction starting from dimethyl 2-oxoglutarate. The S...O distance here is somewhat shorter (2.39 Å), which could be due to the increased electrophilic character of the 1,2,3-thiadiazoline sulfur atom.[87]



216



217

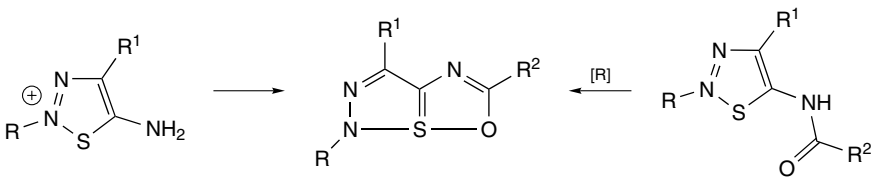


218

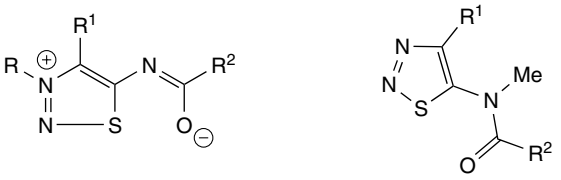
R = H, Ph; $R^1 = COR^2$, CN; R^2 = OEt

The thiadiazolium salts **219**, which are easily obtained starting from α-thioamide hydrazones by oxidation (see Chapter 1), can be converted into thiapentalene derivatives by electrophilic reactions of the exocyclic amine function. For instance, acylation gives the oxathiatriazapentalenes **220**, as described by Gewald.[88] An alternative synthesis for these compounds starts from the 5-acylamino-1,2,3-thiadiazoles **221**. Goerdeler *et al*. have reacted the thiadiazoles **221** with Meerwein's reagent and claimed to obtain the thiapentalenes **220**.[89] An X-ray structure of the product from the reaction of **221** with diazomethane showed it to have the mesoionic structure **222**.[90] Later, it was proven by Masuda *et al*. that the product Goerdeler obtained was actually the mesoionic compound **222**, which could also be obtained by alkylation of **221** with dimethyl sulfate. The use of methyl fluorosulfate yielded, next to the mesoionic **222** as the major product, small amounts of the 2-methyl-substituted derivative **220**. The same workers found that the reaction of **221** with diazomethane gives three products including **220** and **222**, and small amounts of the side chain–methylated **223**. Reaction of benzyl bromide affords only 3-substituted derivatives **222**.[91]

We used imidoyl chlorides as the electrophilic reagent in combination with the salts **219** to afford the thiatetraazapentalenes **224**, which were also obtained using an alternative route starting from 1,2,4-thiadiazole hydrazones.[92] Reaction of the salts **219** with isothiocyanates in the presence of base gave the aminodithiatriazapentalenes **225**.[3] Furthermore, the reaction of **219** with arenediazonium salts gave thiapentaazapentalenes **226**. X-ray crystallographic analysis showed these

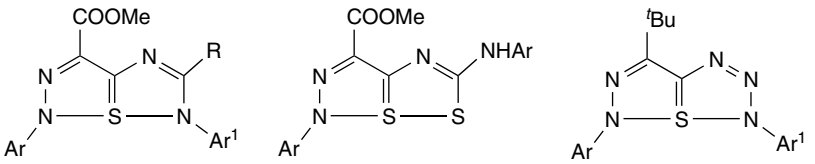


219 **220** **221**



222 **223**

R = Me, CH_2Ph; R^1 = H, CO_2Me, *t*-Bu, Ar;
R^2 = Ar, Alk



224 **225** **226**

compounds to be more biased to a thiadiazoletriazene structure with an S. . .N distance of 2.06 Å, corresponding to a bond dissociation energy of 11 kcal/mol.[93]

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CHAPTER 5

Synthesis and Properties of 1,2,3-Selenadiazoles

We have included in this monograph a chapter on the synthesis and properties of 1,2,3-selenadiazoles because of the similarity with the 1,2,3-thiadiazole ring system. Indeed, in many publications, both 1,2,3-selenadiazoles and 1,2,3-thiadiazoles appear together and are compared with regard to their synthesis and properties. As it will be clear from this chapter, besides the common points there are also many differences between the two ring systems, mostly having to do with the relatively low stability of the 1,2,3-selenadiazole ring.

Earlier reviews or accounts on 1,2,3-selenadiazoles[1,2] cover only a part of the literature.

5.1. SYNTHESIS OF 1,2,3-SELENADIAZOLES

5.1.1. Oxidative Cyclization of Hydrazones by Se-containing Reagents

Almost all of the 1,2,3-selenadiazoles **1** reported in the literature have been prepared by the reaction of semicarbazone derivatives **2** with selenium dioxide. The first article on this was published in 1969 by Lalezari, Shafiee and Yalpani. The discovery was serendipitous as, in fact, the authors had wanted to oxidize a methyl group adjacent to the hydrazide to an aldehyde function.[3] These Iranian researchers have been very active in this field since then. Gleiter referred to this reaction as the Lalezari reaction.[4] The method is analogous to the Hurd–Mori method for 1,2,3-thiadiazole synthesis, as first recognized by Meier.[5] Thus, one can assume that after addition of selenous acid onto the nitrogen of the semicarbazone, intermediate **A** cyclizes via its enehydrazide tautomer **B** to a dihydroselenadiazole-Se-oxide that may be in tautomeric equilibrium between forms **C** and **D**. The intermediate **D** then readily eliminates water and hydrocyanic acid, leading to the 1,2,3-selenadiazole **1**. Ammonium carbonate, possibly a decomposition product of the hydrocyanic acid, separated in the reflux condenser when dioxane was used as the solvent. Moreover, *sym*-diphenylurea was isolated when *N*-phenylsemicarbazone was used as the substrate.

The Chemistry of 1,2,3-Thiadiazoles, by Vasiliy A. Bakulev and Wim Dehaen
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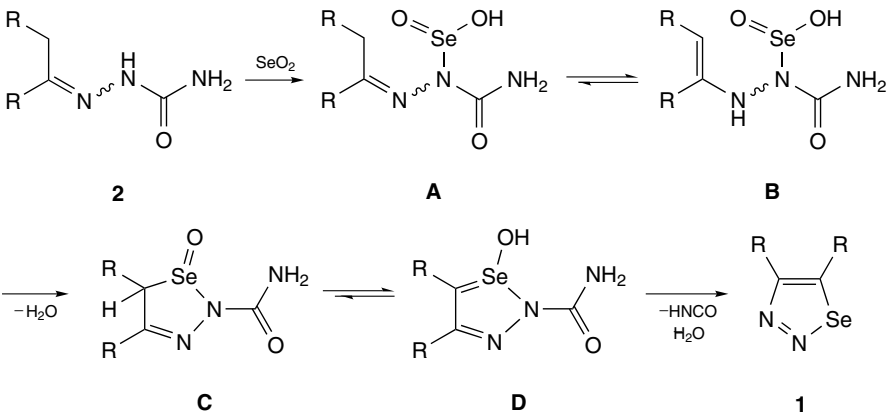
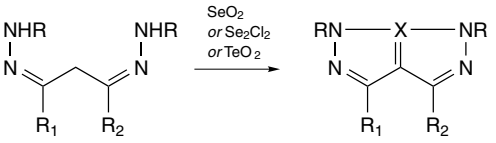


The reaction was carried out, according to Lalezari *et al.*, in hot acetic acid with heating being continued until gas evolution ceased.[3] In the early reports, the data of reaction temperature and time are rather vague, but later authors seem to agree on heating at 50–60°C for about 1 h. Heating for too long a time would lead to decomposition of the relatively unstable 1,2,3-selenadiazole **1**. The same authors, and, later, also Meier described the use of dioxane as the solvent. In general, reactions are carried out at room temperature (10–15 h or several days), in the dark and in combination with a saturated aqueous solution of selenium dioxide.[5,6] In difficult cases, a second portion of selenium dioxide solution was added after one day. The "selenium dioxide/dioxane/water method" seems to be the most accepted nowadays, although many researchers continue to use the "acetic acid method". Common side products in any conditions are the starting ketone and products of overoxidation or decomposition of the 1,2,3-selenadiazole. For fused derivatives, aromatization of the other ring may occur.[7] An improved procedure for the parent selenadiazole **1** (35%, R = H) was reported by Cava *et al.* from acetaldehyde semicarbazone and aqueous selenium dioxide (17 wt %) in dichloromethane containing acetic acid (20:1) under phase-transfer conditions.[8]

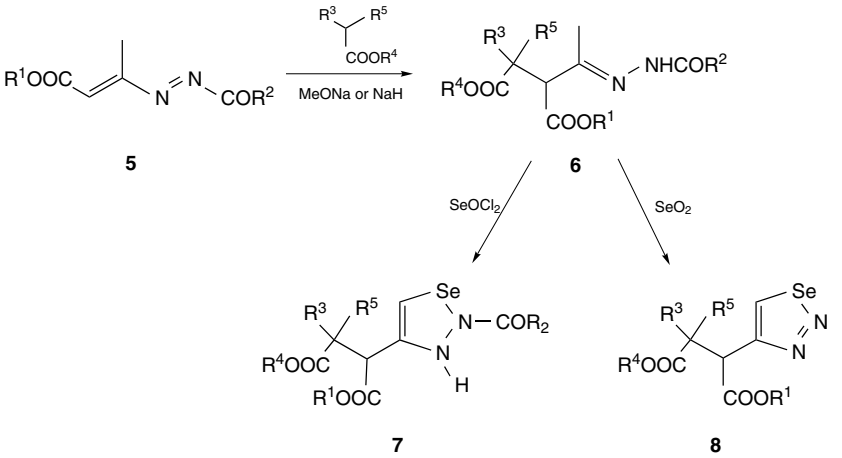
The selenapentalenes **4** (X = Se) were prepared from bishydrazones **3** with either selenium dioxide (SeO_2) or selenium monochloride (Se_2Cl_2) as the source of selenium.[9,10] The latter method gave a better yield. Apart from this report, selenium monochloride seems not to have been used much as a source of selenium in 1,2,3-selenadiazole synthesis. Meier noted a few years later that yields of 1,2,3-selenadiazoles are lower with selenium monochloride than selenium dioxide due to side reactions.[11] This was confirmed by Grandi *et al.*[12] Remarkably, the corresponding tellurium derivatives **4** (X = Te) were prepared from the same intermediates **3** with tellurium dioxide.[9,10] The 1,2,3-telluradiazole ring system is very rare and seems to be stabilized here by the nonbonded interaction between tellurium and the heteroatom (N or O).



3 **4**

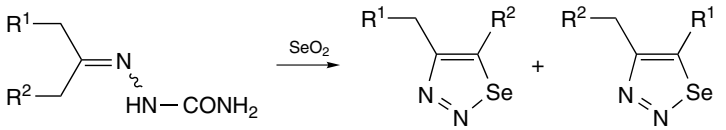
X = Se, Te

A third reagent, seleninoyl dichloride ($SeOCl_2$), was used by Grandi *et al.* in combination with tosyl hydrazones at low temperature (−15°C) to prepare 1,2,3-selenadiazoles **1** with better yield as compared to the more convenient selenium dioxide method.[12] Since this report, this reagent has not been used much. Attanasi *et al.* described the formation of 4-substituted 2,3-dihydro-1,2,3-selenadiazoles **7** from the corresponding hydrazones **6** with $SeOCl_2$ in mild conditions (dichloromethane, −20°C to room temperature), while the expected 1,2,3-selenadiazoles **8** were formed from **6** with selenium dioxide at 90°C in acetic acid. The hydrazones **6** themselves are obtained by the condensation of 1,2-diaza-1,3-butadienes **5** with activated methylenes or methines.[13]



5 **6** **7** **8**

A study of the regioselectivity of ring closure of unsymmetrical semicarbazones with selenium dioxide/dioxane/water was carried out by Meier.[11] In contrast with the corresponding 1,2,3-thiadiazoles, the ratio of the two isomers **9** and **10** is not influenced by the Z/E ratio of the hydrazones as these are in fast equilibrium under the conditions of the ring formation. In general, methyl groups seem to be favored for ring closure unless there are activating groups (ester, sulfonyl and aryl) on the methylenes.[11] Shafiee reported regioselectivity for thiophenoxy derivatives **9** and **10** ($R^1 = H$, $R^2 = SPh$, 9:1), and only the phenoxy derivative **9** was formed ($R^1 = H$, $R^2 = OPh$).[14]

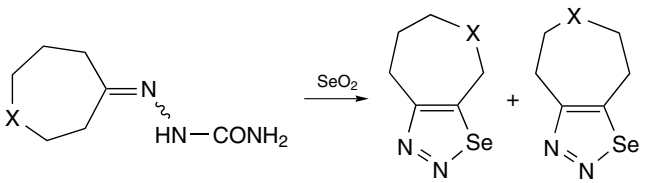


Z/E isomers **9** **10**

Maryanoff reported an unusual medium effect on the distribution of 1,2,3-selenadiazoles regioisomers in the reaction of *N*-benzyl-4-homopiperidone semicarbazone **11** (X = N-benzyl) and its analogs with selenium dioxide.[15] Again, the Z/E ratio was shown to have very little effect on the distribution of products **12a** (the "proximal" isomer) and **12b** (the "distal" isomer"). More important for the regiochemistry was the solvent used and the amount of water present. The experiments were conducted at room temperature, and the ratio of **12a** to **12b** was determined by ^{1}H NMR. High selectivity for the proximal isomer **12a** (20:1) was found in dioxane/water (5:1). A lower dioxane/water ratio (1:5) gave a lower selectivity (9:1), and in dry dioxane, there was hardly any preference for the proximal regioisomer (1.5:1). High selectivities for **12a** were also reached in neat acetic acid (>25:1) or THF/water (5:1 mixture, 9:1 product ratio). Other solvents, including dimethylformamide, acetonitrile, dichloromethane, chloroform or *t*-butanol, gave only fair selectivities, between 5:1 and 2:1. There is also a temperature effect, as the ratio of products in acetic acid at reflux changes to 3.4:1. The authors concluded that small changes in the reaction medium had a large effect on the regiochemistry, but to make predictions based on general trends was not possible.

Earlier, Grandi *et al*. had reported reverse selectivities in the reaction of seleninoyl chloride with tosyl hydrazones, compared to those for selenium dioxide with semicarbazones.[12] Maryanoff argued that this was in fact a solvent effect, rather than the effect of the reagent, because the ratio of products **12a:12b** was similar (2:1) when the reaction was carried out with either selenium dioxide or selenoyl chloride in dichloromethane.[15]

Analogs of **11** (X = N-COOMe, S, CMe_2) gave fair to low regioselectivities, with, in all cases, a bias to the proximal isomer **12a**.



11, Z/E isomers **12a** **12b**

X = N-$CH_2C_6H_5$, N-COOEt, S, CMe_2

5.1.2. Cycloaddition Reactions of Diazoalkanes with Compounds Containing C=Se Bonds

This method toward 1,2,3-selenadiazoles, analogous to the Pechmann reaction, has only been used in a few cases. The reason is given by the difficulties involved in working with compounds containing C=Se bonds, together with the instability of the intermediates.

L'abbé *et al*. reported the 1,3-dipolar cycloaddition of diphenyldiazomethane **13** (R = R′ = Ph) to *in situ* generated benzoyl isoselenocyanate **14**. The intermediate unstable 1,2,3-selenadiazoline **15** could not be isolated and decomposed to a benzoselenophene-2-amine derivative **16**.[16] Heimgartner argued that the results might as well be explained starting from the isomeric 1,3,4-selenadiazoline isomer.[17]

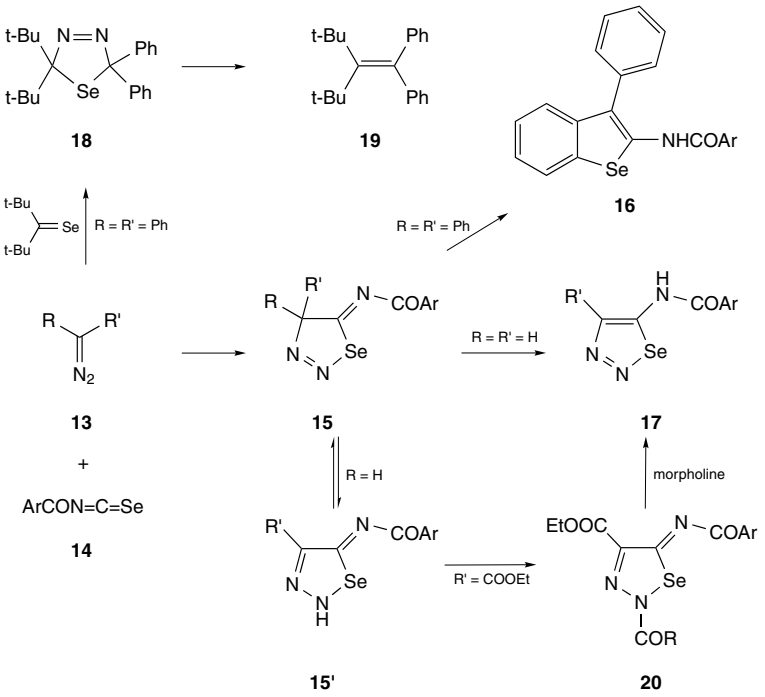
A second example is the similar cycloaddition of diazomethane **13** (R = R′ = H) to **14**, with the formation of stable 5-amino-1,2,3-selenadiazoles **17** that were formed from the tautomerization of intermediate **15** (R = R′ = H). Reactions of diazomethane **13** (R = R′ = H) with aryl isoselenocyanates gave analogous *N*-(1,2,3-selenadiazol-5-yl)anilines of limited stabilities. The decomposition products were not characterized.[18]

Di(*t*-butyl)selenoketone gave the 1,3,4-selenadiazoline regioisomer **18** on cycloaddition with diphenyldiazomethane **13** (R = R′ = Ph). After twofold extrusion of nitrogen and selenium, a tetrasubstituted olefin **19** was formed.[19,20]

Heimgartner described the cycloaddition reaction of aroyl isoselenocyanates **14** (again prepared *in situ* from the corresponding acid chloride) with ethyl diazoacetate **13** (R = H, R′ = COOEt). In this case, the products were the 2-aroyl-1,2,3-selenadiazole-5-imines **20**. Apparently, acylation of the intermediate **15** (R = H, R′ = COOEt) or its tautomer occurs very fast. It is interesting to note that in the case of the corresponding reaction with potassium thiocyanate, benzoyl chloride and ethyl diazoacetate **13**, only the nonacetylated 1,2,3-thiadiazole was formed.[21] Heimgartner concluded that selenadiazolines of type **15** must be more nucleophilic than the corresponding thiadiazoles. One could as well argue that the aromatization of the sulfur analog of intermediate **15** is faster in the case of 1,2,3-thiadiazoles, preventing acylation. The 2-aroyl derivatives **20** were transformed into 1,2,3-selenadiazoles **17** by treatment with morpholine.[17]

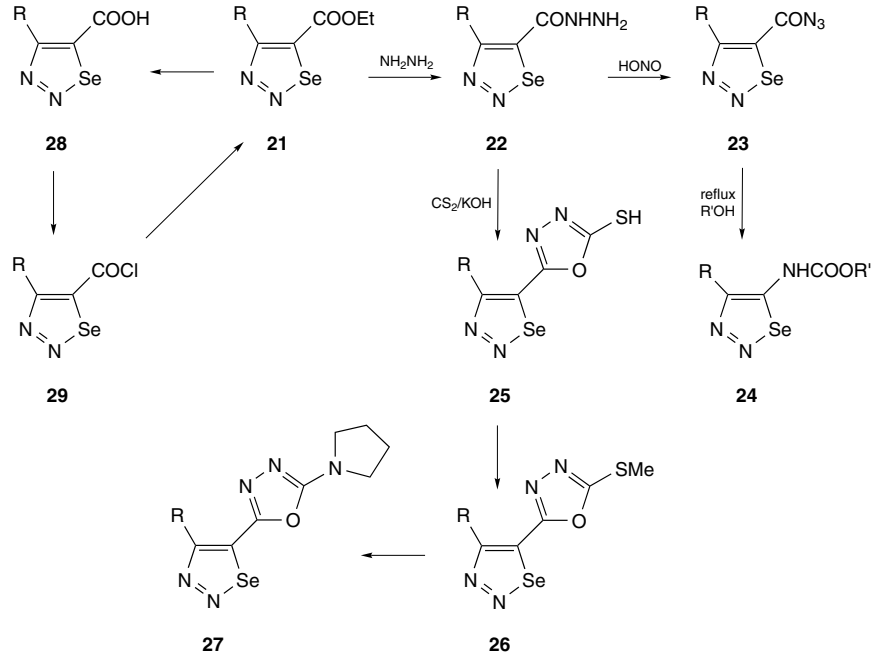
5.1.3. Elaboration of Preformed 1,2,3-Selenadiazoles

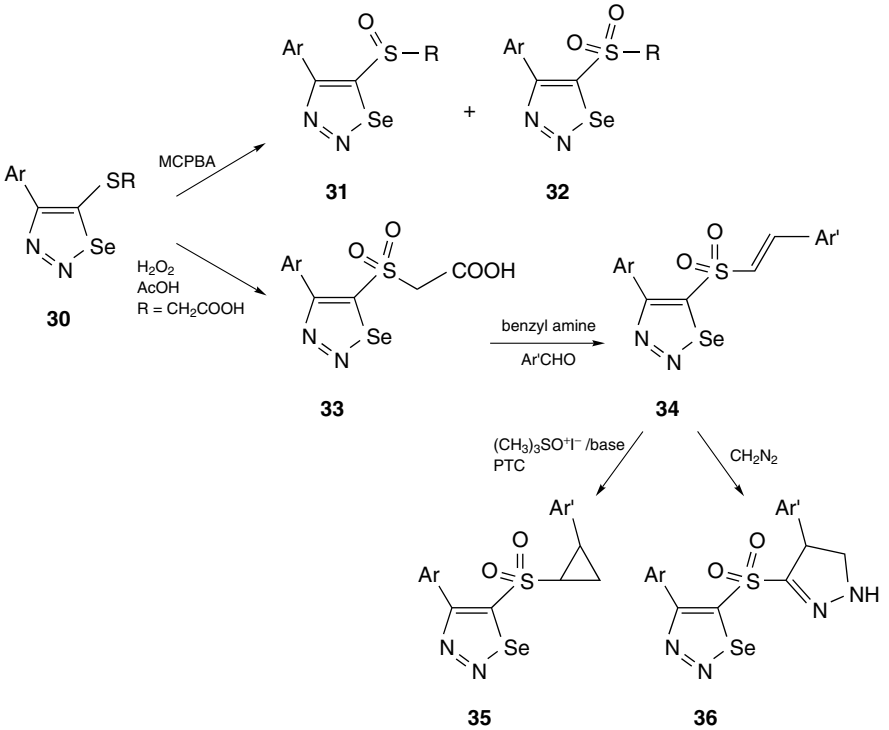
Because of the inherent thermal and chemical instability of the 1,2,3-selenadiazoles, most authors prefer to generate the ring at the last step of the synthesis, or just previous to cleavage of the heterocyclic ring. Therefore, the examples of elaboration of the 1,2,3-selenadiazole heterocycle are rather rare. Nevertheless, there are some surprising examples in the literature, where the ring remains intact during chemical modification of the 4- or 5-substituents.



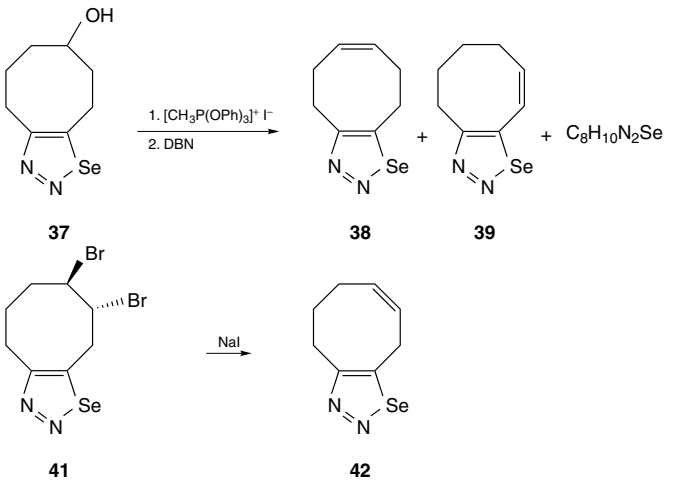
A first example is the Curtius rearrangement of the carbonyl azides **23**, which were formed from the corresponding esters **21** (R = Me, Ph) by hydrazinolysis and treatment of hydrazides **22** with sodium nitrite. The rearrangement of **23** occurs in the presence of alcohols to afford the carbamates **24** in 40–50% yield.[22] The hydrazides **22** were also condensed with carbon disulfide and KOH as the base (ethanol at reflux, 4 h) by Shafiee *et al*. to prepare oxadiazolethiol conjugates **25**, that could be methylated to sulfides **26**, and then aminated (benzene, reflux, 14 h) to pyrrolidine **27**.[23] Also, the ester **21** (R = Me) could be saponified to the acid **28** (R = Me) in 75% yield, converted to the acid chloride **29** (R = Me) and re-esterified to **21** (R = Me). Analogously, 5-(4-phenyl-1,2,3-selenadiazol-5-yl)valeric acid was obtained in 90% yield from the saponification (50% aqueous ethanol, KOH, reflux, 5 h) of the corresponding ethyl ester.[24]

The sulfides **30** could be oxidized with *m*-chloroperbenzoic acid to a mixture of the sulfoxide **31** (major) and sulfone **32** (minor) that were separated by chromatography.[14] Later, Reddy *et al*. reported the use of 30% hydrogen peroxide in acetic acid for the complete oxidation of sulfides **30** (R = CH_2COOH) to sulfones **33**. These sulfones **33** undergo Knoevenagel condensation with aromatic aldehydes to give the 2′-(1,2,3-selenadiazol-5-yl)-styrenes **34**.[25] In a following publication of the same group, compounds **34** were reacted with dimethylsulfonium methylide under phase-transfer conditions to give the cyclopropyl derivative **35**. On the other hand, cycloaddition of diazomethane gave the pyrazolines **36**.


R
COOH
COOEt
CONHNH2
CON3
NH2NH2
HONO
N
Se
28
21
22
23
CS2/KOH
reflux
R'OH
SH
NHCOOR'
COCl
29
25
24
SMe
27
26

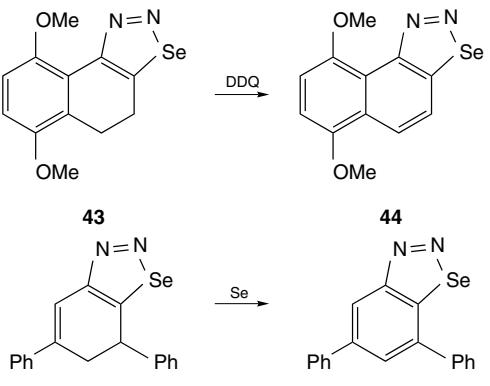

Ar
SR
MCPBA
O
S
R
+
30
31
32
H2O2
AcOH
R = CH2COOH
COOH
benzyl amine
Ar'CHO
Ar'
33
34
(CH3)3SO+I− /base
PTC
CH2N2
NH
35
36

The fused cyclooctanol **37** was iodinated with methyl triphenoxyphosphonium iodide, and the resulting iodide was dehydrohalogenated to the cyclooctene derivative **38** (30%) and its conjugated isomer **39** (20%). The main product (50%) had the bruto formula $C_8H_{10}N_2Se$, but did not contain an olefinic double bond. The authors claimed that it might be a tricyclic compound and referred to an ongoing research, but unfortunately no further results were published.[26] The octanol **37** could be oxidized to the corresponding ketone **40** with chromic acid.[6] Dibromocyclooctano-1,2,3-selenadiazole **41** was debrominated to the alkene **42** with sodium iodide.[26]



37 **38** **39** **41** **42**

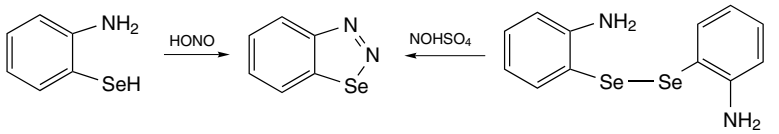
Aromatization of dihydronaphtho[1,2-*d*][1,2,3]selenadiazole **43** to the corresponding fused naphthalene **44** occurred in 55% yield with DDQ.[27] Alternatively, selenium has been used for aromatization of cyclohexeno[1,2,3]selenadiazoles **45** to the 1,2,3-benzoselenadiazoles **46**.[7]



43 **44** **45** **46**

5.1.4. Miscellaneous Syntheses

Benzo-1,2,3-selenadiazole **47** was prepared in 1935 by S. Keimatsu *et al*. by nitrosation of 2-aminobenzeneselenol **48** and was in fact the first 1,2,3-selenadiazole derivative ever reported.[28] Later, Nunn *et al*. described a similar transformation of diselenide **49** with nitrosylsulfuric acid.[29]



47 **48** **49**

5.2. STRUCTURAL DATA OF 1,2,3-SELENADIAZOLES

The structural data on the 1,2,3-Selenadiazole system are of an experimental nature.

5.2.1. Mass Spectrometry

The mass spectra of the 1,2,3-selenadiazoles show the molecular ions with a specific pattern, according to the isotopic abundance for the selenium isotopes. The data mentioned in experimental parts correspond to the ^{80}Se isotope. Important fragment ions are M-$N_2^{+\cdot}$ and M-N_2-$Se^{+\cdot}$.[5] The latter peak M-N_2-$Se^{+\cdot}$, corresponding to the resulting acetylene, is very often the most abundant fragment ion.

5.2.2. Proton NMR Spectroscopy

The ^1H NMR spectrum of the parent 1,2,3-selenadiazole **1** (R = H) in CCl_4 has two doublets at 6.66 and 7.47 ppm for H-4 and H-5, respectively, with a coupling constant of 3.8 Hz. A weak doublet of doublets centered around the larger doublet at 7.47 ppm, with a coupling constant of around 40 Hz, was observed because of the ^{77}Se isotope with natural abundance of 7.5%.[24] Cava *et al*. reported the spectrum of **1** (R = H) in deuterated chloroform as having two doublets (J = 3 Hz) at 8.81 and 9.56 ppm for H-4 and H-5, respectively.[8] Meier *et al*. reported 8.69 and 9.38 ppm for the same hydrogens (J = 3.8 Hz) in the same solvent. The coupling constants between H-4 and H-5 and the ^{77}Se isotope were in the order of 6 and 40 Hz respectively. The spectrum of 4-methyl-1,2,3-selenadiazole ($CDCl_3$) had a H-5 signal at 8.83 ppm (J with ^{77}Se = 41.1 Hz). The spectrum of the isomeric 5-methyl-1,2,3-selenadiazole showed an H-4 signal at 8.25 ppm (J with ^{77}Se = 9.0 Hz).[30]

Caplin reported a detailed study of the ^{1}H NMR spectral parameters for a series of 4-(4-substituted phenyl)-1,2,3-selenadiazoles. The chemical shift of H-5 of the 1,2,3-selenadiazole ring in different solvents can be subjected to a Swain–Lupton multiple correlation analysis, and field and resonance parameters would be obtained. Solvents shifts are strong and also influenced by the substituent.[31]

4-Phenyl-1,2,3-selenadiazole and other 4-(substituted phenyl)-1,2,3-selenadiazoles had a shift of 9.24–9.67 ppm (H-5).[32] The chemical shift of H-5 for 4-monosubstituted 1,2,3-selenadiazoles seems to be about 0.40–0.75 ppm higher (lower field) than the corresponding 1,2,3-thiadiazoles.[11,33]

Duddeck reported (in $CDCl_3$) spectra for several 4-alkyl-1,2,3-selenadiazoles (R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *t*-Bu) with signals for H-5 at 8.79–8.82 ppm ($^{2}J_{H,Se}$ = 39.3–42.1 Hz) and for several 5-alkyl-1,2,3-selenadiazoles (R = Me, Et, *n*-Pr, *i*-Pr, *t*-Bu) with signals for H-4 at 8.22–8.30 ppm.[34]

5.2.3. Carbon-13 NMR Spectroscopy

Meier carried out a ^{13}C NMR spectroscopical study on 37 different 1,2,3-selenadiazoles. All spectra were taken in $CDCl_3$. The parent 1,2,3-selenadiazole **1** (R = H) had signals for C-4 and C-5 at 147.1 ($^{1}J_{CH}$ = 191.1 Hz, $^{2}J_{CH}$ = 9.2 Hz) and 143.7 ppm ($^{1}J_{CH}$ = 191.7 Hz, $^{2}J_{CH}$ = 13.2 Hz), respectively. Most of the 1,2,3-selenadiazoles studied by Meier were fused cycloalkaselenadiazoles. A "zigzag" effect was seen on the shifts of C-4 and C-5, as also found in cycloalkenes. For 30 different 1,2,3-selenadiazoles, fused with six- or higher-membered cycloalkanes (or cycloalkenes), the shifts of C-4 are between 155.4 and 165.0 ppm and those of C-5 between 152.5 and 162.9 ppm.[30] This was confirmed by Duddeck *et al.*[34] Therefore, the report of Reddy *et al.* that several derivatives of cyclohexa-1,2,3-selenadiazole (in $CDCl_3$) had signals for C-4 at 125.24–129.68 ppm, and signals for C-5 at 126.25–129.46 ppm, has to be erroneous.[35]

A later systematic study of Duddeck gave spectra ($CDCl_3$) for several 4-alkyl-1,2,3-selenadiazoles (R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *t*-Bu) with signals for C-4 and C-5 at 158.7–173.4 and 135.3–138.6 ppm, respectively, and for several 5-alkyl-1,2,3-selenadiazoles (R = Me, Et, *n*-Pr, *i*-Pr, *t*-Bu) with signals for C-4 and C-5 at 144.6–148.3 and 161.3–180.5 ppm, respectively. The ^{13}C, ^{77}Se coupling constants for all 1,2,3-selenadiazoles in this study were in the ranges ^{1}J(Se, C-5) = 131.0–137.4 Hz, and ^{2}J(Se, C-4) = 28.0–33.7 Hz.[36]

5.2.4. Nitrogen-15 NMR Spectroscopy

Duddeck reported a ^{15}N NMR spectroscopic study (in $CDCl_3$) on the parent 1,2,3-selenadiazole **1** (R = H) and some fused derivatives. The spectra were resolved by observing the ^{77}Se satellite, with coupling constants $^{1}J_{N\text{-}2,Se}$ = 83.4–92.2 Hz. The parent compound had signals at 454.6 and 466.8 ppm (relative to 1M $^{15}NH_4NO_3$ reference) for N-2 and N-3, respectively. The cycloalka-1,2,3-selenadiazoles had signals for N-2 and N-3 in the range 450.9–481.8 and 445.3–466.3 ppm.[34]

5.2.5. Selenium-77 NMR Spectroscopy

The ^{77}Se nucleus (S = 1/2) has a reasonable abundance (7.5%), and the sensitivity is about three times that of ^{13}C. The chemical-shift dispersion is very large with a range of 3000 ppm. This was used by Maryanoff to determine the ratios of regioisomeric mixtures of fused 1,2,3-selenadiazoles **8a** and **8b**. Two clean singlets were obtained that could be integrated.[15] ^{77}Se NMR spectra are strongly temperature dependant. Duddeck reported a ^{77}Se NMR signal at ambient temperature of the parent 1,2,3-selenadiazole **1** (R = H) at 1498.9 ppm, relative to a reference sample of dibenzyldiselenide (460.0 ppm). For cycloalka-1,2,3-selenadiazoles, the values are between 1404.7–1532.9 ppm.[34] In a later publication, Duddeck reported ^{77}Se NMR data (relative to diphenyldiselenide at 463.0 ppm) of **1** (R = H) at 1502 ppm and alkylselenadiazoles and cycloalkaselenadiazoles in a range of 1418–1525 ppm. It was shown that the ^{77}Se chemical shifts were suitable tools for chiral discrimination in diastereoisomeric compounds.[36]

5.2.6. X-ray Crystallography

Not so many X-ray structures of 1,2,3-selenadiazole derivatives have been described, and most of them are of the more stable N-substituted derivatives. We can compare the distances between the ring atoms for structures **A**–**E** (see Table 5.1).

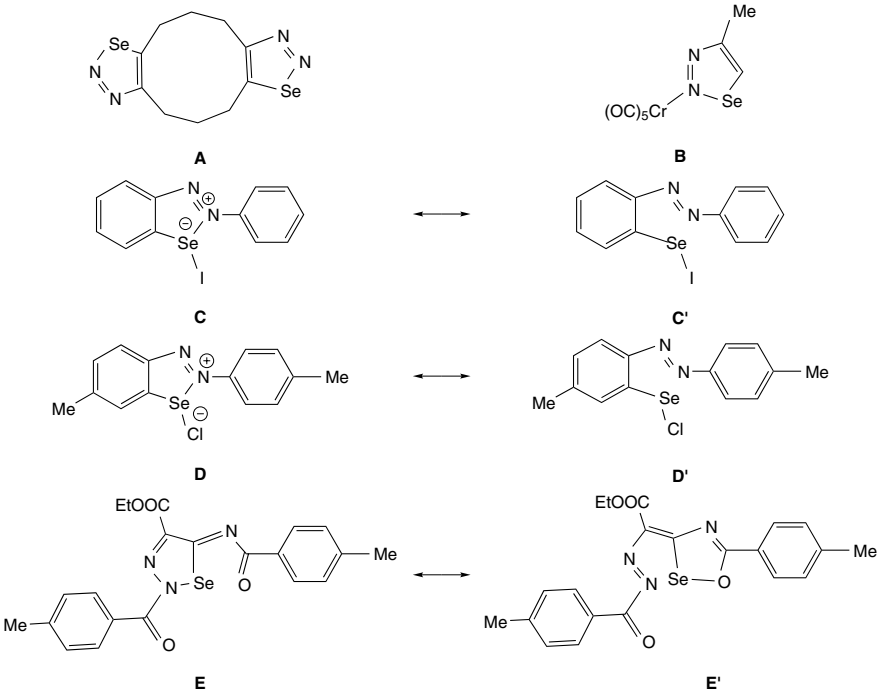


TABLE 5.1. DISTANCES (Å) BETWEEN RING ATOMS OF 1,2,3-SELENADIAZOLES **A**–**E**

	N_2-Se	N_2-N_3	N_3-C_4	C_4-C_5	C_5-Se
A	1.888	1.251	1.384	1.368	1.850
B	1.838	1.272	1.364	1.312	1.817
C	2.052	1.262	1.379	1.395	1.881
D	2.025	1.278	1.379	1.398	1.889
E	1.914	1.313	1.324	1.440	1.877

Comparison between the bond distances of structures **A** and **B** shows that metal complexation has only a slight effect, with mainly a shortening of the N_2-Se bond, and a lengthening of the C_4-C_5 bond. The data for structures **C**, **D** are dramatically different from **A**, **B**, and we can assume that these structures may be partially described by an open resonance form **C′**, **D′**, explaining the long N_2-Se bond. This is a case of single bond–no bond resonance. The latter also occurs for the structure **E**, that shows a selenapentalenic interaction (resonance form **E′**), manifested by the elongated N_2-Se bond. Moreover, the Se–O distance is only 2.242 Å.[37–40]

5.2.7. Miscellaneous

Heat of combustion and formation of 4-phenyl-1,2,3-thiadiazole was determined by calorimetry to be 1097 kcal/mol. The heat of sublimation for the same compound was 22.5 kcal/mol. The bond energies of C–Se and N–Se were estimated to be 71 and 66 kcal/mol, respectively.[41,42]

UV spectra of 1,2,3-selenadiazoles show bands around 240 nm, together with broad absorption bands of low intensity at around 280–330 nm, that may be extending in the near visible and responsible for a slight yellow color.[5,24]

5.3. REACTIVITY OF 1,2,3-SELENADIAZOLES

Most studies on the reactivity of 1,2,3-selenadiazoles are descriptions of the ring cleavage and of the formation of resulting products. For instance, no rearrangements were reported for 1,2,3-selenadiazoles to our knowledge, in contrast with the 1,2,3-thiadiazole analogs. Possibly, this is the result of the low stability of the former heterocycles, as described below. The formation of salts and ylids stabilizes the 1,2,3-selenadiazole ring and is discussed at the end of this subchapter.

5.3.1. Ring Cleavage

5.3.1.1. Thermal Reactions

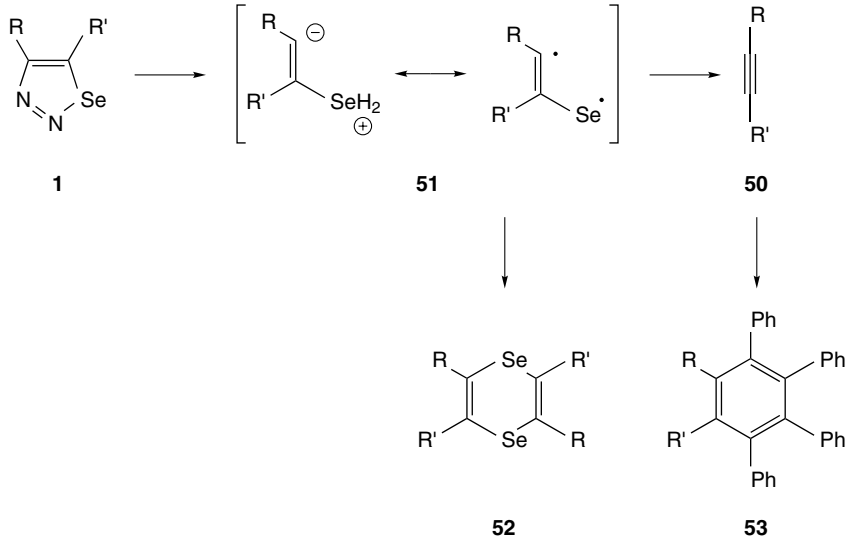
Lalezari *et al*. in 1970 reported the thermal cleavage of 1,2,3-selenadiazoles **1** as a new synthesis for aromatic alkynes **50**. The ring cleavage was observed after

an attempt to crystallize 4-phenyl-1,2,3-selenadiazole **1** (R = Ph, R′ = H) from water. Good yields were obtained after pyrolysis of a 1:5 mixture of the selenadiazole **1** and sand, followed by vacuum distillation.[43] A more detailed procedure for ethyl but-2-ynoate from 4-methyl-5-ethoxycarbonyl-1,2,3-selenadiazole **1** (1:5 mixture with sand) gave 160°C as the temperature and 10 min as the time for pyrolysis.[44] Later reports mention a decomposition temperature of 180°C, and 10 times the amount of sand was added.[45] Many authors used catalysis with electrolytic copper.[26] Arylthio-, aryloxy and arylsulfonylacetylenes were formed in good to very good yield by pyrolysis (120–180°C) of the corresponding neat 1,2,3-selenadiazoles.[14] This was confirmed by Reddy *et al*.,[46] who also used copper catalysis for the thermolysis at 180–200°C.[25,47]

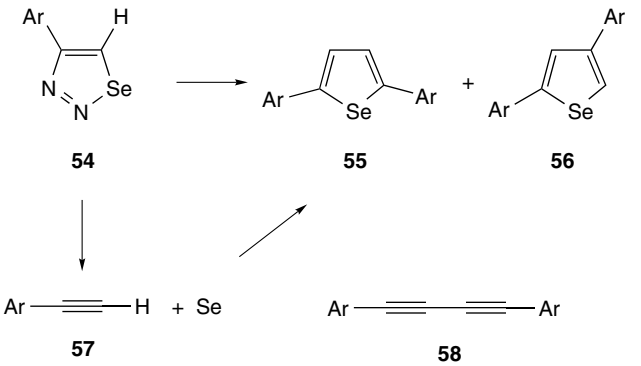
Meier reported that cycloalka-1,2,3-selenadiazoles **1** (R = R′ = cycloalkane) decomposed on heating below the boiling point *in vacuo*, (water aspirator) and observed nitrogen evolution, followed by separation of selenium at higher temperature. A biradical intermediate **51** was supposed, that could dimerize to a 1,4-diselenine **52**. The possibility of formation of the isomeric 1,2-diselenines was excluded by ^{13}C NMR spectroscopy. For the larger rings, selenium separated when the bicyclic selenadiazole **1** (R = R′ = cycloalkane) was thermolyzed in ethylene glycol at reflux and normal pressure. The reactive-strained cycloalkyne **50** (R = R′ = cycloalkane) formed could be reacted *in situ* with tetraphenylcyclopentadienone to give the stable tetraphenylbenzenes **53**. The *in situ* formation of the very strained cyclopentyne was not observed. On the other hand, cyclooctyne was the lowest stable cycloalkyne that could be obtained by this method. This strained cycloalkyne was formed in 49% yield by thermolysis of cycloocta-1,2,3-selenadiazole at 170–220°C over glass pearls in a nitrogen stream.[5]

Lalezari *et al*. reported independently on the thermolysis of cycloocta-1,2,3-selenadiazole in boiling toluene, to give 55% of cyclooctyne. The corresponding bis(cycloocta)diselenine **52** (R = R′ = hexamethylene) was formed in 75% yield on thermolysis, and this was the only product for lower ring sizes. The less-strained cyclododecyne was formed on thermolysis from the corresponding 1,2,3-selenadiazole **1** (R = R′ = decamethylene) in 90% yield.[45]

Lalezari *et al*. also reported that the prolonged heating of 4-aryl-1,2,3-selenadiazoles **54** afforded high yields of 2,5-diarylselenophenes **55** and small amounts of 2,4-diarylseleno-phenes **56**. In the case of 4-phenyl-1,2,3-selenadiazole **54** (Ar=Ph), only the 2,5-disubstituted isomer **55** was formed, while at higher temperatures some 2,4-disubstituted product **56** was also present. The explanation given was that the arylacetylene **57** recombined with selenium to give an intermediate **51** of either radical or bipolar nature that then undergoes a regioselective cycloaddition to a second equivalent of acetylene **57**. In fact, heating of selenium and arylacetylene **57** at 140°C also gave 2,5-diarylselenophene **55**.[48] Later, the formation of 2,5-diarylselenophenes **55** in fair to good yields was described from 4-phenyl-1,2,3-selenadiazole **54** (Ar=Ph), or the 4-(2-thienyl) analog **54** (Ar=2-thienyl), and 10 equiv of an arylacetylene **57**. Two equivalents of arylacetylene **57** gave statistical mixtures of three different selenophenes. In this case, the

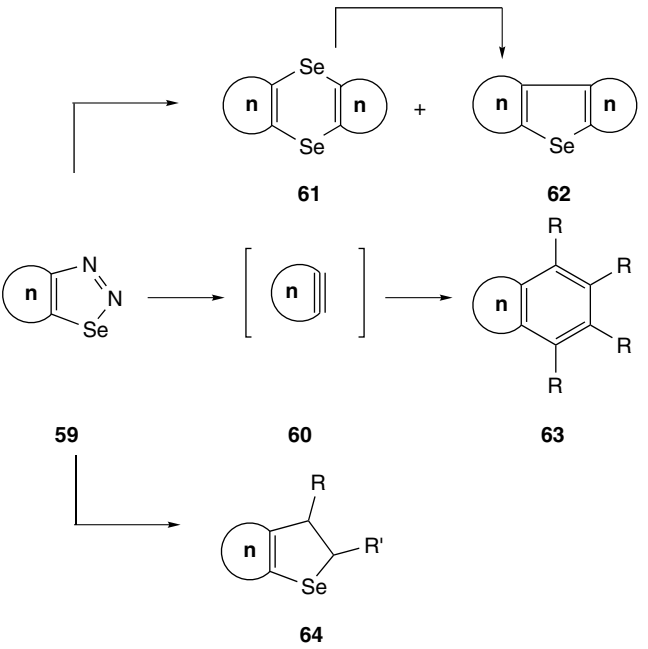


1,2,3-selenadiazoles **54** acted only as the source of selenium. The 1,4-diarylbuta-1,3-diynes **58** were obtained as by-products.[49]



Meier *et al*. described in a series of articles, the formation of novel strained cycloalkynes **60** from the corresponding fused 1,2,3-selenadiazoles **59**. Since this goes beyond the scope of this book, we will give only the highlights. Benzocycloalka-1,2,3-selenadiazoles on thermolysis at 150–190°C gave, depending on the ring size, the corresponding cycloalkynes **60**, the diselenines **61** or the selenophenes **62**. Benzocyclooctyne was isolated (6%) or trapped as the tetraphenylcyclopentadienone adduct **63** (54%, R = Ph). Lower cycloalkyne rings **60** are not stable but can be trapped *in situ*, but the diselenines **61** are the major products. The selenophenes **62** are formed at higher temperatures, and heating

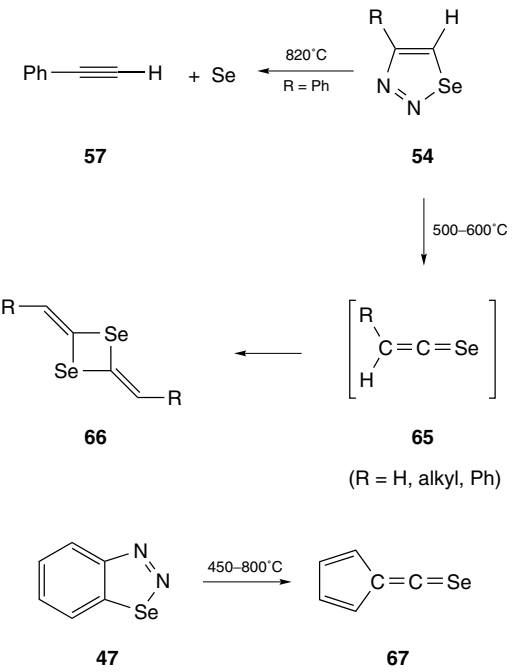
of diselenine **61** leads, in fact, to the selenophene **62** in 67% yield.[50] Numerous other examples of strained cycloalkynes were described by Meier[6,51–64] and others.[4,65–77] Cycloadditions of these cycloalkynes **60**, formed *in situ* by thermolysis of fused 1,2,3-selenadiazoles **59** in the presence of α-pyrones gave the corresponding fused benzenes **63** (R = H) after extrusion of carbon dioxide.[78] The fused 1,2,3-selenadiazoles **63** afforded the corresponding dihydroseleophenes **64** on thermolysis in excess olefin at 130°C. Products **61** and **62** were the by-products. Monocyclic 1,2,3-selenadiazoles, derived from aromatic and linear ketones, only gave the corresponding alkynes.[79]



Pyrolysis of 1,2,3-selenadiazole **54** and its 4-alkyl derivatives in the vapor phase at 500–600°C forms purple to blue selenoketenes **65** that are isolated at −196°C. They dimerized rapidly to yellow 1,3-diselenetes **66**.[88,81] Bock *et al.* investigated selenoketene formation from pyrolysis above 720 K of the parent 1,2,3-selenadiazole **1** (R = R′ = H) by photoelectron and mass spectroscopy. Traces of ethyne and H_2Se were detected. 4-Phenyl-1,2,3-selenadiazole **54** forms, on thermolysis above 820 K, phenylacetylene **57** (Ar=Ph) rather than the phenylselenoketene **65**.[82,83]

The flash vacuum pyrolysis of 1,2,3-benzoselenadiazole **47** at 450–800°C resulted in the formation of 6-fulveneselenone **67** rather than benzyne. The instable fulveneselenone **67** was characterized by photoelectron spectra.[84]

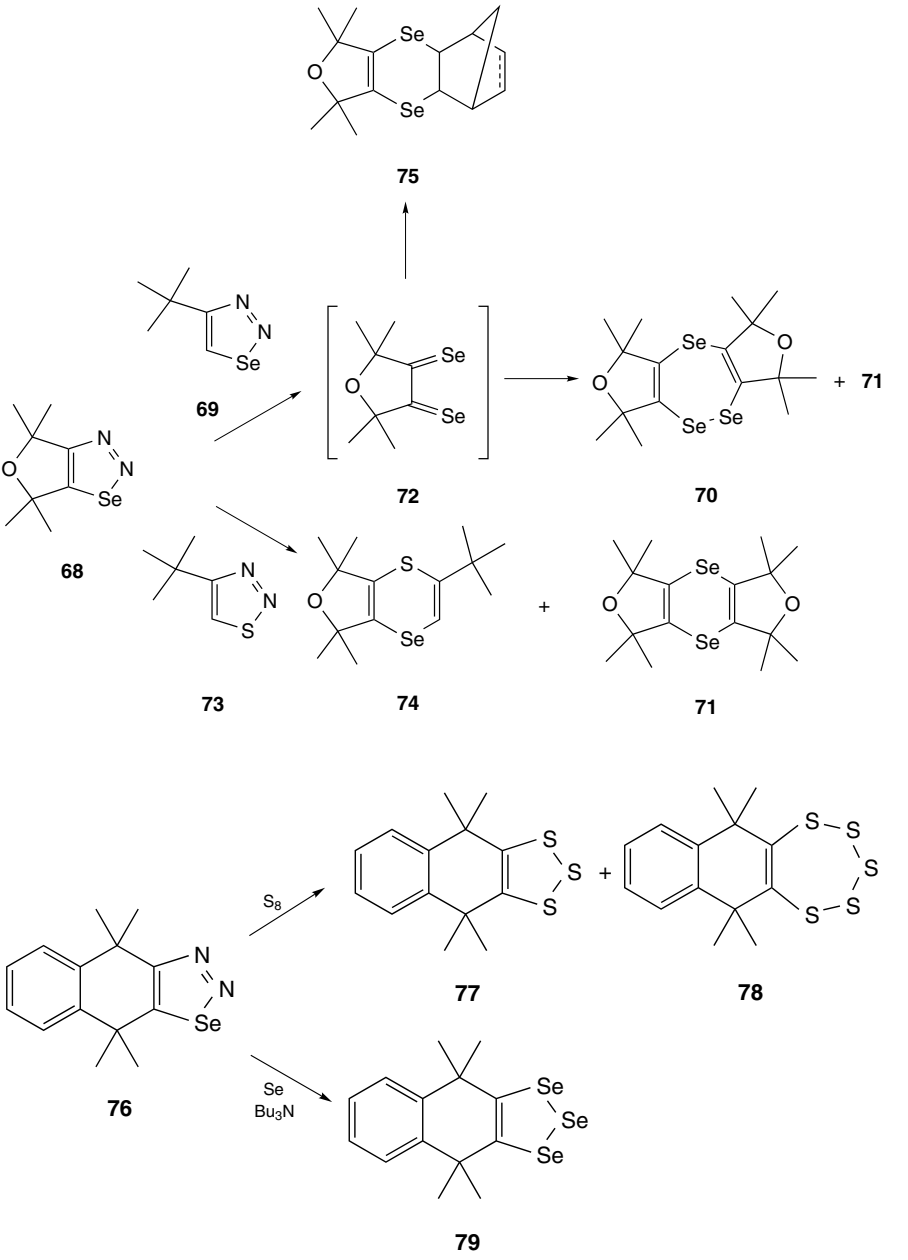
The sterically protected 1,2,3-selenadiazole **68** was thermolyzed at 80°C in the presence of 4-*t*-butyl-1,2,3-selenadiazole **69** to afford a 1,2,5-triselenepin **70**



(58%) together with 1,4-diselenin **71** (30%). The latter was prepared in high yield on thermolysis without 4-*t*-butyl-1,2,3-selenadiazole **69** or in the presence of elemental selenium. The authors discussed the formation of a 1,2-diselenone intermediate **72** after selenium transfer from the second selenadiazole **69** to the zwitterionic species (analogous to **51**) obtained after loss of nitrogen. In the presence of 4-*t*-butyl-1,2,3-thiadiazole **73**, a mixture of thiaselenine **74** (14%) and diselenine **71** (70%) is formed. When olefins such as norbornene or norbornadiene are present *in situ*, the two selenadiazoles **68** and **69** afford dihydrodiselenins **75**, resulting from hetero-Diels–Alder cycloaddition of 1,2-diselenone **72** to the strained olefin.[85]

Thermolysis of sterically protected 1,2,3-selenadiazole **76** at 140°C in the presence of elemental sulfur gave 1,2,3-trithiole **77** (25%) and 1,2,3,4,5-pentathiepine **78** (11%) with remarkable stability as compared to other cyclic polysulfides. Thermolysis of **76** at 130°C with elemental selenium in Bu_3N gave the stable 1,2,3-triselenole **79** (25%).[86]

Thermolysis of 1,2,3-benzoselenadiazole **47** in the presence of an excess CS_2 afforded 1,3-benzothiaselenole-2-thione **80**. A similar reaction occurred starting with cyclopenta-1,2,3-selenadiazole **1** (R = R′ = trimethylene). Reductive coupling of **80** gave dithiadiselena-fulvalene derivatives **81**.[87] In the same way, benzodiselenole-2-selenones **82** were formed from CSe_2 and benzoselenadiazole and converted to the dibenzotetraselenafulvalenes **83**.[88] Tetrathiafulvalenes **85** were formed directly from monothiacycloocta-1,2,3-selenadiazole **84** that was thermolyzed in the presence of carbon disulfide.[60]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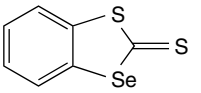

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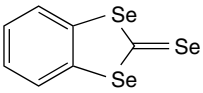

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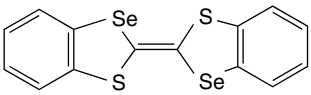

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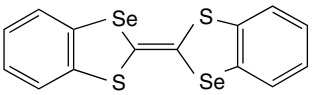

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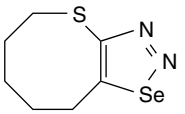

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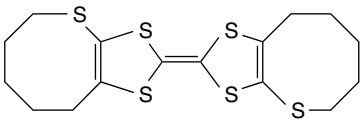

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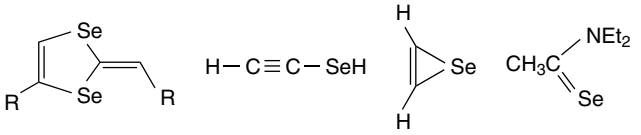
5.3.1.2. Photochemical Reactions

Lalezari *et al*. reported the photochemical cleavage of 1,2,3-selenadiazoles **54** after exposure to daylight "for a long time".[43] The intermediate selenoketenes **65** are formed via a Wolff rearrangement[89] and dimerize with the 1,3-biradical **51** present to form a 1:1 mixture of 1,3-diselenole derivatives **86**.[90]

Krantz *et al*. reported the photolysis of the parent 1,2,3-selenadiazole **1** (R = R′ = H) in an argon or nitrogen matrix at 8 K. Irradiation with a Pyrex-filtered mercury lamp gave ethynyl selenol **87**, selenoketene **65** (R = H) and acetylene. The latter product was not obtained in the photolysis of the corresponding 1,2,3-thiadiazole. The decomposition products were analyzed by IR spectroscopy. Isotopically labeled 4-deutero-1,2,3-selenadiazole **1** (R = D, R′ = H) irradiated under the same conditions gave IR spectra with acetyleneselenol C-H at 3318 cm^{-1} and acetyleneselenol C-D at 2580 cm^{-1} (ratio 0.2), respectively. The 5-deuterated isomer gave the same bands, but in the ratio of 3.5. Therefore, most of the acetyleneselenol **87** is formed in a pathway where the hydrogens are not equilibrated (via the selenirene **88**). Such equilibration was seen to occur effectively in the case of the 1,2,3-thiadiazole isomer. Further irradiation without Pyrex filter resulted in the increase of selenol at the expense of both selenoketene **65** and acetylene, with the ratio of C-H/C-D converging to 1.0. The selenirene **88** was tentatively characterized by IR spectroscopy in subsequent work.[91,92]

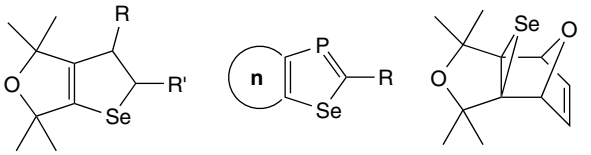
Photolysis of **1** (R = R′ = H) in cyclohexane/diethylamine solution afforded the selenoamide **89** in 95% yield after addition of diethylamine to the selenoketene intermediate **65**.[93]



86 **87** **88** **89**

Photolysis of arylsulfonylselenadiazoles with a 100-W mercury lamp in benzene gave the corresponding acetylenes.[94]

Sterically protected bicyclic 1,2,3-selenadiazole **68** was photolyzed in the presence of olefins, and a regioselective cycloaddition with formation of fused dihydroselenophenes **90** was observed. The high regioselectivity suggests that a zwitterionic intermediate **51** may be involved.[95] Irradiation of fused 1,2,3-selenadiazoles **59** with phosphaalkynes gave the 1,3-selenaphospholes **91**.[96,97] A remarkably stable selenirane **92** was formed in 12% yield when **68** was photolyzed in the presence of furan, possibly via a Diels–Alder reaction to an antiaromatic selenirene analogous to **88**.[98]

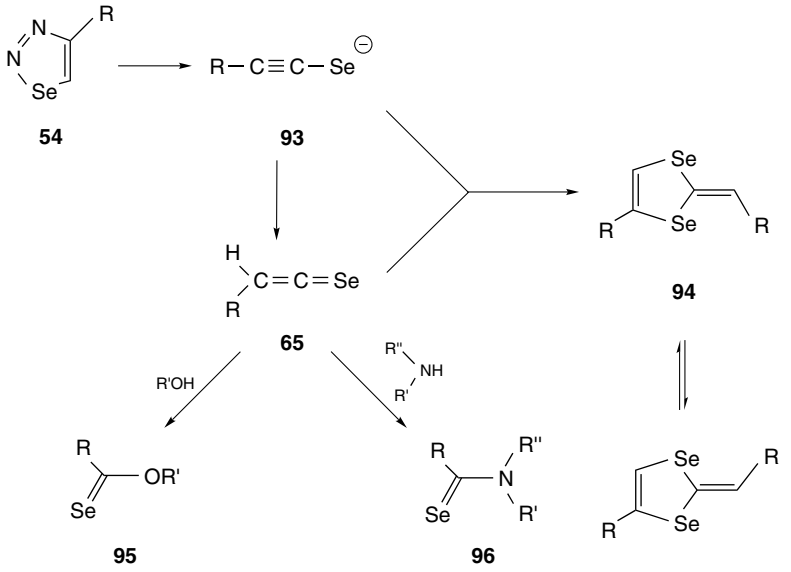


90 **91** **92**

5.3.1.3. Base-catalyzed Reactions

The cleavage of 4-monosubstituted 1,2,3-selenadiazoles **54** in the presence of basic reagents was first reported by Lalezari *et al.* Alcoholic solutions of potassium hydroxide or potassium ethoxide were used. This resulted in the immediate evolution of nitrogen gas and production of a new organoselenium compound, which was found to have a diselenafulvalene structure. Initially, the cis product **94** was formed, but on standing, a mixture of the cis- and trans isomers **94** and **94′** was obtained. Traces of acid speed up the equilibration. The mechanism was shown to involve the formation of an alkyneselenolate **93**, which adds onto a selenoketene **65** formed after protonation of a second equivalent of alkyneselenolate **93**.[99] This dimerization reaction was discussed in terms of a concerted [4 + 2] cycloaddition,[100] explaining the stereoselectivity.[99] The

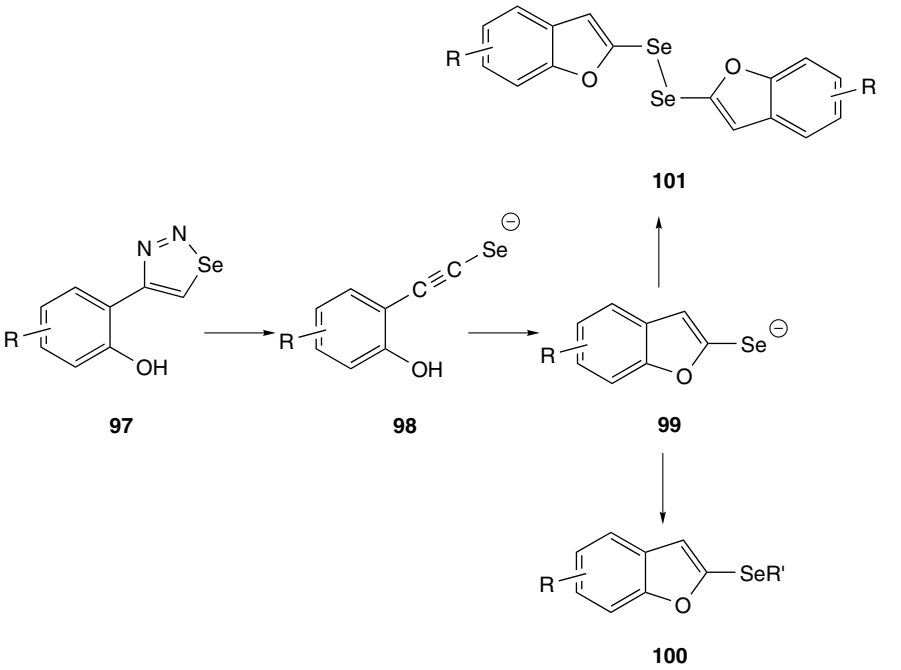
kinetics and mechanism of the base-catalyzed decomposition of 4-aryl-1,2,3-selenadiazoles **54**, with the formation of diselenafulvalene **94** were studied in detail. The arylethynylselenolates **93** could be isolated.[101] Thermal decomposition of potassium 4-phenylselenolate **93** (R = Ph) at 170–180°C gave a mixture of 2,4- and 2,5-diphenylselenophene **55** and **56**.[48] Many other examples of diselenafulvene formation,[102,103] including pyridyl,[104] pyrazine,[105] thiazole,[106] alkene and alkadiene[107] substituents were described.



In low concentrations in alcohols, the unstable selenoesters **95** are formed from the acetyleneselenolates **93** at the expense of the fulvenes **94**. The best yields (about 50%) are obtained by slow addition of the alkyneselenolate **93** to a diluted solution of acid in alcohols[108]. Decomposition of 4-monosubstituted 1,2,3-selenediazoles **54** in primary or secondary amine with potassium hydroxide afforded stable selenamides **96** in good to quantitative yield.[109]

We have generated benzofuran-2-selenolate anions **99** by the decomposition of 4-(2-hydroxyphenyl)-1,2,3-selenadiazoles **97** with bases such as potassium hydroxide or *t*-butoxide. The intermediate alkyneselenolate **98** undergoes an intramolecular cyclocondensation reaction with the phenol function. The selenolate anion can be alkylated to selenides **100** or oxidized to diselenides **101**.[110–115]

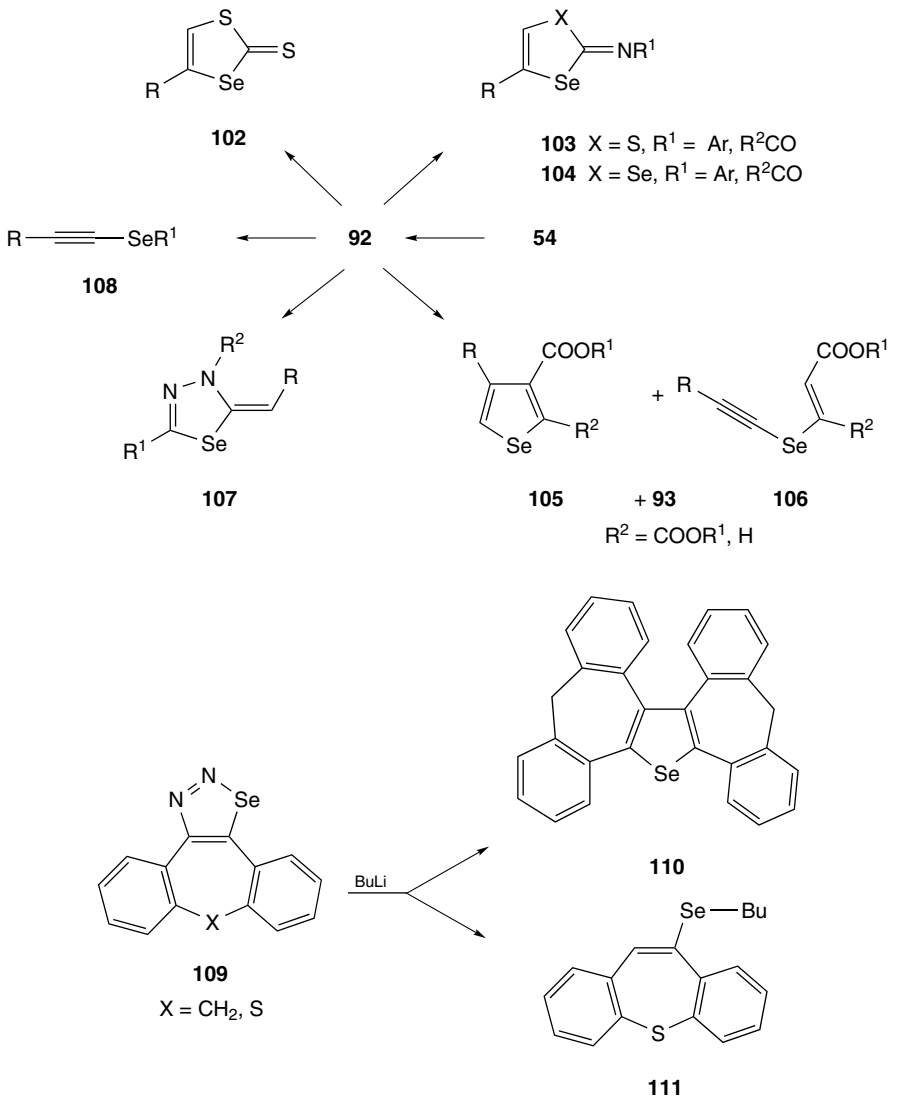
Decomposition of 4-monosubstituted 1,2,3-selenadiazoles **54** with potassium hydroxide in dioxane, followed by the addition of carbon disulfide to the alkyneselenolate solution yielded 5-substituted 2-thioxo-1,3-thiaselenoles **102**. The dimerization to the diselenole **94** was completely suppressed.[8,106,116,117] Other heterocumulenes, such as phenyl isothiocyanate and isoselenocyanate, gave, respectively,



in the reaction with the alkyneselenolate **93** the corresponding 1,3-thiaselenol-2-imines **103** or 1,3-diselenol-2-imines **104**.[118–120] The readily available acyl isothiocyanates and isoselenocyanates also reacted with alkyneselenolates **93** to afford the 1,3-thiaselen-2-imines **103** and 1,3-diselenol-2-imines **104**, respectively.[121] Analogously, the alkyneselenolates **93** were reacted with dimethyl acetylenedicarboxylate to give the selenophenes **105** in fair yield. At the same time, open-chain acetyleneselenides **106** and diselenafulvene **94** were formed. With methyl propynoate and **93**, no selenophenes **105** were formed and only dimer **94** and acetyleneselenide **106** were obtained.[122] The reaction of alkyneselenolates **93** with nitrile imines gave 1,3,4-selenadiazoline **107**.[123]

Alkylation of alkyneselenolates **93** gave the corresponding selenides **108**[118] including carboxylate,[124] glycerol[125] or ketone[126,127] derivatives.

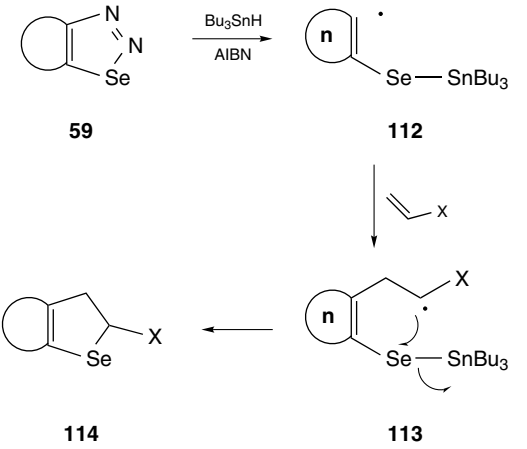
The reaction of cycloalka-1,2,3-selenadiazoles **59** with butyllithium leading to cycloalkynes **60** occurs at $-70^{\circ}C$ and is a good alternative for the thermal decomposition reaction, as the follow-up reactions at higher temperatures are avoided. Cyclooctyne is formed in 85% yield (49% thermally) under these circumstances.[128] Other examples were reported.[26,56,59,64] However, with a smaller ring such as the dibenzocyclohepta-1,2,3-selenadiazole **109** ($X = CH_2$), the selenophene **110** was obtained. The sulfur analog **109** ($X = S$) gave the open-chain butylselenide **111**.[52] Butylselenides were also formed from the reaction of butyllithium and 1,2,3-selenadiazoles fused with five- or six-membered rings.[129]



5.3.1.4. Radical-catalyzed Reactions

When fused 1,2,3-selenadiazoles **59** were treated with an excess of olefin in the presence of a catalytic amount of Bu_3SnH/AIBN, the vinyl radical **112** generated by the loss of nitrogen was added to the olefin double bond. This was followed by intramolecular cyclization of the addition product **113** to afford dihydroselenophenes **114** in moderate to good yield. Without olefin, a mixture of diselenine **61** (major) and selenophene **62** (minor) was formed. The method was proposed as an improved procedure for the ring cleavage of 1,2,3-selenadiazoles.[130] For

nonfused 1,2,3-selenadiazoles **1**, the only products resulting from the treatment with Bu_3SnH/AIBN were the corresponding acetylenes **50**.[131]

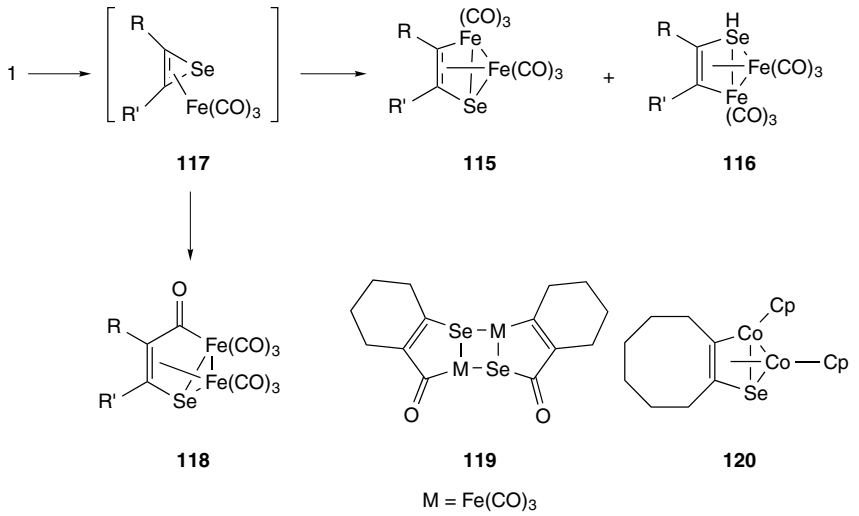


5.3.1.5. Reaction with Metal Complexes

Rees *et al*. treated 1,2,3-selenadiazoles **1** with diiron nonacarbonyl and obtained selenocarbene complexes **115**. The reaction went much faster than with the corresponding 1,2,3-thiadiazoles. Asymmetrically substituted selenadiazoles give a mixture of isomeric complexes **115** and **116**. Therefore, a symmetrical selenirene mono-iron complex **117** was assumed as the intermediate.[132–134] Cycloalka-1,2,3-selenadiazoles **59** react differently with diiron nonacarbonyl, as one of the carbonyls is retained to give a bond with Fe and the delocalized sp^2 carbon atom of the cycloalkene. Heating of the resulting complex **118** at 60°C or its irradiation with UV light gave decarbonylation and formation of selenocarbene complexes analogous to **115/116**.[135,136] Cyclohexa-1,2,3-selenadiazole reacted with diiron nonacarbonyl in the presence of ethyl alcohol to give a dimeric selenoketoketene complex **119**.[137]

Cobaltocene derivatives reacted with cyclooctane-fused selenadiazoles to give dicobalt complexes **120**, similar to the diiron carbonyl complexes **115/116** above.[138,139] Elemental selenium may be inserted into these complexes to form cobaltocene diselenolenes.[140,141]

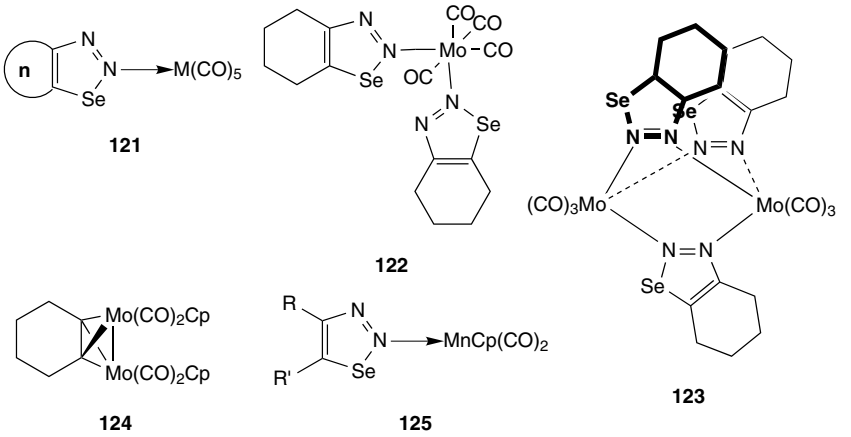
Molybden or tungsten hexacarbonyl was reported to give cleavage of the 1,2,3-selenadiazole ring **1** with trimerization of the acetylene **50** to a hexasubstituted benzene or formation of diselenines **52**. This preliminary report was never confirmed.[142] Later, Panell *et al*. described the formation of complexes **121** of cycloalka-1,2,3-selenadiazoles **59** with $M(CO)_5(THF)$ (M = Cr, Mo, W), where the heterocycle remains intact and merely replaces tetrahydrofuran as a ligand. Reactions between $Mo(CO)_4$(norbornadiene) or $Mo(CO)_3(CH_3CN)_3$ and cyclohexa-1,2,3-selenadiazole gave a $Mo(CO)_4$(selenadiazole)$_2$ complex **122** with two terminal selenadiazole ligands in the cis position, and a $[Mo(CO)_3]_2$(selenadiazole)$_3$ complex **123** with



117 **115** **116**

118 **119** **120**

three bridging ligands, respectively.[143] The nonfused 1,2,3-selenadiazoles form similar complexes with $Cr(CO)_5$ and $WO(CO)_5$. Coordination always occurs via the nitrogen at position 2.[38] The di-molybden complex $[\eta^5\text{-}C_5H_5Mo(CO)_2]_2$ reacted with monocyclic and cycloalka-1,2,3-selenadiazoles **1** and **59**, forming acetylene complexes **124**. Intermediate complexes were isolated in the case of cyclohexa-1,2,3-selenadiazole. [144] Manganese cyclopentadienyldicarbonyl complexes **125** of intact selenadiazole ligands **1** were prepared.[145]



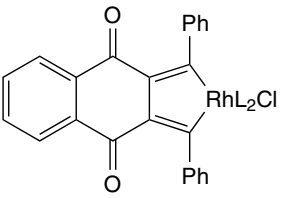
121 **122** **123**

124 **125**

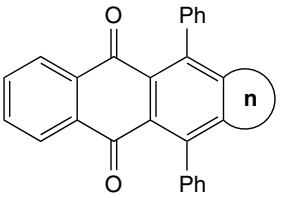
Rhodium phosphine complexes of type **126** were used by Müller *et al* [65,67] or others[52,53] to generate strained cycloalkynes **60** for cycloadditions to the rhodium complexes. The cleavage of the C−Se bond is facilitated by the Se−P interaction.

Even very unstable cycloalkynes **60**, such as cycloheptyne and cyclohexyne can be trapped to the cycloadducts **127**. On the other hand, cyclopenta-1,2,3-selenadiazole **59** gave only diselenine **61**, selenophene **62** and triphenylphosphineselenide. Stable Rh(I) complexes $(CO)_2ClRhL$ were isolated with 4-aryl-1,2,3-selenadiazoles **54** (=L).[146]

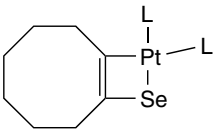
Cycloocta-1,2,3-selenadiazole **59** was combined with tetrakis(triphenylphosphine)platinum to give a selenocarbene complex **128**, together with large amounts of a polymeric complex having cyclooctene-1,2-diselelenolate units.[147]



126
L = PPh_3



127



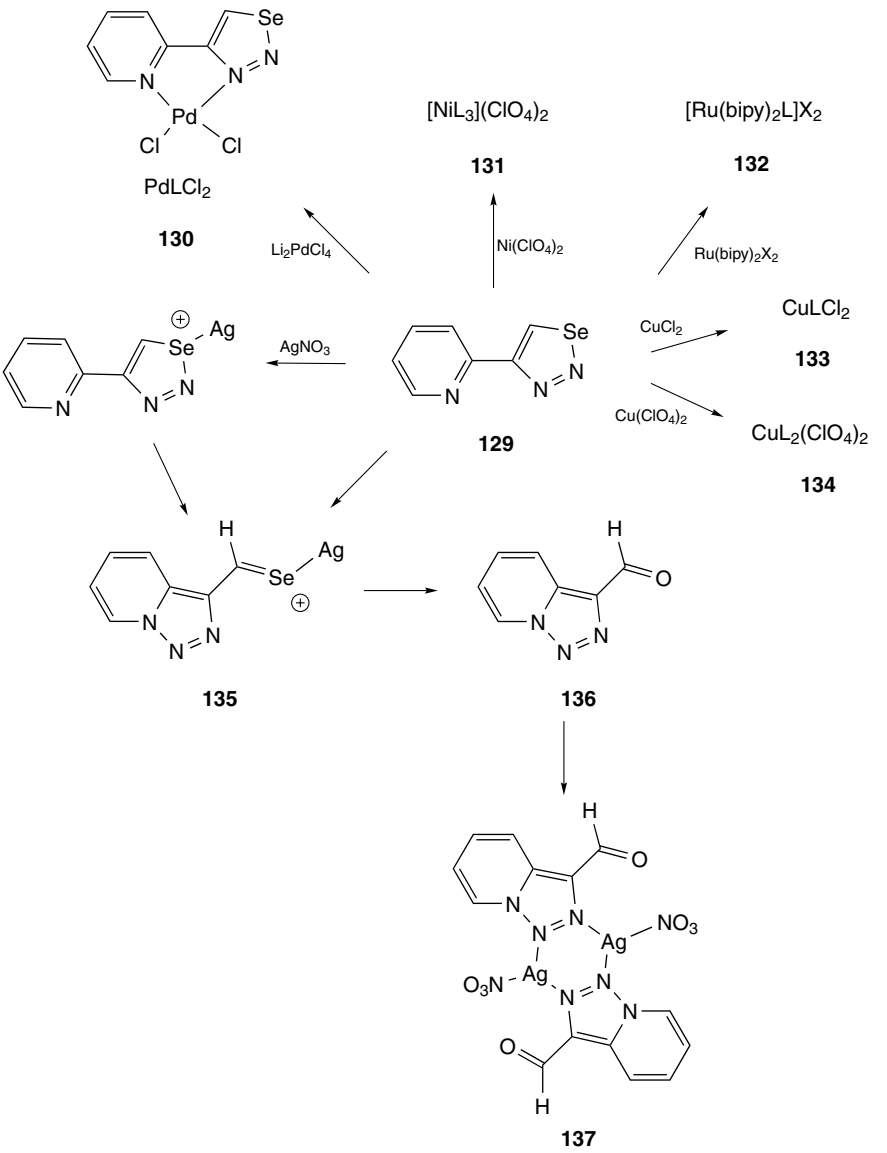
128
L = PPh_3

Complexes of 2-(1,2,3-selenadiazol-4-yl)pyridine **129** with palladium(II), nickel(II), ruthenium(II) and copper(II) were reported. In general, the ligands chelate similar to 2,2′-bipyridine to the metal but are curiously prone to positional disorder in the X-ray crystal structures of their complexes. The stoichiometry of the complexes **130–134** depended on the metal and the counterion used.

Treatment of ligand **129** with excess silver nitrate leads to the formation of metallic silver and an unexpected 2:2 *catena*-complex **137** with 3-formyl-1,2,3-triazolo[1,5-a]pyridine **136**. This ring transformation does not occur for the corresponding 1,2,3-thiadiazole. The authors believe that the reaction proceeds via the initial complexation of silver to selenium, inducing a ring opening and ring closure, with the formation of a complexed selenoaldehyde **136** that is easily hydrolyzed.[148]

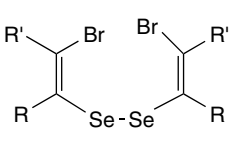
5.3.1.6. Miscellaneous Ring Cleavage Reactions

1,2,3-Selenadiazoles **1** reacted with bromine or *N*-bromosuccinimide, leading to bis(*Z*-2-bromovinyl)diselenides **138** in a regio- and stereospecific manner.[149] The reaction of fused 1,2,3-selenadiazole **68** with soft nucleophiles leads to ring cleavage with addition of the nucleophiles. For instance, trialkyl phosphites at 50°C gave selenophosphonates **139**, whereas benzenethiol at room temperature gave a compound **140** (98%) with Se−S bond. On the other hand, the dihydronaphthalene derivative **76** on treatment with triethyl phosphite at 140°C quantitatively gave a phosphonate product **141** with extrusion of selenium.[129]

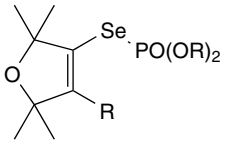


5.3.2. Formation of Salts and Ylides

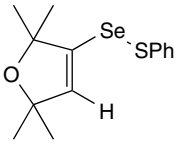
Methylation or ethylation of 1,2,3-benzoselenadiazole **47** with methyl or ethyl 2,4-dinitrophenylsulfonates at 50°C or even room temperature gave quaternary N-alkylated 2,4-dinitrobenzenesulfonate salts **142** (X = $ArSO_2$) in good yields that could be converted to the crystalline iodides **142** (X = I). The 1,2,3-benzoselenadiazole **47** was more reactive than the benzothiadiazole analogs. The quaternary



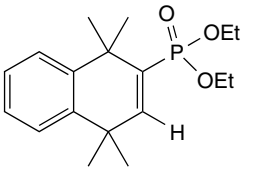
138



139



140

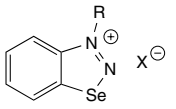


141

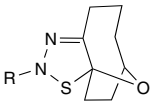
salts **142** were found to be more stable than the starting selenadiazole **47** and melted without decomposition. On treatment with alkali, the parent base **47** was regenerated.[29]

The compounds **4** and **20** are stabilized by a hypervalent selenapentalenic interaction similar to that found in the sulfur analogs. Acylation or tosylation of cyclooctanol **37** occurs at N-2, and stable tricyclic 1,2,3-selenadiazolines **143** were formed. These products are the result of intramolecular ring closure of the selenadiazolium salts **144**. Hydrolysis regenerates **37**.[150]

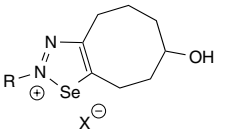
Butler *et al*. reported the alkylation of 4,5-diphenyl-1,2,3-selenadiazole **1** (R = R' = Ph) with trimethylsilylmethyl triflate. The quaternization occurred at N-3, and the salt **145** could be desilylated to form a transient 1,2,3-selenadiazolium ylide intermediate **146**. Trapping of this intermediate **146** with the electron-poor dimethyl acetylenedicarboxylate or methyl propiolate gave the pyrazolylvinyl selenides **147**.[151]



142



143



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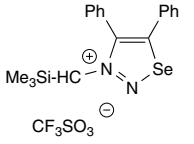
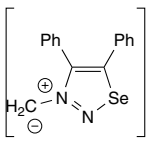


145



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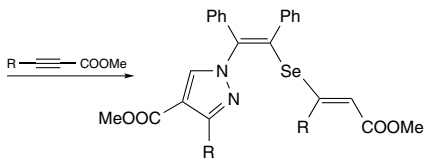
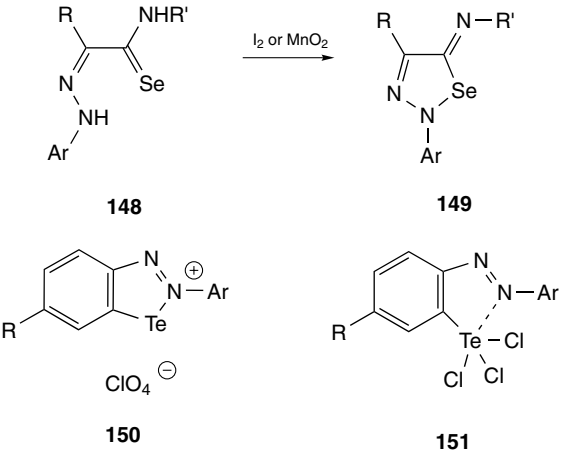


147

Monocyclic 1,2,3-telluradiazoles are unknown, at least in their neutral form, which is logical if we extrapolate the instability of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles. Oxidative cyclization (iodine or MnO_2) of hydrazonoselenamides **148** gave the 2-aryl-1,2,3-selenadiazolium-5-imines **149**.[152] A few papers described the formation of N_2-aryl-1,2,3-benzotelluradiazolium salts **150** by cyclization of tellurated azobenzenes.[153,154] The compound **151** is better described as an intramolecular complex of azobenzene and aryltellurium(IV)trichloride.[155]



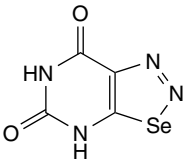
5.4. FUSED 1,2,3-SELENADIAZOLES

The transformation of readily available cyclic ketones via the hydrazone derivative and treatment with SeO_2 or its derivatives is a very attractive way to fused 1,2,3-selenadiazoles. Benzoselenadiazole **47** and cycloalkaselenadiazoles **59** have been mentioned previously, and in this subchapter, we will mainly discuss 1,2,3-selenadiazoles fused to other heterocyclic rings.

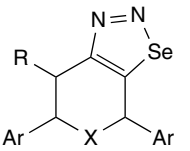
5.4.1. Bicyclic 1,2,3-Selenadiazoles

A pyrimidine derivative **152** was prepared in 67% yield by cyclization of 6-hydrazinouracil **152** and selenous acid in aqueous ethanol for 30 min at room temperature. This is the only report, where an unsubstituted hydrazone is transformed into a 1,2,3-selenadiazole.[156]

Reddy *et al*. transformed in a series of papers[7,35,157–164] a number of 2,6-diarylcyclohexanones and their aza-, spiro-, selenium- and sulfur analogs to the corresponding selenadiazoles **153**–**155**.

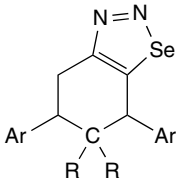


152



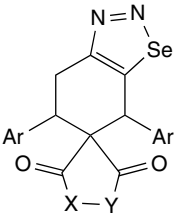
X = CH_2, S, Se, NH

153



R = $COOCH_3$, CN

154

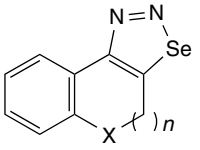


X-Y = $CH_2CR_2CH_2$
NHCONH

155

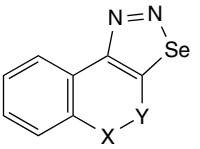
5.4.2. Tricyclic 1,2,3-Selenadiazoles

Tricyclic selenadiazoles **156** were prepared from substituted (thia)chroman-4-ones and their homologs.[165,166] Similar compounds **157** and **158** were prepared later by Reddy and coworkers.[167–169] The benzothiophene **159** (X = S) and its selenium derivative **159** (X = Se) were reported by Reddy *et al*. and Litvinov *et al*. respectively.[170,171] Shafiee *et al*. reported bis(selenadiazolo)cyclohexanes **160**.[172]



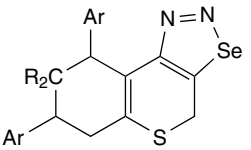
X = O, S
n = 1,2

156

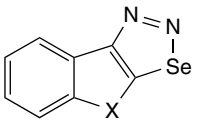


X = S, Y = CH_2
X = CH_2, Y = S

157

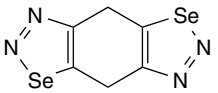


158



X = S, Se

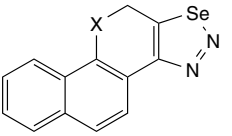
159



160

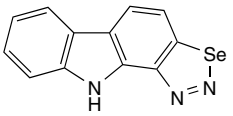
5.4.3. Tetra- and Pentacyclic 1,2,3-Selenadiazoles

1,2,3-Selenadiazole derivatives **161** of naphthopyran, naphthooxepine and naphthocycloheptane were reported by Maiti *et al.*[165] Kirsch and coworkers described carbazole derivatives **162**.[173,174] Polythia heterocycles **163**–**165** were described by Reddy *et al.*[167,170] Steroidal selenadiazoles **166** were prepared in 55% yield from the corresponding cholest-6-one semicarbazone derivatives.[175]

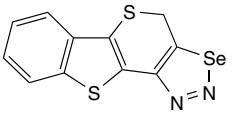


161

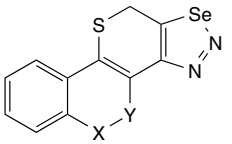
X = OCH_2, CH_2CH_2, O



162



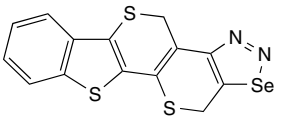
163



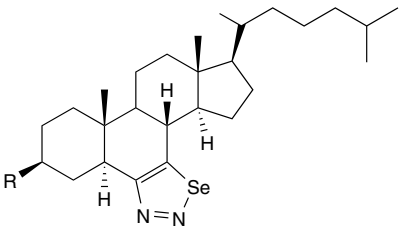
164

X = CH_2, Y = S

X = CH_2, Y = S



165



166

R = OAc, Cl, H

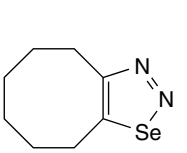
5.5. APPLICATIONS OF 1,2,3-SELENADIAZOLES

The most important use of the 1,2,3-selenadiazole ring is as a synthon for acetylenes or selenium-containing compounds, as described previously in this chapter.

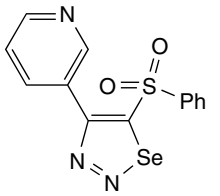
Apart from this, 1,2,3-selenadiazoles have been used as cocatalysts in partial hydrogenation of dinitriles to aminonitriles.[176] 4-Methyl-1,2,3-selenadiazole, one of the few liquid selenadiazoles, was used as a precursor for the low-temperature

plasma-assisted chemical vapor deposition of selenium, with a growth rate of 500 Å/min being achieved with a substrate temperature of 40°C and a plasma power density of 1 W/cm^2.[177] Cadmium selenide, of use in semiconductors, has been prepared as nanoparticles from cadmium chloride and cycloocta-1,2,3-selenadiazole **167** in ethylene glycol. The reduction of cadmium chloride followed by consumption of the selenium released from the selenadiazole led to the formation of CdSe. The selenadiazole was mentioned as a "greener source" of selenium as compared to the more toxic hydrogen selenide.[178]

The biological activities of several 1,2,3-selenadiazoles have been tested, but are probably underexplored. The results so far are not remarkable. Most studies concentrate on the antibacterial and antifungal activities.[22,104,179–184] For instance, 4-(3-pyridyl)-5-phenylsulfonyl-1,2,3-selenadiazole **168**, among a series of sulfonyl derivatives, was shown to have the highest activity of growth inhibition against some bacteria and fungi.[94] Antiaflatoxigenic activities of visnagin conjugates were investigated.[185]



167



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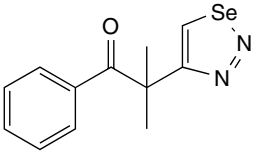
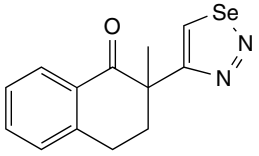
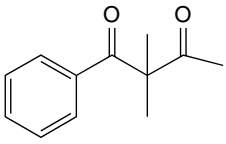


169



170



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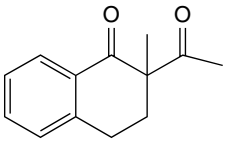

172

The biodistribution of two ^{75}Se-labeled 4-substituted 1,2,3-selenadiazoles **169** and **170**, that are analogs of the corresponding acetyl compounds **171, 172**, which are drugs that inhibit adrenocorticoid biosynthesis,[186] was determined. The conclusion was made that the compounds **169, 170** do not have potential as adrenocorticosteroid-imaging agents.[187,188]

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CHAPTER 6

1,2,3-Thiadiazoles in Medicine and Agriculture

In earlier reviews, it has been mentioned that many 1,2,3-thiadiazole derivatives exhibit various types of biological activities.[1–3]

6.1. MEDICINE

It has been found that the introduction of a 1,2,3-thiadiazole moiety to the molecules of known biologically active compounds changes the spectrum of their activities, and, in some cases, leads to an increase of biological activity. Thus, β-lactam antibiotics derivatized with a 1,2,3-thiadiazole-5-mercapto moiety were active against Gram-negative bacteria, especially resistant pathogens such as *Pseudomonas aeruginosa*.[3–5] A new preparation **1** with the commercial name of Cefuzonam® was introduced to medicinal practice. Fluoroquinolones substituted at the 7-position with the 1,2,3-thiadiazol-5-mercapto moiety also showed a high level of antibacterial activity.[6] Heterocyclic compounds, containing a 1,2,3-thiadiazolyl ring conjugated to a sydnone, were also found to be antibacterial agents.[7] The 3-amino-2-hydroxypropoxyphenyl derivatives of 1,2,3-thiadiazoles **2** and **3** have been found to be β-adrenergic blockers, and therefore these compounds are effective for the treatment or palliation of angina pectoris and several cardiac arrhythmias.[8]

4,5-Di(*p*-methoxyphenyl)-1,2,3-thiadiazole was found to be active as a potent antithrombotic agent.[9] It has been found that 1,2,3-thiadiazoles can act as heme ligands with a novel mechanism comparable to imidazole, and therefore 1,2,3-thiadiazoles have the potential to be used in the design of a new generation of antimycotic agents.[10] 4,5-Diphenyl-1,2,3-thiadiazoles were described to be anti-inflammatory agents.[11] Tetrahydrothiadiazoloisoquinoline **4** was found to inhibit phenylethanolamine-*N*-methyltransferase.[12,13] Such inhibitors might have potential therapeutic effects, especially in the treatment of cardiovascular diseases.

Antiviral activity has been reported in 1999 for the 1,2,3-thiadiazole derivative **5**.[14] These compounds are useful in the treatment of diseases associated with

The Chemistry of 1,2,3-Thiadiazoles, by Vasiliy A. Bakulev and Wim Dehaen
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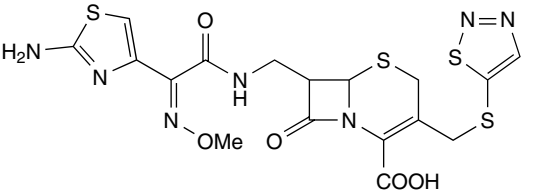

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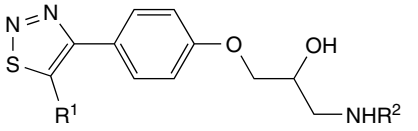
Cefuzonam®



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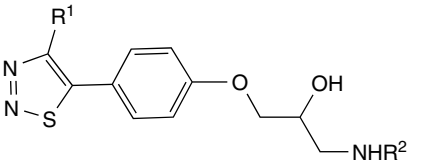

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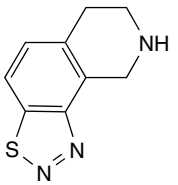

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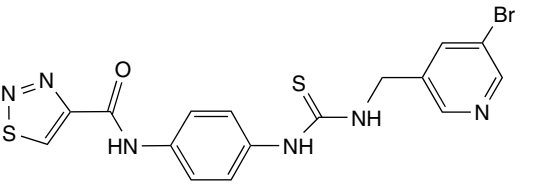
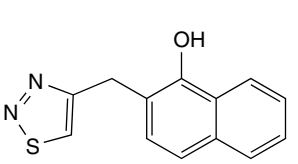


5

herpes viruses, including the human cytomegalovirus, herpes simplex viruses and the varicella-zoster virus.

Compound **6**, containing naphthol and 1,2,3-thiadiazole moieties, was found to be a 5-lipogenase inhibitor. This inhibitor is useful for the treatment of airway disorders, against allergic asthma, bronchitis, inflammation, rheumatism, thrombosis, ischemia, angina pectoris, arteriosclerosis, and skin diseases and as a cytoprotective agent for gastrointestinal tracts.[15] Compounds of type **7** with sulfoxide and sulfone groups are useful for the therapeutic and prophylactic treatment of viral, bacterial, fungal and parasitic infections in humans and animals.[16]

It has been reported that compounds of type **8** inhibit the enzymatic activity of HIV-1 reverse transcriptase, in particular the RNA-dependent DNA polymerase activity of HIV-1 reverse transcriptase.[17]



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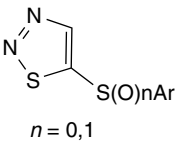

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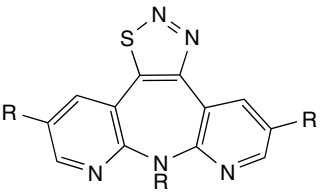

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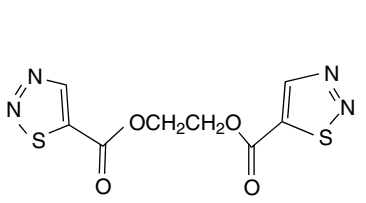
6.2. AGRICULTURE

1,2,3-Thiadiazole derivatives possess various types of pesticide activity, and therefore some of these compounds are useful for agriculture. It is interesting to note in this context that bis-1,2,3-thiadiazole **9** has been patented as a disease-controlling agent in agriculture and horticulture.[18] It has been reported that compound **10** has bactericidal and fungicidal activities.[19] Compound **11** containing 1,2,3-thiadiazole and benzoxazinone rings is patented as a plant disease–controlling agent.[20] It gives complete control over *Pyricularia oryzae*. A similar activity has been exhibited by compound **12**.[21]



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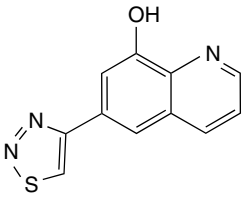

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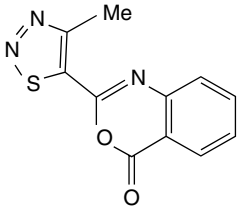

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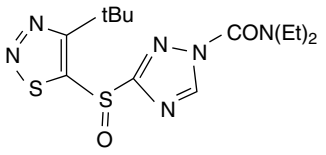

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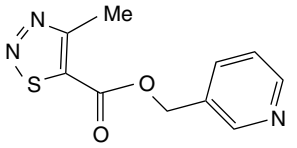
Compound **13** has been reported to be an agrochemical microbiocide.[22] Anilides of 1,2,3-thiadiazole-4- and 5-carboxylic acids exhibit the same activity.[23] Thieno[2,3-*d*][1,2,3]thiadiazoles **14** also have been patented as agrochemical microbiocides.[24] Benzothiadiazole **15** has herbicidal activity.[25]

1,2,3-Thiadiazole-5-ureido derivatives are known to possess various types of pesticide activity.[2,3] Thus, 5-phenylureido-1,2,3-thiadiazole-4-carboxamides



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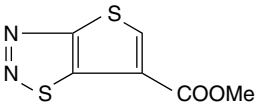

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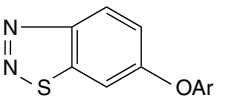

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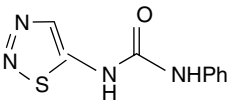
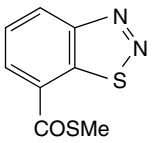


Thidiazuron



Bion

show herbicide activity.[26–29] On the other hand, 5-phenylureido-1,2,3-thiadiazole (Thidiazuron) is a very active cotton defoliant.[30–33]

6.2.1. Thidiazuron

The commercial impact of Thidiazuron has been the strongest in its use for the abscission of green-turgid leaves of cotton to facilitate picking of bolls.[34] Recently, Thiadiazuron has emerged as a highly effective bioregulant in plant tissue of a diverse array of species ranging from herbaceous to tree crops.[35] The defoliating response to Thidiazuron is restricted to a few species of the *Malvaceae* family.[36–38] Treatment with Thiadiazuron has been found to protect chlorophyll from degradation in detached leaves.[39,40] It has been shown that geranium tissues treated with Thiadiazuron have a higher level of chlorophyll than the ones not treated.[41] Examples of the diversity of the physiological effects of Thidiazuron include the following: enhanced seed germination in *Striga asiatica*,[42] lettuce[43] and neem;[35] substitution of the chilling requirement for seed germination in *Pyrus spp*.;[38] accelerated bud break in apple;[40] stimulation of sprouting in potato[42] and pumpkin cotyledon growth;[44,45] formation of branched trichomes and tomato on floral organs;[46] increased cluster and berry weight in grapes[47] and are effected on axillary shoot proliferation of three green ash clones.[48] Saxena and coworkers have reported in their review the intense research efforts directed toward the development of a Thidiazuron-mediated regeneration system.[35] It has been recently shown that Thidiazuron affects fruit growth, ripening and the quality of kiwifruit cropping[49] and induced shoot regeneration in pigeon pea.[50] Using a Thiadiazuron-containing culture, Li *et al*. developed an effective procedure for the regeneration of cacao (*Theobroma cacao*) plants.[51] *In vitro* studies show that Thidiazuron exhibits a high level of activity at concentrations as low as 10 pM for a relatively short period. This distinguishes Thidiazuron from other naturally occurring or synthetic plant-growth regulators. The structure of Thidiazuron is

different from both auxins and adenine-type cytokinins. There are two functional groups in the Thidiazuron molecule, phenyl and thiadiazole ring moieties, and replacement or modification of either of these groups will result in the reduction of activity.[35] It is worth noting that symmetrical *N*,*N*′-dithiadiazolylurea is the compound with the least cytokinin-like activity. This indicates that the two groups have complementary roles in Thidiazuron-induced responses.[35] A review on the regulation of the *in vitro* plant morphogenesis induced by Thidiazuron was published recently by Saxena and coworkers[35] and, earlier, on somewhat similar subjects by Huetteman and Preece[52] and Lu[53].

It has been shown that the application of Thidiazuron induces a diverse array of cultural responses ranging from induction of callus to formation of somatic embrions.[54–56] It exhibits the unique property of mimicking both auxin and cytokinin effects on growth and differentiation of cultured explants, although its structure is different from either auxins or purine-based cytokinins. The role of ethylene in the Thidiazuron-regulated somatic embryogenesis of Geranium hypocotyl cultures is discussed by Hutchinston *et al*.[57] The mechanism of the action of Thidiazuron is still not known. Most probably, Thidiazuron may act through the modulation of the endogenous plant-growth regulators, either directly or as a result of induced stress.[35] The other possibilities include the modification in cell membranes, energy levels, nutrient uptake and assimilation.[35] Recently, Saxena and coworkers have shown the important role of endogenous purine metabolism in the thiadiazuron-induced somatic embryogenesis of peanuts.[58] They have found that the purine analogs 2,6-diaminopurine, azaadenine or azaguanine inhibit the embryogenic response of the seedling induced by Thidiazuron.

6.2.2. Bion

Recently, a class of 1,2,3-benzothiadiazoles was recognized as the first synthetic chemical "plant activators", which can induce disease resistance in plants, the so-called systemic acquired resistance (SAR). The *S*-methyl ester of 1,2,3-benzothiadiazole-7-thiocarboxylic acid (Benzothiadiazole, Acibenzolar-*S*-methyl, CGA 245704) was introduced as the first commercial product of this type by Novartis.[59,60] It has been shown that Benzothiadiazole induces disease resistance in wheat,[61] tobacco,[62] *Arabidopsis*,[63] melons[64] and maize.[65] It can be used as a substitute for antibacterial and antiviral compounds as well as for fungicides.[66] The reduced susceptibility of the cotton plants to *Alternaria* leaf spot, bacterial blight and *Verticillum* wilt is attributed to the SAR following application of Benzothiadiazole.[66,67] Gorard and coworkers have shown that Benzothiadiazole induces resistance in cauliflower (*Brassica oleracera var botrytis*) to the downy mildew of *Crucifers* caused by *Peronospora parasitica*.[68] Brisset *et al*. have found that Benzothiadiazole induces the accumulation of two defense-related enzymes, peroxidases and α-1,3-gluconases, in apples and protects them from fire blight.[69] These results suggest that Benzothiadiazole promotes induced systemic resistance in apple by increasing defense-related compounds. Thomson and

coworkers[70] have investigated the efficacy of Benzothiadiazole in the control of fire blight in pear and apple orchards in USA, New Zealand and France. They have found that it is more active in apples than in pears. Ishi *et al*. have found that Benzothiadiazole induced resistance to cucumber and Japanese pear fungi diseases.[71] The induction of systemic resistance to *Pythium* damping-off in cucumber plants by Benzothiadiazole was also registered earlier by Benhamou and Belanger.[72,73] The same authors have provided evidence that foliar applications of Benzothiadiazole sensitize tomato plants to react more rapidly and more efficiently to *Fusarium oxysporum radicis-lycopersici* attack via the formation of protective layers at the sites of potential fungal entry.[72] Pospieszny and Folkman have shown that Benzothiadiazole protects tomato plants against viruses caused by Benzothiadiazole.[74] Reports have appeared on the suppression of gray mould on strawberry fruit with the chemical plant activator Benzothiadiazole.[75] Romero and coworkers have shown that bell pepper plants sprayed with Benzothiadiazole showed resistance to subsequent infections of the bacterial spot agent *Xanthomonas axonopodis*. In the field, application of Benzothiadiazole every two weeks, alone or in combination with copper, resulted in disease control, similar to the standard treatment of copper plus Menab.[76] The interaction between *Plasmopara helianthi, Glomus mosseae* and Benzothiadiazole in sunflower plants has been studied by Tosi and Zazzerini. They have shown that foliar spray treatment of Benzothiadiazole to mycorrhizal plants provided good protection against *P. helianthi* foliar infections.[77] Dann *et al*. have reported the effect of treating soybean with Benzothiadiazole on seed yields and the level of disease caused by *Sclerotina sclerotiorum* in field and greenhouse studies.[78] The activation of systemic disease resistance in pea by Benzothiadiazole has been shown by Dann and Deverall.[79] The application of Benzothiadiazole in combination with the fungicides Metalaxyl, Fosetyl and copper hydroxide results in synergistic effects on pathogen resistance in wild-type plants and an additive effect in Benzothiadiazole-unresponsive *nim*1 plants.[80] There are few articles on the action mechanism of Benzothiadiazole as a SAR inducer in plants.

Burketova *et al*. have shown that Benzothiadiazole has induced the synthesis of acidic and basic chitinase isozymes and a basic α-1,3-glucanase isozyme.[81] These chemical compounds have been proposed as being able to degrade the polysaccharides of fungal cell walls and in this way inhibiting fungal growth. They could also cleave bacterial cell walls and inhibit bacterial growth. Thomson and coworkers presented evidence that induced resistance was indicated by the enhanced activities of the defense-related peroxidase and glutathione-*S*-transferase enzymes in plants protected with Benzothiadiazole.[70] Interestingly, the prospective signal, which induces systemic resistance, can be transferred from leaves treated with Benzothiadiazole to the untreated upper and lower leaves where systemic resistance is elicited.[82] The same authors have shown that the expression of resistance-related genes, that is, genes of acidic peroxidase, acidic class III chitinase and acidic β-1,3-glucanase[83] was also induced by treatment

with Benzothiadiazole. Kauss and coworkers have demonstrated that inducers of acquired resistance can affect expression of the cucumber chitinase gene and not only as direct inducers. They can also act synergistically with fungal elicitors and, in addition, condition the hypocotyls in a developmental manner for potentiated elicitation.[84–87] Conrath and coworkers have found that pretreatment with Benzothiadiazole augmented the sensitivity for low-dose elicitation of coumarin phytoalexin secretion by cultured parsley cells.[88,89] This enhanced coumarin secretion was associated with the potentiated activation of the genes encoding Phe ammonia-lyase (PAL). Because, in contrast to the PAL genes, those for anionic peroxidase were directly induced by Benzothiadiazole in the absence of an elicitor, a conclusion has been made on a dual role for Benzothiadiazole in the activation of plant diseases.[88] In a recent publication, Conrath *et al.* considered priming as a mechanism in induced systemic resistance in plants.[89] Strikingly, a similarity was found between the administration of defense responses in primed cells of plants and humans. Thus, pretreatment of human monocytes/macrophages with interferon augments the induction of defense-related cytokines. On the other hand, preincubation of cultured parsley cells with inducers of induced acquired resistance, for instance, with Benzothiadiazole, enhances the subsequent induction of a variety of defense responses by elicitors, pathogen infections, wounding or osmotic stress. These responses include the activation of defense genes and the accumulation of defense-related compounds.[89] The interesting biological properties of Benzothiadiazole have prompted researchers to elaborate new methods toward novel fused 1,2,3-thiadiazoles (see Chapter 4) and to study their biological activities.[59,191] Kunz *et al.* gave some data on the structure–activity relationship, analyzing the data on the activation of resistance in cucumber plants against pathosystems of a series of Benzothiadiazole derivatives.[59] They have found that 1,2,3-benzothiadiazole and its methyl derivatives are biologically inactive; benzothiadiazole carboxylic acids that are isomeric to Benzothiadiazole are also inactive. Within the series of benzothiadiazole-7-carboxylic acid derivatives, esters, thioesters and hydrazides were found to be more active than amides, and the higher the molecular weight of a carboxylic acid derivative, the lower the activity. Benzothiadiazoles with a sulfonic acid, a sulfonamide or a phosphinic acid functionality at the 7-position as well as the nitro compound were inactive. The homologous carboxylic acid was found to be inactive, whereas the vinylogous derivatives had a moderate activity. The corresponding carboxaldehyde and its acetals as well as the corresponding carbinol or 7-*O*-alkyl and acyl derivatives were less active than 1,2,3-benzothiadiazol-7-carboxylic acid and its *S*-methylester. Kunz *et al.* have also shown that additional substituents at the phenyl ring of Bion generally decreased the activity.[59] 1,2,3-Thiadiazoles with second annulated ring systems were inactive. It is interesting to note that the replacement of the 1,2,3-thiadiazole ring in the Bion molecule with the isomeric 2,1,3-thiadiazole moiety lead to the loss of activity. On the other hand, the corresponding benzoisothiazoles had a moderate activity.[59]

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