CHAPTER 1

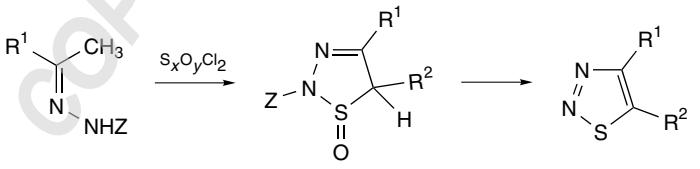
Synthesis of 1,2,3-Thiadiazoles

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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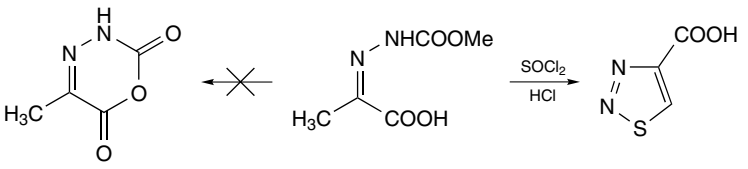


5 **4** **6**

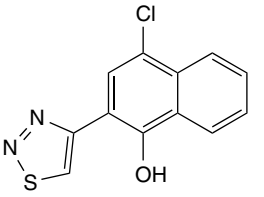
with thionyl chloride. 1,2,3-Thiadiazole-4-carboxylic acid **6** was unexpectedly formed, leading to a new synthetic approach to 1,2,3-thiadiazoles.[10]

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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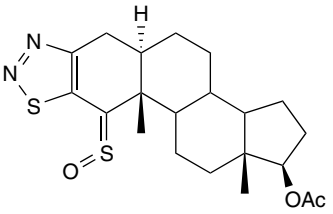
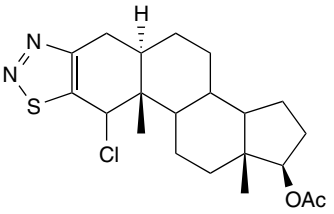


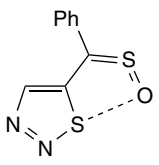
8a



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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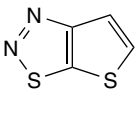

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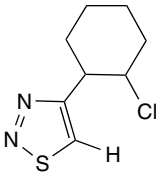

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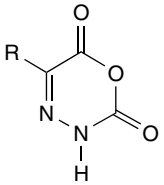
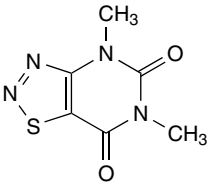


12

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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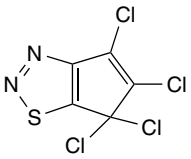

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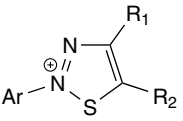
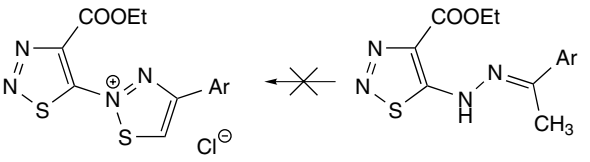
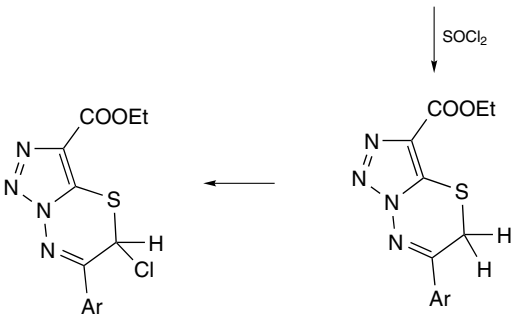


15

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**

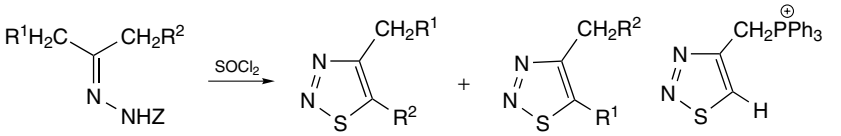


18 **17**

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]



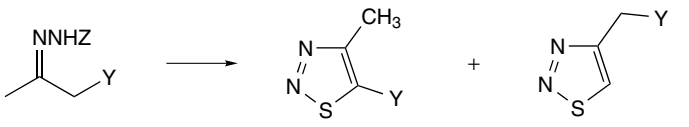
20 **21** **22** **23**

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]

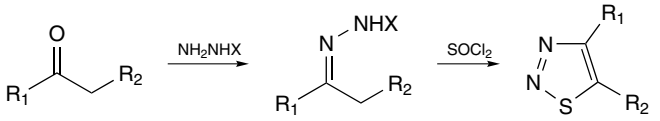


24 **25** **26**

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

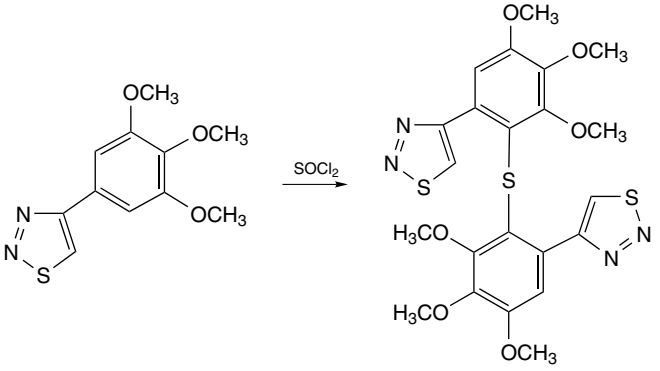
Y = OR, SR, Br, Cl, F

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**.

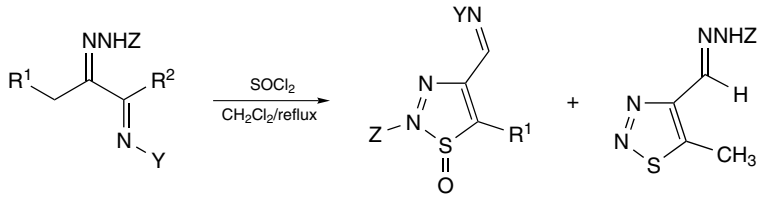


30 **31**

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]

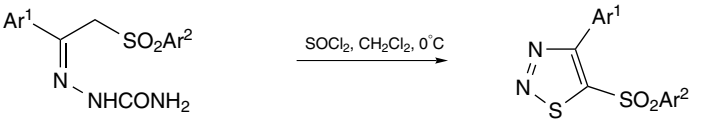
1,2,3-Thiadiazoles containing aryl- (**36**) and alkenylsulfonyl (**38**) groups were recently prepared by the group of D.B. Reddy using the Hurd–Mori reaction.[45,46] Compounds **36** and **38** have been shown to be very useful starting reagents in the synthesis of polyfunctional alkynes.

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**,

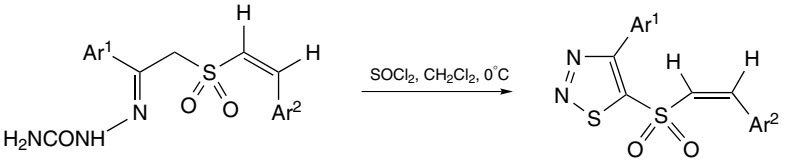


32 **33** **34**

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



35 **36**



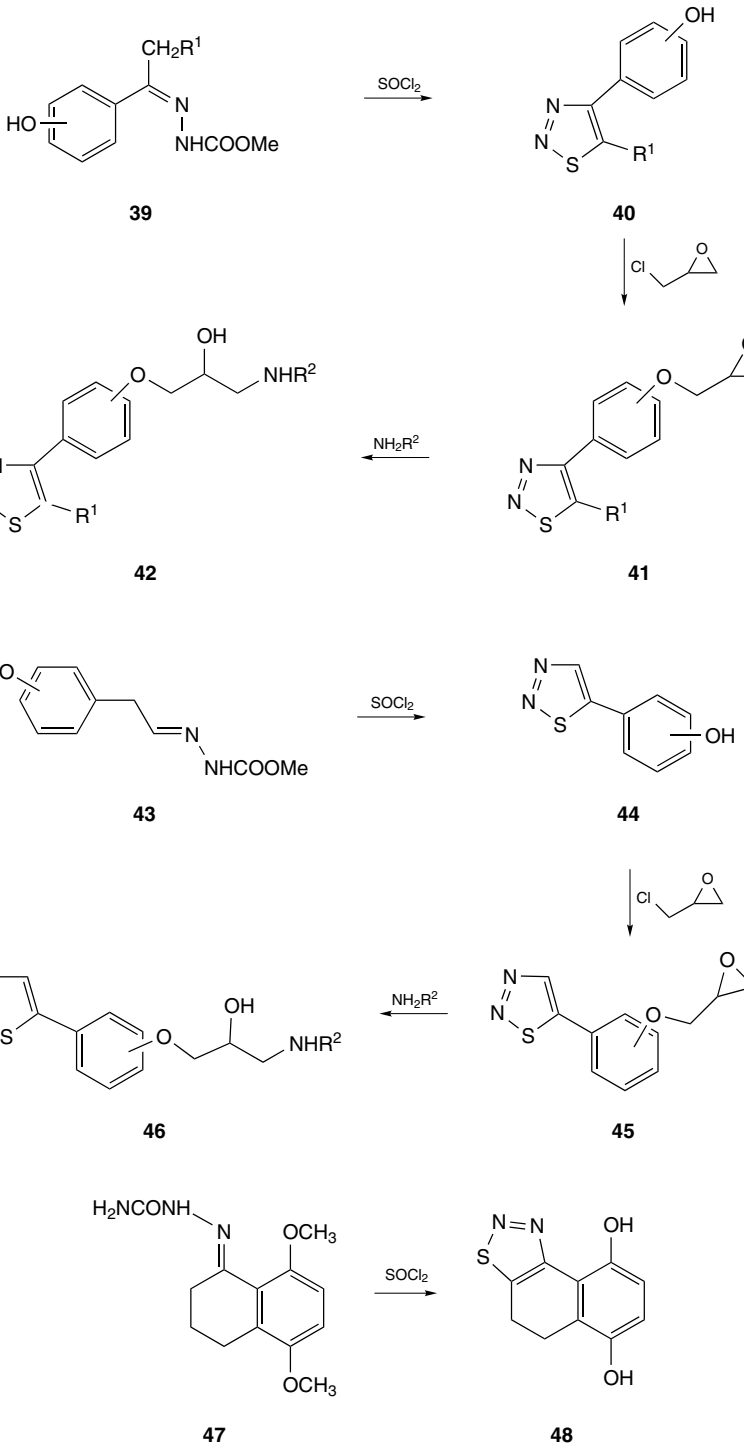
37 **38**

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


CH2R1
HO
N
NHCOOMe
SOCl2
OH
N
N
S
R1
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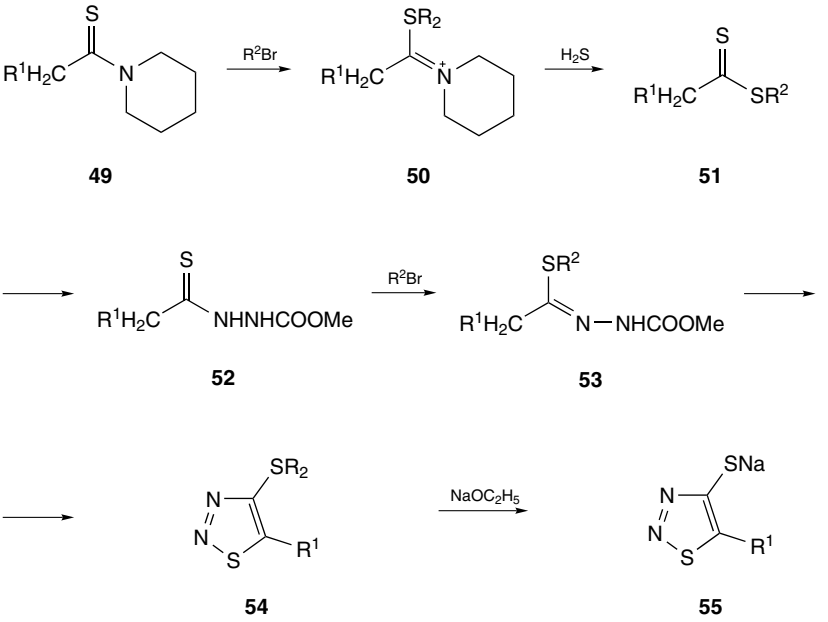
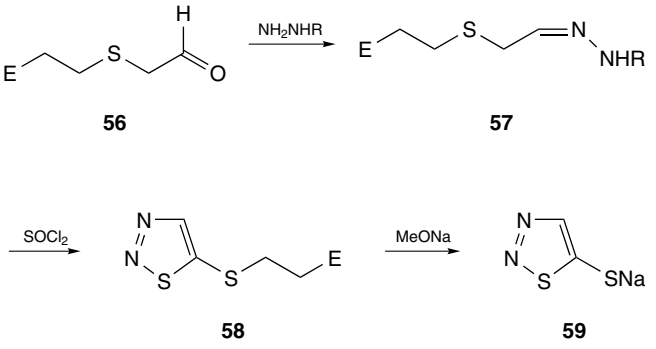
H2NCONH
OCH3

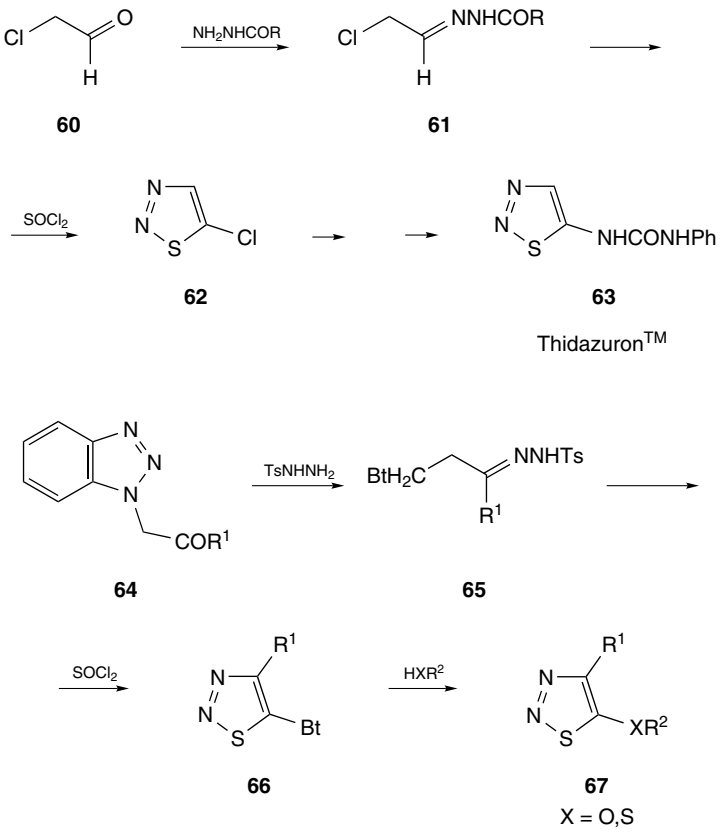


reaction with thionyl chloride. The same thiol protecting group was used in the synthesis of thiadiazoles **59** as in the synthesis of 1,2,3-thiadiazole-4-thiols **55**.[19,49]

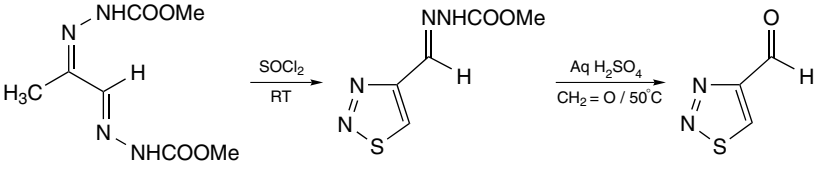


The Hurd–Mori reaction was applied on an industrial scale to prepare 5-chloro-1,2,3-thiadiazole **62**, which is a key intermediate in the synthesis of 5-phenylureido-1,2,3-thiadiazole, a very effective cotton defoliant with the commercial name of thidazuron™.[50]

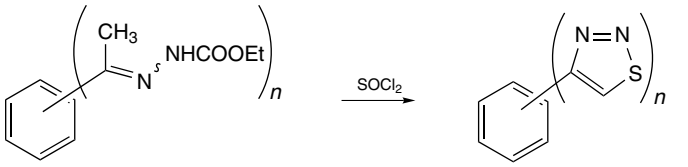
Quite recently, Katritzky and coworkers applied the Hurd–Mori reaction to prepare bicyclic assemblies **66** containing both 1,2,3-thiadiazole and benzotriazole rings[51]. Benzotriazole (Bt) was shown to be a good leaving group, which allowed to prepare 5-aryloxy- and 5-arylthio-1,2,3-thiadiazoles **67**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



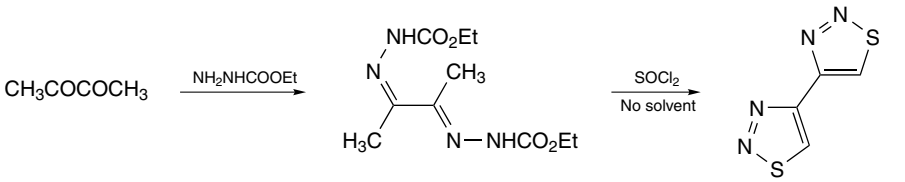
As a part of a program to synthesize new antibacterial cephalosporin analogs, Kobori *et al*. described a two-step synthesis of 4-formyl-1,2,3-thiadiazole **70**. Methylglyoxal was converted with 2 equiv of ethyl carbazate at room temperature into bis(ethoxycarbonylhydrazone) **68**, which was treated 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]

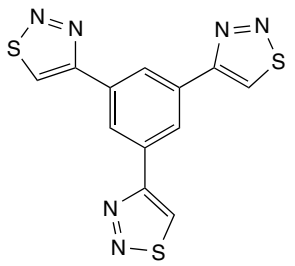


71 **72**



73 **74** **75**

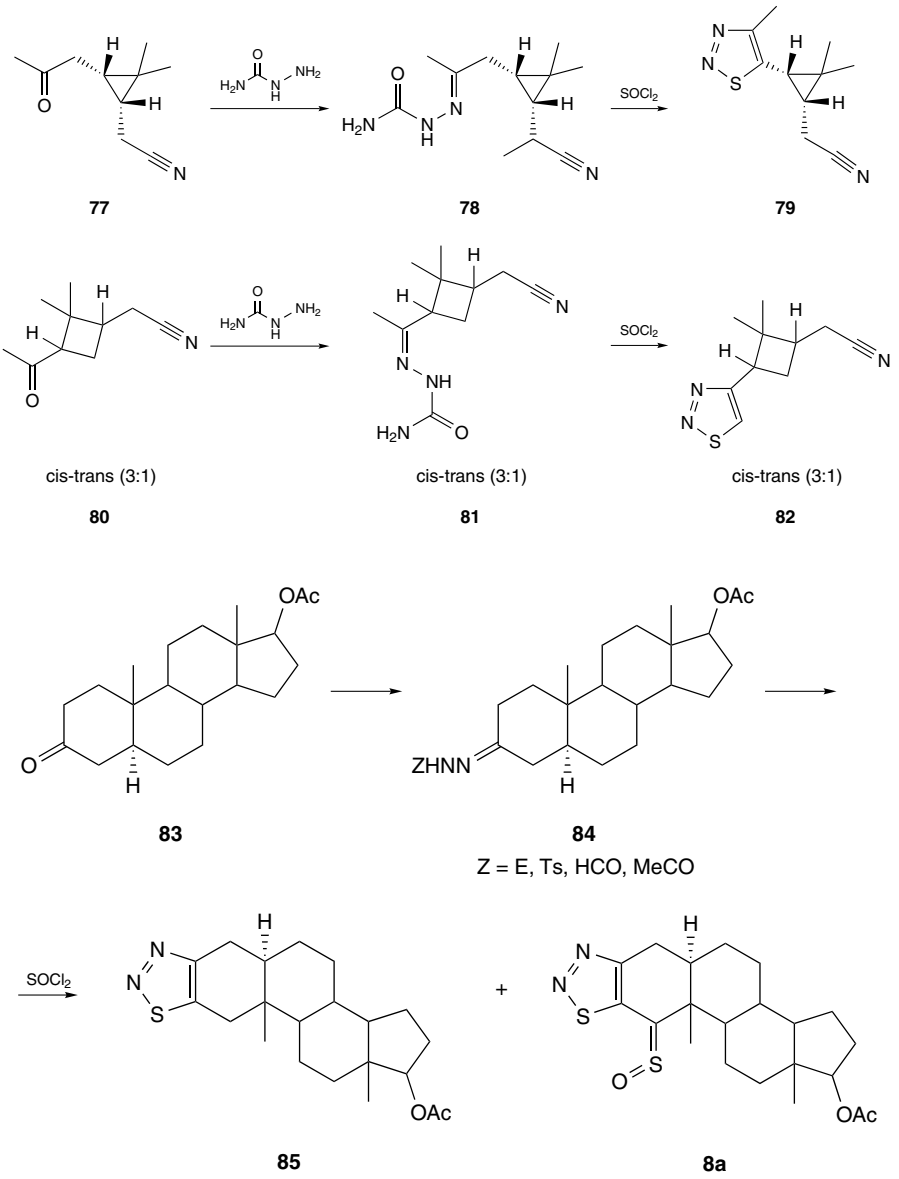
Some years before, we had prepared similar compounds that were used as dendrimer cores and did contain two or three thiadiazole rings (**76**) in one molecule.[23]



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]

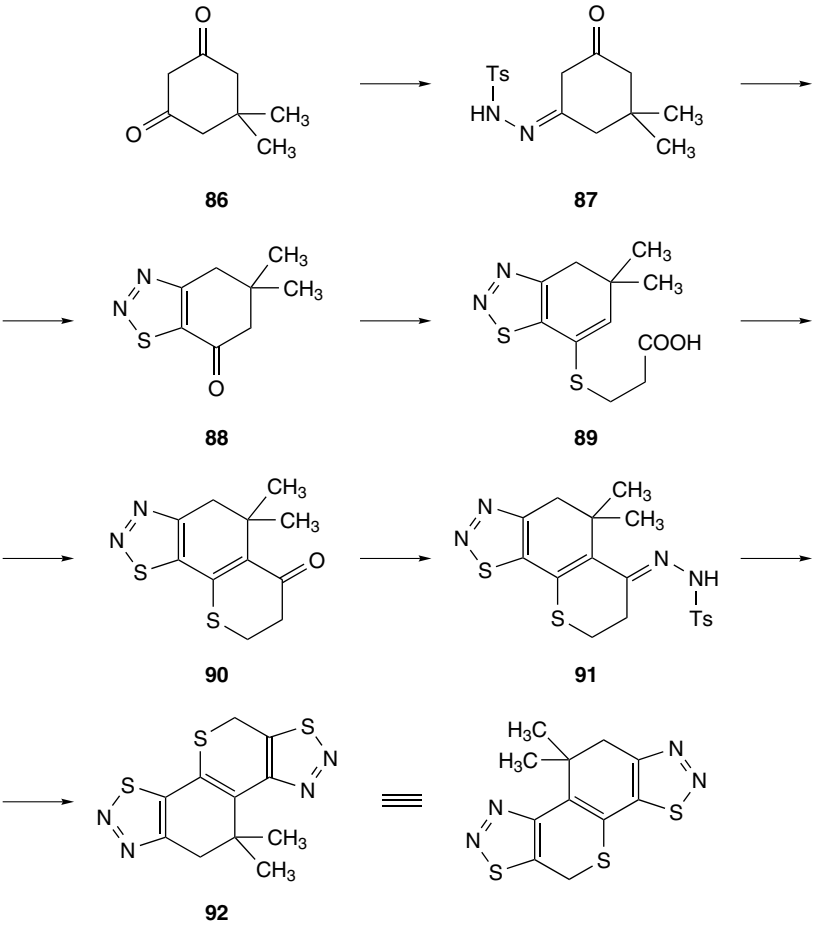
In attempting to prepare novel steroidal [3,2-*d*][1,2,3]-thiadiazoles in support of a program exploring A-ring-fused heterocyclic steroids for use as male contraceptives, Britton *et al.* have found that the reaction of *N*-ethoxycarbonyl hydrazones **84** affords compounds **86** containing a sulfine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

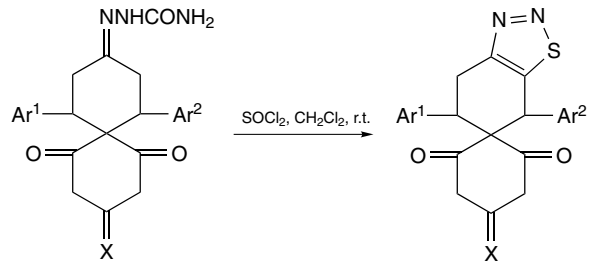
The work of Britton prompted Bakthavatchalam *et al*. to carry out a multi-step synthesis of bisthiadiazolo polycyclic compounds **92**, where both thiadiazole rings were constructed with the Hurd–Mori reaction.[52] The reaction starts from dimedone **86** via the monothiadiazole **88**, which is regioselectively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

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

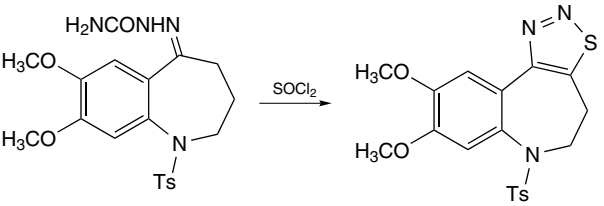


In subsequent work, the same authors prepared compounds, in which one of the thiadiazole rings in **92** was substituted by isoxazole or pyrazole rings.[53] Many other examples of the synthesis of 1,2,3-thiadiazoles fused to other heterocyclic rings by Hurd–Mori reaction were published by Indian chemists.[54–68] 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**

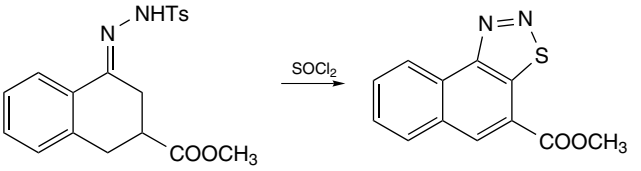
Stanetty and coworkers published data[9,69,70] on the synthesis of structural analogs of Bion™, benzo-[1,2,3]thiadiazole-7-carbothioic acid *S*-methyl ester, the first synthetic chemical, which is recognized as a plant activator.[70]

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.

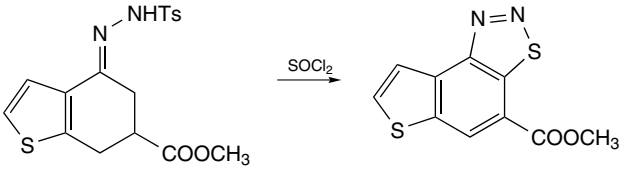
In a related study, the Stanetty group reported an efficient method to prepare thieno[2,3-d][1,2,3]-thiadiazole-6-carboxylic acid derivatives **103**, a new class of compounds biosteric to benzo[1,2,3]thiadiazole-7-carboxylic acid **104**.[69,70]

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**.

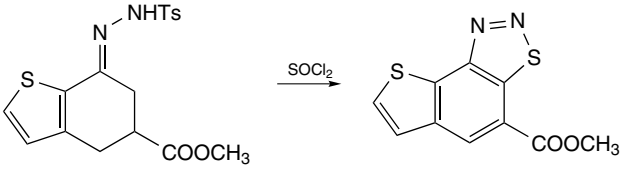
A mixture of the target compound **112** and a by-product, identified as the chlorinated thienothiadiazole **113**, was isolated in a ratio of 8:1 after treatment of the hydrazone **111** with thionyl chloride in dichloromethane at room temperature.



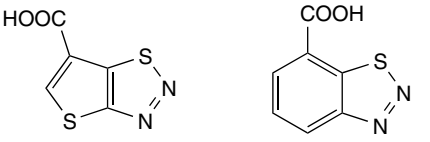
97 **98**



99 **100**



101 **102**



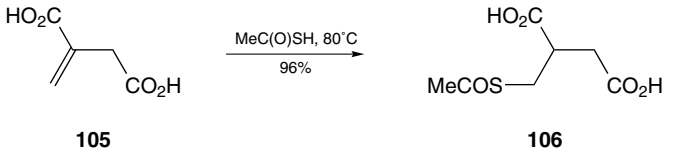
103 **104**

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

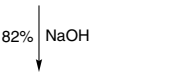
Thienothiadiazole **116**, which is isomeric to **112**, was prepared by Ohno and colleagues from tosylhydrazide **115** by the Hurd–Mori reaction.[71]

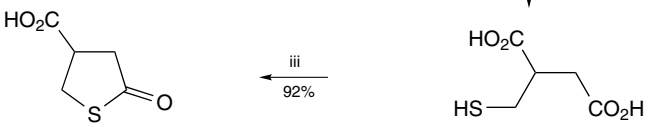
An interesting solid phase synthesis of 1,2,3-thiadiazoles was described. A Merrifield type resin **117**, which was functionalized with sulfonhydrazide groups, was used to "fish out" ketones from a reaction mixture. Subsequent treatment of the isolated resin with thionyl chloride converted the hydrazone 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.

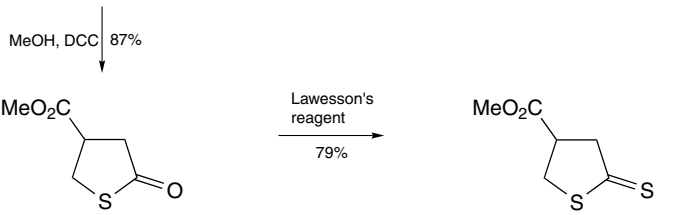


105 **106**

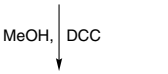


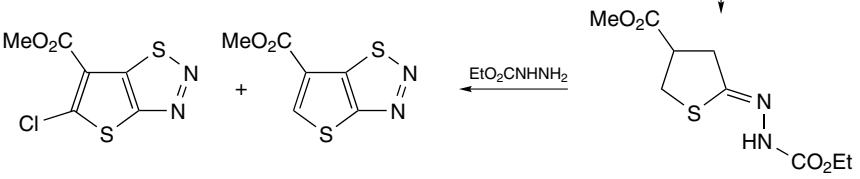


108 **107**



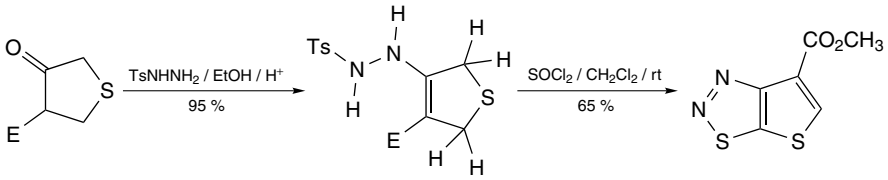
109 **110**



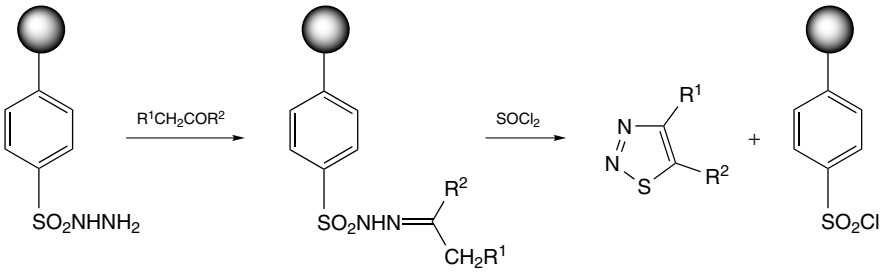


113 **112** **111**

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**

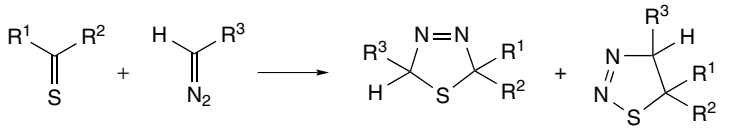


117 **118** **119** **120**

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.

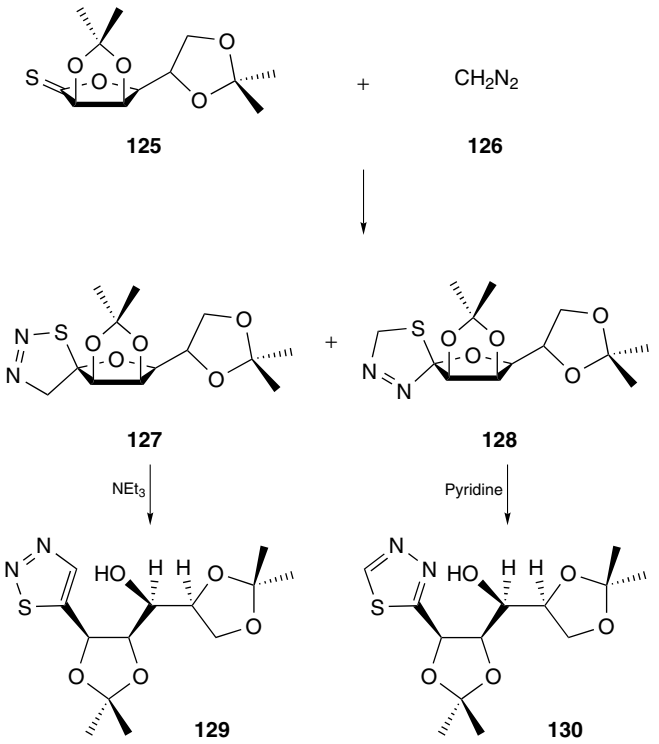
The reaction of diazoalkanes **121** with thioketones **122** gives mixtures of 1,3,4-thiadiazolines **123** and 1,2,3-thiadiazolines **124**. The ratio of the regioisomers depends on the solvent polarity and steric effect. Increasing the solvent polarity and decreasing the steric hindrance favors the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



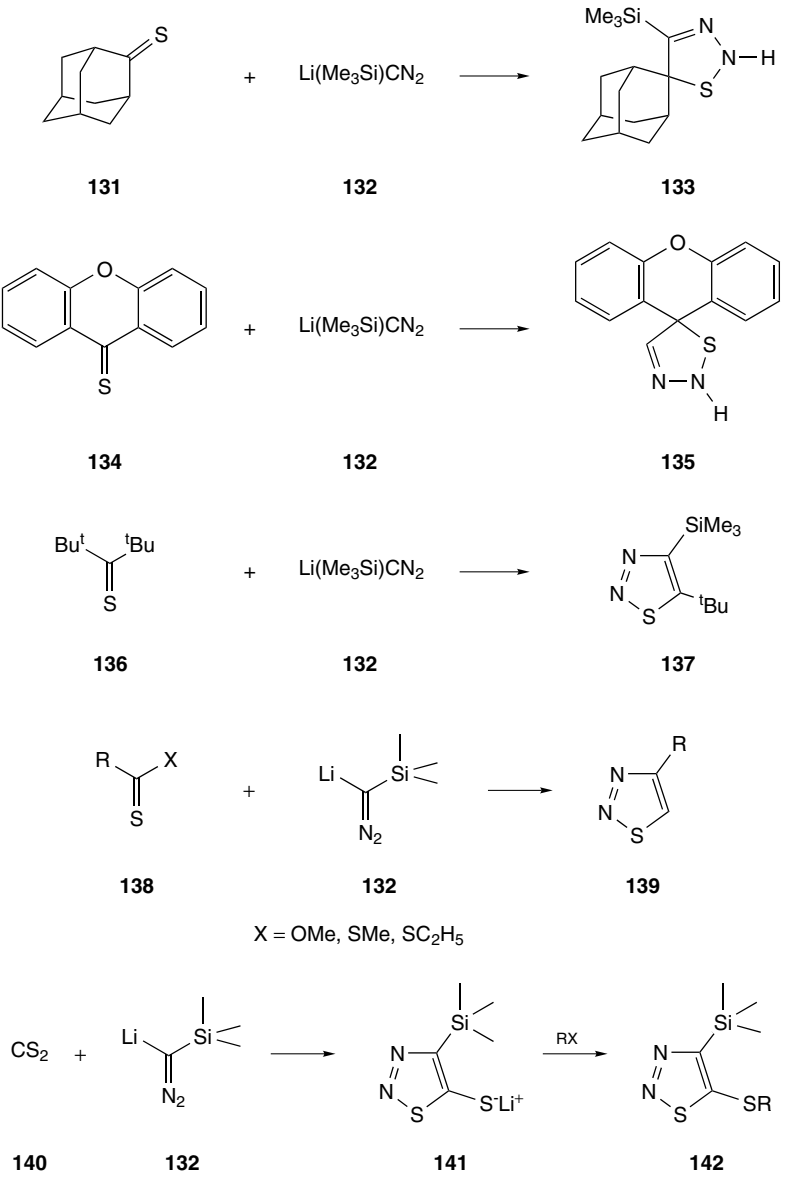
of the adamantyl derivative **131** changes the direction of the reaction drastically to afford the methyleneadamantane, which is a degradation product of the thiadiazoline ring. In the reaction of cyclic ketones, the formation of thiadiazolines **133** and **135** is possible, but in the case of thioketone **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]

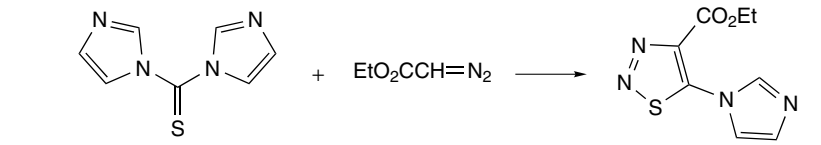
Interestingly, other hindered thiocarbonyl compounds, namely, 1,1′-thiocarbonyl-bis-imidazole **143** and -bis-triazole **145**, reacted with ethyl diazoacetate in a regiospecific manner to give ethyl 5-(imidazol-1-yl)- and 5-(1,2,4-triazol-1-yl)-1,2,3-thiadiazole-4-carboxylates **144** and **146**,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

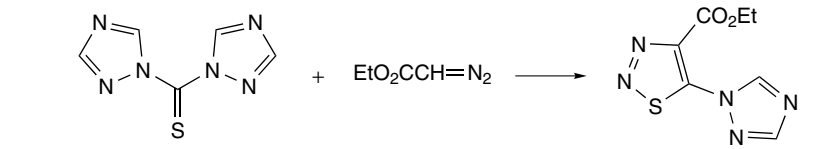


chloride, alcohol or thiol or via a hydrogen shift from the 4-position of the ring to the exocyclic nitrogen atom to form mixtures of aromatic thiadiazoles **149 (153)** and **150 (154)**.[5,79]

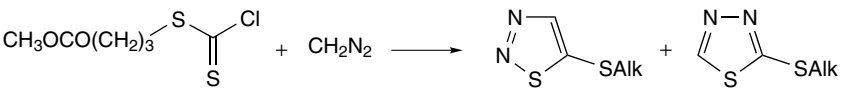
It is interesting to note that ethyl chlorodithioformate **155** preferably affords 1,3,4-thiadiazole **156a** from its reaction with diazoacetic ester in the presence of triethylamine. On the other hand, the isomeric 1,2,3-thiadiazole **156b** was obtained in this reaction when HgO was used instead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



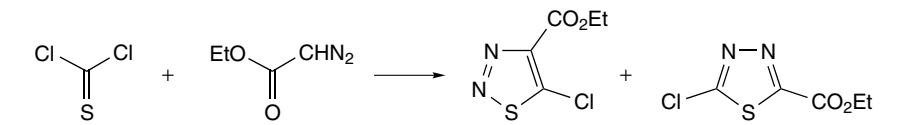
143 **144**



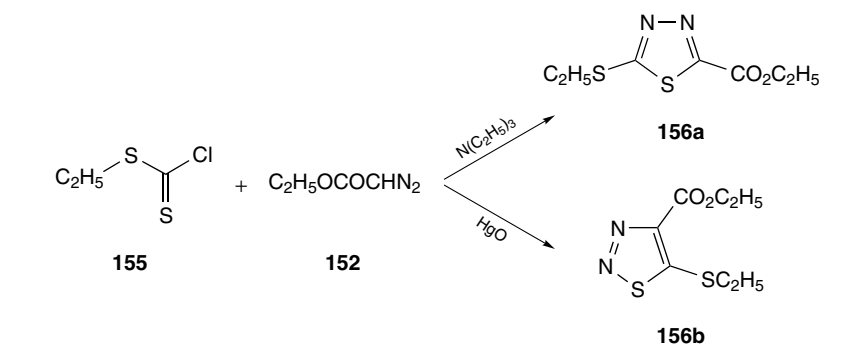
145 **146**



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



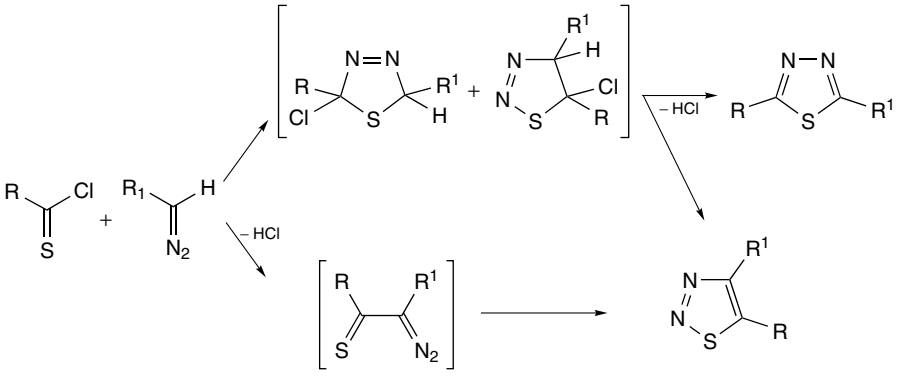
151 **152** **153** **154**



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

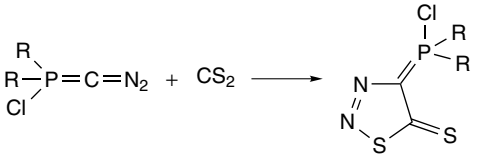
Obviously, the isomeric thiadiazoles are formed *via* different mechanisms. The concerted 1,3-dipolar cycloaddition reaction of diazo compounds onto the C=S double bond takes place regioselectively to give mainly 1,3,4-thiadiazolines, which eliminate hydrogen chloride to afford 1,3,4-thiadiazoles analogous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

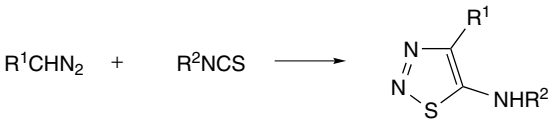
At the same time, only 4-methylene-Δ^2-1,2,3-thiadiazolin-5-thiones **158** were obtained in quantitative yield when diazomethylene phosphoranes **157** were treated with carbon disulfide.[81]



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]

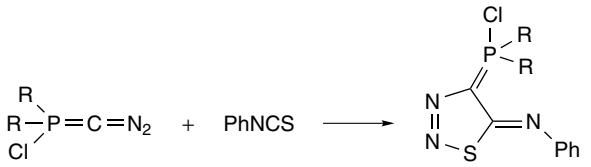
This type of reaction is often accompanied by alkylation of the primary formed 5-amino-1,2,3-thiadiazoles **161** and by the formation of carbene-derived products. Therefore, the yields of the 5-amino-1,2,3-thiadiazoles **161** often are only



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.

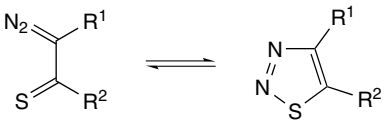
Despite the presence of two cumulated double bonds in the isothiocyanate molecule, the addition of diazo compounds takes place selectively onto the C=S bond to afford only 1,2,3-thiadiazoles. The Pechmann–Nold synthesis of 1,2,3-thiadiazoles is strictly limited to diazomethane or diazo compounds monosubstituted 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]



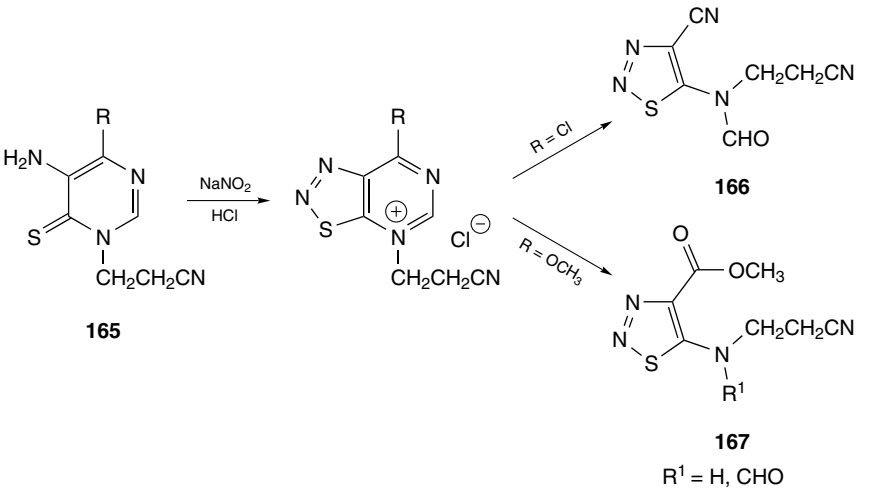
163 **164**

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

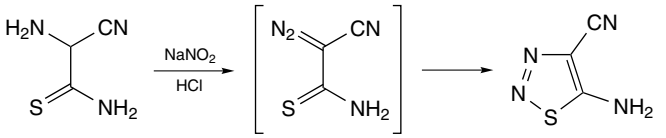
166

167

R^1 = H, CHO

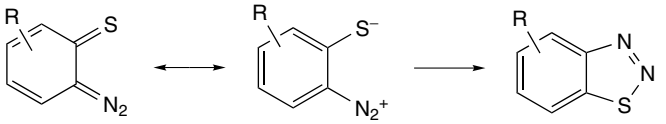
Diazotation of 2-amino-2-cyanothioacetamide **168** under the same conditions proceeds readily to form 5-amino-4-cyano-1,2,3-thiadiazole **170** in good yield.[5,86]

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**.



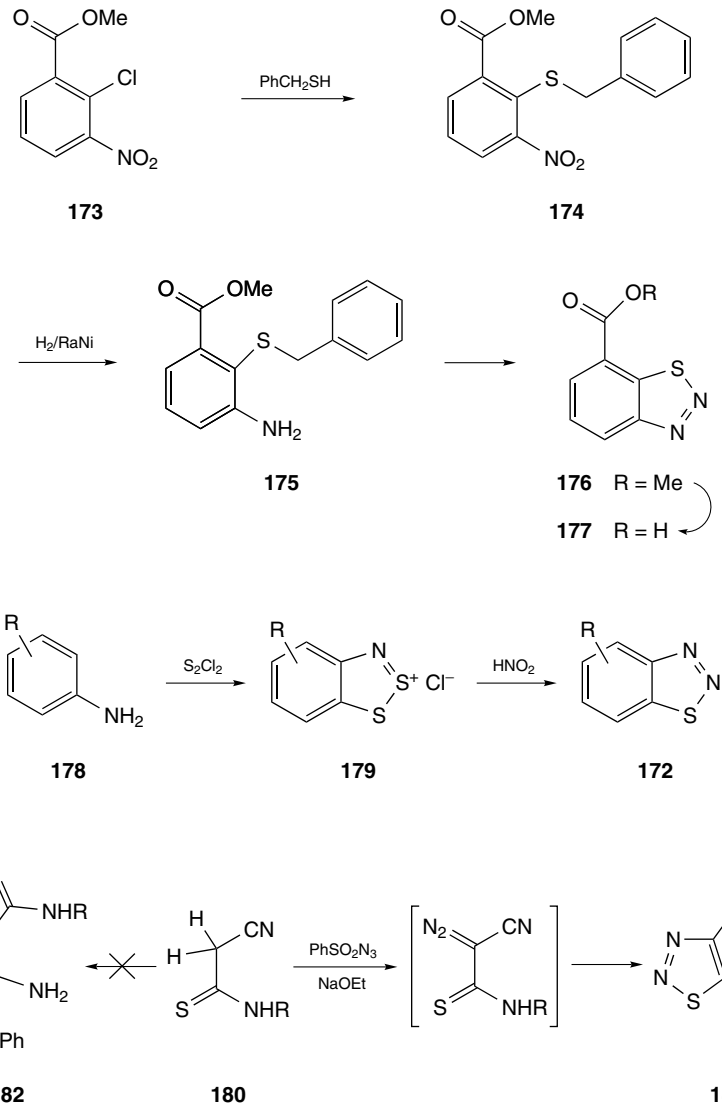
171 **172**

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

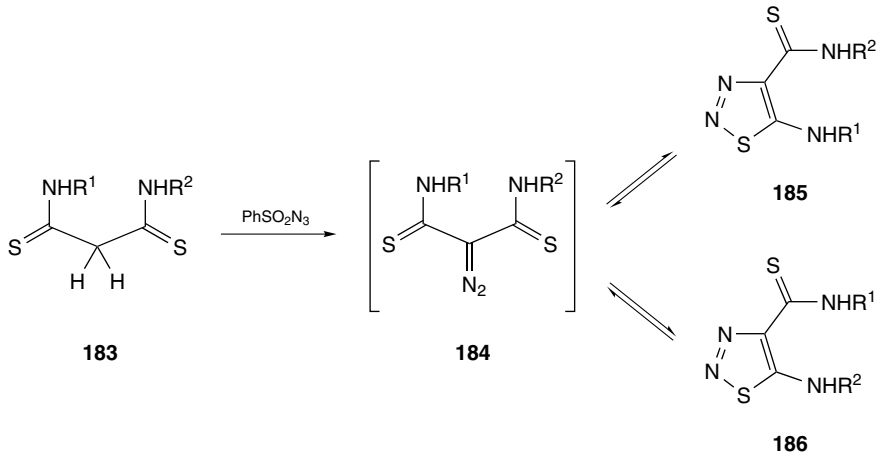


173 **174** **175** **176** **177** **178** **179** **172** **182** **180** **181**

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:

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

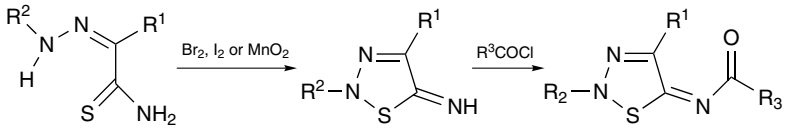
$$\text{Me} < \text{Et} < \text{Bz} < \text{cyclohexyl};$$

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

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

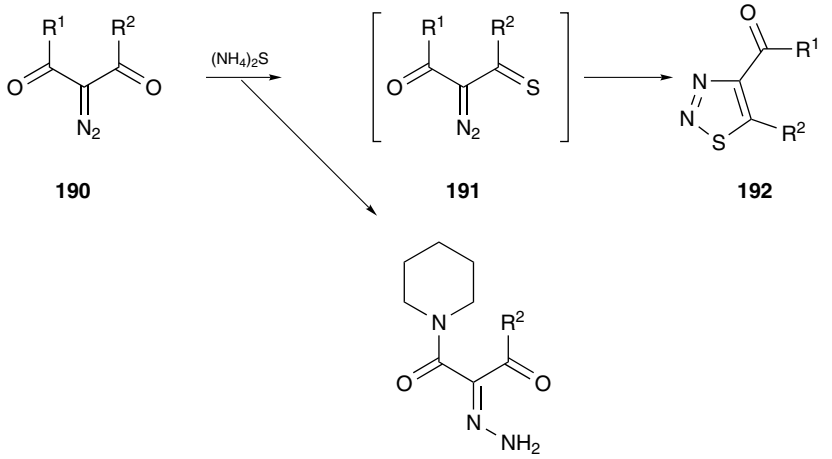
ring takes place here by intermolecular cyclization and, therefore, we can formally classify this approach for the preparation of 2-substituted thiadiazoles **188** as belonging to the Wolff type.

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.

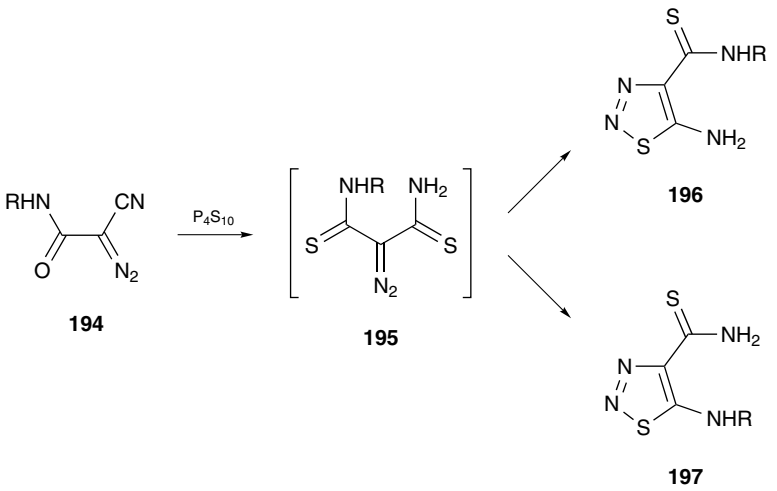


190 **191** **192**

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]

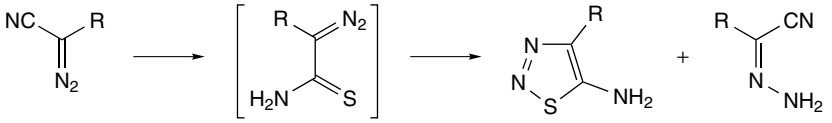
We have found no substantial difference in the results for the reaction of 2-diazo-2-cyanoacetamides **194** with both tetraphosphorous decasulfide and Lawesson's reagent. Both cyano and carboxamide groups of diazo compound **194** take part in the reaction to generate 2-diazomalondithioamide **195**. 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]

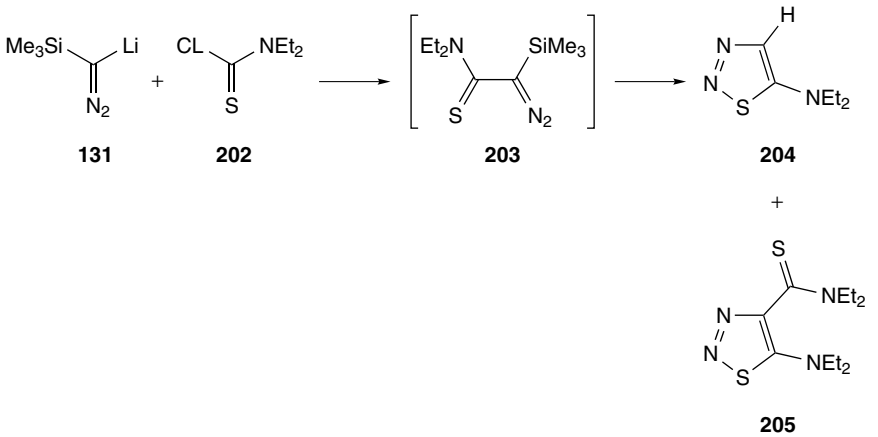


198 **199** **200** **201**

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

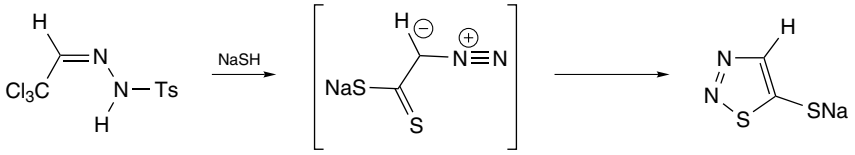
1.3.3. Simultaneous Introduction of Diazo and Thiocarbonyl Functions

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™.

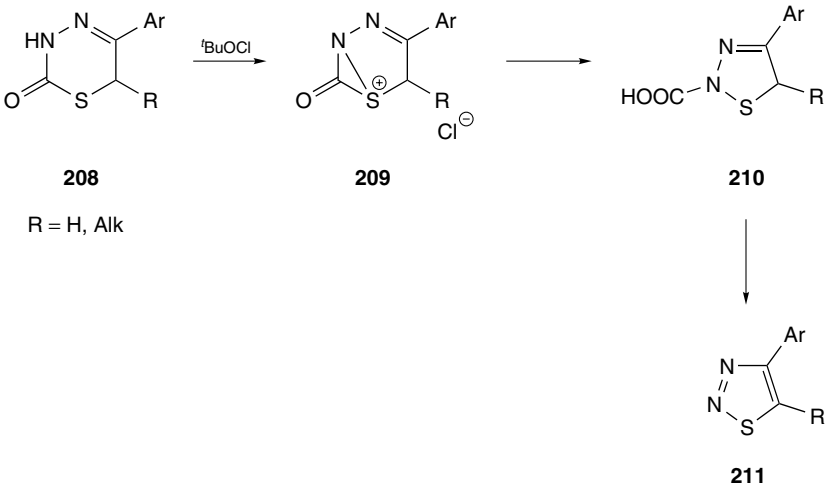


206 **207** **59**

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]

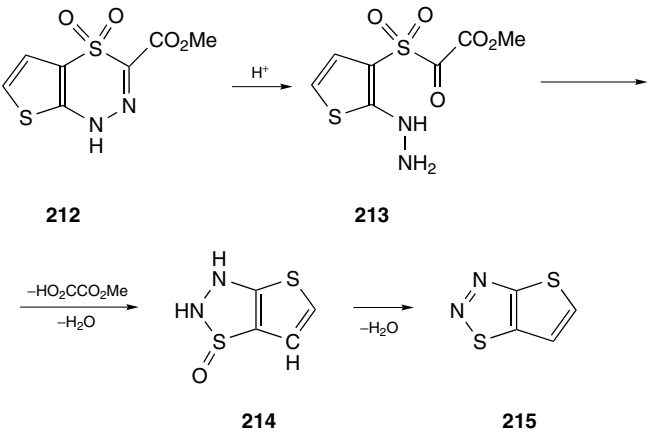


208 **209** **210** **211**

R = H, Alk

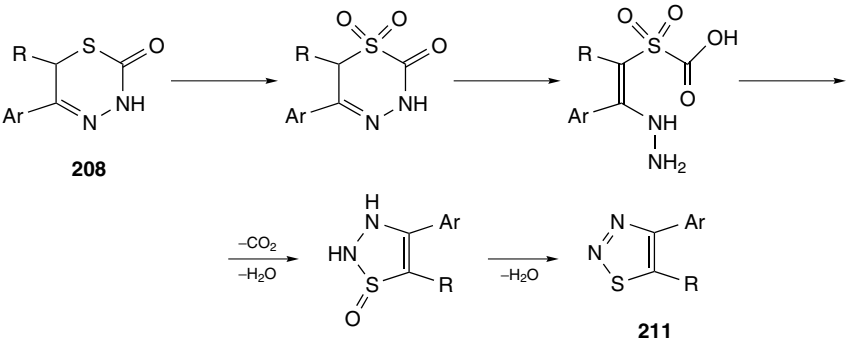
Stephens and Sowell expanded the scope of this reaction to prepare thienothiadiazole **215**.[105] They have found that when a suspension of thienothiadiazine dioxide **212** in a solution of acetic and aqueous sulfuric acid was heated to 100°, thienothiadiazole **215** was obtained in moderate yield.

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

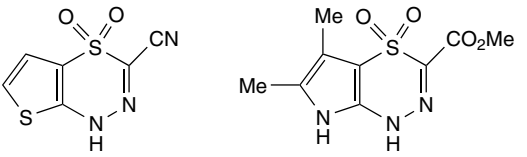


allows to prepare **215** in one pot, instead of the seven-step synthesis based on the Hurd–Mori reaction.[7]

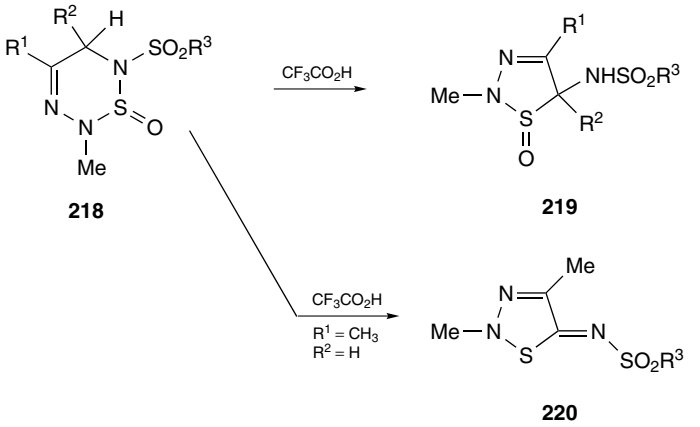
In the light of this work, the mechanism for the transformation of **208** could be reconsidered as including the oxidation of **208** as the first step to afford thiadiazine dioxide **216** which, similar to **213**, undergoes hydrolysis of the imine double bond. Subsequent loss of carbon dioxide and 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]

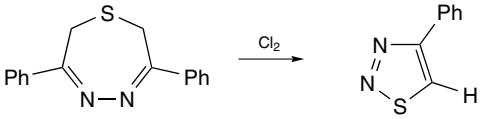


Sommer and Schubert have found that 5,6-dihydro-2H-1,2,3,6-thiatriazine 1-oxides **218** rearrange in the presence of trifluoroacetic acid to give Δ^3-1,2,3-thiadiazoline-1-oxides **219** including fused derivatives in which substituents R^2 and R^3 form a cyclohexyl ring. In a similar reaction of unsubstituted 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**

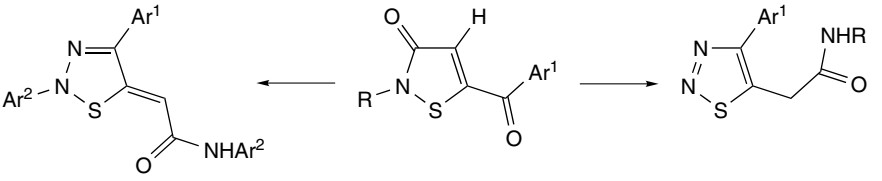
It has been shown that on treatment with chlorine, 2,7-dihydro-3,6-diphenyl-1,4,5-thiadiazepine **221** transforms to 4-phenyl-1,2,3-thiadiazole **222**.[5] The mechanism and scope of this reaction are unclear.



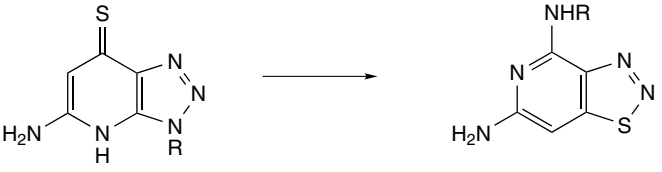
221 **222**

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]

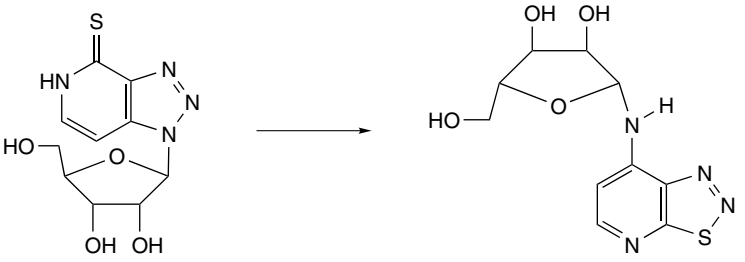
1,2,3-Thiadiazoles can also be prepared by transformation of 1,2,3-triazoles containing a thiocarbonyl group. Thus, in neutral solvents or simply by melting, 1,2,3-triazolo[4,5-*b*]pyridin-4(7*H*)-thiones **226** rearrange to 1,2,3-thiadiazolo[4,5-*c*]pyridines **227**.[5,108–110] It is interesting to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



223 **224** **225**



226 **227**



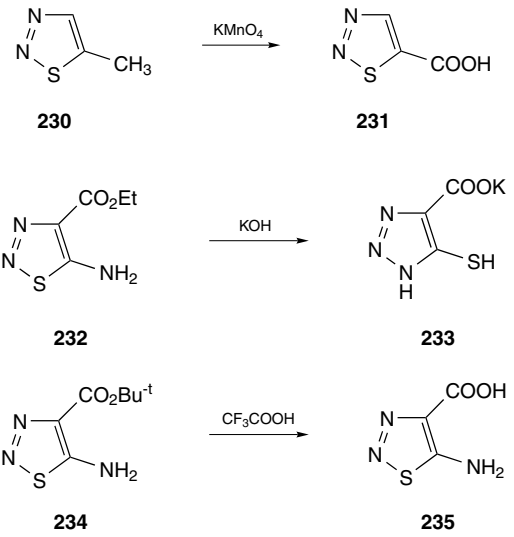
228 **229**

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

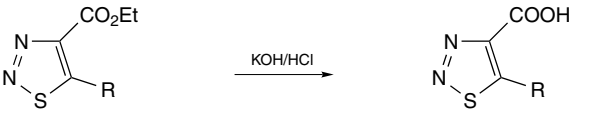
Oxidation of 5-methyl-1,2,3-thiadiazole **230** by potassium permanganate at 100°C in water affords 1,2,3-thiadiazole-5-carboxylic acid **231** in 51% yield.[21] 1,2,3-Thiadiazole-5-carboxylic acid can also be prepared by potassium permanganate oxidation of 5-furyl-1,2,3-thiadiazole-4-carboxylic acid, 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**

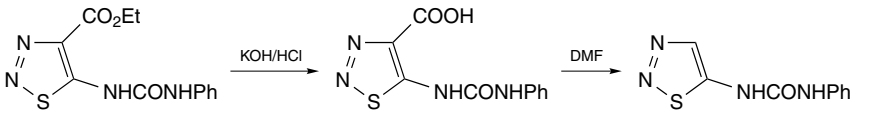
Because of the possibility of a Dimroth rearrangement, the saponification of esters of 5-amino-1,2,3-thiadiazole-4-carboxylic acid in basic solution can be accompanied by the formation of 5-mercapto-1,2,3-triazoles **233**.[112]

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**

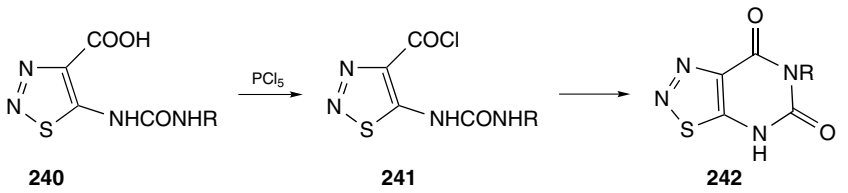
It is interesting to note that saponification of ester **238** with subsequent decarboxylation of primary formed acid **239** was used on an industrial scale to produce urea **63**,[5], which is the main component of the very soft and active cotton defoliant Thidazuron™.



238 **239** **63**

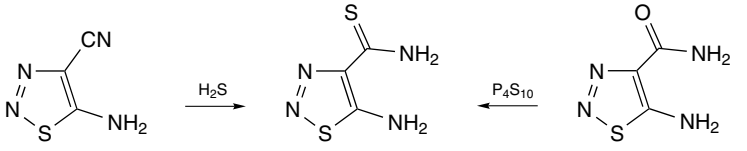
1.5.2. Functional Derivatives of Carboxylic Acids

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**.



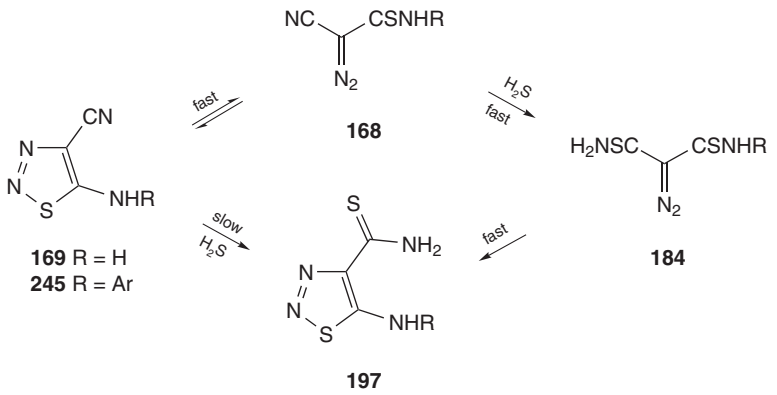
240 **241** **242**

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]



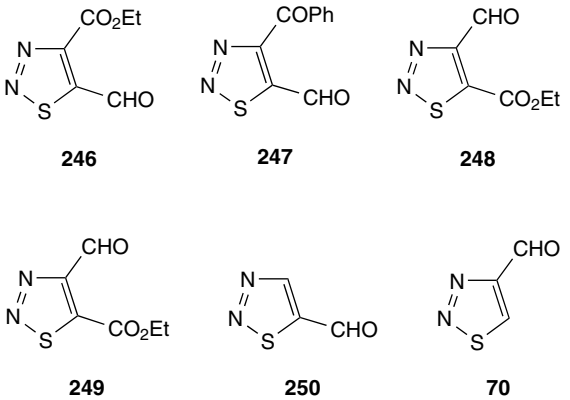
169 **243** **244**

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).



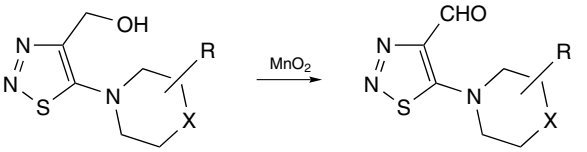
1.5.3. Aldehydes

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]

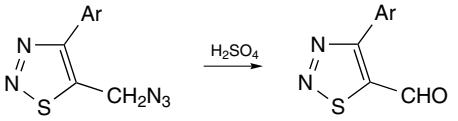


Recently, we prepared a series of 5-cycloalkylamino-1,2,3-thiadiazole-4-carbaldehydes **252** by the smooth oxidation of the corresponding carbinols **251** with active MnO_2. These compounds were shown to be good building blocks to prepare a number of new 1,2,3-thiadiazoles and 1,2,3-triazoles for biological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

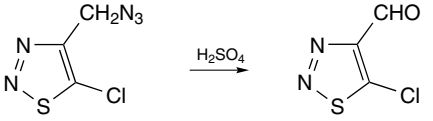
4-Aryl-1,2,3-thiadiazole-5-carbaldehydes **254** and 5-chloro-1,2,3-thiadiazole-4-carbaldehyde **256** were synthesized by the decomposition of the corresponding azidomethyl-1,2,3-thiadiazoles **253** and **255** in concentrated sulfuric acid.[120,121]



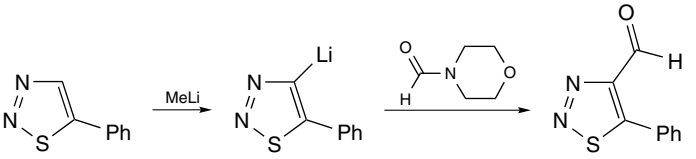
251 **252**



253 **254**



255 **256**



257 **258** **259**

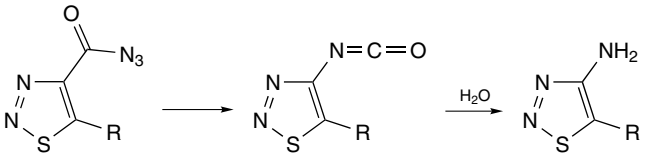
We have found that 5-phenyl-1,2,3-thiadiazole-4-carbaldehyde **259** is formed from 5-phenyl-1,2,3-thiadiazole **257** by the treatment of its 4-lithio derivative **258** with *N*-formylmorpholine in tetrahydrofuran at −70°C.[122]

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]

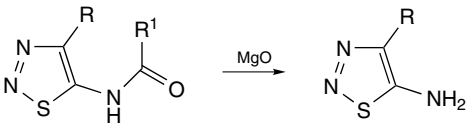
4-Amino-1,2,3-thiadiazole **262** could be prepared by Curtius rearrangement of the corresponding 1,2,3-thiadiazole-4-carbonyl azides **260** followed by the hydrolysis of the intermediate **261**.

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



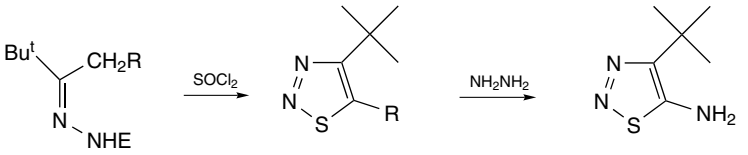
260 **261** **262**

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**

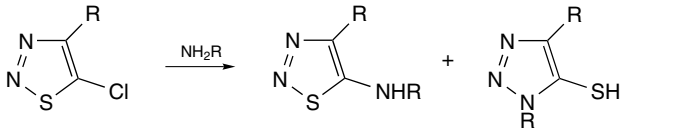
As a part of our program to synthesize thiapentalenes, the 4-*tert*-butyl-5-amino-1,2,3-thiadiazole **267** was obtained, starting from chloropinacolone, which is first converted into hydrazone **265** by successive treatment with potassium phthalimide and then by ethyl carbazate. The latter was transformed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

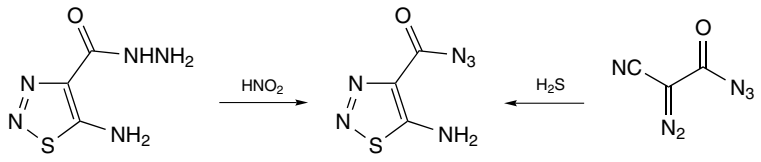
5-Amino-1,2,3-thiadiazole and 5-arylamino-1,2,3-thiadiazoles were prepared in good yield by the nucleophilic substitution of 5-chloro-1,2,3-thiadiazoles by liquid ammonia or anilines, respectively.[101,123] It has been shown that the reaction of the 5-chloro-1,2,3-thiadiazoles with aliphatic amines and 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]

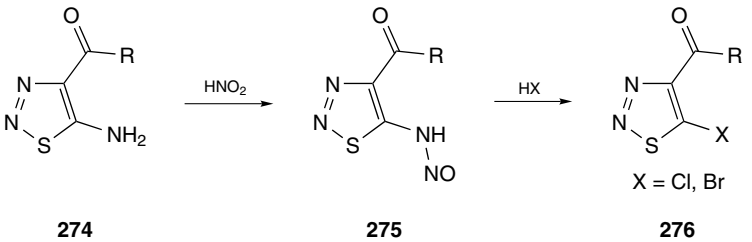
1,2,3-Thiadiazole **272** bearing both an amino and a carboxazide group was prepared by the treatment of 5-amino-1,2,3-thiadiazole-4-carbohydrazide **271** with HNO_2. This compound was also prepared by the reaction of diazonitrile carbonylazide **273** with hydrogen sulfide. We draw attention to the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

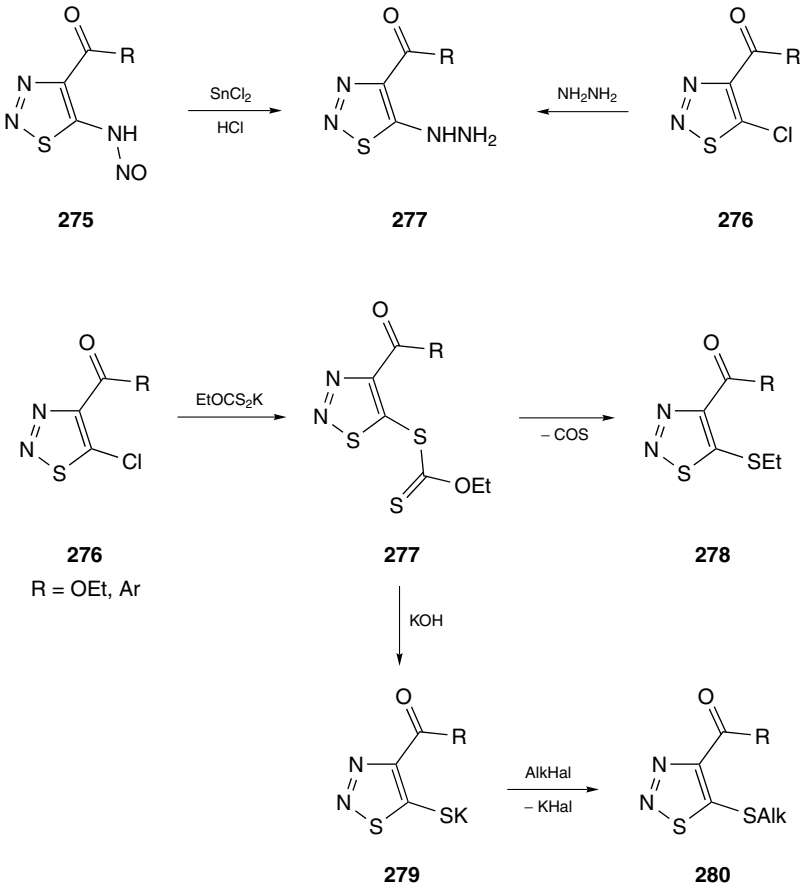
Similar to many other heterocyclic amines, 5-amino-1,2,3-thiadiazoles form isolable 5-nitrosylamino-1,2,3-thiadiazoles **275** by reaction with sodium nitrite in hydrochloric acid. Treatment of the latter with concentrated hydrochloric or hydrobromic acid affords 5-chloro- or 5-bromo-1,2,3-thiadiazoles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

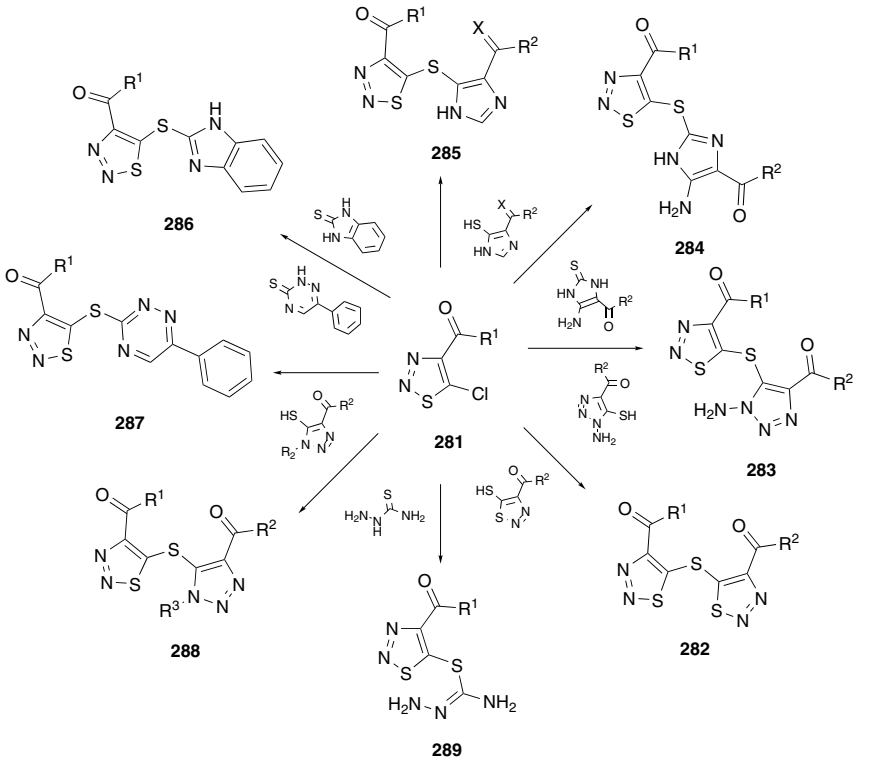


5-Chloro-1,2,3-thiadiazoles **276**, bearing electron withdrawing-acyl and ester groups at the 4-position are also able to react with potassium ethyl xanthate to afford 5 − *S*-dithiocarbonates **277**. These compounds **277** were shown to be very

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]



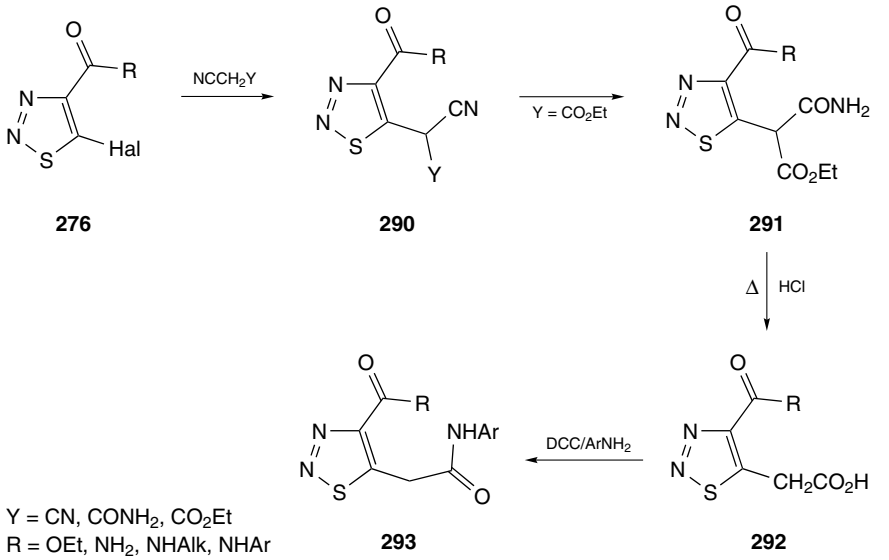
R^1 = OEt , NH_2 , NHMe , NHAr; R^2 = OEt, NH_2, NHMe ; R^3 = H, CH_2Ph ,Me ;
X = O,S

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**

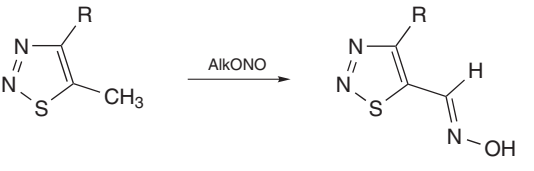
The Pechmann synthesis allows one to prepare ethyl 2-(1,2,3-thiadiazol-5-yl)acetate in 10% yield only.[5]

1.5.8. Alkenyl-1,2,3-Thiadiazoles

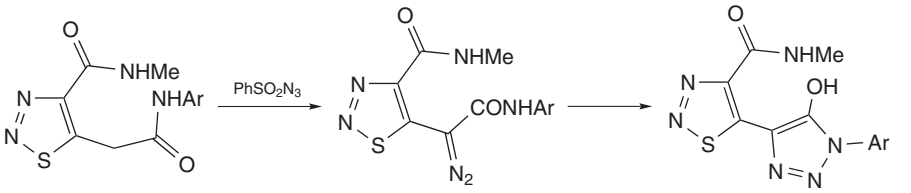
The reaction of either 5-ethyl- or 4-ethyl-1,2,3-thiadiazoles with *N*-bromosuccinimide, followed by treatment with a base, leads to the corresponding alkenyl-1,2,3-thiadiazoles.[128–131] These compounds were subjected to cycloaddition and polymerization reactions.

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**

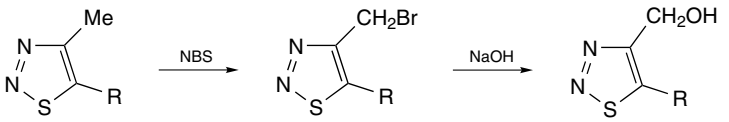


296 **297** **298**

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

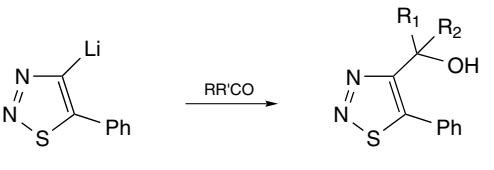
A series of 4-hydroxymethyl-1,2,3-thiadiazoles **301** were obtained by a two-step synthesis from 4-methylthiadiazoles **299** by bromination with *N*-bromosuccinimide, followed by alkaline hydrolysis.[17]



299 **300** **301**

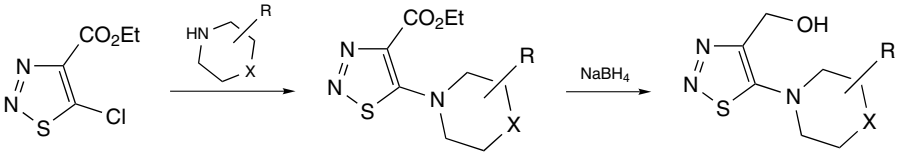
R = CO_2Et

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.

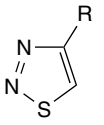


276 **303** **251**

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

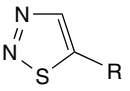


R	Yield (%)	mp (°C)	Other Data	Method	Reference
4-Biphenyl	95	—	NMR, MS	A	8
2-Bromophenyl	100	—	NMR, MS	A	8
3-Bromophenyl	100	—	NMR, MS	A	8
4-Bromophenyl	96	—	NMR, MS	A	8
n-Butyl	20	51–54	—	A	41
Buta-1,3-dien-1-yl	52	—	NMR	A	131
4-Chlorophenyl	91	136–137	NMR, MS	A	44
3-Cyanomethylcyclobutyl	60	Oil	NMR, 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*)

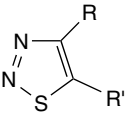
R	Yield (%)	mp (°C)	Other Data	Method	Reference
4-Methylphenyl	51	74–76	NMR, MS	A	44
Penta-1-yn-3-en-1-yl	37	70	NMR	A	131
Phenyl	64	77–78	—	A	10
Phenyl	77	75–77	NMR, MS	A	44
1-Propen-1-yl	8	—	NMR	E	128
n-Propyl	21	30–33	MS	A	41
i-Propyl	87	54–55	NMR	A	16
Triphenylphosphoniummethyl	62	245–250	NMR	A	131
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

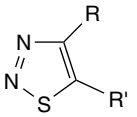


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Aminophenyl	4-Aminophenyl	95	236	NMR, MS	A	44
Benzyl	Phenyl	12	—	NMR, MS	E	134
4-Chlorophenyl	Azidomethyl	67	160	NMR	E	120
4-Chlorophenyl	Bromomethyl	42	140	NMR	E	120
4-Chlorophenyl	Dibromomethyl	21	147	NMR	E	120
4-Chlorophenyl	Methyl	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*)

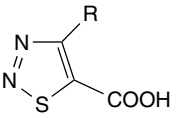
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Phenyl	Bromomethyl	47	101	NMR	E	120
Phenyl	4-Fluorophenyl	87	84	NMR	A	12
Phenyl	2-Methoxyphenyl	89	126	NMR	A	13
Phenyl	4-Methoxyphenyl	82	56.5–58	NMR, MS	A	44
Phenyl	2-Naphthyloxy	11	—	NMR	E	51
Phenyl	Phenoxy	45	101–102	NMR	E	51
Phenyl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



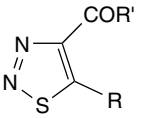
R	Yield (%)	mp (°C)	Other Data	Method	Reference
Amino	—	250	—	E	112
Carboxy	—	98	—	E	2
Carboxymethyl	56	192	NMR	E	133
H	33	227–228	—	A	10
H	—	228	—	E	2
Methyl	—	113	—	E	2
Phenoxymethyl	93	171–172	—	E	110
Phenyl	—	157	—	E	2
Phenyl	45	140–145	NMR, MS	E	134
Phenylcarbonyl	65	248	—	E	112
Phenylsulfonamido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

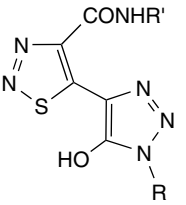


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Amino	*N*-Bromoamino	85	117	NMR, MS	C	94
Amino	Phenylamino	83	124	NMR, MS	C	94
4-Aminophenyl-sulfonamido	Ethoxy	81	—	__	E	112
Benzylamino	Methylamino	98	139	NMR	E	124
Bromo	Amino	—	156	NMR	E	124
Bromo	Methylamino	65	156	NMR	E	124
1-Bromo-1-phenoxymethyl	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*)

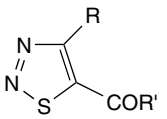
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
H	Chloro	95	52–54	—	E	21
H	Diethylamino	68	85–89	—	E	21
H	Ethoxy	20	86–86.5	—	A	10
H	Ethoxy	48	87–88	—	E	21
H	Ethoxy	59	88–90	—	E	110
H	H	62	86–87	—	A	18
H	Hydrazino	74	214	—	E	21
H	Hydrazino	93	210	—	E	110
H	Methoxy	55	89–90	—	E	21
H	Phenylamino	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



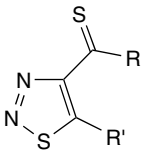
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Amidino	Phenyl	90	222–223	MS	E	136
1,3-Butadien-1-yl	Ethoxy	13	40–47	NMR	A	131

(*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

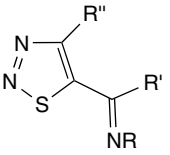


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Amino	Amino	34	171–172	NMR, MS	C	93
Amino	Amino	98	171–172	NMR, MS	E	93
Amino	Acetylamino	77	156	NMR, MS	E	93
Amino	Methylcarbamoyl	77	156	NMR, MS	E	93
Amino	2-Pyridylamino	35	235	NMR, MS	C	93
Methylamino	Amino	65	138–140	NMR, MS	C	93
Methylamino	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

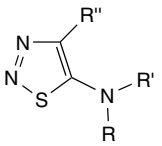


R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Hydroxy	H	Phenyl	49	212	NMR	E	132
Hydroxy	Methyl	H	61	194	NMR, MS	E	117
Hydroxy	Phenyl	H	78	229	NMR, MS	E	117
Methoxy	H	H	58.5	48	NMR	E	132
Phenylamino	H	H	78	184	NMR, MS	E	117
Phenylamino	H	Methoxy	80	141–142	NMR, MS	E	118
Phenylamino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

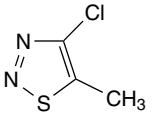
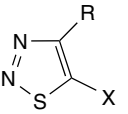
Compound	Yield (%)	mp (°C)	Other Data	Method	Reference
	—	100	—	A	[14]

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



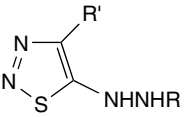
R	X	Yield (%)	Melting Point (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
t-Butyl	Cl	47	62–63	—	A	15
4-Chlorobenzoyl	Cl	35	114	—	B	137
4-Chlorobenzoyl	Cl	13	106–107	—	B	79
H	Cl	—	58–62*	NMR	A	50
H	Br	—	61–64*	—	A	50

(*continued overleaf*)

TABLE 1.15 (*continued*)

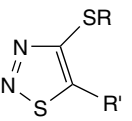
R	X	Yield (%)	Melting Point (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
Methyl	Cl	80	182–183	—	A	14
4-Methylbenzoyl	Cl	30	97	—	B	137
4-Methylbenzoyl	Cl	52	56–58	—	B	79
3-Nitrobenzoyl	Cl	35	124	—	B	137
4-Nitrobenzoyl	Cl	60	113	—	B	137

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

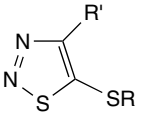


R	R′	Yield (%)	mp (°C)	Other Data	Method	Ref.
1	2	3	4	5	6	7
2-Cyanoethyl	Phenyl	66	—	—	A	20
2-(Ethoxycarbonyl)ethyl	*t*-Butyl	60	Oil	—	A	20
2-(Methoxycarbonyl)ethyl	*t*-Butyl	67	Oil	—	A	20
2-(Ethoxycarbonyl)ethyl	4-*t*-Butylphenyl	83	Oil	—	A	20

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*)

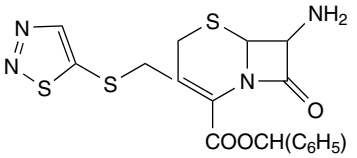
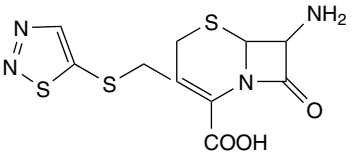
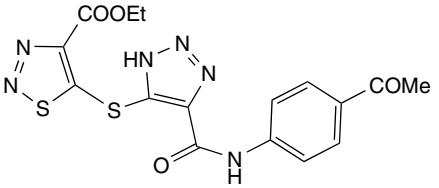
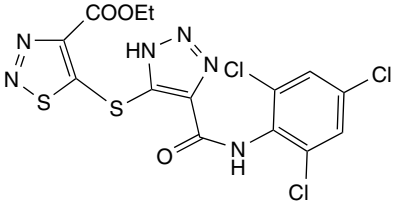
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
Sodium	H	84	—	NMR	C	103
Sodium	H	66	265–267	NMR	C	104
Thienyl	4-Methylphenyl	—	—	NMR	E	51
4-Carbamoylimidazol-5-yl	Carbamoyl	25	285–290	NMR	E	126
4-Thiocarbamoyl-imidazol-5-yl	Carbamoyl	30	250–253	NMR	E	126
		70	—	NMR	E	115
		68	—	NMR	E	115
		72	291–293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

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

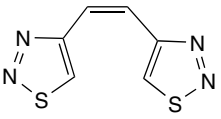
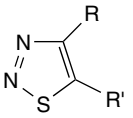
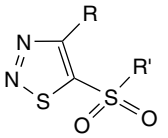
Compound	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6
	32	76	NMR, MS	E	24

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

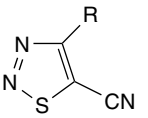


R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Bromophenyl	4-Chlorophenyl	77	108–110	—	A	46
4-Bromophenyl	4-Methylphenyl	70	100–102	—	A	46
4-Bromophenyl	2-(4-Methylphenyl)-1-ethen-1-yl	65	110–111	NMR	A	45
4-Bromophenyl	2-(4-Methylphenyl)cyclopropan-1-yl	60	144–145	NMR	E	45
4-Bromophenyl	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*)

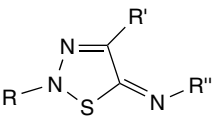
R	R′	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
4-Nitrophenyl	2-(4-Methylphenyl)-1-ethen-1-yl	70	174–175	NMR	E	45
4-Nitrophenyl	4-(4-Methylphenyl)pyrazolin-5-yl	65	271–273	—	A	45
4-Nitrophenyl	Phenyl	79	102–104	—	A	46
Phenyl	4-Chlorophenyl	76	106–108	—	A	46
Phenyl	4-Methylphenyl	78	106–108	—	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

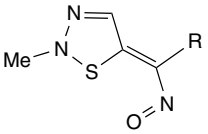
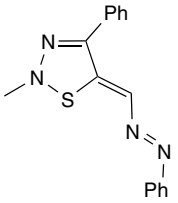
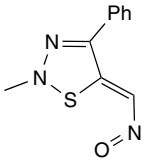
TABLE 1.23. 2-SUBSTITUTED 1,2,3-THIADIAZOLES

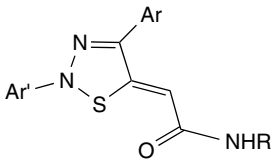


R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Benzoyl	H	Phenoxy-carbonyl	80	193	—	E	112
4-Chlorophenyl	Phenyl	Methyl	86	118	NMR	C	96
H	Benzotriazolyl carbonyl	Acetyl	72	169	—	A	51
Methyl	Phenyl	Methyl	76	—	NMR	C	96
4-Methoxyphenyl	Benzoyl	Acetyl	50–80	119–121	NMR	E	95

(*continued overleaf*)

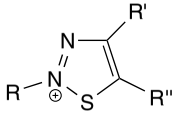
TABLE 1.23 (*continued*)

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*)

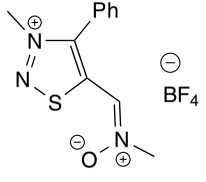
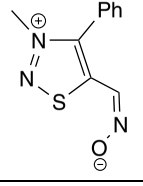
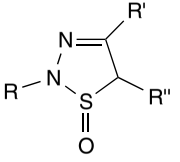
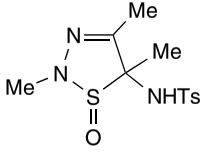
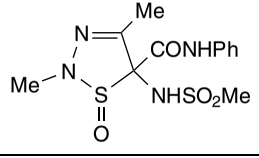
R	R′	R″	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7	8
Phenyl	Ethoxycarbonyl	Acetylimino	50–80	112–113	—	C	95
Phenyl	Ethoxycarbonyl	Amino	75	227–229	—	C	95
Phenyl	H	Ethoxy	97	71–72	NMR, MS	E	22
Phenyl	H	Dicyanomethide	39	255–258	NMR, MS	E	22
Phenyl	H	Methylamino	57	122–124	NMR, MS	E	22
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

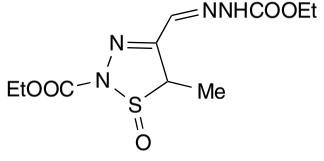
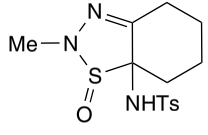
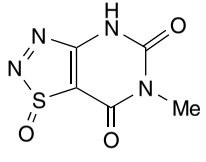
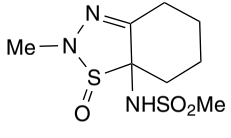
TABLE 1.25. 1,2,3-THIADIAZOLE-1-OXIDES



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

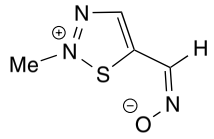
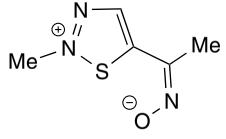
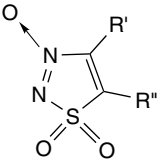
	25	192	NMR, MS	E	117
	41	240	NMR, MS	E	117

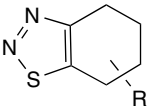
TABLE 1.26. 1,2,3-THIADIAZOLE-1,1,3-TRIOXIDES



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



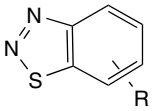
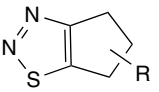
R	Yield (%)	mp (°C)	Other Data	Method	Reference
5,7-Di(4-chlorophenyl)-6,6-diethoxycarbonyl	78	156–157	NMR	A	68
5,7-Di(4-chlorophenyl)-6-oxo	—	169–170	NMR	A	58
5,7-Di(4-methoxyphenyl)-6,6-diethoxycarbonyl	79	168–169	NMR	A	68
5,7-Di(4-methoxyphenyl)-6-oxo	—	174–176	NMR	A	58
6,6-Dimethyl-7-oxo	61	45–46	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

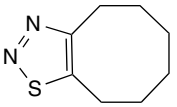
TABLE 1.27 (*continued*)

B. Thiadiazoles fused with five-membered carbocycles

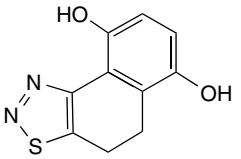
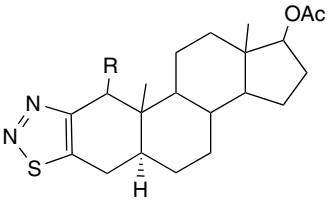


R	Yield (%)	mp (°C)	Other Data	Method	Reference
H	22	42–46	NMR	A	12
H	34	60–62	—	A	12
4,4,5,6-Tetrachloro	—	94–96	NMR, MS, X-ray	A	33

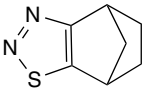
C. Thiadiazoles fused with seven-membered or higher carbocycles

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

D. Thiadiazoles fused with bicyclic or higher carbocycles

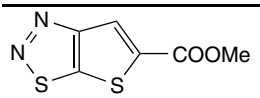
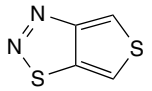
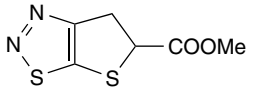
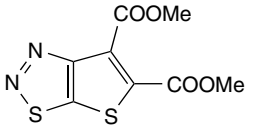
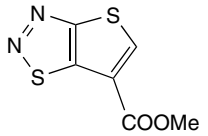
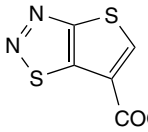
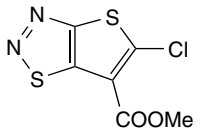
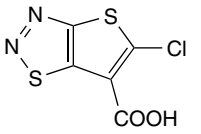
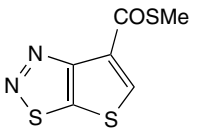
R	Yield (%)	mp (°C)	Other Data	Method	Reference
	47	53–55	NMR, MS	A	48
					
Chloro	5	189–189.5	NMR, MS, X-ray	A	27
H	85	147–149	NMR, MS, X-ray	A	27
Oxo	—	222–224	NMR, MS, X-ray	A	27
Sulfonyl	84	260–262	NMR, MS, X-ray	A	27

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

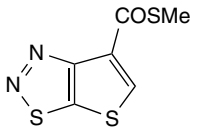
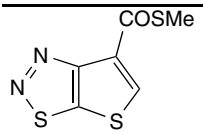
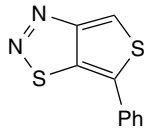
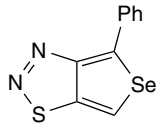
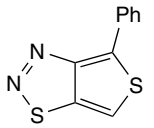
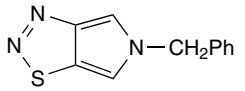
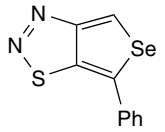
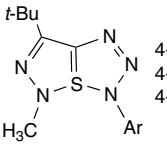
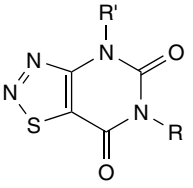
1	2	3	4	5	6
	65	—	NMR	A	71

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*)

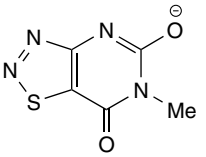
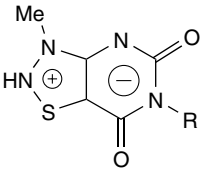
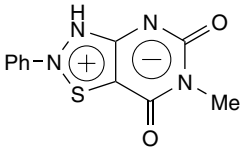
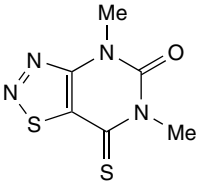
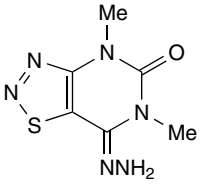
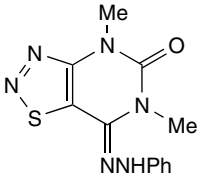
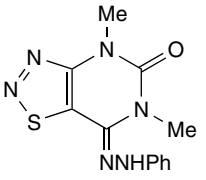
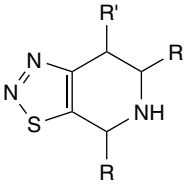
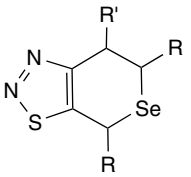
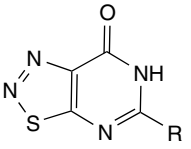
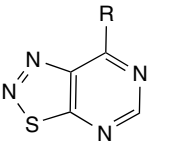
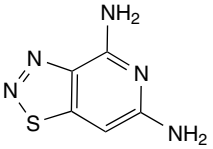
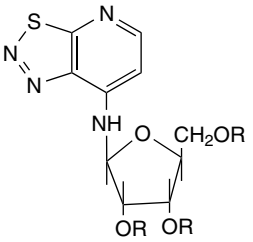
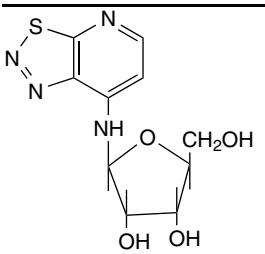
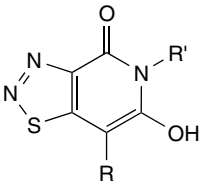
1	2	3	4	5	6	7	8
			70–76	201–203	MS	A	31
	Methyl		67–71	192–193	MS	A	32
	n-Butyl		58	148–149	MS	A	32
	n-Propyl		53	154–155	MS	A	32
			90	294–295	MS	A	32
			85	159–160	MS	E	32
			82	229–230	MS	E	32
			84	135–136	MS	E	32
			81	172–173	MS	E	32

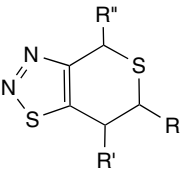
TABLE 1.27 (*continued*)

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-Metho-xyphenyl	50	—	NMR	E	127
	Ethoxycarbonyl	4-Chlo-rophenyl	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

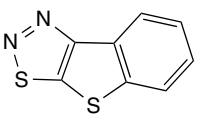
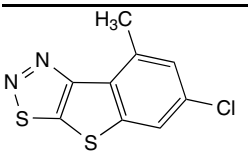
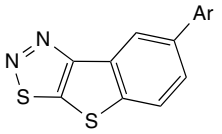
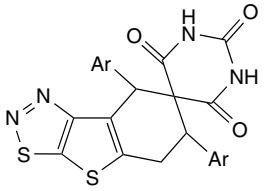
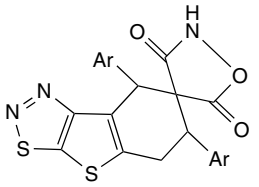
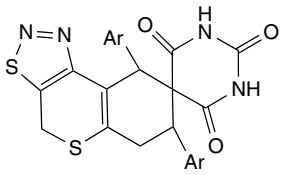
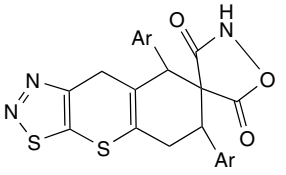
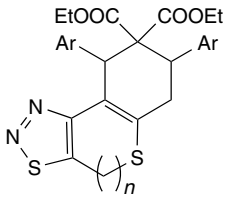
Compounds	R or Ar	Yield (%)	mp (°C)	Other Data	Method	Reference
1	2	3	4	5	6	7
		51	90	NMR, MS	A	12

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*)

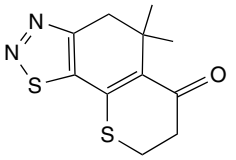
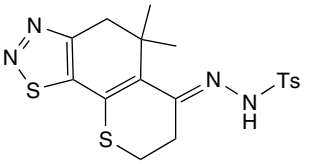
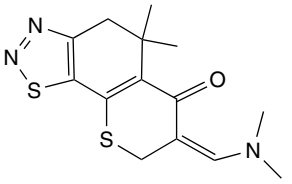
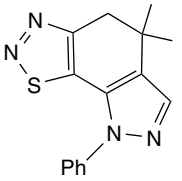
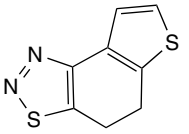
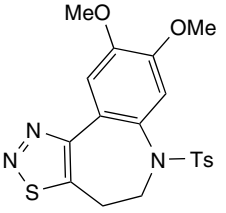
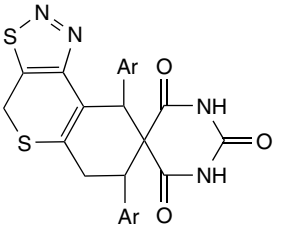
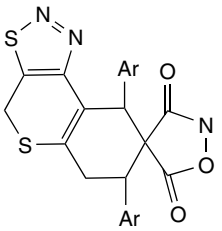
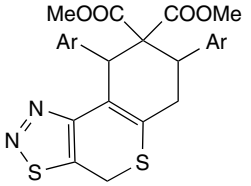
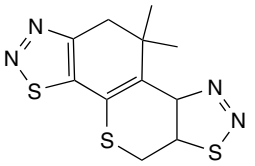
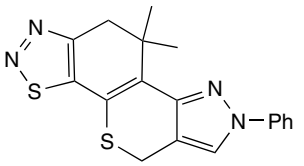
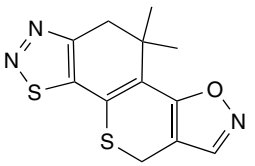
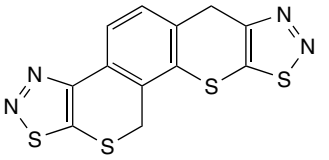
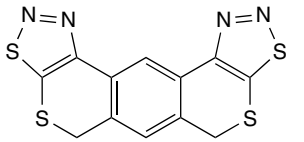
1	2	3	4	5	6	7
		40	148–149	NMR	A	52
		90	181–182	NMR	A	52
		86	163–164	NMR	E	53
		72	179–180	NMR	A	54
		40	98–99	NMR	A	54
		60	134–135	MS	A	56
	Phenyl	59	202–203	NMR	A	66
	4-Methoxyphenyl	55	212–213	NMR	A	66

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*)

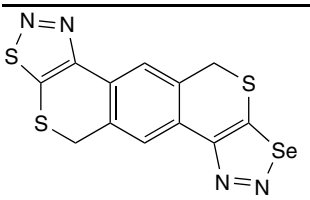
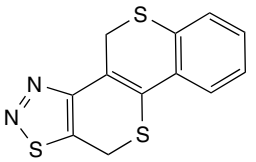
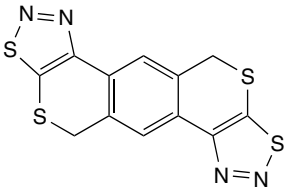
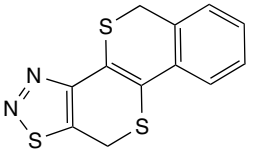
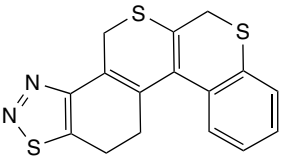
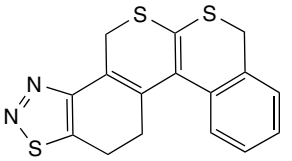
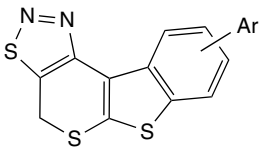
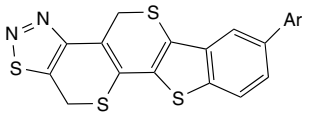
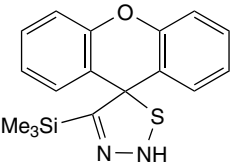
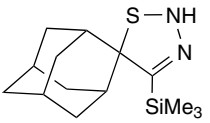
		74	147–149	NMR	A	59
		70	142–144	NMR	A	59
		65	101–102	NMR	A	61
1	2	3	4	5	6	7
		68	114–115	NMR	A	61
		60	112–113	NMR	A	61
		64	107–108	NMR	A	61
	H	59	137–138	NMR	A	65
	Methyl	64	142–143	NMR	A	65
	Chloro	66	140–141	NMR	A	65

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

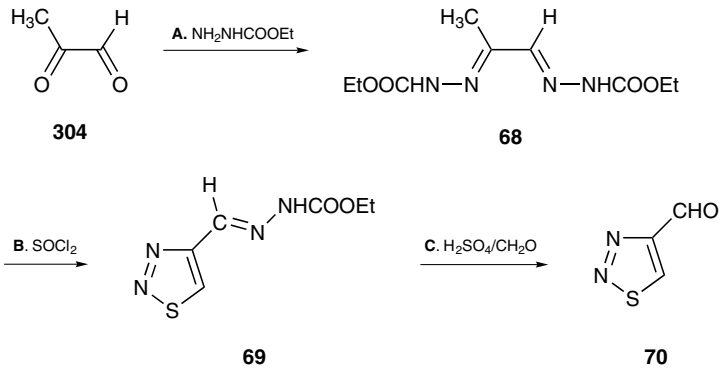
H. Spiro Thiadiazoles

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]



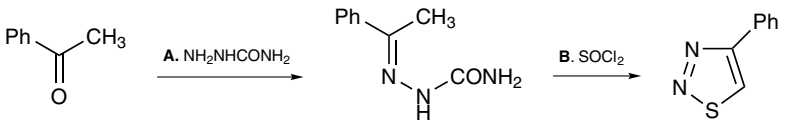
Step A

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

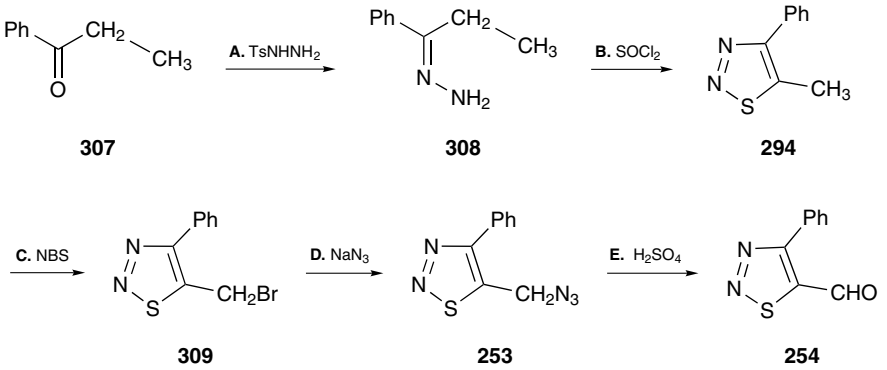
Semicarbazide hydrochloride (67 g, 0.6 mol), together with sodium acetate (67 g, 0.8 mol) in ethanol (500 ml) was heated at reflux. The precipitated sodium chloride was filtered from the hot solution and acetophenone **305** (60 g, 0.5 mol) was added. The mixture was heated at reflux for a further 2 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]



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

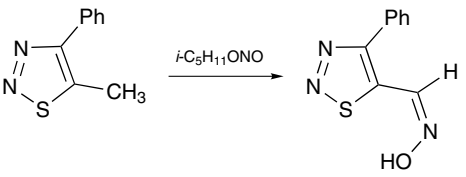
The bromide **309** (10 mmol) was stirred with 4 equiv of sodium azide in a two-phase system of dichloromethane (30 ml) and water (10 ml) at room temperature.

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.

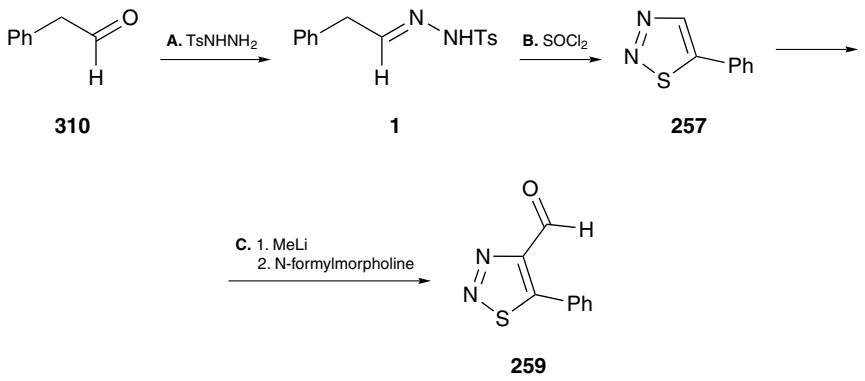
1.7.5. 5-Phenyl-1,2,3-Thiadiazole-4-Carbaldehyde[12,120]

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



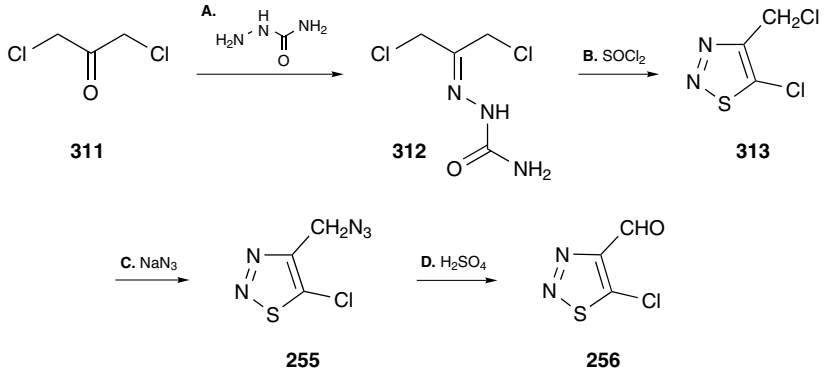
310 **1** **257** **259**

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

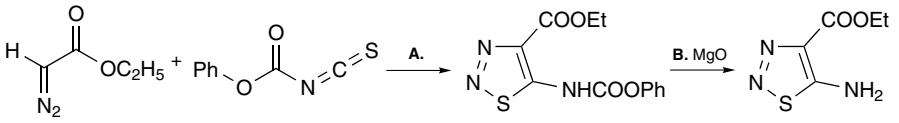
The 4-chloromethyl-5-chloro-1,2,3-thiadiazole **313** (8.2 g, 48.5 mmol) was dissolved in dichloromethane (100 ml) and treated with a solution of sodium azide (11.86 g, 0.182 mol) in water (40 ml), tetrabutylammonium bromide (1.4 g) and sodium iodide (100 mg). The reaction mixture was stirred overnight 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**

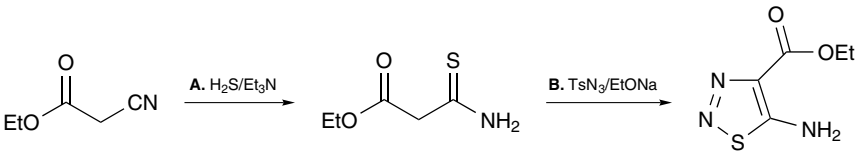
Step A

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

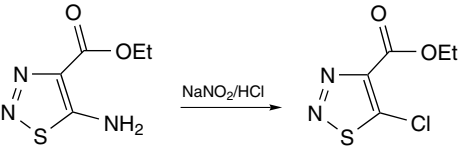
The mixture of anhydrous ethanol (150 ml) and triethylamine (100 ml) was cooled to −15–20°C, and hydrogen sulfide, dried over $CaCl_2$, was bubbled through the solution until the added weight was 15 g. After that, the solution containing triethylammonium hydrogen sulfide was moved into an autoclave, 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.

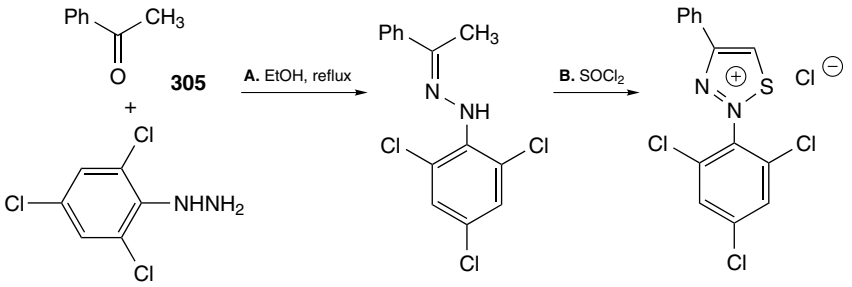
1.7.8. Ethyl 5-chloro-1,2,3-Thiadiazole-4-Carboxylate



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

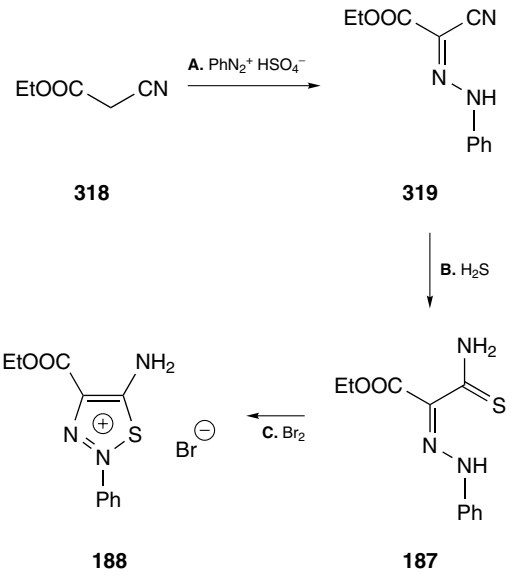
Acetophenone **305** (6 g, 50 mmol) and 2,4,6-trichlorophenylhydrazine **316** (10.5 g, 50 mmol) were dissolved in ethanol (50 ml) and one drop of acetic acid was added.

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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