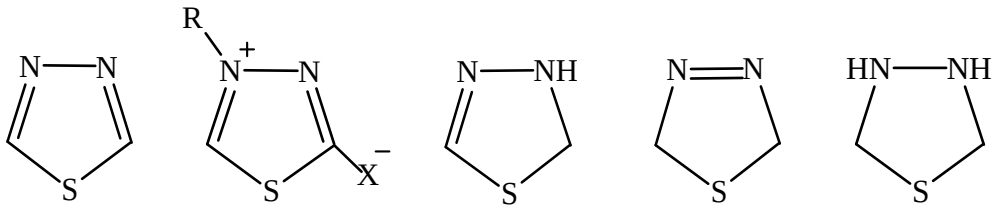
INTRODUCTION

1,3,4-Thiadiazole and its derivatives continue to be of a great interest to a large number of researchers owing to their great pharmaceutical and industrial importance and it is surprising that the synthetic publication far outweigh in numbers those relating to all other fields.

1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Busch and his coworkers .The advent of sulfur drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in this field [73].

1,3,4-Thiadiazoles were conveniently divided into three subclasses:

a) Aromatic systems which include the neutral thiadiazole **1** and constitute a major part of this review.
b) Mesoionic systems **2** which is defined as five-membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring [74].
c) Non aromatic systems such as the 1,3,4-thiadiazolines **3**, **4** and the tetrahydo 1,3,4-thiadiazolidines **5**.



1 **2** **3** **4** **5**

Synthesis of 1,3,4-thiadiazole derivatives

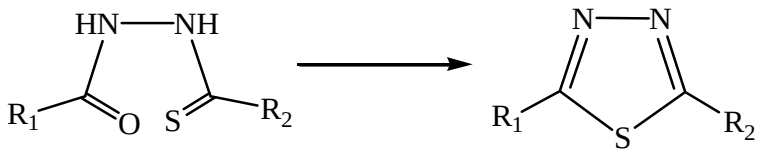
The synthetic procedures of 1,3,4-thiadiazoles could be classified by the number of ring atoms contributed by each component and by the number and types of bond generated in the last reaction step. This is in addition to the synthesis of 1,3,4-thiadiazoles through ring transformation [75].

Synthesis of 1,3,4-thiadiazole via formation of one bond

Fragment S—C—N—N—C: Cyclizations

(i) From monothiodiacylhydrazines:

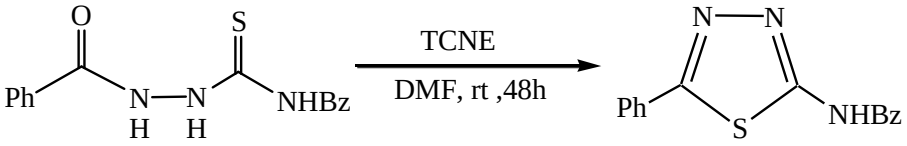
Monothiodiacylhydrazines **6a-c** (prepared from the acylation of thiosemicarbazides or as intermediates in the reactions of thiohydrazides with carboxylic acids and their derivatives) was cyclized through dehydration with sulfuric, polyphosphoric (PPA) or methanesulfonic acids to give 1,3,4-thiadiazoles **7a-c** [76-78]. It is worthy to mention that the use of microwave irradiation [79-81] for the acid-catalyzed cyclizations can increase product yields and reduce reaction times.



6 a -c **7a-c**

	R^1	R^2
a	Ph	PhNH
b	Pyrid-4-yl	EtNH
c	4-Bromo-benzamide	$PhOCH_2$

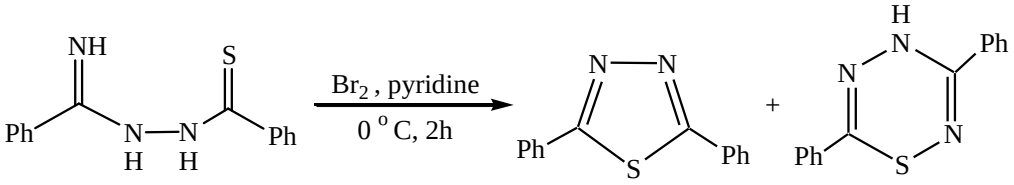
Also, oxidative thermal base-catalyzed cyclization of thiosemicarb-azido arylates **8** in the presence of tetracyanoethylene (TCNE) produce 1,3,4-thiadiazole **9** [82].



8 **9**

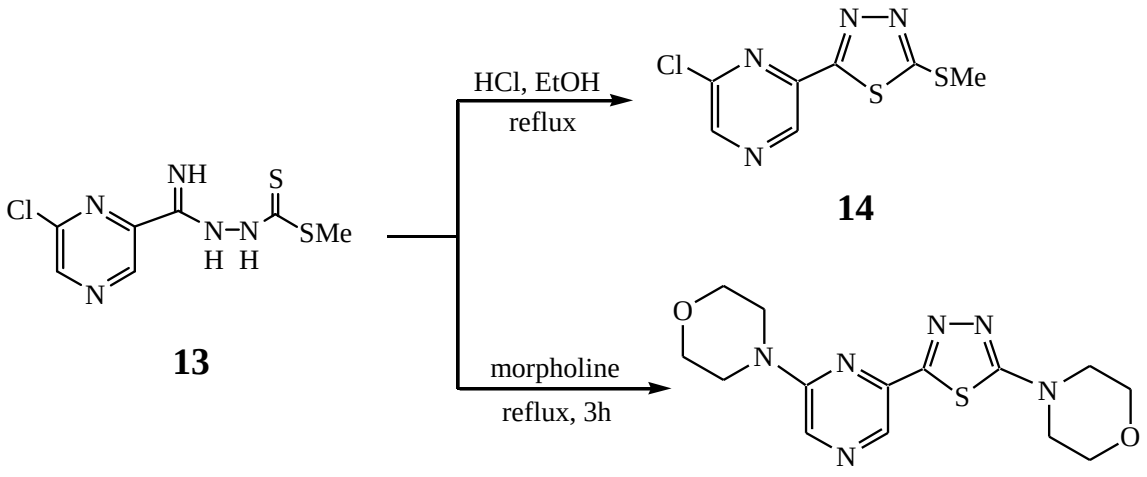
(ii) From *N*'-imidoylthiohydrazide:

The cyclization of *N*'-imidoylthiohydrazide **10** with bromine in the presence of pyridine gave 2,5-diphenyl-1,3,4- thiadiazole **11** along with the 3,6-diphenyl-4*H*-1,2,4,5-thiatriazine **12** in a 13:5 ratio and the yield was enhanced through the treatment with oxidants such as *N*-chlorosuccinamide (NCS) or I_2 /pyridine [83].



10 **11** **12**

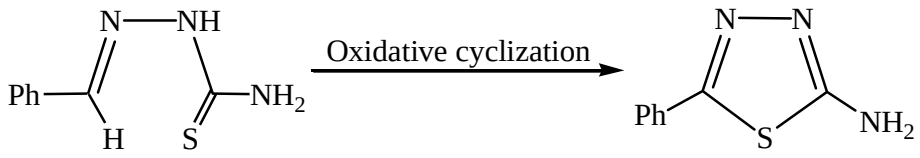
Also, *N*'-Imidoylthiohydrazide **13** was cyclized to 1,3,4-thiadiazole **14** on treatment [84] with HCl (gave the amino-substituted thiadiazole **15** directly on prolonged heating in cyclic secondary amine).



13 **14** **15**

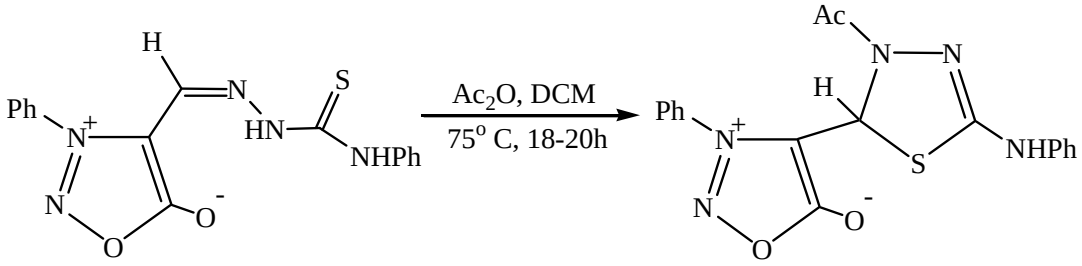
(iii) From thioacylhydrazone:

Oxidative cyclization of thioacylhydrazone **16** by common oxidants include bromine [85], ferric chloride [86, 87], ammonium ferric sulfate [88], or potassium permanganate [89] provided 2-amino-5-phenyl-1,3,4-thiadiazole **17**.



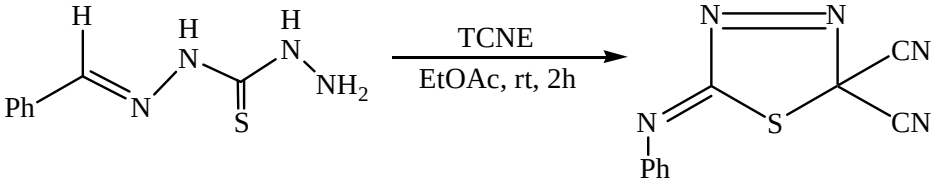
16 **17**

Cyclization of thioacylhydrazone can also be achieved using either Acylating reagents such as acetic anhydride in the presence of dichloromethane (DCM) to afford 1,3,4-thiadiazole derivative; however, in some cases acylation occurred on the ring nitrogen as in compound **18** [90].



18

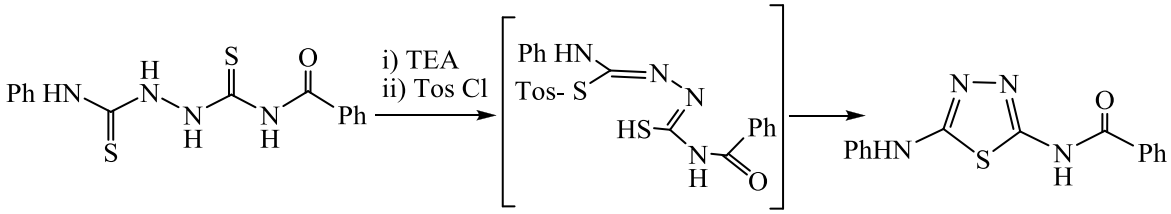
The (TCNE) promoted cyclization of the thioacylhydrazone **19** and gave the phenylimino-5,5-dicyanothiadiazole **20** [91].



19 **20**

(iv) From acylbithioureas:

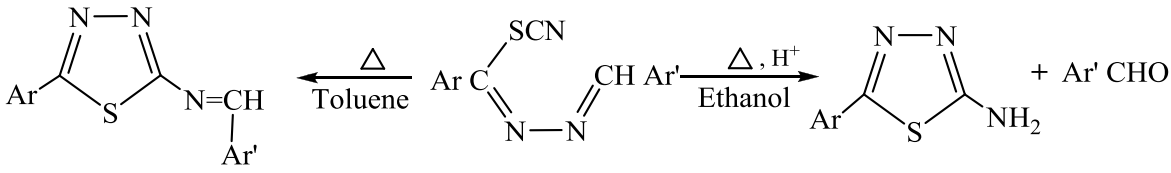
Reaction of acylbithioureas **21** with *p*-tosyl chloride in presence of triethylamine (TEA) provided a 90% yield of the benzoylated thiadiazole **23**, presumably via the intermediate **22** [92].



21 **22** **23**

(v) From hydrazonoyl thiocyanate:

When hydrazonoyl thiocyanates **24a-c** were heated in toluene, they were converted into the thiadiazole derivatives **25a-c**, but on acid hydrolysis in refluxing ethanol it gave aldehyde and the aminothiadiazole derivatives **26a-c** [93].

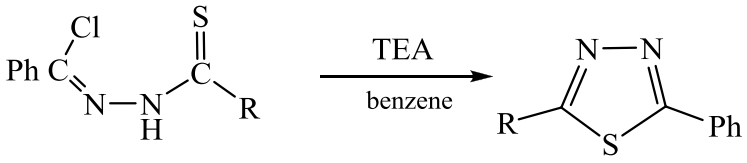


25a-c **24a-c** **26a-c**

	Ar	Ar'
a	4-Cl-C_6H_4	C_6H_5
b	3-Me-C_6H_4	4-OH-C_6H_4
c	4-MeO-C_6H_4	3-NO_2-C_6H_4

(vi) From thioacyl hydrazonoyl chloride:

N-Thiobenzoyl and *N*-thioacetyl hydrazonoyl chlorides **27a,b** gave 1,3,4-thiadiazole derivatives **28a,b** upon treatment with TEA in benzene [94-96].



27a,b **28a,b**

a; R = C_6H_5

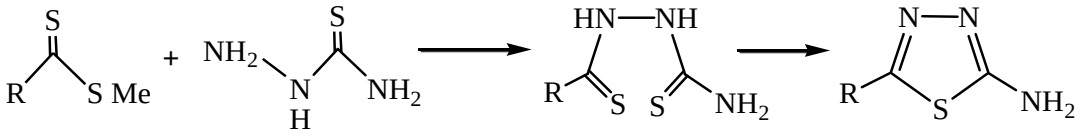
b; R = CH_3

(vii) From thiosemicarbarzide:

The reaction of 4-alkylthiosemicarbazides **29** with trialkyl orthoformate provided an entry into alkylaminothiadiazoles **30** carrying no substituent in the 5-position [97].

29 **30**

The synthesis of numerous thiadiazoles **32a-d** substituted in the 5-position with carbamoyl or heteroaryl moieties and amino groups in the 2-position, was achieved by reacting dithioester **31a-d** with thiosemicarbazide and cyclizing the resulting compound under the usual condition [98].



31a-d **32a-d**

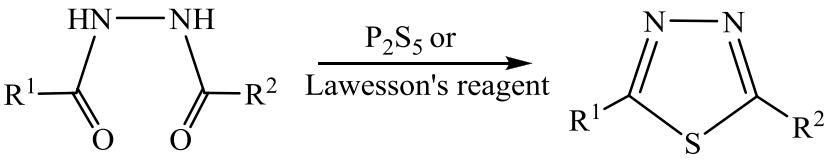
	R
a	Benzoxazol-2-yl
b	Benzimidazol-2-yl
c	Benzthiazol-2-yl
d	Imidazol-2-yl

Recently, 2,5-disubstituted 1,3,4-thiadiazoles have been synthesized in high yield and high purity using an efficient soluble poly(ethyleneglycol) (PEG) polymer support [99]. PEG-bound di(aryloxyacetyl)thiosemicarbazides were refluxed in glacial acetic acid to give the PEG-bound 1,3,4-thiadiazoles which upon purification by precipitation, were cleaved from the support using methoxide in methanol to afford the desired compounds in 76-89% overall yield. Other basic reagents such as sodium hydroxide, ammonia and potassium carbonate were also tested for the cleavage reaction but low yields and some separating problems were encountered.

Synthesis of 1,3,4-thiadiazole via formation of two bonds

Fragments C—N—N—C and S: Diacyl hydrazines with a sulfur source

1,3,4-Thiadiazoles **34a,b** can be prepared from the reaction of diacylhydrazines **33a,b** with a sulfur source. The reaction involves thionation of the carbonyl groups followed by cyclization with loss of H_2S. Phosphorus pentasulfide is commonly used for this cyclization but requires long reaction times and excess reagent, which often leads to low yields and side products [100]. The alternative use of Lawesson's reagent gives higher yields and cleaner reactions [101,102]. This cyclization can also be carried out under microwave and solvent-free conditions to afford 1,3,4-thiadiazoles in high yields and with short reaction times [103,104].



33a,b **34a,b**

	R^1	R^2
a	2-MeO-C_6H_4	C_6H_5
b	4-Br-C_6H_4	n-$C_{13}H_{27}$

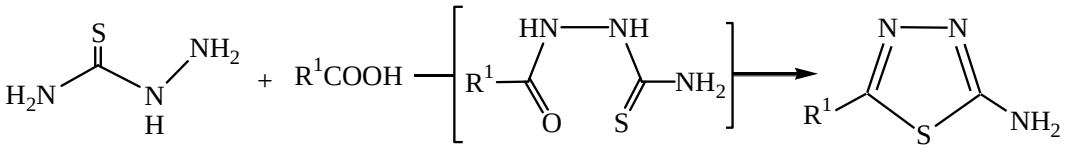
Recently there is a further development, *N*'-Acylbenzohydrazides can be thionated using a fluorous analog of the lawessen reagent to afford 1,3,4-thiadiazoles in high yield by a simple filtration (fluorous solid-phase extraction) [105]. 2,5-Ditolyl-1,3,4-thiadiazole was synthesized in 93% yield by treating the *N*'-acyltolylhydrazide with the fluorous thionated reagents in THF at 55 ^{o}C for 6 h.

Fragments S—C—N—N and C:

Thiohydrazide and/or O-aminothiol derivatives with a carbon source

(i) From Thiohydrazides and carboxylic acid derivatives:

Reaction of thiosemicarbazide with carbon source reagents in the presence of dehydrating agents provides a useful route to 1,3,4-thiadiazoles **36a-d**. The reaction proceeds via the monothiodiacylhydrazines **35**. Carbon source may be aliphatic, aromatic, heterocyclic carboxylic acids, esters or acid chlorides and the dehydrating agents are phosphorus oxychloride [106-108], sulfuric acid [109], and PPA [110].

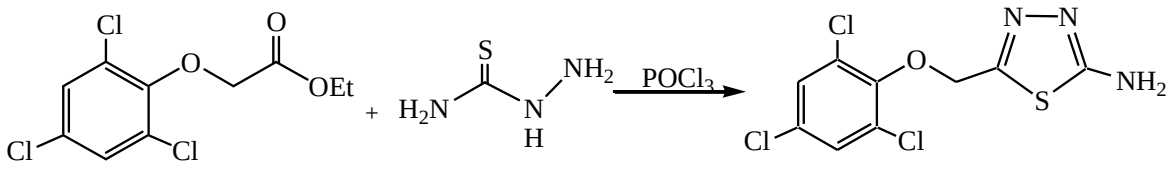


35 **36a-d**

	R^1
a	Phenyl
b	Isopropyl
c	Benzofur-2-yl
d	Methyl

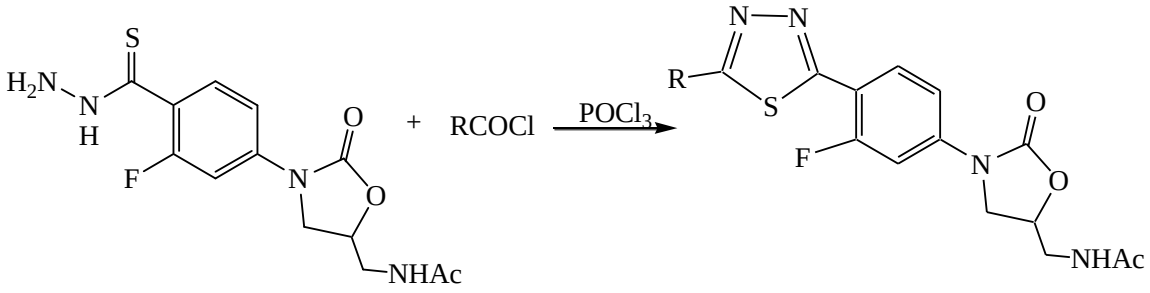
Acid esters react with thiosemicarbazide to afford monothio-diacylhydrazine intermediates which can be isolated and cyclized by concentrated sulfuric acid to 1,3,4-thiadiazoles.

Treatment of the acid ester **37** with thiosemicarbazide in the presence of phosphorus oxychloride affords the 1,3,4-thiadiazole **38** in one step [111,112]



37 **38**

Acid chlorides react with thiohydrazide derivatives **39**in polar solvents to give the corresponding thiadiazoles **40** in a one-pot reaction [113,114].



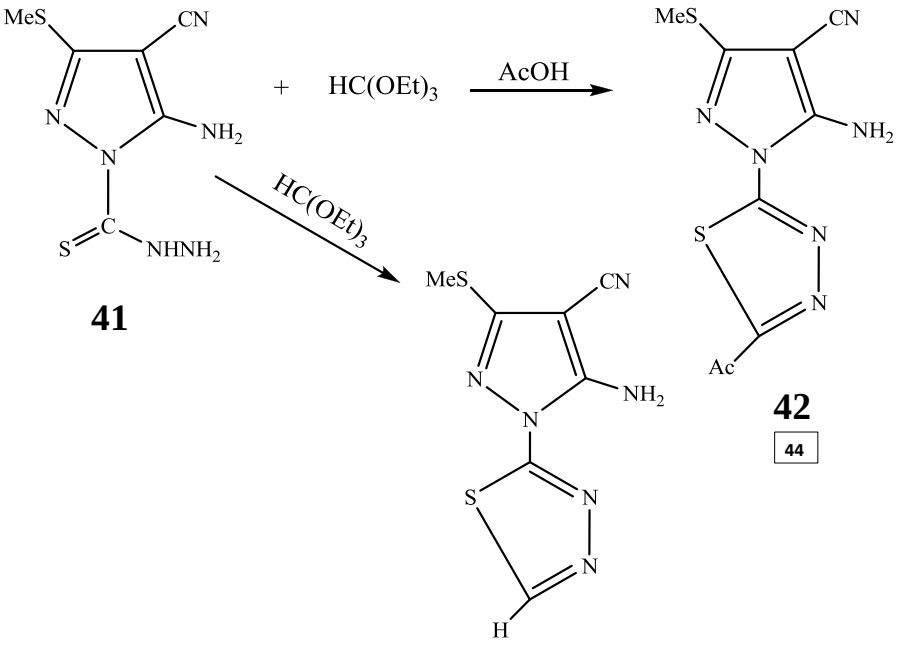
39 **40**

R = H, Me, Et, $MeOCH_2$, $AcOCH_2$, $MeCO(CH_2)_2$, $NCCH_2$, $MeSCH_2$.

(ii) From thiohydrazides and orthoesters:

Alkyl and aryl thiohydrazide derivatives react with orthoesters to afford 1,3,4-thiadiazoles. The reactions proceed via a thiosemicarbazone intermediate which cyclizes to eliminate alcohol or hydrogen.

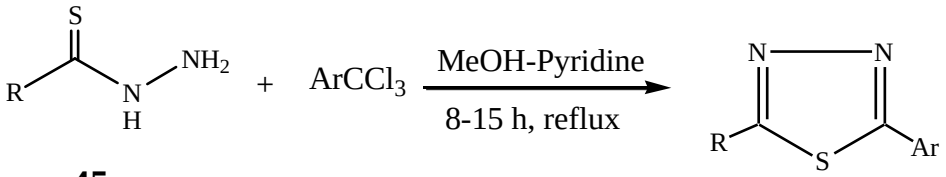
Treatment of the *N*-thiohydrazide pyrazole **41** with triethyl orthoformate in acetic acid under reflux gave the 5-aceto-1,3,4-thiadiazol-2-ylpyrazole **42** and in the absence of acetic acid the 5-amino-1,3,4-thiadiazol-2-ylpyrazole **43** in 76% yield [115].



41 **42** [44] **43**

(iii) From thiohydrazides and trihalomethyls:

The reaction of the trichloromethylarenes **44** with thiosemicarbazide **45a-d** in a boiling methanol-pyridine mixture afforded the diaryl or 2-amino-5-aryl-1,3,4-thiadiazoles **46a-d** [116].

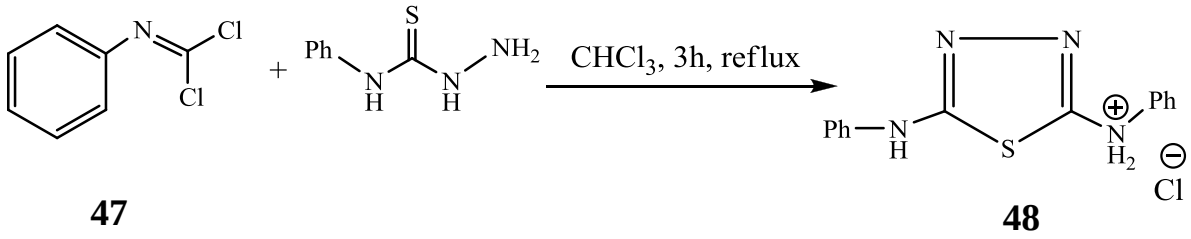


45 **44** **46a-d**

	R	Ar
a	Ph	Ph
b	Ph	2,4-Me_2-C_6H_3
c	NH_2	Ph
d	NH_2	2,4-Me_2-C_6H_3

(iv) From thiosemicarbazide and imines:

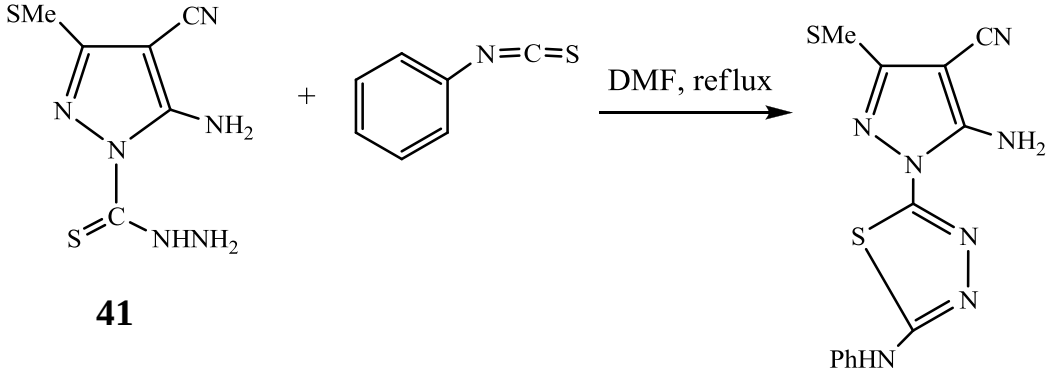
The imidoyl chloride **47** when treated with the *N*-phenylthiosemicarbazide gave the 1,3,4-thiadiazole hydrochloride **48** [117].



47 **48**

(v) From thiohydrazides and isothiocyanates:

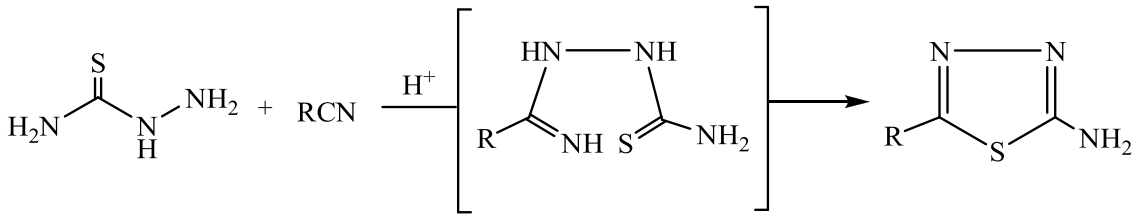
When the *N*-thiohydrazide pyrazole **41** was refluxed in *N*,*N*-dimethylformamide (DMF) in the presence of phenyl isothiocyanate the 5-phenylamino-1,3,4-thiadiazol-2-ylpyrazole **49** is formed [115]. The reaction proceeds via a dithioacylhydrazine intermediate which under the reaction conditions cyclizes with loss of H_2S.



41 **49**

(vi) From thiosemicarbazide and nitriles:

Alkyl and aryl nitriles **50a-c** were reacted with thiosemicarbazide under acidic conditions to give 1,3,4-thiadiazoles **52a-c** [118,119]. The acidic conditions promote the elimination of ammonia from the intermediate imino-thioacylhydrazine **51a-c**.

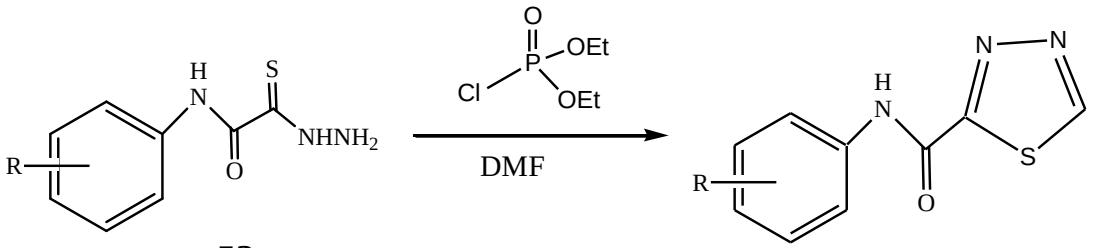


50a-c **51a-c** **52a-c**

	R
a	C_6H_5
b	4-MeO-C_6H_4
c	3-O_2N-C_6H_3

(vii) From thiohydrazides and formamides:

A charge-transfer complex of diethyl chlorophosphate with DMF as the one-carbon source affects the cyclization of thiohydrazides **53** into thiadiazoles **54** [120].

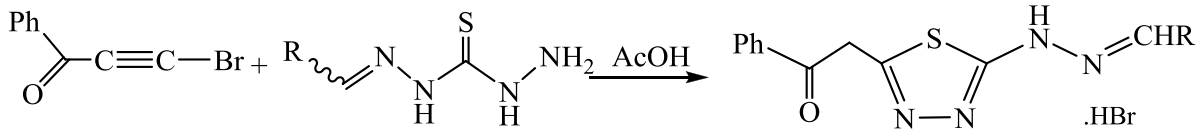


53 **54**

R = H, 4-Cl, 4-Br, 4-F, 4-MeO, 2,3-Me_2

(viii) From thiocarbohydrazones and acetylenic ketones:

When acetylenic ketones **55** was reacted with an equimolar amount of thiocarbohydrazones **56a-d** in acetic acid, thiadiazolyl hydrobromides **57a-d** were obtained [121].



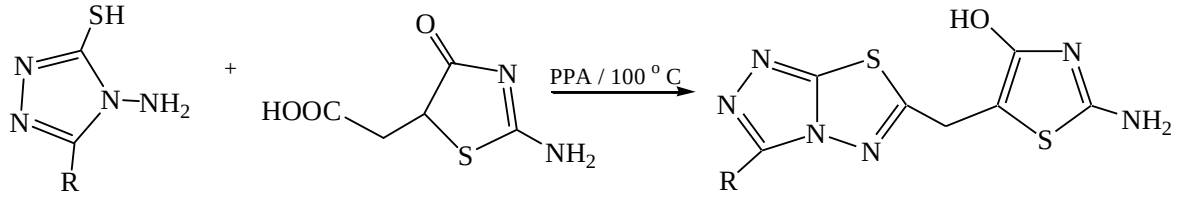
55 **56a-d** **57a-d**

	R
a	C_6H_5
b	4-Cl-C_6H_4
c	4-O_2N-C_6H_4
d	4-Me_2N-C_6H_4

(ix) From *o*-aminothiol and carboxylic acid derivatives:

1,3,4-Thiadiazole derivatives can be synthesized in the one-pot reaction from *o*-aminothiol derivatives with carboxylic acids [56], acid chlorides [58] in the presence of $POCl_3$ or PPA. Also, alkyl or aryl isocyanates [60] were reacted with *o*-aminothiol derivatives in DMF to afford 1,3,4-thiadiazoles [122].

The reaction of 4-amino-5-substituted [1,2,4]triazolo-3-thiols **58a,b** with (2-amino[1,3]thiazol-4-one-5-yl)acetic acid **59** in PPA at 100 ^{o}C afforded 6-(thiazol-5-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives **60a,b** [123].

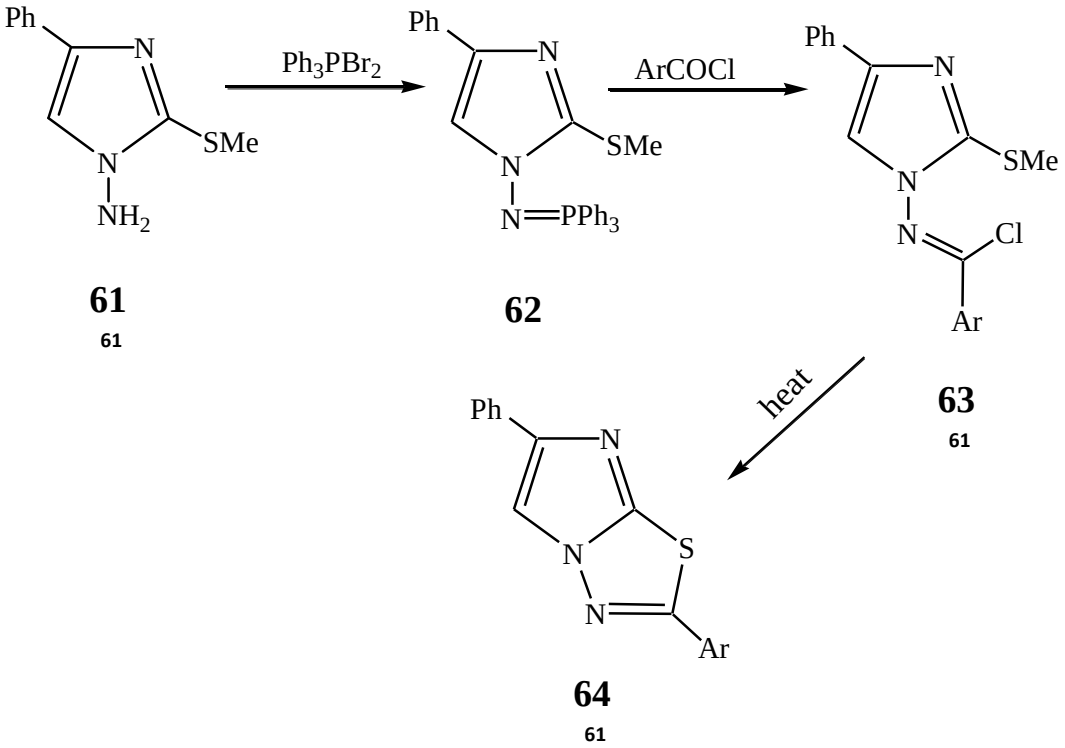


58a,b **59** **60a,b**

a; R = CH_3

b; R = CH_2Ph

Reaction of 1-amino-2-methylthio-4-phenylimidazole **61** with triphenylphosphene dibromide in dry benzene furnished the 2-methylthio-4-phenyl-1-triphenylphosphoranylidenamino imidazole **62** which was reacted with aroyl chlorides at elevated temperature and gave 2-aryl-6-phenylimidazo[2,1-b][1,3,4]thiadiazoles **64** via cyclization of imidoyl chloride intermediate **63** [124].



61

61

62

63

61

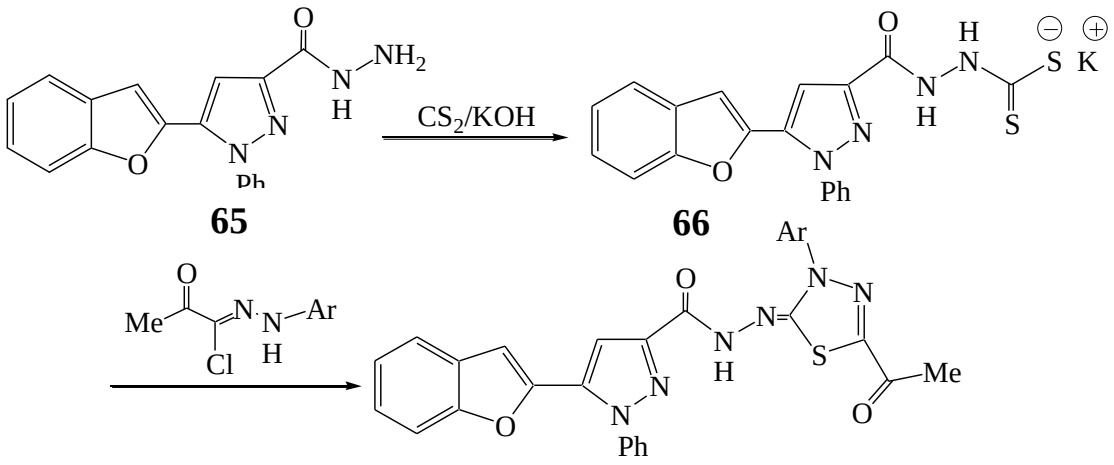
64

61

Fragments N—N—C and S—C:
Hydrazides, amidrazones and diazo compounds with carbon disuphide or thiocarbonyl derivatives

(i) From hydrazides and carbon disulphide:

Acid hydrazide can be regarded as useful intermediate leading to the formation of several heterocycles like 1,3,4-thiadiazoles [125]. Treatment of acid hydrazide **65** with carbondisulfide in ethanol in the presence of potassium hydroxide resulted in the formation of the potassium salt of hydrazinocarbodithioate **66**. Treatment of salt **66** with hydrazonoyl chlorides in aqueous ethanol afforded the production of 1,3,4-thiadiazole derivatives **67a-d** [126,127].



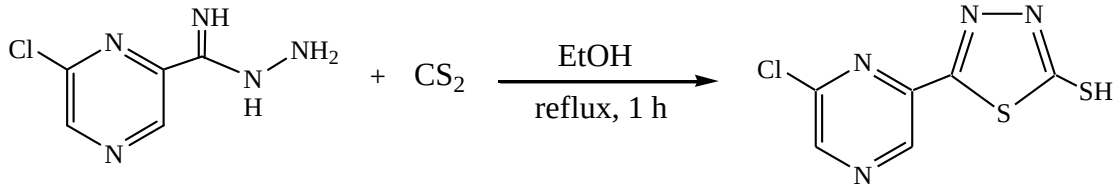
65 **66**

67a-d

	R
a	C_6H_5
b	4-Br-C_6H_4
c	4-Cl-C_6H_4
d	4-F-C_6H_4

(ii) From amidrazones and carbon disulphide:

Amidrazone **68** was reacted with carbon disulfide to give 1,3,4-thiadiazole derivative **69** [84].

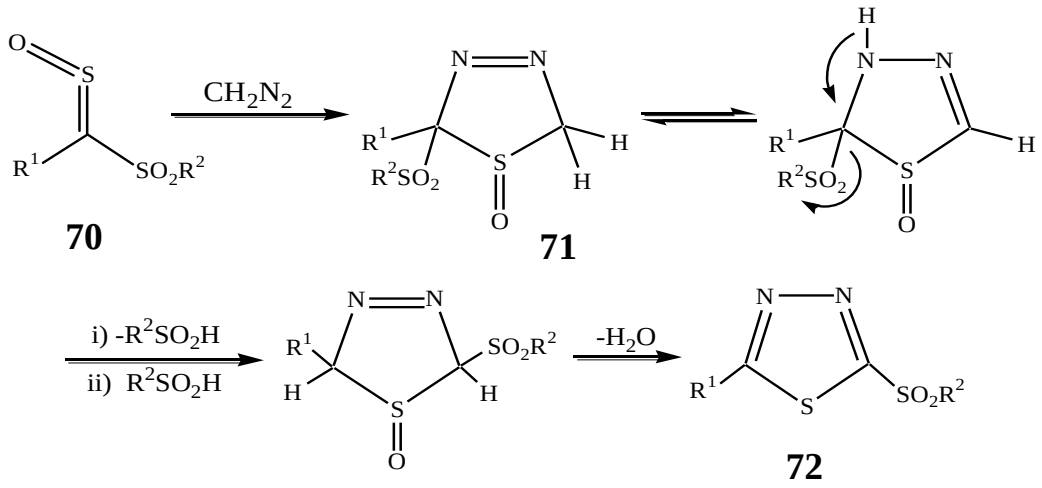


68 **69**

(iii) From diazo compounds and substituted sulfines:

The reaction of arylsulfonyl-substituted sulfines **70** with diazomethane gives 2,5-dihydro-1,3,4-thiadiazole-1-oxides **71** which, however are unstable and rearrange via an isomerization of the 2,5-dihydro to 2,3-

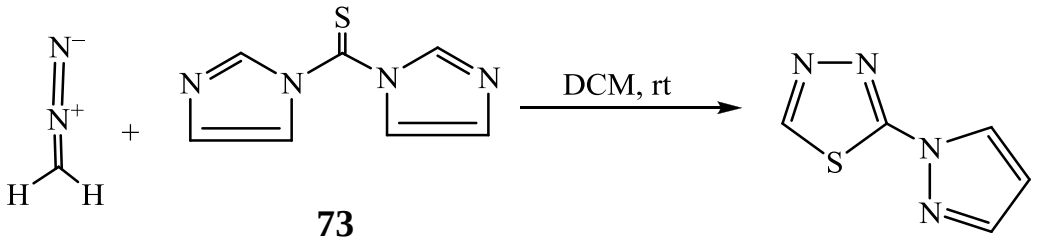
dihydrothiadiazole-1-oxide, this is followed by an elimination and readdition of sulfinic acid followed by loss of water in Pummerer-type aromatization to give the rearranged thiadiazole **72** [128].



70 **71** **72**

(iv) From diazo compounds and thiocarbonyl compounds:

The reaction of 1,1'-thiocarbonyldiimidazole **73** with diazomethane in the presence of DCM gave the 1,3,4-thiadiazole **74** in 64% yield [129].



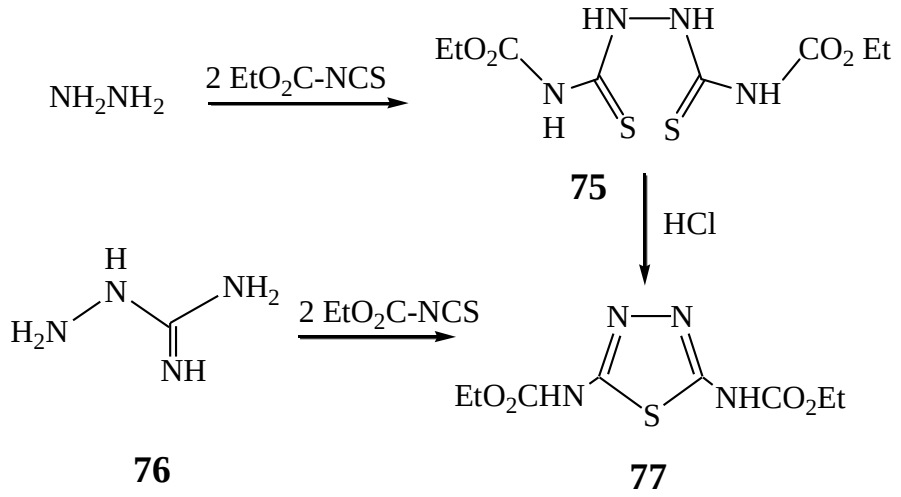
73 **74**

Fragments C—S—C and N—N:

Hydrazines with thiocarbonyl derivatives

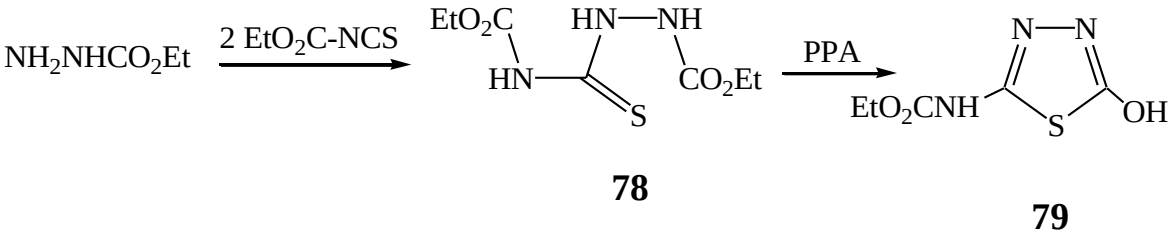
Kurzer and Secker utilized the bifunctional character of ethoxycarbonyl isothiocyanate to prepare a variety of thiadiazoles. The reaction of hydrazine with two moles of ethoxycarbonyl isothiocyanate produced the 1,6 bis(ethoxycarbonyl)bithiourea **75** in high yield which on treatment with ethanolic HCl gave an almost quantitative yield of 2,5-bis(ethoxy-carbonamide)-1,3,4-thiadiazole **77**.

The same compound **77** was obtained from the reaction of ethoxycarbonyl isothiocyanate with **76**, although in a lower yield [130].



76 **77**

Also, the reaction of ethoxycarbonylhydrazine with ethoxycarbonyl isothiocyanate gave the dicarboethoxy derivatives **78**, which required the use of PPA for cyclization to the 2-hydroxy thiadiazole **79** [131].



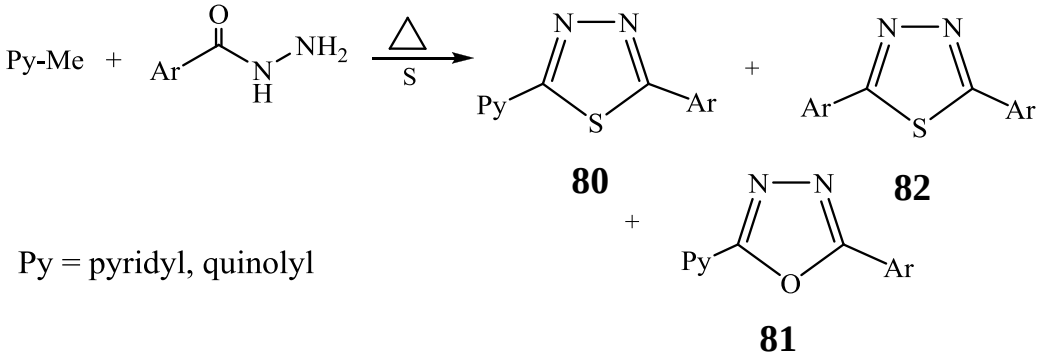
78 **79**

Synthesis of 1,3,4-thiadiazole via formation of three bonds

Fragments N-N-C, S and C:

Aroylhydrazines, sulfur with methyl pyridines or methyl quinolines

Methyl pyridines and methyl quinolines were reacted with aroylhydrazines in the presence of sulfur to afford 5-aryl-1,3,4-thiadiazoles **80** in low yields. This method required high temperatures and long reaction times and gave a mixture of the desired products **80**, 1,3,4-oxadiazoles **81** and symmetrical diaryl- 1,3,4-thiadiazoles **82** [132].

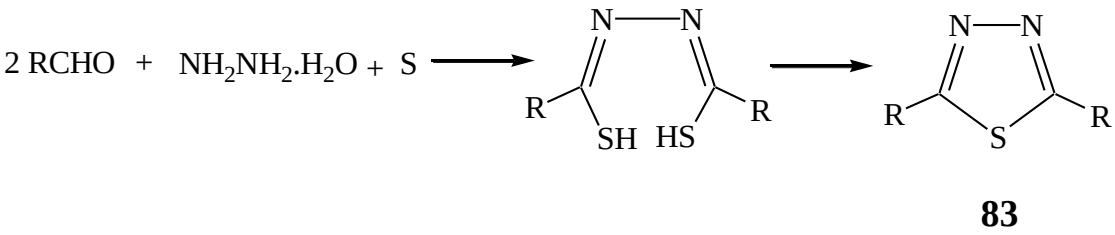


Synthesis of 1,3,4-thiadiazole via formation of four bonds

Fragments N-N, S and two C fragments:

Hydrazine, sulfur and Aldehydes

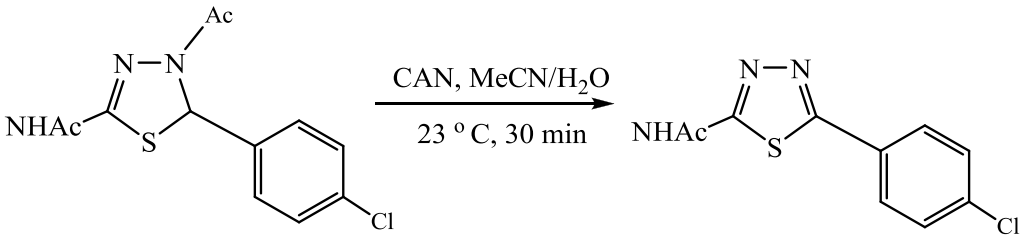
Aldehydes were reacted with hydrazine hydrate and sulfur in one-pot synthesis to give 2,5-dialkyl- and 2,5-diaryl-1,3,4-thiadiazoles **83** in a high yield via a diazene intermediate [133,134].



Synthesis of thiadiazoles by oxidation of fully or partially reduced derivatives.

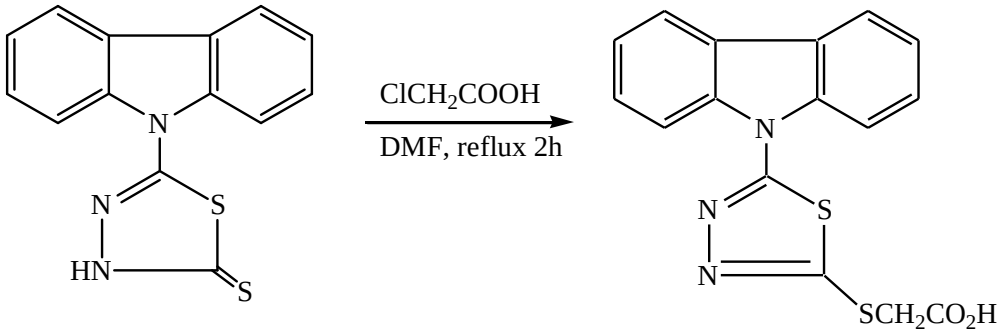
Aromatization

Partially or fully reduced thiadiazoles can be oxidized to yield 1,3,4-thiadiazoles. The 2,5-disubstituted-3-acyl-1,3,4-thiadiazole **85** can be aromatized by numerous methods, oxidative deacylation of compound **84** to thiadiazole **85** can be achieved using oxidants such as $KMnO_4$ and (diacetoxyl)iodobenzene. Better yields and cleaner products using Cerium (IV) ammonium nitrate (CAN) as oxidants [135].



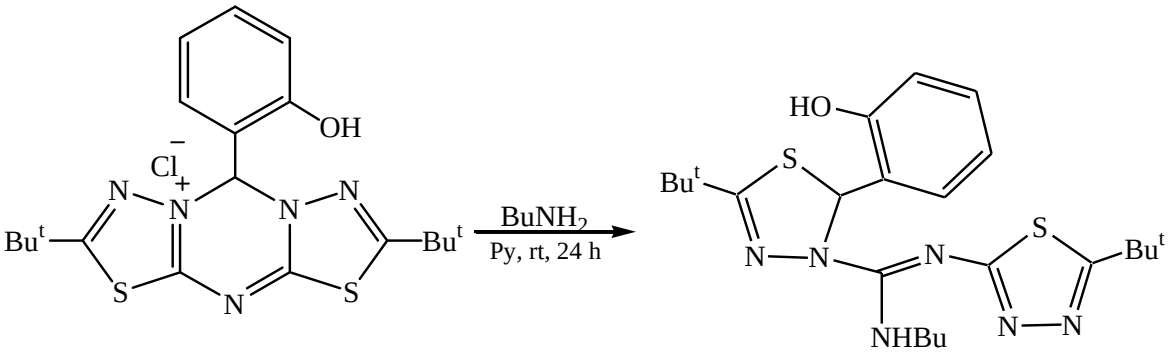
84 **85**

5-(9*H*-Carbazol-9-yl)-1,3,4-thiadiazole-2(3*H*)-thione **86** was S-alkylated and aromatized with monochloroacetic acid to give the 1,3,4-thiadiazole **87** [136].



86 **87**

Another synthesis of 1,3,4-thiadiazoles through aromatization is the cleavage of fused–ring compounds. The reaction of the salt **88** with a primary amine in pyridine at room temperature for 24h results in the ring cleavage of the fused system and the formation of guanidine derivative **89** [137].



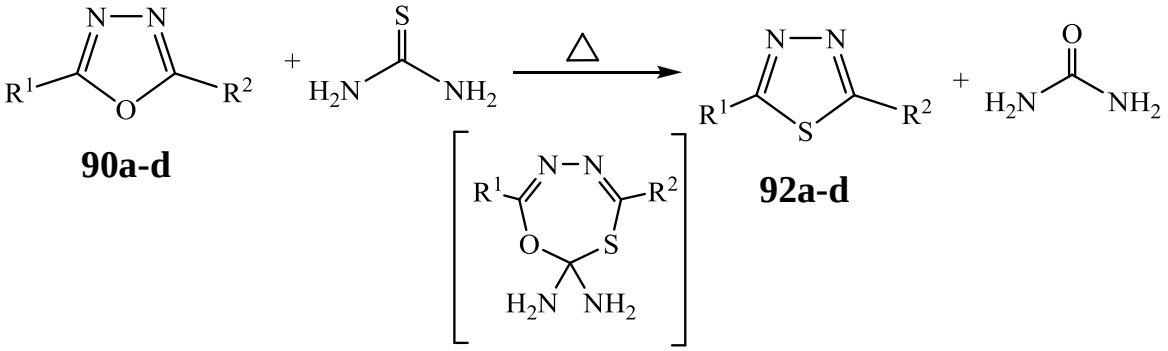
88 **89**

Synthesis of thiadiazoles by transformation of other heterocycles

The direct ring transformations of other heterocycles into 1,3,4-thiadiazoles are briefly summarized as follows:

(i) From 1,3,4-oxadiazoles:

Thiadiazoles can be obtained directly from oxadiazoles [138]. Thus, 2,5-diaryl-1,3,4-oxadiazole **90a-d** was reacted with thiourea to give 2,5-diaryl-1,3,4-thiadiazoles **92a-d**. The proposed mechanism proceeds via ring contraction of an intermediate oxathiadiazepine **91** to give the thiadiazole **92a-d** [139].

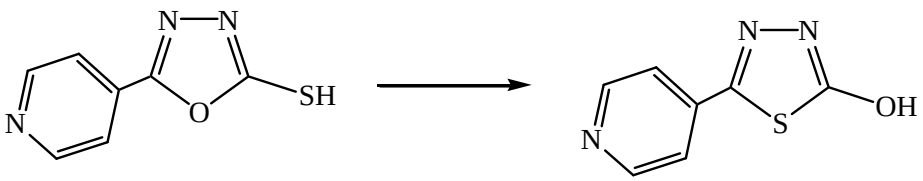


90a-d **92a-d**

91

	R^1	R^2
a	Ph	Ph
b	4-$MeOC_6H_4$	Ph
c	3,4,5-$(MeO)_3C_6H_2$	Ph
d	3,4,5-$(MeO)_3C_6H_2$	4-$O_2NC_6H_4$

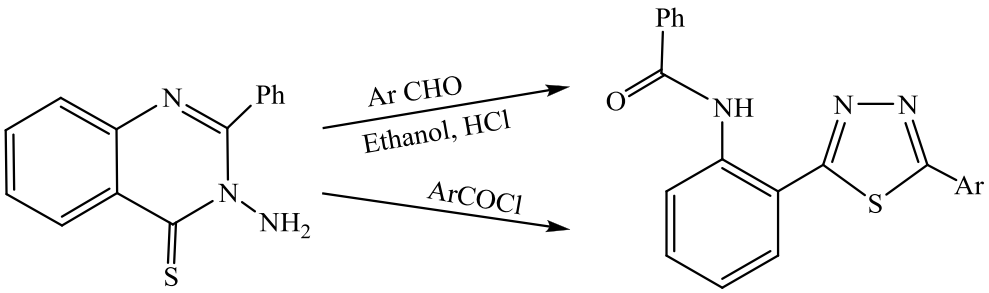
When 2-thio-5-(pyrid-4-yl)-1,3,4-oxadiazole **93** was heated under reflux in ethanolic HCl, it rearranged to the 2-hydroxythiadiazole derivative **94** [140].



93 **94**

(ii) From quinazolines:

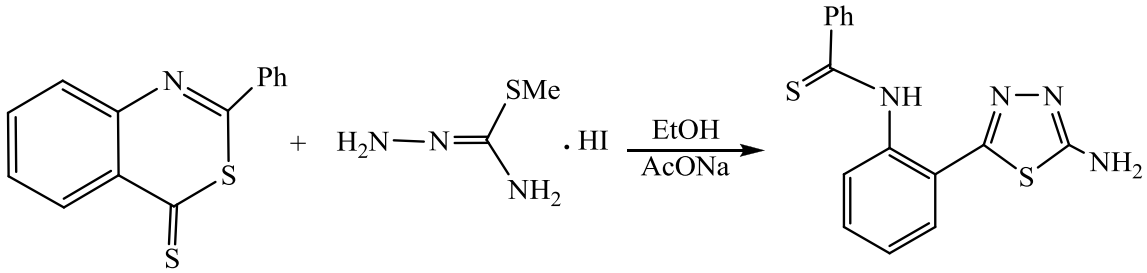
2,5-Disubstitued thiadiazoles **96** was synthesized by prolonged heating of 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline **95** with aromatic aldehydes in ethanol containing HCl [141] or by reaction with acid chlorides [142].



95 **96**

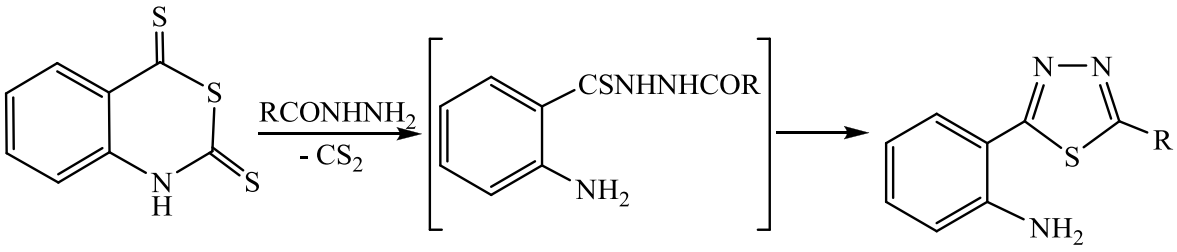
(iii) From benzothiazines:

4*H*-3,1-Benzothiazine-4-thione **97** was treated with S-methyl isothio-semicarbazide hydroioide in ethanol containing sodium acetate to yield the 5-aryl-2-amino-1,3,4-thiadiazole **98**. A suitable mechanism for this transformation requires the addition of one of the amino groups from the thiosemicarbazide to the thiocabonyl group of the benzothiazin-4-thione **97** followed by ring opening and recyclization with elimination of CH_3SH to give the thiadiazole **98** [143].



97 **98**

Also, the reaction of benzothiazinedithione **99** with benzoyl hydrazine yields 2,5-disubstituted thiadiazoles **101**, presumably via the intermediate **100** [144].

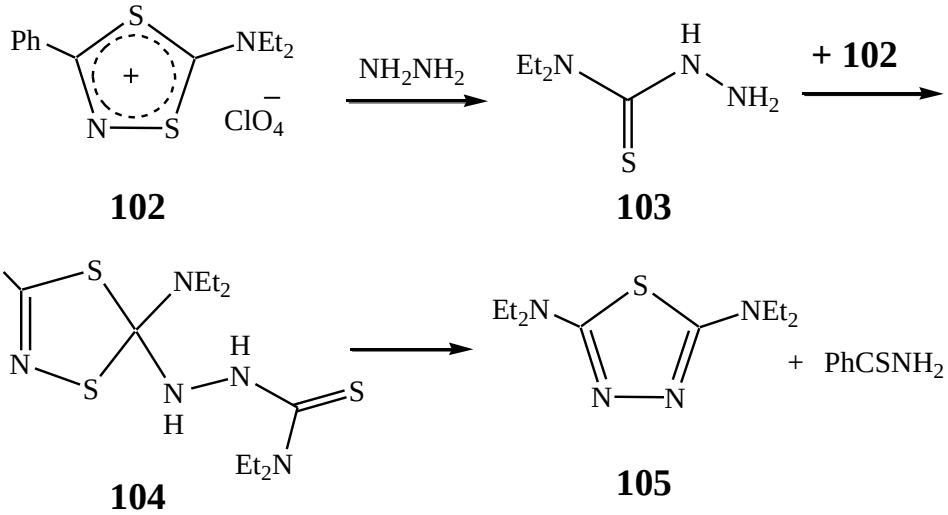


99 **100** **101**

(iv) From 1,4,2- dithiazoles:

The reaction of 1,4,2-dithiazolium salts with hydrazine leads to thiadiazoles. Thus, treatment of *N*,*N*-diethylamino dithaizolium salt **102** with an excess of hydrazine afforded 2,5- bis(diethylamino)-1,3,4-thiadiazole **105** together with thiobenzamide. The mechanism postulated is as follows:

In the first step, hydrazine causes rupture of the ring to liberate *N*,*N*-diethylthiosemicarbazide **103** which in turn reacts with another molecule of **102** to give the intermediate **104**. Opening of the ring and expulsion of thiobenzamide and sulfur leads to the thiadiazole **105** [145].

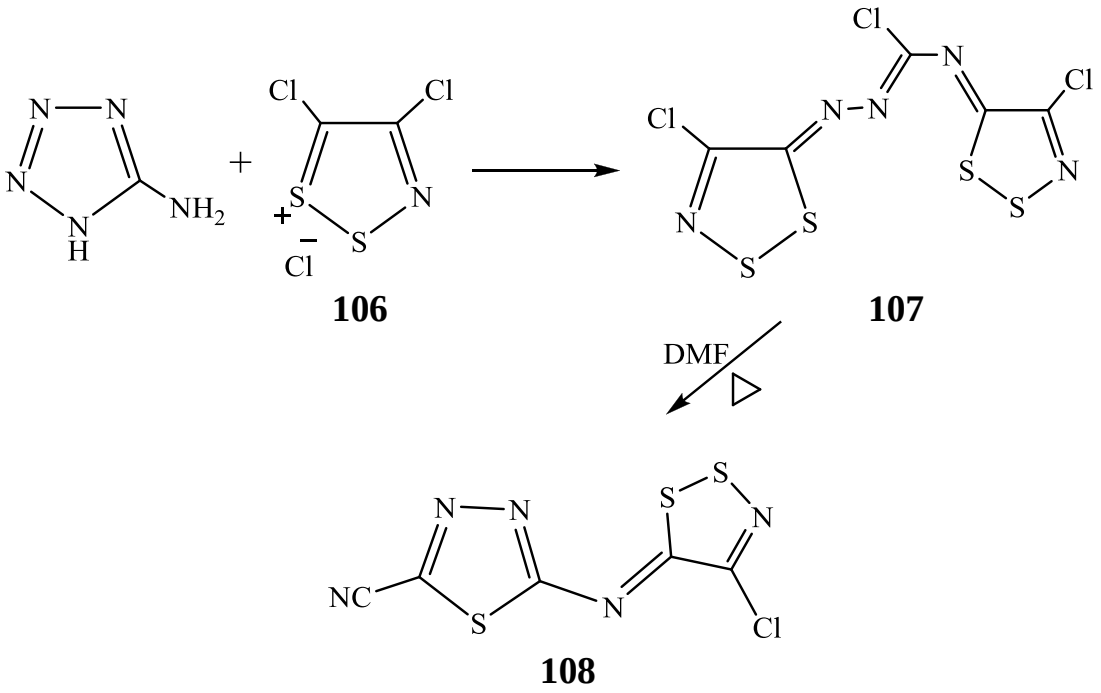


102 **103**

104 **105**

(v) From 1,2,3-dithiazoles:

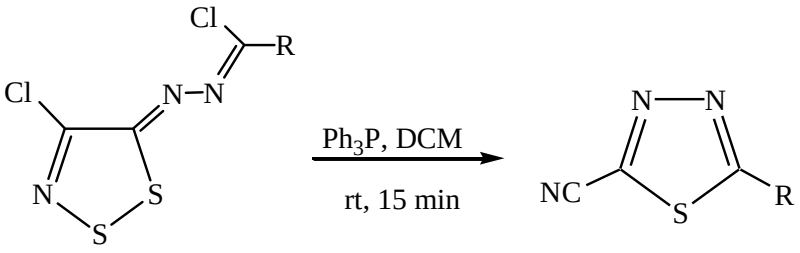
5-Aminotetrazole reacts with 4,5-dichloro -1,2,3-dithiazolium chloride **106** to afford the bis(imino-1,2,3-dithiazole) **107** which in warm DMSO or DMF converts to thiadiazole derivative **108** [146].



106 **107**

108

Also, cyanothiadiazoles **110a-g** were prepard from the reaction of dithiazolimines **109a-g** with triphenyl phosphine in DCM under mild conditions [147].

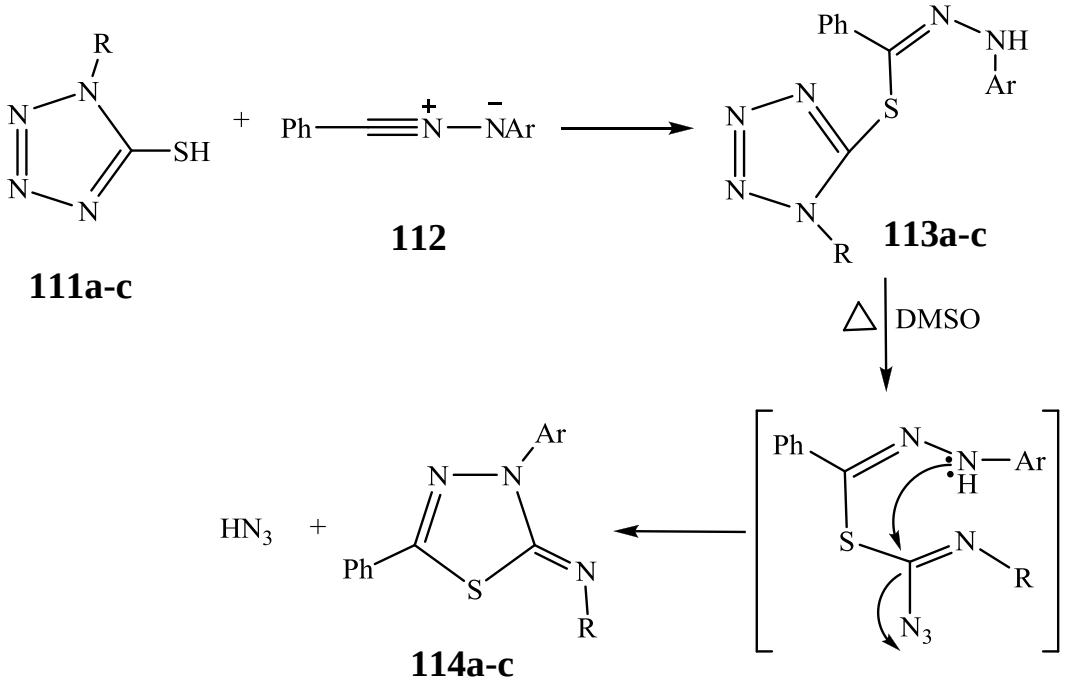


109a-g **110a-g**

	R
a	C_6H_5
b	4-O_2N-C_6H_4
c	4-MeO-C_6H_4
d	2-Thienyl
e	C_6H_5O
f	MeS
g	$ClCH_2CH_2$

(vi) From tetrazoles:

The reaction of a nitrile imide with 1-aryltetrazoles substituted at C-5 with a hydroxyl, thiol or amino group provides means of transforming a tetrazole ring into a 1,3,4-thiadiazole. Thus, electrophilic attack by benzonitrilium-*N*-4-nitrophenylimide **112** on the exocyclic sulfur atom of tetrazole **111a-c** gave the thiohydrazonate **113a-c** which on heating in toluene or dry DMSO is converted to thiadiazoles **114a-c** [148].

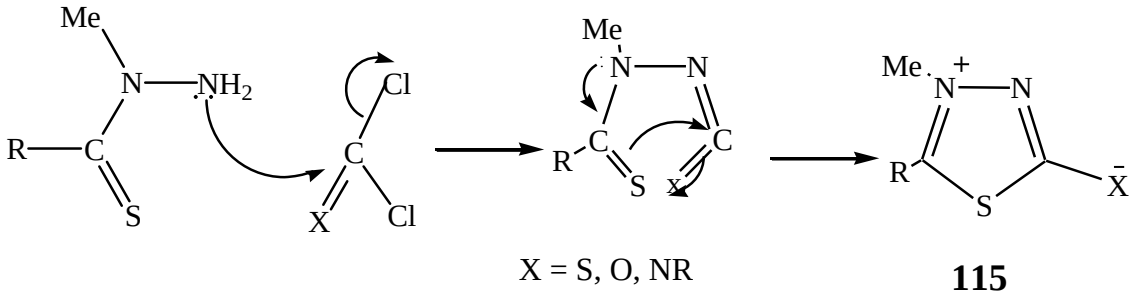


111a-c **112** **113a-c** **114a-c**

	Ar	R
a	4-O_2N-C_6H_4	$C_6H_5CH_2$
b	4-O_2N-C_6H_4	4-O_2N-C_6H_4
c	4-O_2N-C_6H_4	4-Me-C_6H_4

Mesoionic Compounds

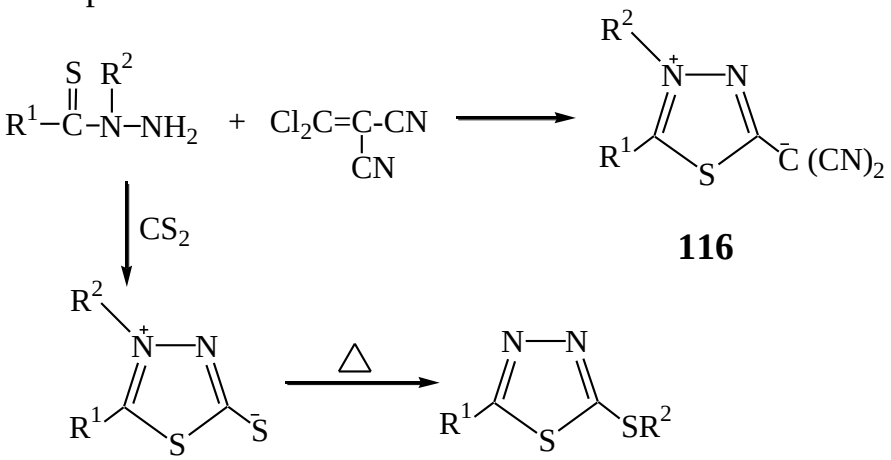
The most common starting materials for the synthesis of mesoionic 1,3,4-thiadiazoles are thioacylated hydrazine derivatives, thus 1-Methyl-1-thioacylhydarzine reacted with thiophosgene or phosgene in the presence of potassium carbonate to give the mesoionic thiadiazole **115** [149].



X = S, O, NR

115

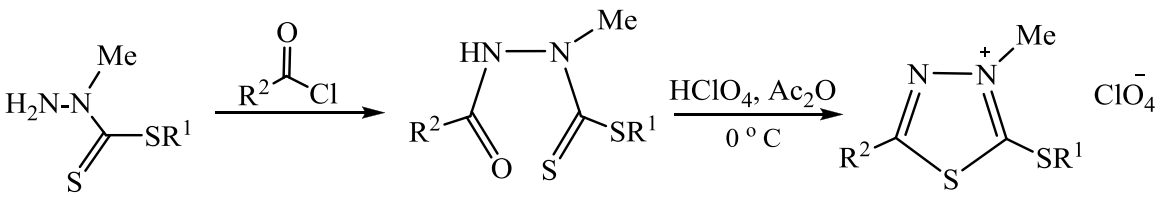
Reaction of thiocarboxylic acid hydrazides with 3,3-dichloro acrylonitrile gave mesoionic compounds, 2-methylene-1,3,4-thiadiazoles **116** [150]. Also, thiocarboxylic acid hydrazides were reacted with CS_2 to produce mesoionic compounds **117** [151].



116

117

Alkyl-2-methyldithiocarbazates **118** were reacted with acyl chlorides and gave high yield of alkyl 3-acyl-2-methyldithiocarbazate **119** which on treatment with a mixture of acetic anhydride and perchloric acid at 0 °C cyclized to 2-alkylthio-3-methyl-1,3,4-thiadiazolium salts **120** in > 90% yield [152].



118 **119** **120**

Reactions of thiadiazole derivatives

Some of the characteristic reactions of the 1,3,4-thiadiazole nucleus are ring opening by strong base, ease of nucleophilic attack and the formation of mesoionic compounds by quaternization. The substituents in the 2- and 5- positions have a large effect in determining the reactivity of the molecule as a whole. Thus, the ambident nucleophilicity of 2- aminothiadiazoles gives rise to electrophilic attack on both the amino group and the nuclear nitrogen atom. Ring formation between these two nitrogen atoms is also a common reaction. 2-Mercaptothiadiazoles reacts similarly to arenethiols while a methyl group on the thiadiazole ring has reactivity similar to that in picoline.

Nucleophiles easily displace halogen atoms from the thiadiazole nucleus. This is due to the electronegativity of the nuclear nitrogen atoms which impart a low electron density to the carbon atom of the nucleus. Selected examples in this part illustrate the general reactivity of 1,3,4-thiadiazole [153].

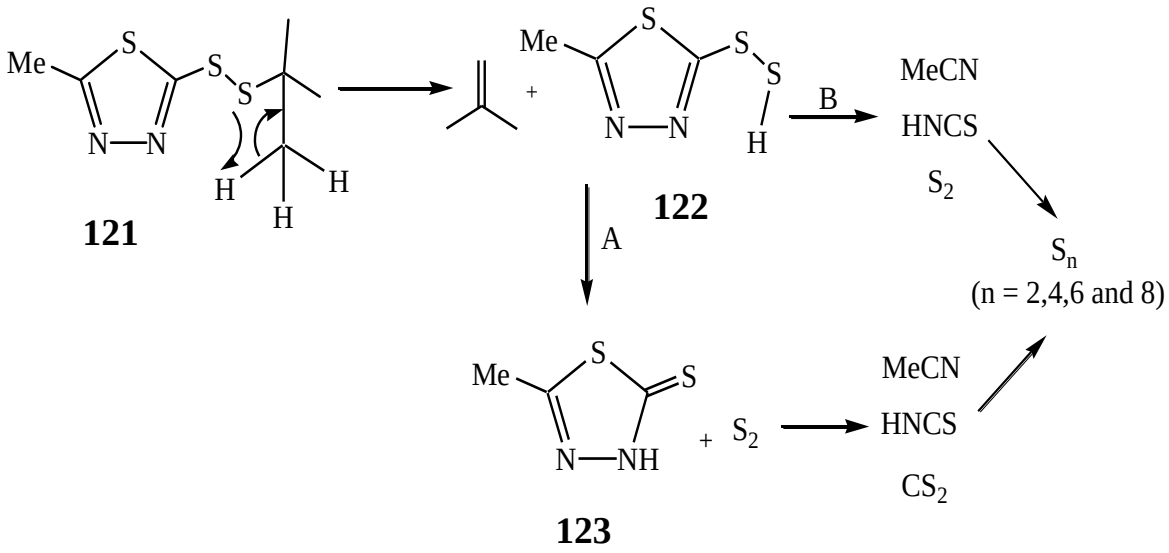
Reactivity of 1,3,4-thiadiazole ring:

(i) Unimolecular thermal and photochemical reactions:

1,3,4-Thiadiazoles often undergo photochemical fragmentation similar to the fragmentation observed in the mass spectrometer [154].

High-vacuum pyrolysis of 2-(*tert*-butyldithio)-5-methyl-1,3,4-thiadiazole **121** between ambient and 900 ^{0}C gave 2-methylpropene, HNCS, thiadiazole **123** ,CS_2, CH_3CN and sulfur species. The presence of 2-methylpropene might be caused by β-hydrogen elimination. This reaction would lead to the disulfanyl **122** which fragments further via two main paths (A and B). In reaction path A the bimolecular fragmentation of **122** gives S_2 and the thiadiazole **123**, which above 500 ^{0}C decomposes to CH_3CN, HNCS,

CS_2 and sulfur. Path B results in direct elimination of S_2 from the disulfanyl **122** to give HNCS and CH_3CN [155].

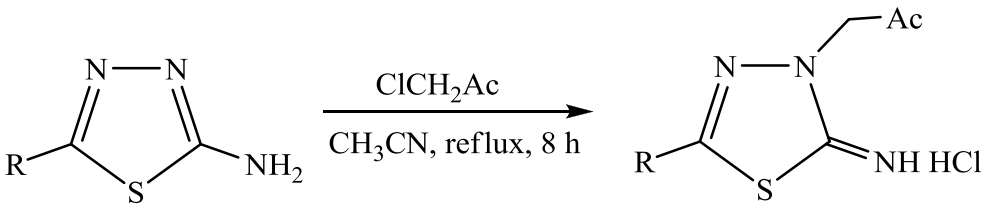


(ii) Electrophilic attack at nitrogen:

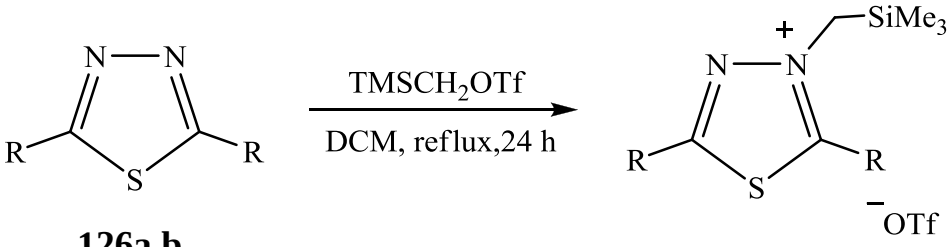
The ring nitrogens react with electrophiles to afford either 1,3,4-thiadiazolium salts or 1,3,4-thiadiazol-2(3*H*)-ones depending on the tautomerisability of the substituents at the C-2 or C-5 positions. While *N*-alkylation is the most common electrophilic reaction of 1,3,4-thiadiazole, reactions with acyl and cyanogen halides as well as Mannich salts have also been reported.

2-Amino-1,3,4-thiadiazole **124** reacts with chloroacetone to give the *N*-alkylated thiadiazolimine **125** [156].

N-alkylation of the 2,5-diphenyl- and 2,5-dimethyl-1,3,4-thiadiazole **126a,b** with trimethylsilyl- methyl trifluromethanesulfanate gave the corresponding 1,3,4-thiadiazolium salts **127a,b** [157].



124 **125**

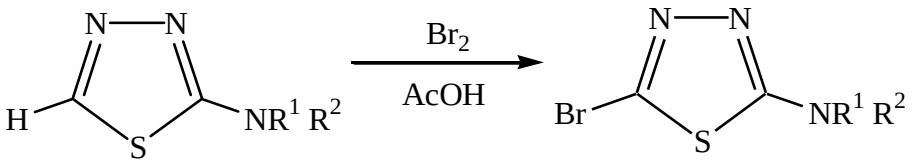


126a,b **127a,b**

	R
a	Me
b	Ph

(iii) Electrophilic attack at carbon:

Due to the low electron density at the carbon atoms in 1,3,4-thiadiazole, such reactions as nitration, sulphonation, acetylation, halogenations, etc. normally do not take place. However, 2- amino-substituted 1,3,4-thiadiazoles **128a-i** react with bromine in acetic acid to give the 5-bromo derivatives **129a-i** [158].



128a-i **129a-i**

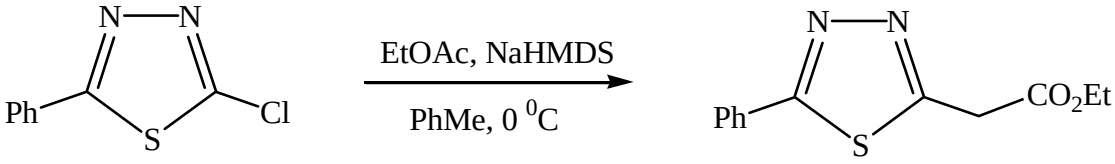
	R^1	R^2
a	H	H
b	H	Me
c	H	NO
d	H	COMe
e	H	COPh
f	Me	Me
g	Me	NO
h	Me	COMe
i	Me	COPh

(iv) Electrophilic attack at sulfur:

The direct oxidation of thiadiazoles to form sulfoxides or sulfones has not been reported [97].

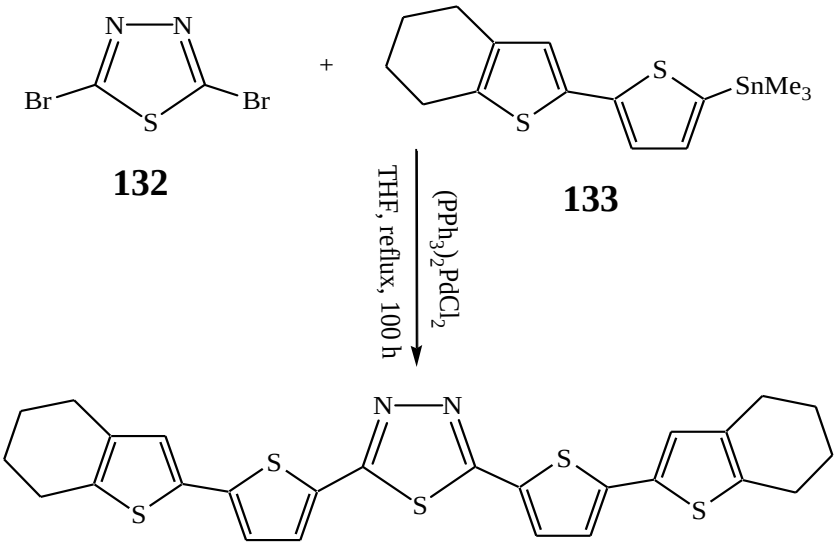
(v) Nucleophilic attack at carbon:

Nucleophilic reactions at the carbon atoms of 1,3,4-thiadiazoles occur readily owing to the electron-deficient nature of the ring. Halo-substituted thiadiazoles are, therefore, highly activated and react with a wide range of nucleophiles. Carbon-based nucleophiles such as malonate have been used in the synthesis of 2-substituted thiadiazoles. When 2-chlorothiadiazole **130** was treated with ethyl acetate in the presence of sodium hexamethyl disilazane (NaHMDS), the 5-phenyl-1,3,4-thiadiazol-2-ylacetic ester **131** was obtained [159].



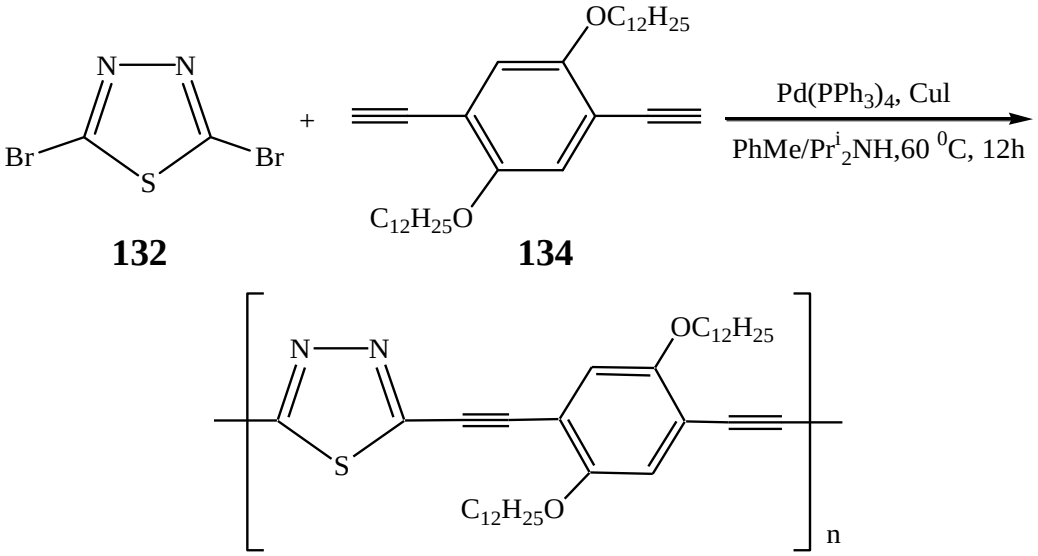
130 **131**

The bromine atoms in 2,5-dibromo-1,3,4-thiadiazole **132** undergo a palladium-catalyzed Stille reaction with the organostannyl derivative **133** [160].



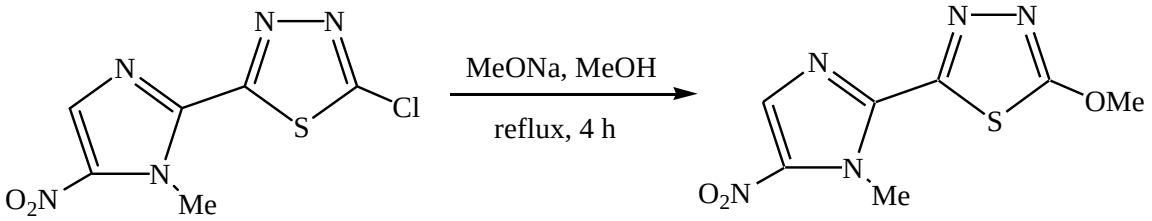
132 **133**

The dibromothiadiazole **132** was co-polymerized with diethynyl benzene derivative **134** in a Sonogashira cross-coupling reaction [161].



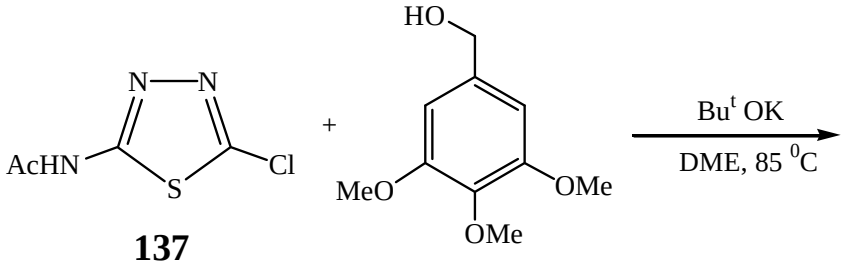
132 **134**

Oxygen, sulfur [162] and nitrogen [163] nucleophiles also react with the halothiadiazoles to give the corresponding halo-displaced products. For example, the chlorothiadiazole **135** reacted with sodium methoxide in methanol to give methoxythiadiazole **136** [88].

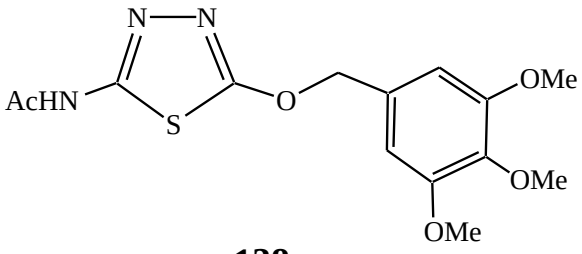


135 **136**

When 2-acetamido-5-chloro-1,3,4-thiadiazole **137** reacted with the 3,4,5-trimethoxybenzyl alcohol in the presence of potassium *tert*-butoxide to afford the substituted trimethoxybenzyl ether **138** [164].

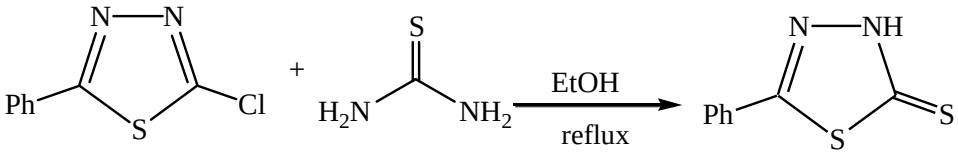


137

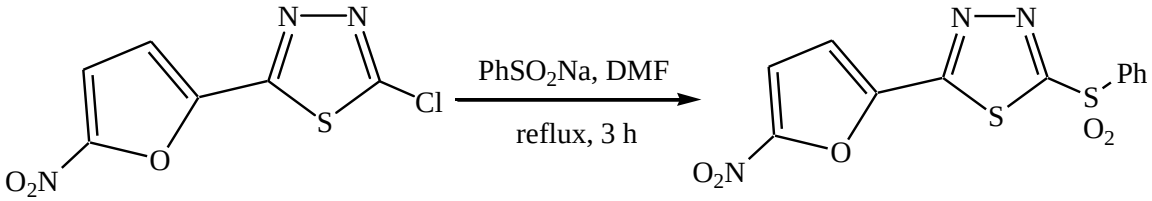


138

2-Chloro-5-phenyl-1,3,4-thiadiazole **130** reacted with thiourea in refluxing ethanol to afford the thione **139** [165]. The reaction of sodium phenylsulfinate with thiadiazole **140** in refluxing DMF gave the 5-phenylsulfonyl-1,3,4-thiadiazole **141** [166].

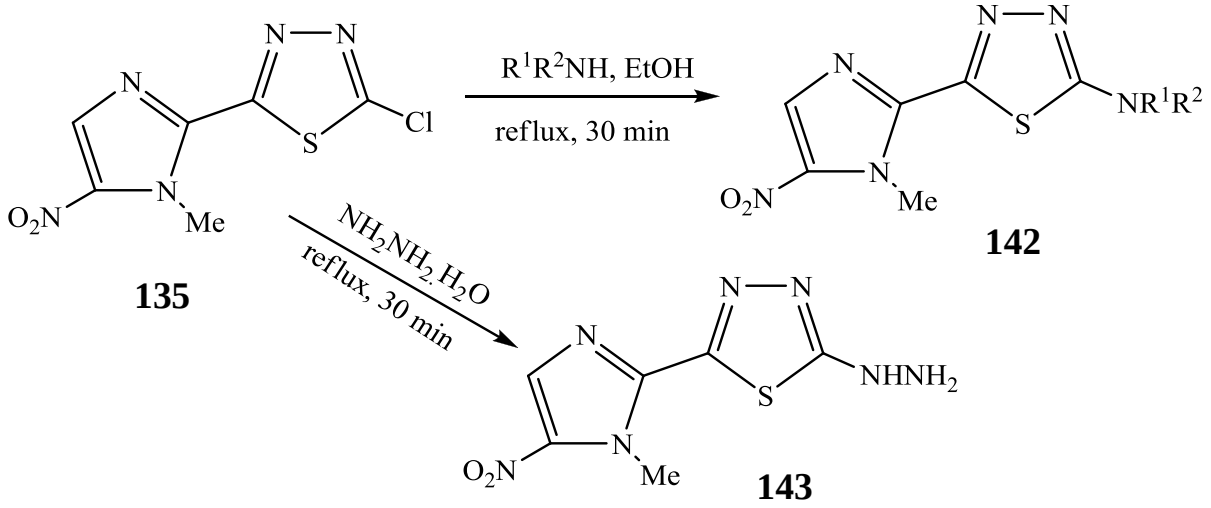


130 **139**



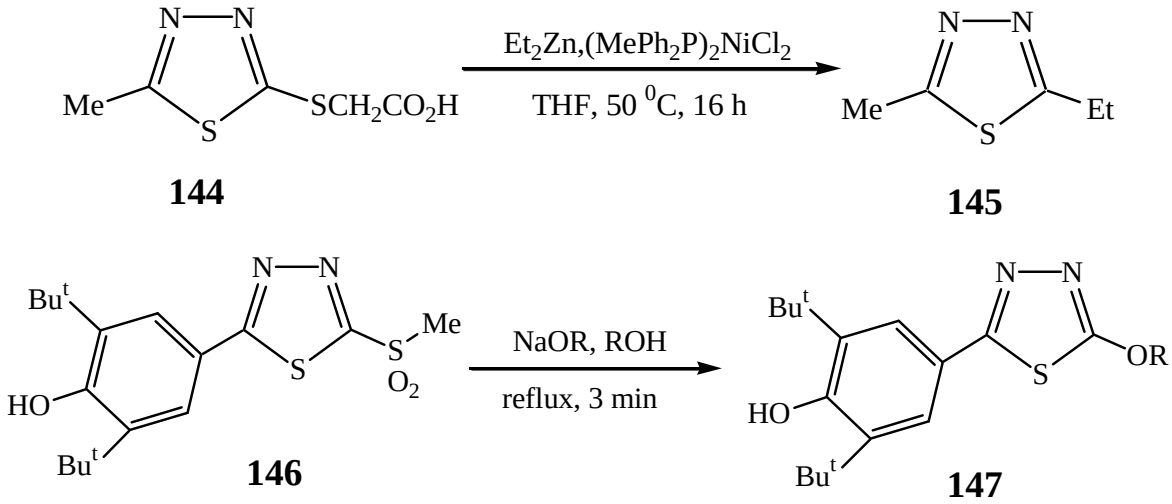
140 **141**

Thiadiazole **135** reacted with cyclic secondary amines such as piperidine, piperazine and morpholine to afford the substituted derivatives **142** in 80-85% yield [167]. Under similar conditions, thiadiazole **135** reacted with hydrazine hydrate to give the hydrazinothiadiazole **143** in 97% yield [106].

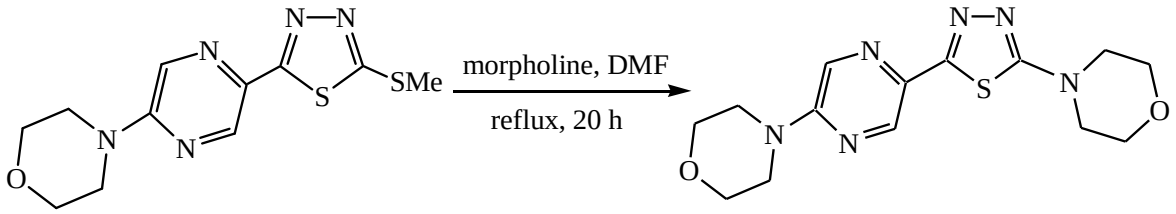


R^1R^2 = -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2OCH_2CH_2$-, -$CH_2CH_2NHCH_2CH_2$-,

Sulfur substituents at either the C-2 or C-5 positions are also activated and can be substituted by a range of nucleophiles. The thioglycolic thiadiazole acid **144** reacted with diethylzinc in the presence of an organo Ni catalyst to give the 2-ethyl-substituted thiadiazole **145** [168]. Sulfonyl substituents **146** can be displaced with sodium alkoxides [169] to give ethers **147**. Also, sulphur substituent at carbon-2 can be displaced by nitrogen nucleophiles to afford the corresponding amino derivatives [170]. The reaction of the thiadiazole **148** with morpholine in refluxing DMF led to substitution of the methylthio group [84].

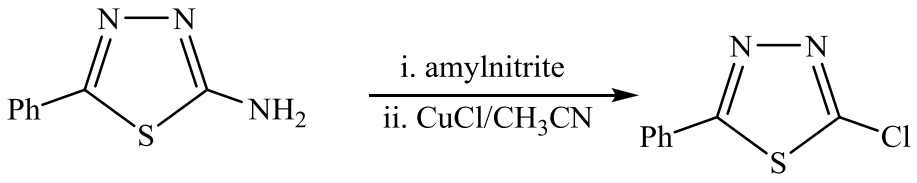


R = Me, Et, Pr^i, Pr^n

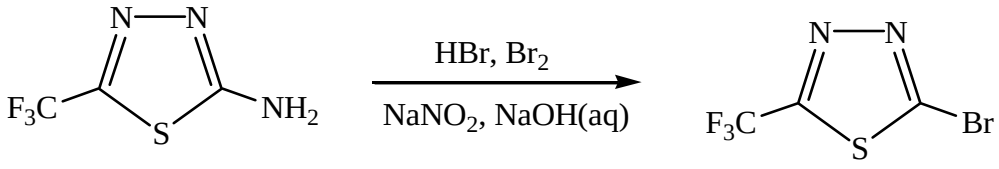


148

2-Amino-1,3,4-thiadiazoles undergo Sandmeyer reactions to afford 2-halo-l,3,4-thiadiazoles [159,163]. Diazotization followed by a Sandmeyer reaction of the 2-amino-5-phenyl-1,3,4-thiadiazole **149** with CuCl generated *in situ* gave 2-chloro-5-phenyl-l,3,4-thiadiazole **130** in 85% yield [106,159] while Sandmeyer bromination of 2-amino-5-(trifluoromethyl)-l,3,4-thiudiazole **150** gave 2-bromo-5-(trif1uoromethyl)-l,3$_s$4-thiadiazole **151** in 54% yield [163].



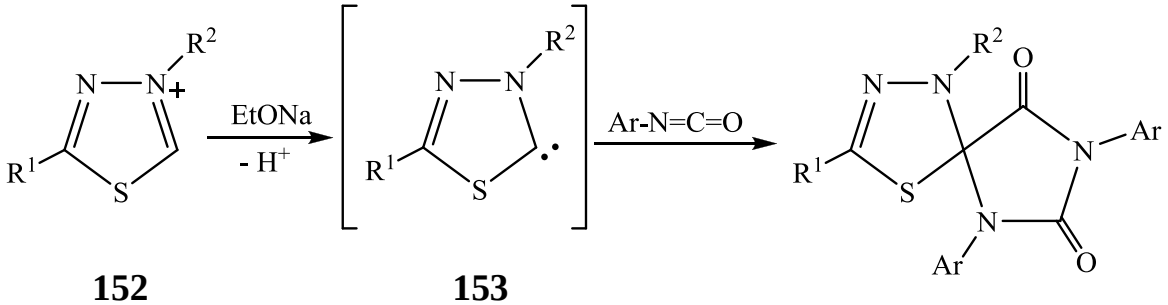
149 **130**



150 **151**

(vi) Nucleophilic attack at hydrogen attached to carbon:

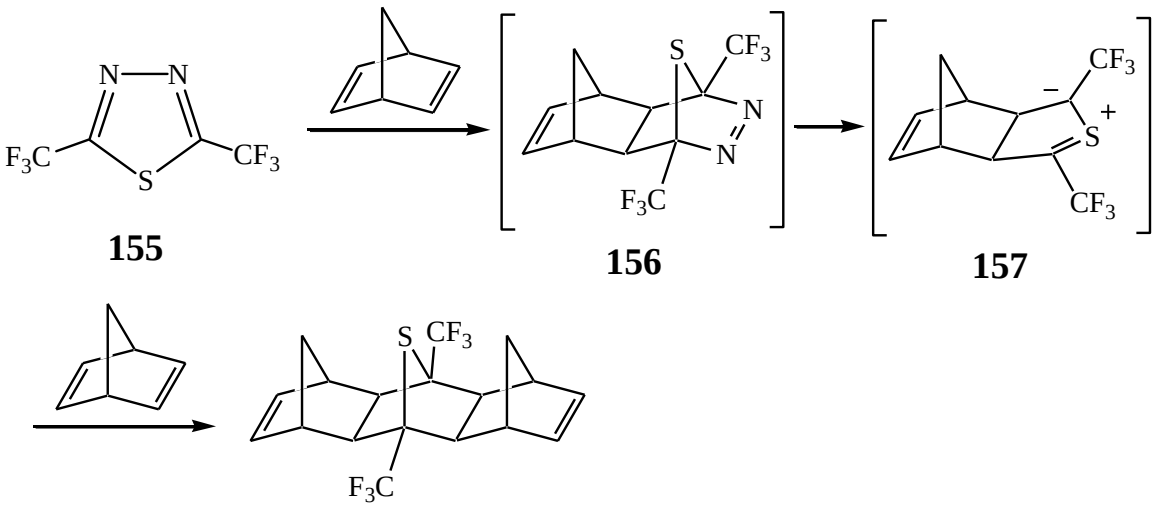
Reaction of various alkylating agents with unsubstituted and 5-substituted thiadiazoles yielded 3-alkyl-1,3,4-thiadiazolium salts; these salts **152** were deprotonated with ethoxide to produce carbenes **153** which were trapped with aromatic isocyanates to yield spirocyclic compounds **154** [171].



152 **153** **154**

(vii) Reaction with radicals and cyclic transition states:

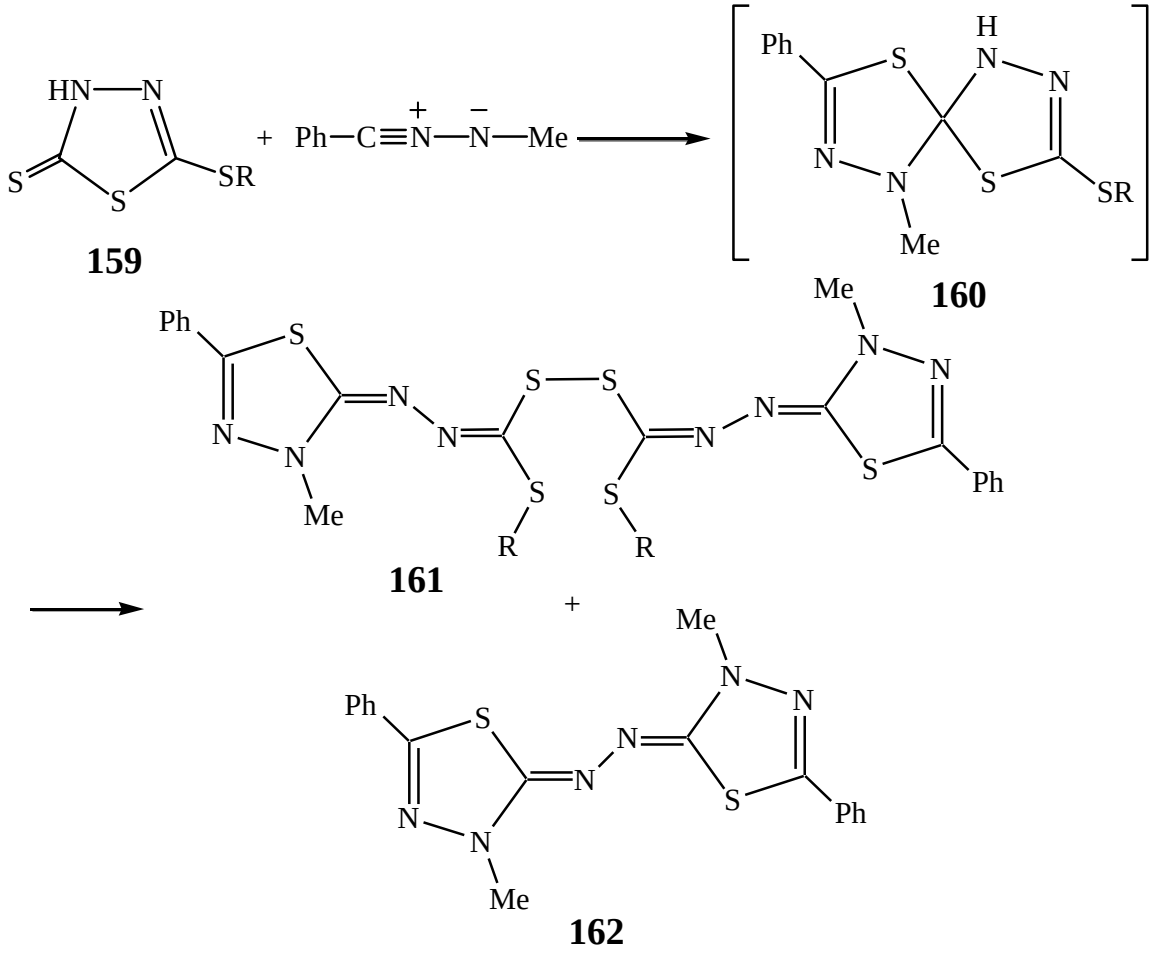
2,5-Bis(trifluoromethyl)-1,3,4-thiadiazole **155** underwent a Diels-Alder reaction with norbornadiene under high pressure to give the unstable cycloadduct **156** which rapidly loses nitrogen molecule forming the 1,3-dipolar intermediate **157**. The [4+2] cycloaddition of the intermediate **157** with a second alkene afforded product **158** in 29% yield [172].



155 **156** **157**

158

The 5-thio-substituted-1,3,4-thiadiazole-2(3*H*)-thiones **159** reacted with *N*-methyl-*C*-phenylnitrilimine in a regiospecific 1,3-dipolar cycloaddition to form not the expected cycloadducts **160** but rather the rearranged products **161** and **162** in 16-28% yields [173].



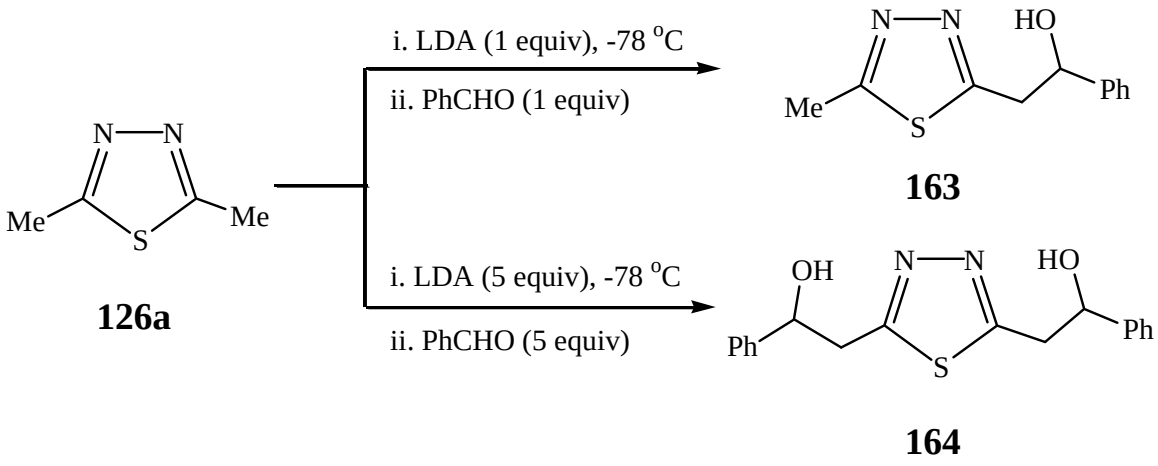
159 **160** **161** **162**

R = Me, Et, Bu^t, $CH_2C_6H_4Me$, $CH_2C_6H_3Cl_2$

Reactivity of substituents attached to ring carbon atoms:

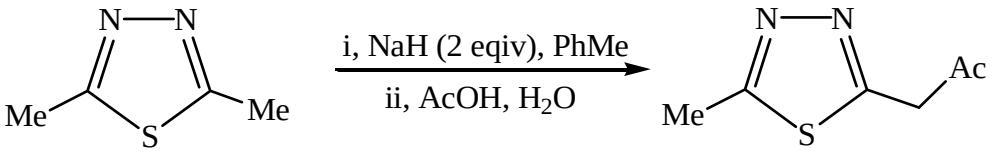
(i) Carbon substituents:

The lithiation of 2-methyl-1,3,4-thiadiazoles can be achieved with strong bases but the corresponding organolithium derivatives are unstable toward dimerization. Nevertheless, functionalization of the methyl groups can be achieved via treatment of methylthiadiazole with a base followed by addition of an electrophile. The lithiation of 2,5-dimethyl-1,3,4-thiadiazole **126a** with lithium diisopropylamide (LDA) followed by quenching with aldehydes or ketones gave either the mono- or bis-hydroxy arylated products **163** and **164** depending on the equivalents of base used [174].



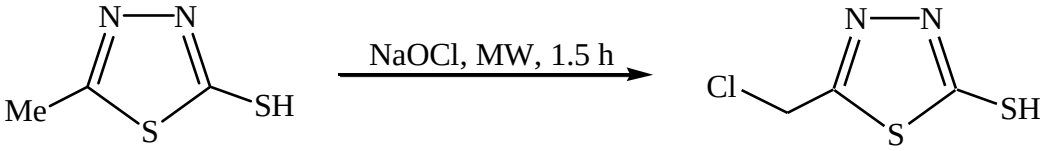
126a **163** **164**

Thiadiazole **126a** was also acetylated when treated with acetic acid in the presence of sodium hydride to give the thiadiazole **165** [175].



126a **165**

Halogenation of 2-methyl-1,3,4-thiadiazole **123** can be achieved under free radical conditions. Rapid and selective free radical monochlorination of the 2-mercapto-5-methyl-1,3,4-thiadiazole **123** was occurred using sodium hypochlorite under microwave conditions to afford **166** [176].

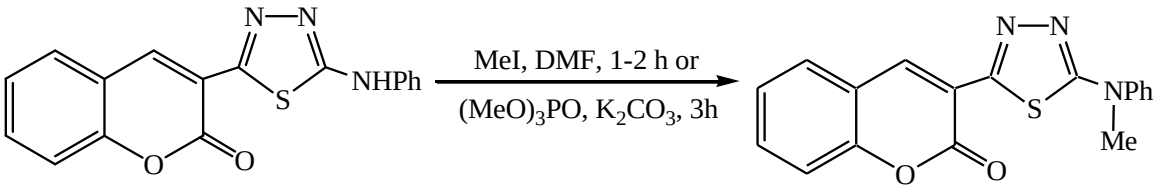


123 **166**

(ii) Nitrogen substituents:

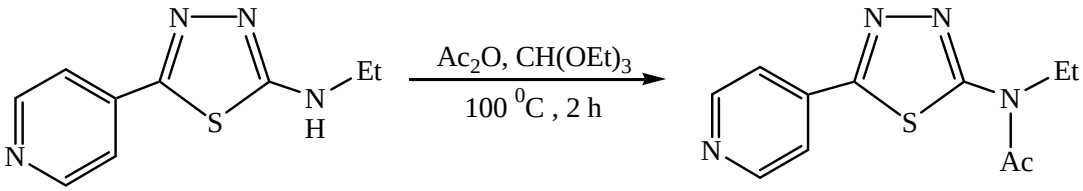
Exocyclic *N*-alkylation gives secondary and tertiary amines [177,69,71,72]. Reaction of secondary amines with nitriles gave amidines [178], acylating agents afforded amides [179] and isocyanates afforded ureas [180]. For example, the

secondary amino group in thiadiazole **167** was alkylated by methyl iodide in 73% yield or by trimethyl phosphate in the presence of anhydrous potassium carbonate to afford the 1,3,4-thiadiazol-2-yl coumarin derivative **168** [78].



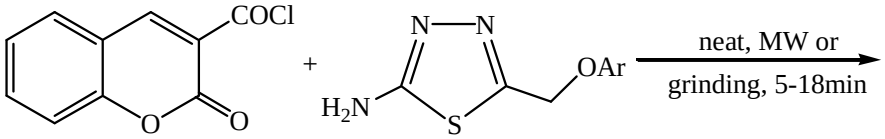
167 **168**

The secondary amine group of the thiadiazole **169** was acylated when heated in the presence of acetic anhydride and ethyl orthoformate to afford the amide **170** in 88% yield [181].

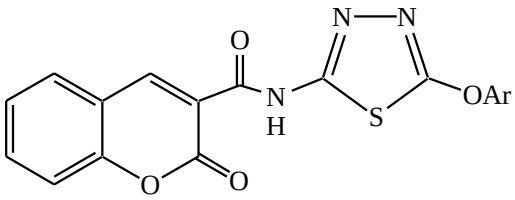


169 **170**

Grinding thiadiazolamines **172** with an equivalent of coumarin-3-carboxylic acid chloride **171** under solvent-free conditions in a mortar gave the corresponding amides **173** in 76-90% yield these amides were obtained when reactants were heated in a microwave oven for 5-18 min [182].

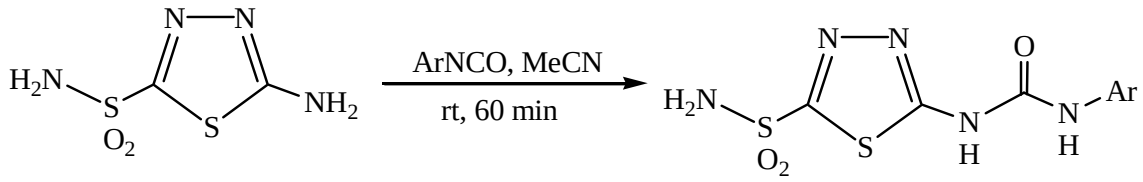


171 **172**

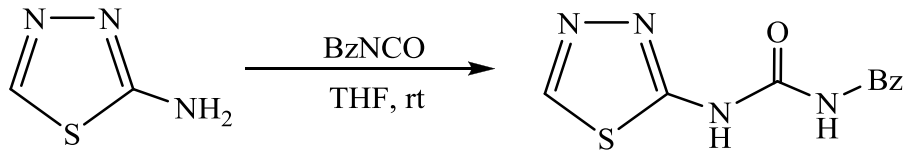


173

The reaction of pentafluorophenyl isocyanate with thiadiazole **174** in acetonitrile at room temperature gave 5-pentafluorophenylureido-1,3,4-thiadiazole-2-sulfonamide **175** [180]. Similarly, 2-amino-1,3,4-thiadiazole **176** reacted with benzyl isocyanate in dry THF to afford the 1,3,4-thiadiazole-2-yl urea **177** in 94% yield [183].

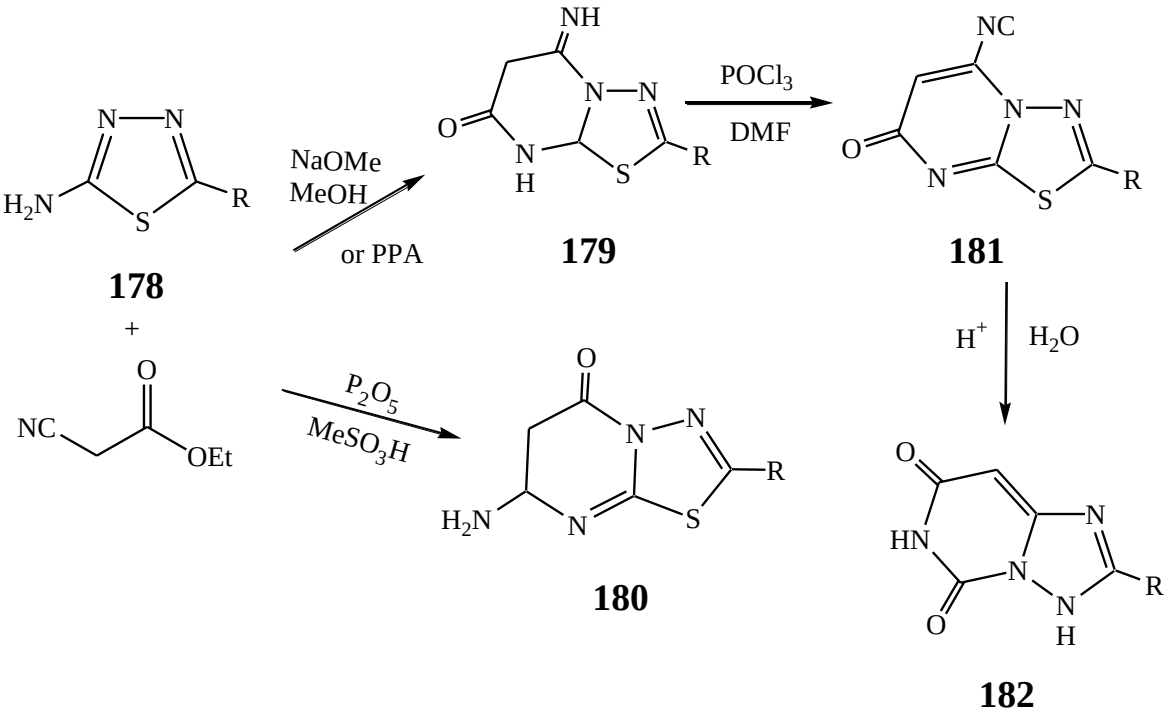


174 **175**



176 **177**

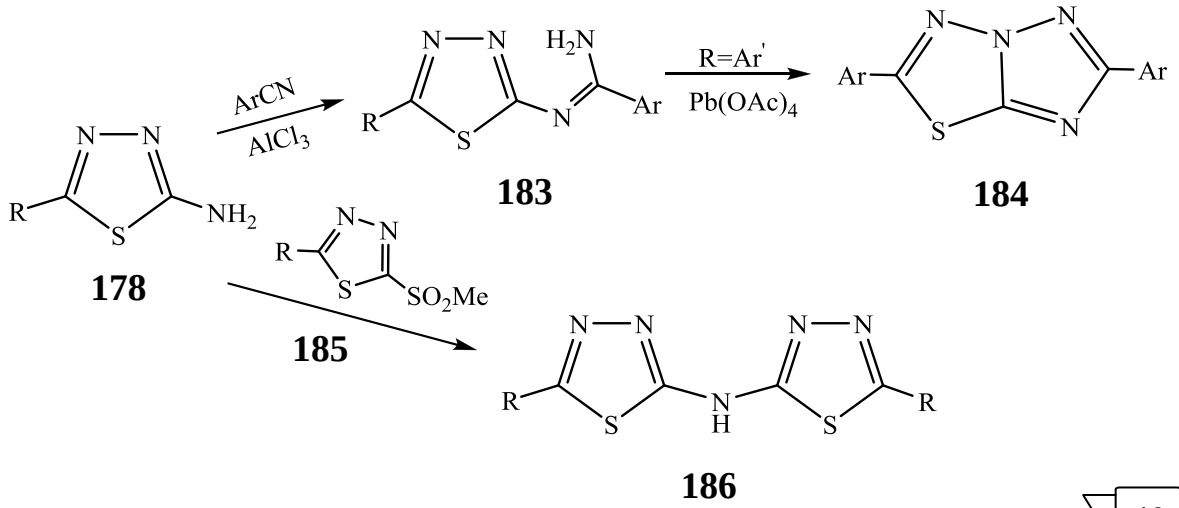
Treatment of 2-amino-5-substituted thiadiazoles **178** with ethyl cyanoacetate in the presence of sodium methoxide gave the 2-substituted- 5-imino-6*H*-[1,3,4]-thiadiazolo[3,2-a]pyrimidine-7-one **179**. When the same reaction was carried out in the presence of P_2O_5 and CH_3SO_3H instead of sodium methoxide, 7-amino[1,3,4]-thiadiazolo[3,2-a]pyrimidine-5-one **180** was obtained. Reaction of **179** with DMF/$POCl_3$ yielded the 5-isocyanide derivative **181** which on HCl hydrolysis gave **182** [184].



178 + **179** **181** **180** **182**

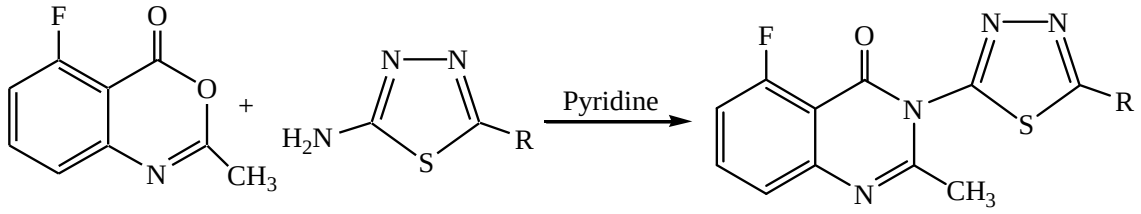
Reaction of 2-amino-5-aryl-thiadiazole (**178**; R=Ar) with aryl nitriles in the presence of aluminum chloride produced the aryl amidine **183** which was oxidized with lead tetraacetate to yield 2,6-diaryl-[1,2,4]-triazolo[5,1-b]-1,3,4-thiadiazoles **184** [185]. The yields of amidines depend on the reactivity of the nitriles. Decreasing the electron density of the cyano group by such electron-withdrawing groups as *p*-nitrophenyl-, and 2- and 4-cyanopyridyl, led to higher yields as compared to unsubstituted benzonitrile.

A bis thiadiazole **186** was prepared by reacting the sodium salt of **178** with 2-methanesulfonyl-5-*t*-butyl-1,3,4-thiadiazole **185** [186].



178 **183** **184** **185** **186**

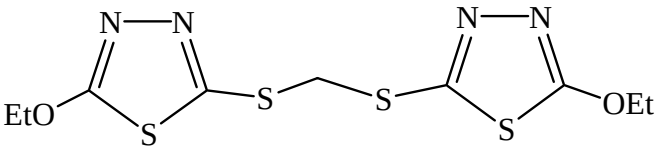
2-Aminothiadiazole (**178**; R=CF_3) condensed with 5-fluoro-2-methyl-benzoxazine-4-one **187** in refluxing pyridine to give 5-fluoro-2-methyl-3-(2-trifluoromethyl-1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinone **188** in about 60% yield [187].



187 **188**

(iii) Oxygen substituents:

2-Alkoxy-1,3,4-thiadiazoles can be dealkylated under acidic conditions to give 1,3,4-thiadiazol-2(3*H*)-ones. The selective and clean dealkylation of the ethoxy group in thiadiazole **189** was achieved with HBr in refluxing ethanol to give the thiadiazolone **190** (90%) [188].



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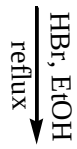
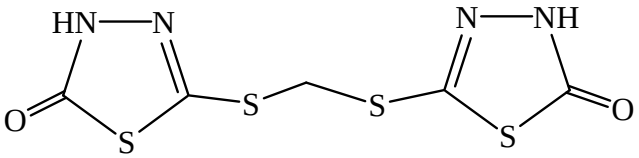




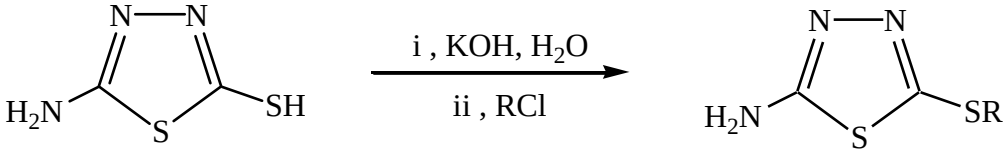
190

(iv) Sulfur substituents:

Sulfur substituent groups at C-2 and/or C-5 undergo alkylation and dealkylation reactions and can be converted into either sulfoxides or sulfones depending on the oxidation conditions. Alkylations [189] are often carried out

by deprotonation with alkali bases and subsequently *S*-alkylated with alkyl halides to give the corresponding thioethers [136].

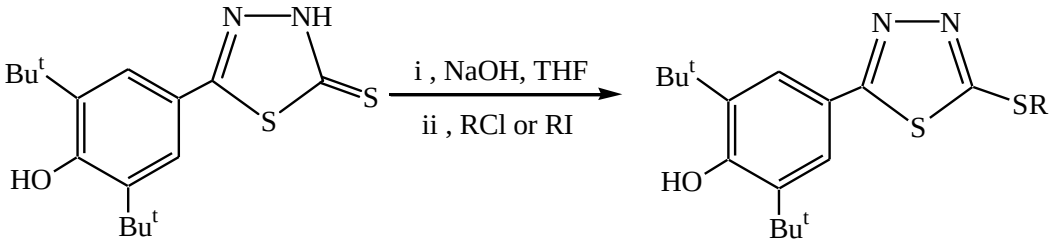
The 5-amino-1,3,4-thiadiazole-2-thiol **191** was suspended in a KOH solution and then treated with alkyl halides to afford the alkylated compounds **192** in 55-91% yields [190].



191 **192**

R = Me, Pr^n, Pr^i, Bz

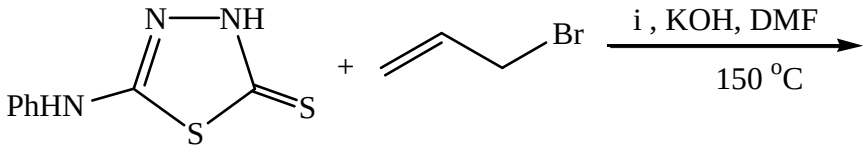
Also, the thiadiazole thione **193** was treated with an alkyl halide in sodium hydroxide to afford the thiadiazole derivatives **194a-d** in 35-92% yields [191].This reaction results in the aromatization of the reduced thiadiazoline ring.



193 **194a-d**

	R
a	CH_2CF_3
b	Pr^n
c	$CH_2CH_2NH_2$
d	$CH_2CH_2NEt_2$

The allylation of thiadiazole-2-thione **195** with allyl bromide gave, as the main product, the *N*-allyl derivative **196** with trace amounts of the corresponding *S*-derivative **197** [192]. Furthermore, it was shown that refluxing the thiadiazole **197** in DMF (3h) gave thiadiazole-2-thione **196** via a thio-Claisen rearrangement.



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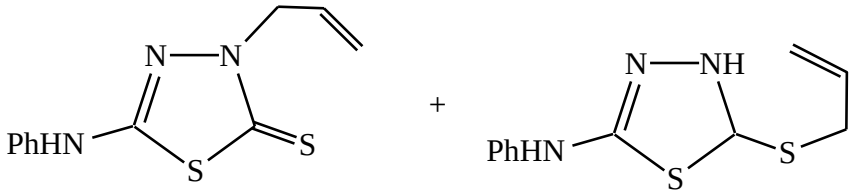
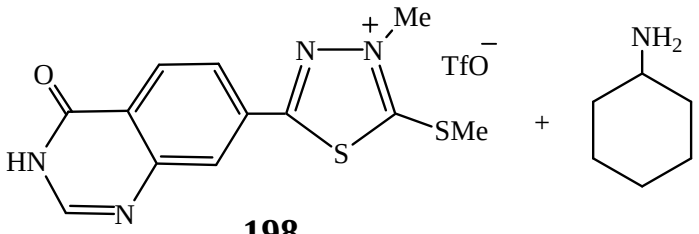


196 **197**

The sulfide group in mesoionic 1,3,4-thiadiazolium salt **198** was displaced by cyclohexylamine to afford the 2*H*-thiadiazolimine **199** because the sulfide group was activated toward nucleophilic substitution [193].



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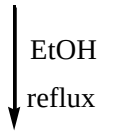
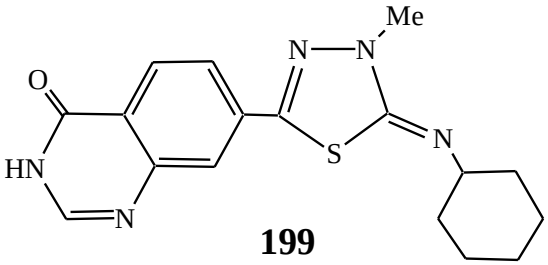
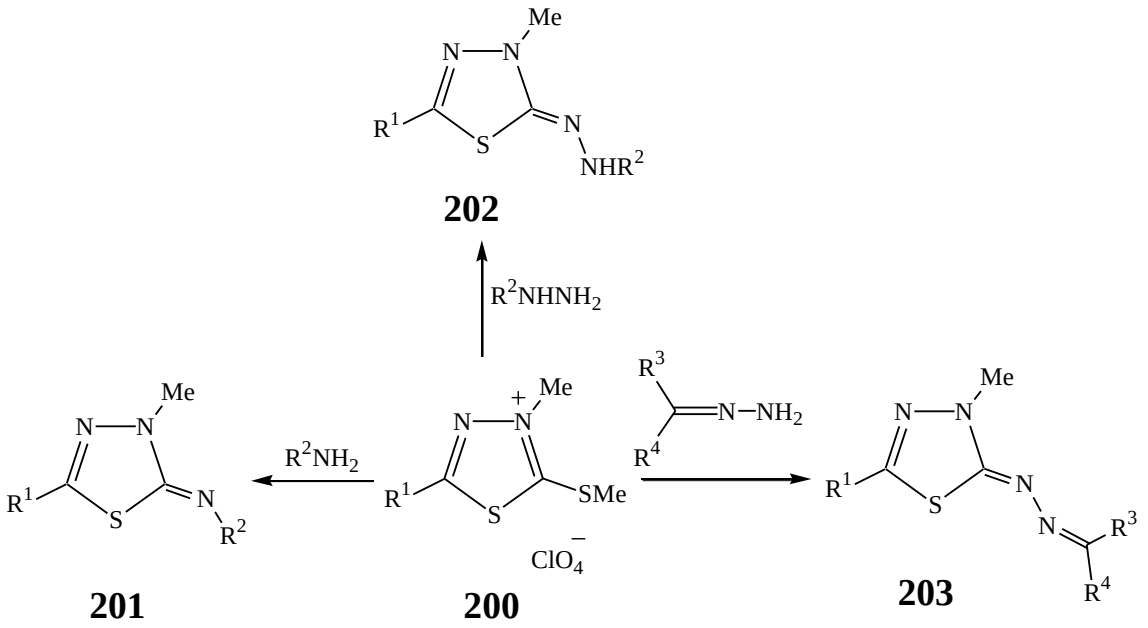


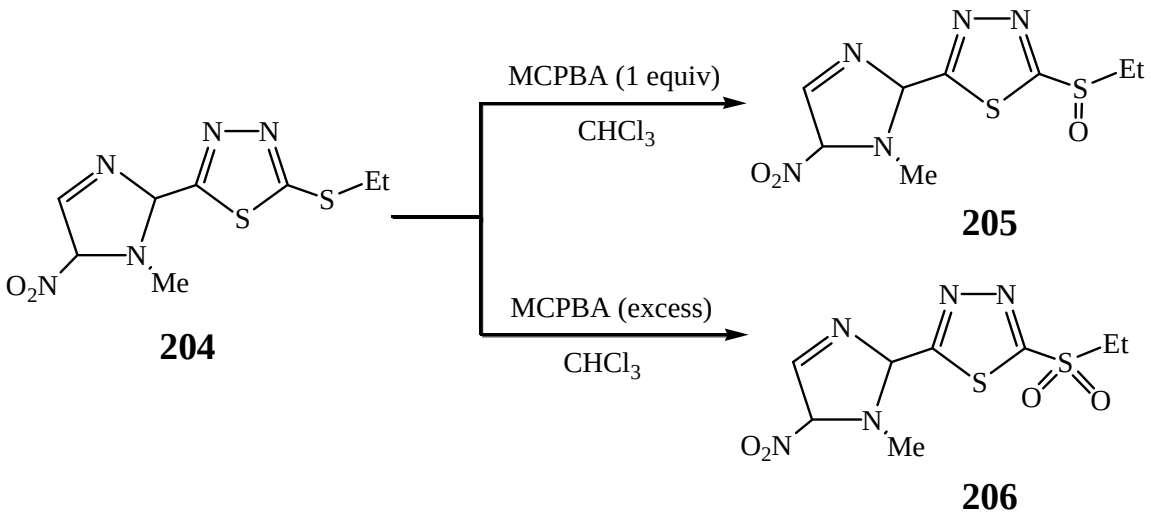


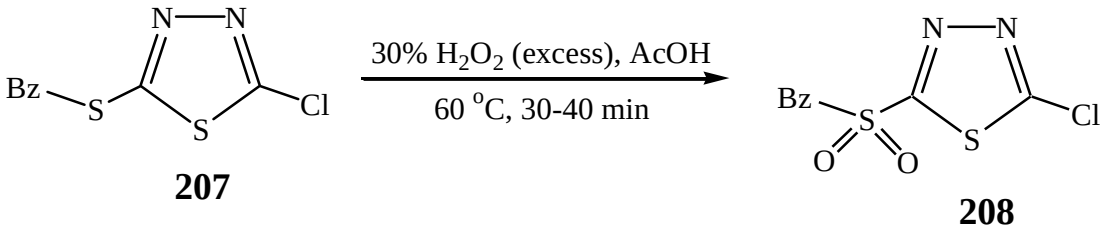
199

The good leaving properties of the thiomethyl group can be utilized for the introduction of various nitrogen functionalities into the 5-position. Thus, treatment of 2-methylthiothiadiazolium salt **200** with various amines led to the imines **201** while hydrazines and hydrazones yielded **202** and **203** respectively [194].



Oxidation of exocyclic sulfides to sulfoxides can be achieved using stoichiometric amounts of *m*-chloroperbenzoic acid (MCPBA) [162], whereas the use of excess MCPBA or hydrogen peroxide leads to the corresponding sulfones [195]. For example, treatment of 2-alkylmercapto-5-aryl-1,3,4-thiadiazole **204** with MCPBA (1 equiv) in chloroform gave the sulfoxide **205** and excess MCPBA gave the sulfone **206** [196]. Similarly, sulfide **207** was reacted with excess 30% hydrogen peroxide in acetic acid to afford the corresponding sulfones **208** [195].

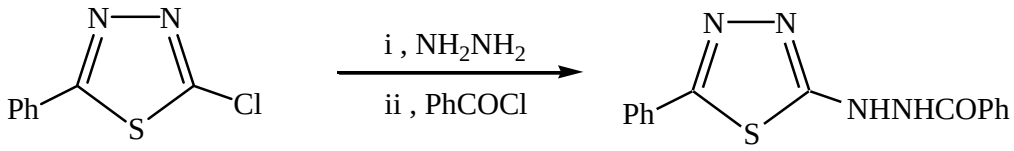




207 **208**

(v) Halogen substituents:

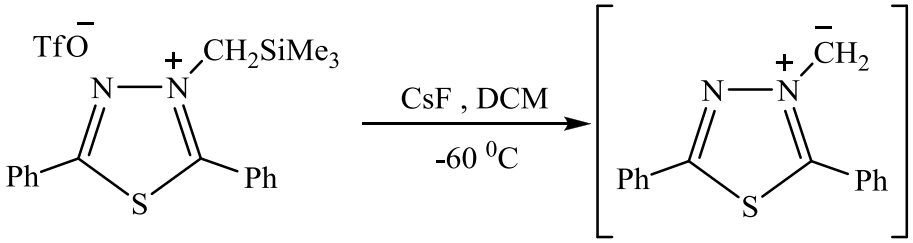
2-Chloro-5-aryl-substituted thiadiazoles were reacted with amines and hydrazines with explosion of chlorine atom. Treatment of 2-chloro-5-phenyl -1,3,4-thiadiazole **209** with hydrazine followed by benzoylation gave the thiadiazole derivative **210** [197].



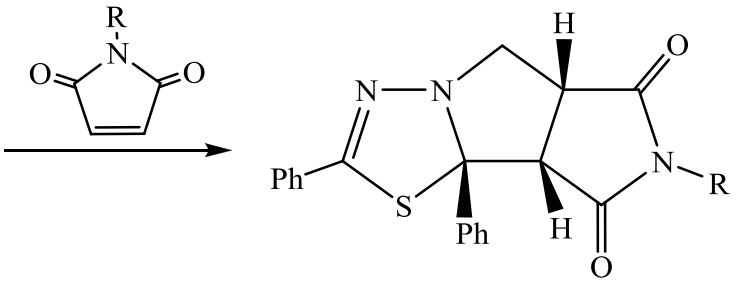
209 **210**

Reactivity of substituents attached to ring hetero atoms:

Very few publications are available on the reactivity of substituents attached to the ring nitrogen and sulfur atoms of thiadiazole. The desilylation of the 1,3,4-thiadiazolium salt **211** by CsF gave the unstable 1,3-dipole **212** which was trapped with *N*-substituted maleimides to afford exclusively the *endo*-pyrrolo[2,1-b][1,3,4]thiadiazoles **213** in 40-69% yields [157].

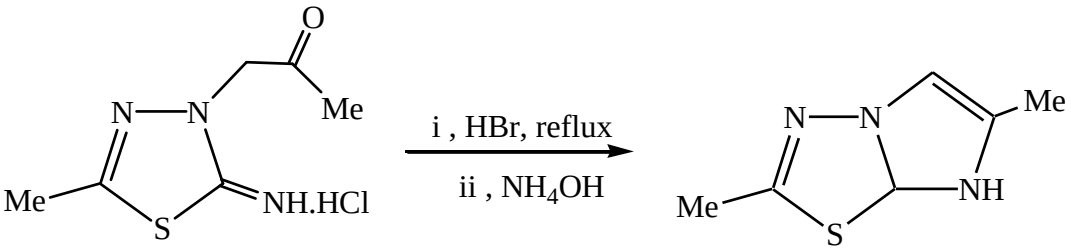


211 **212**



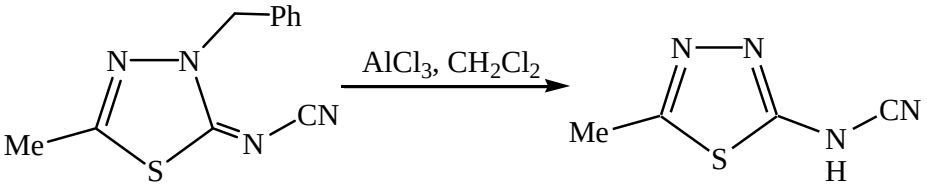
213

Substituents on the ring nitrogen can often cyclize to afford fused 1,3,4-thiadiazoles. The *N*-acetonyl substituent on the 1,3,4-thiadiazole derivative **214** was annulated on the ring when treated with HBr to give the imidazo[2,1-b][1,3,4]thiadiazole derivative **215** [156].

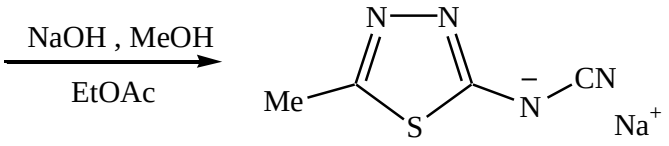


214 **215**

The *N*-benzyl group in **216** can be removed with $AlCl_3$ to give the cyanamide **217** and the antiviral compound **218** on further treatment with base [198].



216 **217**



218

Biological activity of thiadiazole derivatives

Condensed and non-condensed 1,3,4-thiadiazoles are a class of heterocyclic compounds having an important biological activity. 2,5-Disubstituted-1,3,4-thiadiazole derivatives are known to exhibit antibacterial [199-202], antifungal [203,204], antipsychotic [205] and anti-tubercular [206,207] beside it was the best documented as anti-inflammatory [208,209], analgesic [210], anticonvulsant [211], antitumoral [212-214] and antidepressant activity [190,215]. Also, 2,5-disubstituted-1,3,4-thiadiazole derivatives used as effective, cheap, and safe drugs for the treatment of leishmaniasis because of its in *vitro* leishmanicidal activity [167,216].

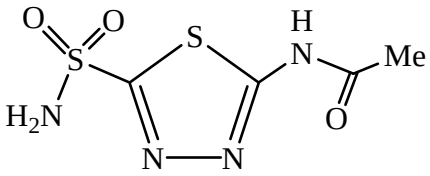
2-Amino-1,3,4-thiadiazole derivatives shows anticonvulsant [217,218], analgesic [219], anti-inflammatory [220,221], antiviral [222], antiprotozoal [44], antimicrobial [223,224] activities.

Recently, condensed and non-condensed thiadiazole derivatives have proved to possess biological activity as highly anticancer [225-227], antimycotic [228], antisecretory [156], anti-trypanosomal [229], antibacterial [230] and anticonvulsant [231] activities, cardiotonic [232], diuretic [233] and Alzheimer diseases [234].

Also, thiadiazole derivatives have been used as antiviral medicants against herpes virus cytomegalovirus (CMV) [235], as medicants for inflammatory disease such as hypersensivity reactions, asthma, rheumatoid, arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications [236] and for many other medical applications.

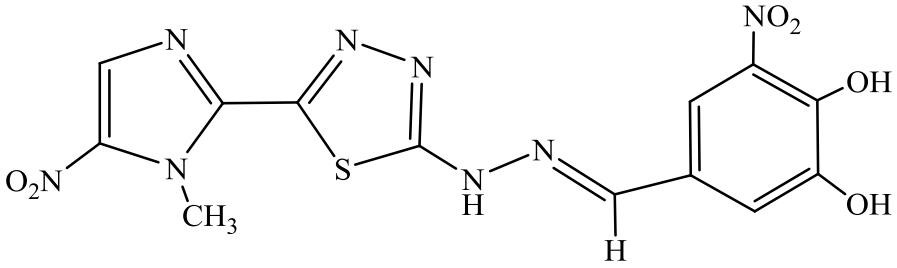
One of the best known drugs based on the thiadiazole molecule is acetazolamide **219**, also called acetazola which is a carbonic anhydrase inhibitor. Its indication and usage are many including glaucoma, epilepsy and

congestive cardiac failure. Although it is an old drug, attempts to improve its efficiency and decrease its side effects continue [237].



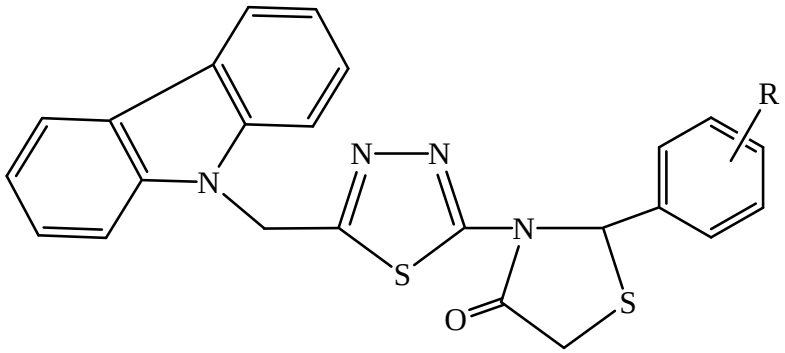
219

3,4-Dihydroxy-5-nitrobenzaldehyde [5-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-1,3,4-thiadiazole-2-yl]hyrazone **220**, which is known as brazilizone A, showed potent in vitro trypanocidal profile. Experimental IC_{50} values for such compound correlate with the predicted by 3D-QSAR CoMFA model [44].



220

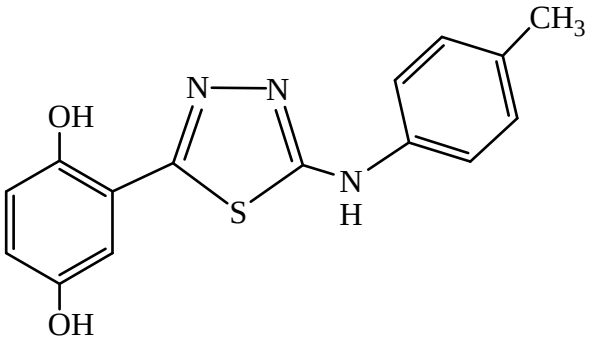
9-[4'-{Substitutedphenyl}-2-oxo-thiazolidin-1''-yl-1',3',4'-thiadiazol-5'-yl]methylene carbazoles **221**showed good antipsychotic and anticonvulsant response when compared to the reference drug, Chlorpromazine (CPZ) [205].



221

1,3,4-Thiadiazole derivatives **222**, **223** and **224** have been shown to possess a promising antileishmanial effect in *vitro*. The high leishmancidal

activity of such compounds led for the development of effective therapeutic agents [167,238].



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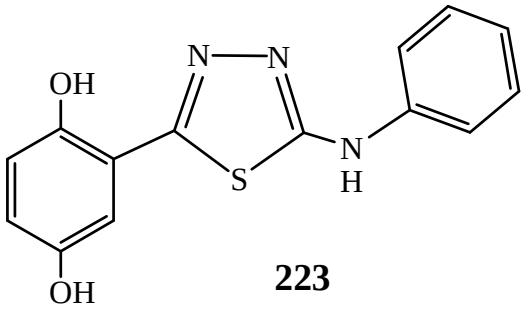

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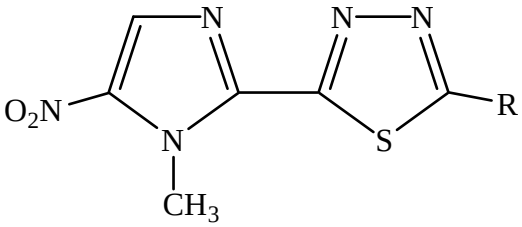
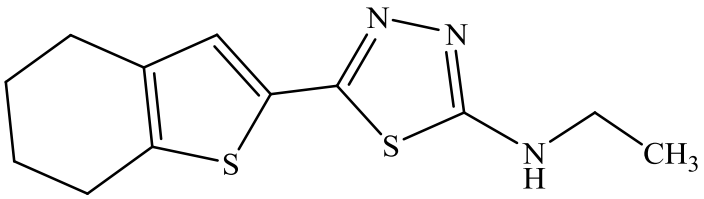


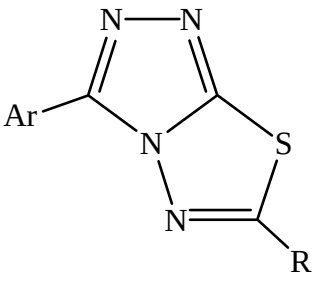
224

N-Ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazol-2-amine **225** was evaluated for cytotoxicity and was found to possess high cytotoxicity in vitro against thymocytes with IC_{50} value of 5.2×10^{-6} µM [239].

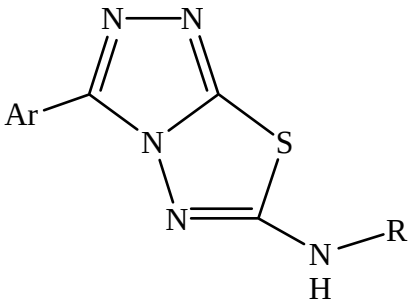


225

3,6-Disubstituted[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives **226** and **227** were found to have dual functional properties (anti-inflammatory, analgesic and antimicrobial) and represent a promising class of compounds with interesting pharmacological profile [240].

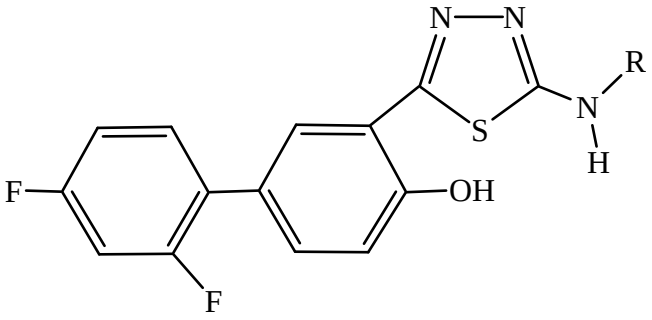


226



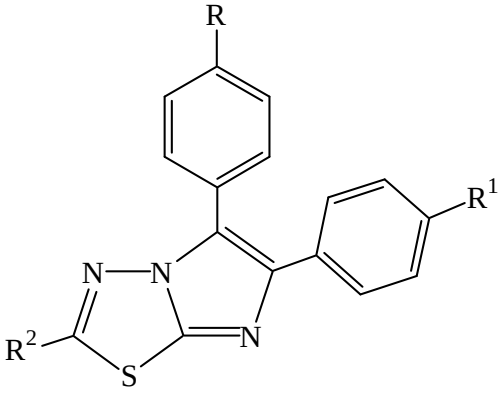
227

The anti-inflammatory activity of thiadiazole derivatives **228** was evaluated and compared with the reference drug diflunisal. Most of the tested compounds showed higher anti-inflammatory (23.85 to 73.03% inhibition) than the reference drug (24.16% inhibition) [220].



228

Imidazo[2,1-b][1,3,4]thiadiazole derivatives **229** showed excellent in *vitro* cyclooxygenase inhibitory activity against COX-1 and COX-2 enzymes [234].

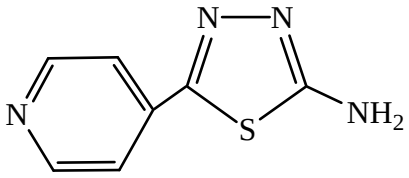


229

Miscellaneous applications of thiadiazole derivatives

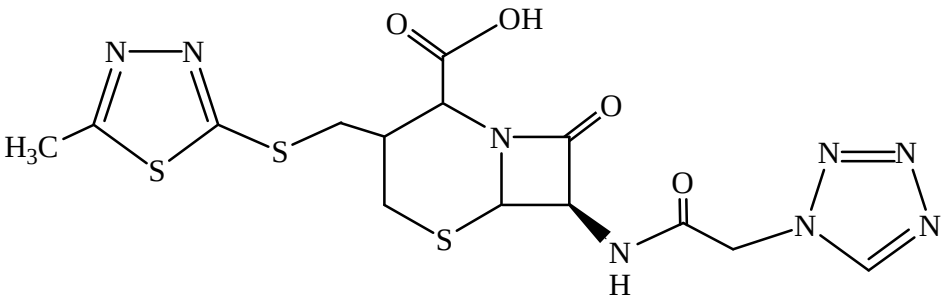
Some of the technological uses of the 1,3,4-thiadiazoles involve dyes, metal complexation agents [241], corrosion and oxidation inhibitors [242], optically active liquid crystals, epoxy resins, photographic materials, lubricating compositions and optoelectronic materials [160].

2-Amino-5-(4-pyridyl)-1,3,4-thiadiazole (4-APTD) **230** was found to be good inhibitor for mild steel corrosion in 0.5 M H_2SO_4 [243].



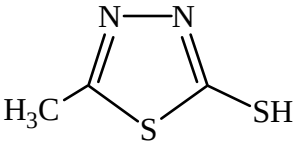
230

Cefazolin **231** acts as a good inhibitor for the corrosion of mild steel in 1.0 M HCl and the inhibition efficiency of this compound decreased with temperature, which leads to an increase activation energy of corrosion process [244].



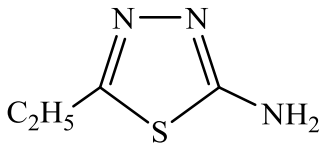
231

2-Mercapto-5-methyl-1,3,4-thiadiazole **232** was used as a hetero-difunctional S,N-donor ligand for the reaction of ruthenium complexes [245].



232

2-Amino-5-ethyl-1,3,4-thiadiazole **233** has been evaluated as a corrosion inhibitor for copper in de-aerated, aerated and oxygenated 3.0% NaCl solution using weight loss and potentiodynamic polarization [246].



233

Further developments

Novel substituted 1,3,4-thiadiazoles were synthesized under both sonication and classical conditions. Generally, improvements in rates and yield of reactions were observed when reactions were carried out under sonication compared with classical condition [247].