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Synthesis of 1,3,4-Thiadiazoles: Review

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Abstract
Molecules with 1,3,4-thiadiazole ring structures have potential biological relevance. These organic molecules have potentially reported for their medicinal importance. In this review, different strategies for the synthesis of biologically important molecules of 1,3,4-thiadiazole ring are briefly summarized and an attempt has been made with recent research findings on this nucleus, to review the structural modifications on different thiadiazole derivatives. Its covers advances made in the last two decades and a brief account of various alterations done on the thiadiazoles nucleus.

Keywords: 1,3,4-Thiadiazole, isomers, isosterism, thiosemicarbazides, 1,2,5-thiadiazole, thiophene, thiazole.

1. Introduction

Thiadiazoles are compounds of azole family and the name originated from Hantzsch-Widman nomenclature. They are five-membered heterocyclic compounds having one sulfur and two nitrogen atoms with formula $C_2H_2N_2S$. It contains aromatic ring by virtue of their two double bonds and the sulfur lone pair. Basically, there are four isomeric forms of thiadiazole *viz*. 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole (**Fig.1**) and exists only depending on relative positions of their heteroatoms. These forms do not interconvert and hence they are structural isomers and not tautomers [1].

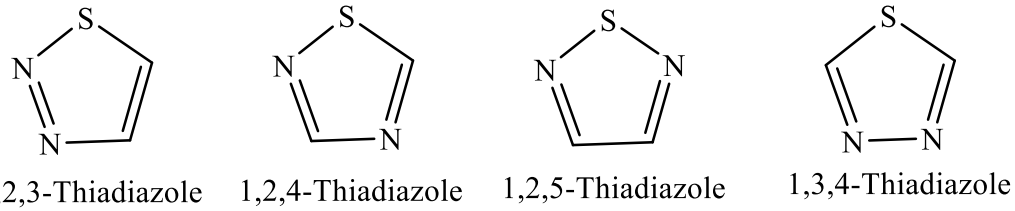


Fig. 1 Structure of thiadiazole isomers

The compounds bearing them as a structural motif are fairly common in pharmacology. In five-membered ring structures one or more heteroatoms are present, such as thiadiazole, oxadiazole, azole, thiazole, pyrrole and triazine. Amongst these, thiadiazole is considered as one of the most significant and well-known heterocyclic nuclei, as it is reported with various pharmacological performance [2]. The compound 1,3,4-thiadiazole was first described in 1882 by Fischer and further developed by Bush and his coworkers [3], its properties of ring system was described by two chemists named Kuh and Freund in 1890 [4], but true nature of the ring system was demonstrated first in 1956 by Goerdler *et al.* [5]. Thiadiazoles possess extensive application as structural units of biologically active molecules and also useful as intermediates in medicinal chemistry [6]. It plays an important role as an organic compound with biological activity as drugs in human and veterinary medicine or as insecticides and pesticides in agriculture along with plastics, polymers and dyes manufacturing [7]. 1,3,4-thiadiazole is the highly useful isomeric form because of its diverse biological actions in body. In particular, compounds bearing the 1,3,4-thiadiazole nucleus is known to have exclusive action as anti-bacterial, anti-cancer, anti-inflammatory, anti-tubercular, molluscicidal, anti-convulsant, anti-leishmanial, anti-viral, anti-fungal, anti-depressant, anti-anxiolytic, anti-diabetic, anti-oxidant, amoebicidal, anti-diuretic, anti-neoplastic and analgesic activities [8]. Drug resistibility is the major problem occurring worldwide and to deal with this, the need of synthesizing new compounds has been become one of the most interesting research areas. It is supposed that 1,3,4-thiadiazole derivatives exhibit various biological activities due to the presence of -N=C-S- moiety in ring of unsaturated structures. Most of the authors assume that the biological activities of 1,3,4-thiadiazole derivatives are due to the strong aromaticity of the ring, which also provides great *in vivo* stability to this five-membered ring system and low toxicity for higher vertebrates, including human beings [9].

There are some studies that show the importance of isosterism (replacement of thiazole moiety) for the pharmacological profile of a compound. According to these studies, the 1,3,4-thiadiazole is the bioisostere of pyridazine through the substitution of -CH=CH- by -S- (**Fig. 2**).

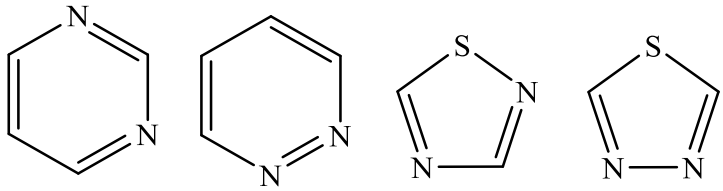


Fig. 2 Isosterism between the diazaheterocycles and thiadiazole derivatives

The thiadiazole ring is also a bioisostere of oxadiazole, oxazole, thiazole and benzene ring. The bioisosteric replacement of a ring with another ring might lead to compounds with enhanced lipophilicity because sulfur atom and improved biological properties [10]. Due to the presence of sulfur atom that gives high liposolubility, show oral absorption and good cell permeability leading to a good bioavailability [11]. In addition, substitution of a homocyclic ring with a heterocycle makes the synthesis of different analogs possible which interact more with the receptors. Considering the high prevalence of pyridazine ring in compounds possessing biological activities and thus the potential of thiadiazole derivatives to exhibit biological activities is very high [12]. Moreover, 1,3,4-thiadiazole derivatives can produce mesoionic salts (**Fig. 3**). Mesoionic system contains a heterocyclic ring which possesses a sextet of *p* and π electrons and positive charge counter balanced by formal negative charge [13]. Despite their internal charges, the mesoionic compounds are neutral and able to cross cellular membranes and this contributes to the good cell permeability of 1,3,4-thiadiazole derivatives. The mesoionic nature of 1,3,4-thiadiazoles enables these compounds to interact strongly with biomolecules [14].

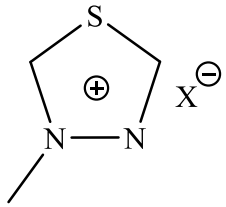


Fig. 3 Structure of the mesoionic salt

The biological importance of 1,3,4-thiadiazole derivatives has been reported following the discovery of heterocyclic sulfonamides as reasonable antimicrobial agents (sulfathiazole). In analogy to sulfathiazole, other sulfonamides showing similar activity such as sulfamethizole, Rufol or sulfaethidole and Globucid. Except sulfathiazole that is still used in the treatment of *Haemophilus vaginalis* vaginitis, sulfamethizole and sulfaethidole currently possess only historical importance [15]. Moreover, the capability of the hydrogen binding domain allows the use of 1,3,4-thiadiazole as one of the potential agents in many drugs (**Fig. 4**) such as Desaglybuzole/Glybuzole/Gludiase (anti-diabetic), Litronesib (anti-cancer), Cefazedone/ Refosporin (anti-biotic), Sulfamethizole (anti-bacterial), Atibeprone (anti-depressant), Cefazoline/Cefazolin (anti-biotic), Sulfaethidole (anti-biotic), Methazolamide/Neptazane (anti-glucoma), Acetazolamide/Diacarb/Diamox (anti-glucoma), Butazolamide (diuretic), Azetepa (anti-neoplastic), Megazol (anti-protozoa) and many more medicines are available in the market [16].

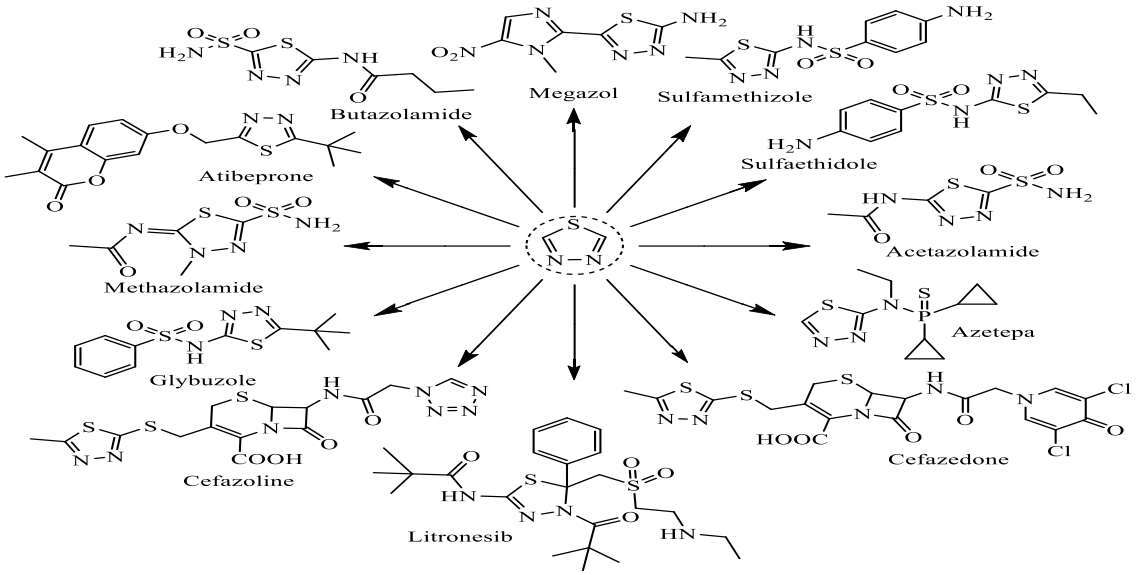


Fig. 4 Biologically relevant drugs of 1,3,4-thiadiazole moiety

The thiadiazole was the most significant nuclei, as a well-known whole characteristic of diversity of natural medicinal agents. Members of this ring system have found their way into such diverse application as pharmaceuticals, oxidation inhibitors, cyanine dyes and metal complexing agents [17]. In view of the standard reference work shows that more work has been carried out on the 1,3,4-thiadiazole than all other isomers combined. 1,3,4-Thiadiazole acts as "hydrogen binding domain" and "two electron donor system" with a constrained pharmacophore. The 1,3,4-thiadiazole isomer of thiadiazole series and its dihydro derivatives provide a bulk of literature on thiadiazole. The researchers are working more on the 1,3,4-thiadiazole isomer than the other three isomers of thiadiazole altogether. The 1,3,4-thiadiazole ring possesses high aromaticity, becoming stable in acid but forming a ring cleavage with base. This scaffold is electron deficient, relatively inert towards electrophilic substitution and displays nucleophilic substitution at 2nd and 5th positions due to which it is highly activated and reacts easily. Because of these properties of 1,3,4-thiadiazole, it is widely used in research by chemists and scientists [18]. The significant biological activities encouraged several research groups to find out different methods for synthesis of new thiadiazoles using different synthones, such as thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines, acylhydrazines, and bithioureas [19]. The uniqueness of these heterocycle systems is based on easy functionalization with the possibility of obtaining various condensed and non-condensed derivatives [20]. The present review, emphasizes on the synthesis and biological activities revealed by substituted 1,3,4-thiadiazoles. The review covers advances made in the last two decades and a brief account of various alterations done on the thiadiazoles nucleus.

2. Chemistry of 1,3,4-thiadiazole

1,3,4-Thiadiazole ring is less aromatic as compared to benzene, thiophene and pyridine. The aromaticity of these rings is measured by delocalization of π electron which is decreases in the order as 1,2,5-Thiadiazole > Thiophene > Thiazole > 1,3,4-Thiadiazole. The electron withdrawing nature of the nitrogen atoms ensures that electrophilic attack at carbon is very rare whereas nucleophilic substitution reactions are common. In addition, electrophilic attack at the sulphur atom has also been observed [21]. 1,3,4-Thiadiazoles are weak base due to the inductive effects of extra hetero atoms and are readily alkylated and acylated at nitrogen. The ring is relatively stable in aqueous acid solutions but the ring gets cleaved in aqueous basic solutions. 1,3,4-Thiadiazole core skeletons are subjected to various substitution reactions with alkyl halides, acid chlorides and sulfonyl chlorides to afford various drug like 2-amino-substituted-1,3,4-thiadiazole derivatives. When substituents are introduced into 2 or 5 position of this ring, the ring is highly reactive and forms different derivatives of thiadiazole easily.

The reactivity of atom nitrogen of ring arises from electrophilic reactions depending on tautomeric equilibrium of thione-thiol or amine-imine. In thione or imine form deprotonation of ring at N-H can take place and ring nitrogen atom becomes vulnerable to alkylation or acylation or transformation to 1,3,4-thiadiazolium salt. The reactions are conducted with electrophiles such as alkyl halides, formaldehyde *etc*. 1,3,4-thiadiazole ring can be classified [22] into three sub-categories: -

(a). Aromatic systems or neutral thiadiazoles **1**.

(b). Non-aromatic systems *i.e.*, Δ^2-thiadiazolines **2**, Δ^3-thiadiazolines **3** and the thiadiazolidines **4**. Systems the non-aromatic such as **5** are aromatic but the tautomeric forms such as **6** and **7** are not aromatic. They are partially reduced systems and the position of the double bond is denoted by the prefix Δ.

(c). Mesoionic systems **8** are neither covalent nor polar with sextet of electrons in the ring. Benzo fusion in 1,3,4-thiadiazoles is not possible.

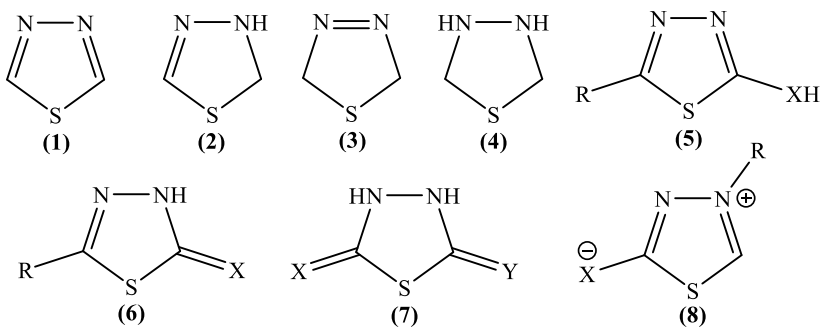


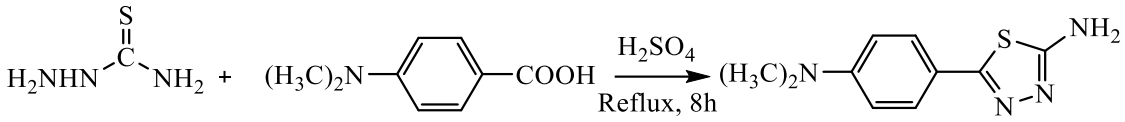
Fig. 5 Subcategories of thiadiazole

3. Synthetic strategies of 1,3,4-thiadiazole

The synthesis methods of 1,3,4-thiadiazole have been reviewed in detail and highlighting the overview of general synthesis methods. There are various strategies for preparing thiadiazole derivatives but few of them are discussed as below:

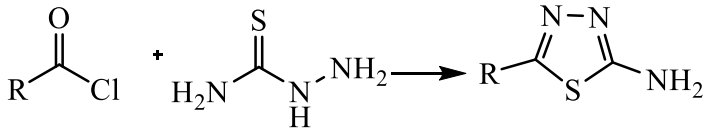
[1]. From thiosemicarbazide: Many syntheses of the 1,3,4-thiadiazoles proceed from thiosemicarbazides or substituted thiosemicarbazides.

[a]. Condensation reaction: The condensation of thiosemicarbazide with carbonyl groups like (carboxylic acid, ester, aldehyde) in presence of sulfuric acid, gives cyclized product of thiadiazole derivatives in acid medium [23] as shown in Scheme 1.



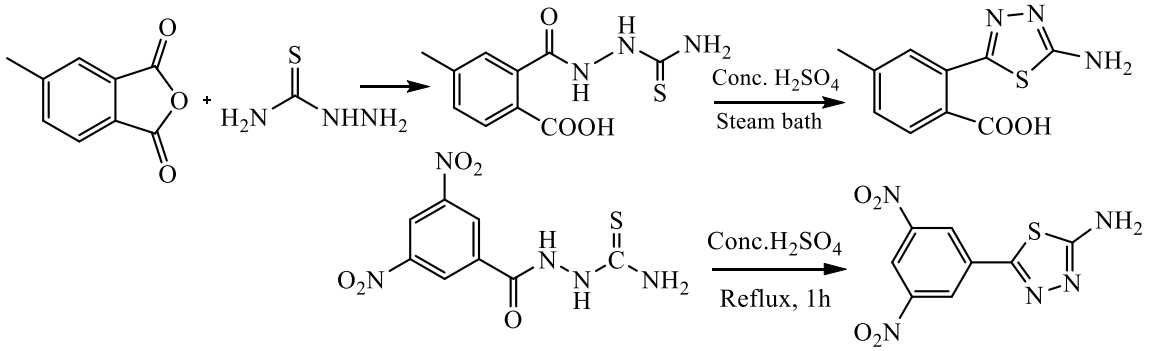
Scheme 1 Condensation of carboxylic group with thiosemicarbazide

Gupta *et al.*, have shown (Scheme 2) that thiosemicarbazide cyclizes directly to 2-amino-5-diazole with acetyl chloride (R = Methyl, benzyl, cyclopropyl). This simple route to 2-amino-5-substituted-1,3,4-thiadiazole seems to be quite general [24].



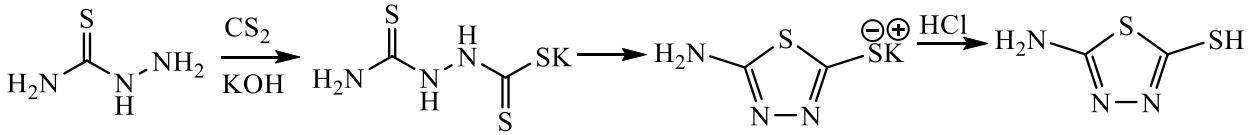
Scheme 2 Condensation of acetyl/aryl chloride with thiosemicarbazide

It has also been observed that 5-(2-carboxy phenyl)-2-amino-4,3,1-thiadiazole was obtained from the interaction of phthalic acid anhydride with thiosemicarbazide in the presence of snowy acetic acid and then the result was converted to 1,3,4-thiadiazole [25] at 90 ^{0}C on reflux 2h with concentrated sulfuric acid shown in Scheme 3.



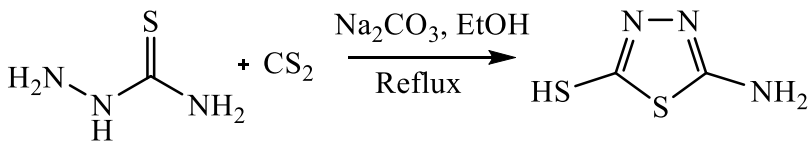
Scheme 3 Cyclization of thiosemicarbazide with H_2SO_4

[b]. Cyclization reaction: Cyclization reaction with CS_2 in special conditions by reaction is ring closure step with carbon disulfide in presence of potassium hydroxide [26], shown in Scheme 4.



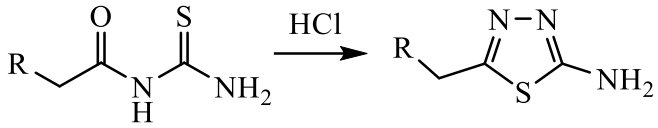
Scheme 4 Cyclization of thiosemicarbazide with CS_2

Petrow *et. al.*, have synthesized the thiadiazole derivative [27] containing the thiol group from the non-compensated thiosemicarbazide interaction with the carbon disulfide in a basic medium shown in Scheme 5.



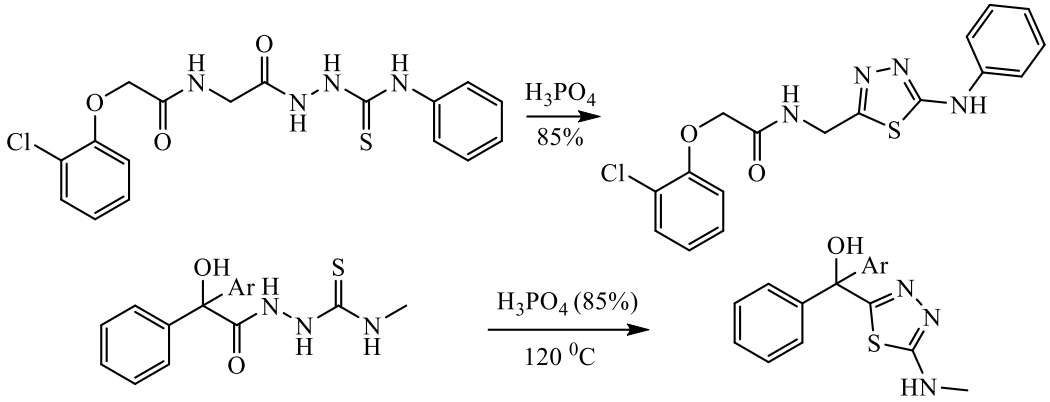
Scheme 5 Cyclization of thiosemicarbazide in Na_2CO_3

Thiosemicarbazide derivatives are important primary compounds for the preparation of the thiadiazole derivatives. These derivatives are prepared in several ways, including the cyclization of thiosemicarbazide [28], shown in Scheme 6.



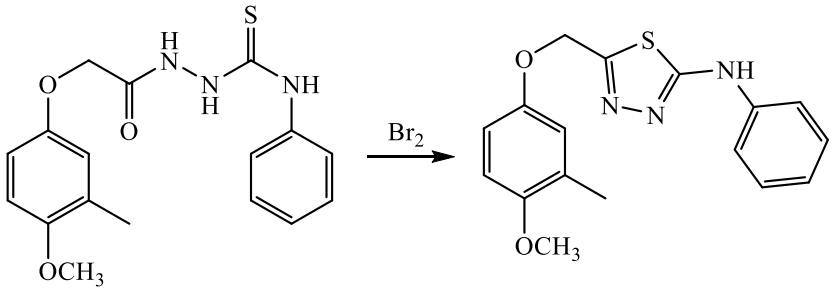
Scheme 6 Cyclization of thiosemicarbazide with HCl

Phosphoric acid was also used as a cyclic closure agent for thiosemicarbazide derivatives to obtain thiadiazole derivatives [29] *via* using closure agents like phosphoric acid in acid medium as a condition of this reaction, shown in Scheme 7.



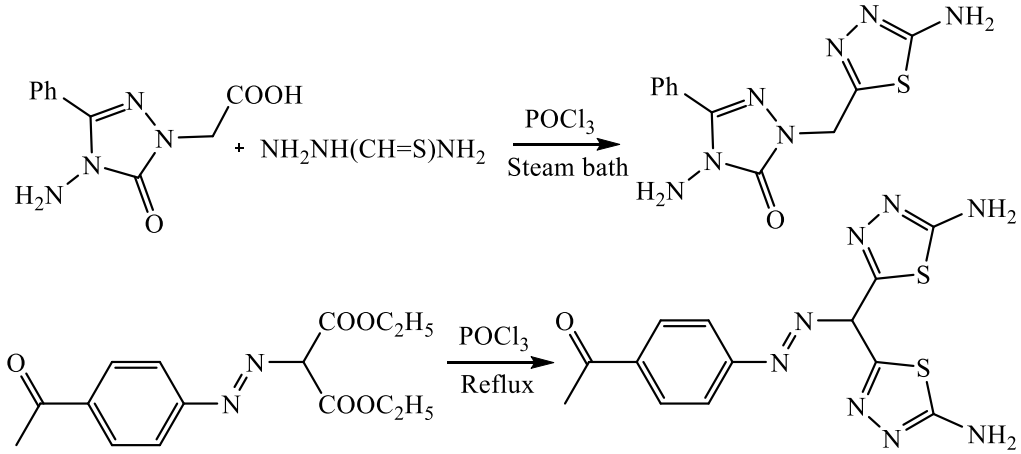
Scheme 7 Cyclization of thiosemicarbazide with Phosphoric acid

There are other methods for preparing (1,3,4-thiadiazole) compensators, including the interaction of thiosemicarbazide compensators with Br_2 also *via* cyclization step, as this method gives product [30] as shown in Scheme 8.



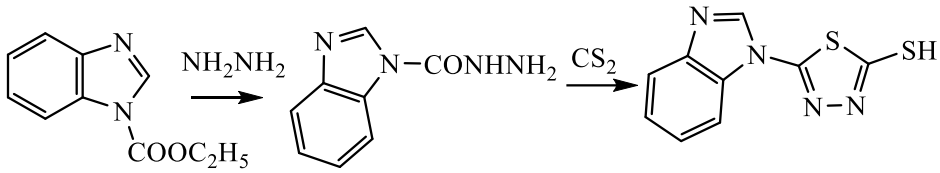
Scheme 8 Cyclization of thiosemicarbazide with Br_2

It is also possible to obtained 5-compensated-2-amino-4,3,1-thiadiazole from the reaction of thiosemicarbazide with the carboxylic acid in the presence of phosphorous chloride and by escalating the mixture in a water bath for two hours [31]. Also, it occurs *via* cyclization of ester with thiosemicarbazide in presence of $POCl_3$ shown in Scheme 9.



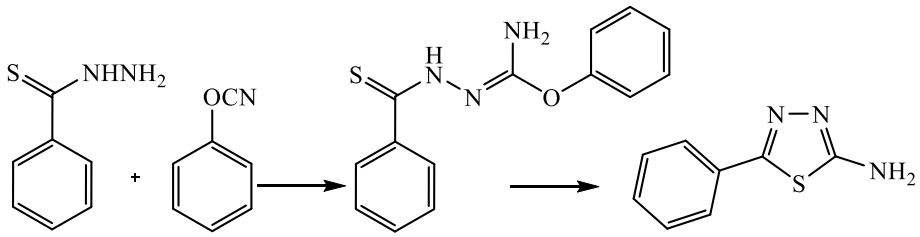
Scheme 9 Cyclization of thiosemicarbazide with phosphorous chloride

Cyclization of carbonyl in ester compound with hydrazine derivatives to yield thiadiazole [32] compound or any amine derivatives by ring closure step with carbonyl of ester, besides that, it can result from reaction with carbonyl of carboxylic acid also, shown in Scheme 10.

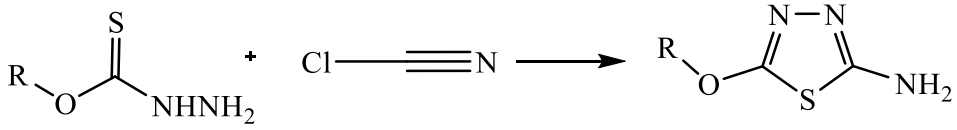


Scheme 10 Cyclization of ester with hydrazine

[2]. From hydrazine: Thiobenzoylhydrazine cyclized to produce 1,3,4-thiadiazole-thiobenzoylhydrazine (Scheme 11). Thionecarbazate are cyclized by cyanogens chloride or bromide to give 1,3,4-thiadiazole [33, 34] (Scheme 12).

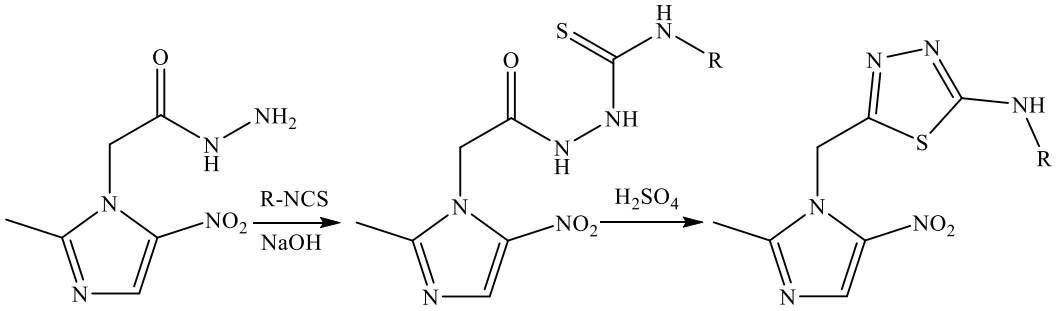


Scheme 11 Cyclization of thiobenzoylhydrazine



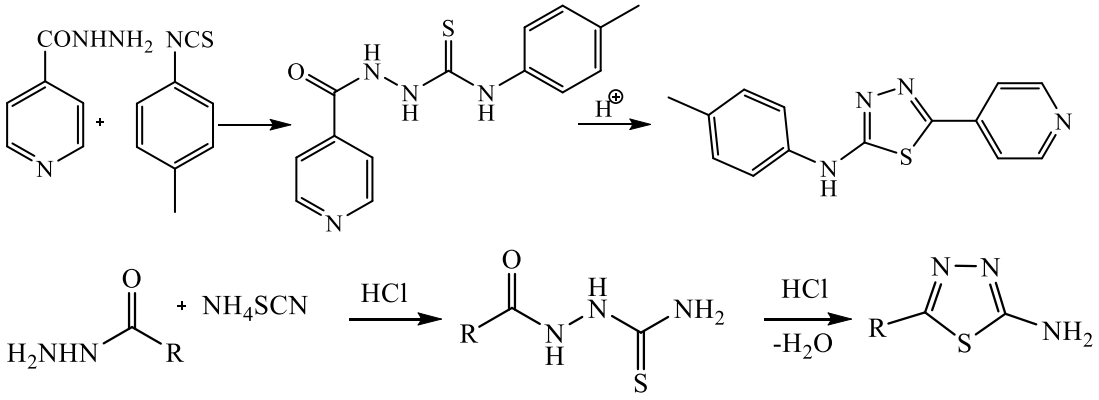
Scheme 12 Cyclization of thionecarbazate

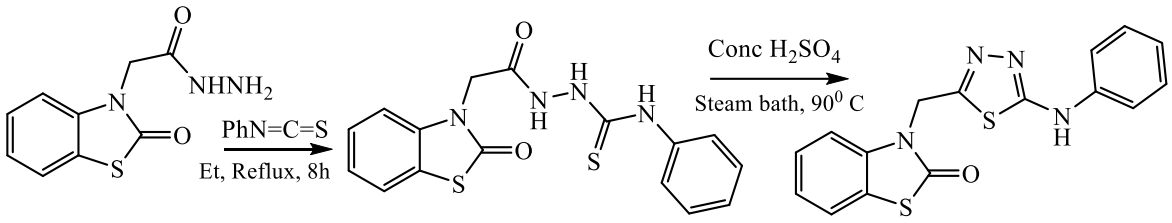
Mirzaei *et al*., synthesizes thiadiazoles from acylhydrazines (Scheme 13). The reaction of acylhydrazine with substituted isothiocyanate and sodium hydroxide in ethanol gives thiosemicarbazide which on cyclization in an acidic medium provided *N*-substituted 2-amino-5-[(2-methyl-5-nitro-1H-imidazol-1-yl)methyl]-1,3,4-thiadiazoles [35].



Scheme 14 Preparation of thiadiazoles from acylhydrazine

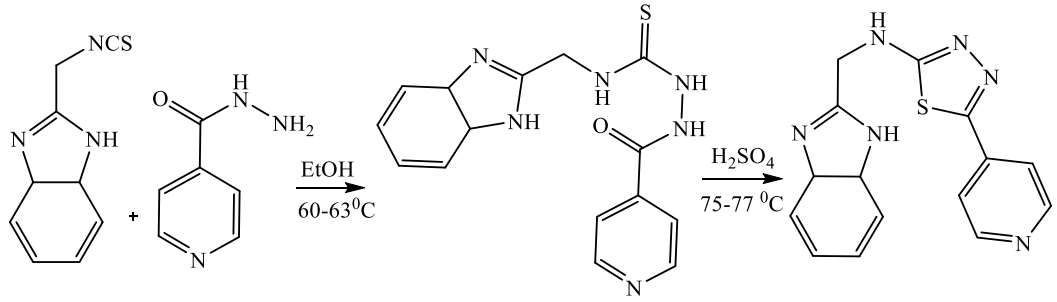
[3]. From thiocyanate derivatives: Condensation of Hydrazo-derivatives with thiocyanate compounds in acid medium to produce thiadiazole compounds *via* ring closure by using conditions and using closure agents for this reaction [36], shown in Scheme 15.





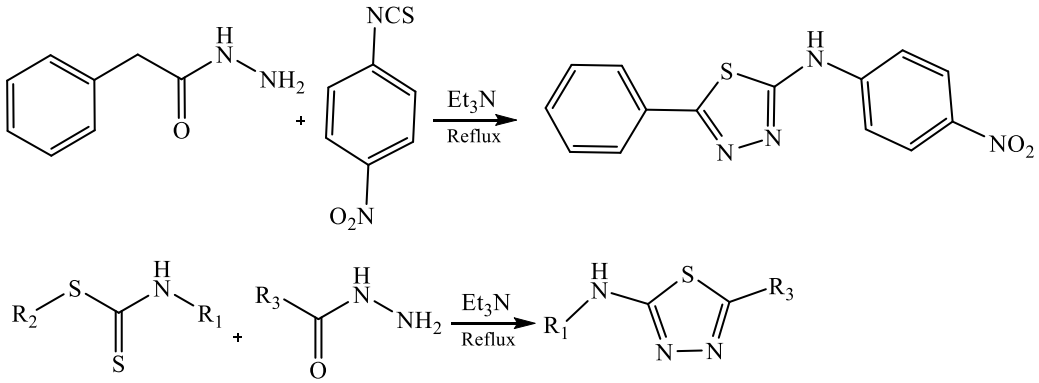
Scheme 15 Condensation with thiocyanate derivatives

Ghate *et al.*, have prepared derivatives of thiadiazoles by two steps, at first step, reaction of isothiocyanate and isoniazide to yield the intermediate as shown in Scheme 16, which then refluxed with 50 % H_2SO_4 [37].



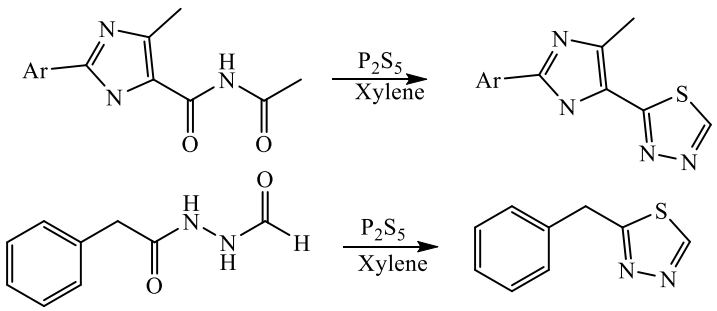
Scheme 16 Preparation of thiadiazole by isothiocyanate and isoniazide

A one-pot synthesis in Scheme 17 has been developed for preparation of 2-substituted-thiadiazole from reaction of acylhydrazide and isothiocyanate with H_2O and Et_3N and similarly, 2-substituted-thiadiazole have prepared from reaction of acid hydrazide and dithiocarbamates [38].

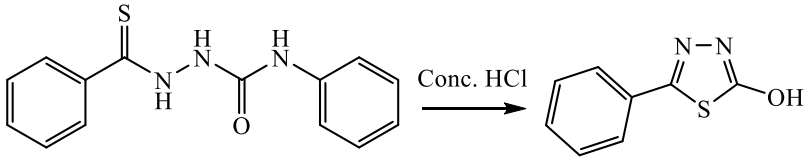


Scheme 17 One pot synthesis of thiadiazole

[4]. Cyclization with P_2S_5: Cyclization of semicarbazide with P_2S_5 in xylene as a solvent *via* substitution of oxygen atom by sulfur atom of P_2S_5 through cyclization reaction or ring closure step [39], shown in Scheme 18. When 4-phenyl-1-(thiobenzole) semicarbazide reacts in the presence of conc. HCl gives 2-hydroxyl-5-phenyl-1,3,4-thiadiazole in Scheme 19.

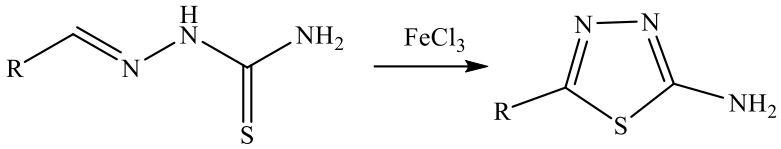


Scheme 18 Cyclization of semicarbazide with P_2S_5



Scheme 19 Cyclization of semicarbazide with HCl

[5]. From Thiosemicarbazone: 2-Amino-5-substituted 1,3,4-thiadiazole [40] have prepared by oxidative cyclization of thiosemicarbazones with ferric chloride shown in Scheme 20.

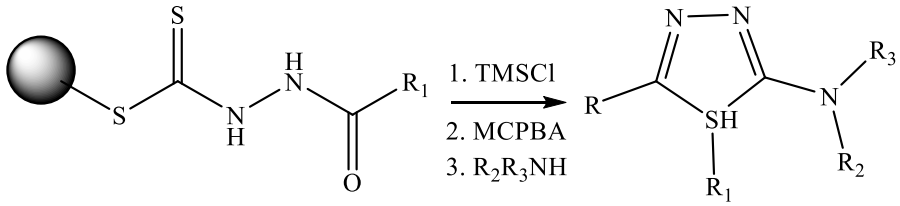


R = Ar, ArCO,CH_3CO, C_2H_5CO

Scheme 20 Cyclization of thiosemicarbazones with $FeCl_3$

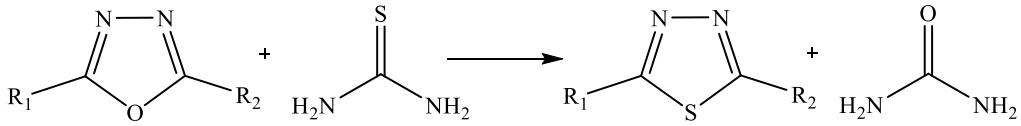
Young *et al.*, have reported the synthesis of 1,3,4-thiadiazole through the oxidation of aryl thiosemicarbazone using $FeCl_3$. According to the authors, the oxidation of thiosemicarbazone by $FeCl_3$ occurs under milder reaction conditions (70-80 °C) as compared to the oxidation of semicarbazone (130-140 °C) [41]. Skagius *et al.*, used the same methodology of Young *et al.*, and the authors reported better oxidation of 5-nitrofurfural thiosemicarbazone with $FeCl_3$, however when thiosemicarbazones derived from 2-furfural and 2-pyridine-carboxaldehyde were used, the yields obtained were less than 40 %. The authors associated the lower yield obtained in the reaction with furfural, compared to 5- nitro-furfural, with the nitro group which prevents the acid cleavage of the furan ring [42].

[6]. From Resin: Resin with TMSCl, MCPBA and R_2R_3NH gives 1,3,4-thiadiazole [43] shown in Scheme 21.



Scheme 21 Synthesis of 1,3,4-thiadiazole from resin

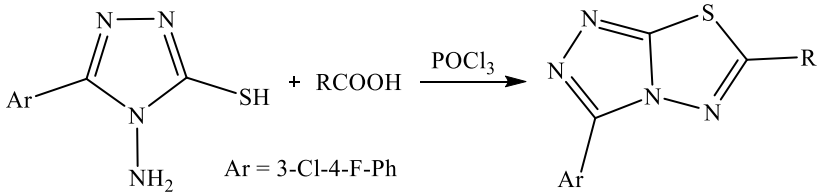
[7]. From 1,3,4-oxadiazoles: An alternative methodology reported in the literature is the conversion of oxadiazole to thiadiazole. The 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring. The idea of bioisosterism is one of the most successful techniques of bioactive compound design. However, the conversion of oxadiazole to thiadiazole is limited due to long time taking. Linganna and Rai have synthesized 1,3,4-thiadiazoles from the oxadiazole reaction with a solution of thiourea in tetrahydrofuran (Scheme 22) in good yields [44]. The mechanism of the reaction is due to the attack of the sulfur atom from thiourea on the heterocycle followed by the ring opening. Although its use is more restricted, in the recent decades.



R_1 = -C_6H_5, -$(NO_2)C_6H_4$; R_2 = -C_6H_5, -$(CH_3O)C_6H_4$, -$(CH_3O)C_6H_2$

Scheme 22 Synthesis of 1,3,4-thiadiazole from 1,3,4-oxadiazole

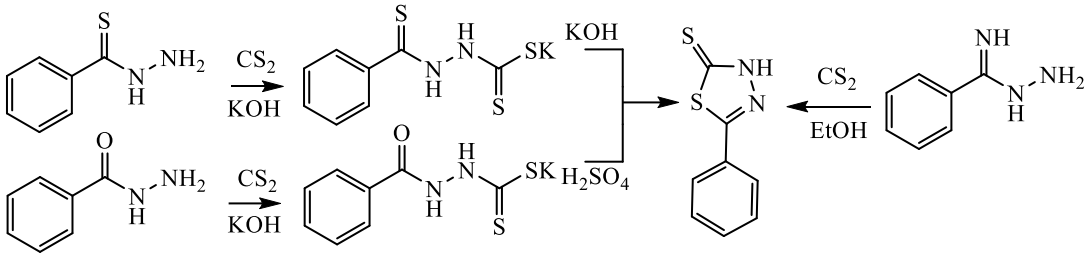
[8]. From 1,2,4-Triazoles: The 1,2,4-triazoles are converted to 1,3,4-thiadiazole by one-pot reaction with substituted aromatic carboxylic acids in the presence of phosphorus oxychloride [45]. The reaction of thiocarbohydrazide with carboxylic acids at the melting temperature allows an improved preparation of the S-substituted 4-amino-3-mercapto-1,2,4-triazole heterocycles. The crude 4-amino-5-mercapto-1,2,4-triazoles react easily with carboxylic acids or carboxylic acid chlorides to afford the 1,2,4-triazolo[3,4-*fc*][1,3,4]thiadiazole ring system [46]. 1,3,4-Thiadiazoles were prepared by condensation of triazole with various carboxylic acids in the presence of phosphorus oxychloride in Scheme 23.



Ar = 3-Cl-4-F-Ph

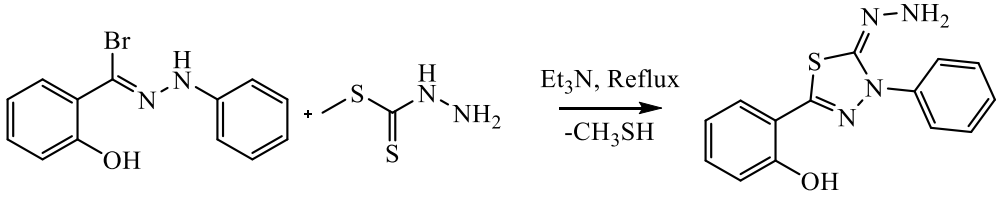
Scheme 23 Synthesis of 1,3,4-thiadiazole from 1,2,4-triazole

[9]. From dithiocarbazates: Kubota *et al.*, have described a reaction between benzamidrazone and carbon disulfide to obtained the thiadiazole with a yield of 82% (Scheme 24). The reaction favored the formation of 1,3,4-thiadiazole in a single step without the formation of the intermediate salt [47].



Scheme 24 Synthesis of 1,3,4-thiadiazole from dithiocarbazates

Gong *et al*. summarized several methods for solid-phase synthesis of 1,3,4-thiadiazoles using CS_2 in the presence of sodium hydride at RT to synthesised various acyldithiocarbazate resins and then cyclodehydrate to generate the 1,3,4-thiadiazole derivatives [48]. Wang *et al.* synthetized 1,3,4- thiadiazoles from dithiocarbazate. Dimethyl sulfate, carbon disulfide and hydrazine hydrate in the presence of potassium hydroxide reacted to generate the intermediate thiohydrazide. This intermediate reacted with chloroacetylchloride at a low temperature to produce compound that was cyclized in sodium bicarbonate to provide (5-methylthio-1,3,4-thiadiazol-2- yl)methylchloride [49]. Sayed *et al.*, reported new thiadiazole derivative as shown in the following Scheme 25 from reaction of hydrazonoyl bromide and methyl hydrazinecarbodithioate.



Scheme 25 Synthesis of thiadiazoles by dithiocarbazates

There are basically four approaches for the cyclization of 1,3,4-thiadiazoles *via* a formation of one bond (**I**), two bonds (**II**, **III**, **IV**), three bonds (**V**) or four bonds through one-pot reaction of three component (**VI**) (**Fig. 6**).

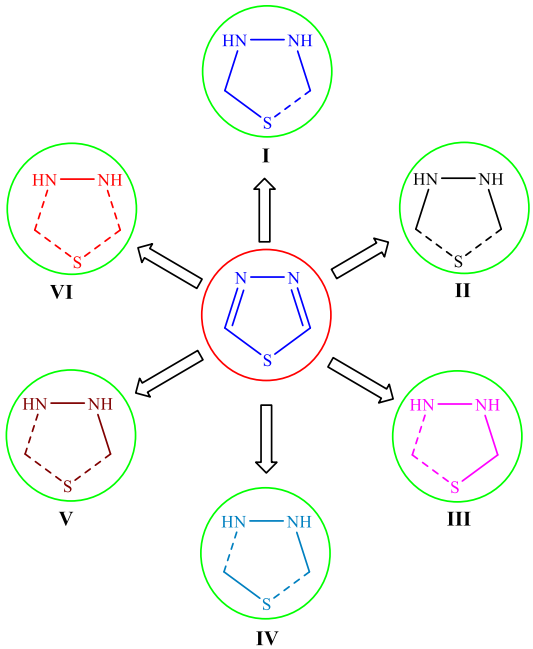
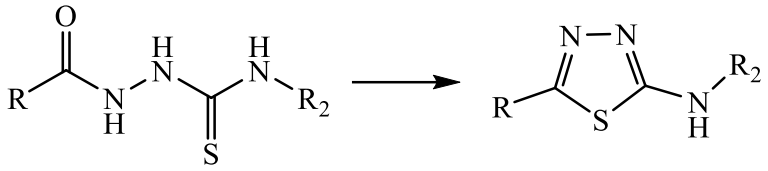


Fig.6 Synthetic routes of 1,3,4-thiadiazoles

[1]. Route (I): Synthesis of 1,3,4-thiadiazole *via* formation of one bond

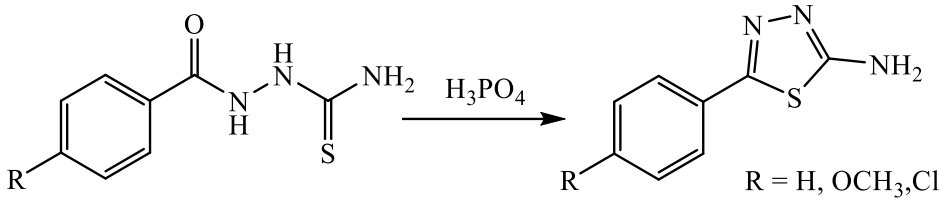
The most common procedure for the synthesis of 5-substituted 2-amino-thiadiazole is the acylation of a thiosemicarbazide followed by dehydration using H_2SO_4, polyphosphoric acid and phosphorous halides. The most recent procedure utilizes methane sulphonic as a dehydrating agent and the thiadiazole obtained in high yield with good purity. 5-Alkyl-2-methyl amino-1,3,4-thiadiazoles [50] have synthesized from a suitable carboxylic acid and methyl

thiosemicarbazide in the presence of polyphosphoric acid and conc. H_2SO_4. Similarily, 2-alkylamino-1,3,4-thiadiazole can also be prepared by the reaction of 4-alkylthiosemicarbazides with orthoformate esters in the presence of small volume of conc. HCl (Scheme 26).

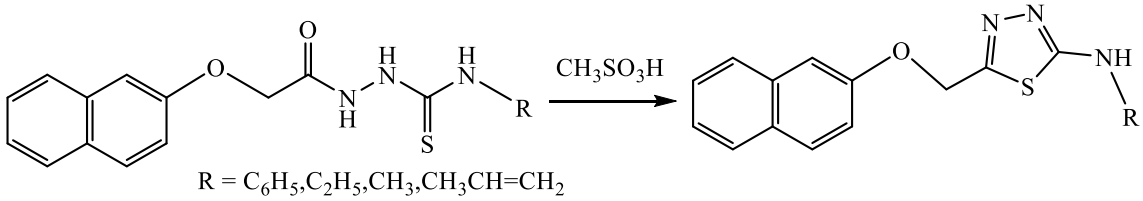


Scheme 26 Synthesis of 1,3,4-thiadiazole *via* formation of one bond

[a]. From Monothiodiacylhydrazines: Monothiodiacylhydrazines were cyclized by dehydrating agents such as sulfuric, phosphorus oxytrichloride, phosphoric acid or methanesulfonic acids to give 1,3,4-thiadiazoles. Several syntheses of 1,3,4-thiadiazoles proceed *via* thiosemicarbazide cyclization in Scheme 27. E. Palaska *et al*., have reported the synthesis of 1,3,4-thiadiazole derivatives from the reaction of thiosemicarbazides with methanesulfonic acid in Scheme 28 [51].

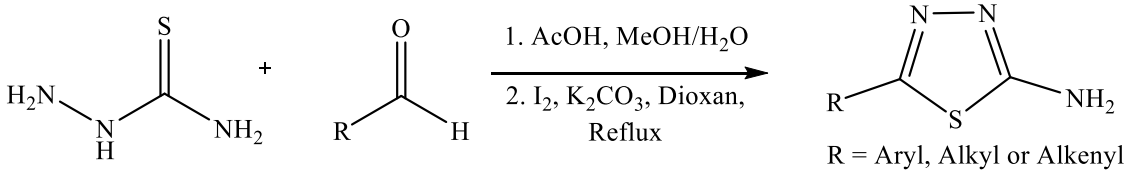


Scheme 27 1,3,4-Thiadiazoles synthesis with phosphoric acid



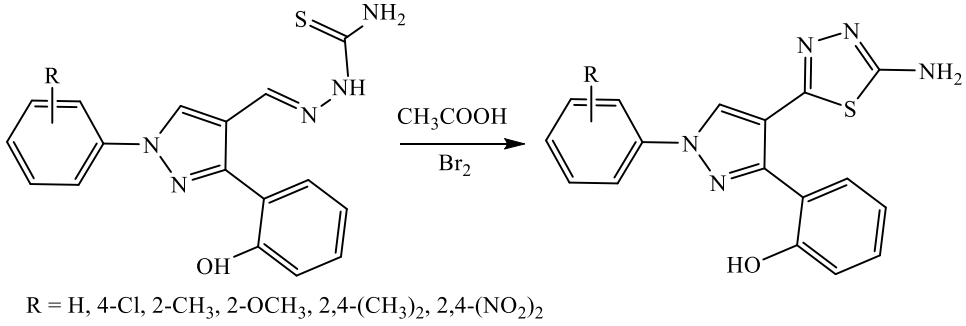
Scheme 28 1,3,4-Thiadiazoles synthesis with methanesulfonic acid

[b]. From Thioacylhydrazone: Cyclization of thioacylhydrazone using common oxidants (Br_2, $FeCl_3$, ammonium ferric sulfate or $KMnO_4$) provided 1,3,4-thiadiazole derivatives. Niu *et al.* reported the synthesis of 2-aminosubstituted 1,3,4-thiadiazoles in Scheme 29 *via* condensation of thiosemicarbazide and aldehydes and with 1,4-dioxane in the presence of I_2 and K_2CO_3 to get the desired thiadiazole derivatives [52].

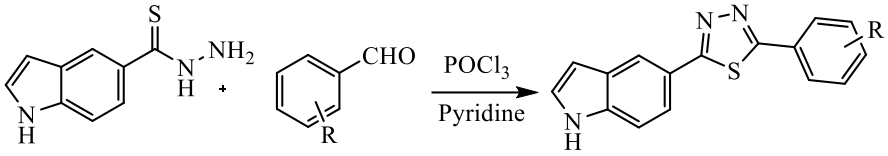


Scheme 29 Cyclization of thioacylhydrazone in presence of oxidants

Kariyappa *et al*., also have reported synthesis of 1,3,4-thiadiazoles by the oxidative cyclization of thiosemicarbazones using Br_2 with glacial acetic acid in the similar way (Scheme 30). A series of indole ring containing thiadiazoles were also synthesized by reaction of thiohydrazide derivative with different aryl aldehydes in pyridine/$POCl_3$ to form 1,3,4-thiadiazole (Scheme 31). A one pot reaction of arylhydrazides and arylaldehydes using Lawesson's reagent is described and 2,5-disubstituted-1,3,4-thiadiazoles [53] in good yields was obtained (Scheme 32).

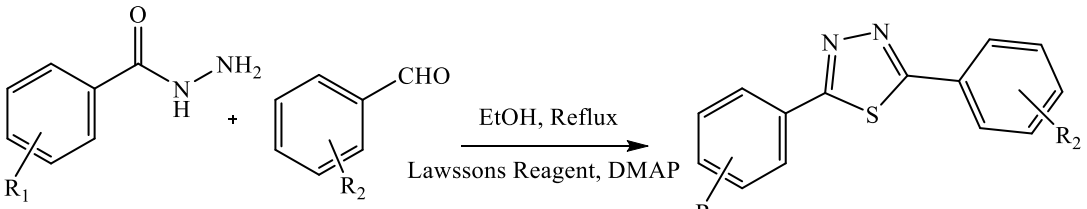


Scheme 30 Cyclization of thioacylhydrazone in presence of Br_2



R = 2-OH, 4-OH, 4-CH_3, 2-Cl, 4-Cl, 2-F, 4-F, 2-NO_2, 4-NO_2

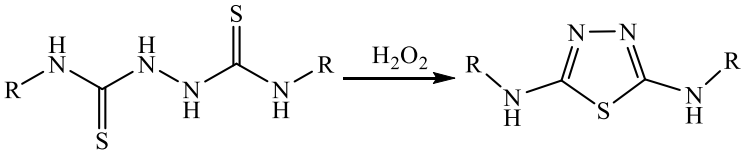
Scheme 31 Cyclization of thioacylhydrazone in pyridine/$POCl_3$



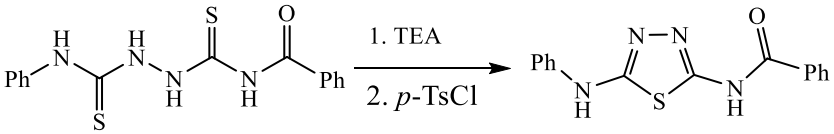
R_1 = H, -OCH_3; R_2 = H, X, -OCH_3, -$(OCH_3)_2$, -C_2H_5

Scheme 32 Cyclization of thioacylhydrazone in Lawesson's reagent

[c]. From acylbithioureas: Bisthioureas and substituted bisthioureas have been converted to 1,3,4-thiadiazole by several methods. The reaction of bisthioureas with 3% H_2O_2 gives 2,5-diamino-1,3,4-thiadiazole derivatives [54] (Scheme 33). Similarily, the reaction of acylbithioureas in Scheme 34 with *p*-tosyl chloride in presence of triethylamine yield ~ 90% of the benzoylated thiadiazole. Acetic anhydride acts on bisthioureas to form a diacetyl derivative of 2,5-diamino-1,3,4-thiadiazole.

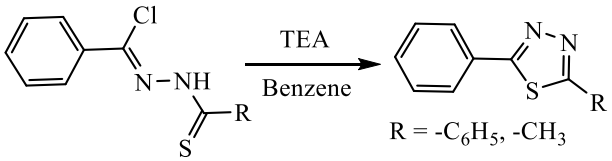


Scheme 33 Thiadiazole synthesis from bisthioureas with H_2O_2



Scheme 34 Thiadiazole synthesis from acylbithioureas

[d]. From thioacylhydrazonoyl chloride: *N*-Thiobenzoyl and *N*-thioacetylhydrazonoyl chlorides gives 1,3,4-thiadiazole derivatives [55] on reaction with TEA in benzene shown in Scheme 35.



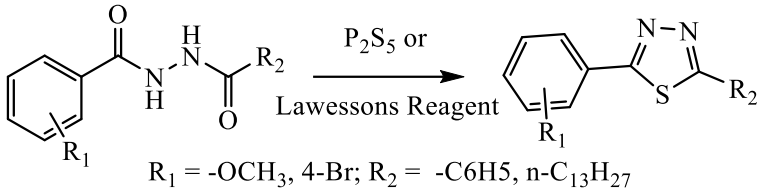
R = -C_6H_5, -CH_3

Scheme 35 1,3,4-Thiadiazole synthesis from thioacylhydrazonoyl chloride

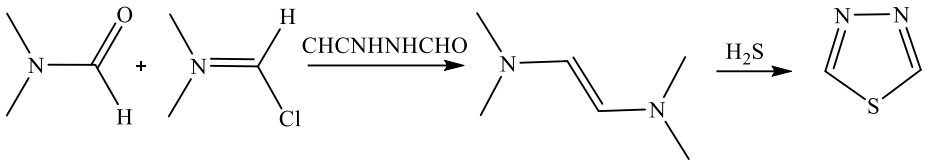
[2]. Route (II): Synthesis of 1,3,4-thiadiazole *via* formation of two bonds

This is the most widely used procedure for the synthesis of thiadiazoles, thiazolidines and mesoionic thiadiazoles. 1,3,4-Thiadiazole was synthesized in 1956 by a four-step reaction sequence start utilizing hydrazine and from thiosemicarbazide. A second procedure utilizes hydrazine and potassium dithioformate.

[a]. From Diacyl hydrazines with a sulfur source: 1,3,4-Thiadiazoles have been prepared from the reaction of diacyl hydrazine with a sulfur source. The reaction involves thionation of the carbonyl groups followed by cyclization with loss of H_2S. P_2S_5 is commonly used for such cyclization but it takes time and excess reagent, which often leads to low yields and side products. The alternative use of Lawesson's reagent [56] gives higher yields and cleaner reactions (Scheme 36). Dehydration of DMF with thionyl chloride or phosgene gives the formamide chloride which on treatment with *N*, *N*-diformyl hydrazine gives the dihydrochloride of the free base which is liberated with sodium ethoxide, which cyclizes to thiadiazole in hydrogen sulphide. 2-Amino-1,3,4-thiadiazole have also synthesized from thiosemicarbazide and a mixture of formic and hydrochloric acid in a tedious procedure with an overall yield of 65% (Scheme 37).



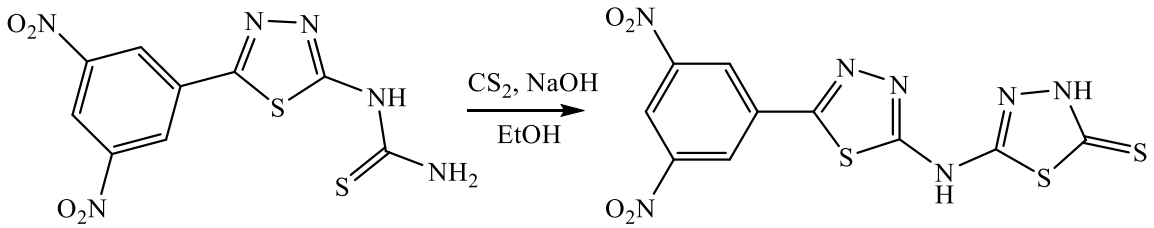
Scheme 36 1,3,4-Thiadiazole synthesis using Lawesson's reagent



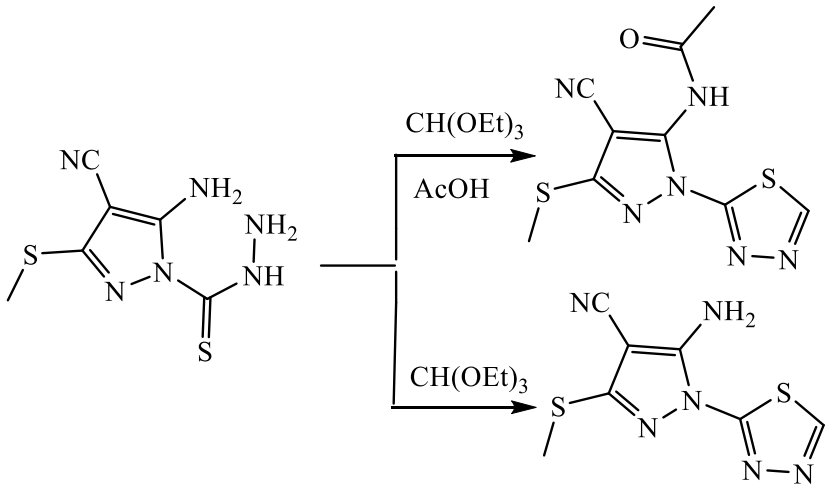
Scheme 37 1,3,4-Thiadiazole synthesis using formic and hydrochloric acid

[3]. Route (III): Synthesis of 1,3,4-thiadiazole *via* formation of two bonds

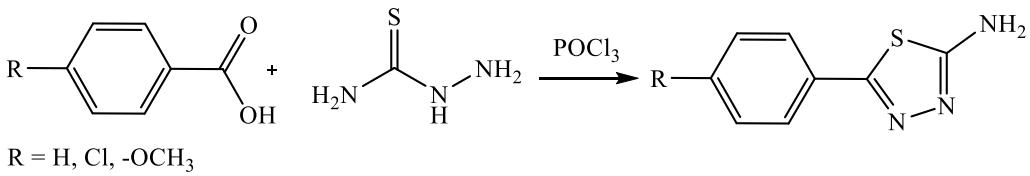
[a]. From Thiohydrazides with a carbon source: Thiosemicarbazide was used as a precursor to prepare thiadiazole through the reaction with CS_2 and NaOH in good yield (Scheme 38). Alkyl and aryl thiohydrazide derivatives react with orthoesters to yield 1,3,4-thiadiazoles *via* a thiosemicarbazone intermediate which cyclizes to eliminate alcohol or hydrogen. The *N*-thiohydrazide pyrazole derivative with triethyl orthoformate in acetic acid under reflux gave the 5-acetylamino-3-methylthio-1-(1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile and in the absence of acetic acid the 5-amino-3-methylthio-1-(1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile in good yield (Scheme 39) [57]. The 5-(4-substituted phenyl)-1,3,4-thiadiazole-2-amine was obtained by the cyclization of aromatic carboxylic acids with thiosemicarbazide reaction in the presence of phosphorus oxytrichloride (Scheme 40).



Scheme 38 1,3,4-Thiadiazole synthesis with CS_2 and NaOH



Scheme 39 1,3,4-Thiadiazole synthesis with triethyl orthoformate in acetic acid

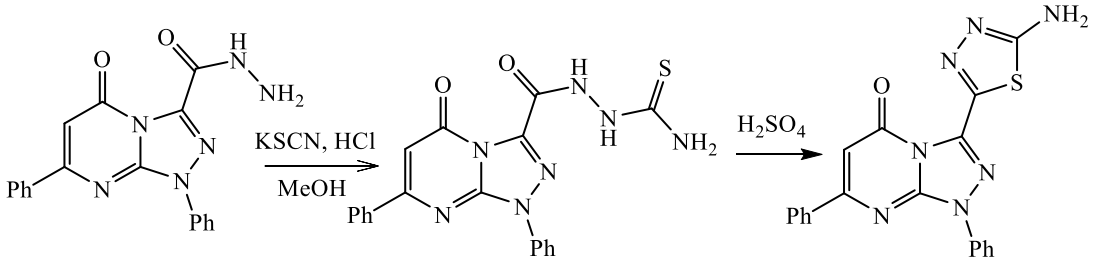


Scheme 40 Cyclization of carboxylic acid in phosphorus oxytrichloride

[4]. Route (IV): Synthesis of 1,3,4-thiadiazole *via* formation of two bonds

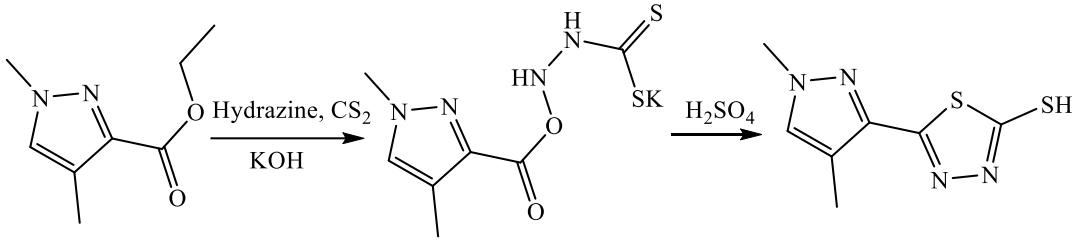
[a]. From Hydrazides with C-S sources: The refluxing of acid hydrazide with KSCN in methanolic medium in the presence of HCl gives 1-(1,5-dihydro-5-oxo-1,7-diphenyl-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carbonyl)thiosemicarbazide.

Dehydrative cyclization of obtained compound [58] in the presence of conc. H_2SO_4 led to the formation of green solid as 1,7-diphenyl-3-(5-amino-1,3,4-thiadiazol-2-yl)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-(1*H*)-one (Scheme 41).

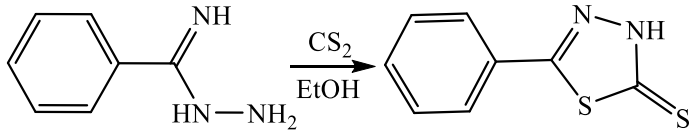


Scheme 41 Dehydrative cyclization thiosemicarbazide with conc. H_2SO_4

The reaction of pyrazole ester with $NH_2NH_2.H_2O$ followed by CS_2 in presence of KOH gives pyrazole salt, which on stirring with conc. H_2SO_4 at RT gives the corresponding 1,3,4-thiadiazole derivative (Scheme 42). Kubota *et. al*, have reported reaction [59] between benzamidrazone and carbon disulfide to obtain the thiadiazole (Scheme 43).



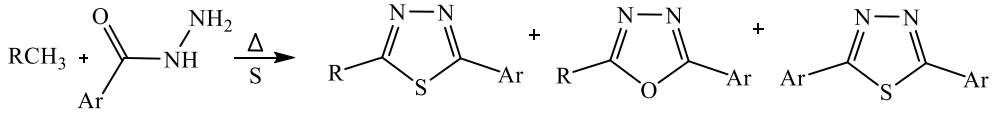
Scheme 42 1,3,4-thiadiazole from pyrazole ester with hydrazine



Scheme 43 1,3,4-thiadiazole from benzamidrazone and carbon disulfide

[5]. Route (V): Synthesis of 1,3,4-thiadiazole *via* formation of three bonds

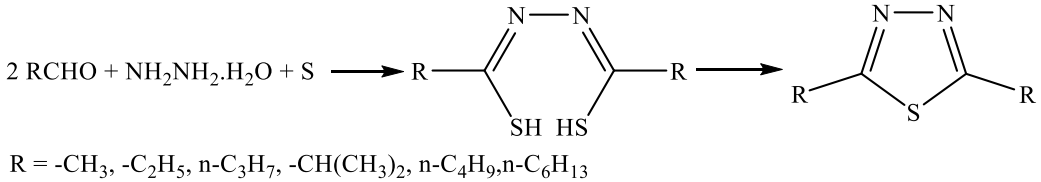
Methyl pyridines and methyl quinolines were reacted with aroylhydrazines in the presence of sulfur to obtained 5-aryl-1,3,4-thiadiazoles. This method required high temperatures and long reaction times to give a mixture of the desired products 1,3,4-thiadiazoles (Scheme 44) along with 1,3,4-oxadiazoles and symmetrical diaryl-1,3,4-thiadiazoles [60].



Scheme 44 Mixed 1,3,4-thiadiazoles, 1,3,4-thiadiazoles synthesis with sulfur

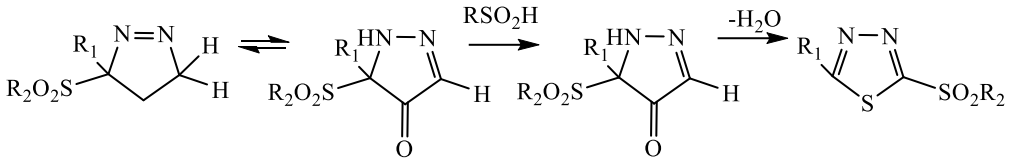
[6]. Route (VI): Synthesis of 1,3,4-thiadiazole *via* formation of four bonds

[a]. From Hydrazine, sulfur and Aldehydes: Aldehydes were reacted with hydrazine hydrate and sulfur in one-pot synthesis [61] to give 2,5-dialkyl- and 2,5-diaryl-1,3,4-thiadiazoles in a high yield *via* a diazene intermediate (Scheme 45).



Scheme 45 One-pot synthesis of 1,3,4-thiadiazoles with aldehyde and hydrazine

[7]. Dipolar Cycloadditions: This procedure has been widely used during the last decade for both synthetic and mechanistic reasons. The reaction of aryl sulphonyl substituted sulfines with diazomethane gives Δ^3-1,3,4-thiadiazole 1-oxide which, however, is unstable and rearranged *via* an isomerization of the Δ^3 to the Δ^2-thiadiazole oxide. This is followed by an elimination and readdition of sulfonic acid and loss of water in a pummerer-type aromatization to give thiadiazole (Scheme 46).



Scheme 46 Synthesis of 1,3,4-thiadiazoles by dipolar cycloaddition

4. Conclusion

This review presents an overview of the various synthetic routes used to prepare 1,3,4-thiadiazoles and their derivatives. Its covers advances made in the last two decades and a brief account of various alterations done on the 1,3,4-thiadiazole nucleus.

Acknowledgement

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