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Review Article

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CONVENTIONAL AND MICROWAVE ASSISTED SYNTHETIC METHOD OF 1,3,4 THIADIAZOLE DERIVATIVES-A REVIEW

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ABSTRACT

The primary techniques used to synthesis the novel compounds comprising 1,3,4-thiadiazole derivatives using both conventional and microwave-assisted methods are highlighted in this review (cyclization, diazotization and etherification respectively). Thiadiazole is a five-membered heterocyclic organic molecule with one sulphur and two nitrogen atoms. With a wide range of physiologically active properties, 1,3,4-thiadiazoles rank among the most active chemical classes.

KEYWORDS: Thiadiazole derivatives, microwave assisted synthesis, one pot synthesis.

INTRODUCTION

Due to their widespread use as medicinal scaffolding for active drugs, heterocyclic compounds especially those containing nitrogen play a significant role in biological processes.[1] The azole group's 1,3,4-thiadiazole nucleus is a flexible pharmacophore that displays a wide range of biological actions.

Three more isomers exist in addition to 1,3,4-thiadiazole (1): 1,2,3-thiadiazole (2), 1,2,4-thiadiazole (3), and 1,2,5-thiadiazole (4). (Figure 1).[2-6]

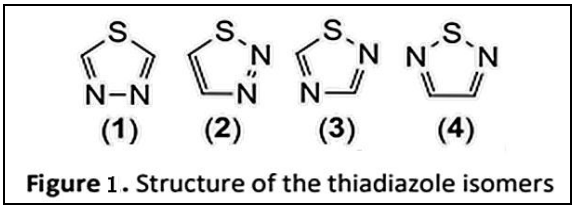


Figure 1. Structure of the thiadiazole isomers

In this instance, the replacement of the sulphur atom with an oxygen atom resulted in the persistence of biological activity and an increase in lipophilicity.[7,8] These chemicals also possess a wide range of biological activities,[6-15] including: antifungal,[16] antiinflammatory,[17] antibacterial,[18] antiparasitic,[19] antioxidant,[20] antidepressant,[20] anticonvulsant,[21] diuretic,[22] and antitumoral agents (Figure 2).[23]

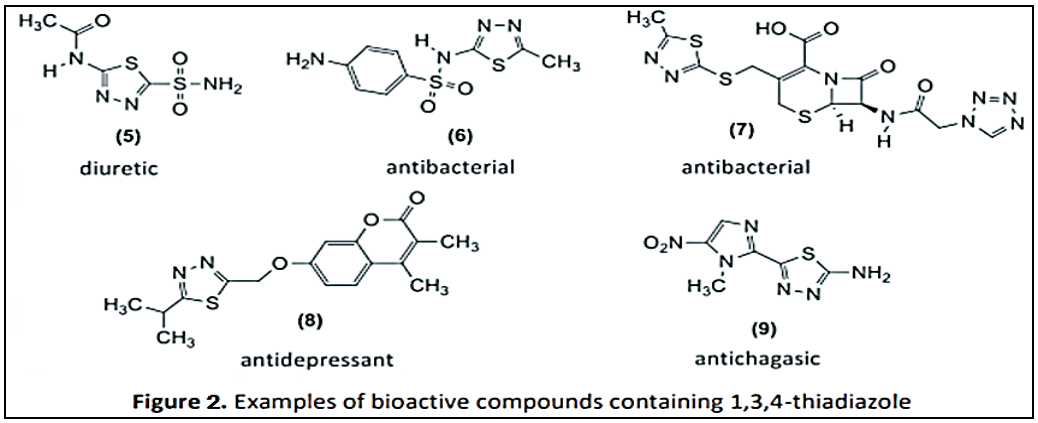


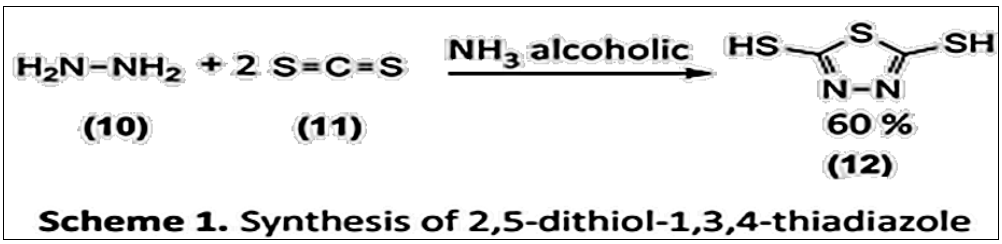
Figure 2. Examples of bioactive compounds containing 1,3,4-thiadiazole

There are already commercially available compounds of this class, including acetazolamide (5), sulfamethiazole (6), cefazolin (7), and atibeprone (8). (Figure 2).[21,24] Megazol (9) was once thought to be a potential substitute for existing Chaga's disease treatments, but it has now

been discovered to be highly mutagenic, which has discouraged further development.[19,25]

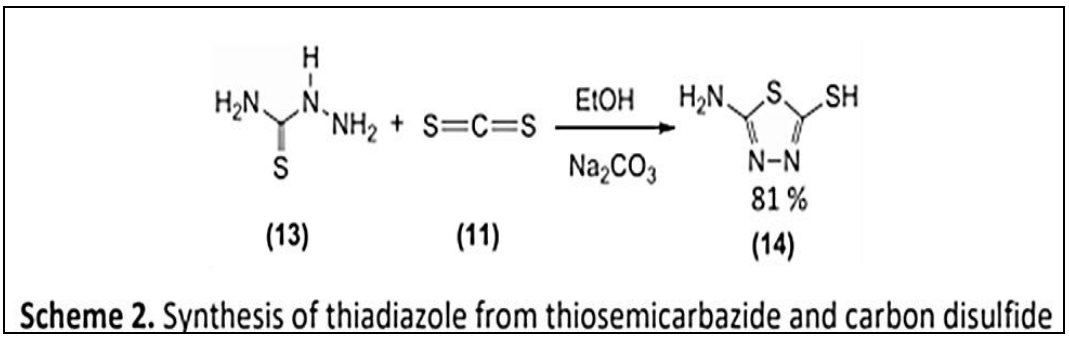
1. Methodologies for the Synthesis of 1,3,4-Thiadiazole

Bush, who reacted hydrazine sulphate with carbon disulfide in the presence of a potassium hydroxide alcoholic solution, was one of the first authors to publish a synthesis of a thiadiazole in 1894.[26] The discovery of hydrazines, in accordance with Losanitch,[26] led to the development of 1,3,4-thiadizole chemistry. The compound 12 was created when strong hydrochloric acid was applied to the 2,5-dithiol1,3,4-thiadiazole hydrazine salt. After combining carbon disulfide (11) and hydrazine hydrate (10) in the presence of alcoholic ammonia, Losanitch modified this procedure to create the heterocycle (12), which he achieved with a 60% yield (Scheme 1).[26]



Scheme 1. Synthesis of 2,5-dithiol-1,3,4-thiadiazole

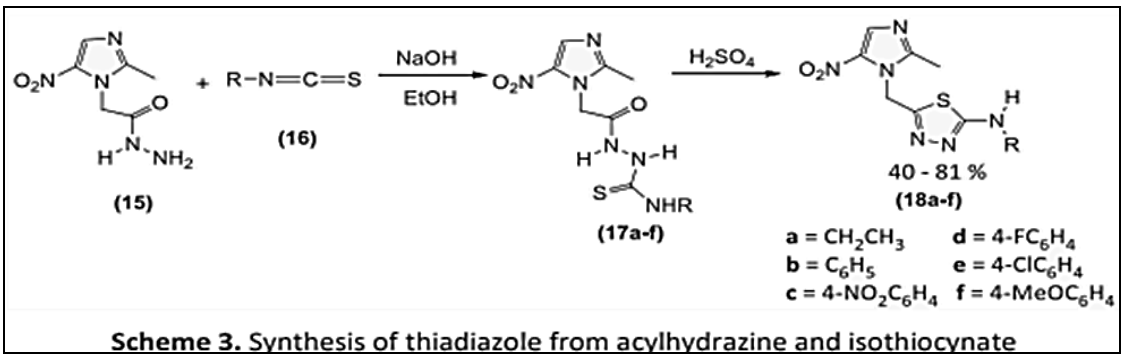
Thiosemicarbazide (13) and carbon disulfide (11) were reported to react in a later investigation by Petrow *et. al.*, (1958), producing compound (14) with a yield (81%) higher than Losanitch's (60%) yield (Scheme 2).[26]



Scheme 2. Synthesis of thiadiazole from thiosemicarbazide and carbon disulfide

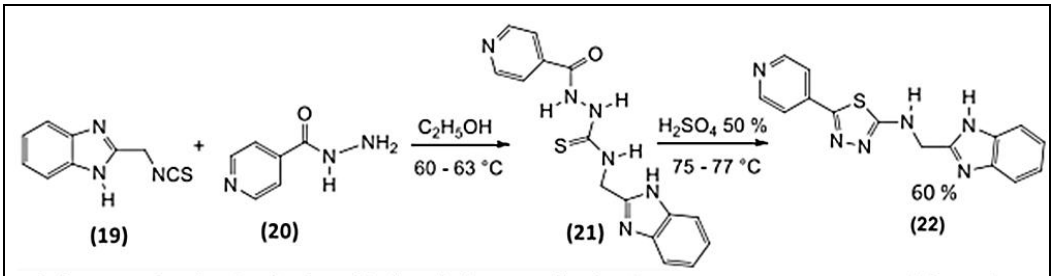
1.1. From acylhydrazines

In most cases, the synthesis of thiadiazoles involves two or more processes, the first of which is the synthesis of the necessary thiosemicarbazides or dithiocarbazides, which can subsequently be transformed into thiadiazoles.[27–29] By converting acylhydrazines into thiadiazoles, Mirzaei *et. al.*, (2008) conducted research (Scheme 3). Thiosemicarbazide (17a-f) was produced by the reaction of acylhydrazine (15), substituted isothiocynate (16), and sodium hydroxide in ethanol, and it was then cyclized in an acidic medium to produce N-substituted 2-amino-5-[(2-methyl-5-nitro-1H-imidazol-1-yl) methyl]-1,3,4-thiadiazoles (18a-f).[27]



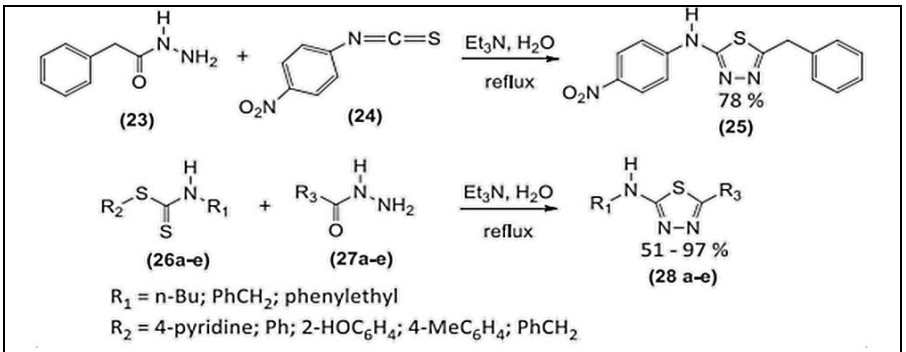
Scheme 3. Synthesis of thiadiazole from acylhydrazine and isothiocynate

In two phases, isothiocynate and isoniazid were used to create 1,3,4-thiadiazoles, according to Ghate *et. al.*, (2017) (Scheme 4). At the beginning, the intermediate (21) was made from isoniazid (20) and 2-methylsulphonitrile-1[H] benzimidazole (19), which was then refluxed with 50% H_2SO_4 to create the 1,3,4-thiadiazole derivatives (22) with a 60% yield.[29]



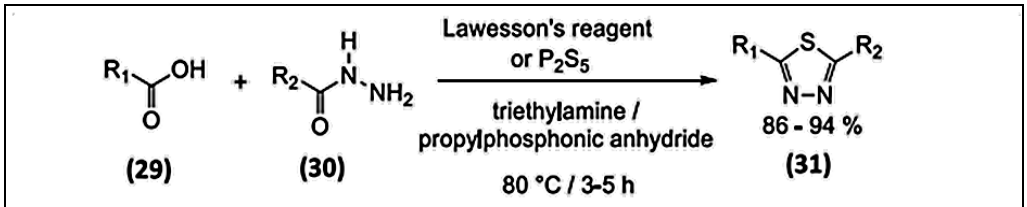
Scheme 4. Synthesis of 1,3,4-thiadiazole from acylhydrazine

To produce 2-substituted 1,3,4-thiadiazoles (25) in the presence of water and triethylamine, Aryanasab devised a one-pot procedure employing isothiocyanate (24) and acylhydrazides (23). The authors produced (28a-e) with good yields (51-97%) under the same conditions by combining acid hydrazides (27a-e) and dithiocarbamates (26a-e) (Scheme 5).[30]



Scheme 5. One-pot synthesis of 1,3,4-thiadiazoles from acylhydrazine and the sulfur reagents

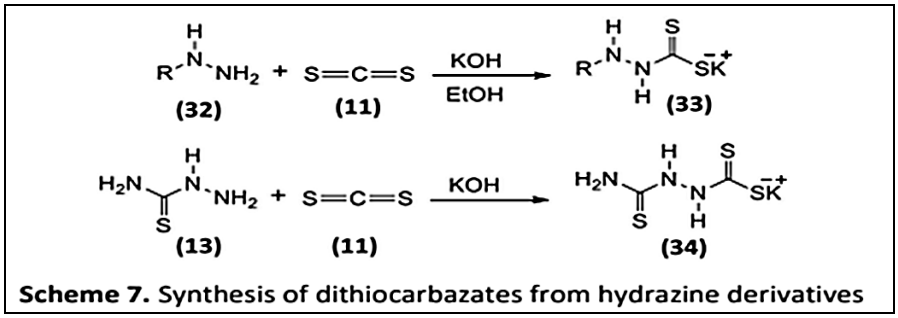
Augustine *et. al.*, created a different kind of one-pot method for producing 1,3,4-thiadiazole derivatives (31) from carboxylic acids (Scheme 6) (2010).[31] These scientists claim that propylphosphonic anhydride (T3P), a coupling agent and water scavenger with low toxicity, has a number of benefits over conventional reagents, including having a wide functional group tolerance, a low tendency to epimerize, and, most importantly, good yields and purity. Hence, assessing the effectiveness of propylphosphonic anhydride (T3P) as a reagent in one-pot synthesis was the main objective of the report.[31] The 1,3,4-thiadiazole derivatives were produced by combining propylphosphonic anhydride (T3P), which has been shown to be an effective reagent, with carboxylic acid (29), hydrazide (30), and Lawesson's reagent or phosphorus pentasulfide (P_2S_5).



Scheme 6. Synthesis of thiadiazoles from carboxylic acids using propylphosphonic anhydride

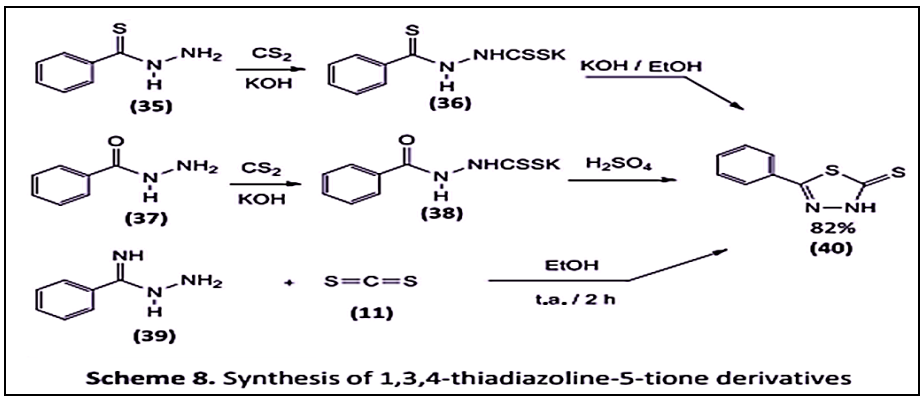
1.2. From dithiocarbazates

At typically basic circumstances, carbon disulfide acts as the sulphur source reagent in the synthesis of dithiocarbazates by interacting with hydrazine (32), hydrazides, thiosemicarbazide (13) or thioacylhydrazine (Scheme 7).[17]



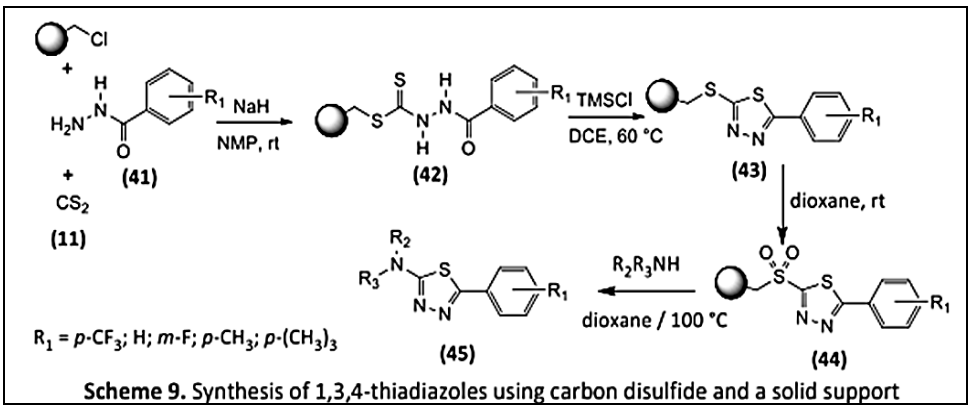
Scheme 7. Synthesis of dithiocarbazates from hydrazine derivatives

According to the literature, the reagents used to create thiadiazole derivatives are thiobenzhydrazide (35) and benzohydrazide (37). When benzamidrazone (39) and carbon disulfide (11) combine, thiadiazole (40) is produced with an 82% yield, according to Kubota and associates (1970).[32] (Scheme 8). Because of its structural resemblance to (35) and (37) the authors chose to employ the benzamidrazone. The authors reaction conditions made it more likely that (40) would arise in a single step without the creation of the intermediate salt.[32] Thiobenzhydrazide (35) and benzohydrazide, according to the literature, are the chemicals used to make thiadiazole derivatives (37). According to Kubota and associates (1970),[32] benzamidrazone (39) and carbon disulfide (11) mix to form thiadiazole (40) with an 82% yield. (Scheme 8).



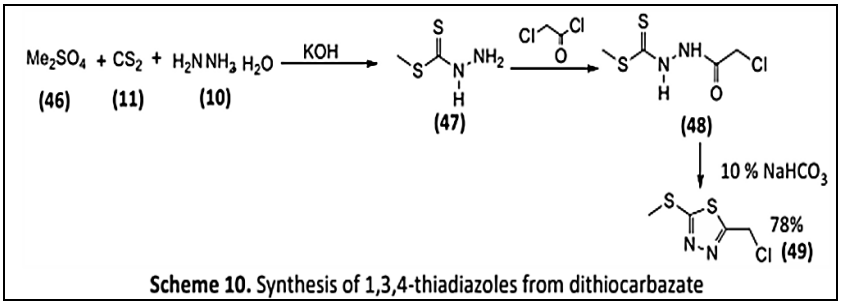
Scheme 8. Synthesis of 1,3,4-thiadiazoline-5-tione derivatives

The preparation of different acyldithiocarbazate resins (42) using CS_2 in the presence of sodium hydride at room temperature, followed by cyclodehydrate to produce the 1,3,4-thiadiazole derivatives, was summarised by Gong *et. al.*, in 2010[33] (43). They created a straightforward and effective solid-phase procedure that made it easier to produce 1,3,4-thiadiazoles and used resin as a solid support (Scheme 9).[33]



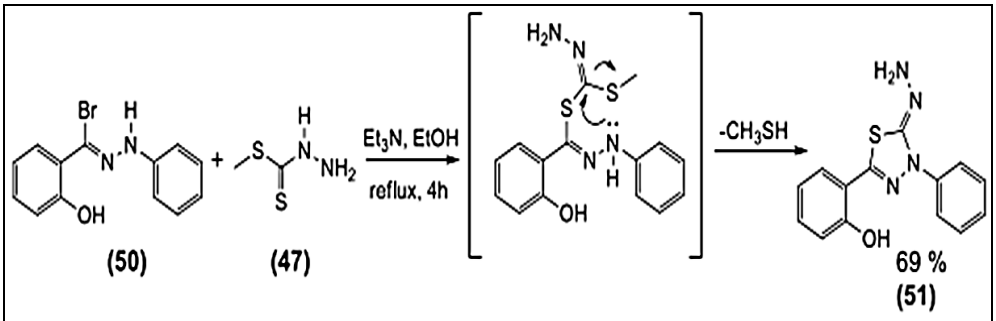
Scheme 9. Synthesis of 1,3,4-thiadiazoles using carbon disulfide and a solid support

Wang *et. al.*,[34] in 2011 produced 1,3,4-thiadiazoles from dithiocarbazate. In the presence of potassium hydroxide, the reaction between dimethyl sulphate (46), carbon disulfide (11) and hydrazine hydrate (10) produced the intermediate thiohydrazide (47). When this intermediate was heated to a low temperature (-15 °C), it combined with chloroacetylchloride to create compound (48), which was then cyclized in 10% sodium bicarbonate to form (5-methylthio-1,3,4-thiadiazol-2-yl)methylchloride (49) with a 78% yield (Scheme 10).[34]



Scheme 10. Synthesis of 1,3,4-thiadiazoles from dithiocarbazate

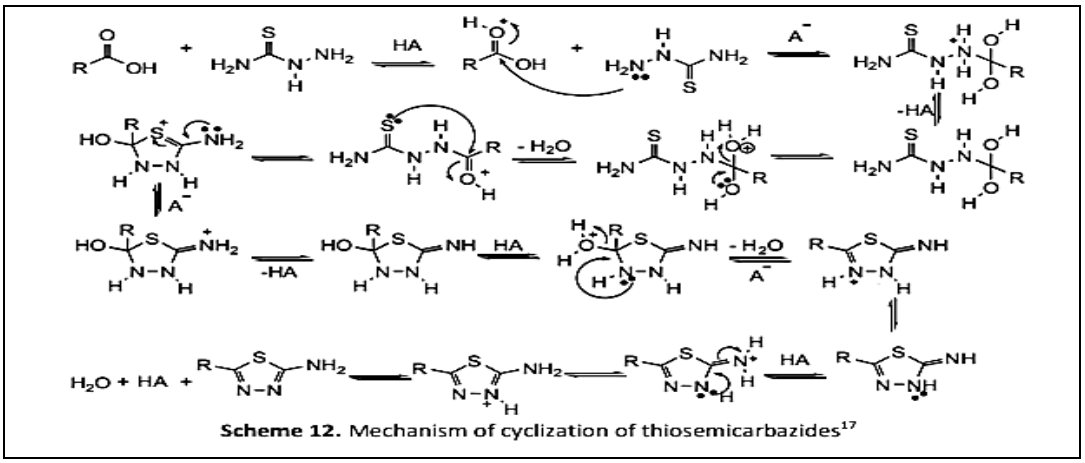
After removing hydrogen bromide and methanethiol, Sayed *et. al.*, utilised the hydrazonoyl bromide (50) and methyl hydrazinecarbodithioate (47) in ethanol to produce the only isolated product, 3-phenyl-5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-(3-amino)-imine (51) (Scheme 11).[35]



Scheme 11. Synthesis of compound **51** from dithiocarbazate and hydrazonoyl bromide

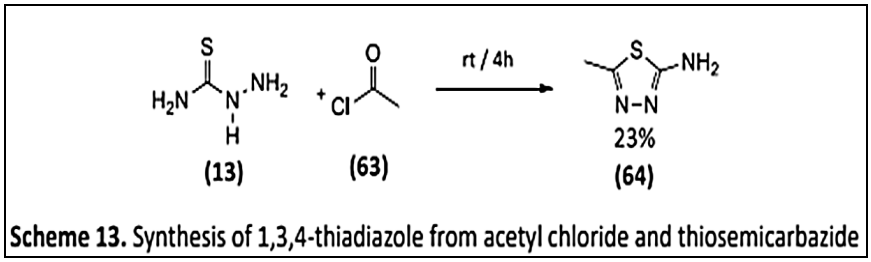
1.3. From thiosemicarbazides

Thiosemicarbazide cyclization, which has been extensively employed and is effective in the synthesis of thiadiazoles, is the starting point for several syntheses of 1,3,4-thiadiazoles. According to the mechanism described in (Scheme 12).[17] this reaction takes place. The nitrogen electron pair from the thiosemicarbazide attacks the carboxylic acid's sp2 carbon nucleophilically in the first step of the proposed mechanism, which is followed by the dehydration of the intermediate. The carbonyl is attacked by an electron pair from the sulphur atom, which leads to cyclization. The resulting intermediate is then dehydrated. Eventually, the aromatic heterocycle is created by an electron migration.



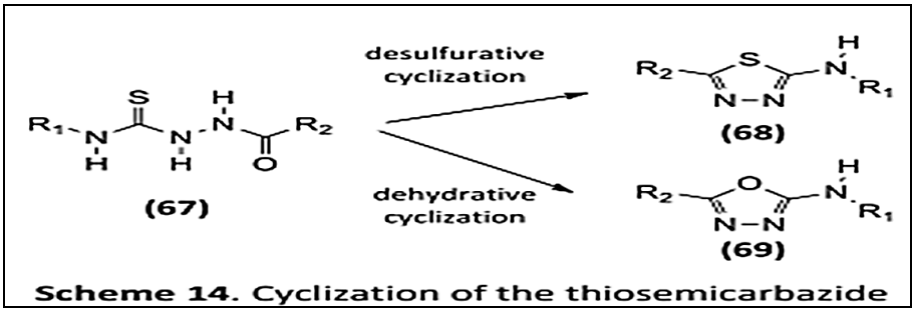
Scheme 12. Mechanism of cyclization of thiosemicarbazides[17]

The acetazolamide derivative (64) was created in 2010 by Schuttelkop *et. al.*, from the reaction of thiosemicarbazide (13) and acetyl chloride (63). The mixture was agitated for 4 hours at room temperature to produce the product, which had a 23% yield (Scheme 13).[36]



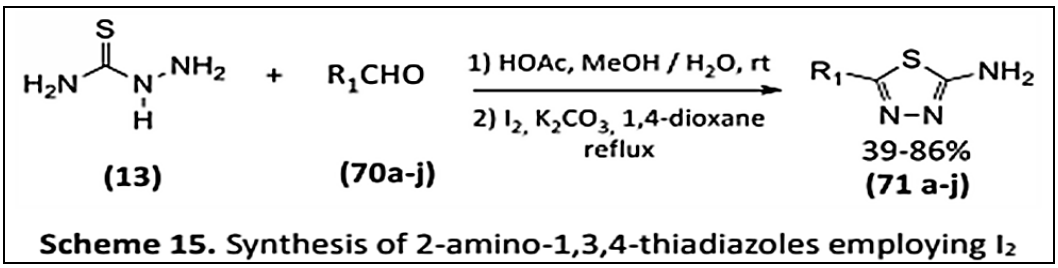
Scheme 13. Synthesis of 1,3,4-thiadiazole from acetyl chloride and thiosemicarbazide

By using cyclodehydration or cyclodesulfurization processes, Yang *et. al.*, created an effective technique for the regioselective synthesis of 1,3,4-thiadiazoles or 1,3,4-oxadiazoles in 2013. (Scheme 14). The interaction of the isothiocyanate starting material with acyl hydrazides results in the production of thiosemicarbazides (67), which act as helpful intermediates in this process.[37]



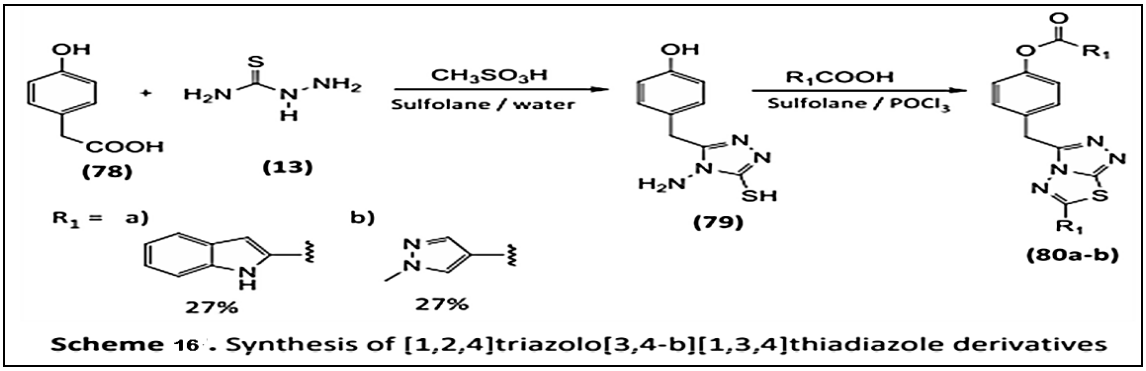
Scheme 14. Cyclization of the thiosemicarbazide

Through condensation of thiosemicarbazide (13) and the corresponding aldehydes (70a–j), followed by I2-mediated oxidative C–S bond formation, Niu *et. al*., (2015) created 2-aminosubstituted 1,3,4-thiadiazoles (71a–j) (Scheme 15).[38] The reaction mixture was concentrated, then redissolved in 1,4-dioxane, followed by treatment with molecular iodine and potassium carbonate to generate the corresponding thiadiazoles after condensation of the thiosemicarbazide and the corresponding aldehyde.[38]



Scheme 15. Synthesis of 2-amino-1,3,4-thiadiazoles employing I_2

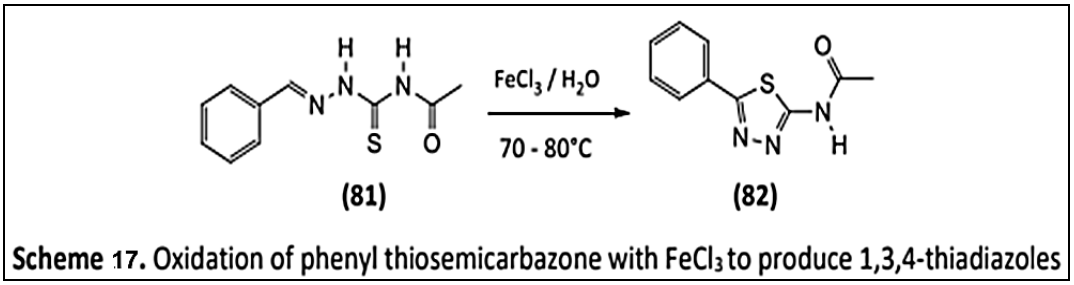
The synthetic approaches for the production of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives were recently described by Yuanet *et. al.,* (2018) (80a-b). Two-step cyclization of 2-(4-hydroxyphenyl)acetic acid (78) with thiocarbohydrazide (13) and carboxylic acids produced the chemicals. Sulfolane/water was combined with 2-(4-hydroxyphenyl) acetic acid, hydrazineca rbothiohydrazide, and methanesulfonic acid, and the mixture was agitated at 90 °C for 24 hours. The resulting intermediate (79) was then subjected to a carboxylic acid reaction with sulfolane and $POCl_3$. At 85 °C, the reaction mixture was agitated for 18 hours. 27% yields were achieved for both products (Scheme 16).[39]



Scheme 16. Synthesis of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives

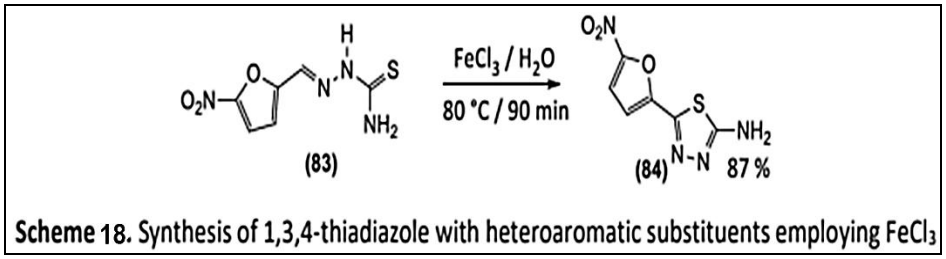
1.4. From thiosemicarbazon

In order to create 1,3,4-thiadiazole (82) from aryl thiosemicarbazone (81) using an aqueous solution of ferric chloride, Young & Eyre (1901) developed a technique (Scheme 17). The oxidation of thiosemicarbazone by ferric chloride, in contrast to the oxidation of semicarbazone, occurs at lower reaction temperatures (70-80 °C), claim the authors.[28]



Scheme 17. Oxidation of phenyl thiosemicarbazone with $FeCl_3$ to produce 1,3,4-thiadiazoles

Years later, Skagius *et. al.,* (1960) used the Young & Eyre (1901) approach to synthesise (84) (Scheme 18).[40] The yields were less than 40% when thiosemicarbazones generated from 2-furfural and 2-pyridine-carboxaldehyde were utilised, despite the authors' reports of good performance in the oxidation of 5-nitrofurfural thiosemicarbazone (83) with ferric chloride.[28,40,41] The nitro group, which prevents the acid cleavage of the furan ring, is attributed by the authors as the cause of the reduced yield obtained in the reaction with furfural as compared to 5-nitrofurfural.[40]



Scheme 18. Synthesis of 1,3,4-thiadiazole with heteroaromatic substituents employing $FeCl_3$

2. Comparative study of one pot synthetic methods of 2-amino-1,3,4-thiadiazole

2.1. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Conventional method using Conc. Sulphuric acid[43] Thiosemicarbazide (0.05mol) was dissolved in water, and an ethanolic solution of aromatic carboxylic acid (0.05mol) was added while stirring constantly and adding a small amount of concentrate. In order to complete the reaction, sulphuric acid was added and heated for 4 hours at 80-90 ºC. After the reaction was complete (TLC), the mixture was cooled and poured into ice-cold water, basified with 10% Na_2CO_3 solution, filtered, dried, and recrystallized using a suitable solvent.

2.2. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Conventional Method by using $POCl_3$.[44] An equimolar amount of mixture of aromatic carboxylic acid (0.1mole) and thiosemicarbazide (0.1mole), in $POCl_3$ (excess), was heated for half an hour, water (90ml) was added and reaction mixture was reflux for another 3 hour, on completion of reaction (TLC), cool to room temperature and poured in ice-cold water, neutralised by saturated KOH solution, filter, dried and recrystalised from suitable solvent.

2.3. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Conventional method using $SOCl_2$[45] A guard tube made of calcium chloride was used to heat aromatic carboxylic acid (0.01mole) and thionyl chloride (0.012) for one hour at 70ºC. This bubbling reaction mixture received 0.012 mole of thiosemicarbazide, which was heated for a further 4 hours at the same temperature. After the reaction (TLC) is finished, basify with aqueous $NaHCO_3$, filter, dry, and recrystallize using a suitable solvent.

2.4. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Microwave method using Conc. Sulfuric acid [46] DMF (10 ml) was used to dissolve a mixture of aromatic carboxylic acid (0.05 mole) and thiosemicarbazide (0.05 mole), which was then added along with concentrated sulfuric acid (10 drops) and microwaved at 480 watts for five minutes. After the reaction is complete, the TLC method calls for pouring ice-cold water, filtering it, drying it off, and recrystallizing the crystals using a suitable solvent.

2.5. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Microwave Method using $POCl_3$[47] A thoroughly mixed catalytic amount of $POCl_3$, thiosemicarbazide, and an aromatic carboxylic acid (0.01 moles each) were then microwaved for 5 minutes at 600 watts. After the reaction was complete, the pH was adjusted to an alkaline value, the mixture was filtered, dried, and recrystallized using an appropriate solvent.

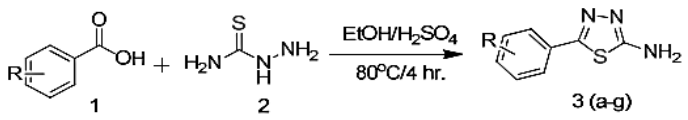
2.6. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by microwave method using $SOCl_2$[48] Thiosemicarbazide (0.012 mole) was added and irradiated (480 watt) for 3 minutes after aromatic carboxylic acid (0.01 mole) and thionyl chloride (0.012 mole) were combined. After the reaction was complete, the TLC was poured into ice cold water, filtered, dried, and recrystallized from a suitable solvent.

2.7. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Microwave method using $MgSO_4$ as a catalyst[49] Magnesium sulphate (2gm) and thiosemicarbazide (0.01mole each) were combined and exposed to radiation for 5 minutes at 250 watts (TLC). The reaction was then put into ice-cold water and neutralised with sodium carbonate solution. Filtered, dried, and recrystallized using a suitable solvent after being obtained solid.

2.8. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine neat reaction condition[50] Thiosemicarbazide (0.1 mol) and aromatic carboxylic acid (0.1 mol) were heated in a solvent-free environment for three hours before the reaction mixture was cooled to ambient temperature. Water was added, filtered, dried, and recrystallized with the use of an appropriate solvent.

2.9. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by ultrasonic irradiation[51] The equimolar amount of aromatic carboxylic acid (0.1 mol), thiosemicarbazide (0.1 mol) in 15ml of ethanol was added conc. Sulphuric acid (10 drops) and the reaction mixture was subjected to Ultrasonic irradiation for 30 minutes at 80ºC, after which the solid obtained was poured into ice cold water, filtered, dried, and recrystalised from suitable solvent.

2.10. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by simple grinding method. Aromatic carboxylic acid (0.01mole), thiosemicarbazide (0.01mole), and a catalytic amount of H_2SO_4 are ground in a mortar and pestle for one and a half hours, then left at room temperature for another four hours with occasional grinding. After the reaction (TLC) was completed, cold water was added and the solid was filtered, dried, and recrystallised in a suitable solvent.



Scheme 19. Selection of appropriate substituted aromatic carboxylic acid for the comparative study of synthesis of 2-amino-1, 3, 4-thiadiazole by conventional method using ethanol and catalytic conc. Sulfuric acid.

CONCLUSION

A significant class of heterocyclic compounds with a variety of pharmacological characteristics are thiadiazoles. Since 1,3,4-thiadiazole is a component of commercial medications and has been the subject of several studies with fruitful outcomes, mostly for microbiological activities, its therapeutic potential is a reality. It is possible to boost lipophilicity without sacrificing pharmacological qualities by acting as a bioisostere for other heterocycles like oxadiazole. In general, the creation and preparation of new antibacterial agents is made possible by the highly efficient synthetic methods for producing a variety of 1,3,4-thiadiazole derivatives. New 1,3,4-thiadiazole-based molecules were created and manufactured in a number of different ways. In this work, conventional and microwave-assisted synthesis techniques were both applied.

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