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METHODS OF SYNTHESIS: 1,3,4-THIADIAZLE-2-THIONES : A REVIEW

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This review article summarizes the literature dealing with synthetic methods for 1,3,4-thiadiazole-2-thione and related compounds. These heterocyclics are obtained from a variety reagents such as thiosemicarbazides, amidrazones, dithiourea, trithiocarbonate, dithiocarbazates, acyldithiocarbazic esters, thiocarbonates etc. The utilization of any of method depends on the structure of the final compounds.

The synthesis of compounds containing 1,3,4-thiadiazoles has attracted widespread attention due to broad spectrum pharmacological applications as antiinflammatory[1-2], antiinfective[3], carbonic anhydrase inhibitors[4], antidepressant[5], antitubercular[6], Metallo-β-lactamases inhibitors[7], matrix metalloproteinase inhibitor[8], antifungal[9] etc. Moreover, sulphur containing heterocycles represent an important group of sulphur compounds that are promising for use in practical applications. The majority of 1,3,4-thiadiazole synthesis are based on cyclization of potassium salt of dithiocarbazates.

In the present review article the most common and useful procedures for the preparation of the mercapto- and thione-substituted 1,3,4-thiadiazole and their utility for the synthesis of well known heterocyclic ring systems are compiled and discussed, therewith the most attention is paid to reports published within the last 50 years.

A. From thiohydrazide

1. Treatment of substituted thiohydrazide **1** with thiophosgene provided the corresponding 1,3,4-thiadiazole-2-thione **2** analogue (Figure 1)[10].

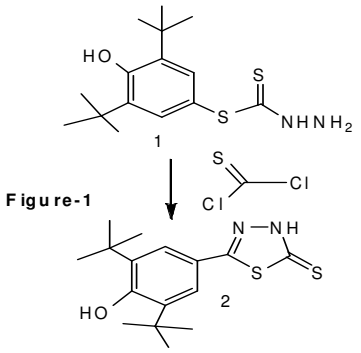


Figure-1

B. From thiosemicarbazide

2. B. Ahmed *et al*[11] synthesized a series of new imine derivatives of 5-amino-1,3,4-thiadiazole-2-thiol **3** using thiosemicarbazide **3**, carbon disulphide, absolute ethanol and anhydrous sodium carbonate (Figure 2).

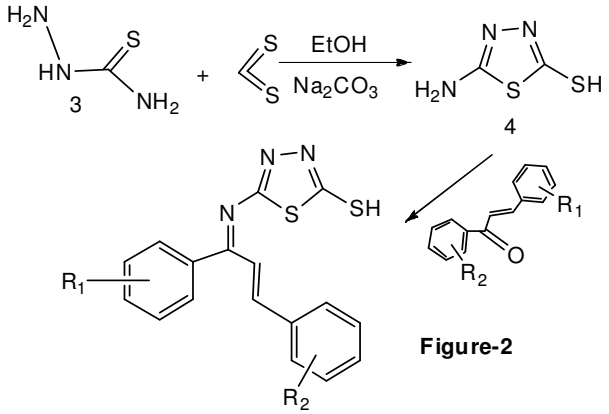


Figure-2

3. Another useful preparative method for 2-amino-5-mercapto-1,3,4-thiadiazole was developed by Guha[12]. When thiosemicarbazide is treated with carbon disulphide and potassium hydroxide, the potassium hydrazothiocarbonamide dithiocarboxylate **5** is formed. Heating this to 140^0 causes cyclization to the salt of 2-amino-5-mercapto-1,3,4-thiadiazole **6** (Figure 3).

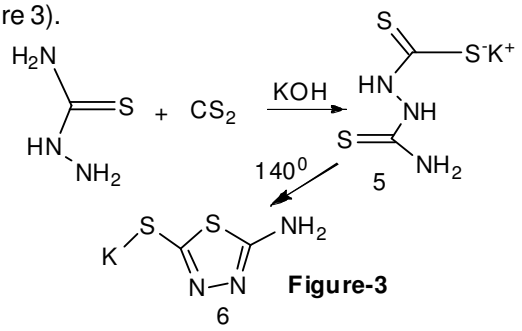


Figure-3

C. From amidrazones

4. Amidrazone **7** reacts with carbon disulfide or isothiocynate to give N-9-imidoylthiohydrazide intermediates which can be isolated and cyclized to afford 1,3,4-thiadiazole **8**. In some cases, the N-9-imidoylthiohydrazides are not isolated prior to cyclization and 1,3,4-thiadiazol-2-thiols or 2-thiones are formed directly (Figure 4)[13].

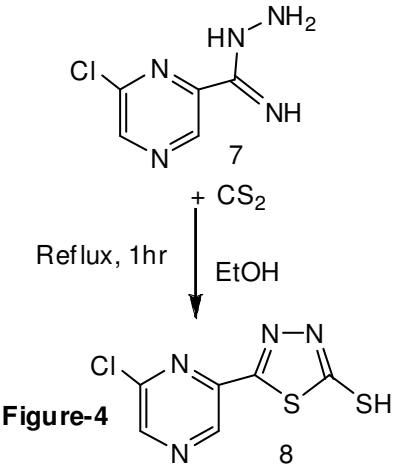


Figure-4

D. Form dithiourea

5. 2-Amino-5-mercapto-1,3,4-thiadiazole **10** was obtained via cyclization of 2,5-dithiobiurea **9** in refluxing hydrochloric acid (Figure 5)[14].

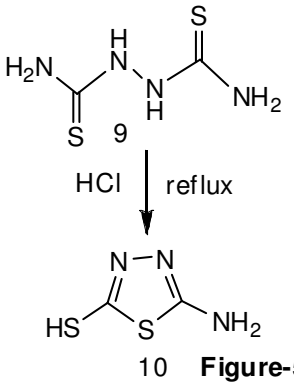
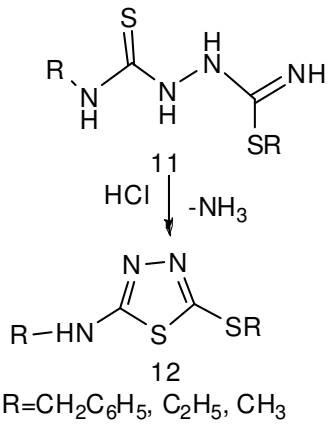


Figure-5

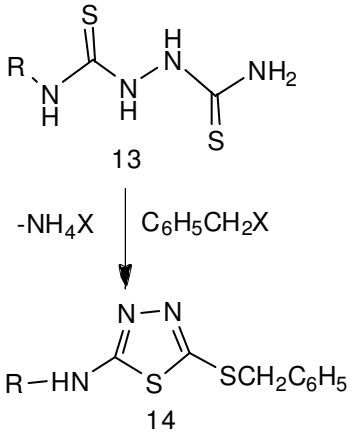
6. On heating 1-substituted-5-*S*-alkyl (aryl) isodithiobiureas **11** in ethanol or water in the presence of hydrochloric acid, 5-alkylmercapto-2-substituted amino-1,3,4-thiadiazoles **12** were obtained (Figure **6**)[15].



R=$CH_2C_6H_5$, C_2H_5, CH_3

Figure-6

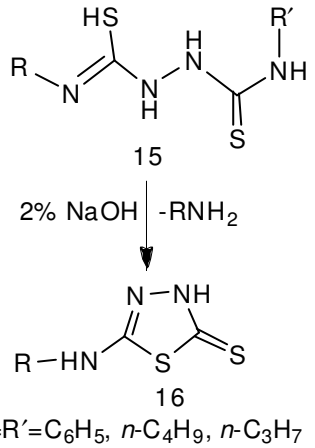
7. Alkylation of 1-substituted-2,5-dithiobiureas **13** with alkyl halide in ethanol gave substituted-1,3,4-thiadiazole **14** (Figure 7)[15].



R=C_6H_5,CH_3,C_2H_5,*p*-Me-C_6H_4

Figure-7

8. Alkali-catalyzed thermal cyclization of 1-alkyl and 1,6-dialkyl-2,5-dithiobiureas **15** gave 2-alkyl amino-1,3,4-thiadiazoline-5-thiones **16** (Figure 8)[16].



R=R′=C_6H_5, *n*-C_4H_9, *n*-C_3H_7

Figure-8

9. Addition of two equivalents of ethenetetracarbonitrile **18** to a solution of 1,6-disubstituted-2,5-dithiobiureas **17** in ethyl acetate at room temp led to the formation of thiadiazole derivatives **19** and **20** as side products (Figure 9)[17].

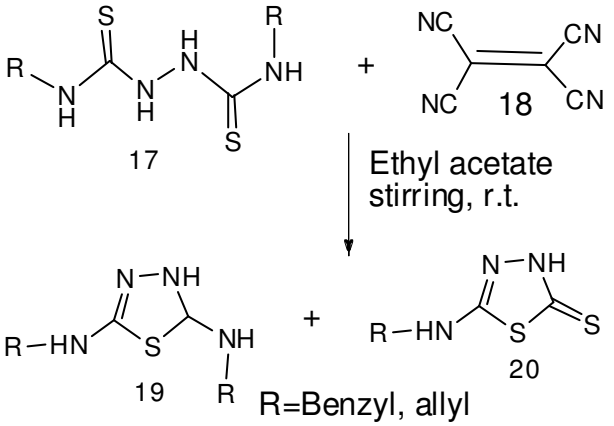


Figure-9

10. Microwave (MW) and thermal heterocyclization of 1,6-disubstituted-2,5-dithiobiureas **21** results in formation of 2,5-disubstituted amino [1,3,4] thiadiazoles **22** and 5-substituted amino [1,3,4] thiadiazole-2-thiones **23** (Figure 10)[18].

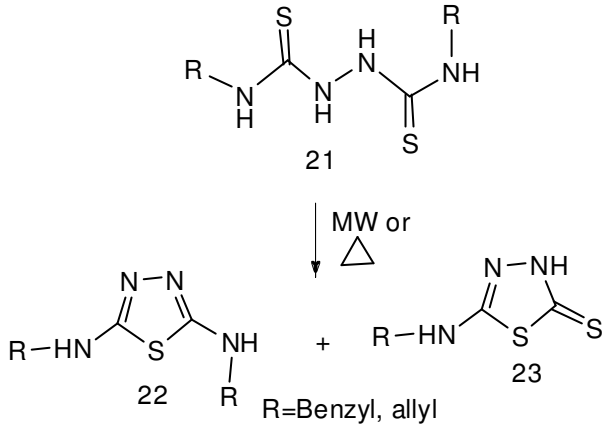


Figure-10

11. On reaction of **24** with methyl iodide in the absence of the base, 2-acylamino-5-methyl-thio-1,3,4-thiadiazoles **26** is formed. This reaction is presumed to be initiated by S- and N methylation to form an intermediate **25**, followed by cyclization through the attack of SH group on C=N with elimination of dimethylaniline to afford **26** (Figure 11)[19].

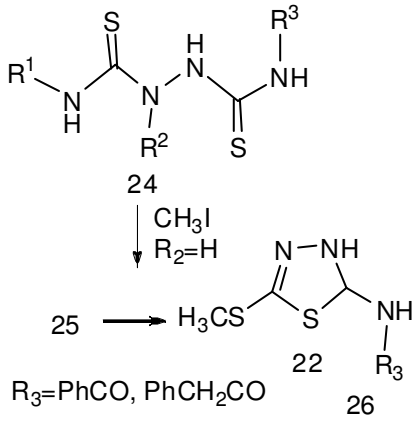


Figure-11

12. The reaction of trifluoroacetic acid with dithiobiureas **27** afforded 1,3,4-thiadiazoline-2-thiones **28** with loss of methylamine (Figure 12)[20].

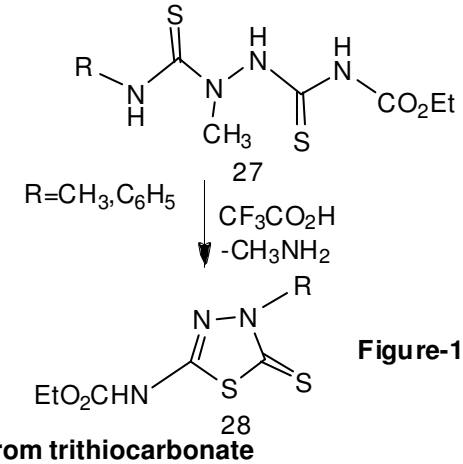


Figure-12

E. From trithiocarbonate

13. Thiocarbohydrazide reacts with dimethyl trithiocarbonate in alkaline solution to form 1-dithiomethoxycarbonylthio-carbohydrazide **29** as a crystalline solid in high yield. The monoadduct **29** is readily cyclized in ethanolic hydrochloric acid to 2-mercapto-5-methylthio-1,3,4-thiadiazole **30** in high yield (Figure 13)[21].

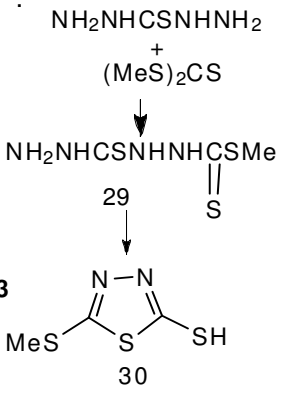


Figure-13

F. From dithiocarbazates

14. Young *et al*[22] reported the preparation of 2-substituted-5-benzylmercapto-1,3,4-thiadiazoles **32** by dissolving the benzyl-3-acyldithiocarbazate **31** in concentrated sulfuric acid and pouring the reaction mixture in ice cold water to get the precipitate (Figure 14). Authors[22] also proposed the reaction mechanism (Figure 15).

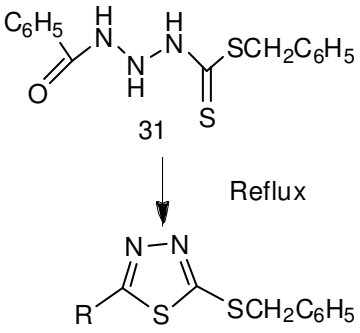


Figure-14

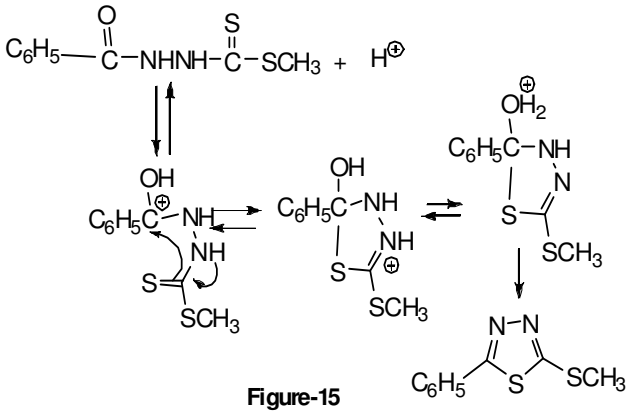


Figure-15

15. Maximo *et al*[23] observed the formation of 5-substituted 1,3,4-thiadiazole-2-thiones **34** on treating the potassium salts of 3-aroyldithiocarbazates **33** with concentrated sulphuric acid (Figure 16).

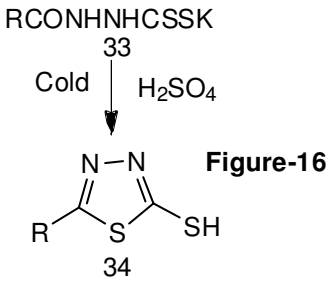


Figure-16

16. Johnson J *et al*[6] have reported the synthesis of 3-[4/3-(5*H*-sulphido-1,3,4-thiadiazolium-4-carbonyl) phenyl] sydnones **36** by cyclization of potassium dithiocarbazates **35** with potassium dithioformate (Figure 17).

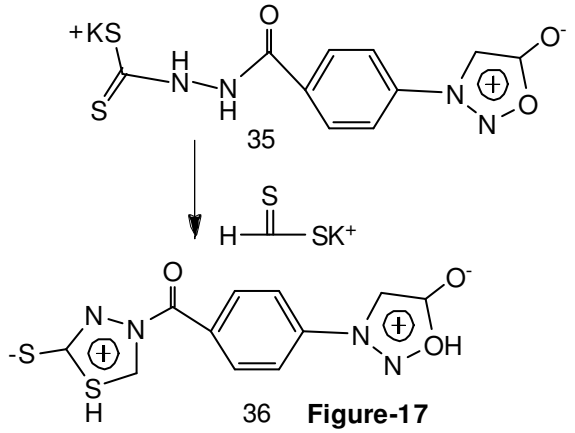


Figure-17

G. From acyldithiocarbazic esters

17. When 3-acyldithiocarbazic esters **37, 39** are treated with acids, they cyclize to form substituted thiadiazole **38, 40**. This is a quite general reaction. Both benzyl and methyl 3-acyldithiocarbazates have been employed (Figure 18)[24].

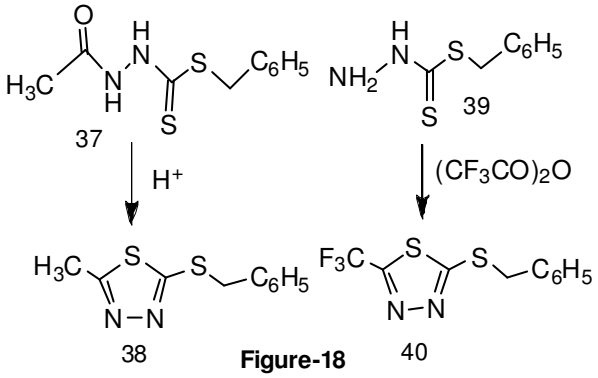


Figure-18

H. From thiocarbonate

18. Treatment of *o*-methyl thiocarbazate **41** with carbon disulphide and alkali gave 5-methoxy-1,3,4-thiadiazole-2(3*H*)-thione **42**. However, addition of the reagents in the inverse order results in the isomeric 5-methylthio **43** compound by a transmethylation process (Figure 19)[25].

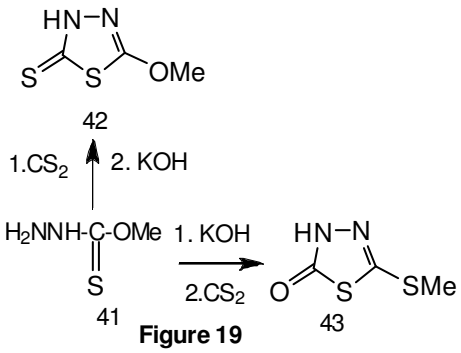


Figure 19

I. Ring transformation

19. The reaction of sodium phenylsulfinate with thiadiazole **44** in refluxing dimethylformamide (DMF) gave the 5-phenylsulfonyl-1,3,4-thiadiazole **45** (Figure 20)[26].

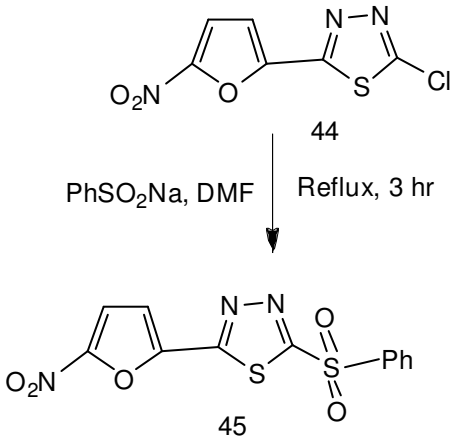


Figure 20

20. The reaction of 2-chloro-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole **46** with thiourea in refluxing ethanol afforded 2-mercapto-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole **47** (Figure 21)[27].

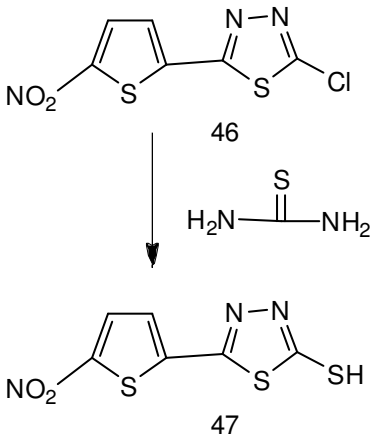


Figure 21

J. Solid phase synthesis

21. The cyclization of the resin bound thiosemicarbazides **48** with a thiocarbonylating agent, di-(2-pyridyl) thionocarbonate (DPT), yielded substituted 5-amino-3*H*-1,3,4-thiadiazole-2-thiones **49** which gave mono S-alkylated product **50** after acid mediated cleavage (Figure 22)[28].

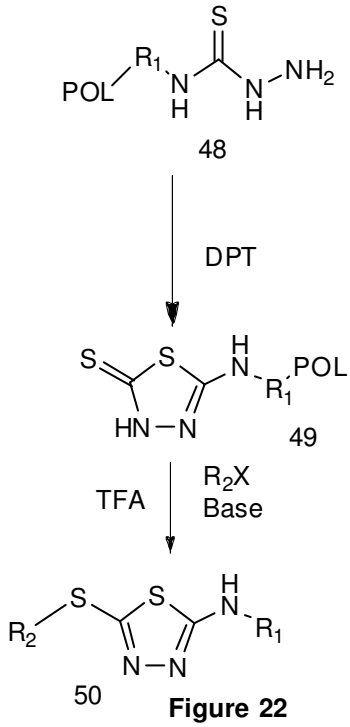


Figure 22

K. Green synthesis

22. A fast, efficient synthesis of 5-substituted-1,3,4-thiadiazole-2-thiols **51** using green chemistry matrices was successfully developed by Rajesh Kumar et al. The developed greener protocol showed 4.7-11.4% increase in overall yield. The greener method was superior with higher energy efficiency, environmental factor, atom economy, atom efficiency carbon efficiency and reaction mass efficiency (Figure 23)[29].

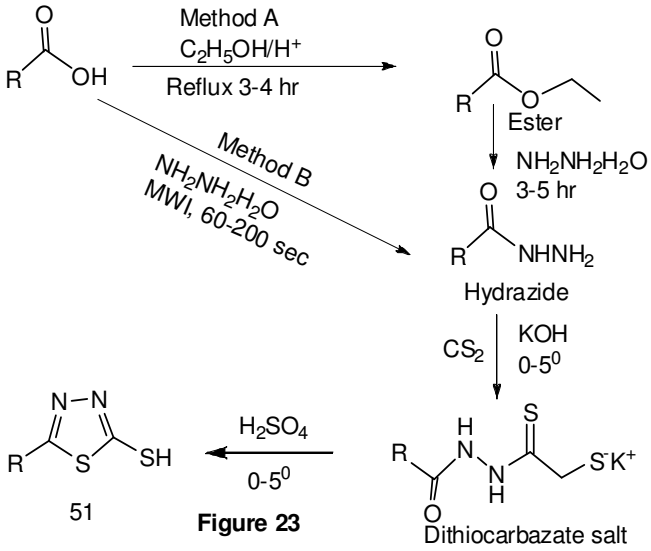


Figure 23

Conclusion

The synthesis of these heterocycles to date, illustrates different approaches to the challenges of preparing these bioactive compounds which can allow the synthesis of many novel medicinally useful chemical derivatives. The selection of method is totally based on ease in availability of the starting material and other chemicals and solvents, time, final workup and yield of the product obtained.

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