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Review Article

Review on Chemistry and Therapeutic activity of the derivatives of Thiadiazole – the Sulphur containing Heterocycle

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Abstract

Heterocycles comprises important pharmacophores in medicinal chemistry. This article focuses on the chemistry and therapeutic activity of the heterocycle thiadiazole, i.e. a sulpher and nitrogen containing five membered ring. The different isomeric forms of the heterocyclic ring, its chemistry, explained briefly. An account of different mode of synthesis from different starting material is shown along with the highlights of the therapeutic activity of thiadiazole derivatives.

Keywords: Thiadiazole, Therapeutic activity, Heterocycle.

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1. Introduction

Thiadiazole is a 5-membered ring system containing hydrogen-binding domain, sulphur atom, and two electron donor nitrogen system (–N=C–S) that exhibit a wide variety of biological activity. They occur in four isomeric forms in the nature viz. 1,2,3-thiadiazole (1); 1,2,5-thiadiazole (2); 1,2,4-thiadiazole (3); and 1,3,4 thiadiazole (4) five member ring. (Figure 1)

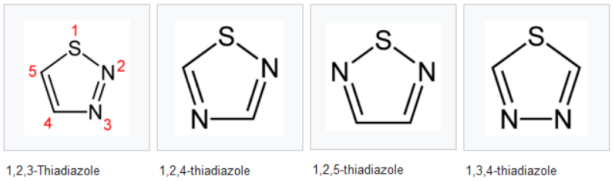
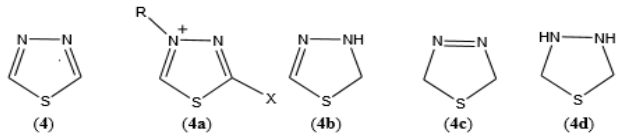


Figure 1: Four Isomeric Form of Thiadiazole

Among these four types of thiadiazole, 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.[1]

1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Busch and his co-workers. The advent of sulfur drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in this field. 1,3,4-Thiadiazoles were conveniently divided into three subclasses:

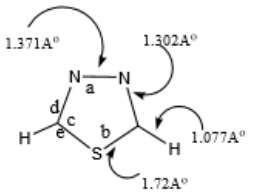
a) Aromatic systems which include the neutral thiadiazole (4) and constitute a major part of this review.
b) Mesoionic systems (4a) which is defined as five membered heterocycles which are not covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring [2].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



Study of different literature shows that various thiadiazoles have resulted in many potential drugs and are known to exhibit a broad spectrum of pharmacological activities. The specific pharmacological activities include antitumor, antiviral, antibacterial, amoebicidal, anti-inflammatory, antitubercular, antipyretic, anticancer, CNS depressant, antischistosomal, herbicidal, insecticidal, pesticidal, hypoglycaemic [4].

Properties of 1,3,4-thiadiazole (4) can be looked upon as 4azathiazole or 3,4- diazathiophene so far as they are electronically isosteric. However, the replacement of –CH= by electronegative –N= atom in the 5-membered thiophene ring changes the chemical/physical behaviour considerably. The structure (4) represents π-excessive ring system as the two adjacent N atoms of the ring carry a lone pair of electrons each. Actually 1,3,4-thiadiazole molecule does not display a true aromatic behavior as do benzene, pyridine and thiophene. Analysis of microwave spectra of these molecule and calculation of bond lengths, bond angles and bond orders conclude that the aromatic character as measured by the π-electron delocalization decreases in the order of 1,2,5-thiadiazole >thiophene>thiazole> 1,3,4 thiadiazole. A series of M.O. was made calculating by HMO method using the Longuet Higgins model for the sulfur atom of thiadiazole isomers and showed that π-electron delocalisation is more in 1,2,5 isomer than in 1,3,4-thiadiazole and thiazole. It has been reported that dipole moment value of 3.25D for 1,3,4-thiadiazole and 1.61D for thiazole [5].

These findings suggested that 1,3,4-thiadiazole is a polar symmetric molecule exhibiting pseudo-aromatic character. The molecular geometry figure for 1,3,4-thiadiazole is given here which are calculated on the bases of M.O. method.[6]



a = 112.2°; b = 86.4°; c = 114.6°;
d = 123.5°; e = 121.9°
(4)

Some important canonical forms of 1,3,4 thiadiazole (Figure 2) are written below, of which 4 with dienic behaviour is the maximum contributing structure.[82]

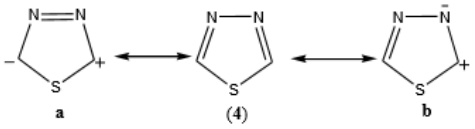
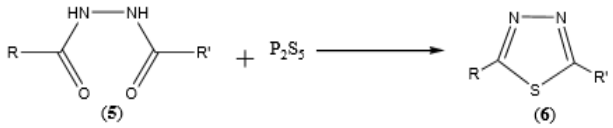


Figure 2 canonical forms of 1,3,4-thiadiazole

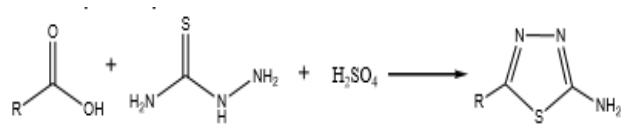
2. Synthetic aspects of 1,3,4-thiadiazoles

The method commonly employed for the synthesis of 1,3,4-thiadiazole is the cyclization of thiosemicarbazide derivatives [7] incorporating the basic structural unit. Other methods involve ring closure of dithiocarbazates, acylhydrazines, bisthioureas or interconversions of oxadiazoles in to 1,3,4-thiadiazoles have also been reported [8].

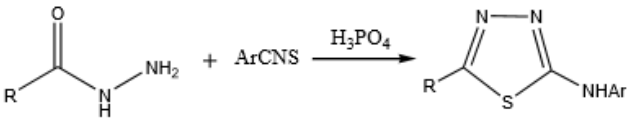
From 1,2-diacylhydrazines Stolle, prepared a number of 2,5-dialkyl-1,3,4thiadiazoles (6) from 1,2-diacylhydrazines (5) and P2S5. Instead of using P2S5, thioacylation of 1,2- diacylhydrazine is effected by carboxymethyldithioate which on heating gives 2,5-disubstituted thiadiazoles [9].



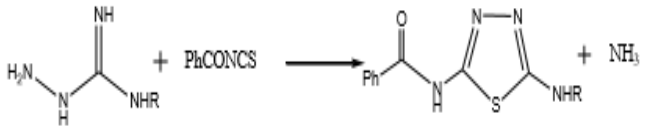
From cyclisation of acylthiosemicarbazides Hoggarth *et al*[10] for the first time reported the synthesis of 2-amino-1,3,4- thiadiazoles, by cyclodehydration of acylthiosemicarbazides in presence of acid catalyst like H_2SO_4, H_3PO_4 etc. The required acylthiosemicarbazides were obtained by treating an acidhydrazide with an isothiocyanate[11]. They were also prepared in situ by heating the carboxylic acid and thiosemicarbazide in the acid medium and were cyclised subsequently.



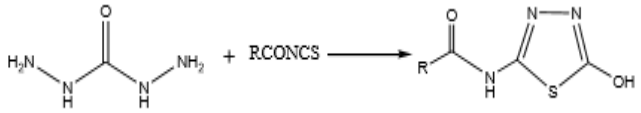
Turner *et al*[12] have prepared 2-amino-5-aryl-1,3,4thiadiazoles directly by heating a mixture of the carboxylic acid and thiosemicarbazide with PPA. Phosphorous oxychloride can also be used instead of PPA. Fullop *et al* [13] used ethanolic HCl for cyclodehydration of acylthiosemicarbazides. Mahajanshetti *et al*[13] synthesized thiadiazoles containing a long alkyl chain by using H_3PO_4 as dehydrating agent.



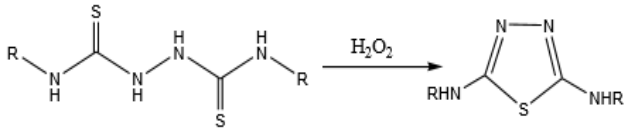
From cyclisation of aminoguinidines and diaminoguinidines Kurzer [14] prepared a number of 1, 3, 4-thiadiazoles by acid catalysed cyclisation of acylthiosemicarbazides obtained from the reaction of aminoguinidine salts and aroylisothiocyanates [15].



From carbohydrazide and acylisothiocyanate Esmail *et al* [16] prepared a number of 2-hydroxy-5acylaminothiadiazoles by heating carbohydrazide with equimolar quantity of an acylisothiocyanate in DMF at 100˚C[17].



From bisthioureas Bisthiourea and substituted bisthioureas when treated with 3% hydrogen peroxide are converted to 2, 5-diamino1, 3, 4-thiadiazole derivatives. [18]

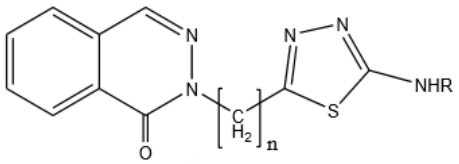


3. Literature survey

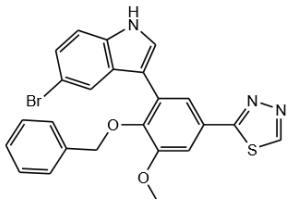
Biological Activity

Antibacterial and Antifungal activity 1, 3, 4-Thiadiazole has shown a broad spectrum of activity against various pathogens, and extensive research has been performed on the synthesis of new potent antibacterial and antifungal agents. A new series of 2-[[1(2H) phthalazinone-2-yl] methyl/ethyl]-5-arylamino-1, 3, 4 thiadiazole derivatives [19] was evaluated in vitro antimicrobial activity against bacterial and fungal species.

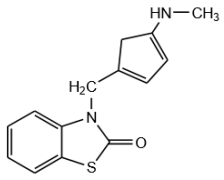
The results showed that the tested compounds possessed weak antibacterial and antifungal activity compared with standard drugs chloramphenicol and rifampicin for antibacterial and ketoconazole for antifungal activity, respectively [20].



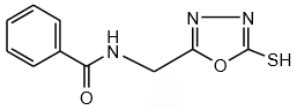
Anticancer activity of 5-(3-indolyl)-1, 3, 4-thiadiazoles are evaluated. Primary screening was performed at a concentration ranging from 100 nM to 1 mM. Change in cell number and cell morphology in 96-well plates was observed at 24 and 48 h had been detected. Compounds that exhibited toxicity to cancer cell lines but not to normal cells were selected for the secondary confirmation assays. It was found that substitution on C-2 position of the 1, 3, 4-thiadiazole ring plays an important role in imparting the cytotoxic activity to the compound. Compound 2-(4-(Benzyloxy)-5-(5-bromo-3-indolyl)-3methoxyphenyl)-1, 3, 4-thiadiazole [21] with 4-benzyloxy-3methoxyphenyl at C-2 position and 5-bromoindole at C-5 position was found to be the most potent compound of the series. [22].



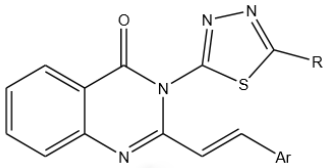
Antihistaminic agents: 2-Oxobenzothiazoline derivatives bearing substituents at position 3 with thiadiazole moiety have reported to exhibit antihistaminic activity [23]. 3-((4-(methylamino) cyclopenta-1, 3 dienyl) methyl) benzo[d]thiazol-2(3H)-one [24] were more potent than others and the standards in tail flick test.



Anthelmintic Activity Shrivastava *et al*, 1,3,4-oxadiazole derivative of hippuric acid, N-((5-mercapto-1,3,4-oxadiazol-2-yl) methyl) benzamide [25] synthesized and were found to possess potential antihelmentic activity against *Pheretima posthuma* as compared to albedazole [26].



Antidepressant agent: A series of novel 3-[5-substituted phenyl-1, 3, 4thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones were synthesized and evaluated for anticonvulsant, sedativehypnotic and CNS depressant activities [27].



4. Conclusions

This review thus gives an overview of the various synthetic routes used to form a biologically rich thiadiazole moiety as well as the reactions the molecule undergoes to yield various other important molecules. It also highlights the therapeutic properties of the thiadiazole ring and the availability of varied drugs in the market containing the ring. Thus this account of thiadiazole shows significant aspect of the bioactive thiadiazole ring.

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