Review on substituted 1, 3, 4 thiadiazole compounds

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ABSTRACT
The review was carried out to discuss in detail about the substituted 1,3, 4 thiadiazole compounds. Heterocyclic compounds such as thiazoles, thiadiazoles, indoles, oxadiazoles, benzisoxazoles and pyrroles have been successfully used as Antibacterial, Anticancer, Antipyretic, Schistosomicidal, Hypoglycemic, Antihypertensive, Anti-tubercular, Anti-inflammatory and Anti-HIV agents. All large number of organo-sulfur compounds occur in living and non-living object. They belong to open chain, alicyclic, aromatic and heterocyclic types of compounds containing sulfur atoms or atoms as a part of chain/ring or both in the structure. In this review briefly study about the Structure and reactivity of 1,3,4-thiadiazoles, Characteristic reactions, Characteristic features of 1,3,4-thiadiazole, Methods of synthesis, biological interest. And in this review can be concluded that many researches had investigated on substituted thidiazole compounds having the biological activities.

Keywords: Thiadiazole, Heterocyclic chemistry, 1, 3, 4 Thiadiazole.

INTRODUCTION
Because of the diversity in synthetic procedures, physiological and industrial significance, heterocyclic chemistry has been and continues to be one of the most active areas of organic chemistry. As a result numerous heterocyclic compounds such as thiazoles, thiadiazoles, indoles, oxadiazoles, benzisoxazoles and pyrroles have been successfully used as antibacterial, anticancer, antipyretic, schistosomicidal, hypoglycemic, antihypertensive, antitubercular, anti-inflammatory and anti-HIV agents. In addition, they have also been used in agriculture, plastics, polymers, dyes and textiles. Hence heterocyclic chemistry still continues to draw the attention of synthetic organic chemists and is of great scientific interest [1, 2, 3].

All large number of organo-sulfur compounds occur in living and non-living object. They belong to open chain, alicyclic, aromatic and heterocyclic types of compounds containing sulfur atoms or atoms as a part of chain/ring or both in the structure. [4, 5] Isolation, identification and applications of these organo-sulfur compounds lead to the fact that some of the compound sare useful in scientific, technical and industrial growth.
the last three decades organo-sulfur chemistry developed at a much faster pace than any other branches of organic chemistry. The role of organic sulphides in rubber vulcanization, hair curling, muscle contraction, natural aromas, vitamins, hormones, antibiotics, radio-protective agents, dye stuffs, binding materials organic semiconducting materials and organic light emitting diodes etc. may be cited. [6, 7]

Among the sulfur containing heterocyclic compounds, lot of research in the field of 1, 3, 4-thiadiazoles and imidazo [2,1-b][1,3,4] thiadiazoles has been reported. Some salient features regarding structure, chemical reactivity, spectral studies, synthetic pathways and biological interest of 1, 3, 4-thiadiazole and condensed imidazo [2,1-b] [1,3,4] thiadiazole are discussed briefly as background information.

**STRUCTURE AND REACTIVITY OF 1, 3, 4-THIADIAZOLE**

Of the four possible thiadiazoles (I, II, III, IV) the chemistry of1,3,4- thiadiazole (I) has attracted maximum attention since its discovery by Emil Fischerin 1882 on account of its compounds finding applications in agriculture, drugs, dyes and photographic materials. [8, 9]

1,3,4-thiadiazole (I) can be looked upon as 4-azathiazole or 3,4- diazathiophene so far as they are electronically isosteric. However, the replacement of z=CH= by electro negative –N= atom in the 5-membered thiophene ring changes the chemical/physical behavior considerably. The structure (I) represents π-excessive ring system as the two adjacent N atoms of the ring carry alone pair of electrons each. Actually 1,3,4-thiadiazole molecule does not display a true aromatic behavior as do benzene, pyridine and thiophene. Bak et al. have made analysis of microwave spectra of this molecule and calculated bond lengths, bond angles and bond orders. They concluded 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. Zahardnik and Koutechy made a series of M.O. calculations 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 I and thiazole. Bak et al. have reported the dipole moment value of 3.25D for 1,3,4-thiadiazole and1.61D for thiazole. [10] 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.

![Figure 1: Four possible thiadiazoles (I, II, III, IV)](image)

![Figure 2: Molecular geometry figure for 1,3,4-thiadiazole](image)
Some important canonical forms of 1,3,4-thiadiazole are written below, of which I with dienic behavior is the maximum contributing structure.

Figure 3: Some important canonical forms of 1,3,4-thiadiazole

CHARACTERISTIC REACTIONS

The chemistry of 1,3,4-thiadiazoles has been well documented in the form of books and review articles. Hence only a brief account of some characteristic reactions of the molecule is given.

Ring cleavage and rearrangement

1,3,4-thiadiazole is susceptible to the attack by strong nucleophiles, at the carbon atoms which is explainable on account of the poor electron density created by electronegative N atoms, e.g. 2-amino and 2-methylamino-1,3,4-thiadiazoles are rearranged to the isomeric S-triazole-3-thiones on heating with methylamine at 150°C. Heating 2-aminothiadiazole with benzyl amine afforded a mixture of 2- benzylamino-1,3,4-thiadiazole and 1-benzyl-S-triazole-3-thione.

Figure 4: Ring cleavage and rearrangement

Such rearrangements are reported to take place via ring opening to an inter mediate thio-carbohydrazone derivative (amidrazone), which further recyclicity to S-triazole-3-thione in the basic medium. [11]

Substitution reactions

Though 1,3,4-thiadiazole is a weak base, it forms hydrochloride salts. It resists electrophilic substitution reactions generally, e.g. bromination, nitration, sulfonation etc. However the presence of strong electron donating groups like NH₂ at Second position activates the 5th position for attack. Bak et.al obtained 2-amino-5-bromo-1,3,4-thiadiazole by bromination and subjected to Sandmeyers reaction to get the corresponding 2-substituted-5-bromo-1,3,4-thiadiazoles. [12]

Halogenation and nitration of 2-arylarnino-5-methyl-1,3,4-thiadiazole occurs in aryl nucleus. The halogen at 2 or 5 position is reactive and undergoes a variety of nucleophilic displacement reactions. In fact 1,3,4-thiadiazole is susceptible to nucleophilic attack at 2 or 5 position as both are activated sites. [12] The sensitivity to nucleophilic attack is further illustrated by direct nuclear amination of certain 2-aryl-1,3,4-thiadiazoles. e.g. the reaction of hydroxyl amine in the presence of alkali leads to the formation of 2-aryl-5-amino-1,3,4-thiadiazoles in about 45-70% yields. Also a substituent like methyl, amino, halo, carboxy present at this position undergo characteristic reactions. Though weak base, amino group of 2-amino-1,3,4-thiadiazole and its 5-substituted derivatives can be readily acylated and diazotized. It undergoes mannich reaction with variety of reactive methylene compounds.

Alkylation takes place on ring nitrogen with alkyl halides in most of the cases suggesting the imino structure or alkylated product.
Burmistrov et al. have reported an interesting reaction of 2-amino-1,3,4-thiadiazole with sec- and tert-alcohols in presence of 80-99% sulfuric acid giving the corresponding 2-alkylamino-1,3,4-thiadiazole in good yields.

Free radical reactions

Butler et al. have reported the following reaction regarded as Gomberg-Bachman reaction involving homolysis to C₆H₅• OH• and nitrogen.

Tautomerism

2-hydroxy-1,3,4-thiadiazole, 2-mercapto-1,3,4-thiadiazole and 2-aminothiadiazole have been reported to exist in the tautomeric forms as shown below.
Both hydroxyl and mercapto-1,3,4-thiadiazoles exist mostly in keto form (I) in free state. But their hydroxyl/thiol function is often elicited during the chemical reactions.

**Mesoionic 1,3,4-thiadiazoles**

The interest in the mesoionic 1,3,4-thiadiazoles is reviewed to study the physico-chemical aspects of varieties of mesoionic compounds containing hetero aromatic rings. F.Kurzer has given a concise account of mesoionic 1,3,4-thiadiazoles in a review article. Some of the mesoionic thiadiazoles are given below.

*Figure 9: Mesoionic 1,3,4-thiadiazoles*

The mesoionic 1,3,4-thiadiazole-2-thiones are reported to display large dipole moment values, which is confirmed by X-ray photoelectron spectroscopy. Their characteristic UV, IR, NMR spectra are reported.

*Formation of macro hetero cycles*

An interesting reaction of 2,5-diamino-1,3,4-thiadiazole and phthalonitrile in ethylene glycol at 120°C, leading to the formation of the following macro heterocyclic product (81%) has been reported.

*Figure 10: Formation of macro hetero cycles*

**SPECTRAL DATA**

Vast information is cited in the literature on spectral investigations of 1,3,4-thiadiazole and its derivatives. Bak *et al.* have recorded the IR and NMR spectra of a number of 1,3,4-thiadiazole derivatives. Reports on the mass spectra of some 2,5-disubstituted-1,3,4-thiadiazole derivatives have provided data for fragmentation patterns in the system.

**CHARACTERISTIC FEATURES OF 1,3,4-THIADIAZOLE**

By the studies on the chemical reactivities and the spectral features of 1,3,4-thiadiazoles we can summarize their properties as below. [13]

- 1,3,4-thiadiazole is a typical pseudo-aromatic molecule with dipole moment value of 3.25D.
- It is stable to acids but affected by strong bases leading to ring cleavage.
• It resists electrophilic substitution reactions. Facile nucleophilic attack takes place at 2- and 5- positions.
• Groups like -CH₃, Halogen, -NH₂, -COOH present in this position are reactive and exhibits their typical reactions.
• 2-hydroxy-, mercapto- and amino derivatives display tautomeric behavior.
• It is susceptible to reduction and oxidation in acids/alkali.
• It forms stable mesoionic betaine type compounds.

METHODS OF SYNTHESIS

The method commonly employed for the synthesis of 1,3,4-thiadiazole is the Cyclisation of thiosemicarbazide derivatives in incorporating the basic structural unit. Other methods involve ring closure of dithiocarbazates, acylhydrazines, bisthioureas or intercom versions of oxadiazoles in to 1,3,4-thiadiazoles have also been reported. [14]

From 1, 2 diacyl hydrazines

Stolle and coworkers prepared a number of 2,5-dialkyl-1,3,4-thiadiazoles from 1,2-diacyl hydrazines and P₂S₅. Instead of using P₂S₅, thioacylation of 1,2-diacyl hydrazine is effected by carboxymethyl dithioate which on heating gives 2,5-disubstituted thia diazoles.

![Figure 11: Formation of 2,5-disubstituted thiadiazoles](image)

From cyclisation of acyl thiosemicarbazides

E. Hoggarth for the first time reported the synthesis of 2-amino-1,3,4-thiadiazoles, by cyclodehydration of acylthio semi-carbazides in presence of acid catalyst like H₂SO₄, H₃PO₄ etc. The required acylthiosemicarbazides were obtained by treating an acid hydrazone with an isothiocyanate. They were also prepared in situ by heating the carboxylic acid and thiosemicarbazide in the acid medium and were cyclised subsequently. [15]

From cyclisation of aminoguanidines and diaminoguanidines

E. Kurzer prepared a number of 1,3,4-thiadiazoles by acid catalysed cyclisation of acyl thiosemicarbazides obtained from the reaction of aminoguanidine salts and aryl isothiocyanates.

![Figure 12: Preparation of a number of 1,3,4-thiadiazoles](image)
THIADIAZOLE DERIVATIVES OF BIOLOGICAL INTEREST

Mohammad amir et al. Have synthesized thiadiazole derivatives of biphenyl-4-yl oxy acetic acid and the targeted compounds were evaluated for their analgesic and anti-inflammatory activities.

where \( R = \text{Ph, p-BrPh, p-FPh, p-ClPh} \)

**Figure 13: Thiadiazole derivatives of biphenyl-4-yl oxy acetic acid**

**Spectral data**

The spectral studies involving UV, IR, \(^1\)HNMR, \(^{13}\)CNMR, Mass spectral data of imidazo[2,1-b][1,3,4]thiadiazoles have been reported by Torogova et al. and the mass spectral fragmentation of some 2-arylamino-5-alkyl-1,3,4-thiadiazoles and 2-alkyl-6-arylimidazo[2,1-b][1,3,4] thia diazoles was studied by Khazi et al. a wherein they observed the Mc Lafferty rearrangement in many of these molecules.

**Figure 14: Mc Lafferty rearrangement**
METHODS OF SYNTHESIS

The bicyclic imidazo[2,1-b][1,3,4]thiadiazole ring system I can be constructed with an appropriately substituted 2-amino-1,3,4-thiadiazole moiety and building the imidazole ring or vice versa. The first method is commonly adopted. [16]

From the condensation of 2-amino-1,3,4-thiadiazoles with α-haloketones

A mixture of an appropriately substituted 2-amino-1,3,4-thiadiazole and α-haloketones is heated in a suitable solvent medium for 6 to 10 hrs. Hydrohalides are obtained in good yields. The respective free bases are obtained by neutralization of salts with sodium carbonate solution. The method provides required substituent at 2-5- and 6-position, by starting with appropriately substituted synthons.

![Figure 15: condensation of 2-amino-1,3,4-thiadiazoles with α-haloketones](image)

The ring nitrogen of the thiadiazole is involved in the nucleophilic displacement of halogen of α-haloketone forming the intermediate as shown above. It undergoes further cyclodehydration on heating in a suitable medium like ethanol, dimethyl formamide to afford imidazo [2,1-b][1,3,4]thiadiazoles in good yields. [17] The cyclodehydration involves intra molecular nucleophilic addition of the 2-imino group to carbonyl function of the intermediate followed by the elimination of water. Various reports are available in the literature which involve this method for the synthesis of imidazo[2,1-b][1,3,4]thiadiazoles.

From cyclisation of n-(1,3,4-thiadiazol-2-yl)formamidines

Fajgelj et al. have reported a method for synthesis of imidazo[2,1-b][1,3,4]thiadiazoles. The method involves the transformation of N-(1,3,4-thiadiazol-2-yl)formamidines to the corresponding bicyclic system by cyclisation with phenacyl bromides.

![Figure 16: cyclisation of N-(1,3,4-thiadiazol-2-yl)formamidines](image)
This route provides a convenient method for the synthesis of imidazo [2,1-b] [1,3,4]thiadiazoles having a benzoyl group at 5-position without any substituent at 6-position. Pyl et al. reported that 2-benzylmercapto-5,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazole on heating with hydrazine hydrate is cleaved into the corresponding 1-amino-2-mercapto-4,5-disubstituted imidazole. Further they built thiadiazole ring on this moiety by cyclisation of 1-acylderivative in phosphorous oxychloride as shown below.

Figure 17: Cyclisation of 1-acylderivative in phosphorous oxychloride

For the present work we have adopted the first method for the synthesis of various imidazo[2,1-b][1,3,4]thiadiazoles. There are number of reports in the literature on the synthesis and biological activities of the condensed imidazo [b] thiazoles appeared particularly after the discovery of novel broad spectrum anthelmintic tetramisole.

After this discovery, research activities started on bioisosteric thiadiazole ring in place of thiazole ring of tetramisole. So, imidazo[2,1-b][1,3,4]thiadiazole nucleus has come into picture and thereafter tremendous work on such molecules being carried out in search of biologically active molecules. An important review article on the chemistry of imidazo[2,1-b][1,3,4]thiadiazoles has been recently published from our group. A series of 2-sulfamoyl-imidazo[2,1-b][1,3,4]thiadiazole derivatives were synthesized by Barnish and associates. They have reported them as carbonic anhydrase inhibitors.

Figure 18: Tetramisole and imidathiadizole ring

Many of these compounds showed the same degree of ionization as acetazolamide and methazolamide with higher lipophilic character. They were tested for anticonvulsant activities, compound I (R = t-butyl and R2 = H) had an anticonvulsant ED50 of 2.6mg/kg when administered orally to mice. This compound selectively increased cerebral blood flow in animals without producing a high level of metabolic acidosis.

CONCLUSION

Hetero cyclic chemistry has been and continues to be one of the most active areas of organic chemistry. As a result numerous heterocyclic
compounds such as thiazoles, thiadiazoles, indoles, oxadiazoles, benzisoxazoles and pyrroles have been successfully used as antibacterial, anticancer, antipyretic, schistosomicidal, hypoglycemic, antihypertensive, antitubercular, anti-inflammatory and anti-HIV agents. In addition, they have also been used in agriculture, plastics, polymers, dyes and textiles. Hence heterocyclic chemistry still continues to draw the attention of synthetic organic chemists and is of great scientific interest. Hence it can be concluded that many researches had investigated on substituted thiodiazole compounds having the biological activities.

Acknowledgement

I thankful to the almighty for blessings in successful completion of this work, my special thanks to Mr.K.Gopalsatheskumar and I would like to thank my friends S.Parthiban, T.Boopathi, G.Sangeetha, M.Thanga Kokila, V.Sanish Devan, M.Sanjay, A.Jeevanantham. My deepest heartfelt gratitude and indebtedness belong to my Parents and Sisters who showed love, affection, encouragement and finally made it possible to complete this work.

REFERENCES

[1]. Otilia Pintilie. Synthesis and Antimicrobial Activity of Some New Moiety 1,3,4-Thiadiazole and 1,2,4-Triazole Compounds Having a D.L-Methionine. Molecule. 12, 2007, 103-113
[3]. Dushyant H Purohit et al. Synthesis and Antimicrobial Activity of Some New 1,3,4-Thiadiazoles and 1,3,4-Thiadiazines Containing 1,2,4-Triazole Nucleus. Acta Chim.slov. 1, 2011, 53-58.
[13]. Patil SG, Girisha M, Badiger J, Kudari SM, Purohit MG. Synthesis and antimicrobial, anticonvulsant activity of some bis-1,3,4-oxadiazole and bis-1,2,4- triazole derivatives from sebacic acid. Ind J Heterocylic Chem. 17, 2007, 37-40
[15]. Silvia Schenone, 3-Arylsulphonyl-5-arylamino-1,3,4-thiadiazol-2(3H)ones as Antiinflammatory and Analgesic Agents, bioorganic and medicinal chemistry. 2001, 2149- 2153.
[16]. Parmar Kokila, A Simple and Efficient Procedure for Synthesis of Biologically Active 1,2,4- Triazole-[3,4-b]-1,3,4-thiadiazole -2-aryl-thiazolidine-4-one Derivatives, Research journal of chemical sciences. 1, 2011, 18-26.