EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 7
118-122
Year: 2024

COMPARATIVE STUDY OF ONE POT SYNTHETIC METHODS OF 2-AMINO-1,3,4-THIADIAZOLE

Ankita Jamale[1]*, Ahilya Mudhe[2], Ajinkya Patil[3], Akshay Khadake[4], Akash Bageli[5], Baliram Sarvade[6], Amit Panaskar[7], Bhagyashri Panaskar[8] and Vishal Ghadage[9]

Asst. Professor Pharmaceutical Chemistry[6], Professor Dr. of Pharmaceutical Chemistry Department[7], Professor Dr. of Pharmacology Department[8],
[1-5,9]Padmini College of Pharmacy, Dighanchi, Tal-Atpadi, Dist-Sangli, Maharashtra, India-415315.

***Corresponding Author: Ankita Jamale**
Padmini College of Pharmacy, Dighanchi, Tal-Atpadi, Dist-Sangli, Maharashtra, India-415315.

Article Received on 30/04/2024 **Article Revised on 20/05/2024** **Article Accepted on 10/06/2024**

ABSTRACT
Thiadiazole derivatives have garnered significant attention in the field of medicinal chemistry due to their diverse pharmacological activities, including anticancer, antimicrobial, antibacterial, antifungal, insecticidal and pesticidal properties. This article presents the synthesis of a series of thiadiazole derivatives and investigates their chemical characterization and potential pharmacological effects on various cell lines. Thiadiazoles belong to the classes of nitrogen–sulfur heterocycles with extensive application as structural units of biologically active molecules and as useful intermediates in medicinal chemistry. The potency of the thiadiazole nucleus is demonstrated by the drugs currently used. 1,3,4-Thiadiazoles and some of their derivatives are extensively studied because of their broad spectrum of pharmacological activities. In this article Substituted Carboxylic acid condensed with Thiosemicarbazide to form 2-amino-5- substituted 1,3,4-Thiodiazole in various reaction conditions. All products are characterized by elemental analysis.

KEYWORDS: 2-Amino-1,3,4-Thiadiazole, Elemental Analysis, Thiosemicarbazide, One Pot Synthetic Methods, Thionyl Chloride, Ultrasonic Irradiation.

INTRODUCTION
Five membered heterocyclic compounds play an important role among organic compounds with biological activity used as drugs in human and veterinary medicines and not only insecticides and pesticides in agriculture but also includes anticancer, antimicrobial, antibacterial, antifungal properties. Chemical rings, which are present in many marketed drugs, may possess pharmacological properties or may serve as a platform for the pharmacophoric groups which will interact with the receptors. They have become an important class of heterocycles of great interest to researchers because of their broad spectrum of biological activities.[3] There are several isomers of thiadiazole including 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5- thiadiazole, and 1,3,4-thiadiazole. Among them, 1,3,4-thiadiazoles are extensively investigated owing to their high reactivity towards nucleophilic substitution reactions and a wide range of biological activities.[1],[2],[3] In addition, 1,3,4-thiadiazole core's have electron-deficient nature and good electron-accepting ability as well as thermal and chemical stability. Thus, possessing these properties, 1,3,4-thiadiazole derivatives are applied widely in pharmaceutical, agricultural, and material chemistry.[4],[5],[6] The presence of nitrogen and sulfur atoms in 1,3,4-thiadiazole moiety as potential binding sites makes them versatile ligands for the syntheses of metal complexes.[4]

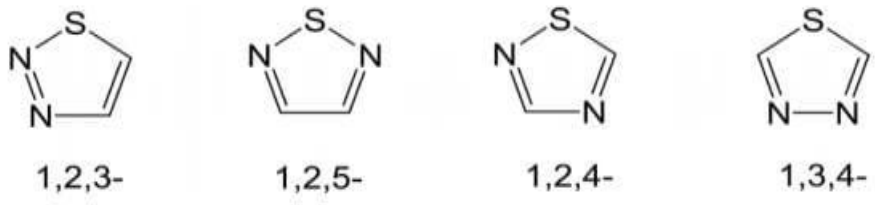


Fig. no. 01: Structures of thiadiazole isomers.

Considering the information provided above, we have hypothesized that exploring cytotoxic compounds within the category of 1,3,4-thiadiazole derivatives holds significant promise as an avenue of research. Consequently, we present our work on the synthesis, characterization of a series of 1,3,4-thiadiazole derivatives which share a central 5-phenyl-1,3,4-thiadiazol-2-amine scaffold. Through a comparative analysis of the effects of the compounds on the growth and survival of cancer cells, we aimed to better understand the structure–activity relationships and the potential mechanistic pathways underlying the action of the novel compounds.

AIMS AND OBJECTIVES

1. This comparative study is used to identify their pharmacological activities, as well as introducing deduced collective structure–activity relationship charts for antimicrobial, anticancer, and antioxidant activities.[3]
2. The main purpose of the study was the development of a new method for synthesis of 1,3,4- thiadiazol-2-amine derivatives in a one-pot manner using the reaction between a thiosemicarbazide and carboxylic acid.[5]
3. The aim of this review was to highlight the main antimicrobial properties exhibited by derivatives possessing 2-amino-1,3,4-thiadiazole moiety.[3]
4. To report the synthesis, spectral, structural investigations of 5-(4-methoxyphenyl)−1,3,4-thiadiazole-2-amine.[2]
5. To perform comparative study of synthesis of 2-amino- 1, 3, 4-Thiodiazole with respect to yield, reaction time and reaction conditions.[2]
6. To characterize all the products by elemental analysis.[2]

MATERIALS AND METHODS

The melting points of all the compounds were determined in open head capillary and are uncorrected. All the compounds were checked for purity by thin layer chromatography (TLC) and elemental analysis requires test tubes, test tube holders, infusion tubes. It require many more materials like beakers, measuring cylinders, pipette, dropper, etc.

Materials

Test tubes, test tube holders, infusion tubes, beakers, measuring cylinders, pipette, dropper, etc.

Methods

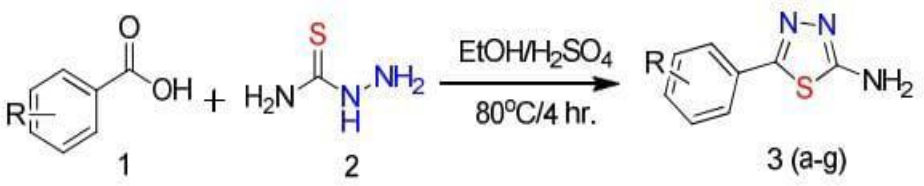


Fig. No. 02

1. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine by Conventional Method Using Conc. Sulphuric Acid:** An ethanolic solution of aromatic carboxylic acid (0.05mol) was added to aqueous solution of Thiosemicarbazide (0.05mole) with constant stirring, few drop of conc. Sulphuric acid was added and heated for 4 hours at 80-900C, after completion of reaction (TLC), cool and poured to ice-cold water, basify with 10% Na2CO3 solution, filter, dried and recrystalised from suitable solvent.[2]

2. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine by Conventional Method Using Socl2:** Aromatic carboxylic acid (0.01mole) and thionyl chloride (0.012) was heated for 1 hour at 700 C with calcium chloride guard tube. Thiosemicarbazide (0.012mole) was added to this hot reaction mixture and heated for another 4 hours at same temperature. On completion of reaction (TLC), basify with aqueous NaHCO3, filter, dried and recrystalised from suitable solvent.[2]

3. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine by Microwave Method Using Conc. Sulfuric Acid:** A mixture of aromatic carboxylic acid (0.05 mole) and thiosemicarbazide (0.05mole) was dissolved in DMF (10ml) to this added conc. sulfuric acid (10 drop) and irradiated in microwave oven (480 watt) for 5 minutes. On completion of reaction (TLC) pour to ice cold water, filter, dried and recrystalised from suitable solvent.[2]

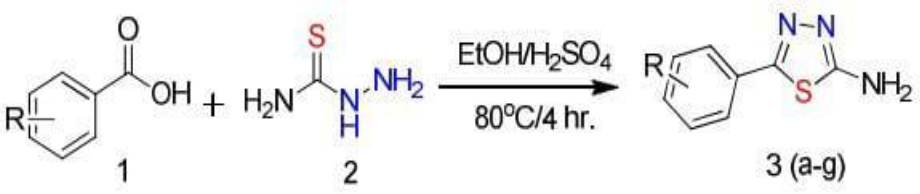
4. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine by Microwave Method Using Socl2:** A mixture of aromatic carboxylic acid (0.01mole) and thionyl chloride (0.012mole) was irradiated at 300 watt for 1 minutes, upon cooling thiosemicarbazide (0.012 mole) was added and irradiated (480 watt) for 3 minute, on completion of reaction (TLC) poured to ice cold water, filter, dried and recrystalised from suitable solvent.[2]

5. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine by Microwave Method Using MgSO4 as a Catalyst:** A mixture of aromatic carboxylic acid (0.01mole) and thiosemicarbazide (0.01mole) was irradiated in presences of magnesium sulphate (2 gm) for 5 minutes (250 watt) (TLC), poured to ice cold water neutralized by sodium carbonate solution. Obtained solid was filter, dried and recrystalised from suitable solvent.[2]

6. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine Neat Reaction Condition:** A mixture of aromatic carboxylic acid (0.1mole) and Thiosemicarbazide (0.1mole) was heated under solvent free condition for 3 hours then reaction mixture was cooled at room temperature. Water was added, filters, dried and recrystalised from suitable solvent.[2]

7. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine by Ultrasonic Irradiation:** The equimolar quantity 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 minute at 800C, on completion of reaction (TLC) solid obtained was poured to ice cold water, filter, dried and recrystalised from suitable solvent.[2]

8. **Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2- Amine by Simple Grinding Method:** Aromatic carboxylic acid (0.01mole), Thiosemicarbazide (0.01 mole) and catalytic amount of H2SO4, grind in mortar and pestle for one and half hour, then stand at room temperature for another 4 hours with occasional grinding. On completion of reaction (TLC) cold water was added, basified with sodium hydroxide (10%), obtained solid was filtered, dried and recrystalised from suitable solvent.[2]



Elemental analysis

Elemental analysis (EA) is an analytical technique applied in chemistry to determine the elemental composition of chemical compounds and their composites. As there are different elements in many different samples, there is a number of techniques more or less suitable for elemental analysis of a sample of interest.

Fig. No. 03

Fig. No. 04

Chromatography

Chromatographic analysis is a method that uses the small differences in the solubility, resolution, adsorption and desorption of each component in the sample between the stationary phase and the mobile phase to realize the separation of each component and then analyse it one by one.

Thin layer chromatography

Thin layer chromatography (TLC), an analytical technique often used to separate and identify compounds present in a given mixture, can also be used to determine the purity of a particular substance within that mixture.

$$\text{Rf Value} = \frac{\text{Distance travelled by solute front from origin line.}}{\text{Distance travelled by solvent front from origin line.}}$$

Where,
Rf =Retention factor
Thin layer chromatography tests were performed on the carboxylic derivative of benzoic acid in order to identify the existence of many substances supported by chemical tests. TLC spot colour and Rf value in Ethyl Acetate:Hexane solvent system (1:4).

RESULT AND DISCUSSION

For comparative study of various synthetic methods of 2-amino-1,3,4-thiadiazole, series of reactions were performed. Among various methods eight methods were taken which are very common. Our study underlines the importance of sulphuric acid and catalysed conventional reaction is most efficient product obtaining method. Unlike sulphuric acid, phosphorus oxychloride improve the yield of reaction when used in microwave irradiation. Ultrasonic method and grinding method gives 2-amino thiadiazole with comparative fewer yield.

Table No. 01

Sr No.	Methods	T.Y(gm)	P.Y. (gm)	%Purity	M.P.	RF Value
1.	Conventional method by using H2SO4	3.84 gm	2.34 gm	60 %	115°	0.66
2.	Conventional method by using SOCL2	3.84 gm	2.39 gm	62 %	118°	0.5
3.	Microwave method by using H2SO4	3.84 gm	2.4 gm	62 %	114°	0.8
4.	Microwave method by using SOCL2	3.84 gm	2.35 gm	61 %	121°	0.6
5.	Microwave method by using MgSO4	3.84 gm	2.19 gm	57 %	120°	0.6
6.	Amine neat reaction	3.84 gm	2.45 gm	63 %	115°	0.4
7.	Ultrasonic irradiation	3.84 gm	2.49 gm	64 %	118°	0.5
8.	Grinding method	3.84 gm	2.92 gm	76 %	115°	0.5

Elemental analysis

Elemental analysis is applied to all the carboxylic derivatives of benzoic acid for each methods performed in this study and underlines the presence of nitrogen, sulfur, and halogen.

Table No. 02

Sr. No.	Tests	Observations	Inference
1.	**Test for nitrogen:** Stock Soln+FeSO4 Soln and Cooled Conc.H2SO4 Till The Soln Is Clear	Green Or Blue Colour	Present
2.	**Test for sulfur:** 2ml Stock Soln+1 Drop of Freshly Prepared Sodium Nitroprusside Soln	Purple Or Violet Colour	Present
3.	**Test for halogen:** 2ml Stock Soln+Add 1ml dil.Nitric Acid And 1ml aq. Silver Nitrate Soln	White ppt. Soluble in Ammonium Hydroxide	Present

CONCLUSION

In conclusion, synthesis of 2-amino-1,3,4-thiadiazole by sulfuric acid conventional method is one of the efficient and simple way to obtained desire product, particularly in term of yield. Unlike any other general synthetic method, this study reports that Sulfuric acid catalyzed conventional way of synthesis of 2-amino-1, 3, 4-thiadiazole is more productive over sulfuric acid MWI method. Thiadiazole ring is present in compounds with various biological activities. Among the different isomers of thiadiazole, 1,3,4-thiadiazole derivatives are most studied due to broad spectrum of pharmacological activities. Although only a few pharmacological effects exhibited by 1,3,4-thiadiazole derivatives are currently clinically used (eg, antibacterial activity and carbonic anhydrase inhibiting activity), the substitution at thiadiazole ring is a challenging approach to obtain agents with improved potency and less toxicity.

ACKNOWLEDGEMENT

I am thankful to the Padmini College of Pharmacy Dighanchi, Tal-Atpadi, Dist- Sangli for providing the necessary facilities. I am also grateful to Dr. Panaskar Sir, Dr. Panaskar Mam, Mr. Sarvade B.B, Ms. Agawane S.S and Ghadage V.A for guiding and supporting me throughout the process.

REFERENCES

1. Stecoza, C. E., Nitulescu, G. M., Draghici, C., Caproiu, M. T., Hanganu, A., Olaru, O. T., Mihai, D. P., Bostan, M., & Mihaila, M. Synthesis of 1,3,4-thiadiazole derivatives and their anticancer evaluation. International Journal of Molecular Sciences, 2023; 24(24): 17476. https://doi.org/10.3390/ijms242417476.
2. (N.d.). Retrieved April, 2024; 23. from http://file:///C:/Users/Admin/Downloads/comparative-study-of-one-pot-syntheticmethods-of-2amino134thiadiazole%20(1).pdf
3. Serban, G., Stanasel, O., Serban, E., & Bota, S. 2-Amino-1,3,4-thiadiazole as a potential scaffold for promising antimicrobial agents. Drug Design, Development and Therapy, 2018; 12: 1545–1566. https://doi.org/10.2147/dddt.s155958
4. Gond, M. K., Pandey, S. K., Chandra, S., Tiwari, N., Bharty, M. K., Maiti, B., Katiyar, D., & Butcher, R. J. Zinc(II) catalyzed synthesis of 2-(4-methoxyphenyl)-5-(2- pyridyl)-1,3,4-thiadiazole:

Characterizations, crystal structure, DFT calculation, Hirshfeld surface analysis, and molecular docking analysis. Journal of Molecular Structure, 2022; 1267(133586): 133586. https://doi.org/10.1016/j.molstruc.2022.133586
5. Kokovina, T. S., Gadomsky, S. Y., Terentiev, A. A., & Sanina, N. A. A novel approach to the synthesis of 1,3,4-thiadiazole-2-amine derivatives. Molecules (Basel, Switzerland), 2021; 26(17): 5159. https://doi.org/10.3390/molecules26175159
6. (N.d.-c).Retrieved April, 2024; 24. from http://file:///C:/Users/Admin/Downloads/A_REVIEW_ON_BIOLOGICAL_ACTIVITIES_134-_THIADIAZOLE%20(2).pdf