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SYNTHESIS OF AN HETEROCYCLIC COMPOUND 5-PHENYL-1, 3, 4-THIADIAZOLE-2-AMINE

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ABSTRACT- *The present work describes an efficient synthetic approach for the preparation of 5-phenyl-1,3,4-thiadiazole-2-amine using phenyl hydrazine as the starting material. The synthesis was carried out through a multi-step reaction involving cyclization, acidification, and animation processes. Initially, phenyl hydrazine was reacted with carbon disulfide in ethanol in the presence of sodium hydroxide under reflux conditions to form an intermediate salt, which subsequently underwent intermolecular cyclization to generate the thiadiazole framework. Controlled acidification with hydrochloric acid facilitated the isolation of the thiol intermediate. The obtained intermediate was then subjected to amination using ammonia under reflux to afford the desired amine derivative. The crude product was isolated by filtration and purified by recrystallization form ethanol to obtain the final compound in good purity. The synthesized 5-phenyl-1,3,4-thiadiazole-2-amine was characterized by infrared (IR) spectroscopy, which confirmed the formation of the thaiodiazole nucleus and functional groups. The adopted synthetic route is simple, cost-effective, and reproducible, making it suitable for laboratory scale preparation. This methodology also provides a convenient platform for the synthesis of related 1,3,4-thiadiazole derivatives with potential pharmaceutical significance.*

Keywords: Cyclization, Acidification, Amination, Recrystallization, Infrared spectroscopy.

INTRODUCTION

In recent years, heterocyclic compounds have attached considerable interest owing to their vital role in the synthesis of novel derivatives and their wide-ranging applications in the pharmaceutical and chemical industries [1-3]. Numerous heterocyclic systems have been developed and assessed for their biological and medical relevance. Among them, thiadiazole is a notable five-membered heterocyclic containing two nitrogen atoms and one sulphur atom. Various structural isomers of thiadiazole, including 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, have been extensively investigated for their diverse biological activities. [4]

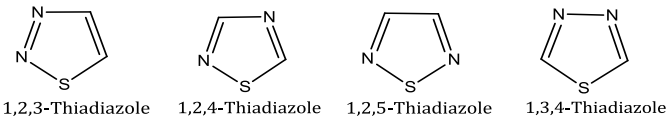


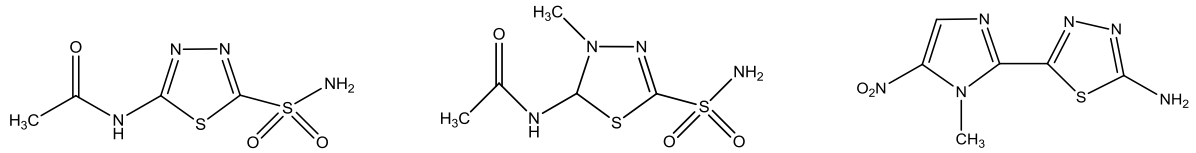
FIG 1: Structural isomers of thiadiazoles

1, 3, 4-thiadiazole

Previous literature surveys indicate that 1,3,4-thiadiazole is the most promising isomer among thiadiazole derivatives. The presence of a sulphur atom in the 1,3,4-thiadiazole ring induces an inductive effect, resulting in very weak basic character and comparatively high aromaticity. Among the various isomers, 1,3,4-thiadiazoles in particular exhibit a broad spectrum of biological activities, including antimicrobial, antitubercular, antioxidant, anti-inflammatory, anticonvulsant, antidepressant and anxiolytic, antihypertensive, anticancer, and antifungal properties. [5,6,7]

1,3,4-thiadiazole drugs

Till the date, several drugs containing the 1,3,4-thiadiazole nucleus are available in the market, including acetazolamide, methazolamide, and megazol, whereas cefozopran is an antibiotic that contains the 1,2,4-thiadiazole ring. [8,9]



Acetazolamide Methazolamide Megazol

FIG 2: 1,3,4-thiadiazole drugs

SYNTHESIS

a) Synthesis of 1,3,4-thiadiazole.

b) Synthesis of 5-phenyl-1,3,4-thiadiazole-2-amine.

Synthesis of 1,3,4-thiadiazole

Structure and Characteristics: 1,3,4-thiadiazole is a five-membered heteroaromatic ring containing two nitrogen atoms and one sulphur atom. The ring system is planar and conjugated, following Huckle's rule and exhibiting aromatic character. Substitution generally occurs at the 2- and 5- positions, enabling structural variation. These structural features provide high stability and make the 1,3,4-thiadiazole scaffold valuable in medical chemistry.

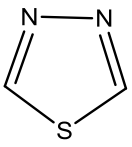
Synthesis: 1,3,4-thiadiazole derivatives are commonly synthesized by cyclization of thiosemicarbazides using dehydrating agents. The reaction usually involves condensation of carboxylic acids or acid chlorides with thiosemicarbazide to form intermediates.

Chemical and physical properties: It has a molecular weight of approximately 102.12 g/mol and exists as a stable heteroaromatic compound. It exhibits a relatively high melting point and low volatility due to strong intermolecular interactions, including dipole-dipole forces. These interactions contribute to its solid-solid stability, density, and well-defined physiochemical behaviour.

Uses

- Pharmaceuticals: antimicrobial, anticancer, anti-inflammatory, and antitubercular.
- Industry: used in agrochemicals, dyes, polymers, and functional material.

This 1,3,4-thiadiazole plays a vital role in chemical synthesis, pharmaceutical development, and as a solvent. Its synthesis, applications, and toxicity require careful handling and analysis.



1,3,4-Thiadiazole

FIG 3: Structure of 1,3,4-thiadiazole

Synthesis of 5-phenyl-1,3,4-thiadiazole-2-amine

Chemicals and reagents:

- Phenyl Hydrazine
- Carbon disulfide
- Hydrochloric acid
- Ethanol
- Ammonia
- Sodium hydroxide

Equipment and Instruments

- Magnetic stirrer
- Thermometer
- Laboratory condenser
- Heating mantle

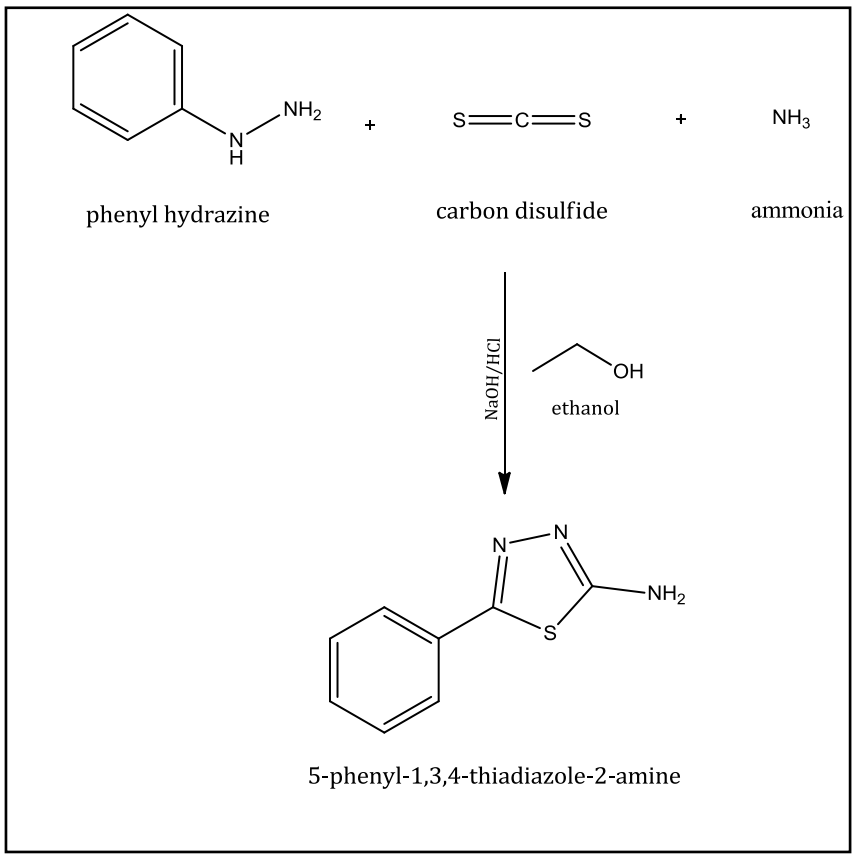


FIG 4: Scheme of the preparation

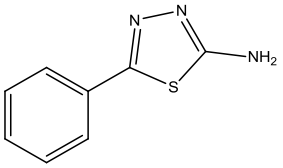
PROCEDURE:

Phenyl hydrazine was reacted with carbon disulfide in absolute ethanol in the presence of a base such as anhydrous sodium carbonate to form a Di thiocarbamate intermediate. The reaction mixture was refluxed for 4-8 hours, reading to the formation of a potassium hydrazothicarbonamide dithiocarboxylate salt, which subsequently underwent cyclization to yield 5-phenyl-1,3,4-thiadiazole-2-thiol or its salt form. After completion of the reaction, the mixture was cooled in an ice bath, and concentrated hydrochloric acid was added slowly with continuous stirring to control the exothermic process and precipitate the thiol intermediate. The resulting solid was collected and dissolved in ethanol, followed by the addition of ammonia solution. The mixture was then refluxed for 8-10 hours, allowing nucleophilic substitution of the sulphur atom by an amine group to form 5-phenyl-1,3,4-thiadiazole-2-amine. Upon completion, the reaction mixture was cooled or poured into ice water to induce precipitation. If required, the solution was neutralized to pH 8-9 using a mild alkaline solution. The precipitated product was filtered, washed thoroughly, and recrystallized from ethanol to obtain the final compound in high purity.

RESULT:

In this experiment, the 5-phenyl-1,3,4-thiadiazole-2-amine were successfully synthesized using the outlined synthetic routes. The compound was obtained in a satisfactory yield and characterized based on its physical and chemical properties. The structure of the compound, identified as 5-phenyl-1,3,4-thiadiazole-2-amine, was confirmed using its molecular formula and chemical name. The synthesized product exhibits the expected characteristics, including its physical properties appearance, high melting point, and molecular weight, all of which were consistent with the expected properties of 5-phenyl-1,3,4-thiadiazole-2-amine. The details of the compound's properties are summarized in the following table.

TABLE 1

Structure	 5-phenyl-1,3,4-thiadiazole-2-amine
Molecular formula	$C_8H_7N_3S$
Chemical Name	5-phenyl-1,3,4-thiadiazole-2-amine
Yield	78%
Melting Point	168-172° C
Molecular Weight	177.23 g/mol

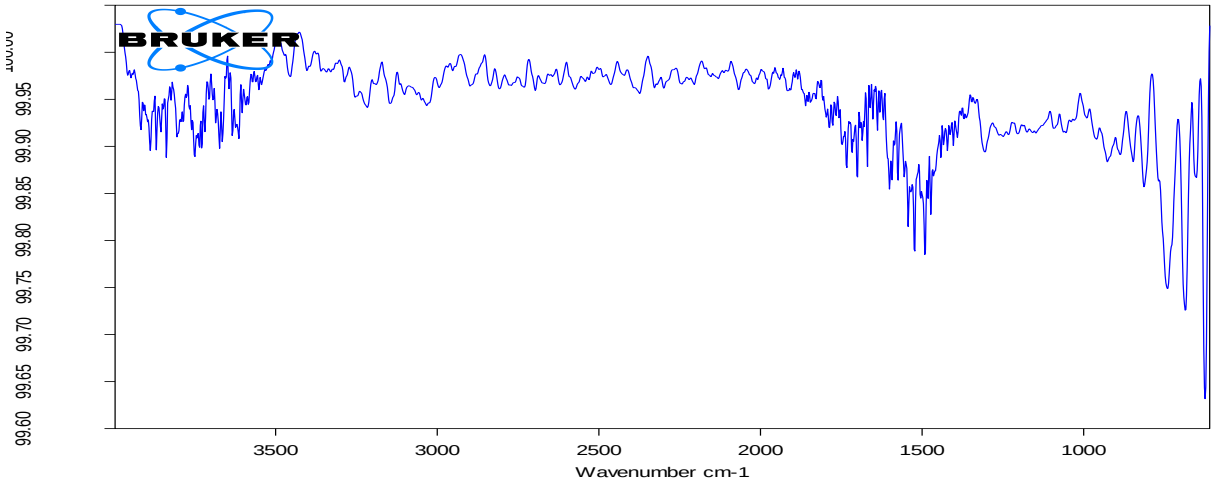


FIG 5: FT-IR Spectroscopy of 5-phenyl-1,3,4-thiadiazole-2-amine

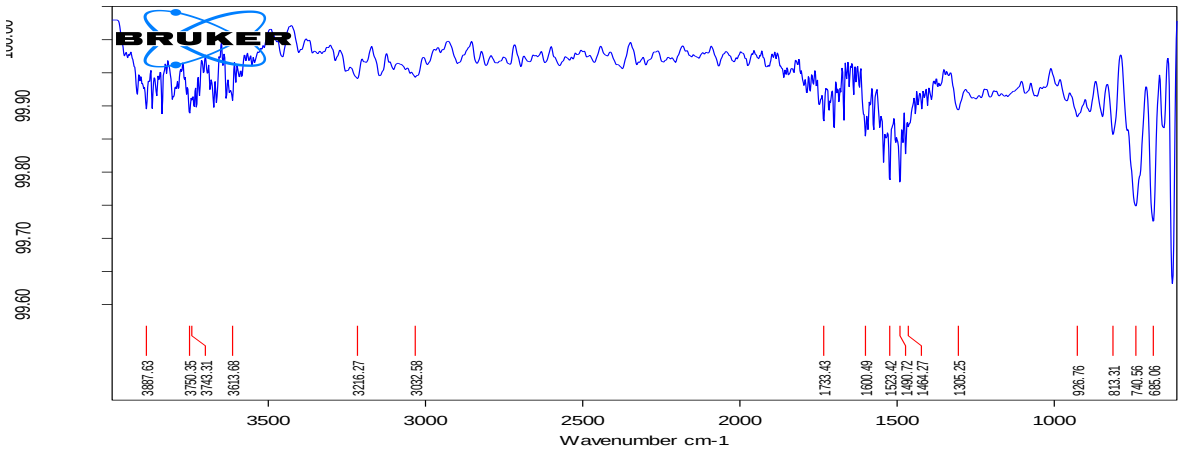


FIG 6: FT-IR spectroscopy of 5-phenyl-1,3,4-thiadiazole-2-amine with peak lines

DISCUSSION:

The test compounds were synthesized by adopting the synthetic route depicted in the scheme. The key intermediate was Di thiocarbamate prepared by reacting phenyl hydrazine, anhydrous sodium hydroxide and ammonia solution in the presence of ethanol and hydrochloric acid. The IR spectrum of the synthesized compound, 5-phenyl-1,3,4-thiadiazole-2-amine, was analysed to confirm its structure. The spectrum exhibited characteristic absorption bands that are consistent with the expected functional groups. The spectrum data for 5-phenyl-1,3,4-thiadiazole-2-amine is given below.,

TABLE 2

(cm^{-1})	Assignment
3029 cm^{-1}	Aromatic C-H stretching
1584 cm^{-1}	C-N stretching
1622 cm^{-1}	N-H bending
1248 cm^{-1}	C-N stretching
1078 cm^{-1}	C-S and N-N stretching
864 cm^{-1}	C-H out of plane bending

The IR spectrum data provides strong evidence for the successful synthesis of the 5-phenyl-1,3,4-thiadiazole-2-amine. The presence of characteristics absorption bands corresponding to the expected functional groups confirms the structure of the compound.

CONCLUSION:

The 5-phenyl-1,3,4-thiadiazole-2-amine was successfully synthesized through a well-defined multi-step procedure involving intermediate salt formation, controlled acidification, and amination. The reaction conditions were optimized to ensure smooth cyclization and high product stability. The synthesized compounds were subjected to IR spectroscopic analysis, which confirmed the presence of the thiadiazole framework and functional groups, supporting the successful formation of the target molecule. The overall procedure was found to be reproducible and operationally simple. The final product was isolated as a solid and purified effectively by recrystallization, yielding a compound of high purity. The synthetic route employed is cost-effective and suitable for laboratory-scale preparation. This method also offers flexibility for further structural modifications. Hence, the approach is promising for the synthesis of related 1,3,4-thiadiazole derivatives with potential biological applications.

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