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Synthesis of 1,3,4-thiadiazole Derivative Using Appropriate Reaction Conditions

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Abstract: ***Five membered heterocyclic rings possessing a mixture of different heteroatoms like S, N, O, etc. not only possess interesting chemical properties but also have a myriad number of biological activities. Of these, 1,3,4-thiadiazole moiety and its derivatives have gained a deep interest in recent year due to their crucial role in wide variety of drugs, dyes, and other substances of high interests. The present work is focussed on the different methods of their synthesis. The review highlights the key features of their synthesis.***
Keywords: Thiadiazole, synthesis,

I. INTRODUCTION

Heterocyclic organic compounds are those that have heteroatoms like O, N, S, or P as one of the ring members. Modern organic chemistry includes the chemistry of heterocyclic compounds as a fundamental component. One of the most important factors that determines a heterocyclic molecule's physical characteristics, reactivity, and ease of synthesis is its ring size. The most common and dominant class of heterocyclic compounds contains those with heterocyclic rings made of nitrogen, oxygen, and sulphur. There are many heterocyclic compounds with rings containing three to six carbons, but five and six membered rings are by far the most significant. Thiophene, furan, and pyrrole are the three most basic and extensively researched single heteroatoms with five membered heterocyclic rings. Azole, thiazole, thiadiazole, oxadiazole, etc. are examples of five-membered rings that contain two or more heteroatoms. A five-membered ring having two or more heteroatoms, one of which being Nitrogen, is described by the suffix -azole.

Due to their distinct chemical characteristics and diverse biological activities, heterocyclic rings and their many derivatives have garnered the majority of chemists' attention in recent years. These rings have also found applications in the chemical and pharmaceutical industries. Despite tremendous advancements in the study of heterocyclic ring systems, work is still being done to find new heterocyclic compounds that have strong bioactivities. Numerous heterocyclic compounds, including imidazole, oxazole, thiazole, oxadiazole, and thiadiazole, have been the subject of research. These molecules frequently have biological effects. In the past, the thiadiazole ring has been used to bind substances like antiparasitic and antibacterial agents, and some of the resulting medicines are still in use today [1-3]. Recent studies have shown that the thiadiazole ring is a significant structural element with wide-ranging biological action.

Thiadiazole and its derivatives have received attention of researchers due to ease of synthesis, stability and wide spectrum of biological applications. Thiadiazole is a five membered heterocyclic ring system containing one sulphur and two nitrogen atoms. Thiadiazoles are derivatives of thiophene, formed by replacing the two –CH= (methine) groups by pyridine-type nitrogen (-N=).

The numbering of monocyclic azole system commences with the heteroatom from highest group in the periodic table with the element of lowest atomic number in same group. Consequently, the numbering of 1,3,4-thiadiazole **4** is done in the following manner. This designated that one sulphur atom is present in the ring.

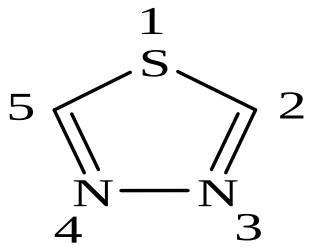


Figure 1. Numbering used in 1,3,4-thiadiazole ring.

Four isomeric forms are possible for thiadiazole ring system *viz.*, 1,2,3-thiadiazole **1**, 1,2,4-thiadiazole **2**, 1,2,5-thiadiazole **3**, and 1,3,4-thiadiazole **4**. The IUPAC and common names are same for these isomeric forms.

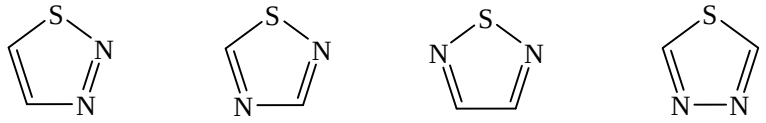


Figure 2. Different isomeric forms of thiadiazole ring.

1,3,4-Thiadiazole and its derivatives have received considerable interests in last decade due to their significant pharmaceutical and industrial importance along with low toxicity for higher vertebrates like Humans. Therefore, it is not surprising that the synthetic publication far outweighs in numbers those relating to all other fields.

1,3,4-Thiadiazoles have been found to exist as:

1) Aromatic systems which include the neutral thiadiazole **5**.

2) Mesoionic systems **6** 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.

3) Non aromatic systems such as the 1,3,4-thiadiazolines **7, 8** and the tetrahydro- 1,3,4-thiadiazolidines **9**.

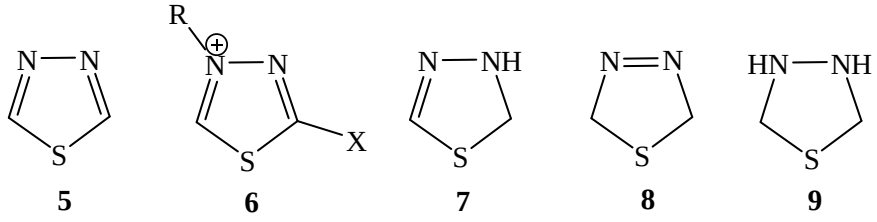
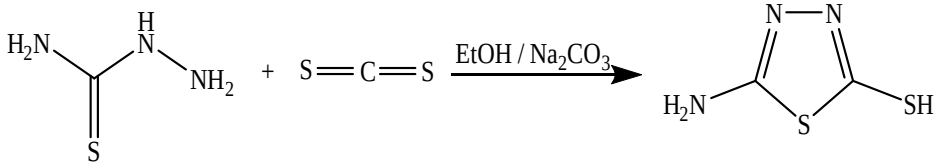


Figure 3. Structures of neutral, mesoionic and non-aromatic 1,3,4-thiadiazoles.

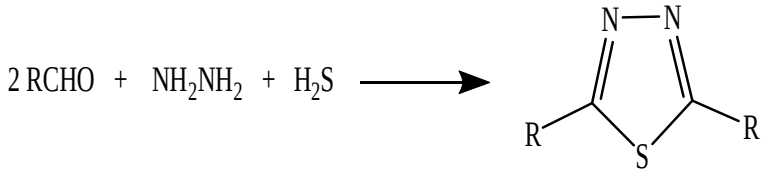
II. SYNTHETIC STRATEGIES FOR 1,3,4-THIADIAZOLES

1,3,4-Thiadiazoles are synthesized by different methods:

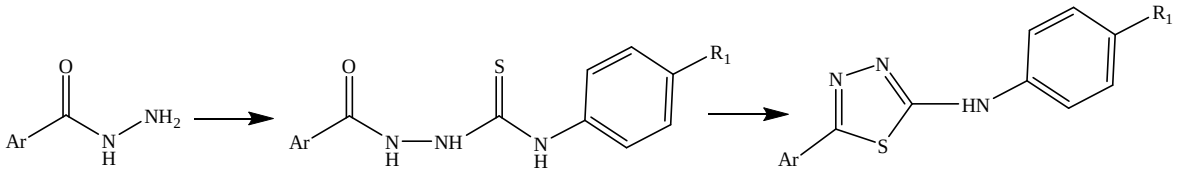
In a study, Barbosa & Palermo [4] highlighted the main methodologies for the synthesis of 1,3,4-thiadiazoles derivatives using acylhydrazines, dithiocarbazates, thiosemicarbazides, 1,3,4-oxadiazoles. Additionally, 2,5-disubstituted-1,3,4-thiadiazole derivatives with antimicrobial action were discussed.



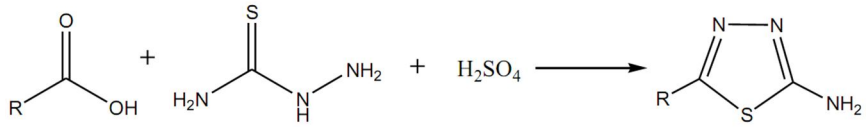
In 1959, Ruhlmall *et al.* [5] reported the synthesis of 2,5-dialkyl-1,3,4-thiadiazoles in good yields via thiadiazolidines, which were synthesized using hydrazine, aliphatic aldehyde and hydrogen sulfide. Further treatment of thiadiazolidinones with sulfur in boiling pyridine caused dehydrogenation which then led to the formation of 2,5-dialkyl-1,3,4-thiadiazoles.



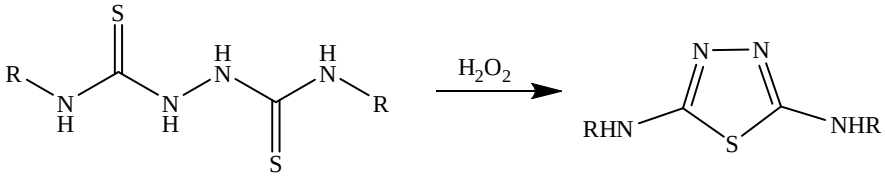
A good number of 2,5-disubstituted-1,3,4-thiadiazoles were synthesized by Oruç, E. E. *et al.* [6]. The compound structures were confirmed and then screened for the antituberculosis activity against mycobacterium tuberculosis H37Rv using the BACTEC 460 radiometric system. One of the tested compounds, 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole showed the highest inhibitory activity.



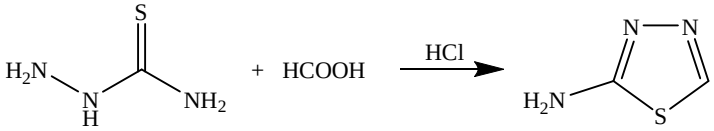
An easy and feasible method for synthesis of 2-amino-1,3,4-thiadiazoles from readily accessible starting materials was described by Hoggarth *et al.* [7]. The method is based on dehydration leading to cyclization by heating suitable carboxylic acid with thiosemicarbazide in the presence of an appropriate Lewis catalyst like H_2SO_4, H_3PO_4, etc.



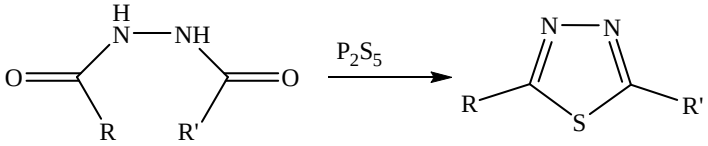
Alternative process was reported by Fromm *et al.* [8]. The method is based on reaction of bisthiourea and substituted bisthioureas with 3% hydrogen peroxide leading to 2,5-diamino-1,3,4-thiadiazole derivatives.



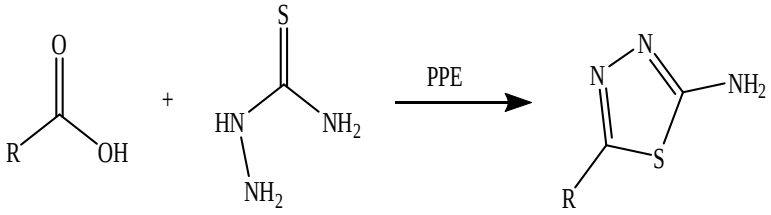
In 2013, Harish *et al.* [9] reported new pyrazine substituted 1,3,4-thiadiazole derivatives in good yields by the reaction of pyrazine substituted 1,3,4-thiadiazoles with various sulfonyl chlorides. The new compounds were screened for their anticonvulsant activity against maximal electroshock (MES) seizure method.



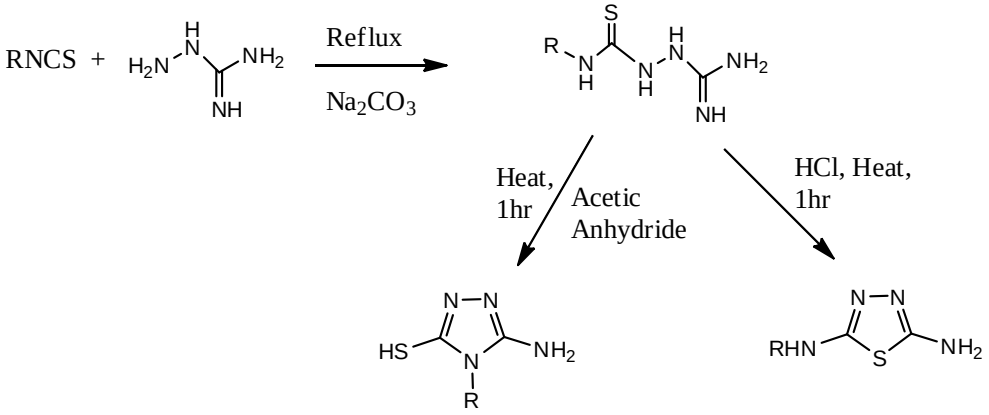
Earlier in 1899, Stolle reported the synthesis of 2,5-dialkyl-1,3,4- thiadiazoles from 1,2-diacylhydrazines and P_2S_5 [10]. The synthesis of 1,3,4-Thiadiazoles due to the inclusion of sulfur drugs and the anion discovery of mesoionic compounds meaningfully enhanced the rate of development in this field.



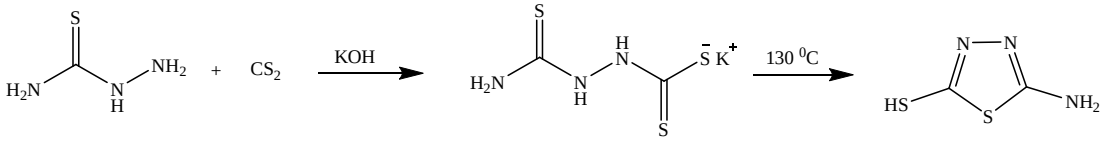
Kokovina *et al.* [11] developed a new method for synthesis of 1,3,4-thiadiazol-2-amine derivatives in a one-pot manner using the reaction between a thiosemicarbazide and carboxylic acid without toxic additives such as $POCl_3$ or $SOCl_2$. The reaction was investigated in the presence of polyphosphate ester (PPE). It was found that, in the presence of PPE, the reaction between the thiosemicarbazide and carboxylic acid proceeds in one-pot through three steps with the formation of corresponding 2-amino-1,3,4-thiadiazole.



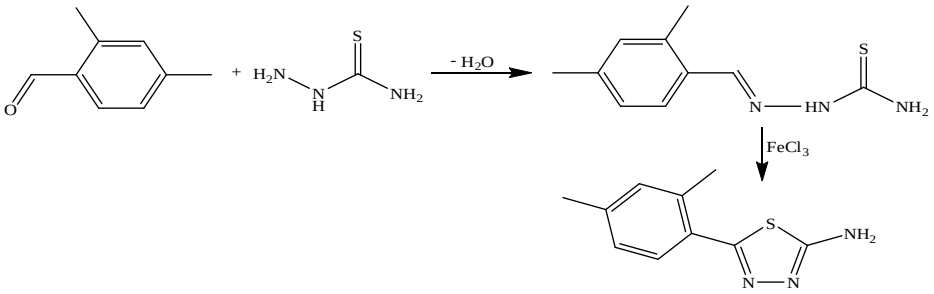
Kurzer and Canell reported a number of 4-substituted-3-amino-5-mercapto-1,2,4-triazoles and 2-amino-5-alkyl (or aryl)amino-1,3,4-thiadiazoles [12]. The preparation route encompassing cyclization of 4-substituted-l-amidinothiosemicarbazides in different media with improvement in the yields.



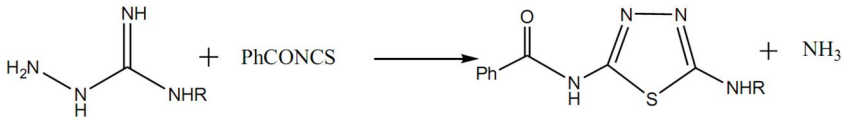
Guha *et al.* [13], in 1922, described simple and effective synthesis for 2-amino-5-mercapto-1,3,4-thiadiazoles by reacting thiosemicarbazide with carbondisulfide (CS_2) in the presence of a strong base viz. KOH, followed by heating the intermediate potassium dithiocarbazate. The route is simple but with moderate yields.



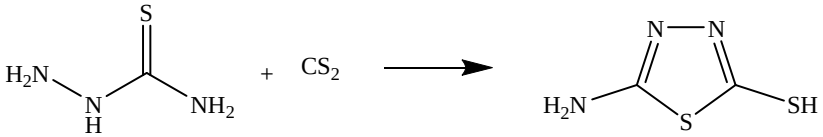
Sahu *et al.* [14] synthesized a series of 1,3,4-Thiadiazole derivatives by cyclization of a group of various benzaldehyde with thiosemicarbazide in the presence of various reagent like $FeCl_3$, HCHO by losing a molecule of water. These derivatives were found to possess prominent antimicrobial activity.



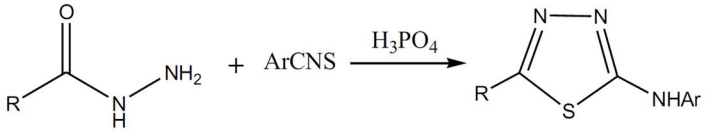
Kurzer *et al.* [15] produced several 1,3,4-thiadiazole derivatives by Lewis acid promoted cyclisation of acylthiosemicarbazides, which itself was obtained from the reaction of aminoguinidine salts and aroylisothiocyanates.



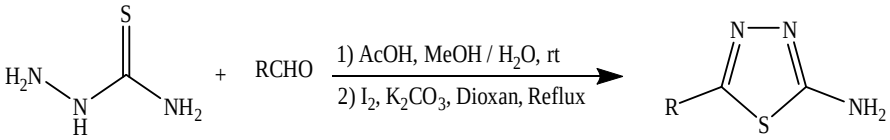
A series of novel 1,3,4-thiadiazole derivatives bearing an amide moiety were designed, synthesized, and evaluated by Almasirad *et al*. [16] for their *in vitro* antitumor activities against HL-60, SKOV-3 and MOLT-4 human tumor cell lines by MTT assay. Ethyl 2-((5-(4-methoxybenzamido)-1,3,4-thiadiazol-2-yl)thio)acetate showed the best inhibitory effect against SKOV-3 cells.



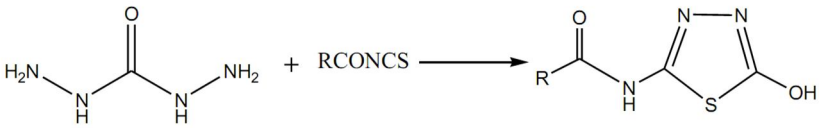
Mahajanshetti *et al*. [17] prepared 1,3,4-thiadiazole derivatives using a long alkyl chain from acid azide using phosphoric acid (H_3PO_4) as a dehydrating cum cyclizing agent.



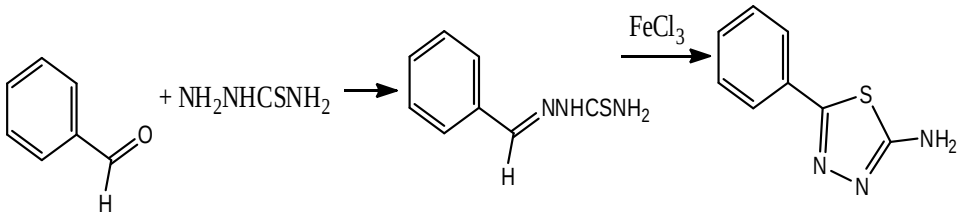
In 2020, Hegab [18] highlighted the recently synthesized 1,3,4-thiadiazole derivatives possessing important therapeutic activities and computational studies.



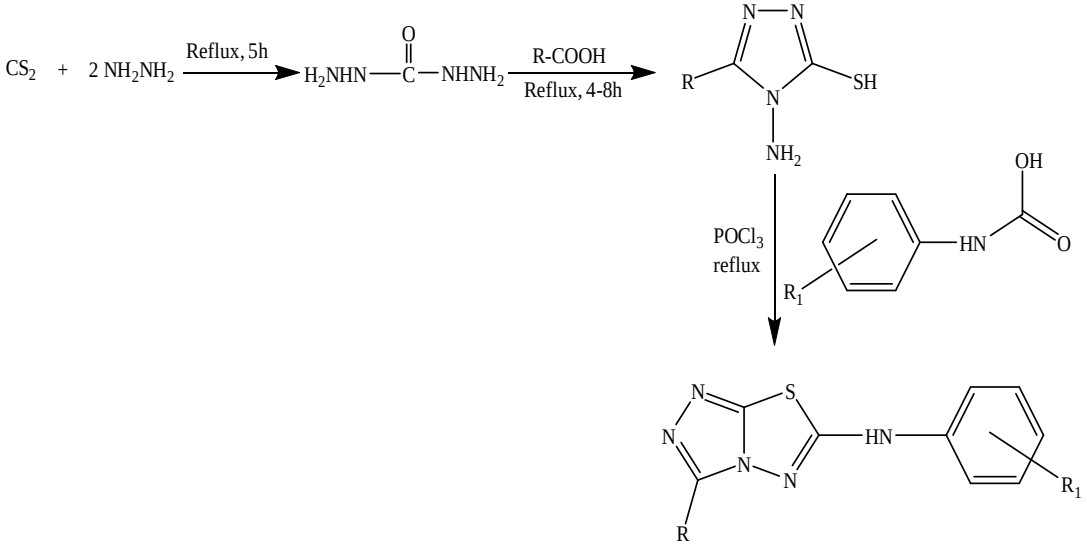
Different 2-hydroxy-5-acylaminothiadiazole derivatives were synthesized by heating carbohydrazide with equal amount of an acylisothiocyanate in dimethylformamide at 100˚C by Esmail *et al.* [19].



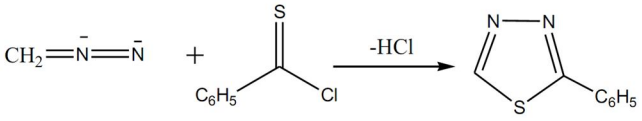
Young *et al.* [20] synthesized 2-amino-5-phenyl-1,3,4-thiadiazole by using thiosemicarbazone of an aldehyde and Lewis acid viz. $FeCl_3$, the mechanism involved oxidative cyclization.



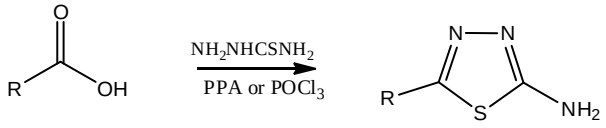
The preparation of a novel series of 6-arylaminomethyl-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles by the cyclo-condensation of 5-substituted-4-amino-3-mercapto-1,2,4-triazoles with appropriately substituted anilino acetic acids employing phosphorous oxychloride was reported by Kalluraya [21].



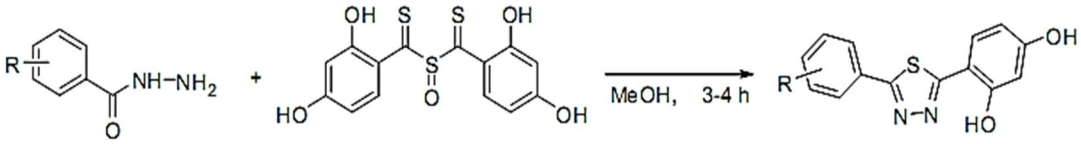
A novel and interesting reaction to formulate 2-aryl-1,3,4-thiadiazole that includes the addition of diazomethane (CH_2N_2) to an opposite thiobenzoylchloride was described by Bhargava *et al.* [22].



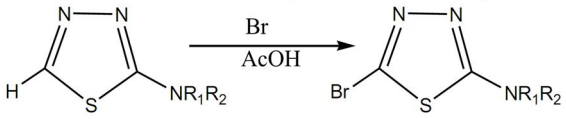
Turner *et al*. [23] prepared 2-amino-5-aryl-1,3,4-thiadiazole derivatives. The method involved heating carboxylic acid and thiosemicarbazide with polyphosphoric acid (PPA) and Phosphorous oxychloride ($POCl_3$) to give moderate to high yields.



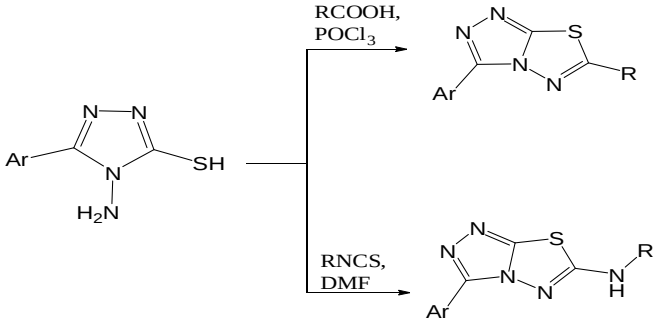
Skrzypek *et al.* [24] successfully synthesized a good number of 1,3,4-thiadiazole derivatives Then, they were evaluated as the acetyl- and butyrylcholinesterase inhibitors.



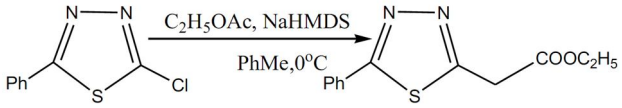
Interestingly, it is difficult to accomplish aromatic electrophilic substitution reactions like nitration, sulphonation, acetylation, halogenations, etc., due to scarce electron density at the carbon atoms in 1,3,4-thiadiazole nucleus. However, 2-amino-substituted 1,3,4-thiadiazoles respond to bromination (bromine in acetic acid) leading to 5-bromo derivatives [25]. Thus, the amino group enhanced its reactivity.



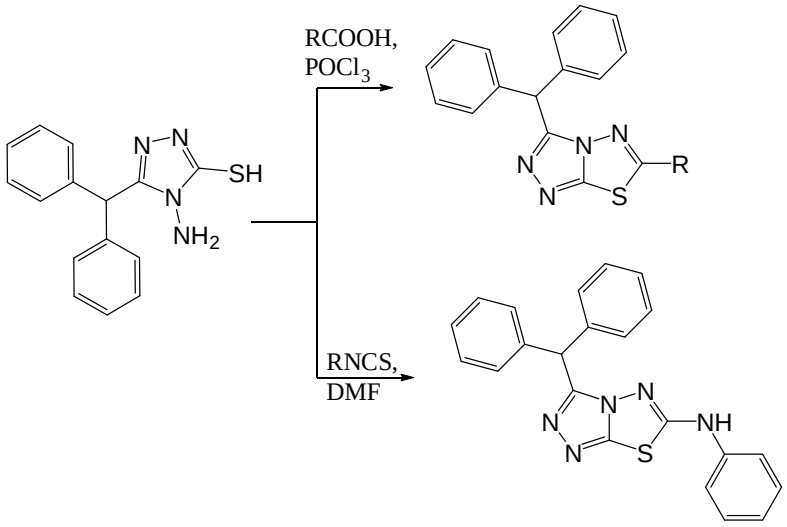
A single step and one-pot synthesis of several 3,6-disubstituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles by treating 4-amino-5-substituted-3-mercapto-(4H)-1,2,4-triazoles with various substituted aromatic acids and aryl/alkyl isothiocyanates was reported by Amir *et al*. [26].



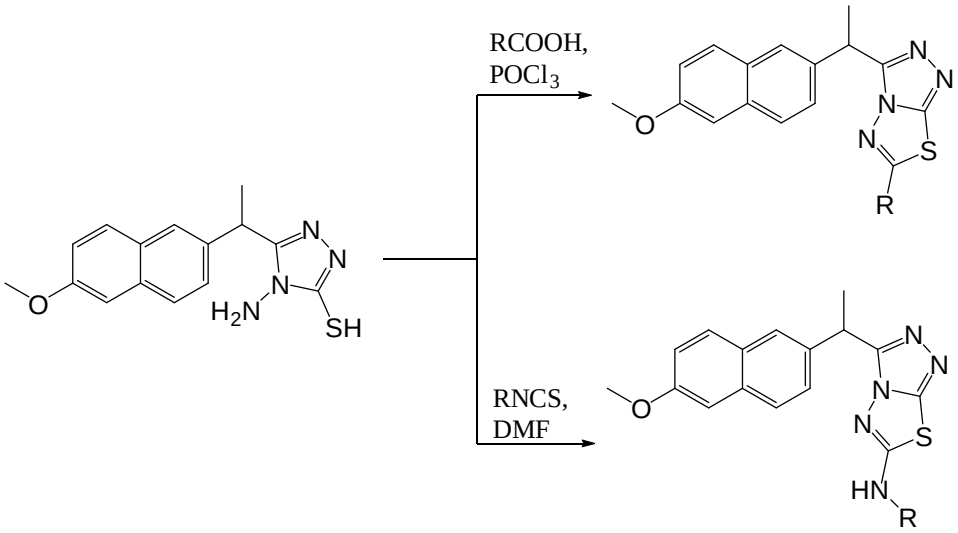
The treatment of 2-chlorothiadiazole with ethyl acetate in the presence of sodium hexamethyl disilazane (NaHMDS) led to formation of 5-phenyl-1,3,4-thiadiazol-2-ylacetic ester [27]. This opened new ways to accomplish the nucleophilic reactions at the carbon atoms of 1,3,4-thiadiazoles. The reaction happened straightforwardly due to the electron-deficient nature of the ring. Hence, the halo-substituted thiadiazoles are considerably active and react with a wide variety of nucleophiles.



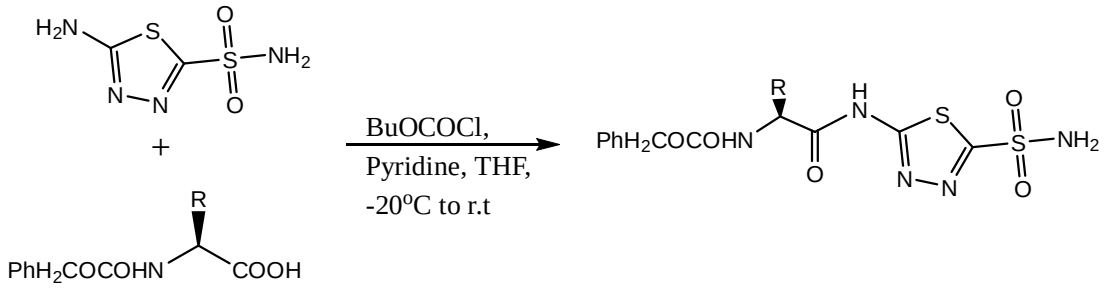
4-amino-5-diphenylmethyl-4H-1,2,4-triazole-3-thiol with numerous substituted aromatic acids and aryl/alkyl-isothiocyanates condensed to 3-diphenylmethyl-6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives was reported by Akhter *et al.* [28].



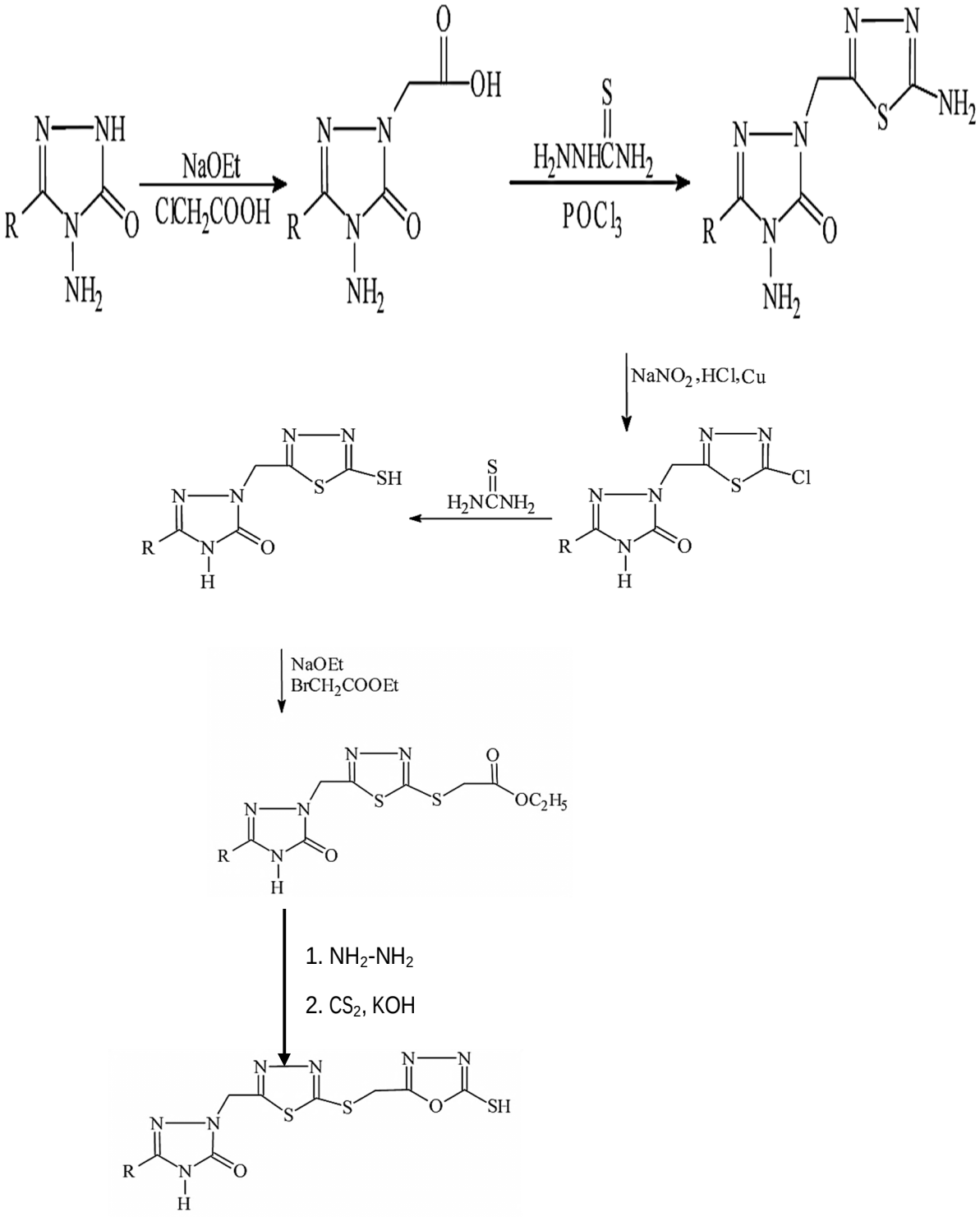
Amir *et al.* [29] successfully accomplished the synthesis of novel 6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives by cyclisation of 4-amino-5-[1-(6-methoxy-2-naphthyl)ethyl]-3-mercapto-(4H)-1,2,4-triazole using diverse substituted aromatic carboxylic acids with aryl/alkyl isothiocyanate. The novel produced compounds were found to have substantial anti-inflammatory and analgesic activity with very little ulcerogenic profile. One of the derivatives showed extreme reduction of severity index along with minimum lipid peroxidation, with no hepatocyte necrosis or degeneration.



Jayaweera *et al* [30] reported synthesis and *in vitro* activity as inhibitors of carbonic anhydrase by 2-substituted-1,3,4-thiadiazole-5-sulphonamides. The compounds found to have good water-solubility and activity in nanomolar.



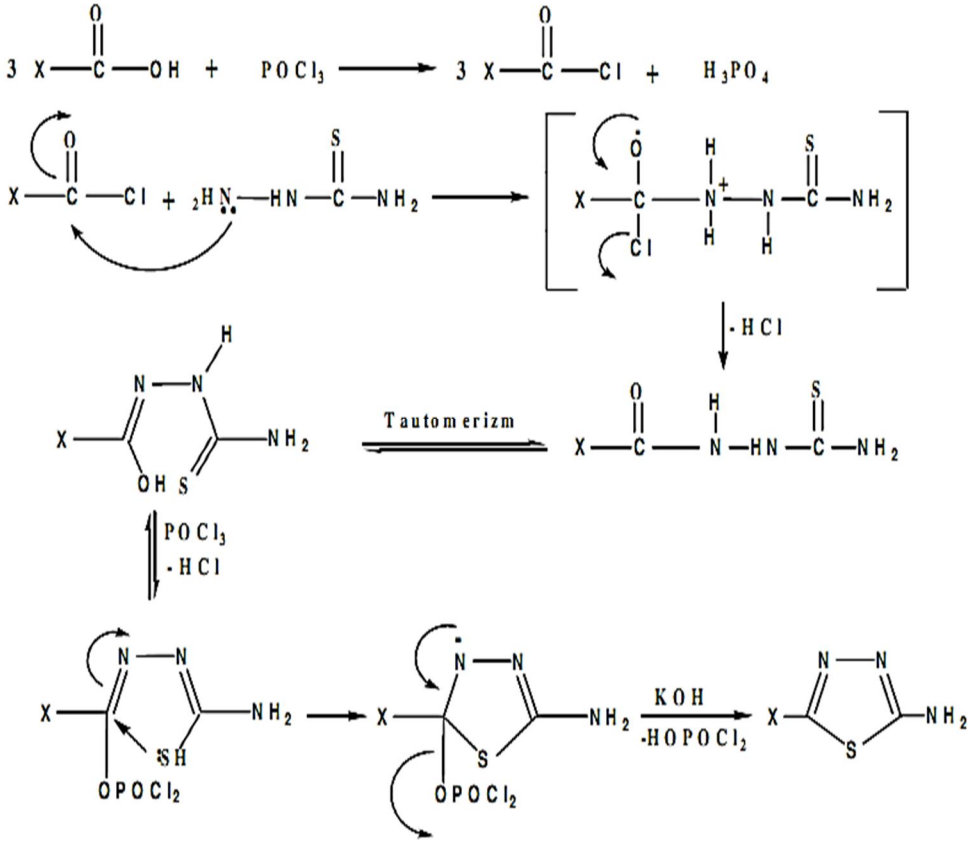
Triheterocyclic compounds comprising 1,2,4-triazol-3-one,1,3,4-thiadiazole and 1,3,4-oxadiazole rings were reported by Demirbas [31]. The scheme is as follows:



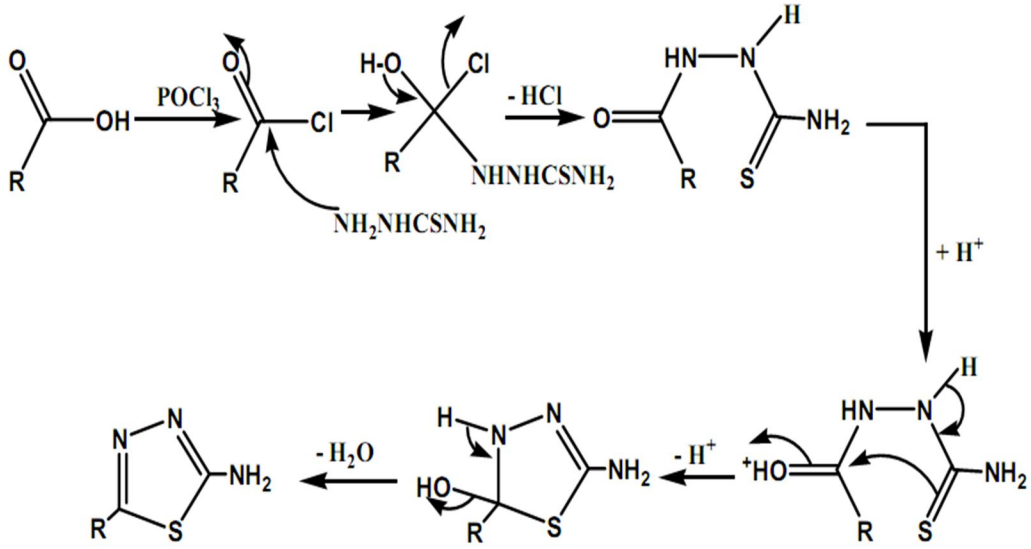
III. PROPOSED MECHANISMS FOR THE FORMATION OF 1,3,4-THIADIAZOLE RING

Thiosemicarbazide must be cycled with an adequately substituted carboxylic acid in the presence of various dehydrating agents in order to produce 1,3,4-thiadiazole. The following mechanisms have been put forth by several researchers when applying various cyclizing agents [32,33].

A. Mechanism 1



B. Mechanism 2



IV. CONCLUSIONS

1,3,4-thiadiazole and its derivatives are prepared by a variety of methods and reaction conditions. In general, different Lewis's acids like $POCl_3$, PPA dry $ZnCl_2$, etc. are commonly employed to get a good yield of 1,3,4-thiadiazole and its derivatives. Their role is highly crucial as dehydrating or cyclizing agents. The present work offered an insightful understanding of synthesis of 1,3,4-thiadiazole and its derivatives.

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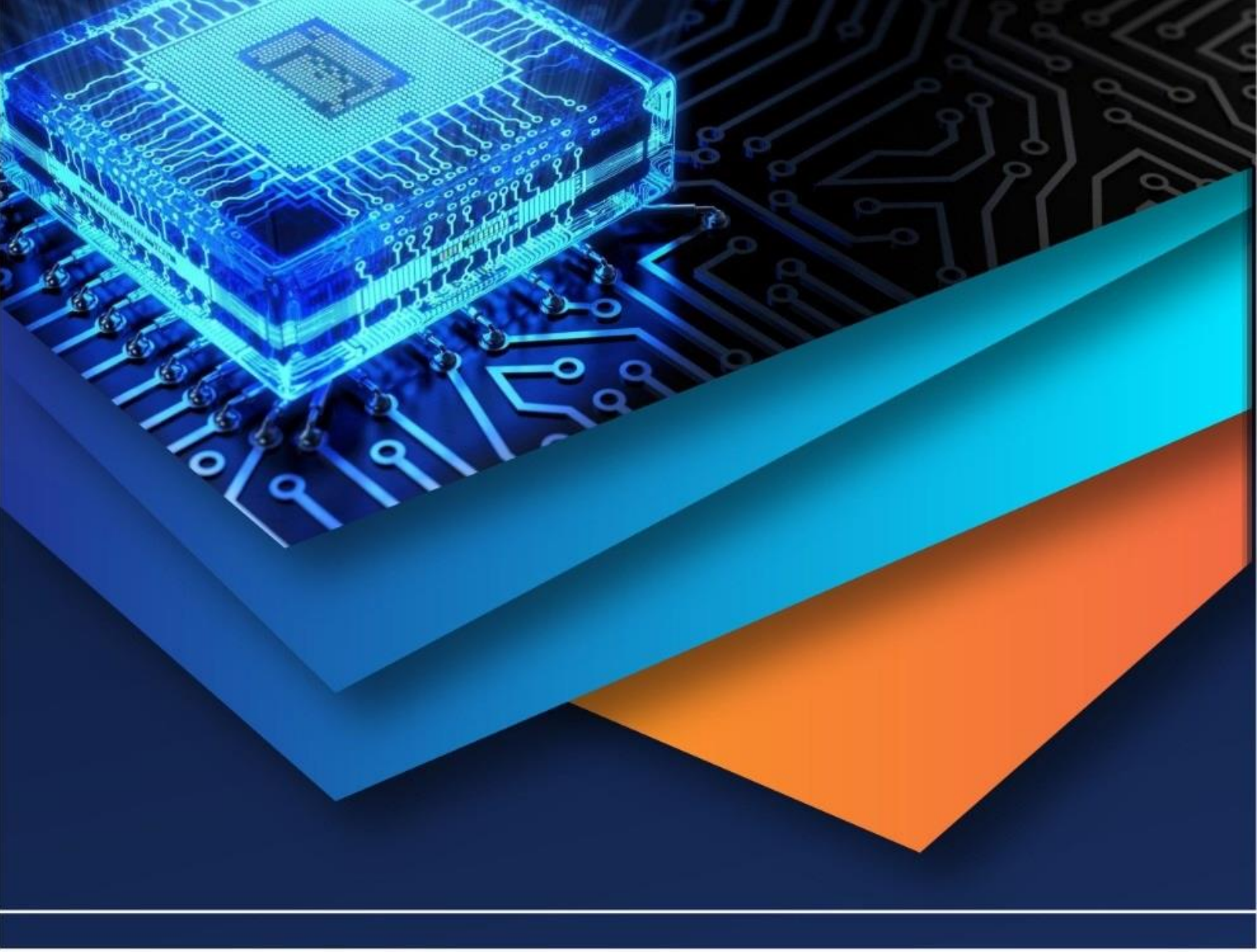

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