Review Article

# Greener Approach as a Recent Advancement in the Synthesis of Thiadiazole

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**ABSTRACT**

Impetus of green synthesis is to proceed with all the synthetic procedures which are eco-friendly, nonhazardous, reproducible and economic. The utilization of green chemistry techniques is substantially reducing chemical waste and reaction times than conventional methods, are observed in several organic synthesis and chemical transformations. In medicinal chemistry 1,3,4-Thiadiazole are source of overwhelming medicament for different pharmacological activities. Therefore, this review provides readers with an overview of the main greener synthetic methodologies for 1, 3, 4-Thiadiazole derivatives.

**Keywords:** Conventional, Green Chemistry, Thiadiazole

## INTRODUCTION

In chemical technology field, the green chemistry provides a set of clear guidelines for the development of chemical processes and the evaluation of their potential for environmental impact[1,2]. Green chemistry is the most important class of chemistry which help to utilize eco-friendly, reduces the harmful substances from the design, manufacture and application of chemical products[3-5].

Here we discussed different methods of greener approach in drug discovery; sonochemistry is the study of effects of ultrasound in making acoustic cavitations in water[16]. It proved to be an important for meeting the goal of green chemistry, to reduce the energy required, and to minimise the waste[1]. Sonochemistry is the effect of sonic waves and wave properties on chemical systems. The chemical effect of ultrasound does not interact directly with molecular species. But it arises from the formation, growth, and implosive collapse of bubbles in liquid. This is shown by ultrasound, sonication and sonic cavitations[18]. The sonic waves travelled through water was first reported by Robert Williams Wood in (1868-1955) and later was given by Alfred Lee Loomis in (1887-1927). They study how the energy of sonic waves pass or enter through the barrier of liquid. They found that sound travel faster in water but due to the density of water as compared to atmosphere was extremely difficult to get sonic waves into the water. They did research and found a way to get the sonic waves in water by creating bubbles at same time with sound[19].

Microwave is another method for the development of drug discovery. It is used in such areas, where high temperature is required, for long time and also shortens the length of reaction and increases their selectivity and product yields[2]. The application of microwave irradiation is used for carrying out chemical transformations, which are pollution free and echo friendly[9a]. It is used in various organic syntheses, especially for the solvent free reactions, since the solvent free microwave assisted reaction may provide an opportunity to work with open vessels which reduces the risk of high pressure development and increases the potential of reactions to upscale[6].

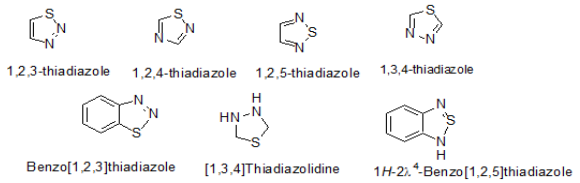
Microwave provides quick results for the reaction which take long time from hours to days[8,9]. In research of the drug, microwave is used in three areas for screening of organic drug, peptide synthesis and for DNA amplification[7]. Maximum number of organic molecule are synthesised by this method because of this method is simple, fast and clean. Today microwave is more beneficial for green chemistry, because it do not affect the environment and a cleaner process[8]. Microwave have some advantages over conventional heating like uniform heating throughout the material, process of speed is fast, high efficiency of heating, reduces the unwanted side reaction, purity in the final product, improve reproducibility, loss of environment heat can be avoided, reduction of wastage of heating during reaction, cost of operating is low[6]. Recently microwave assisted synthesis has attracted the researcher throughout the world for its less time consumption, minimum usage of solvents and increased yield of the compounds[10a]. For this reason microwave method is used for organic synthesis[8,10].

### Chemistry of Thiadiazole

Thiadiazole is a heterocyclic compound which contains a five member aromatic ring having two nitrogen and one sulfur atom. It acts as "hydrogen binding domain" and "two-electron donor system", which replaces the thiazole moiety by acting as bioisostere. It also acts as a bioisostere of oxadiazole, oxazole and benzene. Thiadiazole give better activity by the replacement of heterocycles due to the presence of sulfur which increases liposolubility[11,12]. Due to their application in pharmaceutical and medicinal chemistry they are tested against different diseases. Thiadiazoles and their derivatives can be considered as simple five membered

heterocycles possessing one sulphur and two nitrogen atoms[48-50].

There are four isomeric forms of thiadiazole like 1, 2, 3-thiadiazole[8] and their benzo derivatives[34] 1, 2, 4-thiadiazole; 1, 3, 4-thiadiazole; 1, 2, 5-thiadiazole[8] and their benzo derivatives[34]. Among these 1, 2, 4- and 1, 3, 4-thiadiazole have more activity, substitutions of thiadiazole at different position have different activity[11,12].

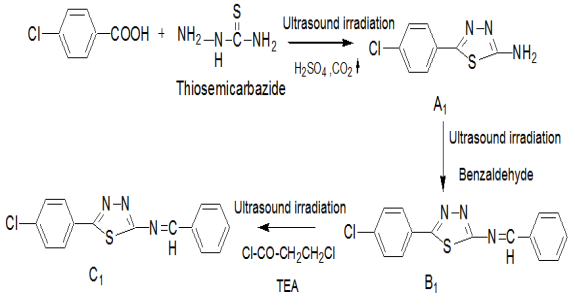



Literature survey revealed that 1, 3, 4-thiadiazole moiety had used medicinally in past to explore its biological activities.1, 3, 4-Thiadiazole had various therapeutic activities like[8], antimicobacterial[35,36], antituberculosis[37-39], anticonvulsant[40], antitumor agents[41], fungicidal activity[42], antibacterial[43,44], CNS depressants[45], herbicidal[46], antiviral[47], antileishmanial, anti-inflammatory, analgesic, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertension, diuretic, analgesic[48], antipanosomal, anticoccoidal, insecticidal, herbicidal, antiacetylcholine, transquillizer, sedative[51] radio protective, diuretic, antiarrhythmic, antimetastastic, psychoneurosis, schistosomicidal and pesticidal[44].

## Physical Properties of Thiadiazole

Thiadiazole is yellowish liquid having pyridine odour. It has soluble in alcohol and ether and slightly soluble in water. The compound having metal complexes which contain 1, 3, 4-thiadiazole nucleus is used as anti-corrosion paints and anti-fouling in marine. Derivatives of thiadiazole have fluorescence properties[11,14,15]. Thiadiazole exhibit varied physical properties such as anticorrosion, liquid crystal, optical brightening and fluorescent properties[50].

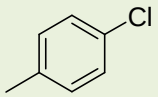
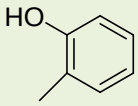
## Synthetic Review of 1,3,4-Thiadiazole




Synthetic scheme of U.S method for thiadiazole derivatives

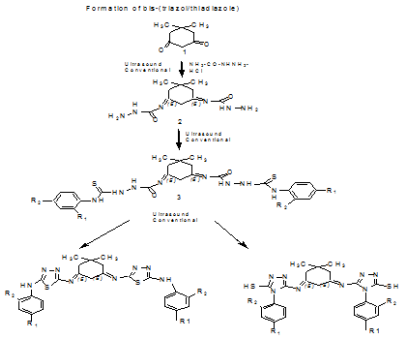
**Scheme 1[20]:** Synthetic scheme of U.S method for thiadiazole derivatives

Kekare Prajact G synthesized a series of new substituted 1, 3, 4-thiadiazole derivatives using Ultrasound irradiation technique. The structures of these compounds were established by means of FTIR, $^1$H-NMR and elemental analysis. All the compounds were evaluated for antibacterial, antifungal and antitubercular activities. Most of the compounds have shown significant antibacterial, antifungal and antitubercular activities when compared with the standard drug.

| Comp | Ar | Ar |
|---|---|---|
| C 1 | p-chlorobenzene |  |
| C 2 | 1'3-dichlorobenzene | |
| C 3 | p-nitrobenzene | |
| C 4 | p-chlorobenzene |  |
| C 5 | 1'3-dichlorobenzene | |
| C 6 | p-nitrobenzene | |
| C 7 | Anisole |  |
| C 8 | Benzene | |
| C 9 | Aniline | |

**Scheme 2[21]**

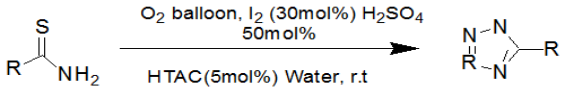
Vijay V. Dambolkar, studied synthesis of bis (Thiadiazole/Triazoles) by sonication. 5,5-Dimethylcyclohexane-1,3-dione was treated with semicarbazide to yield its acid hydrazide, which on further reaction under ultrasound condition with aryl isothiocynates gave 1,3-bis-imino-[1-(carboxy)-4-substituted phenylthiosemicarbazide]-5,5-dimethylcyclohexane. This compound in acidic medium gave 1,3-bis-imino-[5-(substituted) phenylamino-1,3,4-thiadiazol-2-yl-]-5,5-dimethylcyclohexane, whereas in basic medium 1,3-bis-imino-[4-(substituted) phenyl-5-mercapto-1,2,4-triazol-3-yl-]-5,5-dimethylcyclohexane was obtained. The synthesized compounds were investigated for their antibacterial activities. The results indicated that the compounds show convincing activities against Gram-positive bacteria (*S. aureus, C. diphtheriae and S. cerevisiae*) when compared with standard drug (Ampicillin trihydrate). These compounds were also synthesized by conventional method and their structures have been elucidated on the basis of spectral analysis and chemical reactions.



**Scheme 3[22]**

Jin-Wu Zhao [2014], studied green synthesis of 1, 2, 4-thiadiazole from thioamide, they synthesized 1, 2, 4-thiadiazoles via iodine-catalyzed, oxidative dimerization of thioamides in water using molecular oxygen as a

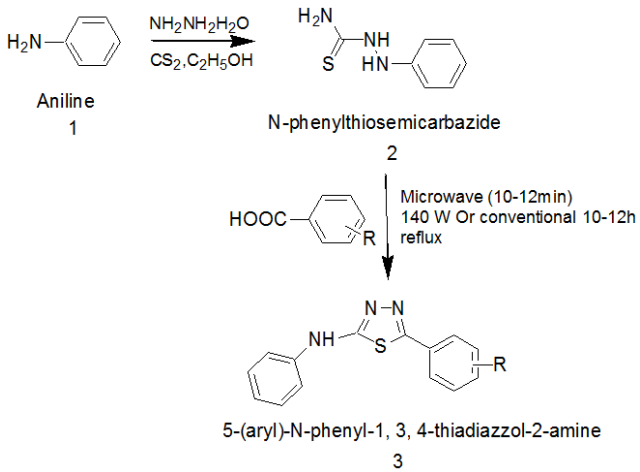
terminal oxidant. Under the optimized reaction conditions, aryl thioamides produced 3, 5-diaryl-1, 2, 4-thiadiazoles in good to excellent yields. Alkyl thioamides and substituted thioureas could also provide corresponding 1, 2, 4- thiadiazole products.




Green process for the synthesis of 1, 2, 4-thiadiazole

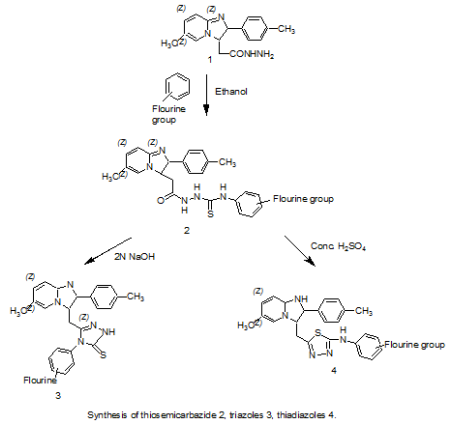
**Scheme 4**[23]

Biswa Mohan Sahoo studied synthesis and antiepileptic evaluation of 5-(aryl)-N-phenyl-1, 3, 4-thiadiazole-2-amine. Epilepsy is one of the leading neurological disorders, which is a major threat to public health. Though, several new antiepileptic drugs are developed, the treatment of epilepsy remains still inadequate, and the patient suffers from a lot of side effects. Therefore, it is essential to search for newer chemical entities for the treatment of epilepsy. So here an indirect type of molecular modelling study was carried out to find out the 3D structural similarity between some reported antiepileptic drugs and the newly designed 1, 3, 4-thiadiazole derivatives. Thus, a new series of 1, 3, 4-thiadiazole derivatives were synthesized by cyclization of N-phenylthiosemicarbazide with various aromatic acids. Both conventional and microwave irradiated synthesis of 1, 3, 4-thiadiazole derivatives have been carried out to compare their yield and reaction time. Microwave technology enables the reaction to be simple, rapid, high yielding with most pure and led environment benign synthesis. All the newly synthesized compounds were characterised by IR, $^1$HNMR and LC-Mass and also evaluated for their antiepileptic activity by MES model in rats.



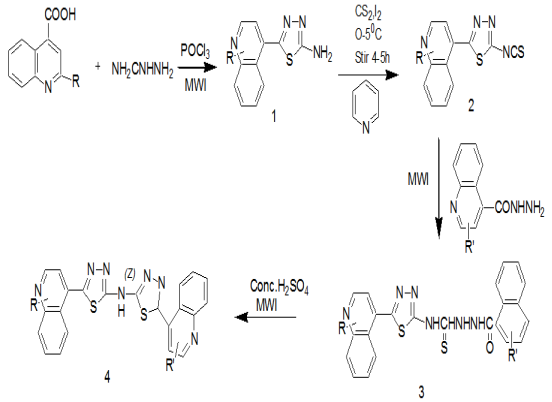

**Scheme 5**[24]

Nilesh G.Salunkhe studied green synthesis, characterisation and biological evaluation of some triazoles and thiadiazole. A series of fluorine-containing triazoles 3 and thiadiazoles 4 were synthesized from thiosemicarbazides 2. These reactions were carried out by green synthesis method such as ultrasonication and microwave technique. All products have been characterized by IR, $^1$H NMR, and Mass spectral study. All the compounds were screened for their antimicrobial activity using *Bacillus cereus* and *Klebsiella pneumoniae* bacteria.




**Scheme 6**[25]

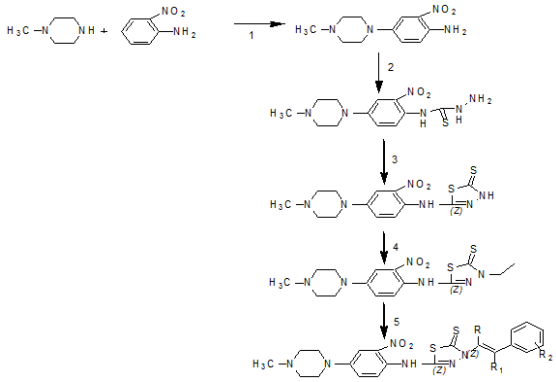
I.R Siddiqui studied novel 1, 3, 4 - thiadiazole derivatives synthesis by MAOS. 1, 3, 4-thiadiazole nucleus was therapeutically interesting drug candidate as anti-inflammatory, antimicrobial, anticonvulsant, antihypertensive, analgesic, antiepileptic, antiviral, antineoplastic and antitubercular agents. Therefore thiadiazole derivatives IVa-k were synthesized. The structures of the synthesized compounds were confirmed by spectral data and elemental analysis. The synthesized compounds were screened for antifungal activity by using Minimum Inhibitory Concentration (MIC) by serial dilution method against Staphylococcus aureus ATCC 9144, Bacillus Cereus ATCC 11778, Escherichia coli ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853., *Aspergillus niger* and *Aspergillus flavus*.




**Scheme 7**[26]

Chandra Prakash Ghuru synthesized a new class of thiadiazole having combination of Schiff base and Mannich base containing N-methyl piperazine moiety by an efficient microwave assisted green synthetic approach. Antioxidant activity of methanolic solutions of synthesized compounds was determined by reducing power assay and Hydrogen peroxide scavenging activity at 700 nm and 250 nm respectively. The synthesized

compounds were also screened for antibacterial activity and were characterized by FTIR, $^{1}$HNMR and elemental analysis.

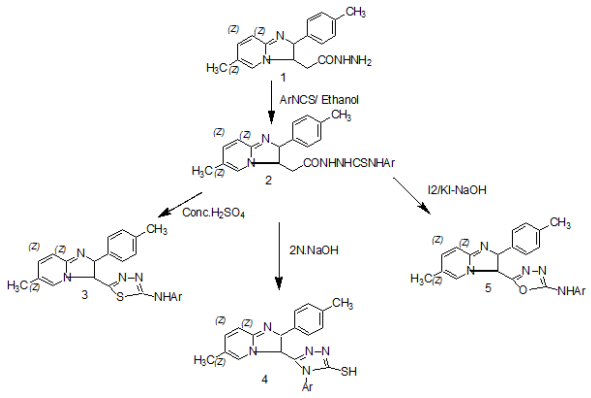


**Systematic reaction of synthesized compounds**

1. Benzene, 2. $CS_2$, $NH_2$-$NH_2$ and $ClCH_2COONa$ in $NH_3$, 3. $CS_2$ in DMF, 4. HCHO and Substituted amines in ethanol, 5. Carbonyl compound and anhydrous sodium acetate in acetic acid, R = anisidino/morpholino/piperidino, $R_1$=H, $CH_3$, $R_2$=4-hydoxy, 3-methoxy-benzilidene, 4-hydroxy-benzilidene.

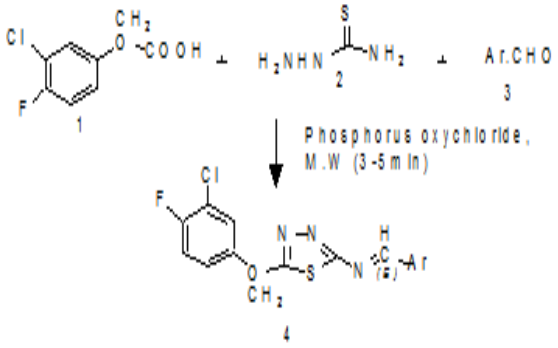
**Scheme 8[27]**

S.K Narwade studied conventional and ultrasound mediated synthesis of thiadiazole, triazoles and oxadiazole, acid hydrazide 1 when treated with aryl isothiocyanates gives compound 2. The compound 2 on ultrasound irradiation give compound 3 i.e. thiadiazole and on basic media give compound 4 i.e. triazoles. These compound 2 on treated with $I_2$/KI and NaOH resulted in compound 5 i.e. oxadiazole. These compounds were synthesized by conventional and ultrasound irradiation method.



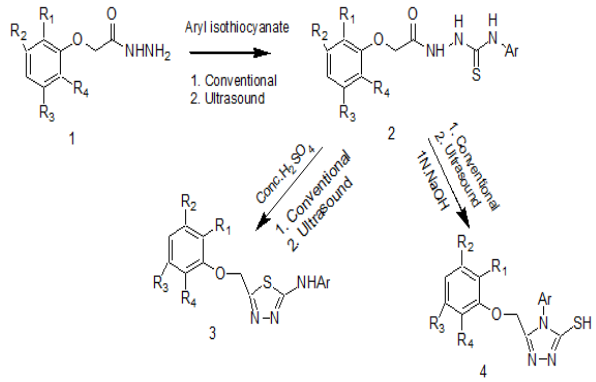

**Scheme 9[28]**

Dr. Shalini Jaiswal studied synthesis and antimicrobial activities of 5-subtituted-2-arylbenzalamino-1, 3, 4-thiadiazole, there is a growing need for more environmentally acceptable processes in the chemical industry. The fields of combinatorial and automated medicinal chemistry have emerged to meet the increasing requirement of new compounds for drug discovery. Microwave-assisted organic synthesis is an enabling technology for accelerating drug discovery and development processes. In the family of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes. Thiosemicarbazides belongs to thiourea group, whose biological activity is due to the presence of aldehydes or ketone moiety. Thiosemicarbazides derivatives exhibit a great variety of biological activities, such as antitumor, antifungal, antibacterial, and antiviral. Here we developed a, novel, solvent free, microwave assisted synthesis of hitherto unknown 5-subtituted-2aryl benzalamino-1, 3, 4- thiadiazole 4a-h with excellent yield.




**Scheme 10[29]**

PV Randhavan studied synthesis and biological screening of some halogenated thiadiazoles and triazoles. Acid hydrazide is treated with aryl isothiocyanate to get thiosemicarbazides 2. Compound 2 in acidic media give thiadiazole and in basic media give triazoles 3. These compound were synthesized by conventional and ultrasound irradiation method. Some of these compounds are tested for their antioxidant, antiviral and antimicrobial activity.

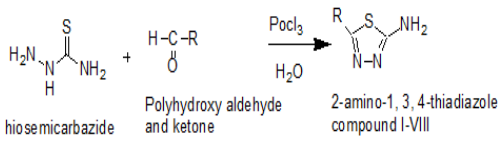



**Scheme 11[30]**

Deepika Koti synthesised 2-amino-1, 3, 4-thiadiazole derivatives, a series of 1, 3, 4-thiadiazole derivatives from different Polyhydroxylated aldehydes and ketones. The structures were characterized by IR, $^{1}$HNMR and $^{13}$CNMR spectral data.

The compounds were evaluated for antibacterial activity against gram-positive and gram-negative bacteria. *Insilco* evaluation was carried, aiming to present potential

selective activities as enzyme inhibitors. These activities were suggested by the score values using Mol inspiration Cheminformatics program.



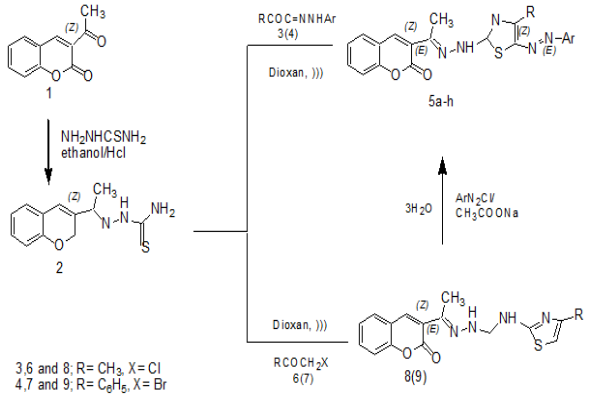

**Scheme 12**[31]

Sobhi M. Gomha studied Convenient Ultrasound-Promoted Synthesis of Some New Thiazole Derivatives Bearing a Coumarin Nucleus and their Cytotoxic Activity. Successful implementation of ultrasound irradiation for the rapid synthesis of a novel series of 3-[1-(4-substituted-5-(aryldiazenyl) thiazol-2-yl) hydrazono) ethyl]-2Hchromen-2-ones 5a–h, via reactions of 2-(1-(2-oxo-2H-chromen-3-yl) ethylidene) thiosemicarbazide (2) and the hydrazonoyl halides 3(4), was demonstrated. Also, a new series of 5-arylidene-2-(2-(1-(2-oxo-2H-chromen-3-yl) ethylidene) hydrazinyl) thiazole (5H)-ones 10a–d were synthesized from reaction of 2 with chloroacetic acid and different aldehydes. Moreover, reaction of 2-cyano-N'-(1-(2-oxo-2H-chromen-3-yl) ethylidene) acetohydrazide (12) with substituted benzaldehydes gave the respective arylidene derivatives 13a–c under the conditions employed.

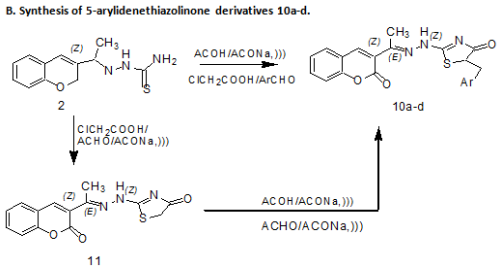
The structures of the synthesized compounds were assigned based on elemental analyses and spectral data. Also, the cytototoxic activities of the thiazole derivative 5a were evaluated against HaCaT cells (human keratinocytes). It was found that compound 5a possess potent cytotoxic activity.

**A. Synthesis of 5-arylazothiazole derivatives.**

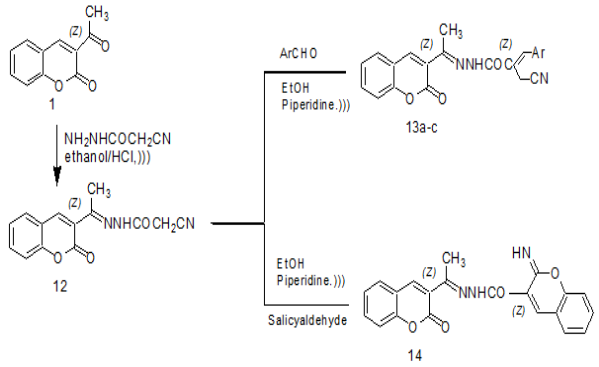
| 5a-h | R | Ar |
|---|---|---|
| a. | $CH_3$ | $C_6H_5$ |
| b. | $CH_3$ | 4-$MeC_6H_4$ |
| c. | $CH_3$ | 4-$ClC_6H_4$ |
| d. | $CH_3$ | 4-$NO_2C_6H_4$ |
| e. | $CH_3$ | $C_6H_5$ |
| f. | $CH_3$ | 4-$MeC_6H_4$ |
| g. | $CH_3$ | 4-$ClC_6H_4$ |
| h. | $CH_3$ | 4-$NO_2C_6H_4$ |




**B. Synthesis of 5-arylidenethiazolinone derivatives 10a-d.**

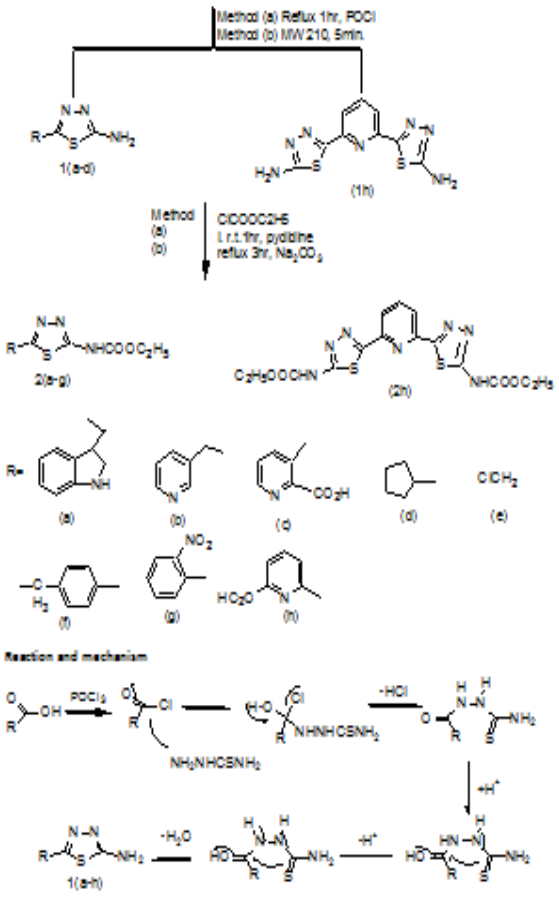



**C. Reaction of acetohydrazide 12 with aromatic aldehydes.**



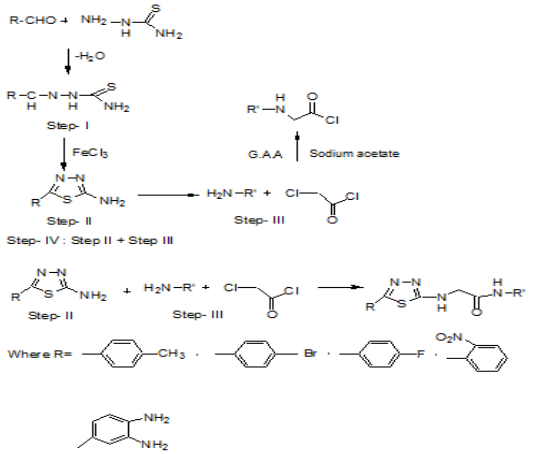

**Scheme 13**[32]

**A. 2-Amino-5-substituted-1, 3, 4 – thiadiazoles (ATDA) (1 a-g) and 2, 6-bis (5-amino-1, 3, 4-thiadiazol-2yl) pyridine 1(h):**



Moayed S.A.L-Gwady [2009] studied synthesis of 2-Amino-5-Substituted-1,3,4-Thiadiazoles (ATDA) and their Derivatives Using Conventional and Microwave Techniques. A variety of 2-Amino-5-substituted-1,3,4-thiadiazoles (ATDA) were prepared by the reaction of thiosemicarbazide with different substituted carboxylic acids and phosphorous oxychloride as catalyst using conventional methods in comparison with the advantages of microwave techniques. The 5-(substituted-1,3,4-thiadiazol-2-yl) carbamates derivatives were prepared by refluxing these (ATDA) with ethyl chloroformates using pyridine as a base to neutralize the acid produced which gave higher yield than sodium carbonate. The structures of the products were supported by IR spectroscopy.

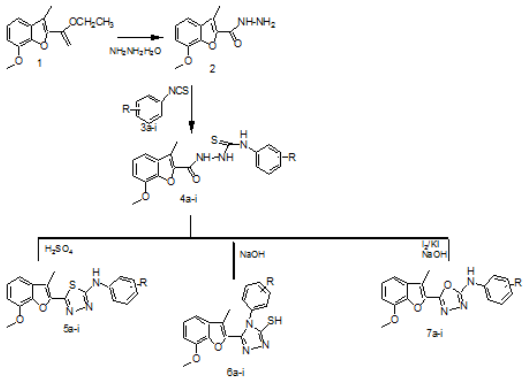
**Scheme 14**[33]




Mohammed Ashraf studied synthesis and antimicrobial activity of some thiadiazole derivates. Small and simple heterocyclic structures often have surprising complex biological properties. Many compounds containing this heterocyclic are having pharmaceutical importance. The hetero cyclic compound thiadiazole and its derivatives are reported to possess varied biological activities. Heterocyclic compounds like Thiadiazole plays a vital role owing to its wide range of therapeutic activities like fungicidal activity, antimicrobacterial activity, antibacterial, antituberculosis, anticonvulsant, anti-microbacterial, anti-tumour agents, CNS depressants, herbicidal and antiviral activity. In the present project, an attempt was made to synthesize some of newer 1, 3, 4-thiadiazole derivatives and evaluate their antimicrobial activity quantitatively and qualitatively. All synthesized compounds were prepared by reaction of N-Substituted-α-Chloroacetanilides in presence of aqueous potassium hydroxide solution with aromatic aldehydes substituted 1, 3, 4-thiadiazole-2-amine. N-Substituted-α-Chloroacetanilides were prepared by reaction of aromatic amines with chloroacetylchloride in presence of glacial acetic acid and saturated solution of sodium acetate. Aromatic aldehydes substituted 1, 3, 4-thiadiazole-2-amine was prepared by cyclization of arylthiosemicarbazide. The synthesized compounds were characterized by TLC, Melting point and Spectral data. Melting points were determined by using Precision melting point apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using methanol: chloroform (1:9) solvent system iodine chambers used as a visualizing agent. Characterization of compounds is done by IR, $^1$HNMR and Mass analysis. Antimicrobial activities of thiadiazole derivatives also reported.

**Scheme 15**[34]

Anata D. Shinde studied synthesis and characterization of 1-Benzofuran-2-yl thiadiazoles, Triazoles and oxadiazole by Conventional and Non-conventional methods. The synthesis of benzofuran based 1, 3, 4-thiadiazoles, 1, 3, 4-triazoles and 1, 3, 4-oxadiazole via cyclocondensation of thiosemicarbazides have been carried out by conventional and non-conventional methods in excellent yields of product.




## CONCLUSION

In this review, we summarized information about synthesis of 1,3,4-thiadiazole and its derivatives, using Greener synthesis based upon the most recent literature study.

By using green chemistry approach, we can minimize the waste of time, materials, maintain the atom economy and prevent the use of hazardous chemicals.

Microwave method was improved process as compare to conventional method for purity of compound and should be used in future because it is inexpensive and more reliable.

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