

2.0. LITERATURE METHODS FOR THE SYNTHESIS 1,3,4-THIADIAZOLE AND 1,3-THIAZOLE DERIVATIVES

2.1. Synthetic review of 1,3,4-Thiadiazole derivatives

Yang Hu et al., (2014) reported that cyclization of acylhydrazines including N,N'-diacylhydrazines and monoacylhydrazines or transformation from 1,3,4-oxadiazoles (Scheme 1) are the general route to obtain 1,3,4-thiadiazoles. Synthesis of 1,3,4-thiadiazoles from thiohydrazines including thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines, and bithioureas (Scheme 2).

![Scheme 1](image1.png)

**Scheme-1: General preparation of 1,3,4-Thiadiazoles from acylhydrazines or 1,3,4-Oxadiazoles**

![Scheme 2](image2.png)

**Scheme-2: General Preparation of 1,3,4-Thiadiazoles from Thiohydrazines**
2.1.1. Synthesis of 1,3,4 thia diazoles from Acid Hydrazides

In the past decades reports have indicated that one-pot syntheses of 1,3,4-thiadiazoles avoids multistep syntheses. Among these methods, modulations of harsh conditions are notable in some. Augustine et al., reported one-pot synthesis of 1,3,4 thiadiazoles from carboxylic acids using propylphosphonic anhydride (T3P) (Scheme 3a)\(^{2}\) which acts as both coupling and cyclodehydration reagent. Reaction was highly efficient and tolerant to broad functional group but was contaminated with small percentage of byproduct (i.e) 1,3,4-oxadiazole (3–5%) further purified by recrystallization or column chromatography. Microwave radiation single step synthesis from acid hydrazide was reported by Polshettiwar et al., (Scheme 3b)\(^{3}\).

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\begin{align*}
\text{Scheme-3: Synthesis of 1,3,4-Thiadiazoles Directly from Carboxylic Acids and Acid Hydrazides}
\end{align*}
\]

2.1.2. Synthesis of 1,3,4 thia diazoles from Thiosemicarbazides

All forms of thiosemicarbazides are basis for synthesis of 1,3,4 Thiadizoles. 2-amino-1,3,4-thiadiazoles, intermediate for 1,3,4- thia diazole derivatives, is prepared by cyclization of thiosemicarbazides or substituted thiosemicarbazides. Scheme 4 represents thiadiazole formation
by acylation/schiff base formation on α-amino group initiates cyclization of thiosemicarbazides and on dehydrating agent (i.e) EDCI, DCC, TMSCl, TsCl, PPh3, SOCl2, PCl5, and diphenyl chlorophosphate.

Scheme- 4: Mechanism of Cyclization of Thiosemicarbazide

Variations in Acylating agents (Scheme 5a and 5b) as carboxylic acid⁴, acid halide⁵, and acid anhydride⁶ and Schiff base formation (Scheme 5c and 5d) by metal oxidants (acidic aluminum oxide and ferric chloride and aldehydes) were reported⁷.

Scheme – 5a: Synthesis of 1,3,4 thiadiazoles from Thiosemicarbazide(5a-5d)

Sulfinyl-bis((2,4-dihydroxyphenyl) methanethione) (STB) with thiosemicarbazides or hydrazides in methanol resulted in N-substituted 5-amino- 1,3,4-thiadiazole 12 or analogue 13.
devoid of amine group (Scheme 5e). During reaction of STB with nucleophiles, linear product of thioacyl derivative is converted to thiol form and H2S or H2O molecule removal yields 1,3,4-thiadiazole ring. Thus, electrophilic substrate STB acts as endogenous cyclising reagent. Additionally, nitriles 14 in PPA (phenylpropanolamine) are converted to iminoesters of PPA, which are converted into amidazones 15 on reacting with thiosemicarbazide, followed by loss of ammonia to give compounds 16 (Scheme 5f).

**Scheme – 5b: Synthesis of 1,3,4-Thiadiazoles from Thiosemicarbazide(5e-5f)**

Yusuf M et al., (2008) reported the synthesis of 5-amino-1,3,4-thiadiazole-2-thiol imines and thiobenzyl. In first step the preparation of 5-amino-1,3,4-thiadiazole-2-thiol by the adding up of carbon disulfide to thiosemicarbazide under reflux. In second step addition of different chalcones to form a 2-amino-5-mercapto-1,3,4-thiadiazoles under reflux for 5 to 8 hrs.
R’=H, OCH₃, Cl

Scheme -6: Synthesis of 1,3,4-Thiadiazoles from Thiosemicarbazide

Pattan S.R. *et al.*, (2009), reported synthesis and biological evaluation of some 1, 3, 4 – thiadiazole derivatives. A mixture of thiosemicarbazide and aryl carboxylic acid, in the presence of sulphuric acid was refluxed for 1 hr and poured onto crushed ice. The solid separated out was filtered, washed with water and recrystallized with ethanol\(^1\).

\[
\text{Ar COOH} + \text{H₂N N₂S NH₂} \xrightarrow{\text{H₂SO₄}} \text{Ar S-N-NH₂}
\]

Scheme -7: Synthesis of 1,3,4-Thiadiazoles from Thiosemicarbazide

Alok Pandey *et al.*, (2012), reported Schiff bases of 2-amino-5-aryl-1, 3, 4-thiadiazole. First they synthesized corresponding thiosemicarbazone with substituted aldehyde. Further 2-amino-5-aryl-1, 3, 4-thiadiazole were synthesized by condensing thiosemicarbazone with slow addition of bromine in acetic acid in presence of sodium acetate as a catalyst\(^2\).

Scheme -8: Synthesis of 1,3,4-Thiadiazoles from Thiosemicarbazide
Biswa Mohan Sahoo et al., (2012) reported synthesis of 5-(Aryl)-N-Phenyl-1,3,4-Thiadiazol-2-Amine for Antiepileptic activity. In that paper they first synthesized various N-phenylthiosemicarbazide. Aniline was taken for starting material and further it’s condensed with hydrazine hydride with CS$_2$ in presence of ammonia under reflux in water bath. Further the N-phenylthiosemicarbazide reacted with various aromatic acids in DMF were taken and refluxed on water bath for 10-12 h$^{13}$.

**Scheme-9: Synthesis of 1,3,4-Thiadiazoles from thiosemicarbazone**

El-Rahman et al., (2009), reported 1,3,4-Thiadiazole derivatives were synthesized by the reaction of 1-methyl-5-oxo-3-phenyl-2-pyrazolin-4-thiocarboxanilide with a series of hydrazonyl halides or $N,N'$-diphenyl-oxalodihydrazoneyl dichloride in the presence of triethylamine (TEA) under ultrasonic irradiation (3-15min). The products were obtained in excellent yields in short reaction times$^{14}$.

**Scheme-10: Synthesis of 1,3,4-Thiadiazoles from Hydrazonyl halides**
Meng-Xue Wei et al., (2009), reported synthesis of new chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing γ-butenolide moiety. Chiral 2,5-disubstituted 1,3,4-thiadiazoles were synthesized by sequentially adding a solution of 0.1 N NaOH (11 mL) in tetrabutyl ammonium bromide (TBAB) (0.11 mmol), with 5-substituted-2-mercapto-1,3,4-thiadiazoles (1.1 mmol) and γ-substituted butenolides in PhH or CHCl₃ (5 mL) with stirring at room temp (2-48h)\(^1\). 

![Scheme-11: Synthesis of 1,3,4-Thiadiazoles from γ-butenolide moiety](image)

Tai-Bao et al., (2006) reported synthesis of 2,5-disubstituted 1,3,4-Thiadiazoles by cyclisation of 1-acyl-4-aroylthiosemicarbazides with glacial acetic acid at microwave irradiation within 5 min\(^2\).
Kumar.D et al., (2010) reported synthesis of the indolyl-1,3,4-thiadiazoles from indoles. In that studies the indole-3-carboxylic acids were prepared from the reaction of with trifluoroacetic anhydride followed by hydrolysis with sodium hydroxide. Reaction of 3 with arylhydrazides in the presence of versatile coupling reagents 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and 1-hydroxybenzotriazole in dry tetrahydrofuran afforded diacylhydrazines. Thionation of diacylhydrazine with Lawesson’s reagent followed by oxidative cyclization in dry tetrahydrofuran led to the indolyl-1,3,4-thiadiazoles in good yields.\(^{17}\).

Naskar et al., (2015) reported Schiff bases containing 1, 3, 4-thiadiazole. In this studies aldehyde based thiosemicarbazone has been synthesized by condensation of aromatic aldehyde with thiosemicarbazone in presence of alcohol. The cyclized product of 2-amino-5-aryl-1, 3, 4-thiadiazoles were prepare with ferric chloride in the presence of buffer containing citric acid under reflux(80-90\(^{\circ}\)C). Later on the product of 2-amino-5-aryl-1, 3, 4-thiadiazoles were condensed with various aromatic aldehyde under 6 hours reflux, the corresponding Schiff bases containing 1, 3, 4-thiadiazole.\(^{18}\).
Fatondji, H. R. et al., (2011) were reported aromatic 1,3,4 thiadiazoles. In this report the aromatic thiosemicarbazone was dissolved in 0.5 ml of pyridine and 0.5 ml of acetic anhydride and the mixture was heated at 110°C during 3 h with magnetic stirring to give the 1,3,4-thiadiazoline derivative which is filtered and purified by flash chromatography.  

Scheme-15: Synthesis of Schiff bases 1,3,4-Thiadiazoles from aromatic aldehyde or ketones
2.1.3. Literature review for synthesis of thiazole

Hantzsch thiazole synthesis is a reaction between α-halo ketones and thioamides which is common. High yield and efficient synthesis of 2-Aminothiazoles 43 can be obtained via Hantzsch thiazole synthesis (Scheme-16). Thiazole ring with bromoketones in R2 and R3 position offer diversity.

![Scheme-16: An example of Hantzsch thiazole synthesis](image)

Deau et al., (2014) reported microwave-assisted synthesis of novel N-(4-phenylthiazol-2-yl)-carboximidamides 44 (Scheme-17) by preparing the intermediates (4-phenylthiazol-2- amines) by irradiating a mixture of thiourea and substituted a bromoacetophenone, in ethanol for 15 min in excellent yields.

![Scheme-17: An example of microwave-assisted Hantzsch thiazole synthesis](image)

Gabriel synthesis (Scheme-18) is reaction of an acylamino-ketone with phosphorus pentasulfide yields the corresponding 2,5-disubstituted thiazole. Compound 46.

![Scheme-18: Gabriel synthesis of thiazoles](image)
The Cooke-Heilbron thiazole synthesis (Scheme-19) describes the reaction of α-aminonitriles with carbon disulfide to form 5-amino-2-mercaptothiazoles$^{23}$.

**Scheme-19: Cooke-Heilbron thiazole synthesis**

Simple, rapid and efficient synthesis of 4,5-disubstituted thiazoles is obtained by reacting isocyanides containing active-methylene with methyl carbodithioates in the presence of NaH (base) 48 (Scheme-20)$^{24}$.

**Scheme-20: Synthesis of 4,5-disubstituted thiazoles**

2-aminothiazoles is a domino alkylation cyclization reaction of propargyl bromide derivatives with thioureas yields 49 (Scheme-21) performed under microwave irradiation in presence of K2CO3 in few minutes and high yields, Compound 49$^{25}$.

**Scheme-21: Synthesis of 2-aminothiazoles from propargyl bromide derivatives and thioureas**

Varma.R.S et al., (1998) reported Thiazole and its derivatives are simply obtained by the reaction of α-tosyloxyketones, which are generated in situ from arylmethyl ketones and [hydroxy(tosyloxy)iodo]benzene (HTIB) with thioamides in the presence of K 10 clay using microwave irradiation, in a process that is solvent-free in both steps$^{26}$. 
Scheme-22: Synthesis of 1,3-Thiazoles from tosyloxyketones

Varma.R.S et al., (1998) reported the case of corresponding bridgehead heterocycles, however, is a special one where microwave effects really become apparent since the reactions of α-tosyloxyketones with ethylenethioureas remain incomplete in an oil bath whereas in a microwave oven they are completed in a short time.

Scheme-23: Synthesis of 1,3-Thiazoles from tosyloxyketones and ethylene thiourea

Noei and Khosropour et al., (2009) reported a high yield, green protocol for the synthesis of 2,4-diarylthiazole derivatives via the reaction of arylthioamides with α-bromoacetophenones under ultrasonic irradiation in the ionic liquid [bmim]BF4.

Scheme-24: Synthesis of 1,3-Thiazoles from arylthioamides with α-bromoacetophenones
Among the natural products containing a 1,3-thiazole ring, thiamine (aneurine, vitamin B1) is of great importance (Eicher and Hauptmann, 2003). Several 2-(N-arylamino)-4-arylthiazoles were prepared by the reaction of α-bromoacetophenones with N-aryl substituted thioureas, as in the classical Hantzsch synthesis, but using ultrasonic irradiation (Gupta et al., 2010). This further confirmed that thiazole heterocycles can be conveniently synthesized in good yields (88-97%) by the application of sonochemistry. The insecticidal activity of these 1,3-thiazoles was evaluated.

![Scheme-25: Synthesis of 1,3-Thiazoles from N-aryl substituted thioureas with α-bromoacetophenones](image)

Boja poojary et al., (2012) reported that the synthesis of 2,4-disubstituted-[1,3]-thiazoles by an equimolar mixture of 2-chloro-6-fluoro/2-fluorobenzyledened) hydrazine carbothioamide (2a, b) (0.01 mol) and substituted phenacyl bromides (0.01 mol) in ethanol was refluxed for 4 h.

![Scheme-26: Synthesis of 1,3-Thiazoles from substituted phenacyl bromides with hydrazine carbothioamide](image)

Liaras.K et al., (2011), reported Thiazole-based chalcones. The target chalcones was accomplished by a Claisen–Schmidt condensation of 1-(4-methyl-2-(methylamino) thiazol-5-
yl)ethanone with various aromatic aldehydes, in methanol, and 10% aq NaOH, the reaction proceeded smoothly and in good yields (32–84%)\(^31\).

![Scheme-27: Synthesis of 1,3-Thiazoles from various aromatic aldehydes](image)

Santhosh penta et al., (2012), reported synthesis of thiazoles and thiazolyl-pyrazole derivatives via multi component approach. They reported equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2\(H\)-pyran-2-one with thiosemicarbazide and various carbonyl compounds on stirring at room temperature for period of 10 min resulted in the formation of 4-hydroxy-3-[2-(N-substitutedhydrazino)-thiazol-4-yl]-6-methyl-pyran-2-one with the yield of more than 80\%\(^32\).

![Scheme-28: Synthesis of 1,3-Thiazoles from thiosemicarbazide with pyran-2-one](image)
2.2. References

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