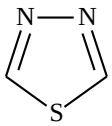
Introduction

Chemistry of 1,3,4-thiadiazoIes

1.1- Structure of 1,3,4-thiadiazoIes

The chemistry of 1,3,4-thiadiazole and its derivatives has been previously covered.[1-3] Since 1991 advances in the chemistry of l,3,4-thiadiazole compounds have been annually reviewed in Progress in Heterocyclic Chemistry. [4]

The numbering of the 1,3,4-thiadiazole ring is given below. The chemistry of derivatives of the aromatic 1,3,4-thiadiazole **1**, the nonaromatic 2-thiadiazolines **2**, 3-thiadiazolines **3**, the thiadiazolidines **4**, the tautomeric forms **5** and **6**, and the mesoionic systems **7** will be covered by this part .



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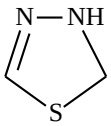

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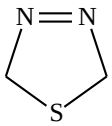

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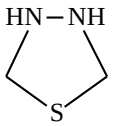

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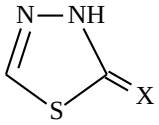

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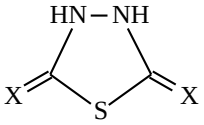

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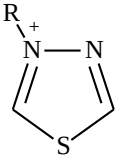

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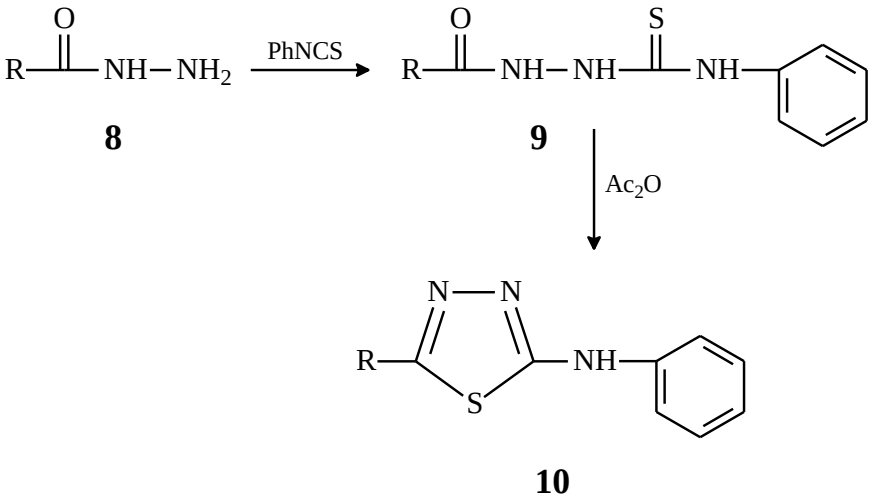
1.2- Synthesis of 1,3,4-thiadiazoles

1.2.1- From Acid Hydrazide

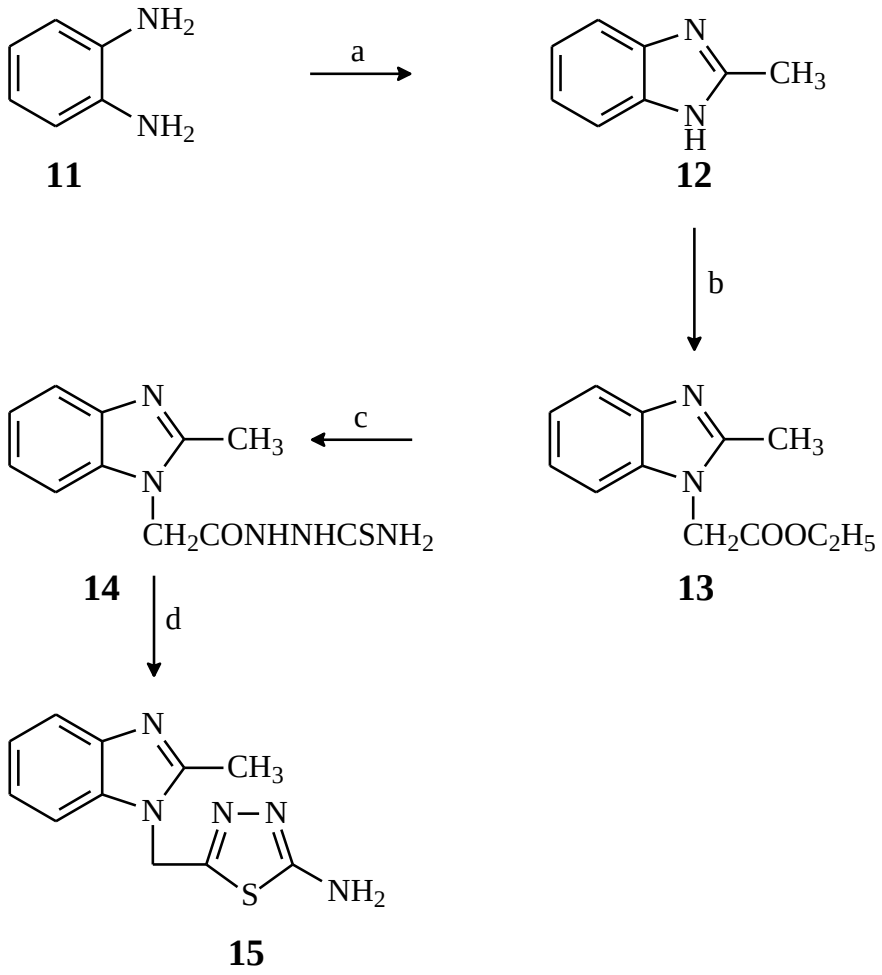
The reaction of along-chain alkenoic acid hydrazide **8** with phenyl isothiocyanate gave the corresponding thiosemicarbazides **9** which on dehydrative cyclization by Ac_2O produced 2,5-disubstituted-1,3,4-thiadiazoles **10** in excellent yields (Scheme 1). [5]



Scheme 1: Synthesis of 2,5-disubstituted-1,3,4-thiadiazoles

1.2.2- From benzimidazoles

2-Methyl-l*H*-benzimidazole **12** was prepared according to the reported method.[6] Compound **12** on *N*-ethoxylation with ethyl chloroacetate in the presence of anhydrous K_2CO_3 in dry acetone gave ethyl (2-methyl-l*H*-benzimidazol-l-yl)acetate **13** which on treatment with thiosemicarbazide resulted in the formation of 2-[(2-methyl-1*H*-benzimidazol-l-yl)acetyl]hydrazinecarbothioamide **l4**. Dehydrated annulation of compound **14** with concentrated H_2SO_4 followed by NH_3 treatment yielded 5-[(2-melhyl-l*H*-benzimidazol-l-yl)methyl]-l,3,4-thiadiazol-2-amine **15** (Scheme 2) .[7]

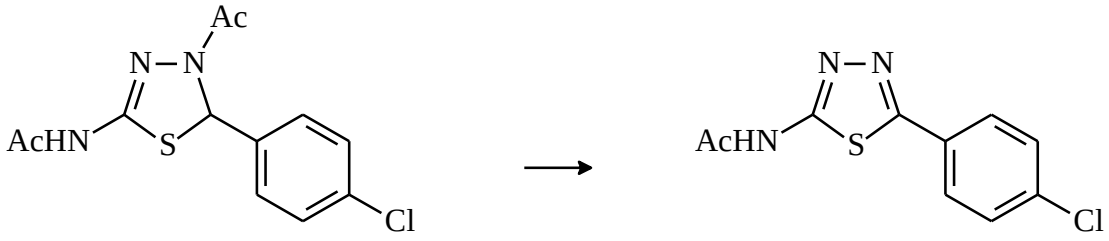


Reaction conditions (a) CH_3COOH; (b) $ClCH_2COOC_2H_5$; (c) $NH_2NHCSNH_2$; (d) $H_2SO_4.NH_3$

Scheme (2) for synthsis of 2,5-disubstituted -1,3,4- thiadiazole derivatives

1.2.3- Synthesis of thiadiazoles by oxidation of fully or partially reduced derivatives (Aromatization)

Partially or fully reduced thiadiazoles can be oxidized to yield 1,3,4-thiadiazoles. The 2,5-disubstituted-3-acyl-l,3,4-thiadiazole can be deacylated by numerous methodes.[8] The oxidative deacylation of compound **16** to thiadiazole **17** can be achieved using oxidants such as $KMnO_4$, cerium(IV) ammonium nitrate (CAN), and (diacetoxy) iodobenzene (Scheme 3). Better yields and cleaner products are obtained using CAN as oxidant.



16 **17**

Condition	Yield %
$KMnO_4$, $AcOH.H_2O$, 20 ^oC, 1.5-3h	70
CAN, $MeCN/H_2O$, 23 ^oC, 0.3-0.75h	94.5
$C_6H_3I[(OAc)_2$, MeOH, 23 ^oC, 2-36h	93

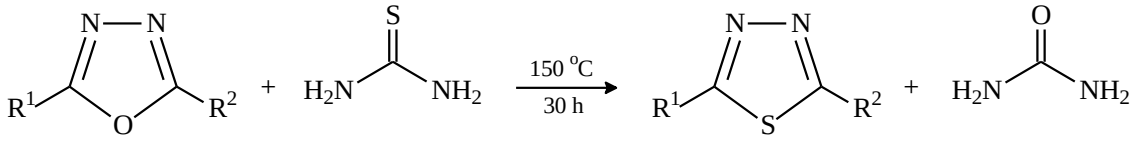
Scheme 3

1.2.4. Synthesis of thiadiazoles by transformation of other heterocycles

The direct ring transformations of other heterocycles into 1,3,4-thiadiazoles that appeared in the literature prior to 1995 are reviewed. [1,2] 1,3,4-Oxadiazoles are converted into 1,3,4-thiadiazoles when treated with phosphorus pentasulfide[9] or sodium sulfide.[10] 5-Substituted tetrazoles when treated with thiobenzoyl chloride, phenyl isothiocyanate[11] or benzonitrilium *N*-(4-nitrophenyl)imide[12] gave 2-substituted-5-phenyl-1,3,4-thiadiazoles. Mesoionic1,3,4-oxadiazoles are converted into 1,3,4-thiadiazoles when heated in ethanol or ethanethiol,[13] while 1,4,2-dithiazolium salts upon treatment with amines give 1,3,4-thiadiazoles.[14] Other transformations include the ring contraction of the six-membered l,3,4-thiadiazin-6-ones.[15]

I.2.4.1- From 1,3,4-oxadiazoles

2,5-Diaryl-1,3,4-oxadiazoles **18** react with thiourea to give 2,5-diaryl-1,3,4-thiadiazoles **19** (Scheme 4) the prepared derivatives are shown in (Table 1).[16]



18 **19**

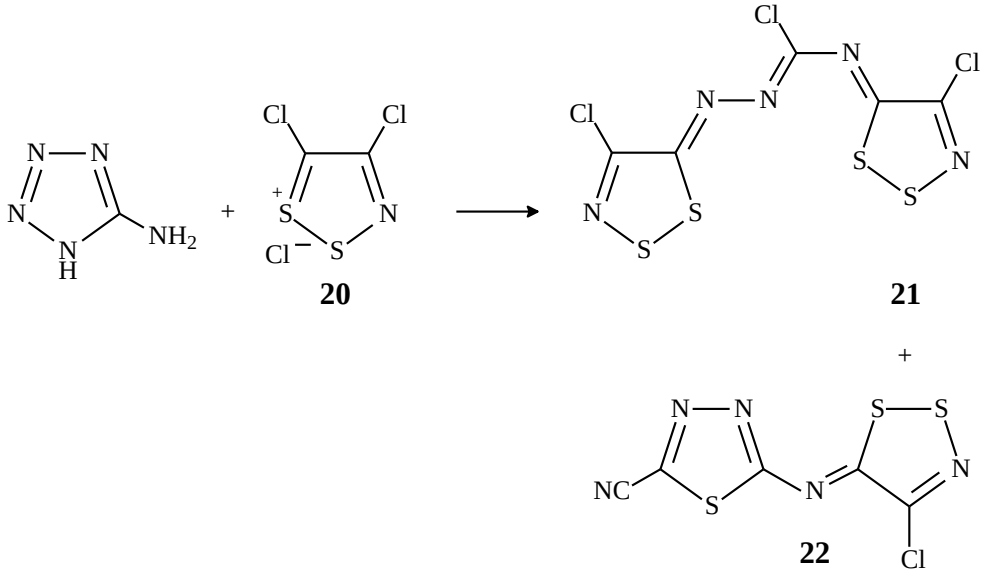
Scheme 4

Table 1: Preparation of 2,5-diaryl-l,3,4-thiadiazoles from 2,5-diaryl-1,3,4-oxadiazoles using thiourea.

R^1	R^2	*Yield*
Ph	Ph	65
4-$MeOC_6H_4$	Ph	60
3,4,5-$(MeO)_3C_6H_2$	Ph	69
3,4,5-$(MeO)_3C_6H_2$	4-$O_2NC_6H_4$	55

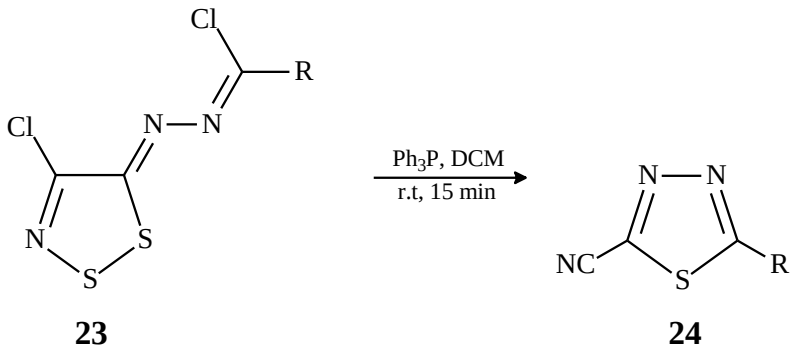
1.2.4.2- From 1,2,3-dithiazoles

5-Aminotetrazole react with 4,5-dichloro-l,2,3-dithiazolium chloride **20** to afford the bis(imino-l,2,3-dithiazole) **21** (20%) which in warm DMSO or DMF converted into the l,2,3-dithiazolimine **22** (25%) (Scheme 5).[17]



Scheme 5

The scope of this reaction has been extended to other 5-substituted tetrazoles, readily prepared by the reaction of nitriles with aluminium azide.[18] Using triphenylphosphine and dichloromethane under mild conditions; the resulting dithiazolimines **23** are rapidly converted into cyanothiadiazoles **24** in high yield (Scheme 6)and (Table 2).

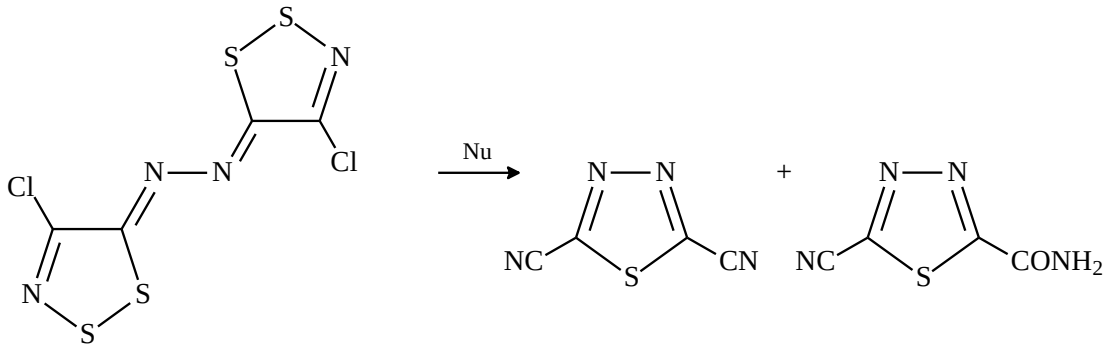


Scheme 6

Table 2: Preparation of 5-cyano-l,3,4-thiadiazoles from dithiazolimines using Ph_3P.

R	*Yield*
Ph	82
4-$O_2NC_6H_4$	92
4-$MeOC_6H_4$	99
2-Thienyl	76
PhO	75
MeS	73
$ClCH_2CH_2$	90

The thiadiazolecarbonitriles **24** can be further sequentially treated with azide, dithiazolium chloride **20** and triphenylphosphine to afford unsymmetrical bi- and tri-l,3,4-thiadiazolyl oligomers. Hydrazine react with dithiazolium chloride[19] to give the bisdithiazole **25** which react with $BnEt_3NI$ to give l,3,4-thiadiazole-2,5-dicarbonitrile **26** (Scheme 7).[20] Thiadiazole **26** prepared previously via a laborious multistep synthesis[21] suffer hydration during chromatographic isolation to afford the carboxamide **27** the formation of which can be avoided when polymer-bound triphenylphosphine is used as nucleophile (Scheme 7).



25 **26** **27**

Nu	*Yield*	
	%	*%*
$BnEt_3NI$	79	19
Ph_3P-Polymer bound	69	0

Scheme 7

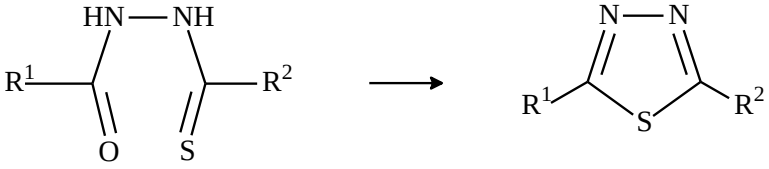
1.2.5- Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

The synthetic procedures in this section are classified by the number of ring atoms contributed by each component and by the number and types of bond generated in the last reaction step.

I.2.5.1- Formation of One Bond

Fragment **S-C-N-N-C***: Cyclizations*

Monothiodiacylhydrazines **28**, derived from the acylation of thiosemicarbazides or as intermediates in the reactions of thiohydrazides[1] with carboxylic acids and their derivatives or hydrazides[2] with thiocarbonyl compounds cyclize in the presence of an acid catalyst to give 1,3,4-thiadiazoles **29** (Scheme 8).

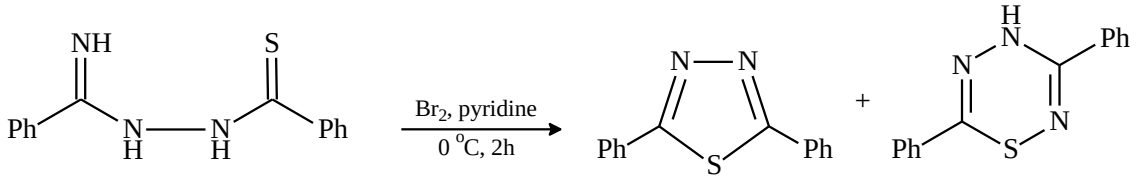


28 **29**

Scheme 8

The cyclization of *N*'-imidoylthiohydrazide **30** with bromine in the presence of pyridine gave 2,5-diphenyl-l,3,4- thiadiazole **31** along with the 3,6-diphenyl-4H-l,2,4,5-thiatriazine **32** in a 13:5 ratio (Scheme 9).[21]

The product ratio was sensitive to the reaction conditions and when compound **30** was treated with oxidants such as NCS, Bu^tOCl, I_2/pyridine, or, if deprotonated, with NaH and then treated with I_2 or SO_2Cl_2, thiadiazole **31** was the major product[22]. *N*'-Imidoylthiohydrazide **30** was converted to thiadiazole **31** in 80% yield upon storage at room temperature for over a year and gave product **31** exclusively when treated with either pyridine or an acid.



30 **31** **32**

Scheme 9

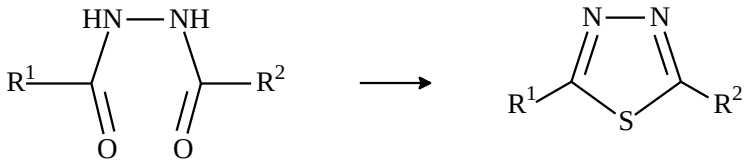
1.2.5.2- Formation of Two Bonds

Fragments C-N-N-C and S: Diazenes and hydrazines with a sulfur source

The reaction of 2,3-diazabuta-l,3-dienes with sources of active sulfur to prepare 1,3,4-thiadiazoles has been reviewed.[1,2] A variety of sulfur-

releasing reagents can be used depending on the nature of the diazene. The most common sulfur sources include phosphorus pentasulfide, sodium thiolate, and hydrogen sulfide. Using this strategy, 2,5- diphenyl-l,3,4-thiadiazole **31** was prepared from the reaction of diphenyl diazene with O,O-diethyl dithiophosphate.[23]

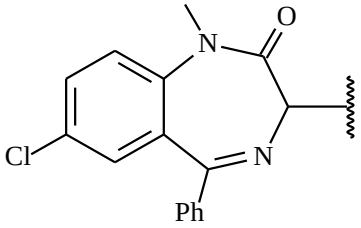
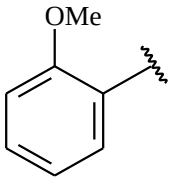
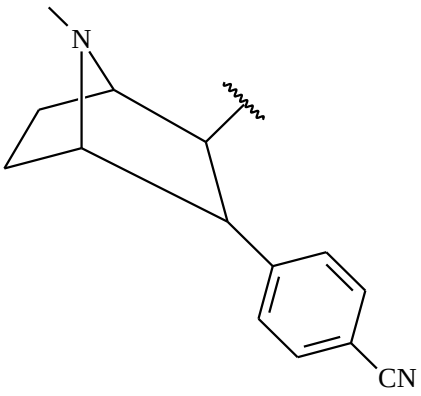
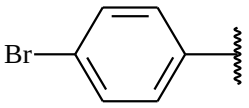
1,3,4-Thiadiazoles **34** can also be prepared from the reaction of diformyl- or diacylhydrazines **33** with a sulfur source (Scheme 10). The reaction involves thionation of the carbonyl groups followed by cyclization with loss of H_2S (Table 3). Phosphorus pentasulfide is commonly used for this cyclization but requires long reaction times and excess reagent, which often leads to low yields and side products such as 1,3,4-oxadiazole.[24-26] The alternative use of Lawesson's reagent gives higher yields and cleaner reactions.[27-29] This cyclization can also be carried out under microwave and solvent-free conditions to afford 1,3,4-thiadiazoles in high yields and with short reaction times.[30]



33 **34**

Scheme 10

Table 3: Preparation of 1,3,4-thiadiazoles from diformyl-and diacylhydrazines and a sulfur

R^1	R^2	Conditions	Yield 137 (%)
	Me	P_2S_4, 150-160 oC, 2h	40
	Ph	P_2S_4, xylene, 140^{o}C, 4h	65
	Ph	Lawesson's reagent, PhMe, reflux, 4h	58
	n-$C_{13}H_{23}$	Lawesson's reagent, PhMe, reflux, 4h	91

1.3- Thermodynamic Aspects

1.3.1- Physical Properties

The melting, boiling points, and solubility of many thiadiazoles have been reviewed.[1] Thiadiazoles, thiadiazolines, and thiadiazolidines can have high melting points, especially if they create inter- or intramolecular hydrogen bonds. Thiadiazoles substituted in the 2- and 5-position with

small polar groups like amines are soluble in water but generally the water solubility decreases as substituents increase in size, while solubility in organic solvents increases. Solubility for many 1,3,4-thiadiazoles have been previously recorded. [31]

1.3.2- Aromaticity

The aromaticity of 1,3,4-thiadiazole have previously discussed and studied.[32-33] The average ring bond order deviation computed for 1,3,4-thiadiazole was found to be 0.22562 and supports the relative high aromaticity of 1,3,4- thiadiazole. [34] Studies on energy and magnetic criteria based on computationally obtained geometries also supported the relatively high aromaticity of 1,3,4-thiadiazole.[35-36] Aromaticity related parameters such as the aromatic stabilization energy (ASE), the nucleus-independent chemical shift (NICS), the harmonic oscillator model of aromaticity (HOMA) have been examined with respect to chemical reactivity of 1,3,4-thiadiazoles and 3-methyl-2-methylthio-l,3,4-thiadiazolium salts.[37] An NICS aromaticity study was also performed on the biologically important compound megazol.[38] HOMA index calculations were used as a quantitative measure of aromaticity for four bisubstituted 1,3,4-thiadiazole derivatives.[39] The calculated HOMO indices were substituent dependent and an increase in the substituent electrophilicity led to an increase in aromaticity. The aromaticity of 1,3,4-thiadiazole-1,1-dioxide was estimated based on the N, MDQ, $\Delta E_{\pi L}$(NLMO), and $\delta E_{\pi L}$(Boys) criteria as well as comparing with total energies.[40] 1,3,4-Thiadiazole-1,1-dioxide was concluded to be less aromatic than the 1,1-dioxides of the 1,2,5-, 1,2,4-, and 1,2,3-thiadiazoles.

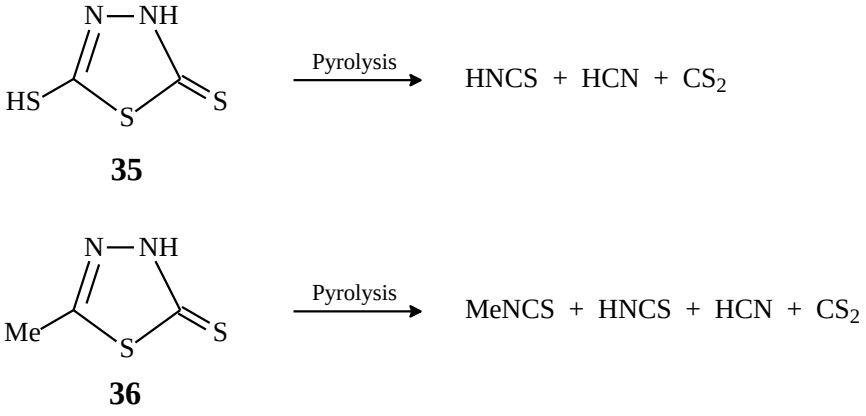
1.4- Reactivity of Fully Conjugated Rings

1.4.1- Survey of Reactivity

1,3,4-Thiadiazole is less aromatic than thiophene and electrophilic attack at carbon is rare due to the electron withdrawing effect of the nitrogen atoms. Thiadiazoles suffer electrophilic attack on the ring nitrogens and can be readily *N*-alkylated or *N*-acylated and mesoionic thiadiazoles can be prepared in this manner. Electrophilic attack at the sulfur atom has not been observed. Nucleophilic substitution of leaving groups present at either the C-2 or C-5 positions dominates the reactivity of the molecules. While 1,3,4-thiadiazoles are relatively stable, strongly basic conditions can lead to ring fission.

1.4.2- Unimolecular Thermal and Photochemical Reactions

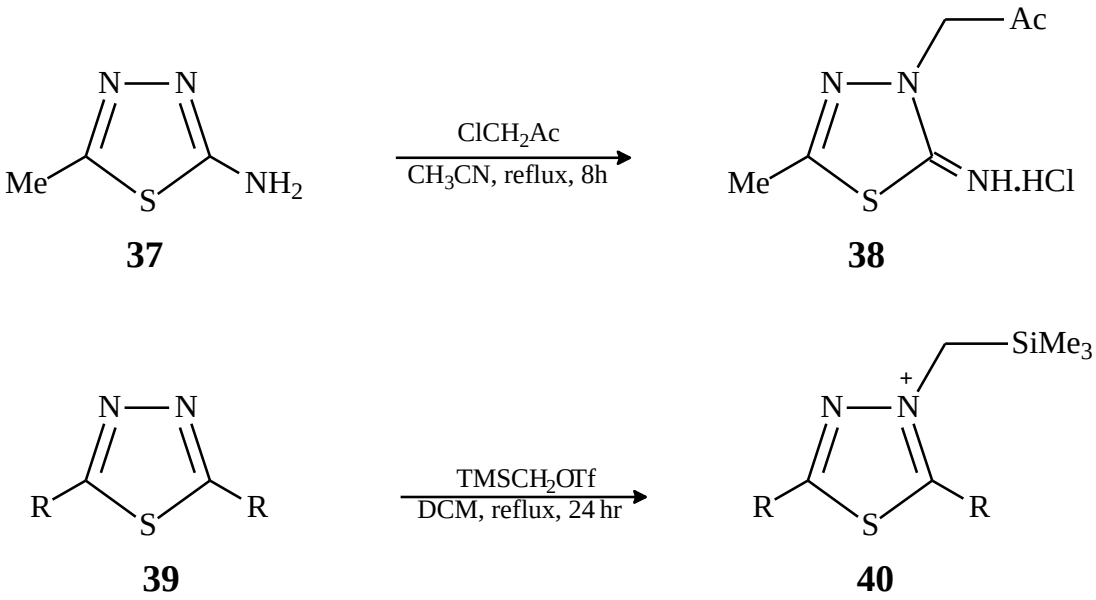
High-vacuum pyrolysis of 2,5-dimercapto-l,3,4-thiadiazole **35** and 2-mercapto-5-methyl-l,3,4-thiadiazole **36** performed between ambient and 800 °C gave products that were trapped by matrix-isolation techniques and characterized by IR spectroscopy. Pyrolysis of the dimercaptothiadiazole gave HNCS, CS_2, and HCN, whereas the thiadiazolethione showed a more complex fragmentation pattern forming HNCS, CH_3NCS, HCN, and CS_2 (Scheme 11) .[41]



Scheme 11

1.4.3- Electrophilic Attack at Nitrogen

The ring nitrogens react with electrophiles to afford either 1,3,4-thiadiazolium salts or l,3,4-thiadiazol-2(3*H*)-ones depending on the tautomerisability of the substituents at the C-2 or C-5 positions. While *N*-alkylation is the most common electrophilic reaction of 1,3,4-thiadiazoles, reactions with acyle and cyanogene halides as well as Mannich salts have also been reported. 2-Amino-5-methyl-l,3,4-thiadiazole **37** reacts with chloroacetone to give the *N*-alkylated thiadiazolimine **38** (Scheme 11)[42] and *N*-alkylation of the 2,5-dimethyl-1,3,4-thiadiazole with trimethylsilylmethyl trifluoromethanesulfonate gave the corresponding 1,3,4-thiadiazolium salts **40** (Scheme 12).[43]



37 **38**

39 **40**

Scheme 12

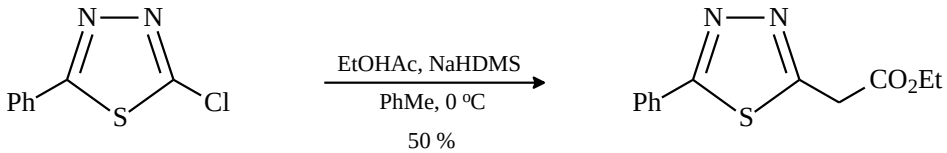
1.4.4- Electrophilic Attack at Carbon

Electrophilic substitution reactions on the carbon atoms of 1,3,4-thiadiazoles are rare due to the low electron density of ring carbons. *C*-Acylation can be accomplished via rearrangement of intermediate *N*-

acylthiadiazolium salts while radical halogenation can give chlorinated or Dominated 2-halo-5-substituted thiadiazoles.

1.4.5- Nucleophilic Attack on Carbon

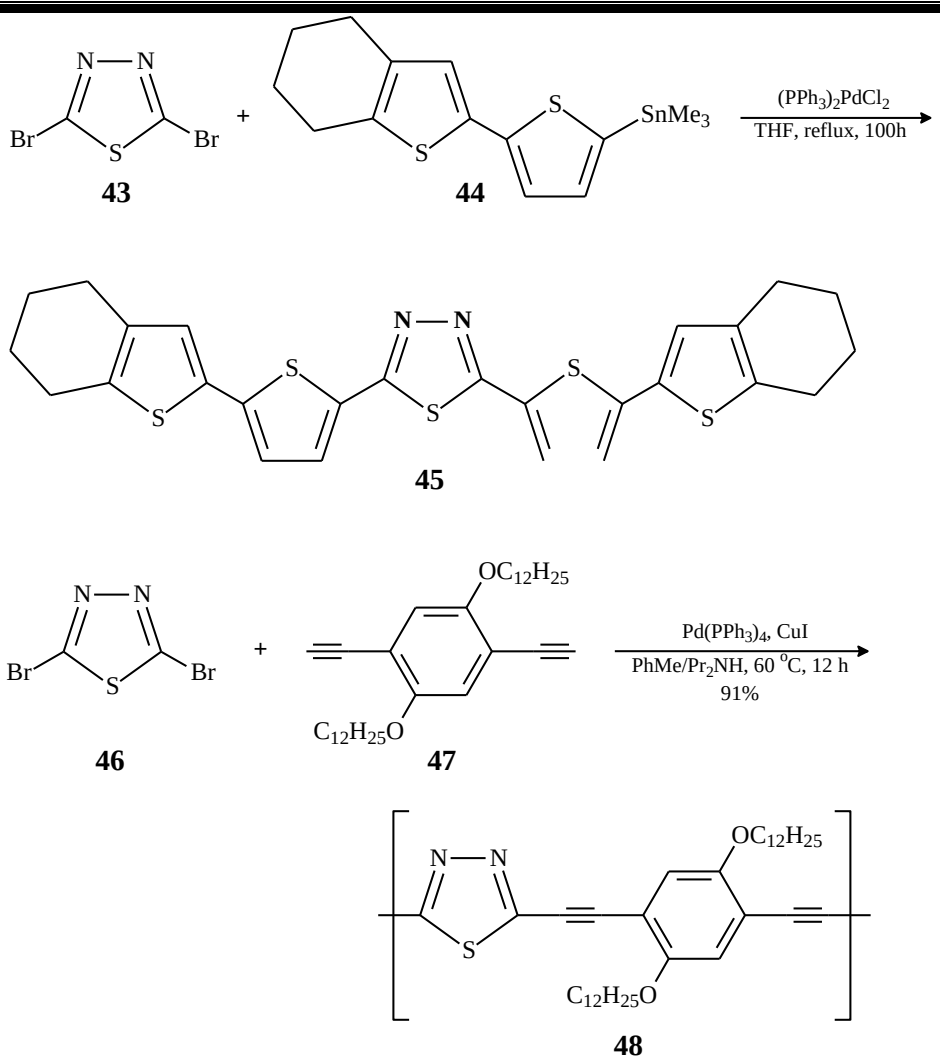
Nucleophilic reactions at the carbon atoms of 1,3,4-thiadiazoles occur readily owing to the electron-deficient nature of this ring. Halo-substituted thiadiazoles are therefore highly activated and react with a wide range of nucleophiles. Carbon-based nucleophiles such as malonates have been used in the synthesis of 2-substituted thiadiazoles. When chlorothiadiazole **41** was treated with ethyl acetate in the presence of Sodium Hexamethyldisilazane, the 2-phenyl-l,3,4-thiadiazol-5-ylacetic ester **42** obtained (Scheme 13). [44]



41 **42**

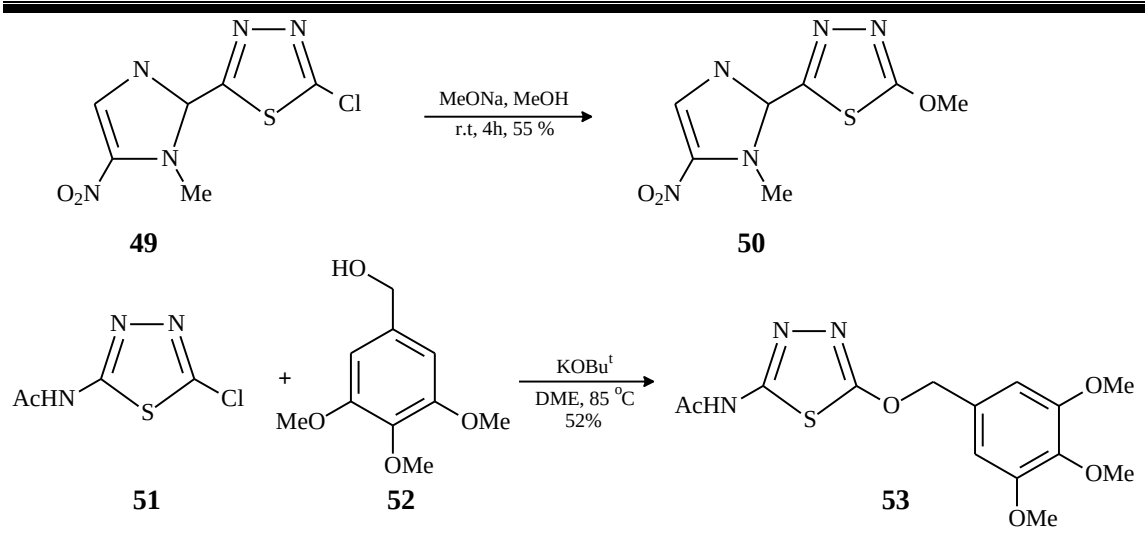
Scheme 13

The bromine atoms in 2,5-dibromo-l,3,4-thiadiazole **43** undergo a palladium-catalyzed Stille reaction[45] with the organostannyl derivative **44**. The thiadiazole **43** was co-polymerized with diethynyl benzene **47** and diethynyl pyrrole in a Sonogashira cross-coupling reaction (Scheme 14). [46]



Scheme 14

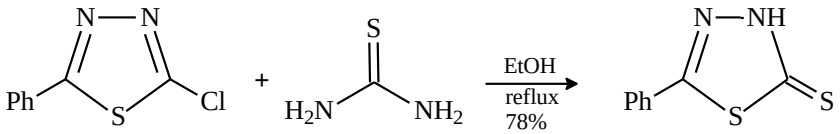
Oxygen, sulfur[47] and nitrogen[48-55] nucleophiles also react with the halothiadiazoles to give the corresponding halo-displaced products. For example, the thiadiazole **49** reacts with sodium methoxide in methanol to give thiadiazole **50** [56] and 2-acetamido-5 -chloro- 1,3,4-thiadiazole **51** reacted with the 3,4,5-trimethoxybenzyl alcohol **52** in the presence of potassium *t*-butoxide to afford the substituted trimethoxybenzyl ether **53** (Scheme 15).[57]



49 **50** **51** **52** **53**

Scheme 15

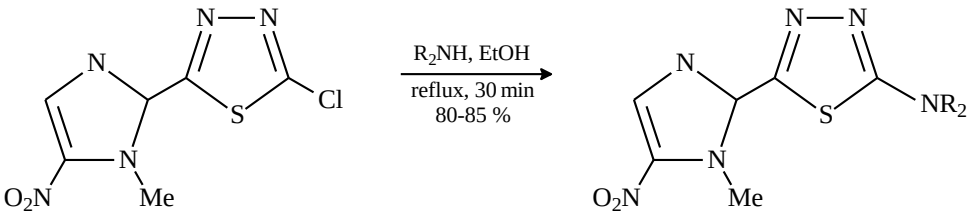
2-Chloro-5-phenyl-l,3,4-thiadiazole **54** reacts[58] with thiourea in ethanol under reflux to afford the thione **55** (Scheme16).



54 **55**

Scheme 16

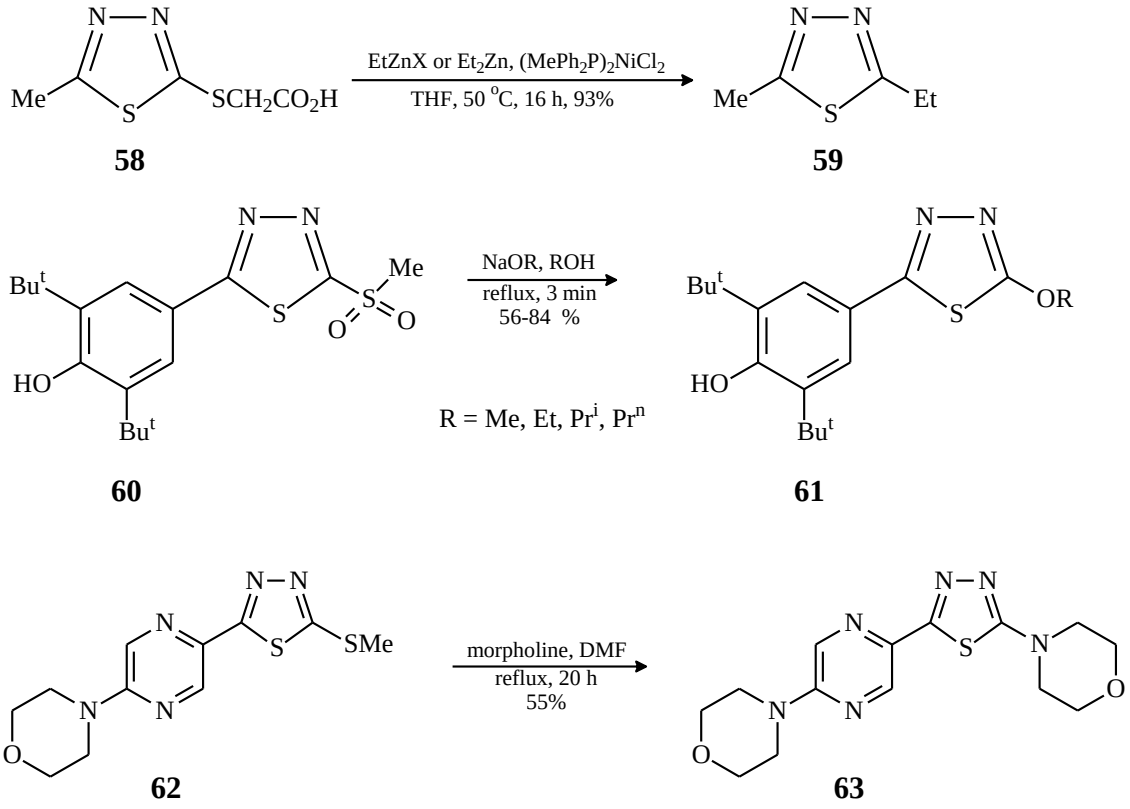
Thiadiazole **56** reacts with cyclic secondary amines such as piperidine, piperazine, and morpholine to afford the substituted derivatives[59] **57** in 80-85% yield (Scheme 17).



56 **57**

Scheme 17

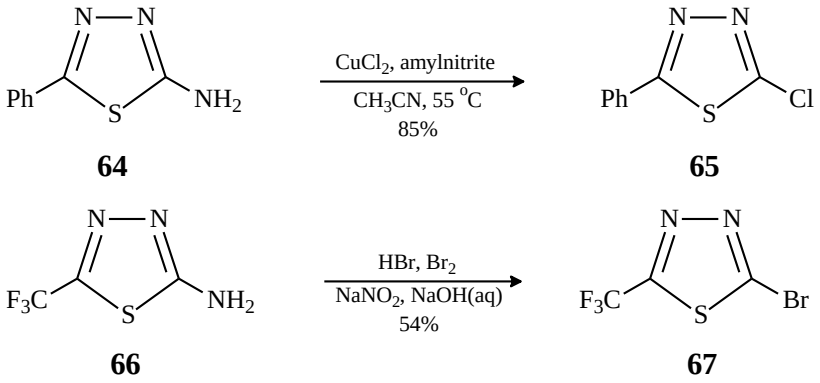
Sulfur substituents at either the C-2 or C-5 positions are also activated and can be substituted by a range of nucleophiles. The thioglycolic thiadiazole acid **58** reacts with diethylzinc in the presence of an Ni catalyst to give the 2-ethyl-substituted thiadiazole **59**.[60] Sulfonyl substituents can be displaced with sodium alkoxides to give ethers,[61,62] or by nitrogen nucleophiles to afford the corresponding amino derivatives.[63,64] The reaction of the thiadiazole **62** with morpholine in refluxing DMF led to substitution of the methylthio group **63** (Scheme 18).[65]



Scheme (18)

2-Amino-l,3,4-thiadiazoles undergo Sandmeyer reactions to afford 2-halo-l,3,4-thiadiazoles.[66-69] Diazotization followed by a Sandmeyer reaction of the 2-amino-5-phenyl-l,3,4-thiadiazole **64** with CuCl generated in situ gave 2-chloro-5-phenyl-l,3,4-thiadiazole **65** in 85% yield.[70] while Sandmeyer bromination of 2-amino-5-(trifluoromethyl)- l,3,4-thiadiazole

66 gave 2-bromo-5-(trifluoromethyl)-1,3,4-thiadiazole **67** in 54% yield (Scheme 19). [71]



Scheme 19

1.4.6. Nucleophilic Attack at Hydrogen Attached to Carbon

Deprotonation of 1,3,4-thiadiazolium salts affords carbenes that can be trapped with aromatic isocyanates to yield spirocyclic compounds. These reactions have been reviewed.[1,72]

1.5. Important Compounds and Applications

1,3,4-thiadiazoles are important compounds in medicine, agriculture, and in many fields of technology. A large number of thiadiazoles have been patented in the medical field for the treatment of a wide variety of diseases and some of them have become commercial products. Many 1,3,4-thiadiazoles derivatives have been patented as useful antagonists. 1,3,4-thiadiazoles 599 platelet glycoprotein IIb/IIIa fibrinogen receptor complexs[73,74] have been found to be inhibitors of 5-Lipoxygenase and /or cyclooxygenase providing trearment of conditions advantageously affected by such inhibition including inflammation ,arthritis,pain fever,and the like,[75] as antiviral mendicants against herpes virus cytomegalovirus(CMV),[76] as antagonists of alpha V beta 3 and related

integrin receptors,[77] as medicants for inflammatory disease such as, hypersensitivity reaction, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications,[78] and for many other medical applications. A large number of thiadiazoles have also been patented in the agriculture field as herbicides, insecticides, fungicides, and bactericides. 2-Alkylthio1,3,4-thiadiazoles have been patented as crop protection agents ,[79] and acylated 5-amino-thiadiazoles as pesticides and fungicides.[80]

Some of the technological uses of the 1,3,4-thiadiazoles involve dyes or metal complexation agents,[81-84] corrosion and oxidation inhibitos,[85] and optically active liquid crystals and optoelectronic materials.[86,87] Drug resistance is a steadily increasing process that is reaching alarming level in the treatment of infectious caused by pathogenic bacteria, fungi, parasites and viruses. Over the past few years, steadily increasing drug resistance in the treatment of infectious disease pose a serious problem in antimicrobial therapy and necessitates continuing research into novel classes of antimicrobials[88] a number of researchers have reported antimicrobial activities in 2,5- disubstituted-1,3,4-thiadiazoles.[89,90] Recently, several compounds from 1,3,4-thiadiazole series that exhibited significant anti-H. pylori activity.[91–93] There are also several reports regarding the antimicrobial properties of 1,3,4-thiadiazoles with different substitutions at 2 and 5 positions.[94] Furthermore, the synthesis and antimicrobial activity of some pyridyl and naphthyl substituted 1,2,4-triazole and 1,3,4- thiadiazole derivatives containing a benzylthio group have also been reported.[95]

Moreover, the synthesis of 2-acylamino, 2- aroylamino, and ethoxycarbonyl imino-1,3,4-thiadiazoles as antitumor agents is reported.[96]

It is known that many1,3,4- thiadiazole and 1,2,4-triazole derivatives have biological activity, with their antibacterial,[97-99] antimycobacterial,[100,101] antimycotic,[102] antifungal,[103,104] antidepressive,[105] and cardiotonic[106] action being notable.

Recent research has also established for these heterocycles an analgesic[107] and anti-inflammatory[108,109] activitie. A diversity of useful biological effects is possessed by heterocyclic compounds containing the five membered oxadiazole nucleus.[110] In particular, compounds bearing 1,3,4-oxadiazole nucleus are known to exhibit unique antiedema and antinflammatory activity.[111-114]

2,5-Disubstituted-1,3,4-thiadiazoles are active against drug resistant wild type species related to cutaneous and visceral leishmaniasis; L. major, and L. tropica, even though exhibited different growth inhibition profiles for different concentrations.[115] 4-Thiadiazolidinones have been reported as novel inhibitors of the bacterial enzyme.[116] 2- Amino-5-substituted-1,3,4-thiadiazoles are very useful starting materials for the synthesis of various bioactive molecule and applied in medicine and agriculture.[117–120] A large number of imidiazo[2,1-b][1,3,4]thiadiazole properties such as anticancer,[121] antitubercular,[122] antibacterial,[123] antifungal,[124] anticonvulsant, analgesic [125] and antisecretory[126] activities. Moreover, much interest has also been focused on the anti- inflammatory, [127] cardiotonic,[128] diuretic[129] activities displayed by compounds incorporating this heterocyclic system.

Substituted 1,3,4- thiadiazoles have become very useful compounds in medicine, agriculture, and in many fields of technology such as dyes,[130] lubricating compositions,[131] optically active liquid crystals,[132] photographic materials,[133] Acetazolamide (acetazol), a carbonic anhydrase inhibitor

launched in 1954, is a well-known drug based on the 1,3,4-thiadiazole ring.[134] Clubbed1,2,4-triazole and 1,3,4-oxadiazole are new classes of azole anti-mycobacterials, which are proved to be highly active both in vitro and in vivo. [135,136]In continuation of our research on clubbed triazolyl-thiazoles[137–140] and clubbed triazolyl-isopropylthiazole, in previous communication it was proved isopropylthiazole moiety on coupling with other heterocyclic rings provides novel biologically active compounds that could be explored as potent antimicrobial and antitubercular agents.[141] Substituted oxadiazole and thiadiazole derivatives are potent cyclooxygenase/5-lipooxygenase inhibitors.[142–146]