1 GENERAL

Five-membered heterocycles with more than two heteroatoms are considered to be derived from pyrrole, furan and thiophene by the replacement of methine groups (–CH=) by pyridine-type nitrogen (–N=) atoms from the different positions and are named as (Fig. 1)[1] :

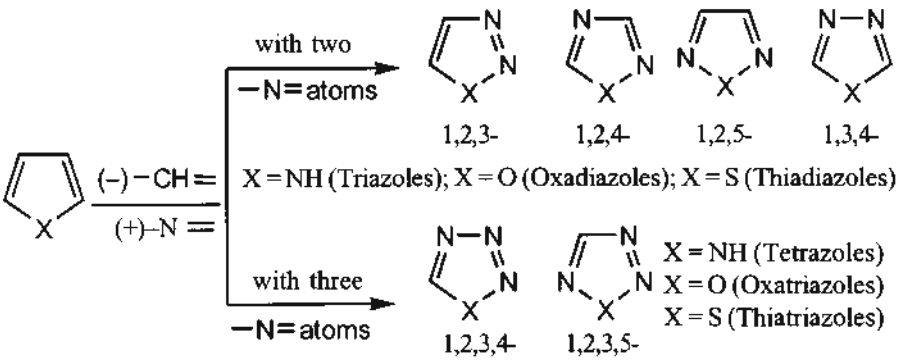


Fig. 1. Heterocycles with more than two heteroatoms

1.1 Effects of Additional Nitrogen Atoms[2–5]

(i) **Basicity** : The base strength generally decreases with increasing the number of nitrogen atoms because of inductively electron-withdrawing effect of the pyridine-type nitrogen atoms (diazines are weaker bases than pyridine). The additional nitrogen atoms in these heterocycles, therefore, have base-weakening effect as a result of which these systems are with lower basicity

(ii) **Acidity** : The acidity of the ring system increases with the number of nitrogen atoms as tetrazoles are more acidic than triazoles. Triazoles are comparable with phenol in acid strength, while 1*H*-tetrazole behaves as an acid (acetic acid). The positions of nitrogen atoms (orientation) do not affect considerably the acid strength as 1,2,3-triazole is slightly more acidic than 1,2,4-triazole. But the effect of orientation on acidity is much less than the effect of the total number of nitrogen atoms.

(iii) The tendency of the ring system towards electrophilic attack falls off with the introduction of additional pyridine-type nitrogen atoms. Triazoles, oxadiazoles and thiadiazoles are, therefore, resistant towards electrophilic attack and undergo electrophilic substitutions only if powerful electron-releasing substituents are present.

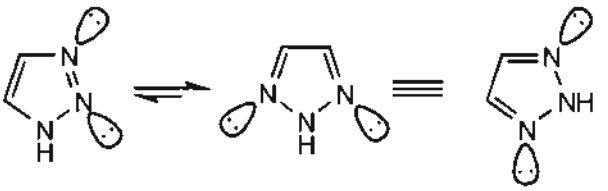
(iv) The introduction of pyridine-type nitrogen atoms in the ring system affects the ease of quaternization. The quaternization of triazoles, oxadiazoles thiadiazoles and tetrazoles requires stronger reagents and reaction conditions.

2 TRIAZOLES AND TETRAZOLES

2.1 1,2,3-Triazoles[6–9]

2.1.1 General

1,2,3-Triazole 1 is a planar five-membered heterocyclic system with two carbon and three nitrogen atoms (one pyrrole-type and two pyridine-type) in the 1-,2- and 3-positions. It was also named as v-triazole (v for vicinal) to distinguish it from s-triazole (s for symmetrical). 1,2,3-Triazole exists in two tautomeric forms; 1*H*- and 2*H*-froms, in which 1*H*-form was initially considered more stable than the 2*H*-form, but spectral studies have confirmed the predominance of symmetrical 2*H*-form. The destabilization of 1*H*-form is considered to be due to repulsive forces between the nonbonding electron pairs on the nitrogen atoms at positions-2 and -3 (Fig. 2).



1*H*-form 2*H*-form
1*H*-1,2,3-Triazole 2*H*-1,2,3-Triazole (2,1,3-triazole or osotriazole or 1,2,5-triazole)

Fig. 2. Tautomeric forms of 1,2,3-triazole

The fusion of a benzene ring with both the forms of 1,2,3-triazole results in benzotriazoles which are named and numbered as shown in structures **2** and **3.** Benzotriazole also exists in two tautomeric forms, but 1*H*-form predominates over the 2*H*-form (Fig. 3).

2 **3**

1*H*-form 2*H*-form
1*H*-Benzo[*d*][1,2,3-triazole] 2*H*-Benzo[*d*][1,2,3-triazole]
(1,2,3-Benzotriazole) (2,1,3-Benzotriazole)

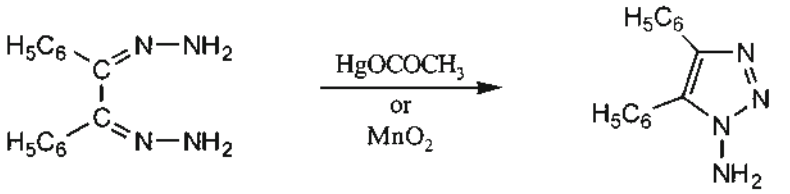
Fig. 3. Tautomeric forms of benzotriazole

1,2,3-Triazoles find their applications in medicines as sedatives, antiinflammatory, analgesics etc. and in agriculture as herbicides, fungicides and antibacterial agents. The industrial applications of 1,2,3-triazoles include their uses as fluorescent whiteners, light stabilizers and optical brightners.

2.1.2 Synthesis

2.1.2.1 Oxidative Cyclization of bis-Hydrazones of α-Diketones

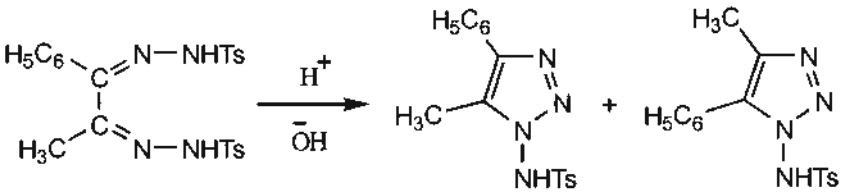
Bis-hydrazones of α-diketones **4** undergo oxidative cyclization when treated with mercury acetate or manganese dioxide to provide 1-amino-1,2,3-triazoles **5** involving N_1–N_2 bond formation (scheme-1)[10,11].



4 5

Scheme-1

However, with unsymmetrical bis-hydrazone **6**, both possible 1,2,3-triazoles; **7** and **8**, are obtained (scheme-2)[12].

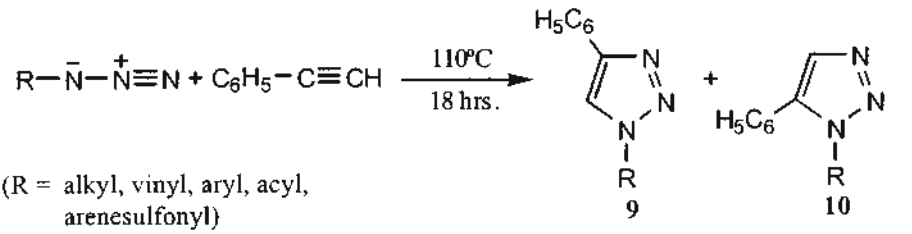


6 7 8

Scheme-2

2.1.2.2 Cycloaddition of Azides with Alkynes

This is the most versatile route to synthesize 1*H*-1,2,3-triazoles and involves thermal 1,3-dipolar cycloaddition of a wide variety of organic azides to alkynes with the formation of C_5–N_1 and C_4–N_3 bonds (scheme-3)[6,9,13]. However, the

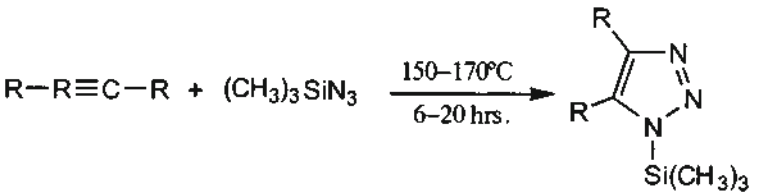


(R = alkyl, vinyl, aryl, acyl, arenesulfonyl)

9 (major product) 10 (minor product)

Scheme-3

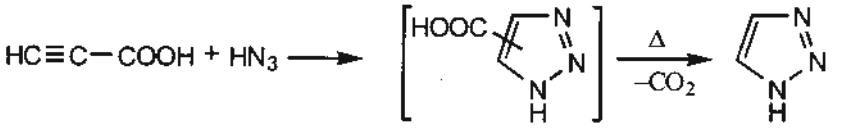
cycloaddition of trimethylsilyl azide to alkynes at higher temperature produces N-trimethylsilyl-1,2,3-triazoles. The silyl group can be easily removed to obtain 1*H*-1,2,3-triazoles in good yields (scheme-4)[14].



11

Scheme-4

The parent compound 1,2,3-triazole **1** is obtained by the direct addition of hydrazoic acid to alkynes substituted with an electron-withdrawing group (scheme-5).



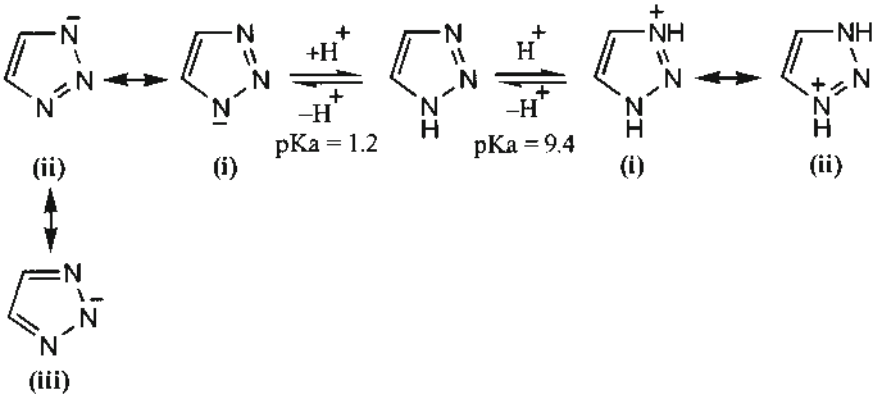
1

Scheme-5

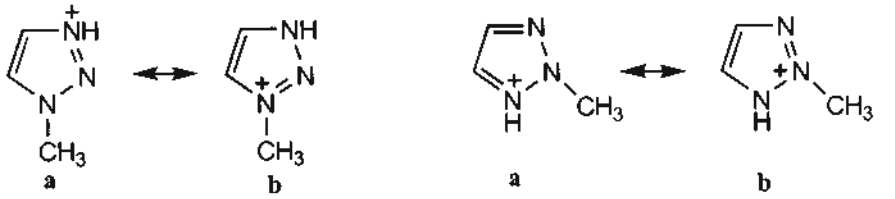
2.1.3 Reactions

2.1.3.1 Amphoteric Nature

1,2,3-Triazole is a weak base but it can also behave as a weak acid with comparable strength to phenol (scheme-6). The presence of methyl group at the position-1 does not affect base strength considerably as 1-methyl-1,2,3-triazole exhibits basicity comparable to 1,2,3 triazole. But with methyl group at the position-2, basicity is decreased. 2-Methyl-1,2,3-triazole is therefore a much weaker base. The base-weakening effect of methyl group in 2-methyl-1,2,3-triazole can be explained by the formation of pyrazolium-type cation **13**, while very weak base strengthening effect of the methyl group in 1-methyl-1,2,3-triazole is atributed to the formation of imidazolium-type cation **12** (Fig. 4).



Scheme-6



imidazolium-type cations — **12**

pyrazolium-type cations — **13**

Fig. 4.

2.1.3.2 Electrophilic Substitutions

1,2,3-Triazole undergoes electrophilic substitution at a ring carbon or at a ring nitrogen as three-hydrogen atoms are available (two-hydrogen atoms on ring carbons and one-hydrogen atom on nitrogen) for the electrophilic replacement (Fig. 5). Moreover, in unsymmetrical 1,2,3-triazole, N–H is present at three different

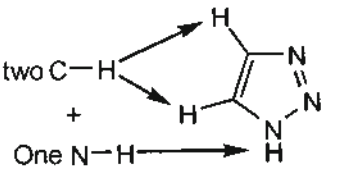


Fig. 5. Three replaceable hydrogens

positions due to tautomerism and therefore three different N–substitutions are possible with the formation of three possible isomers (Fig. 6). But in symmetrical

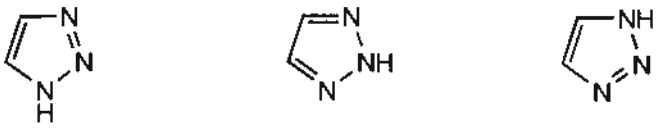


Fig. 6. Three N–H positions

1,2,3-triazole two N–H positions result in two different N-substitutions with the formation of two isomeric N-substituted derivatives (Fig. 7).

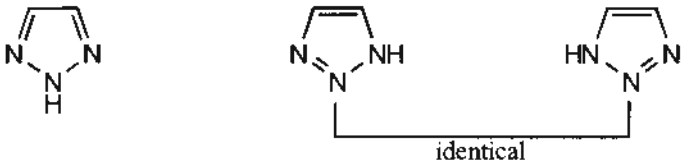
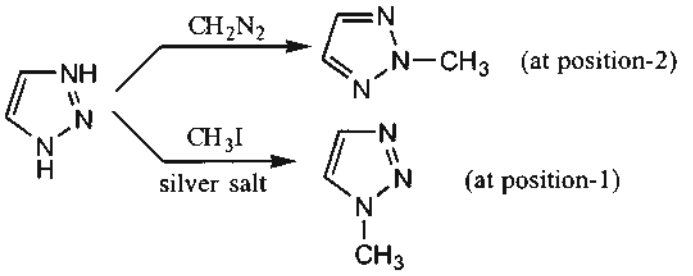


Fig. 7. Two N–H positions

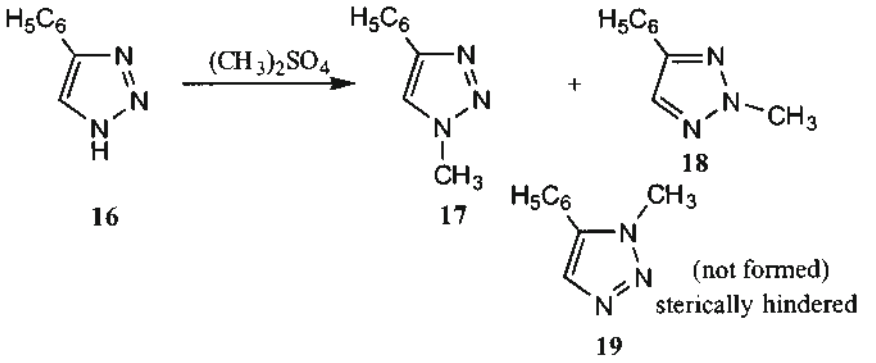
2.1.3.2.1 Alkylation

1,2,3-Triazoles undergo N-alkylation with a variety of alkylating agents. The ratio of isomers depends upon the nature of alkylating agents and the reaction conditions. Methylation of 1,2,3-triazole with diazomethane occurs preferentially at N-2 with the formation of 2-methyl-2*H*-1,2,3-triazole **14**. But methylation with methyl iodide in the presence of silver salt takes place preferentially at the position-1 (scheme-7).



Scheme-7

The steric effects of the substituents also affect the formation of products. Methylation of 4-phenyl-1*H*-1,2,3-triazole **16** with dimethyl sulfate occurs at N-1 and N-2 to provide 1-methyl- **17** and 2-methyl- **18** isomers in 62% and 38% yields, respectively, but sterically hindered 1-methyl-5-phenyl derivative **19** is not formed (scheme-8).

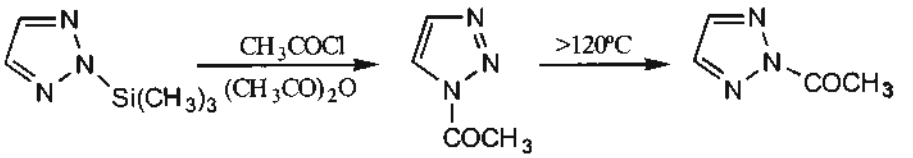


16 **17** **18** **19**

Scheme-8

2.1.3.2.2 Acylation

Acylation of 1,2,3-triazoles with acyl halides or acid anhydrides occurs initially at the position-1, but in some cases acyl group may migrate from the position-1 to the position-2 when 1-acyl derivative is heated above 120°C or treated with a base (scheme-9).

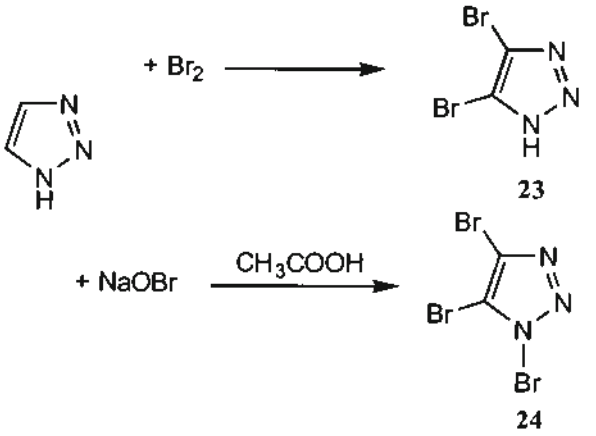


20 **21** **22**

Scheme-9

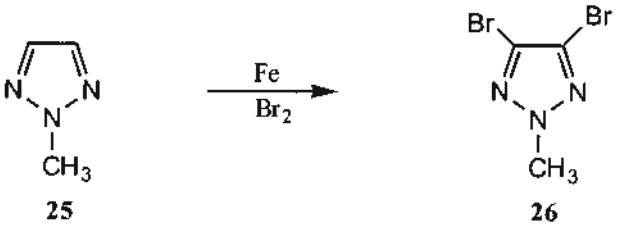
2.1.3.2.3 Bromination

Bromination of 1,2,3-triazole with bromine occurs at the positions-4 and -5 with the formation of 4,5-dibromo-1,2,3-triazole **23**, but with an excess of sodium hypobromite in acetic acid 1,4,5-tribromo-1,2,3-triazole **24** is formed (scheme-10). The high



Scheme-10

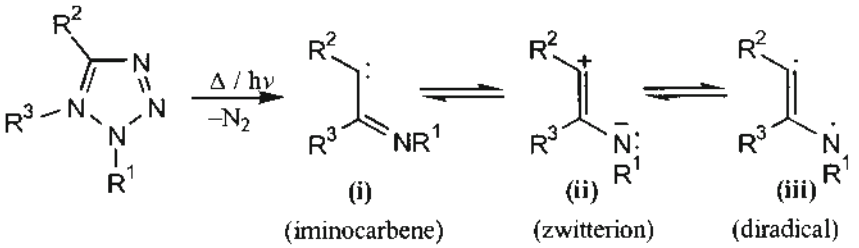
reactivity of 1,2,3-triazole towards bromination is due to the pyrrole-type nitrogen because bromination of 2-methyl-1,2,3-triazole **25** occurs comparatively very slowly. However, the presence of iron filings as catalyst facilitates bromination to occur readily at the positions-4 and -5 with the formaion of 2-methyl-4,5-dibromo-1,2,3-triazole **26** (scheme-11).



Scheme-11

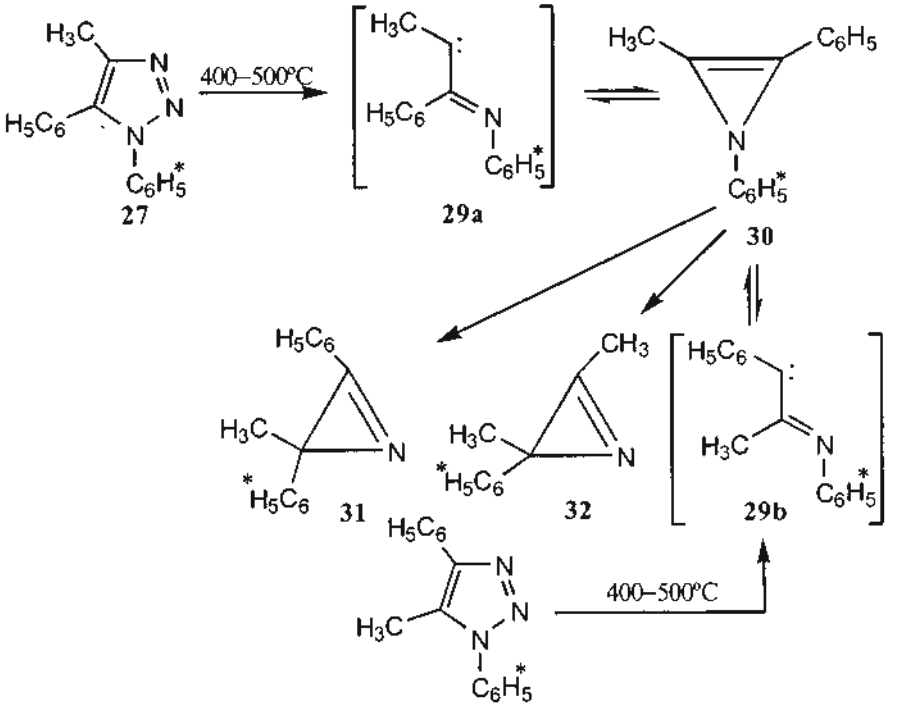
2.1.3.3 Thermal and Photochemical Reactions

1,2,3-Triazoles are stable towards oxidation and reduction, but undergo thermal and photochemical reactions under forcing conditions with the extrusion of nitrogen. The reactions proceed with the involvement of an intermediate in any one of the three mesomeric forms: (i) iminocarbene, (ii) zwitterion or (iii) diradical, depending on the nature of substituents and the reaction conditions (scheme-12)[12,15].



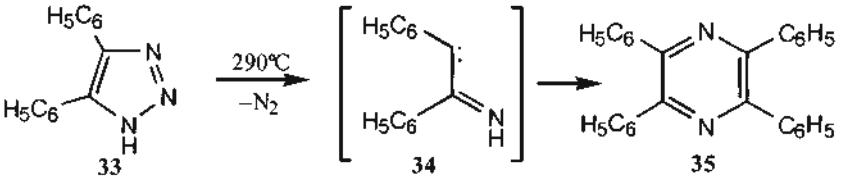
Scheme-12

(i) Vapour phase pyrolysis of unsymmetrically substituted 1,2,3-triazoles **27** and **28** proceeds via iminocarbene intermediates **29a** and **29b** with the formation of 1*H*-azirine derivative **30** which rearranges to two isomeric 2*H*-azirines **31** and **32** (scheme-13).



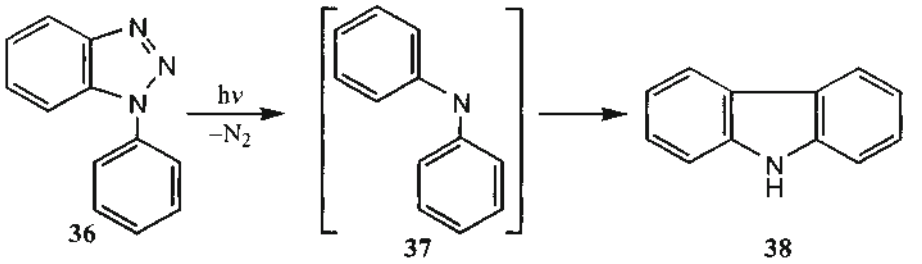
Scheme-13

(ii) Pyrolysis of 4,5-diphenyl-1,2,3-triazole **33** also proceeds via iminocarbene intermediate **34** with the extrusion of nitrogen to provide 2,3,5,6-tetraphenylpyrazine **35** (scheme-14)[16].



Scheme-14

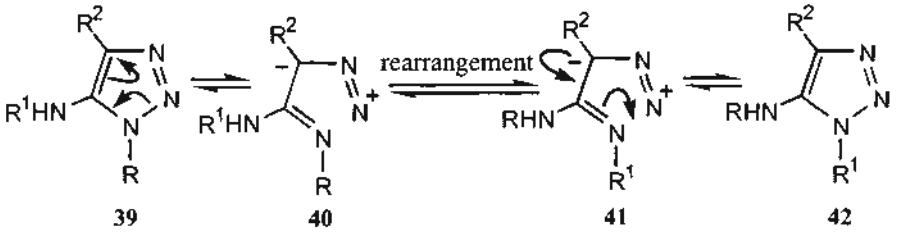
(iii) Irradiation of 1-phenylbenzo-1,2,3-triazole **36** produces carbazole **38** via a diradical intermediate **37** with the elimination of nitrogen (scheme-15).



Scheme-15

2.1.3.4 Dimroth Rearrangement[17]

5-Amino-1,2,3-triazoles **39** undergo Dimroth rearrangement[17] in which ring nitrogen and its attached substituent is exchanged with an imino group at an α-position. The rearrangement proceeds to involve ring opening by cleavage of the N–N bond and subsequent cyclization via diazoimine intermediates **40** and **41** (scheme-16).



Scheme-16

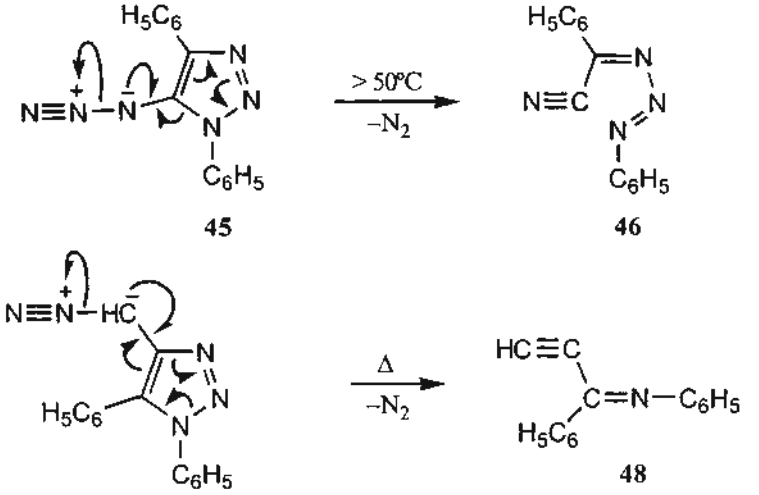
The position of the equilibrium is influenced by the nature of the substituents and also by the solvent basicity (pH of the solvent). The presence of electron-attracting and large groups favours the tautomeric form in which these groups are on the exocyclic nitrogen, while the alkyl groups prefer to be on cyclic nitrogen (scheme-17). More basic solvent shifts the equilibrium to the more acidic NH-triazole.

43 **44**

Scheme-17

2.1.3.5 Ring Cleavage Reactions

Amino-, azido- and diazomethyl-1,2,3-triazoles undergo ring cleavage reactions with the evolution of nitrogen at elevated temperatures involving concerted processes (scheme-18)[18].



45 **46**

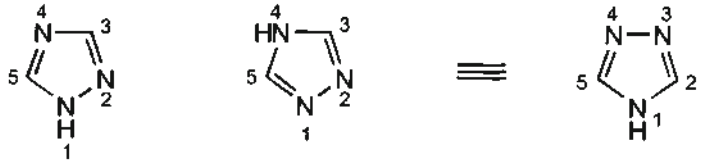
47 **48**

Scheme-18

2.2 1,2,4-Triazoles[5,19–21]

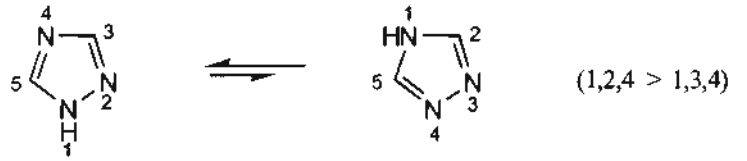
2.2.1 General

1,2,4-Triazoles are cyclic hydrazidines with hydrogen atom (or substituent) on either hydrazide nitrogen **49** or on amide nitrogen **50.** Parent 1,2,4-triazole (1*H*-form) is in tautomeric equilibrium with 1,3,4-triazole (4*H*-form). The interconversion



1*H*-1,2,4-Triazole **49** | 4*H*-1,2,4-Triazole **50** | (1*H*-1,3,4-triazole)

of two tautomeric forms occurs rapidly and their separation is difficult, however, 1,2,4-triazole tautomer is preferred over 1,3,4-triazole tautomer (less symmetrical 1*H*-form is favoured over symmetrical 4*H*-form) (scheme-19).



1,2,4-Triazole | 1,3,4-Triazole | (1,2,4 > 1,3,4)

Scheme-19

N-Unsubstituted 1,2,4-triazoles exist in two tautomeric forms (if substituents R_3 and R_5 are different) with the predominance of 1*H*- or 2*H*- form depending on the conditions (scheme-20).

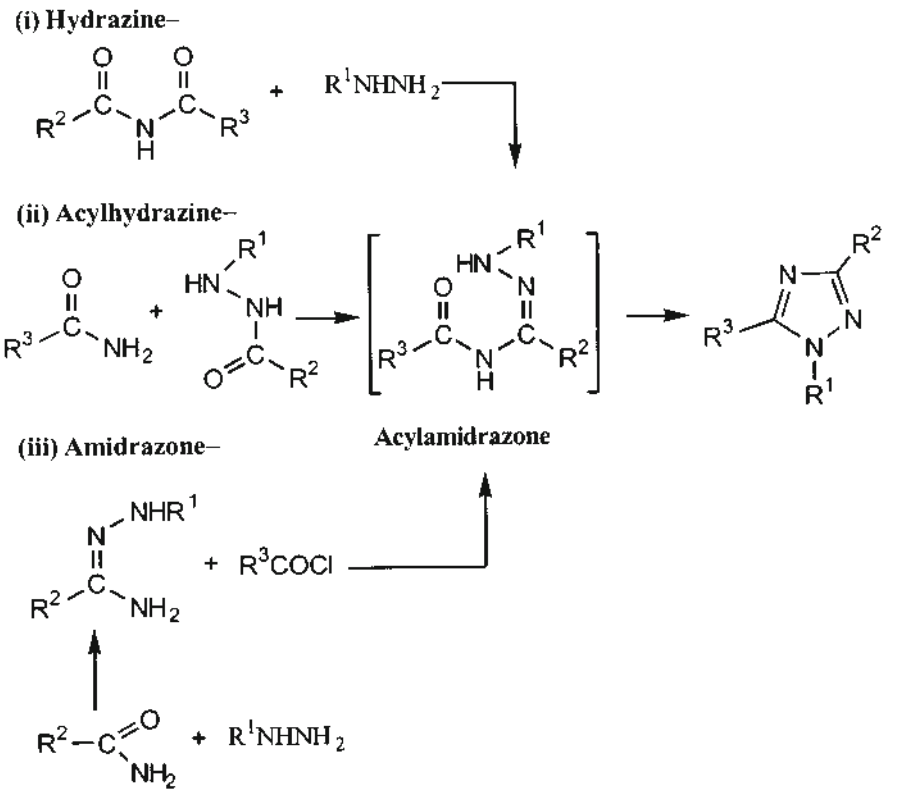
1*H*-form | 2*H*-form

Scheme-20

2.2.2 Synthesis

2.2.2.1 From Hydrazine Derivatives

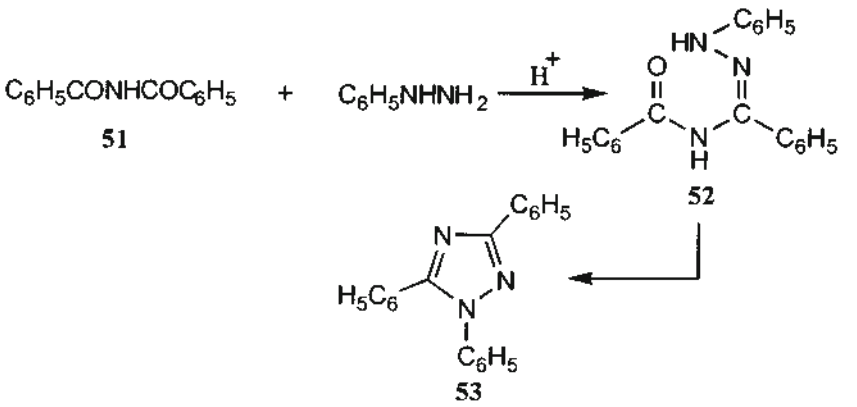
Synthesis of 1,2,4-triazoles involves the use of (i) hydrazine, (ii) acylhydrazine, (iii) amidrazone or (iv) acylamidrazone and represented schematically in (scheme-21).



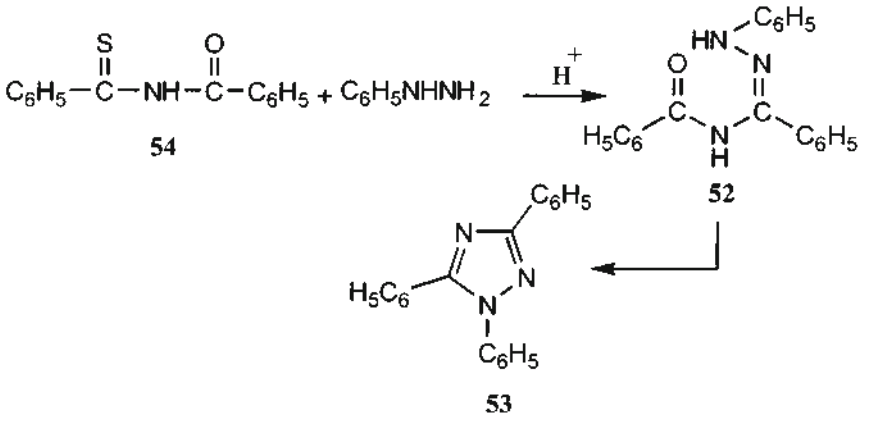
Scheme-21

Einhorn–Brunner Reaction

This reaction involves the condensation of diacylamines **51** with monosubstituted hydrazines in the presence of a weak acid and proceeds via an amidrazone intermediate **52** (scheme-22). If N-acylthioamide **54** is used instead of diacylamines, the acylamidrazone formation occurs on the thione group (scheme-23).



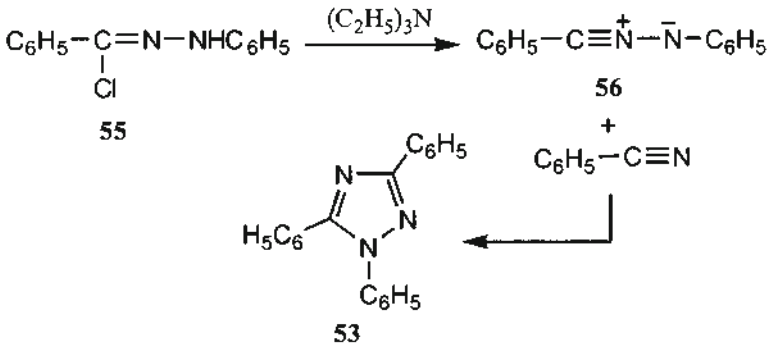
Scheme-22



Scheme-23

2.2.2.2 From Nitrilimines

1,3-Dipolar cycloadditions of nitrilimines **56**, obtained by dehydrohalogenation of C-halobenzylidenephenylhydrazones **55**, with nitriles leads to the formation of 1,2,4-triazoles (scheme-24).



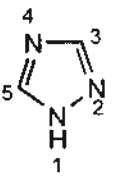
Scheme-24

2.2.3 Structure

1,2,4-Triazole has a planar structure with the following structural parameters[22]:

Bond lengths (Å)

N_1-N_2	=	1.359
N_2-C_3	=	1.323
C_3-N_4	=	1.359
N_4-C_5	=	1.324
N_1-C_5	=	1.331
N_1-H	=	1.030
C_3-H	=	0.930
C_5-H	=	0.930



Bond angles (°)

$C_5-N_1-N_2$	=	110.2
$N_1-N_2-C_3$	=	102.1
$N_2-C_3-N_4$	=	114.6
$C_3-N_4-C_5$	=	103.0
$N_4-C_5-N_1$	=	110.1

Fig. 8. Structural parameters of 1,2,4-triazole

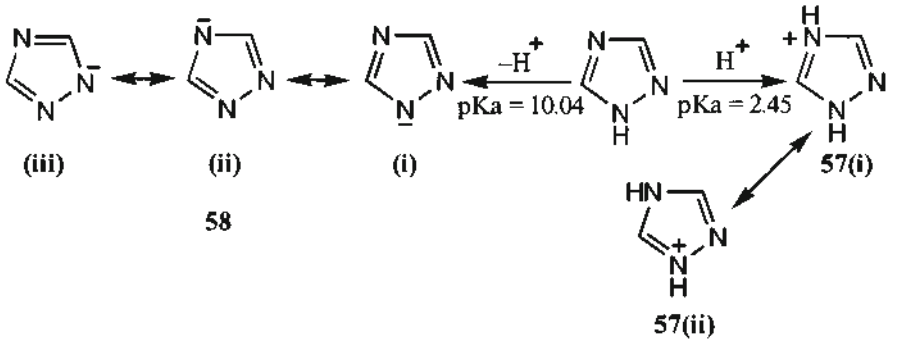
1,2,4,Triazole is aromatic and its resonance energy has been estimated to be 205.9 kJ/mol which is comparable with that of pyrazole. The calculated energy difference between two tautomers of 1,2,4-triazole also supports the preference of 1*H*-tautomer over the 4*H*-tautomer[23].

2.2.4 Reactions

2.2.4.1 Acidity–Basicity

1,2,4-Triazole is slightly less acidic (pKa = 10.04 for proton loss), but more basic

(pKa = 2.45 for proton addition) than 1,2,3-triazole. The basicity of 1,2,4-triazole is attributed to the mesomeric stabilization of the imidazolium type cation **57** formed on protonation. Moreover, the maximum separation of protonated nitrogens (N_1 and N_4 rather than N_1 and N_2) makes the cation most stable (scheme-25).



Scheme-25

2.2.4.2 Reactivity

1,2,4-Triazole is considered to be derived from benzene by replacement of –CH=CH– by –NH– and the replacement of two –CH= by two –N= atoms (Fig. 9) :

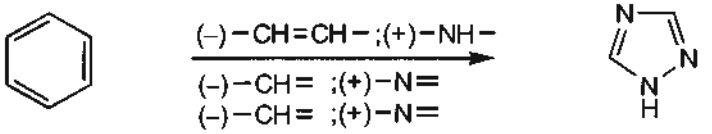


Fig. 9.

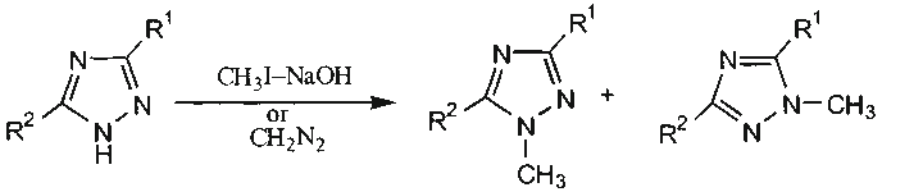
The replacement of –CH=CH– in benzene by -NH- enhances the electron density and hence makes 1,2,4-triazole susceptible towards electrophilic attack as compared to benzene. But the replacement of two –CH= by two –N= atoms causes the resulting 1,2,4-triazole to be nearly unreactive towards electrophiles. Therefore, 1,2,4-triazoles fail to undergo nitration, sulfonation and N-oxidation. However, 1,2,4-triazole anion undergoes alkylation and acylation very readily.

1,2,4-Triazoles undergo nucleophilic substitutions, if substituted with electron-withdrawing substituents. The reactivity of 1,2,4-triazole ring towards nucleophiles is enhanced in 1,2,4-triazolium cations and mesoionic 1,2,4-triazoles.

2.2.4.2.1 Reactions with Electrophiles

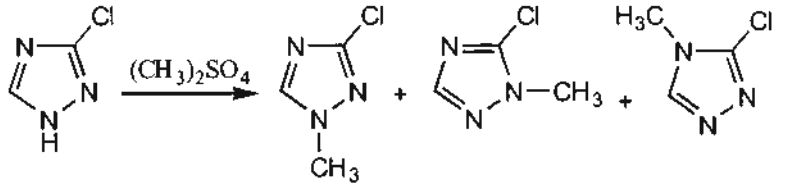
2.2.4.2.1.1 Electrophilic Attack at Nitrogen

Alkylation of N-unsubstituted 1,2,4-triazoles generally occurs at N-1 rather than at N-4. If there is choice of alkylation between N-1 and N-2 due to the nature of substituents at the positions-3 and -5, the alkylation occurs at both the positions (N-1 and N-2) with the formation of both N-alkylated products in a ratio depending on the alkylating agent (scheme-26). However, alkylation of 3-halo-1,2,4-triazoles with dimethyl sulfate in the absence of a base occurs at N-1, N-2 and N-4 (scheme-27)[24].



59 **60** **61**

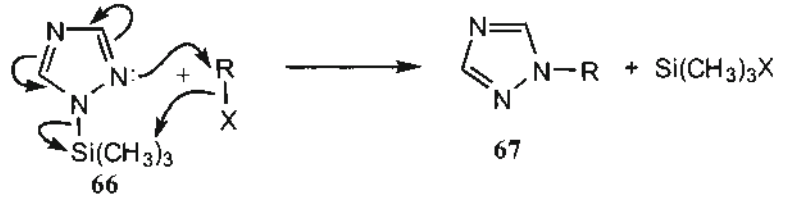
Scheme-26



62 **63** **64** **65**

Scheme-27

If trimethylsilyl group is present at N-1, the alkylation occurs selectively at N-2 with the removal of trimethylsilyl group (scheme-28)[25].

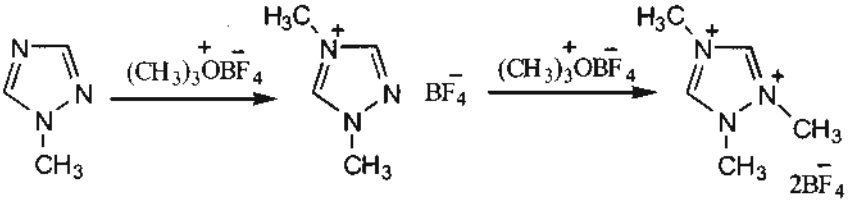


66 **67**

Scheme-28

2.2.4.2.1.2 Quaternization

1,2,4-Triazoles substituted with alkyl, aryl or acyl substituents on N-1 or N-4 undergo quaternization when treated with powerful quaternizing reagents, trialkyloxonium tetrafluoroborates. The quaternization occurs on the nitrogen atom furthest away from the substituted nitrogen (maximum distance between substituents on annular nitrogen atoms). Thus 1,2,4-triazole substituted on N-1 is quaternized on N-4 and *vice-versa*. 1-Substituted and 4-substituted 1,2,4-triazoles are, therefore, quaternized at N-4 and N-1 positions, respectively (scheme-29)[26]. Diquaternization is also possible with an excess of trimethyloxonium tetrafluoroborate.

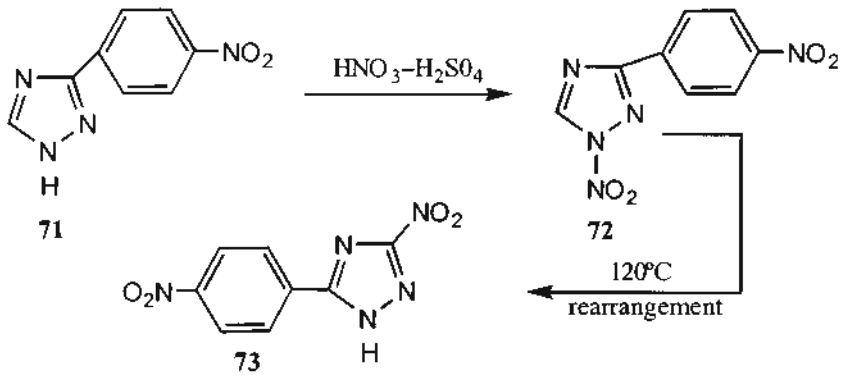


68 **69** **70**

Scheme-29

2.2.4.2.1.3 Electrophilic Attack at Carbon

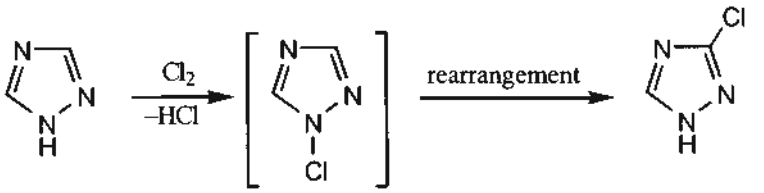
1,2,4-Triazole and its C-monoalkyl derivatives fail to undergo nitration. If 1,2,4-triazole is substituted with an aryl group on carbon, nitration occurs on the benzene ring. But in 3-*p*-nitrophenyl-1,2,4-triazole **71** in which benzene ring is deactivated by the nitro group, the nitration results in C-nitro derivative **73** via N-nitro derivative **72** (scheme-30)[27].



71 **72** **73**

Scheme-30

Halogenation of 1,2,4-triazole is considered to proceed via N-halo-1,2,4-triazole **74** with the formation of 3-halo-1,2,4-triazole **62** (scheme-31).

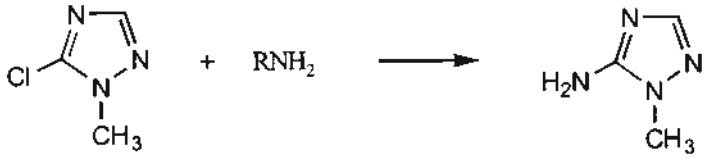


49 **74** **62**

Scheme-31

2.2.4.2.2 Reactions with Nucleophiles

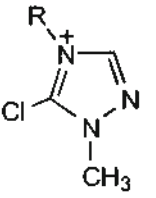
1,2,4-Triazoles substituted with halo-group at the position-3 or-5 undergo nucleophilic substitution reactions (scheme-32). The ease of nucleophilic



75 **76**

Scheme-32

displacement is increased with the quaternization of nitrogen or by the presence of an additional electron-withdrawing substituent on the other ring carbon atom.

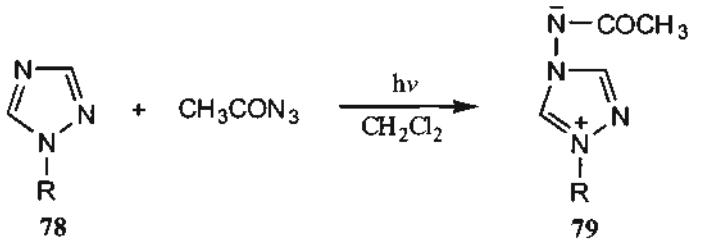


77

2.2.4.2.3 Reactions with Electron-Deficient Species

2.2.4.2.3.1 Reactions with Nitrenes

The reaction of 1-alkyl-1,2,4-triazoles **78** with nitrenes, generated by irradiation of azides, results in the formation of N-imines **79** (scheme-33)[28].

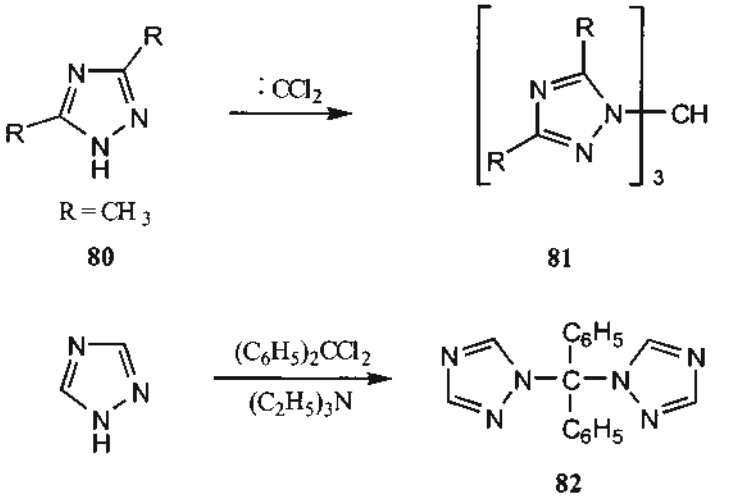


78 **79**

Scheme-33

2.2.4.2.3.2 Reactions with Carbenes

The reaction of 1,2,4-triazoles **80** with dichlorocarbene does not proceed with the ring expansion as in pyrazole and imidazole, but results in the formation of *bis*-or tris-1,2,4-triazoles (scheme-34)[29].



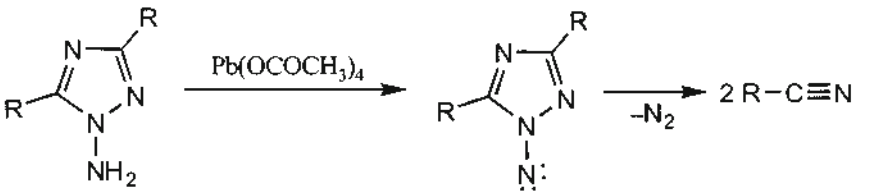
80 **81**

82

Scheme-34

2.2.4.2.4 Oxidation

1,2,4-Triazole ring is resistant to oxidation, but N-aminotriazoles **83** undergo oxidative fragmentation via a nitrene intermediate **84** when treated with lead tetraacetate. The formation of nitrene intermediate from N-aminotriazoles causes destabilization of the triazole ring scheme-35)[30].

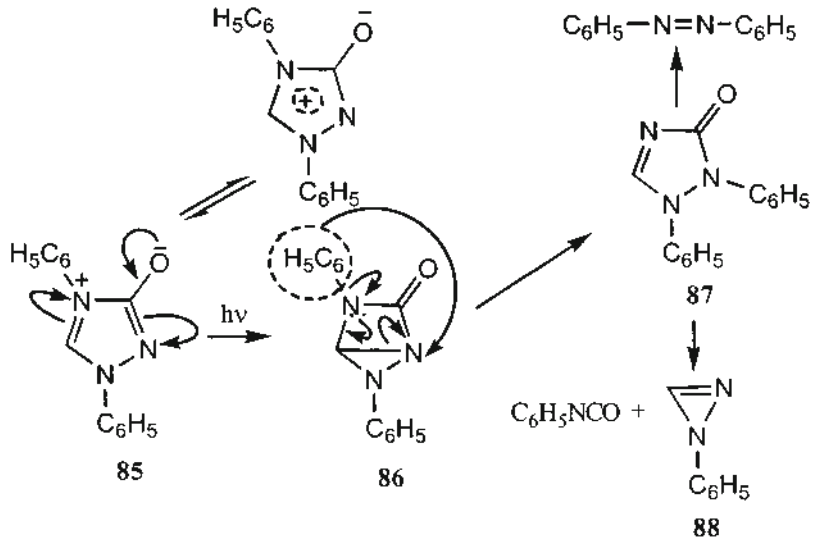


83 **84**

Scheme-35

2.2.4.2.5 Thermal and Photochemical Reactions

1,2,4-Triazole ring is thermally stable, however mesoionic 1,2,4-triazolium-3-olates **85** undergo photochemical fragmentations as shown in (scheme-36)[31].



85 **86** **87** **88**

Scheme-36

2.3 Tetrazoles[32-34]

2.3.1 General

Tetrazole is six π-electron heteroaromatic system and contains three pyridine-type and one pyrrole-type nitrogen atoms. Tertrazole exists in two tautomeric forms; 1,2,3,4-tetrazole (1*H*-form) **89** and 1,2,3,5-tetrazole (2*H*-form) **90**, with the predominance of 1,2,3,4-tetrazole (1*H*-form) (Fig. 10). The numbering in the tetrazole ring system is adopted as in 1*H*-form.

1,2,3,4-Tetrazole (1*H*-form) **89**

1,2,3,5-Tetrazole (2*H*-form) **90**

Fig. 10. Tautomeric forms of tetrazole

Tetrazole ring represents tetrazolic acid functional group (CN_4H) of carbazolic acids (RCN_4H). Tetrazoles are, therefore, considered nitrogen analogues of carboxylic acids (RCOOH) with comparable acidity. The tetrazole ring exhibits strong electron-withdrawing inductive effect (–I effect) which is more effective than its weak mesomeric effect (+M effect). The tetrazole ring, therefore, behaves as a deactivating group and the flow of the electrons is towards the ring if substituted with strong activating group[35].

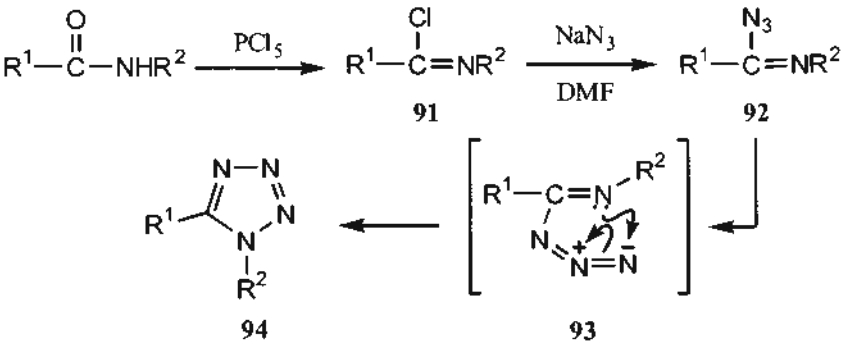
Tetrazoles exhibit potential biological activity because of being tetrazole ring isosteric with carboxylic acid group and metabolically more stable than the carboxylic acid group. The replacement of carboxylic acid group in the biologically active compounds by the tetrazole ring, therefore, produces possibly more effective tetrazole derivatives. Tetrazole analogues of amino acids, aminotetrazolic acids, with comparable biological activity have been synthesized and exist similarly in the zwitterionic form[32].

2.3.2 Synthesis

2.3.2.1 From Imidoyl Chlorides

The reaction of imidoyl chlorides **91** with azides (sodium azide or hydrazoic acid) in the presence of DMF produces imidoyl azides **92** which undergo 1,5-

heteroelectrocyclization to provide 1,5-disubstituted tetrazoles **94**. The cyclization of imidoyl azides occurs via an activated complex **93** with the movement of imino lone pair towards azido terminal nitrogen and at the same time the shifting of π-electrons of azido terminal π-bond to the central azido nitrogen as a lone pair (scheme-37)[32].



Scheme-37

The cyclization of the imidoyl azides depends on the following factors :

(i) **Stereoelectronic effect :** *cis*-Orientation of the imino lone-pair and azido group is required for the cyclization of imidoyl azide. The *trans*-orientation does not favour cyclization without prior inversion. If intramolecular hydrogen bonding stabilizes the imidoyl azide, the tetrazole formation occurs only if the treatment of reagent brings about the required geometrical isomerization of the imino group (scheme-38).

Scheme-38

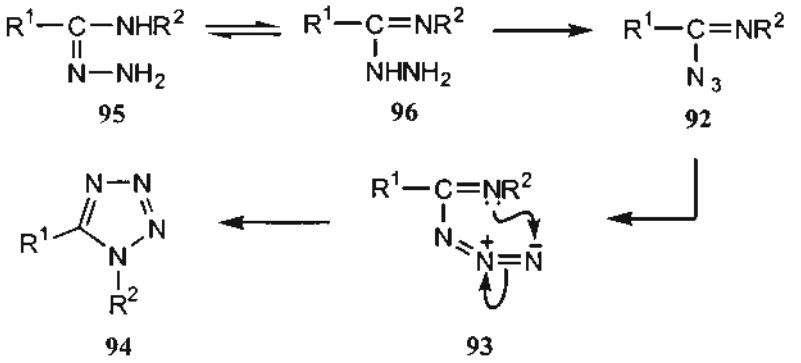
(ii) **Electronic effects :** The presence of electron-withdrawing substituents around the imino group does not favour the cyclization, but electron-releasing substituents facilitate cyclization.

(iii) Solvent effect : The acidic media inhibits cyclization due to the protonation of imidoyl azide, while basic media favours tetrazole formation because of the increased electron density on the imino moiety.

(iv) Temperature : Higher temperature restricts the cyclization of imidoyl azide, but favours instead tetrazole ring cleavage.

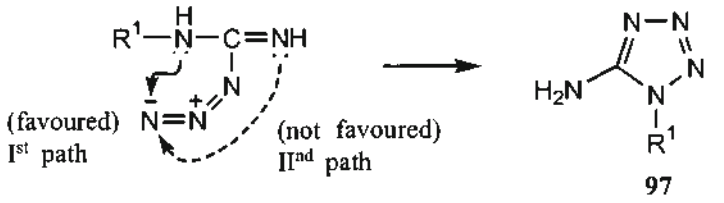
2.3.2.2 From Amidrazones

The reaction of amidrazones **95** via the hydrazine form **96** with nitrous acid (diazotization) results in imidoyl azides which undergo cyclization immediately with the formation of 1,5-disubstituted tetrazoles **94** (scheme-39).



Scheme-39

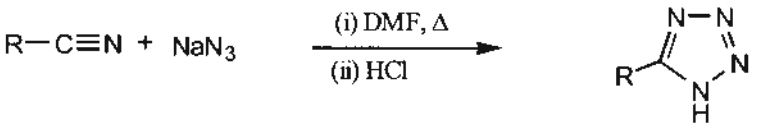
If R^1 substituent is an aminoalkyl and R^2 is a hydrogen atom in imidoyl azide **92**, the cyclization involving imino nitrogen of highest electron density is favoured (scheme-40).



Scheme-40

2.3.2.3 From Nitriles

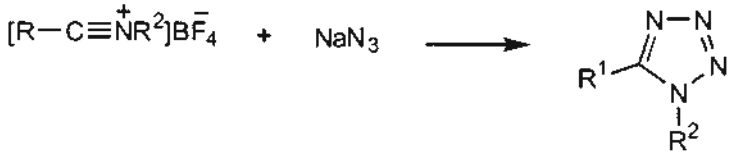
It is the most widely used method and involves reaction of nitriles with sodium azide in the presence of dipolar aprotic solvent (DMF) to provide 5-substituted tetrazoles (scheme-41). The reaction is sensitive to the nature of the solvent as in hydroxylic or alcoholic solvents the product is formed in poor yield, while optimum yield of the product is obtained with dipolar aprotic solvents.



Scheme-41

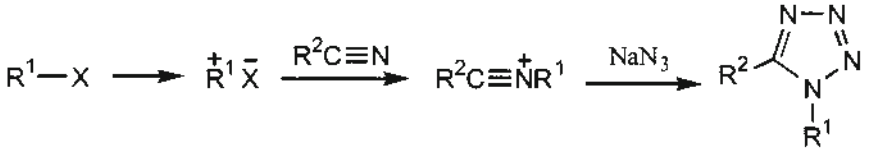
2.3.2.4 From Nitrilium Salts

The reaction of nitrilium salts with sodium azide also leads to the formation of 1,5-disubstituted tetrazoles (scheme-42)[37].



Scheme-42

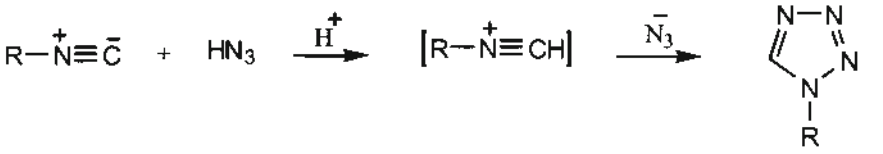
This reaction has been extended to the nitrilium ions generated in solution by the reaction of nitriles with carbocations in the presence of sodium azide (scheme-43)[38].



Scheme-43

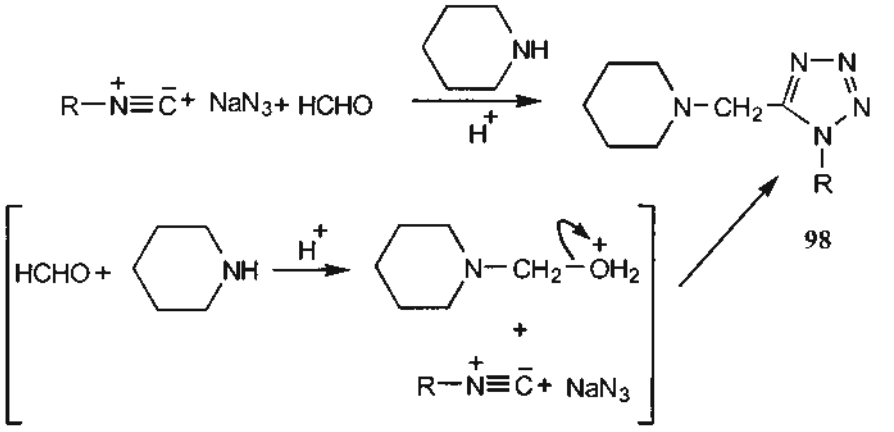
2.3.2.5 From Isonitriles

The acid catalyzed reaction of isonitriles with hydrazoic acid affords 1-substituted tetrazoles. The reaction proceeds to involve protonated isonitrile followed by the attack of azide ion (scheme-44).



Scheme-44

However, the reaction of isonitriles with azide in the presence of Mannich type reagent (formaldehyde + piperidine) results in the formation of 1,5-disubstituted tetrazoles **98**. The reaction is known as Ugi reaction and proceeds with the addition of Mannich type carbocation moiety at C-5 (scheme-45)[32].



Scheme-45

2.3.3 Structure

Tetrazole molecule is planar with the following structural parameters (Fig. 11) :

Bond lengths (Å)			**Bond angles (°)**		
N_1–N_2	=	1.347	C_5–N_1–N_2	=	105.3
N_2–N_3	=	1.283	N_1–N_2–N_3	=	106.9
N_3–N_4	=	1.345	N_2–N_3–N_4	=	112.2
N_4–C_5	=	1.290	N_3–N_4–C_5	=	104.2
N_1–C_5	=	1.351	N_4–C_5–N_1	=	111.4

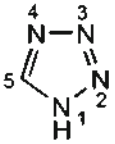


Fig. 11. Structural parameters of 1,2,3,4-tetrazole

Tetrazole is aromatic because it contains six delocalized π-electrons. Dipole moment of tetrazole (μ_D = 5.11D in dioxane) has also suggested to exist it predominantly in the 1*H*-form (calcd μ_D = 5.22D) rather than in the 2*H*-form (calcd μ_D=1.63D).

2.3.3.1 Hydrogen Bonding

N-Unsubstituted tetrazoles exhibit intermolecular hydrogen bonding because of the presence of three pyridine-type nitrogens (–N=) in the ring as proton acceptors and the availability of the active hydrogen at the position-1. The intermolecular hydrogen bonding in tetrazoles influence their melting and boiling points (Fig. 12).

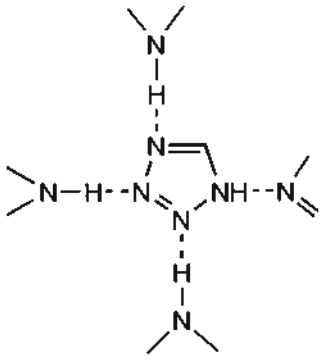


Fig. 12. Hydrogen bonding in N-unsubstituted tetrazoles

The replacement of hydrogen attached to the nitrogen at the position-1 by a small substituent causes large decrease in the melting point due to the absence of intermolecular hydrogen bonding (tetrazole; m.p. = 156°C and 1-methyltetrazole; m.p. = 39°C).

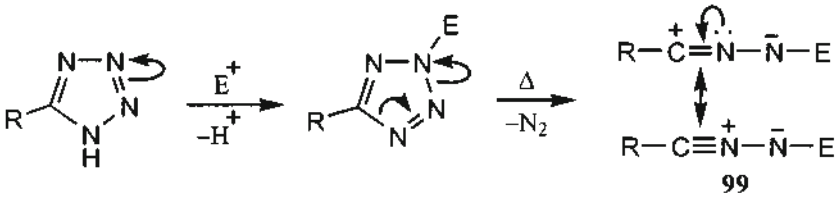
The introduction of substituents with N–H or O–H bonds at C–5 generally raises melting points due to extra intermolecular hydrogen bonding (5-amino-1,2,3,4-tetrazole; m.p. = 203°C)

2.3.4 Reactions

Tetrazole ring contains both types of nitrogen atoms; one pyrrole-type and three pyridine-type . The pyrrole-type nitrogen exerts electron-releasing effect and thus activating effect, while pyridine-type nitrogens exert electron-withdrawing effect and thus deactivating effect which makes the tetrazole ring π-electron deficient. The π-electron deficiency in tetrazole ring causes it to undergo reactions with nucleophiles readily. Electrophilic attack in the tetrazole ring generally occurs on the nitrogens and results in the ring fragmentation with the loss of nitrogen (dediazoniation).

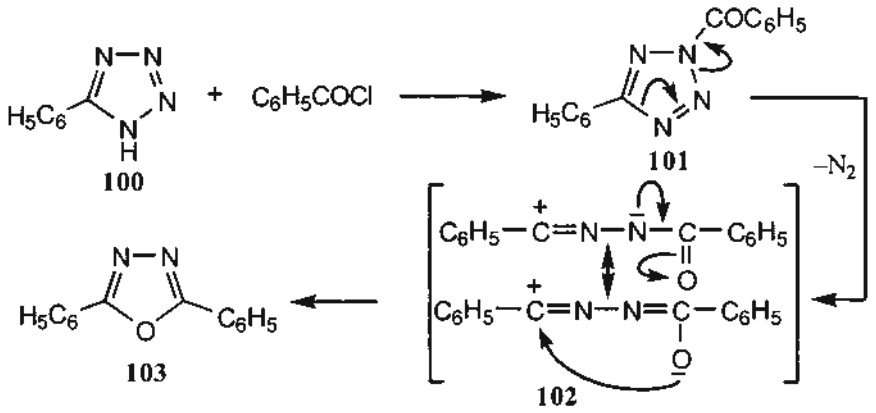
2.3.4.1 Reactions with Electrophiles

Tetrazole ring undergoes electrophilic substitutions with the attack of electrophiles preferentially at N-2 which facilitates fragmentation of the ring providing nitrilimines **99** with the loss of nitrogen (N_2) (scheme-46)[32]. This type of mechanism



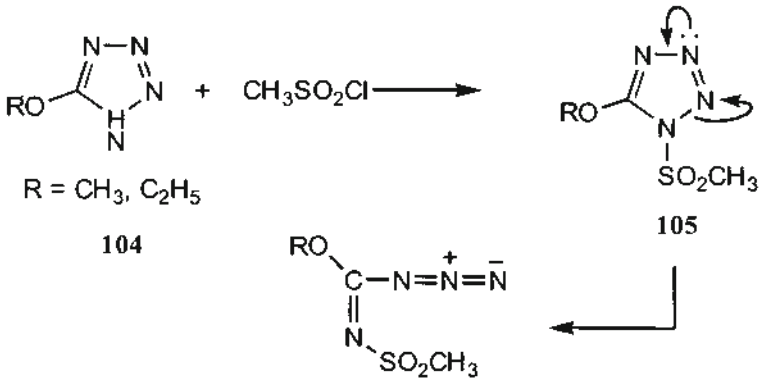
Scheme-46

can be evidenced by the reaction of 5-phenyltetrazole **100** with benzoyl chloride. The reaction proceeds with the electrophilic attack at N-2 to provide 2,5-diphenyl-1,3,4-oxadiazole **103** involving intramolecular cyclization of nitrilimine intermediate **102** (scheme-47)[39].



Scheme-47

If position-5 is substituted with strongly activating substituent (alkoxy or amino), the preferred site of electrophilic attack is changed and occurs at N-1. The reaction of 5-alkoxytetrazoles **104** with methanesulfonyl chloride involves electrophilic attack at N-1 and proceeds with the cleavage of the ring (N–N bond) to provide imidoyl azides **106** (scheme-48)[40].



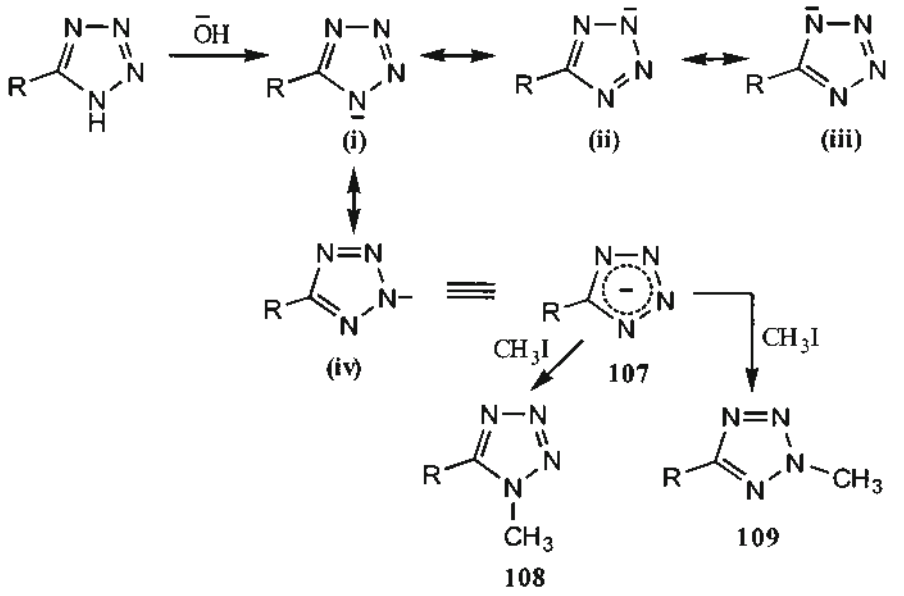
Scheme-48

2.3.4.2 Reactions with Nucleophiles

2.3.4.2.1 Nucleophilic Attack at Hydrogen

2.3.4.2.1.1 Acidity

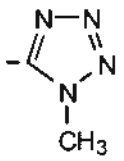
The tetrazole ring (–CN_4H, tetrazolic acid group) is considered as the nitrogen analogue of the carboxylic acid group (-COOH). In general, 5-substituted tetrazoles represent nitrogen analogues of the carboxylic acids and are called as the tetrazolic acids. But 5-phenyltetrazole is relatively more acidic than benzoic acid because of the enhanced resonance stabilization and greater solvation of the tetrazolate anion than the carboxylate anion. The nature of the substituents at C-5 influences the acidity of the tetrazole ring. The acidity of the tetrazole ring is increased with the substitution of electron-withdrawing substituents at C-5, while electron-releasing substituents cause decrease in acidity. 5-Substituted tetrazoles (tetrazolic acids) form stable tetrazolate anions when treated with bases. The tetrazolate anions exhibit ambident character and therefore can react at N-1 or N-2. The alkylation of the tetrazolate anion with alkyl halides produces 1-alkyl- or 2-alkyltetrazole depending on the reaction conditions and the nature of the substituent at C-5 (scheme-49).



Scheme-49

2.3.4.2.1.2 H ⇌ D Exchange

N-Substituted tetrazoles undergo base-induced H ⇌ D exchange readily at C-5 via a carbanionic type intermediate **110**. The rate of H ⇌ D exchange is 10^5 times faster in 1-methyltetrazole **110** than in 2-methyltetrazole **111** and attributed to the greater reactivity of the α-position as compared to β-position to the pyrrole-type nitrogen[32].



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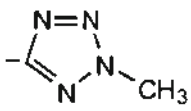
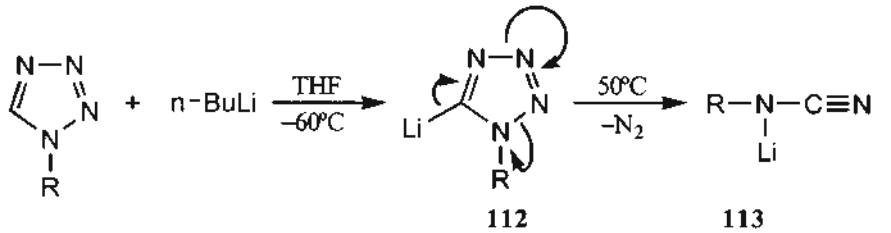


111

2.3.4.2.1.3 Metallation

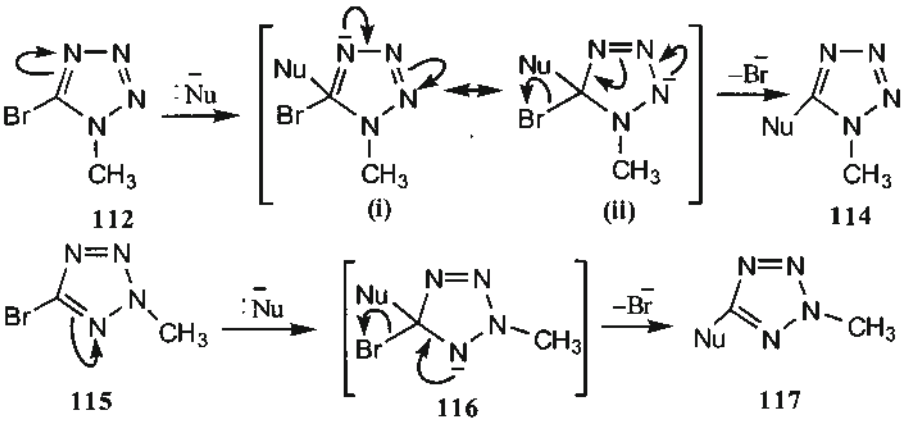
The reaction of substituted tetrazoles with n-butyllithium in the presence of THF at −60°C results in C-lithiation at the position-5 with the formation of 5-lithio derivatives **112** which undergo ring cleavage at higher temperature providing the corresponding lithium cyanamides **113** with the loss of nitrogen (scheme-50)[32].



Scheme-50

2.3.4.2.2 Nucleophilic Attack at C-5 (Nucleophilic Substitutions)

Because of the π-deficient deactivated nature of the tetrazole ring, 5-halotetrazoles undergo nucleophilic substitutions with the replacement of halogen atom from the position-5. The kinetic studies have shown 1,5-disubstituted tetrazoles (5-bromo-1-methyltetrazole **112**) to undergo nucleophilic substitution reactions more readily than 2,5-disubstituted tetrazoles (5-bromo-2-methyltetrazole **115**) probably because of greater stabilization of the intermediate **113** resulting from the 1,5-disubstituted tetrazoles as compared to that **116** resulting from 2,5-disubstituted tetrazoles (scheme-51)[32].



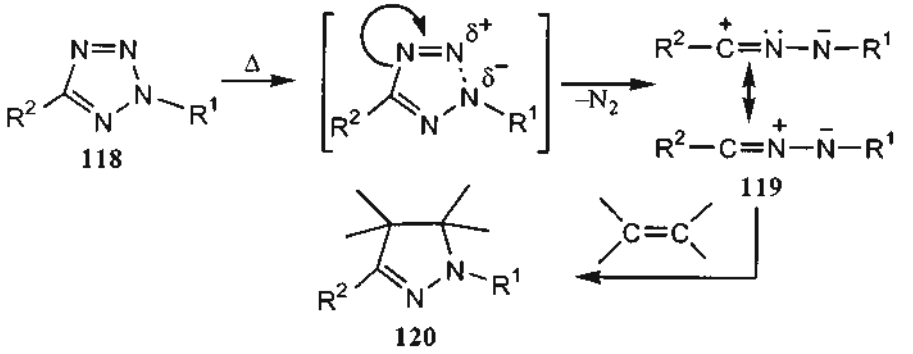
Scheme-51

2.3.4.3 Thermal and Photochemical Reactions

2.3.4.3.1 Reactions Involving Nitrilimine Intermediates

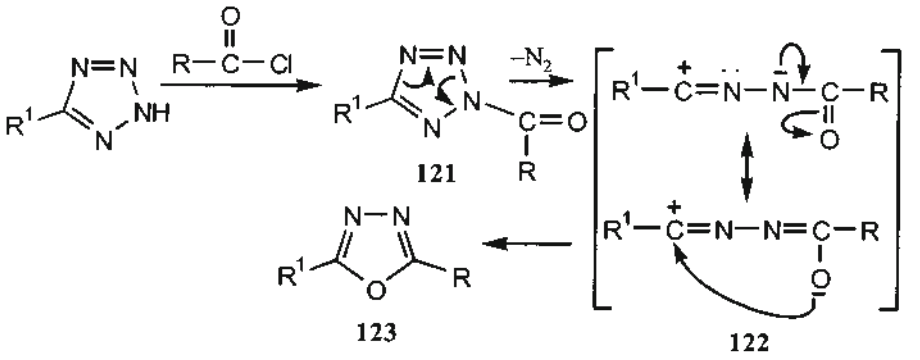
(i) 2,5-Disubstituted tetrazoles **118** undergo thermal fragmentation with the extrusion of nitrogen (N_2) and the formation of a reactive nitrilimine

intermediate **119** which can undergo 1,3-cycloaddition with alkenes, imines, alkynes and nitriles (scheme-52). If intramolecular cyclization is possible



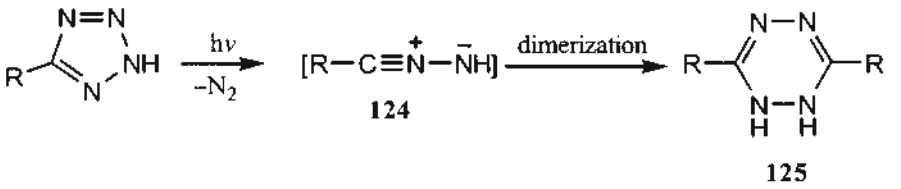
Scheme-52

with the involvement of substituent in nitrilimine intermediate **122**, five-membered heterocycles **123** with three heteroatoms (oxadiazoles, thiadiazoles and triazoles) are obtained involving 1,5-heteroelectrocyclization and the reaction is referred to as the Huisgen reaction (scheme-53)[41,42].



Scheme-53

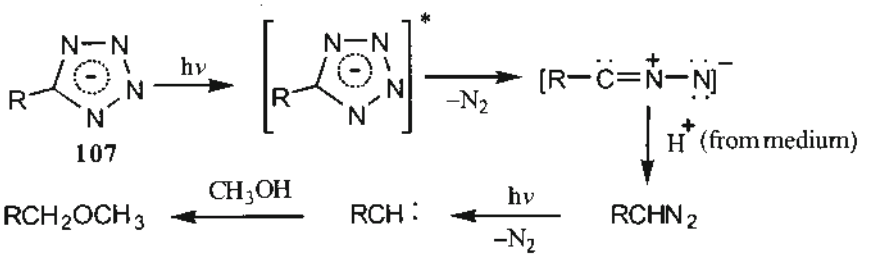
(ii) Photochemical fragmentation of 5-substituted tetrazoles in THF also proceeds to involve a nitrilimine intermediate **124** with the extrusion of nitrogen (N_2) and leads to the formation of tetrazine derivative **125** involving dimerization of the nitrilimine intermediate (scheme-54).



Scheme-54

2.3.4.3.2 Reactions Involving Carbene Intermediates

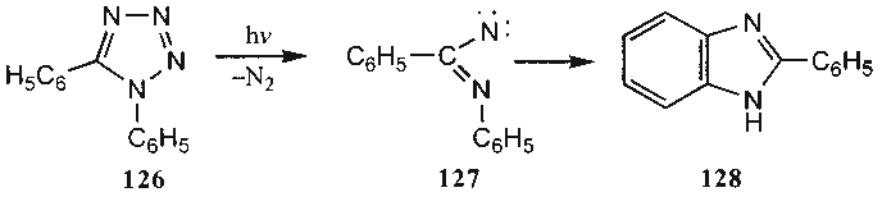
Photochemical fragmentation of 5-substituted tetrazolate anions **107** involves photochemical excitation of the tetrazolate anion with the extrusion of two molecules of nitrogen and generation of carbene intermediate which undergoes insertion reactions (scheme-55).



Scheme-55

2.3.4.3.3 Reactions involving Nitrene Intermediates

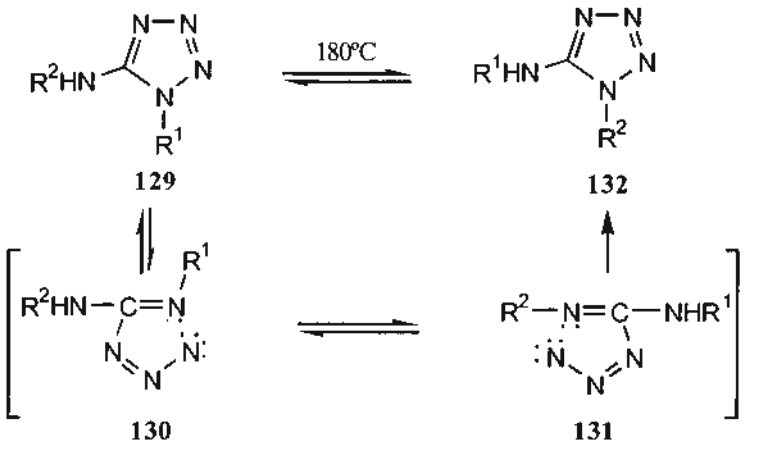
1,5-Disubstituted tetrazoles **126** are photolyzed with the loss of nitrogen molecule and the reaction proceeds to involve an iminonitrene intermediate **127** (scheme-56).



Scheme-56

2.3.4.4 Rearrangements

Substituted 5-aminotetrazoles undergo thermal rearrangements with the existance of both the forms **129** and **132** in equilibrium. The rearrangement proceeds via a reactive imidoylazide intermediate **130** involving rotation of the C_5–N_4 bond and an amino–imino proton tautomeric change (scheme-57). The 6π-heteroelectrocyclization occurs preferentially on the imino nitrogen with higher electron density.



Scheme-57

3 OXADIAZOLES

Oxadiazoles are considered to be derived from furan by the replacement of two methine (–CH=) groups by two pyridine-type nitrogens (–N=). There are four isomeric types of oxadiazoles depending on the positions of the nitrogen atoms in the oxadiazole ring and are numbered as shown in (Fig. 13).

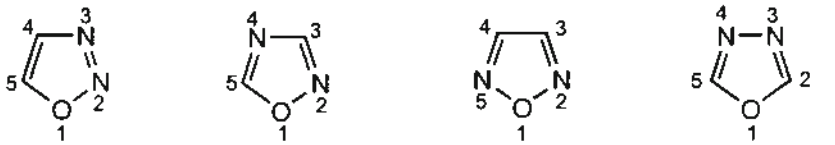


Fig. 13. Isomeric oxadiazoles

The replacement of two –CH= groups in furan by two pyridine-type nitrogens (–N=) reduces aromaticity of the resulting oxadiazole ring to such an extent that the oxadiazole ring exhibits character of the conjugated diene. The electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atoms because of relatively low electron density on the carbon atoms due to electron-withdrawal effect of the pyridine-type nitrogen atoms. However, the attack of electrophiles occurs at the nitrogens, if oxadiazole ring is substituted with an electron-releasing group. Oxadiazole ring is generally resistant to the nucleophilic attack. Halo-substituted oxadiazoles, however, undergo nucleophilic substitutions with the replacement of halogen atom by nucleophiles. Oxadiazoles undergo nucleophilic substitutions similarly as occurring at an aliphatic sp^2-carbon atom, but not as aromatic nucleophilic substitutions.

3.1 1,2,3-Oxadiazoles

1,2,3-Oxadiazoles are not known as these exist entirely in the diazoketone tautomeric form **134** (Fig. 14). 1,2,3-Oxadiazoles occur only in the form of mesoionic

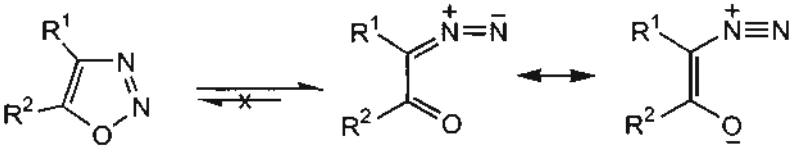


Fig. 14. Diazoketone form of 1,2,3-oxadiazole

heterocycles known as sydnones. Sydnones are represented by mesoionic form and are considered to be contributed by resonating structures (Fig. 15).

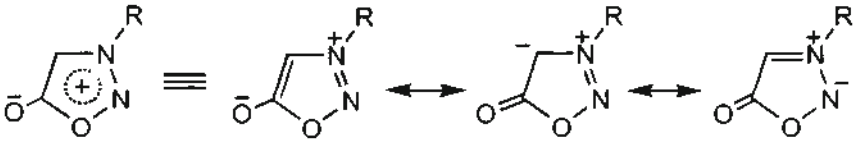
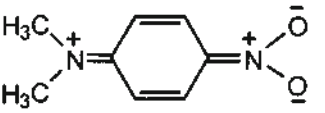


Fig. 15. Resonating structures of sydnones

The higher dipole moments of the sydnones, generally greater than 6D and comparable with that of 4-Nitro-N,N-dimethylaniline **136** (6.87D), also support strongly polar character of the sydnones.

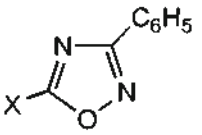


136

3.2 1,2,4-Oxadiazoles[43,44]

3.2.1 General

1,2,4-Oxadiazoles find their uses as anaesthetics, analgesics, antispasmodics, antitussives, anthelmintics and antiinflammatory. Some of the 1,2,4-oxadiazoles with their activity are as follows :

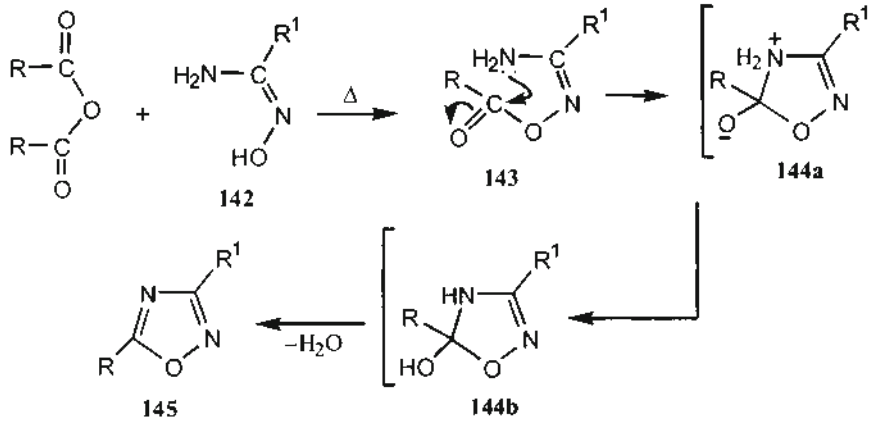


X= $-(CH_2)_2N(C_2H_5)_2$	Oxalmine, Bredon, Perebron	anaesthetic, antiinflammatory
X= $-NH(CH_2)_2N(C_2H_5)_2$	Irrigor	anaesthetic
X= $-CH_2N(C_2H_5)_2$		anaesthetic, analgesic
X= $-(CH_2)_3NC_5H_{10}$		anaesthetic, antiinflammatory
X= $-(CH_2)_2N(C_4H_9)_2$		anaesthetic, antispasmodic, antiinflammatory

3.2.2 Synthesis

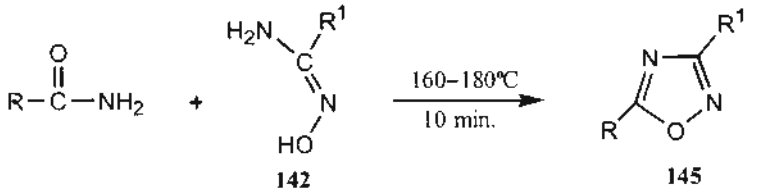
3.2.2.1 Cyclization Reactions (From Amidoximes)

The reaction of amidoximes **142** with an anhydride results in dehydrative cyclization providing 1,2,4-oxadiazoles **145** (scheme-58)[45]. The reaction proceeds to involve O-acylation in the first step and followed by dehydrative cyclization in



Scheme-58

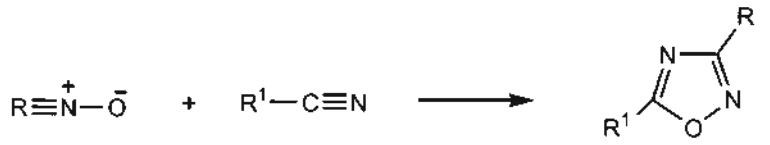
the second step to afford the corresponding 1,2,4-oxadiazoles in which C-5 carbon is furnished by an anhydride. However, acid chlorides, ketones, esters and amides can also be used to furnish C-5 carbon in 1,2,4-oxadiazoles (scheme-59)[46].



Scheme-59

3.2.2.2 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloaddition of nitrile oxides (4π-electron–three atom system) to nitriles (2π-electron system–dipolarophile) leads to the formation of 1,2,4-oxadiazoles **146** (scheme-60).



146

Scheme-60

3.2.3 Structure

1,2,4-Oxadiazole ring is planar with high degree of diene character (little aromatic) as both C–N bond lengths reflect conjugated double bond character. 1,2,4-Oxadiazole ring system is therefore conisdered to be a conjugated system rather than an aromatic system. The structural parameters in 1,2,4-oxadiazole are summarized as (Fig. 16) :

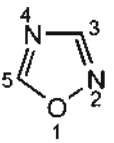
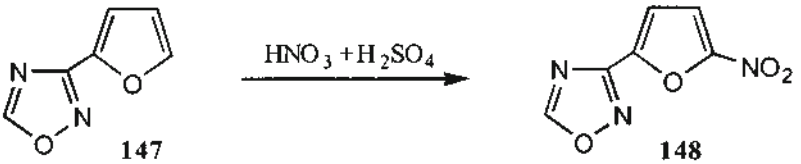
Bond lengths (Å)				**Bond angles (°)**		
O_1–N_2	=	1.418		O–N_2–C_3	=	103.2
N_2–C_3	=	1.303		N_2–C_3–N_4	=	114.2
C_3–N_4	=	1.380		C_3–N_4–C_5	=	102.8
N_4–C_5	=	1.287		N_4–C_5–O	=	113.8
O_1–C_5	=	1.332		N_2–O–C_5	=	106.1

Fig. 16. Structural parameters in 1,2,4-oxadiazole

3.2.4 Reactions

3.2.4.1 Electrophilic Substitution Reactions

1,2,4-Oxadiazole ring is less susceptible towards electrophilic attack. If 1,2,4-oxadiazole ring is substituted with an aromatic ring at C-3 or C-5, the oxadiazole ring behaves as an electron-withdrawing group and directs the incoming electrophile to the *meta*-position (scheme-61).

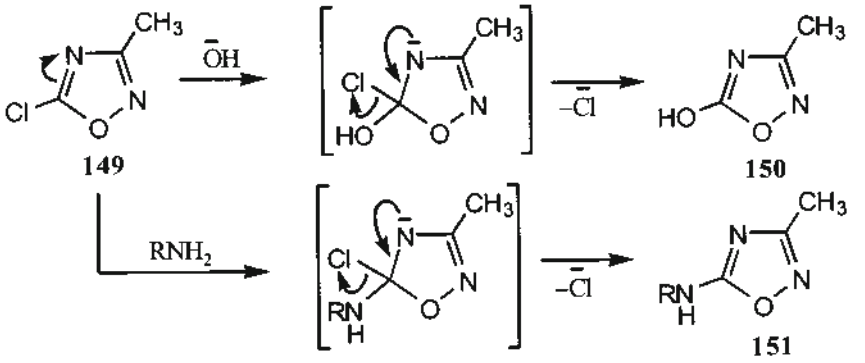


147 **148**

Scheme-61

3.2.4.2 Nucleophilic Substitution Reactions

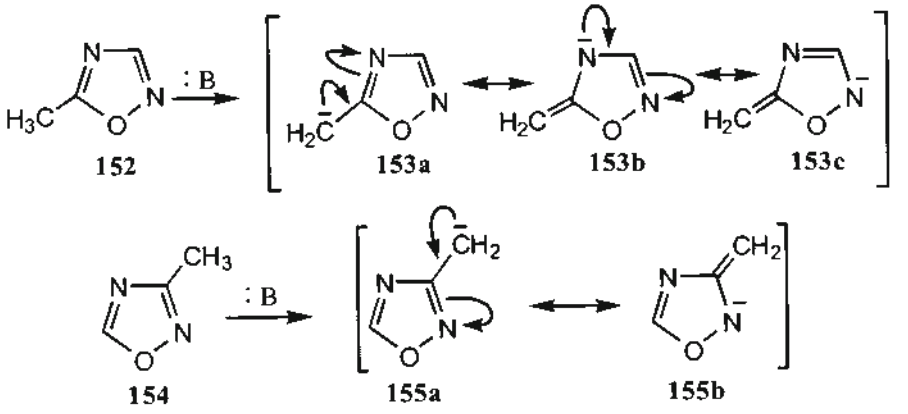
1,2,4-Oxadiazoles undergo nucleophilic substitutions with the replacement of a halogen atom from C-5 involving nucleophilic addition–elimination mechanism (scheme-62).



Scheme-62

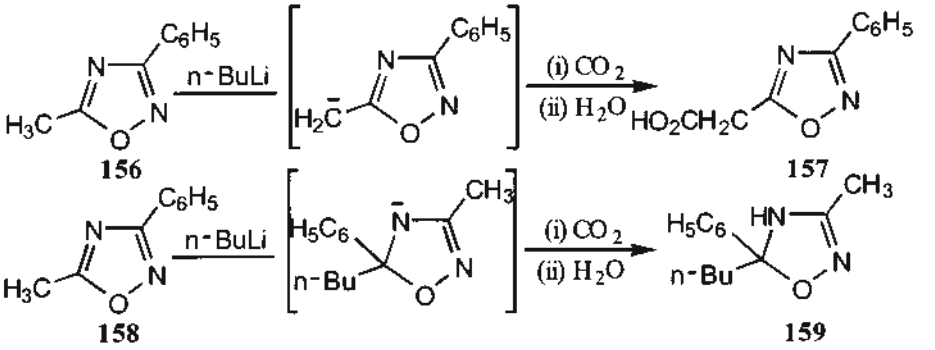
3.2.4.3 Reactions of Substituents

The methyl group at C-5 of the 1,2,4-oxadiazole ring is more reactive than that at C-3. The greater reactivity of the methyl group at C-5 is attributed to the greater stabilization of anion **153** resulting from 1,2,4-oxadiazole **152** with methyl group at C-5 than **155** obtained from 3-methyl-1,2,4-oxadiazole **154** (scheme-63).



Scheme-63

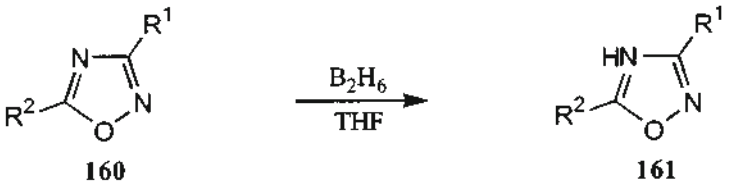
The greater reactivity of the methyl group at C-5 can be explained by the reactions depicted in (scheme-64).



Scheme-64

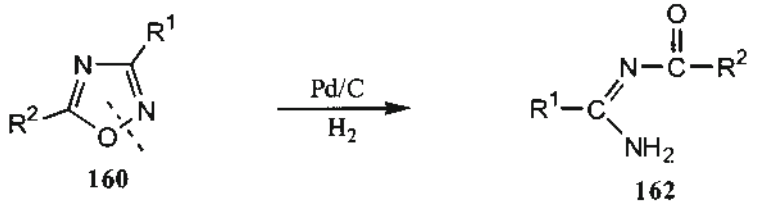
3.2.4.4 Reduction

(i) The reduction of 1,2,4-oxadiazole with diborane in the presence of tetrahydrofuran leads to the formation of Δ^2-oxadiazoline **161** (scheme-65)[47].



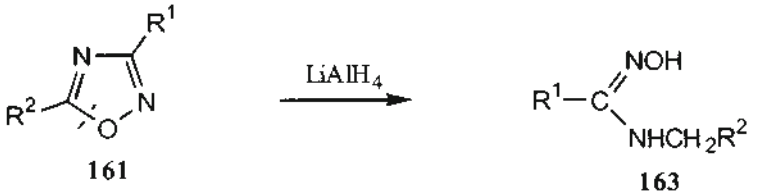
Scheme-65

(ii) Neutral catalytic reduction of 1,2,4-oxadiazole with platinum oxide, Raney nickel or palladium–carbon occurs with the cleavage of N–O bond (scheme-66)[43].



Scheme-66

(iii) Reduction with lithium aluminium hydride, in contrast, proceeds with the cleavage of C–O bond to provide amidoximes **163** (scheme-67)[43].

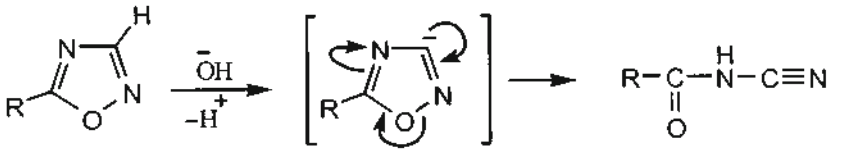


161 **163**

Scheme-67

3.2.4.5 Ring Cleavage via C-Deprotonation

1,2,4-Oxadiazole ring is readily cleaved via C-deprotonation in alkaline solution with the formation of corresponding cyanamide **164** (scheme-68).

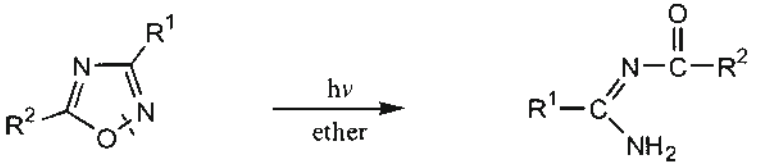


164

Scheme-68

3.2.4.6 Photochemical Reactions

Photolysis of 1,2,4-oxadiazoles involves cleavage of N–O bond with the formation of **165** in which extra hydrogens are taken from the solvent (scheme-69).

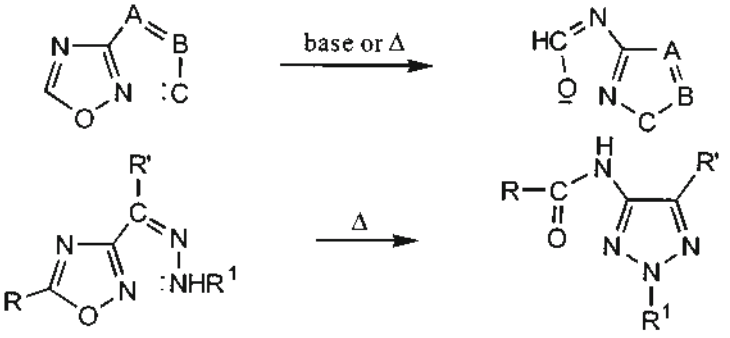


165

Scheme-69

3.2.4.7 Rearrangements

1,2,4-Oxadiazoles **166** containing a suitable side chain at an α-position to the pyridine-type nitrogen undergo base catalyzed or thermal rearrangement which is generalized by (scheme-70).



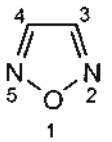
166 **167**

Scheme-70

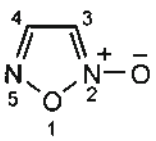
3.3 1,2,5-Oxadiazoles[48-50]

3.3.1 General

1,2,5-Oxadiazole **168** and its N-oxide, 1,2,5-oxadiazole 2-oxide **169**, are known by their trivial names; furazan and furoxan, respectively and are numbered as follows :

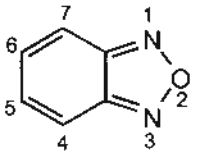


168

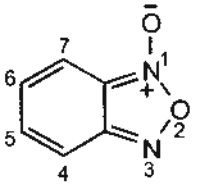


169

The fusion of a benzene ring with furazan **168** and furoxan **169** at the 3,4-positions leads to benzofurazan **170** and benzofuroxan **171**, respectively. Benzofurazan is also named as 3,4-benzo-1,2,5-oxadiazole or 2,1,3-benzoxadiazole and benzofuroxan is named as 3,4-benzo-1,2,5-oxadiazole 2-oxide or 2,1,3-benzoxadiazole 1-oxide.



170



171

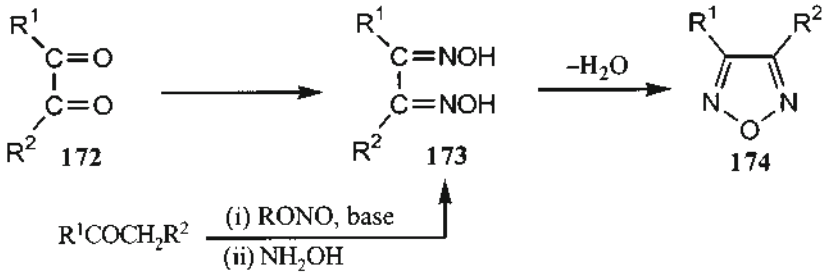
1,2,5-Oxadiazole ring system is incorporated into many compounds with wide spectrum of biological activity. 1,2,5-Oxadiazoles have found their uses as plant growth regulators, pesticides, herbicides, rhodenticides, anticancer agents, anti-convulsants and muscle relaxants. The presence of nitro- and N-oxide groups in 1,2,5-oxadiazoles makes them effective against cancer.

3.3.2 Synthesis

3.3.2.1 Furazans

3.3.2.1.1 Dehydration of α-Dioximes

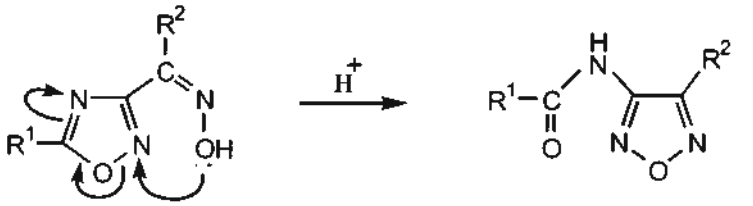
This is the most widely used method and involves dehydration of suitably substituted α-dioximes **173** which are obtained by oximation of 1,2-diones **172** or nitrosation–oximation of ketones (scheme-71). However, the reaction conditions vary with the nature of the substituents.



Scheme-71

3.3.2.1.2 Ring Transformations

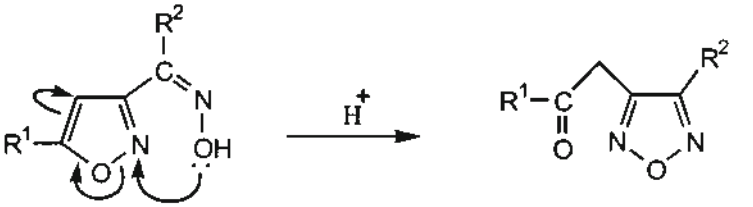
1,2,4-Oxadiazoles **175** containing an oxime side chain at the position-3 undergo a special type of heterocyclic rearrangement involving side chain when heated in hydrochloric acid and provide 3-acylamino-1,2,5-oxadiazoles **176** (scheme-72)[51].



175 **176**

Scheme-72

Isoxazoles **177** also undergo this type of rearrangement providing 1,2,5-oxadiazoles **178** (scheme-73).



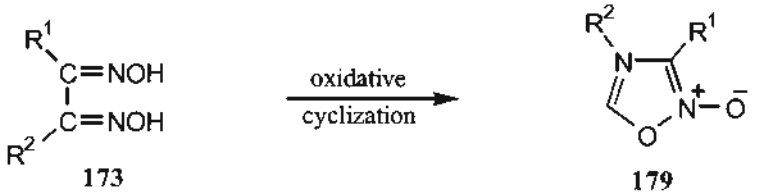
177 **178**

Scheme-73

3.3.2.2 Furoxans

3.3.2.2.1 Oxidation of α-Dioximes

Oxidative cyclization of α-dioximes with oxidizing agents such as potassium ferricyanide, lead tetraacetate, N-iodosuccinimide, alkaline hypohalites and cerium (IV) ion leads to the formation of furoxans **179** (scheme-74). Electrochemical oxidation of α-dioximes is also possible[52].

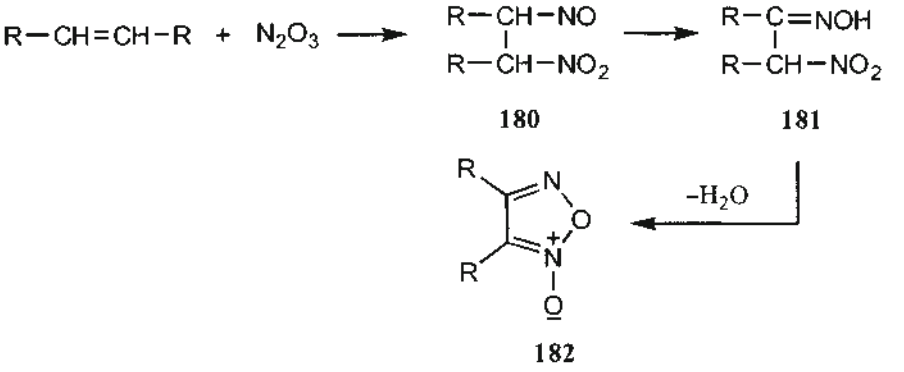


173 **179**

Scheme-74

3.3.2.2.2 Dehydration of α-Nitro Ketone Oximes

Dehydrative cyclization of α-nitro ketone oximes **181** with sulfuric acid or phosphoric acid at 110–120°C results in furoxans **182**. α-Nitro ketone oximes are obtained by thermal isomerization of nitro-nitroso adducts **180** which in turn are prepared by treatment of alkenes with dinitrogen trioxide (scheme-75). However, sulfur trioxide and chlorosulfonic acid in DMF are used as effective dehydrating agents for the preparation of furoxans which are thermally sensitive to the ring cleavage.



Scheme-75

3.3.3 Structure

1,2,5-Oxadiazole ring is planar and symmetrical with following structural parameters (Fig. 17) :

Bond lengths (Å)			**Bond angles (°)**		
$O–N_2$	=	1.38	$N_2–O–N_5$	=	110.4
$N_2–C_3$	=	1.30	$O–N_2–C_3$	=	105.8
$C_3–C_4$	=	1.42	$N_2–C_3–C_4$	=	109.0
$C_4–N_5$	=	1.30	$C_3–C_4–N_5$	=	109.0
$O–N_5$	=	1.38	$C_4–N_5–O$	=	105.0

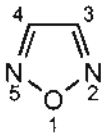


Fig. 17. Structural parameters in 1,2,5-oxadiazole

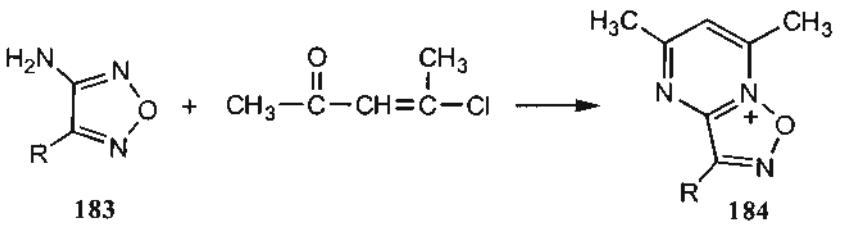
The C=N bond length (C_3–N_2 and C_4–N_5) (1.30Å) is intermediate between that of formaldoxime (1.27Å) and pyridine (1.34Å) and suggests high degree of diene character in 1,2,5-oxadiazole. However, comparison with cyclopentadiene indicates small degree of aromatic character in 1,2,5-oxadiazole ring. The C_3–C_4 bond acquires double bond character. The bond lengths, therefore, reflect π-electron delocalization with small degree of aromatic character in 1,2,5-oxadiazole.

In 1,2,5-oxadiazole 2-oxide (furoxan), the exocyclic oxygen at N-2 causes distortion in the ring from planarity. However, C_3–C_4 bond acquires double bond character and suggests π-electron delocalization as in 1,2,5-oxadiazole. The O_1–N_2 bond (1.42–1.46Å) is longer than N_2–O (exocyclic) bond (1.18–1.25Å).

3.3.4 Reactions

3.3.4.1 Reactions with Electrophiles

1,2,5-Oxadiazoles exhibit very low reactivity towards electrophiles as benzo-fused 1,2,5-oxadiazoles undergo electrophilic substitutions in the benzene ring and 1,2,5-oxadiazole ring remains intact. The quaternization of the ring nitrogen is also difficult, but occurs only if the ring is substituted with an electron-releasing substituent. The reaction of amino-1,2,5-oxadiazoles **183** with 2-chloro-1-acylalkenes in the presence of perchloric acid results in quaternization of the ring nitrogen with the formation of oxadiazolopyrimidinium salts **184** (scheme-76)[53].

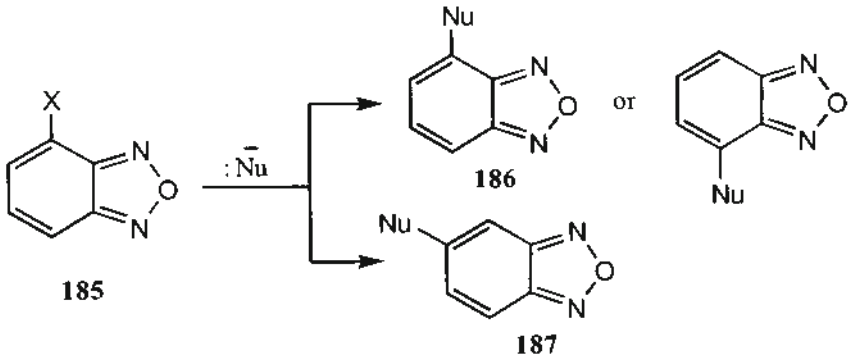


183 **184**

Scheme-76

3.3.4.2 Reactions with Nucleophiles

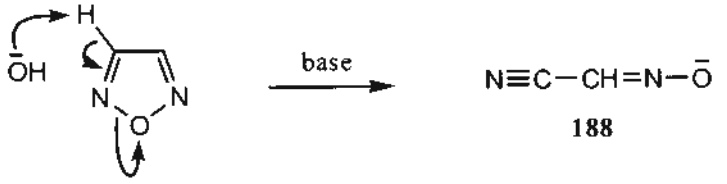
In spite of the low π-electron density on the carbon atoms, 1,2,5-oxadiazole ring is generally resistant to nucleophilic attack. However, benzo-fused 1,2,5-oxadiazoles **185** substituted with halogen atom undergo nucleophilic substitutions with the replacement of a halogen atom by nucleophiles involving 'normal' and '*cine*'-substitutions (scheme-77). The relative amounts of the normal **186** and cine **187** products depend on the polarity of the solvent and on steric effects. The presence of electron-withdrawing substituent facilitates nucleophilic attack.



Scheme-77

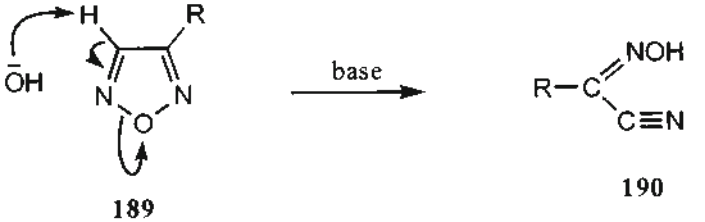
3.3.4.3 Ring Cleavage via C-Deprotonation

The hydrogen atoms in 1,2,5-oxadiazole can be abstracted as protons by a strong base with the cleavage of the ring providing α-oximinoacetonitrile **188** (scheme-78).



Scheme-78

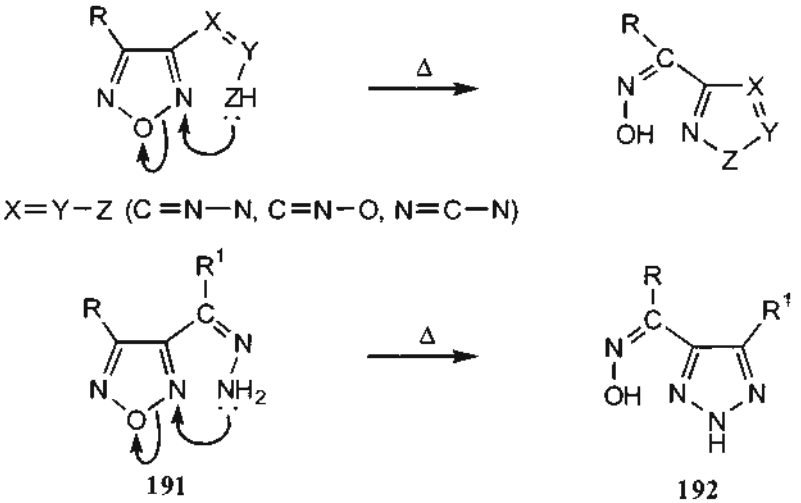
Similarly, monosubstituted 1,2,5-oxadiazoles **189**, irrespective of the nature of the substituent, undergo ring opening reactions in the presence of a strong base with the formation of oximes **190** of α-ketonitriles. The reaction proceeds to involve C-deprotonation of 1,2,5-oxadiazole ring (scheme-79).



Scheme-79

3.3.4.4 Rearrangements

1,2,5-Oxadiazoles **191** substituted at position-3 with side chains such as hydrazone, oxime and amidine are thermally transformed into new heterocyclic systems containing hydroximino substituent. The transformation is generalized as depicted in (scheme-80)[51].

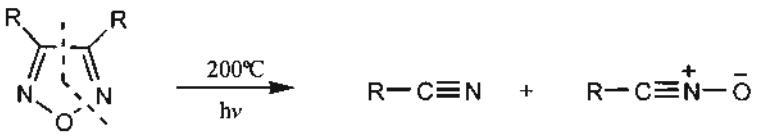


191 **192**

Scheme-80

3.3.4.5 Thermal and Photochemical Reactions

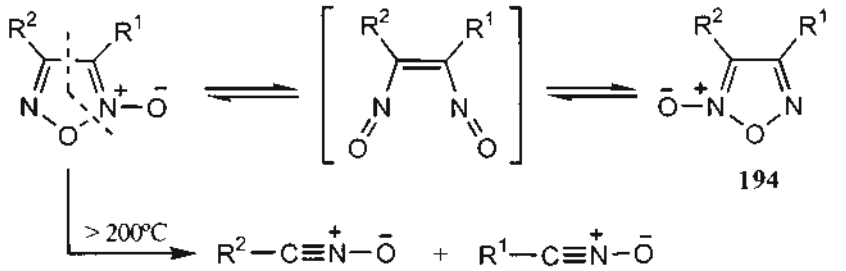
1,2,5-Oxadiazoles undergo thermal and photochemical reactions with the cleavage of O_1–N_2 and C_3–C_4 bonds providing nitriles and nitrile oxides (scheme-81).



Scheme-81

1,2,5-Oxadiazole 2-oxides are thermally or photochemically isomerized into 1,2,5-oxadiazole 5-oxides **194** via a dinitroso intermediate **193**. But at high temperature (>200°C), furoxan (1,2,5-oxadiazole N-oxide) ring is cleaved at the O–N_2 and C_3–C_4

bonds to provide two nitrile oxide fragments (scheme-82). If furoxan ring is substituted with bulky groups or the ring is strained, the process of the ring cleavage becomes easier and requires low temperature (scheme-82).

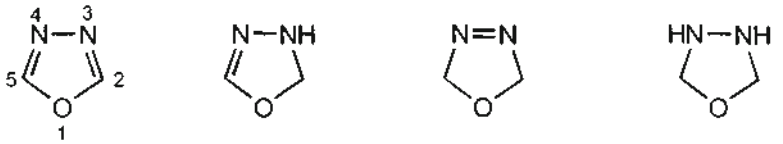


Scheme-82

3.4 1,3,4-Oxadiazoles[54–56]

3.4.1 General

1,3,4-Oxadiazole **195** is a thermally stable aromatic heterocycle and exists in two partially reduced forms; 2,3-dihydro-1,3,4-oxadiazole (Δ^2-1,3,4-oxadiazoline) **196** and 2,5-dihydro-1,3,4-oxadiazole (Δ^3-1,3,4-oxadiazoline) **197** depending on the position of the double bond. The completely reduced from of 1,3,4-oxadiazole is designated as 2,3,4,5-tetrahydro-1,3,4-oxadiazole (1,3,4-oxadiazolidine) **198**.



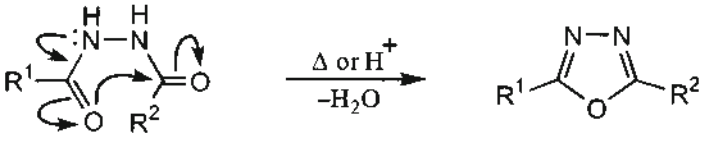
195 **196** **197** **198**

1,3,4-Oxadiazoles find their medicinal applications and are used as analgesics, antipyretics, diuretics, antiinflammatory, hypnotics and sedatives. 1,3,4-Oxadiazoles have also been used as herbicides, fungicides, bactericides and insecticides. 1,3,4-Oxadiazole ring is incorporated to synthesize heat resistant polymers because of thermal stability of 1,3,4-oxadiazole ring. 1,3,4-Oxadiazoles are also used as dyestuffs, fluorescent whiteners and scintillators.

3.4.2 Synthesis

3.4.2.1 From Diacylhydrazines

Thermal or acid catalyzed intramolecular cyclization of diacylhydrazines **199** results in 2,5-disubstituted 1,3,4-oxadiazoles **200** (scheme-83). The reaction is considered to involve nucleophilic attack of carbonyl oxygen of an amide group at the carbon of the second amide group with the formation of C_2–O bond. It can also be used to synthesize monosubstituted 1,3,4-oxadiazoles.

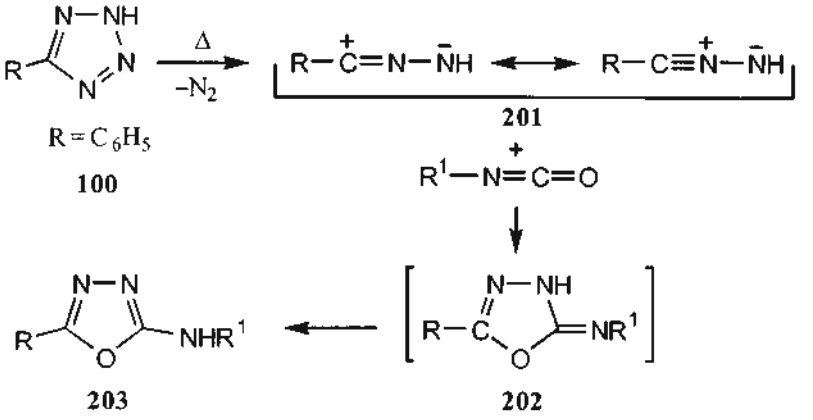


199 **200**

Scheme-83

4.3.2.2 Ring Transformation

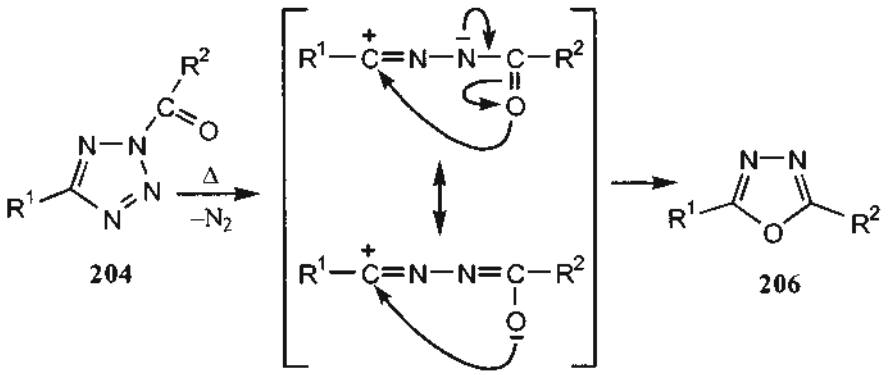
Thermal fragmentation of 5-substituted tetrazoles **100** with the extrusion of nitrogen results in the generation of nitrilimine intermediate **201** which undergoes 1,3-dipolar cycloaddition with isocyanates to provide 1,3,4-oxadiazoles **203** (scheme-84).



100 **201** **203** **202**

Scheme-84

However, 2-acyltetrazoles **204** on thermal fragmentation extrude nitrogen with the formation of nitrilimines **205** which undergo heteroelectrocyclization directly with the formation of 2,5-disubstituted 1,3,4-oxadiazoles **206** (scheme-85). The reaction is widely referred to as the Huisgen reaction.



204 **205** **206**

Scheme-85

3.4.3 Structure

1,3,4-Oxadiazole ring is symmetrical and planar with the following structural parameters (Fig. 18) :

Bond lengths (Å)			**Bond angles (°)**		
N_3–N_4	=	1.399	C_2–O–C_5	=	102.0
C_2–N_3	=	1.297	O–C_2–N	=	113.4
N_4–C_5	=	1.297	C_2–N_3–N_4	=	105.6
O–C_2	=	1.348	N_3–N_4–C_5	=	105.6
O–C_5	=	1.348	O–C_5–C_4	=	113.4

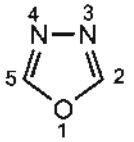


Fig. 18. Structural parameters in 1,3,4-oxadiazole

1,3,4-Oxadiazole is an aromatic, molecule with resonance energy 167.4 kJ/mol. The bond lengths in 1,3,4-oxadiazole reflect π-electron delocalization. However, the C=N bond lengths are very close to that in acyclic compounds (1.27Å) and therefore indicate some dienic character in 1,3,4-oxadiazole.

2-Hydroxy-, 2-mercapto- and 2-amino-1,3,4-oxadiazoles exist in equilibrium with the tautomeric oxadiazolines (Fig. 19).

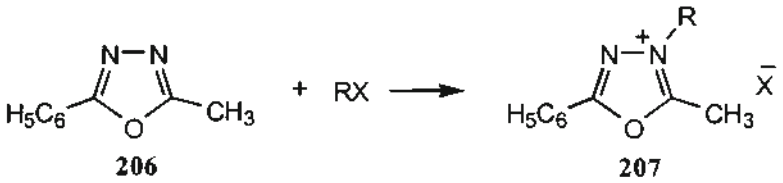
Fig. 19. Tautomeric equilibrium

3.4.4 Reactions

1,3,4-Oxadiazole contains pyridine-type nitrogen atoms at the positions-3 and -4 which cause electron-withdrawal from the carbon atoms at the positions-2 and -5. 1,3,4-Oxadiazoles, therefore, have low electron density on the carbon atoms and relatively higher electron density on the nitrogen atoms. The reactions of 1,3,4-oxadiazoles involve (i) attack of electrophiles at the nitrogen atom and (ii) attack of nucleophiles at the carbon atoms.

3.4.4.1 Reactions with Electrophiles

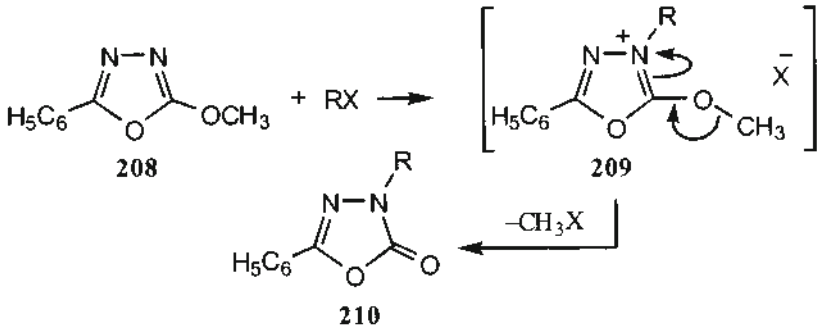
Because of very low π-electron density on the carbon atoms, the attack of electrophiles preferentially occurs at nitrogen. Alkylation of 1,3,4-oxadiazoles **206** occurs at the position-3 with the formation of 1,3,4-oxadiazolium salts **207** (scheme-86).



206 **207**

Scheme-86

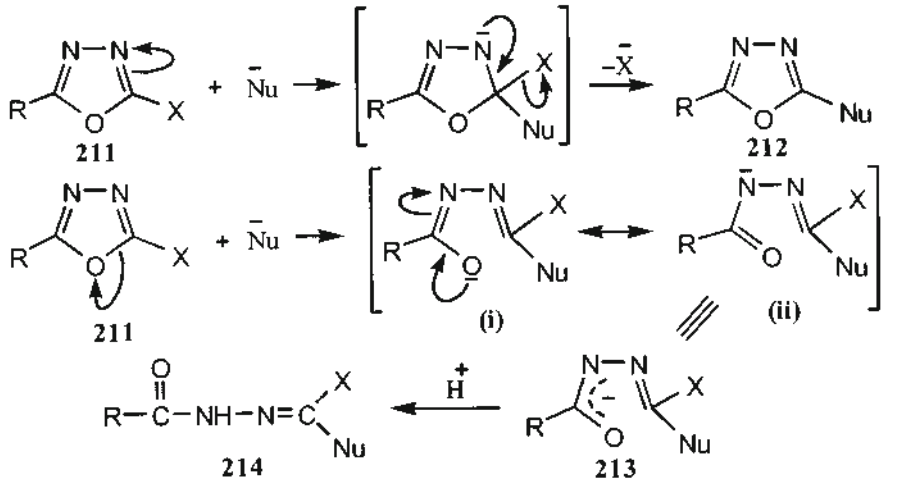
However, the alkylation of 2-alkoxy-1,3,4-oxadiazoles **208** with alkyl halides produces labile oxadiazolium salts **209** which undergo O-dealkylation to provide 4-alkyloxadiazolin-5-ones **210** (scheme-87)[57].



Scheme-87

3.4.4.2 Reactions with Nucleophiles

The carbon atoms in 1,3,4-oxadiazole ring are relatively with low π-electron density and therefore attack of nucleophiles occurs at the carbon atoms. The reaction proceeds either with nucleophilic substitution or with ring cleavage as represented (scheme-88).

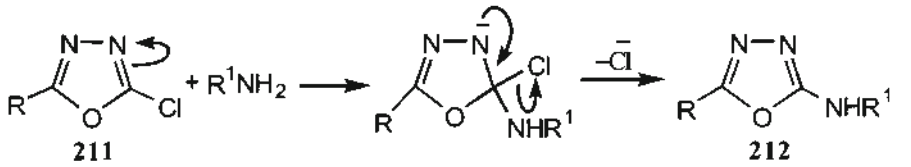


Scheme-88

3.4.4.2.1 Nucleophilic Substitution Reactions

1,3,4-Oxadiazoles substituted with chloro- or sulfonyl group at the postion-2 undergo nucleophilic substitution reactions. The reaction of 2-chloro-1,3,4-

oxadiazoles **211** (X=Cl) with nucleophiles such as amines, thiourea or azide ion proceeds with the substitution of chloro group by nucleophile and results in the corresponding 2-substituted 1,3,4-oxadiazoles **212** (scheme-89).

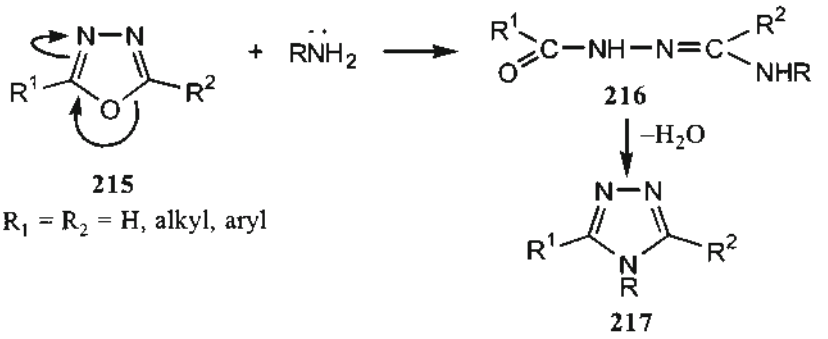


211 **212**

Scheme-89

3.4.4.2.2 Nucleophilic Attack with Ring Cleavage

The reactions of alkyl-or aryl-1,3,4-oxadiazoles **215** with nucleophiles involve the cleavage of 1,3,4-oxadiazole ring with the formation of hydrazine derivatives **216** which may recyclize to provide 1,2,4-triazoles **217** (scheme-90).



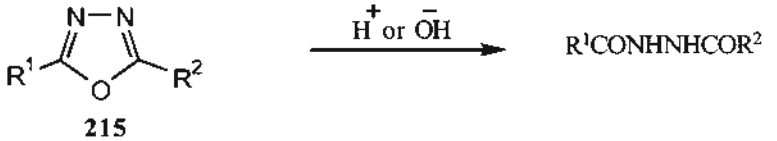
215

$R_1 = R_2$ = H, alkyl, aryl

216 **217**

Scheme-90

Alkyl- and aryl-1,3,4-oxadiazoles undergo acid or base catalyzed ring opening reactions in aqueous solution with the formation of diacylhydrazines (scheme-91). This reaction is the reverse of the intramolecular cyclization of diacylhydrazines (scheme-83) for the synthesis of 1,3,4-oxadiazoles.

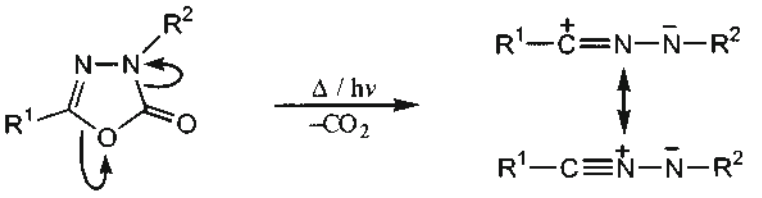


215

Scheme-91

3.4.4.3 Thermal and Photochemical Reactions

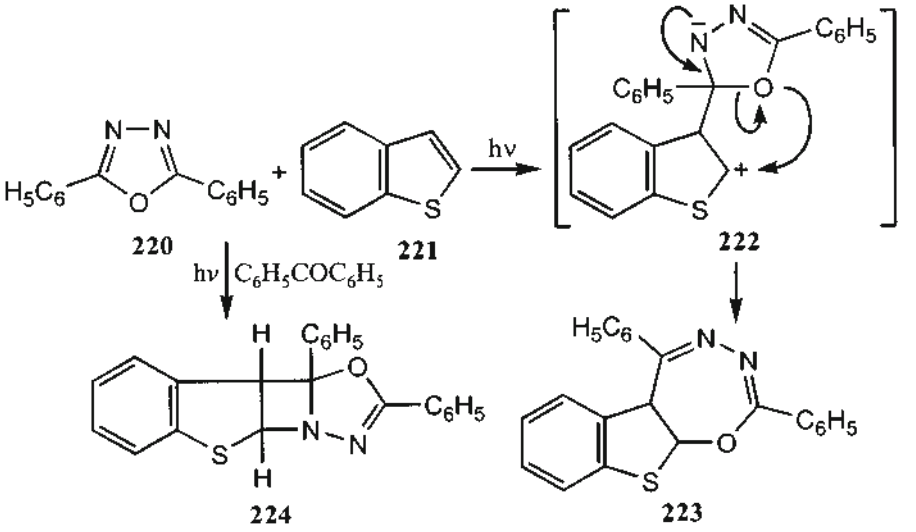
(i) 1,3,4-Oxadiazole is thermally stable and the stability of the ring is increased with the substitution of the aryl groups. However, 1,3,4-oxadiazolin-5-ones **218** undergo thermal and photochemical ring opening reactions with the loss of carbon dioxide to provide nitrilimines **219** (scheme-92).



218 **219**

Scheme-92

(ii) Photochemical irradiation of 2,5-diphenyl-1,3,4-oxadiazole **220** with benzo[*b*]thiophene **221** leads to the formation of oxadiazepine **223** as a major product. But irradiation of 2,5-diphenyl-1,3,4-oxadiazole and benzo[*b*]-thiophene with benzophenone as a sensitizer results in (2 + 2) cycloadduct **224** (scheme-93)[58].

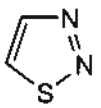


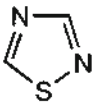
220 **221** **222** **224** **223**

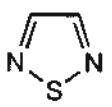
Scheme-93

4 THIADIAZOLES

Thiadiazoles are considered to be derived from thiophene by replacing two –CH= (methine) groups by pyridine-type nitrogens (–N=) and include four isomeric members depending on the relative positions of the nitrogen atoms. Thiadiazoles are named as shown in (Fig. 20) :


1,2,3-Thiadiazole


1,2,4-Thiadiazole


1,2,5-Thiadiazole

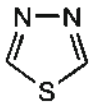
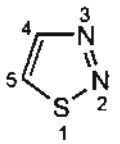

1,3,4-Thiadiazole

Fig. 20. Isomeric thiadiazoles

4.1 1,2,3-Thiadiazoles[59–61]

4.1.1 General

1,2,3-Thiadiazole **225** is a neutral five-membered aromatic heterocycle with three contiguous heteroatoms and is numbered as shown in structure **225**.

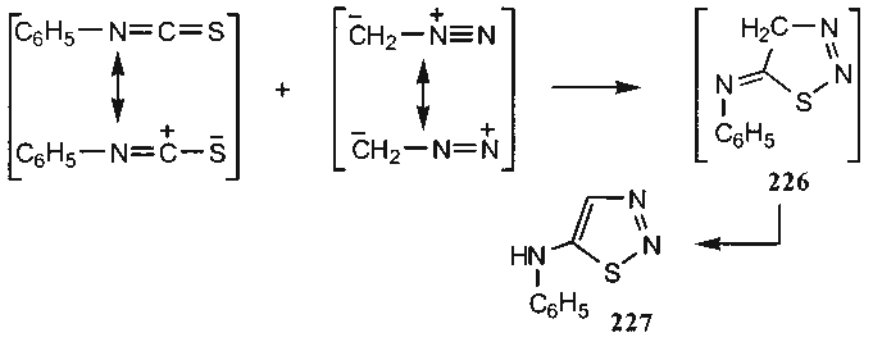

225

1,2,3-Thiadiazoles have been found to possess antibacterial, insecticidal and herbicidal activity. The analogues of 1,2,3-thiadiazole-4-carboxylic acid exhibit sedative and hypnotic activity comparable to benzodiazepines.

4.1.2 Synthesis

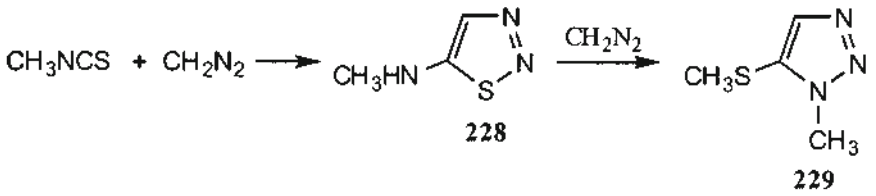
4.1.2.1 Pechmann and Nold Synthesis

This method involves dipolar cycloaddition of diazomethane to phenyl isothio cyanate to provide 1,2,3-thiadiazoles **227** (scheme-94). It has some limitations as



Scheme-94

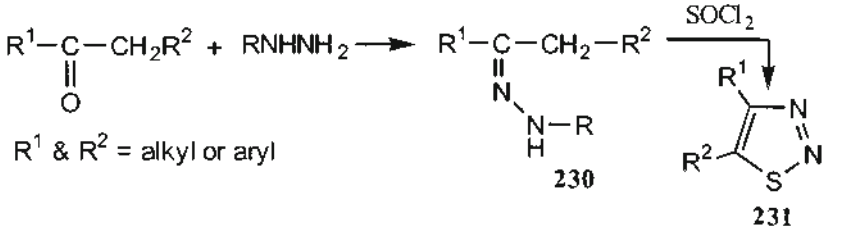
methyl isothiocyanate does not react with diazomethane at room temperature but at higher temperature 1,2,3-thiadiazole **228** produced reacts further with the second molecule of diazomethane and provides 1,2,3-triazole **229** involving Dimroth rearrangement (scheme-95).



Scheme-95

4.1.2.2 Hurd–Mori's Classical Synthesis (From Hydrazones)

This is the most widely used method for the synthesis of 1,2,3-thiadiazoles and involves cyclocondensation of α-methylene hydrazones **230**, (derived from α-methylene ketones) with thionyl chloride (scheme-96)[62]. The cyclization occurs



Scheme-96

predominantly at the more reactive methylene site rather than at the methyl site (if R_1=CH_3). However, sulfur dichloride (SCl_2) has also been used in place of thionyl chloride to obtain 1,2,3-thiadiazoles in improved yield[63].

4.1.3 Structure

1,2,3-Thiadiazole is a planar molecule with the following structural parameters (Fig. 21):

Bond lengths (Å)			**Bond angles (°)**		
$S–N_2$	=	1.692	$N_2–S–C_5$	=	92.9
$N_2–N_3$	=	1.290	$N_2–N_3–C_4$	=	114.0
$N_3–C_4$	=	1.366	$S–N_2–N_3$	=	111.2
$C_4–C_5$	=	1.369	$N_3–C_4–C_5$	=	114.2
$S–C_5$	=	1.689	$C_4–C_5–S$	=	107.8

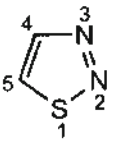


Fig. 21. Structural parameters in 1,2,3-thiadiazoles

The bond lenghts in 1,2,3-thiadiazole indicate considerable π-electron delocalization in 1,2,3-thiadiazole. The interesting structural features exhibited by 1,2,3-thiadiazole molecule include the nearly equal bond lengths of $S–N_2$ and $S–C_5$ bonds and very short $N_2–N_3$ bond.

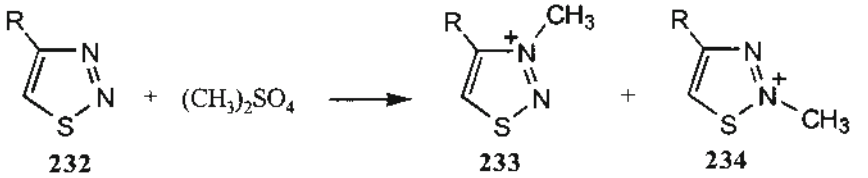
4.1.4 Reactions

1,2,3-Thiadiazole is a π-excessive heterocycle in which the nitrogen atoms particularly N-3 are comparatively with higher electron density and the carbon atoms are with lower electron density. The attack of electrophiles at carbon is very rare and therefore occurs at the nitrogen atoms. The attack of nucleophiles occurs at the carbon atoms and results in either nucleophilic substitution or ring cleavage.

4.1.4.1 Reactions with Electrophiles

4.1.4.1.1 Electrophilic Attack at Nitrogen

The reaction of 1,2,3-thiadiazoles with dimethyl sulfate results in N-alkylation with the formation of a mixture of quaternary salts **233** and **234** (scheme-97). However, in some cases, alkylation occurs exclusively at the position-3[64,65].



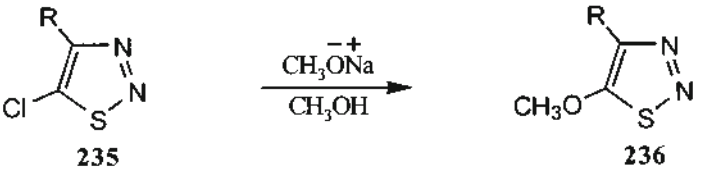
232 233 234

Scheme-97

4.1.4.2 Reactions with Nucleophiles

4.1.4.2.1 Nucleophilic Substitutions

The halogen atom in 1,2,3-thiadiazoles at the position-5 is reactive and can be replaced by nucleophiles. The reaction of 5-chloro-1,2,3-thiadiazole **235** with sodium methoxide proceeds with the replacement of chlorine substituent (scheme-98)[66].

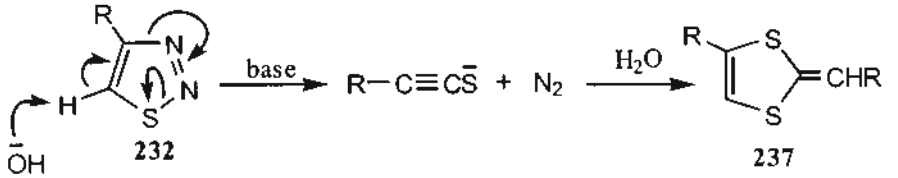


235 236

Scheme-98

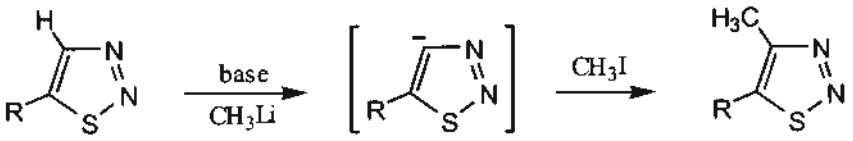
4.1.4.2.2 Ring Cleavage via C-Deprotonation

The C_5–H in 1,2,3-thiadiazole is reactive and can be abstracted as a proton by a base. Deprotonation of 1,2,3-thiadiazole ring occurs at C-5 under strongly basic conditions and leads to the ring cleavage with the extrusion of nitrogen (scheme-99). However, 1,2,3-thiadiazoles substituted at C-5 can be deprotonated at C–4 and the resulting anion **239** can be alkylated (scheme-100).



232 237

Scheme-99

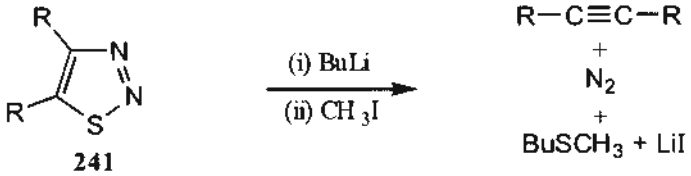


238 **239** **240**

Scheme-100

4.1.4.2.3 Nucleophilic Attack at Sulfur

If 1,2,3-thiadiazole is substituted at both the carbons (C-4 and C-5), the reaction with n-butyllithium followed by methyl iodide proceeds with the initial attack of nucleophile at sulfur and results in the fragmentation of the ring with the evolution of nitrogen (scheme-101).

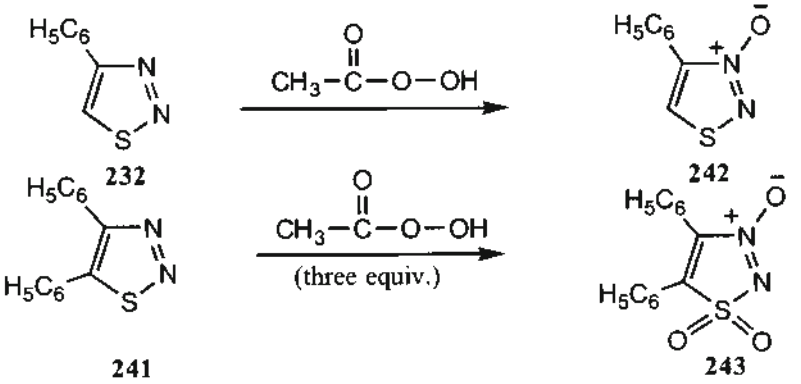


241

Scheme-101

4.1.4.3 Oxidation

Oxidation of 1,2,3-thiadiazole with one equivalent of peracid occurs at N-3 with the formation of 1,2,3-thiadiazole 3-oxide **242**, but with three equivalent of peracid 1,2,3-thiadiazole trioxide **243** is produced involving oxidation of N-3 and of the sulfur atom (scheme-102)[67].



232 **242**

241 **243**

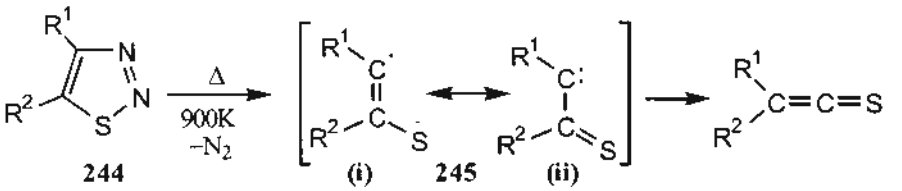
Scheme-102

4.1.4.4 Thermal and Photochemical Reactions

Thermal and photochemical reactions are considered to proceed via diradical intermediates with the extrusion of nitrogen.

4.1.4.4.1 Thermal Reactions

Thermal decomposition of 1,2,3-thiadiazoles leads to the formation of thioketenes via a diradical intermediate **245** (scheme-103).

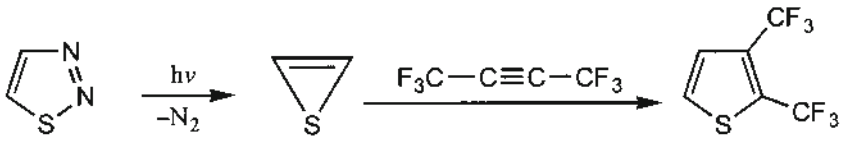


244

Scheme-103

4.1.4.4.2 Photochemical Reactions

Photolysis of 1,2,3-thiadiazole produces thiirene **246** which can be trapped by an alkyne to provide thiophene **247** (scheme-104)[68].



225 **246** **247**

Scheme-104

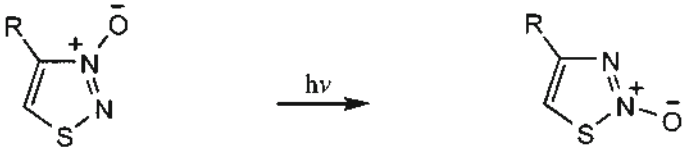
However, irradiation of 1,2,3-thiadiazole in an argon matrix at 8K gives thiirene which upon further irradiation affords thioketene (scheme-105)[69,70].

225 **246**

Scheme-105

4.1.4.4.3 Rearrangements

1,2,3-Thiadiazole 3-oxides **242** are isomerized into 1,2,3-thiadiazole 2-oxides **248** when photochemically irradiated (scheme-106).



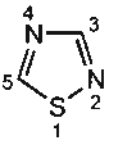
242 **248**

Scheme-106

4.2 1,2,4-Thiadiazoles[59,71–74]

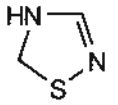
4.2.1 General

1,2,4-Thiadiazole **249** is a sulfur and nitrogen containing π-excessive aromatic heterocycle and is numbered as shown in structure **249**. The partially reduced



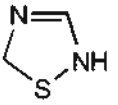
249

1,2,4-thiadiazoles are known as dihydro-1,2,4-thiadiazoles (thiadiazolines) and are named according to the position of the double bond. The fully reduced ring system of 1,2,4-thiadiazole is referred to as 2,3,4,5-tetrahydro-1,2,4-thiadiazole (thiadiazolidine) **253**.



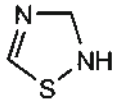
Δ^2–1,2,4–Thiadiazoline (4,5-dihydro-)

250



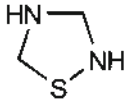
Δ^3–1,2,4–Thiadiazoline (2,5-dihydro-)

251



Δ^4–1,2,4–Thiadiazoline (2,3-dihydro-)

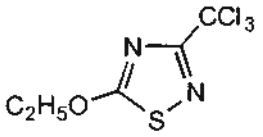
252



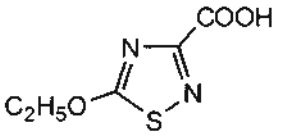
1,2,4-Thiadiazolidine (2,3,4,5-tetrahydro-)

253

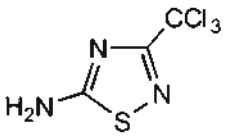
1,2,4-Thiadiazoles have been used mainly as fungicides **254**, **255** and **256** under a viariety of names such as Terrazole, Pansoil, Truban, Aaterra etc. 1,2,4-Thiadiazoles also find their uses as herbicides, insecticides and bactericides.



254



255

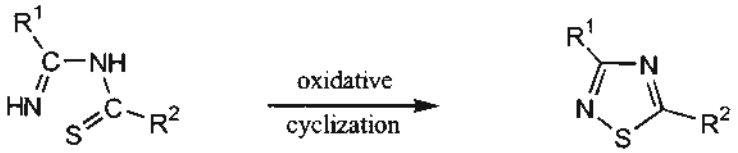


256

4.2.2 Synthesis

4.2.2.1 Oxidative Cyclization of Thioacylamidines

Oxidative cyclization of thioacylamidines **257** with oxidizing agents such as bromine, iodine, nitric acid, acidic hydrogen peroxide and arylsulfonyl halides in the presence of pyridine leads to the formation of 1,2,4-thiadiazoles **258** (scheme-107)[71].

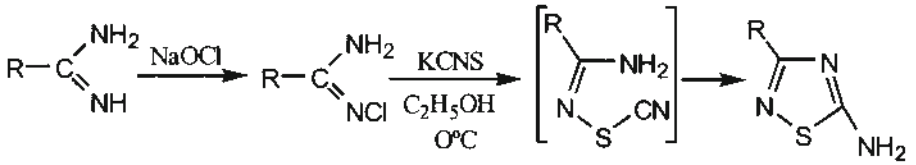


257 **258**

Scheme-107

4.2.2.2 From Amidines

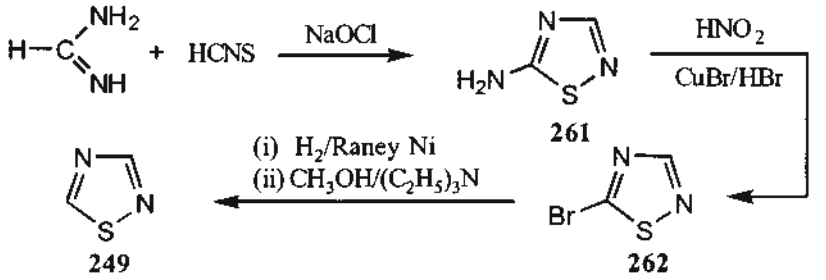
The reaction of amidines with sodium hypochlorite followed by potassium thiocyanate results in 5-amino-1,2,4-thiadiazoles **260** (scheme-108)[71]. However,



259 **260**

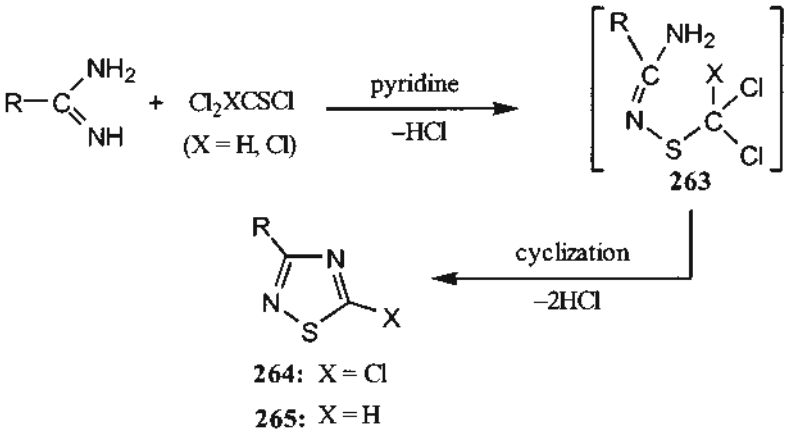
Scheme-108

parent 1,2,4-thiadiazole is obtained by the following course of reactions (scheme-109). But the reaction of amidines with trichloromethylsulfenyl chloride in



Scheme-109

the presence of a base produces 5-chloro-1,2,4-thiadiazoles **264** and with dicholoromethylsulfenyl chloride 3-substituted 1,2,4-thiadiazoles **265** are obtained (scheme-110)[71].

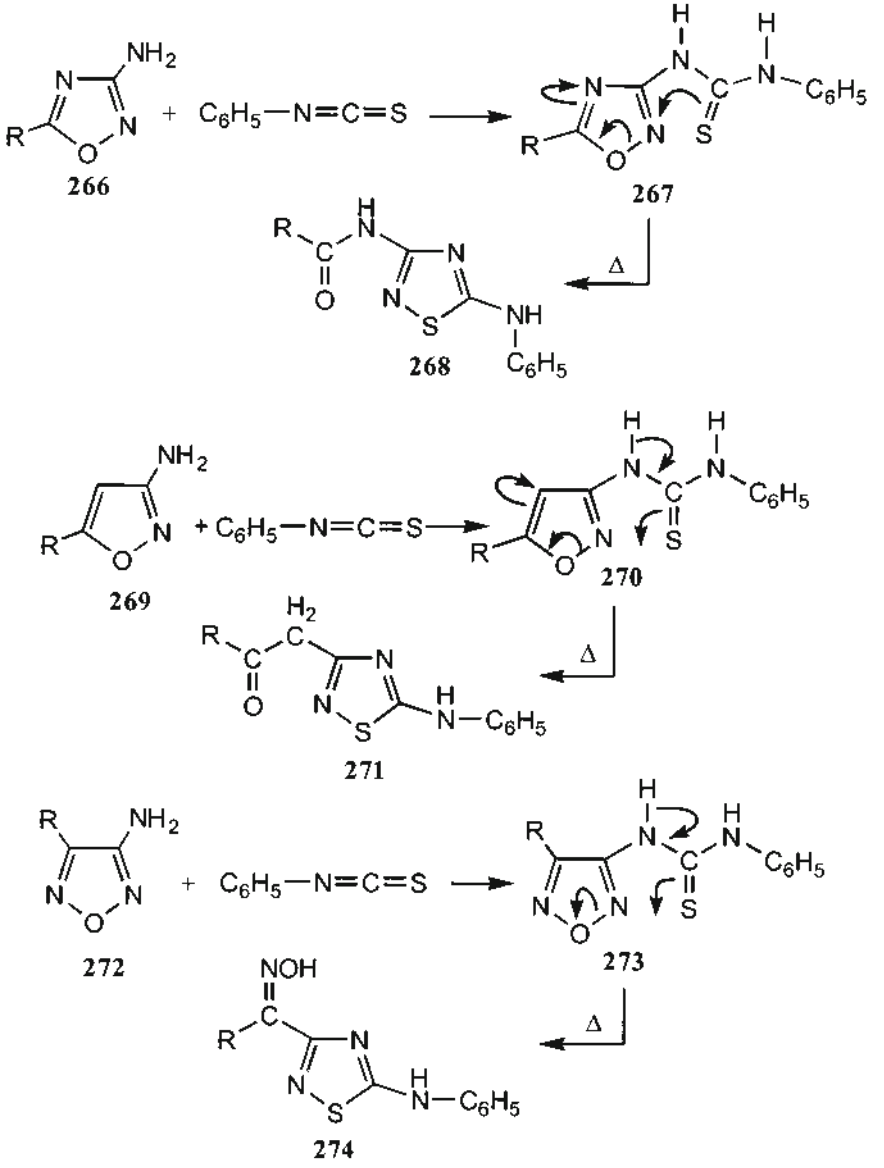


Scheme-110

4.2.2.3 Heterocyclic Ring Transformations (Oxazole and Oxadiazole Rearrangements)

Thermal rearrangements of thioureas **267**, **270** and **273**, resulting by treating 5-alkyl-3-amino-1,2,4 oxadiazoles **266**, 5-alkyl-3-aminoisoxazoles **269** and 4-alkyl-3-

amino-1,2,5-oxadiazoles **270** with phenylisothiocyanate, proceed through a common mechanism involving cleavage of the N–O bond to provide 1,2,4-thiadiazoles **268**, **271** and **274**, respectively (scheme-111).



Scheme-111

4.2.3 Structure

1,2,4-Thiadiazole is a planar molecule with the following structural parameters (Fig. 22):

Bond lengths (Å)			Bond angles (°)		
$S–N_2$	=	1.649	$C_5–S–N$	=	92.8
$N_2–C_3$	=	1.317	$S–N_2–C_3$	=	107.1
$C_3–N_4$	=	1.366	$N_2–C_3–N_4$	=	120.1
$N_4–C_5$	=	1.313	$C_3–N_4–C_5$	=	107.7
$C_5–S$	=	1.707	$N_4–C_5–S$	=	112.3

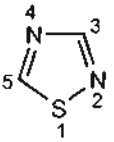


Fig. 22. Structural parameters in 1,2,4-thiadiazole

4.2.4 Reactions

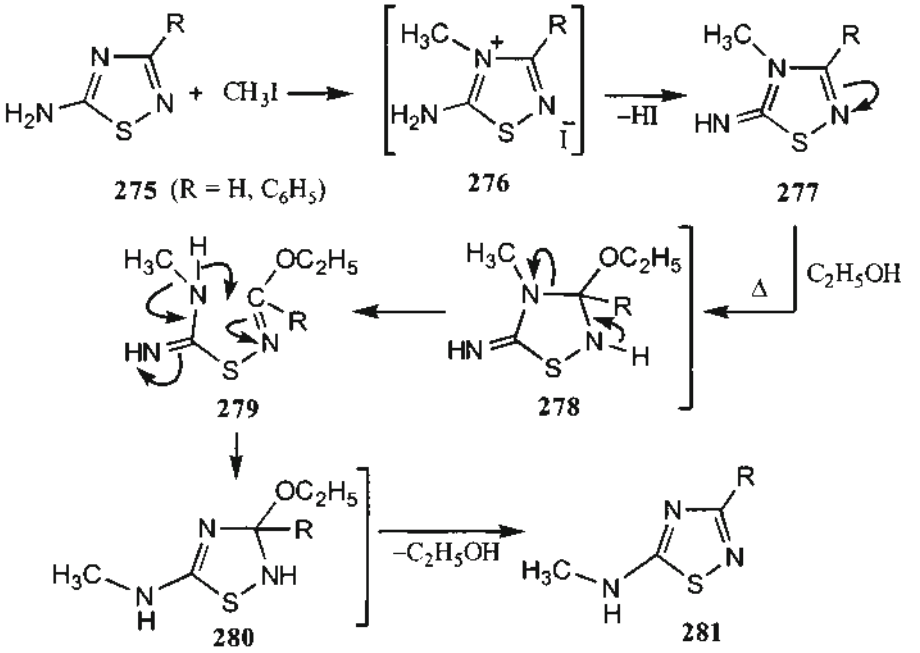
4.2.4.1 Reactivity

1,2,4-Thiadiazole is sensitive to acid and alkali. 1,2,4-Thiadiazole is easily oxidized by 30% hydrogen peroxide and is reductively cleaved readily by reducing agents. However, the substituents at the positions-3 and -5 of 1,2,4-thiadiazole ring exert stabilizing influence and stabilize the ring towards acid, alkali, oxidizing and reducing agents.

The presence of two pyridine-type nitrogen atoms which exhibit inductively electron-withdrawing effect make the ring carbons least reactive towards electrophiles. However, quaternization occurs with the attack of electrophiles at the nitrogen atoms, if the ring is activated by electron-releasing substituents. 1,2,4-Thiadiazole ring is reactive towards nucleophiles and the attack of nucleophiles generally results in nucleophilic substitution or ring cleavage.

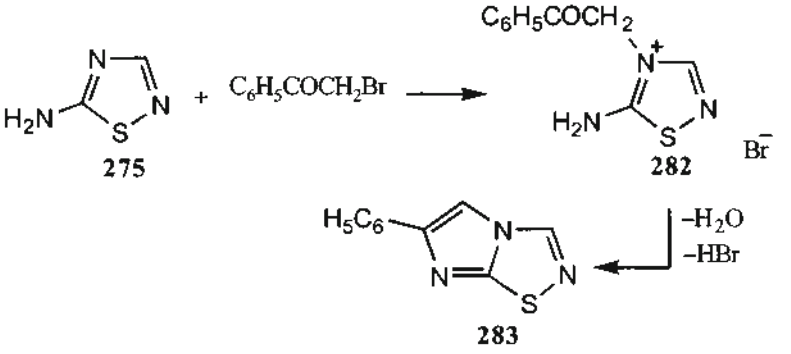
4.2.4.2 Reactions with Electrophiles

1,2,4-Thiadiazoles substituted with an electron-releasing substituent ($-NH_2$) at the position-5 are alkylated by alkyl halides initially at N-4 with the formation of N-4-alkyl derivatives which on warming with ethanol undergo Dimroth rearrangement to provide 5-alkylamino-1,2,4-thiadiazoles **281** (scheme-112). But with phenacyl bromide the initially formed N-4 derivative **282** undergoes cyclization with the



Scheme-112

formation of fused imidazolothiadiazoles **283** (Scheme-113)[71]. However, the reaction of 1,2,4-thiadiazole with trimethyloxonium tetrafluoroborate [$(CH_3)_3O^+ BF_4^-$] results in diquaternary salt (scheme-114)[76].



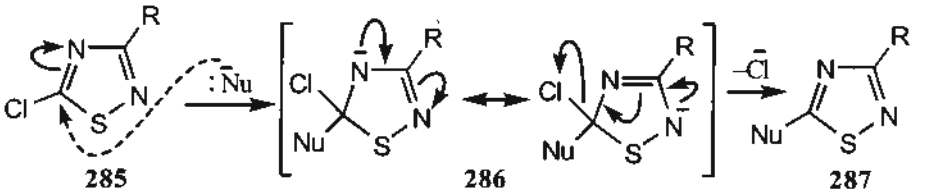
Scheme-113

Scheme-114

4.2.4.3 Reactions with Nucleophiles

4.2.4.3.1 Nucleophilic Substitution Reactions

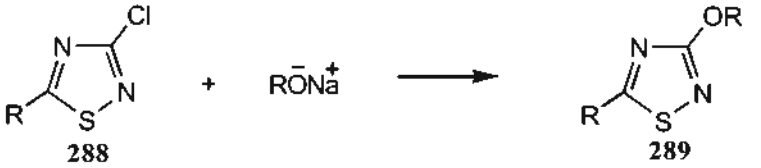
The position-5 in 1,2,4-thiadiazole is more reactive towards nucleophilic attack because of being relatively with lower electron density as compared to the position-3. The halogen atom at the position-5 can be replaced by nucleophiles involving addition–elimination mechanism (scheme-115).



Scheme-115

The nucleophilic substitution in 5-chloro-1,2,4-thiadiazoles **285** is faster than in six-membered heteroaromatics. The higher reactivity towads nucleophilic substitutions is attributed to the greater stabilization of the intermediate **286** (additionally by inductive effect of sulfur).

The halogen atom at position-3 of 1,2,4-thiadiazoles exhibits inertness and is much more difficult to replace by nucleophiles because delocalization of negative charge on both the nitrogen atoms is not possible. However, it can be replaced only under drastic conditions (scheme-116).

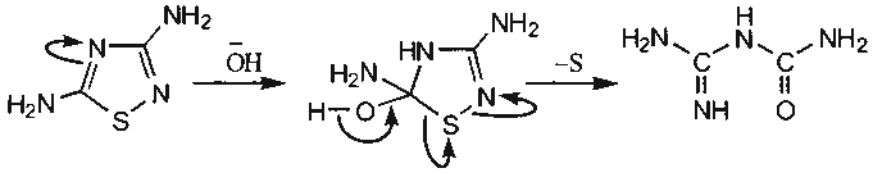


Scheme-116

4.2.4.3.2 Ring Cleavage

4.2.4.3.2.1 Nucleophilic Attack at Carbon

The presence of substituents at the positions-3 and -5 in 1,2,4-thiadiazoles exert stabilizing influence, however the reactions leading to ring cleavage occur with the attack of nucleophiles at C-5 (scheme-117).

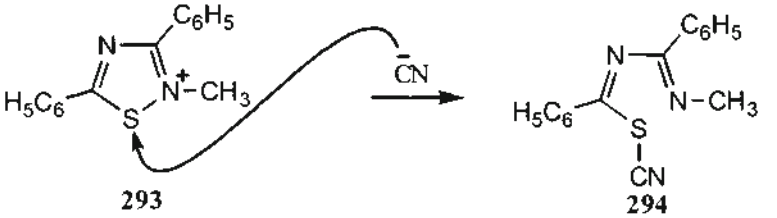


290 **291** **292**

Scheme-117

4.2.4.3.2.2 Nucleophilic Attack at Sulfur

Soft nucleophiles attack at the sulfur atom of 1,2,4-thiadiazoles with the cleavage of the ring (scheme-118).

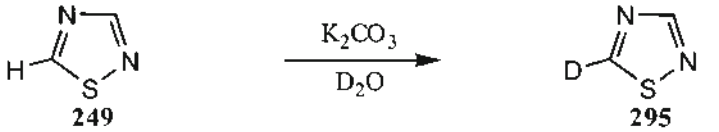


293 **294**

Scheme-118

4.2.4.3.3 Nucleophilic Attack at Hydrogen

1,2,4-Thiadiazole when treated with a weak base (K_2CO_3) in D_2O is deuterated at the position-5 with the formation of monodeutero 1,2,4-thiadiazole **295** (scheme-119)[77].

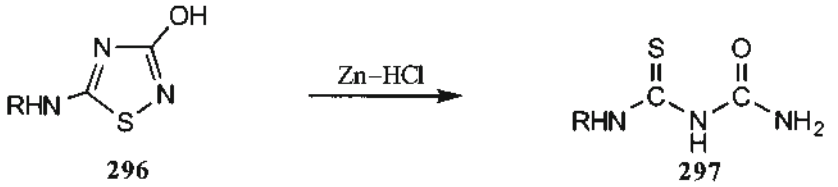


249 **295**

Scheme-119

4.2.4.4 Reduction

1,2,4-Thiadiazoles are catalytically reduced with the cleavage of nitrogen–sulfur bond (scheme-120).



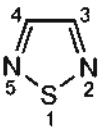
296 **297**

Scheme-120

4.3 1,2,5-Thiadiazoles[61,78–80]

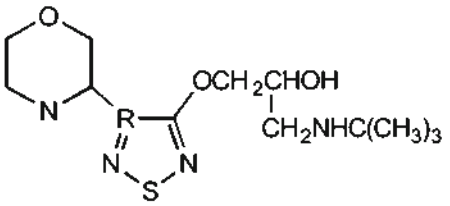
4.3.1 General

1,2,5-Thiadiazole is an aromatic heterocycle and is numbered as shown in its structure **298**. 1,2,5-Thiadiazole does not exist in the reduced forms as the reduced systems are much less stable and are readily hydrolytically desulfurized to the open chain compounds with N–C–C–N structural skeleton.



298

1,2,5-Thiadiazoles find pharmaceutical, agricultural and industrial applications. The pharmaceuticals incorporating 1,2,5-thiadiazole ring system are used as antibiotics, histamine H_2-receptor antagonists and β-adrenergic blocking agents (Timolol). Timolol **299** (hemimaleate salt) is used as an active chemotherapeutic agent in Blocadren and Timoptic. Blocadren is used for the treatment of high blood pressure and Timoptic is used as eye drops in the treatment of eye disease glaucoma. 1,2,5-Thiadiazoles are also used as herbicides, fungicides, bactericides, insecticides and plant growth regulators. 1,2,5-Thiadiazole ring system is also involved into a number of polymers with desirable chemical and thermal stability.

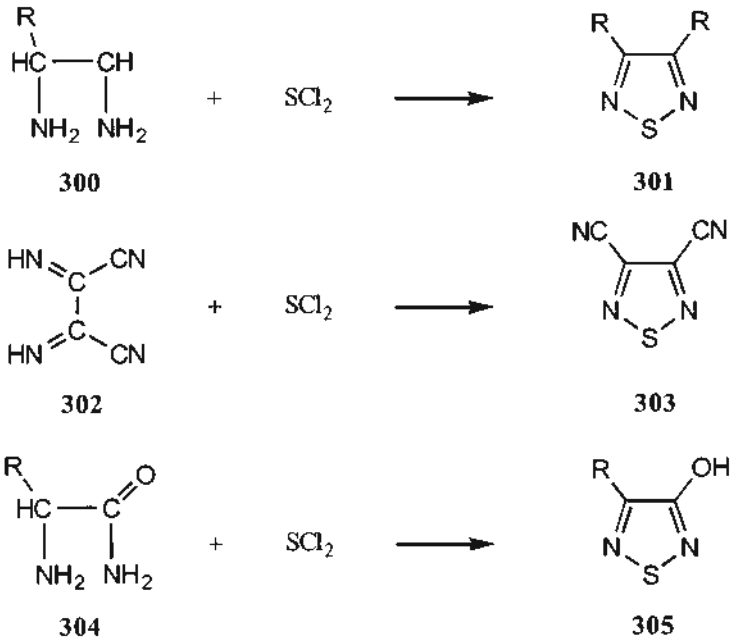


299

4.3.2 Synthesis

4.3.2.1 From *o*-Diamines [(4 + 1) Cyclization]

This is the most widely used and versatile method and involves the reaction of *o*-diamines (acyclic N–C–C–N system with N–C groups sp, sp^2 or sp^3 hybridized) with sulfur monochloride or sulfur dichloride to provide appropriately substituted 1,2,5-thiadiazoles (scheme-121)[78,81–84].



Scheme-121

4.3.3 Structure

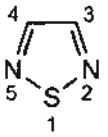
1,2,5-Thiadiazole is a planar heterocycle with C_2v symmetry. The structural parameters for 1,2,5-thiadiazole are as (Fig. 23) :

Bond lengths (Å)

S–N = 1.631

C=N = 1.328

C–C = 1.420



Bond angles (°)

N–S–N = 99.6

S–N–C = 106.4

N–C–C = 113.8

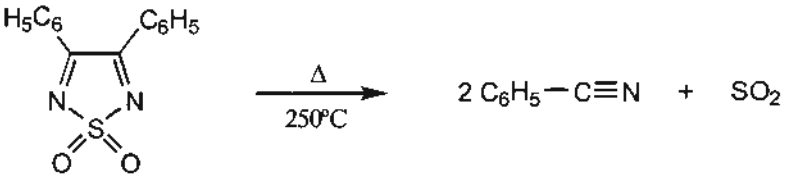
Fig. 23. Structural parameters in 1,2,5-thiadiazole

The structural parameters indicate that the carbon–carbon bond length is nearly the same as C_3–C_4 in thiophene (1.423Å). It is longer than that in benzene (1.397Å), while shorter than the carbon–carbon single bond in cyclopentadiene (1.46Å). Thus, carbon–carbon bond (C_3–C_4) in 1,2,5-thiadiazole exhibits double bond character. The C–N bond length (1.328Å) in 1,2,5-thiadiazole is intermediate between that of pyridine and oxadiazole and, therefore, reflects to acquire partial single bond character also. Similarly, the S–N bond length in 1,2,5-thiadiazole indicates the presence of double bond character. The bond lengths in 1,2,5-thiadiazole predict π-electron delocalization and hence the aromaticity in the ring.

4.3.4 Reactions

4.3.4.1 Stability

1,2,5-Thiadiazole is a weak base with pKa = 11.90. 1,2,5-Thiadiazole ring system is generally stable to mineral acids, but slightly sensitive to bases. 1,2,5-Thiadiazole is thermally stable, but 3,4-diphenyl-1,2,5-thiadiazole 1, 1-dioxide **306** is decomposed into benzonitrile and sulfur dioxide when heated at 250°C (scheme-122)[78].



306

Scheme-122

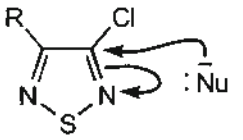
4.3.4.2 Reactions with Electrophiles

1,2,5-Thiadiazole ring system is with very low electron density at the nitrogen and sulfur heteroatoms and is therefore relatively inert towards electrophilic attack. However, electrophilic substitutions can occur only if 1,2,5-thiadiazole ring is substituted with electron-releasing substituents ($-NH_2$ or $-CH_3$)[78,79].

4.3.4.3 Reactions with Nucleophiles

1,2,5-Thiadiazole ring is susceptible towards nucleophiles with the attack either at carbon, sulfur or a ring proton.

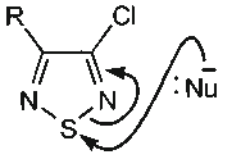
(i) The attack of nucleophile at carbon results in nucleophilic substitution with the formation of a substituted product (Fig. 23).



(attack at carbon)

Fig. 23. Nucleophilic attack at carbon

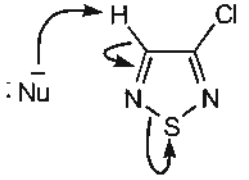
(ii) The attack of nucleophile at sulphur leads to the formation of rearranged product or causes ring cleavage (Fig. 24).



(attack at sulfur)

Fig. 24. Nucleophilic attack at sulfur

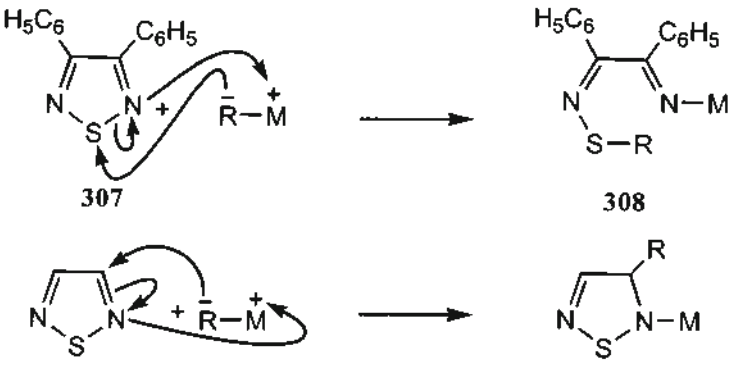
(iii) The attack of nucleophile at a ring hydrogen proceeds with the abstraction of a proton providing ring cleaved product or involves proton exchange (Fig. 25).



(attack at ring hydrogen)

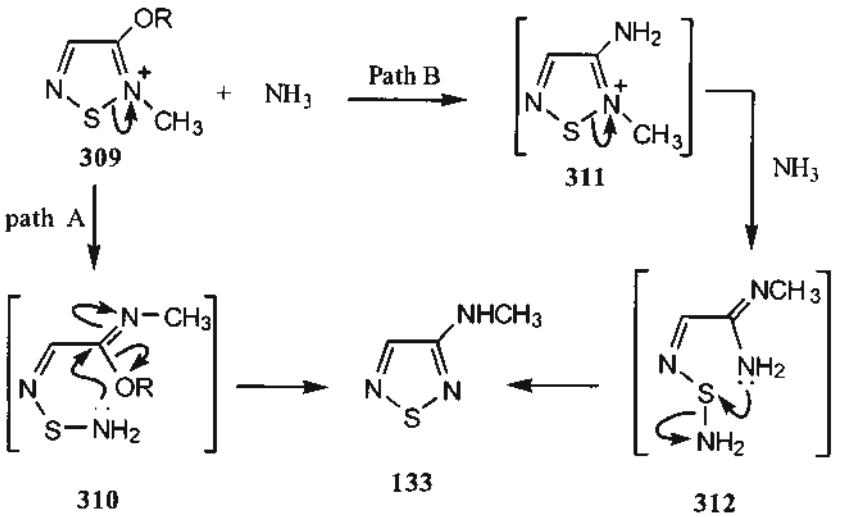
Fig. 25. Nucleophilic attack at hydrogen

The reaction of 1,2,5-thiadiazoles with organometallics (n-butyllithium or Grignard reagents) involves the attack of nucleophile usually at the ring sulfur, but the attack at the ring carbon also occurs providing a different product (scheme-123)[85].



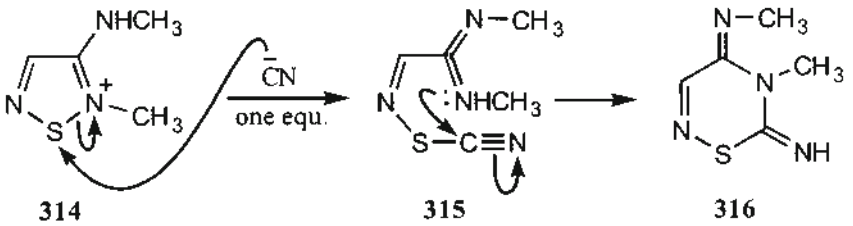
Scheme-123

The reaction of quaternary compound **309** with ammonia (nitrogen nucleophile) in acetonitrile proceeds to involve attack at sulfur or carbon (path A or B) with the formation of rearranged product **313** (scheme-124)[83].



Scheme-124

But the reaction of quaternary compound **314** with carbon nucleophile (CN) involves the attack at sulfur followed by ring cleavage and subsequent cyclization to provide ring expanded product **316** (scheme-125)[86].



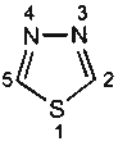
314 **315** **316**

Scheme-125

4.4 1,3,4-Thiadiazoles[61,87–90]

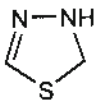
4.4.1 General

1,3,4-Thiadiazole is a sulfur-containing aromatic heterocycle with nitrogen atoms at the 3-and 4-positions and is numbered as shown in its structure **317**.

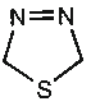


317

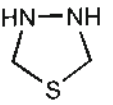
1,3,4-Thiadiazole exists in two partially reduced (dihydro-) forms, **318** and **319** and named as 1,3,4-thiadiazolines depending on the position of the double bond. The completely reduced (tetrahydro-)1,3,4-thiadiazole is known as 1,3,4-thiadiazolidine **320**.



Δ^2-1,3,4-Thiadiazoline
(2,3-dihydro-)
318

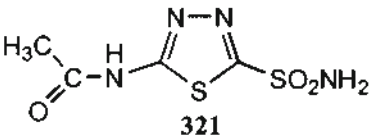


Δ^3-1,3,4-Thiadiazoline
(2,5-dihydro-)
319

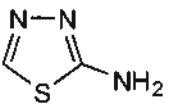


1,3,4-Thiadiazolidine
(2,3,4,5-tetrahydro-)
320

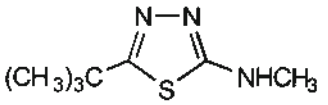
1,3,4-Thiadiazoles exhibit varying biological activity and are, therefore, find their uses in the fields of pharmaceuticals (acetazolamide **321** as diuretic and 2-amino-1,3,4-thiadiazole **322** as antitumor agent in dogs) and agrochemicals (methidathion **323** as an insecticide and **324** as herbicide).



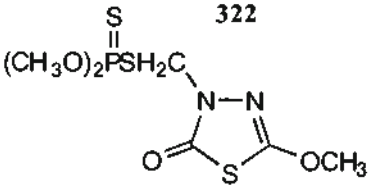
321



322



323

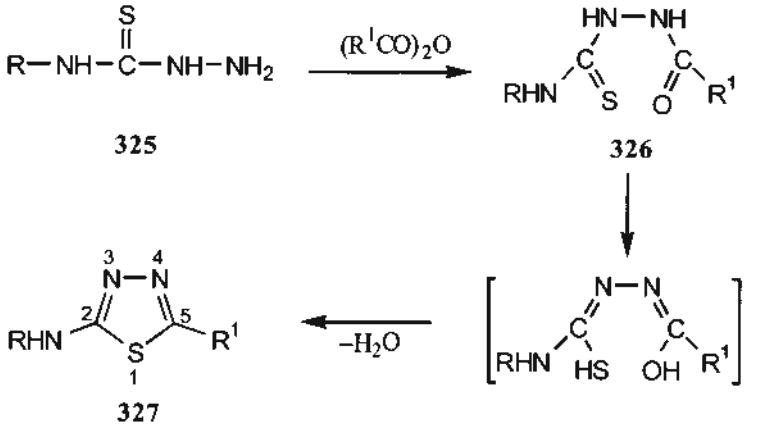


324

4.4.2 Synthesis

4.4.2.1 From Thiosemicarbazides

This is the most common method to synthesize 5-substituted 2-amino-1,3,4-thiadiazoles and involves acylation of thiosemicarbazide **325** followed by dehydrative cyclization using sulfuric acid, polyphosphoric acid, phosphorus halides or more recently methane sulfonic acid (scheme-126)[91]. However, 2-amino-



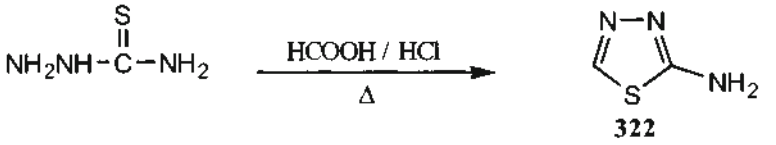
325

326

327

Scheme-126

1,3,4-thiadiazole is obtained by heating thiosemicarbazide with a mixture of formic acid and hydrochloric acid (scheme-127)[92].

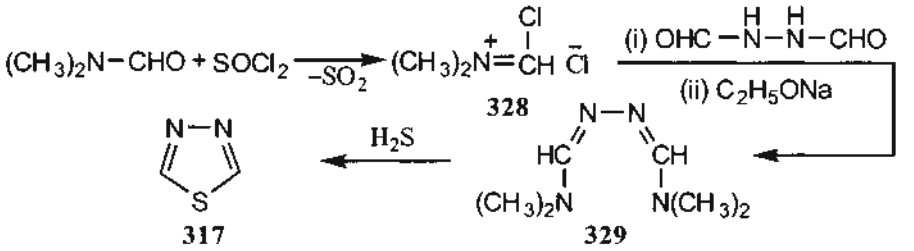


322

Scheme-127

4.4.2.2 From Dimethylformamide

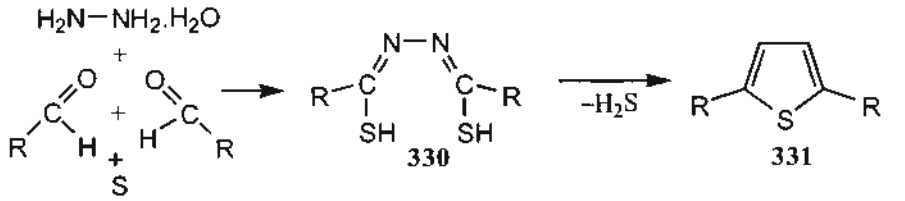
The reaction of N,N-dimethylformamide with thionyl chloride produces formamidoyl chloride **328** which on treatment with N,N-diformylhydrazine and with sodium ethoxide gives a free base **329**. The free base **329** obtained undergoes cyclization in the presence of hydrogen sulfide with the formation of parent 1,3,4-thiadiazole **317** (scheme-128).



Scheme-128

4.4.2.3 From Hydrazine

This is the one pot-synthesis of 2,5-dialkyl-1,3,4-thiadiazoles **331** and involves the reaction of hydrazine with aldehyde and elemental sulfur. The reaction proceeds via an intermediate **330** which is subsequently cyclized to **331** with the evolution of hydrogen sulfide involving the formation of C–S bond (scheme-129).



Scheme-129

4.4.3 Structure

1,3,4-Thiadiazole is a planar molecule with C_2v symmetry and the structural parameters are summarized as (Fig. 26) :

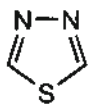
Bond lengths (Å)		**Bond angles (°)**
C–N = 1.302		C–S–C = 86.4
C–S = 1.721		S–C–N = 114.6
N–N = 1.371		C–N–N = 112.2

Fig. 26. Structural parameters in 1,3,4-thiadiazole

The C–N bond length in 1,3,4-thiadiazole is very close to that in thiazole and the C–S bond length is nearly similar to that in thiophene. The N–N bond in 1,3,4-thiadiazole also acquires some double bond character. The bond lengths in 1,3,4-thiadiazole reflect that the single bonds acquire double bond character while double bonds acquire some single bond character and therefore suggest larger delocalization of π-electrons in 1,3,4-thiadiazole than in 1,3,4-oxadiazole. But 1,3,4-thiadiazole exhibits lower aromaticity than that in 1,2,5-thiadiazole.

4.4.4 Reactions

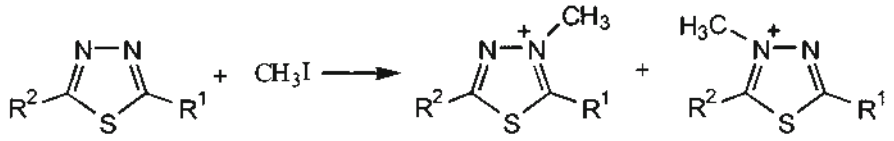
4.4.4.1 Reactivity

1,3,4-Thiadiazole ring is π-electron deficient because of the presence of two pyridine-type nitrogen atoms and hence does not react readily with electrophiles at nitrogen or at carbon. If the ring is substituted with the electron-releasing substituent, the attack of electrophile occurs at nitrogen with quaternization. 1,3,4-Thiadiazole ring is susceptible towards nucleophiles and the attack of nucleophile occurs with the nucleophilic displacement or ring cleavage. The reactions involving ring formation between two nitrogens (ring nitrogen and amino group nitrogen) are common, if 1,3,4-thiadiazole ring is substituted with an amino group at the position-2.

4.4.4.2 Reactions with Electrophiles

4.4.4.2.1 Electrophilic Attack at Nitrogen (Quaternization)

The attack of electrophiles in 1,3,4-thiadiazole ring occurs at both ring nitrogen atoms. The reaction of 1,3,4-thiadiazoles with methyl iodide results in quaternization at N-3 and N-4 and the ratio of the products depends upon the substituents present at the positions-2 and -5 (scheme-130)[93].



332 R^1=H; R^2=CH_3 **334** (55%) **335** (45%)
333 R^1=C_2H_5; R^2=CH_3 **336** (43.5%) **337** (56.4%)

Scheme-130

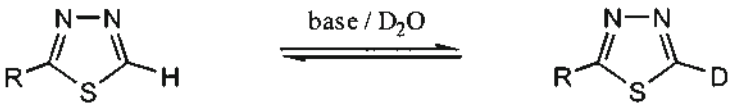
4.4.4.2.2 Electrophilic Attack at Carbon

1,3,4-Thiadiazole does not undergo electrophilic substitutions at the ring carbon atoms because of the low electron density due to the presence of electron-withdrawing nitrogen atoms at the positions-3 and -4.

4.4.4.3 Reactions with Nucleophiles

4.4.4.3.1 H ⇌ D Exchange

1,3,4-Thiadiazoles undergo base induced H ⇌ D exchange at the position α- to the sulfur when treated with D_2O under strongly basic conditions (scheme-131).

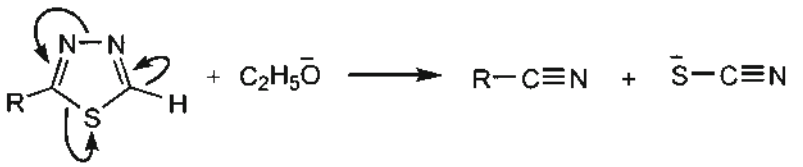


338 **339**

Scheme-131

4.4.4.3.2 Ring Cleavage via C-Deprotonation

1,3,4-Thiadiazoles unsubstituted at least at one α-position undergo ring opening reaction via C-deprotonation when treated with a strong base (scheme-132).

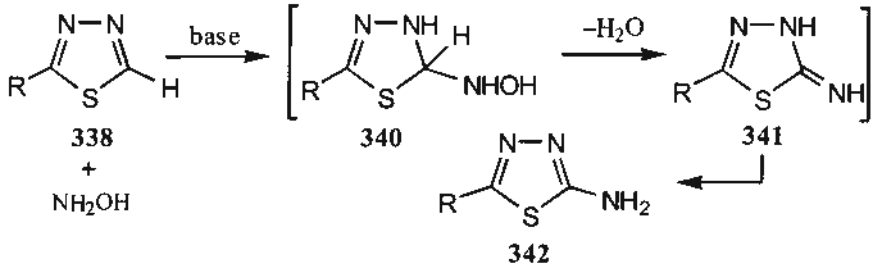


338

Scheme-132

4.4.4.3.3 Amination

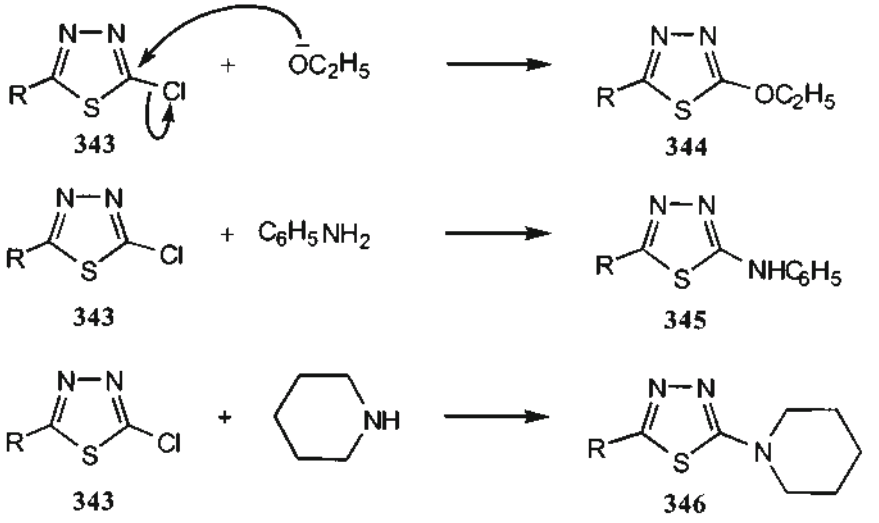
The reaction of 1,3,4-thiadiazoles (containing one free α-position) with hydroxylamine in the presence of a base results in nuclear amination via an imine intermediate **341** with the formation of 2-amino-1,3,4-thiadiazoles **342** (scheme-133)[90].



Scheme-133

4.4.4.3.4 Nucleophilic Substitutions

Halo-1,3,4-thiadiazoles **343** undergo nucleophilic substitution reactions readily with the replacement of halogen atom (α-to ring sulfur) by nucleophiles. The replacement of halogen atom in 1,3,4-thiadiazole nucleus is easier because of the presence of electronegative nitrogen atoms which inductively attract electrons from the ring carbon atoms and make them with low electron density (scheme-134).

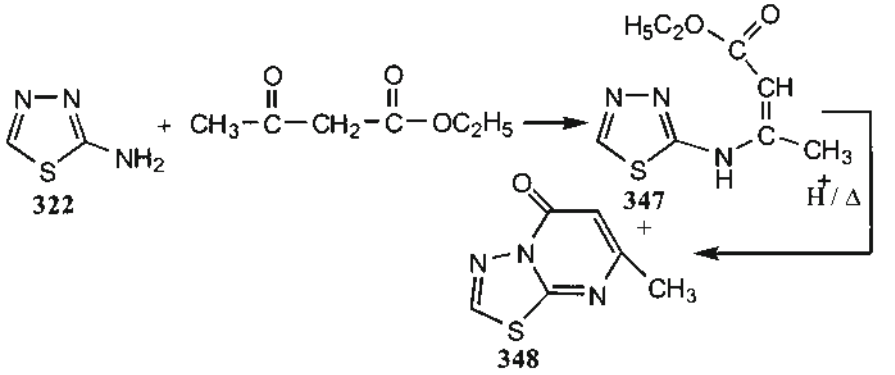


Scheme-134

4.4.4.4 Reactions Involving Ring Formation

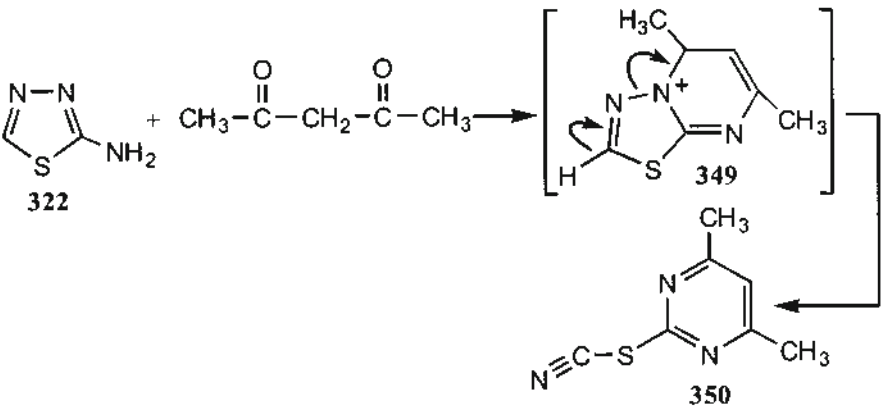
In 2-amino-1,3,4-thiadiazoles, the presence of nitrogen atom at the position-3 facilitates ring formation involving nitrogen of an amino group. The reaction of 2-amino-1,3,4-thiadiazole with β-diketones results in the formation of bicyclic compounds. The reaction, however, depends on the nature of the ß-diketones.

The reaction of 2-amino-1,3,4-thiadiazole **322** with ethylacetoacetate produces a mixture of **347** and **348**, but **347** is converted into **348** (bicyclic compound) on heating (scheme-135). However, the reaction with pentane-2,4-dione results in 4,6-



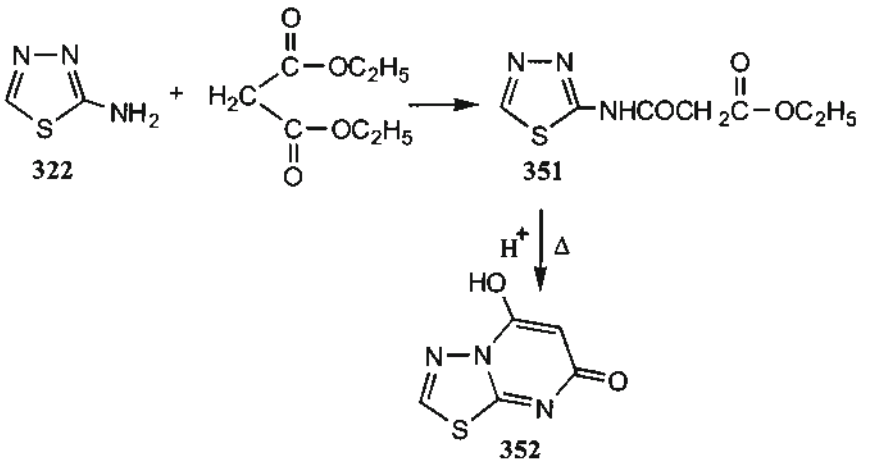
Scheme-135

dimethyl-2-thiocyanopyrimidine **350** via a bicyclic intermediate **349** (scheme-136).



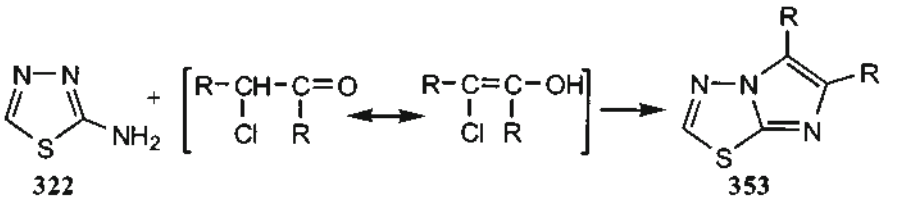
Scheme-136

The reaction of 2-amino-1,3,4-thiadiazole **322** with diethyl malonate proceeds initially with the formation of an ester **351** which is then cyclized to bicyclic compound **352** on heating (scheme-137).



Scheme-137

The reaction of 2-amino-1,3,4-thiadiazole **322** with haloaldehydes and haloketones also provides bicyclic compounds, imidazo[2,1-*b*][1,3,4]thiadiazoles **353** incorporating both the nitrogens in the ring (scheme-138)[94].



Scheme-138

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1. A. R. Katritzky and J. M. Lagowski in A. R. Katritzky and C. W. Rees (Eds.), *Comprehensive Heterocyclic Chemistry* Vol. **5**, Pergamon Press, Oxford, 1984, pp. 1.