ISSN (Online): 2455-7838
SJIF Impact Factor (2015): 3.476

EPRA International Journal of

Research & Development

(IJRD)

Volume:1, Issue:9,November 2016

Published By :
EPRA Journals

SJIF Impact Factor: 3.476 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 1 | Issue : 9 | November | 2016

REVIEW: METHOD OF SYNTHESIS OF TRIAZOLE DERIVATIVES

Shinde Pooja. N[1]
[1]College of pharmacy, Akluj, Dist-Solapur, Maharashtra, India

ABSTRACT

Triazole is an aromatic compound 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 1,2,4-triazole also supports the preference of 1H-tautomer over the 4H-tautomer. 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. Its ionization potential is 10.00 ev. Therefore, its HOMO is low than of 1,2,3- triazole. The dipole moment in the gas phase is 2.72D and in dioxane 3.27D. The absorption maximum in the UV (measured in dioxane) is 205 nm. The H^1NMR spectrum of 1,2,4-triazole (in HMPT) shows a CH-signal at δ-15.1. Only one signal at δ 1474 is observed in the ^{13}C-NMR spectrum because of tautomerism. At -34°C, however, the CH-signal split in to two peaks, namely δ= 7.92 for 3-H and 8.85 for 5-H. 1,2,4-triazoles have not yet been found in nature.

We have discussed here various methods used for the preparation of triazole derivatives.

KEYWORDS: *triazole, mercapto, osotriazole, molecular nitrogen*

MERCAPTOTRIAZOLE

The triazoles are said to be isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen atom. According to position of nitrogen atoms the triazoles are exists in isomeric forms. Two structural isomeric triazoles are known, 1,2,3-(1,2,5) and 1,2,4-(1,3,4) the former being known as *osotriazole*, and the latter as *triazole.* Each exists in two dissimilar tautomeric forms[19]. The different isomeric triazoles are characterised by the position of the nascent hydrogen. Thus 1,2,4-triazoles are exist in two forms i.e.*1H* and *4H.*(Figure 5.1)

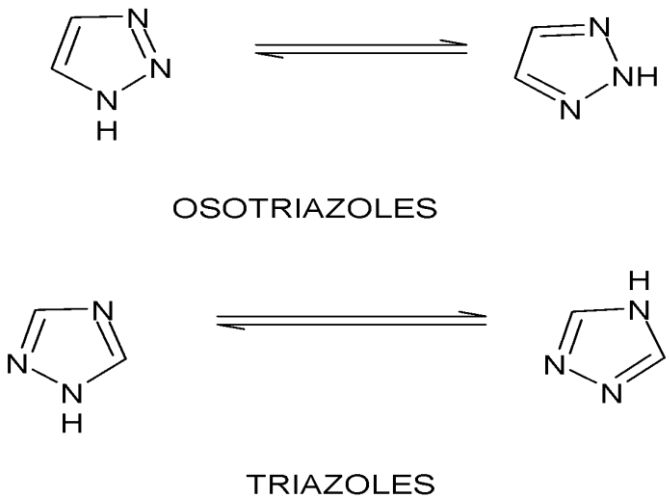


Figure 5.1

Replacement of the imino hydrogen atom by an alkyl or aryl group prevents the tautomerism, and there by gives rise to the possibility of two 1-substituted triazoles and 1-substituted osotriazoles. However, flash vaccum pyrolysis at 500^{o}C leads loss of molecular nitrogen (N_2) to produce aziridines.

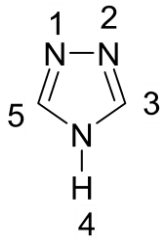


Figure 5.2

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

Bond length(A^{o})	Bond angles(^{o})
N_1-N_2 = 1.359	C_5-N_1-N_2 = 110.2
N_2-C_3 = 1.323	N_1-N_2-C_3 = 102.1
C_3-N_4 = 1.359	N_2-C_3-N_4 = 114.6
N_4-C_5= 1.324	C_3-N_4-C_5 = 103.0
N_1-C_5 = 1.331	N_4-C_5-N_1 = 110.1
N_1-H = 1.030	
C_3-H = 0.930	
C_5-H = 0.930	

We have discussed here various methods used for the preparation of 1,2,4-triazolone-5-thione derivatives. The initial products were thiosemicarbazide, thiosemicarbazone, amidrazones salts, aminoguanidine salts and their derivatives.

a. 1,2,4-Triazolone-5-thione

The condensations of hot formamide with thiosemicarbazide give a 90% yield of s-triazolone-5-thione. Also the preparation of s-triazolone-5-thione can be accomplished by the cyclization of thiosemicarbazide either with ethyl formate in the presence of sodium methoxide (65%) or by heating with s-triazine (63%). In addition both the 1-formyl and 1-(ethoxymethylene) derivatives of thiosemicarbazide can be converted to s-triazolone-5-thione with aqueous sodium carbonate with excellent yields. Rearrangement of 2-amino-1,3,4-thiadiazole to s-triazolone-5-thione in 52% yields was effected in methanolic methyl amine at 160 ° C (**Figure 5.3**).[1]

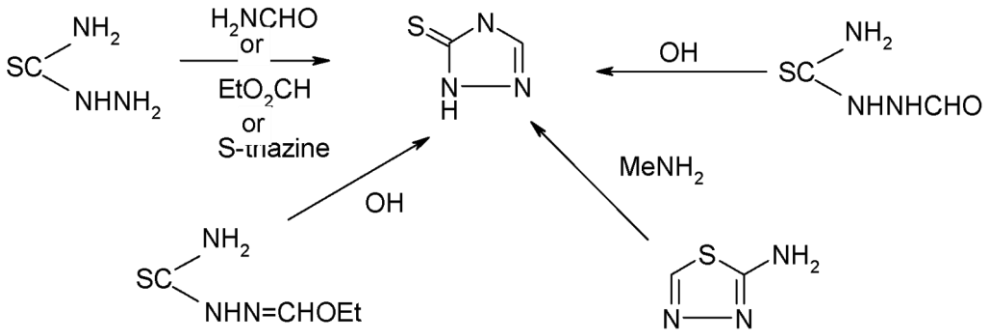


Figure 5.3

In a basic medium a number of types of 1-acyl and 1-aroyl-3-thiosemicarbazides are dehydrated by the condensation of the 4-amino group with the carbonyl moiety to give yield of triazoline-5-thiones. Although dehydration can occur in the presence of a strong mineral acid, the products are usually 1,3,4-thiadiazoles. A simple explanation for the different modes of cyclization is provided by the condensation of the relative nucleophilicity of the atoms of the terminal thioamide function of the 1-substituted 3-thiosemicarbazide. In strong acid the 4-amino group is protonated and cannot enter into the condensation reaction. Whereas in base the sulfur function is ionized, this increases the nucleophilicity of the 4-amino group and promotes triazolines-5-thiones formation.

b. 3-Substituted-1,2,4-triazoline-5-thione

The majority of the monosubstituted 1,2,4-triazoline-5-thione are 3-alkyl and 3-aryl derivatives which are readily obtained from thiosemicarbazide and its acylated products. The methoxide catalyze reaction of thiosemicarbazide with aliphatic carboxylic esters gave 3-alkyl-triazoline-5-thiones in 45-95% yields. Similarly, aromatic carboxylic esters give 3-aryl-triazoline-5-thione in 54-86% yields. In addition the thermal condensation of the dithiocarboxylic acid esters with thiosemicarbazide at 155 °C give the corresponding 3-(3- pyrazoline-4-yl)-triazoline-5-thione (**Figure 5.4**).[1]

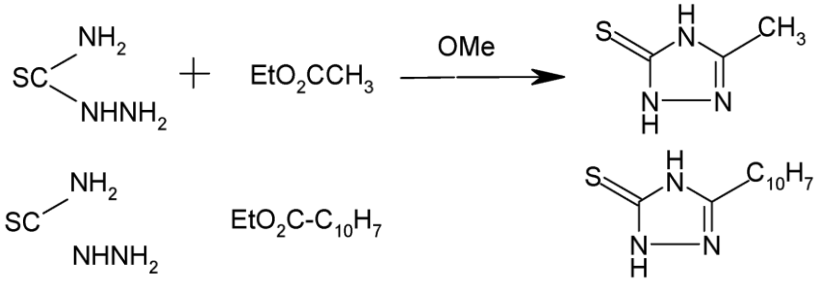


Figure 5.4

The 1-acyl-3-thiosemicarbazides are converted in good yields with aqueous base to 3-alkyltriazoline-5-thiones (**Figure 5.5**).[1]

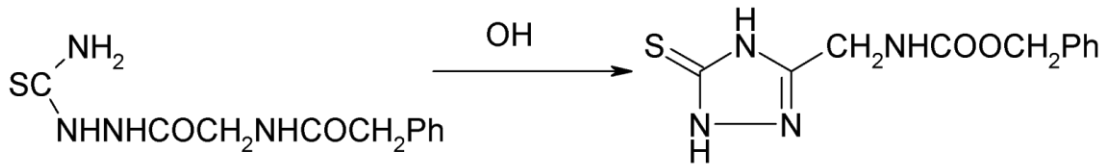


Figure 5.5

Another route to the acylthiosemicarbazide is offered by the reaction of thiosemicarbazide with aliphatic anhydrides, with one mole of propionic anhydride, 1-propionylthiosemicarbazide is obtained and cyclization to 3-ethyl-1,2,4-triazoline-5-thione is effected by boiling with 10% sodium carbonate solution for 1 h (**Figure 5.6**).[2]

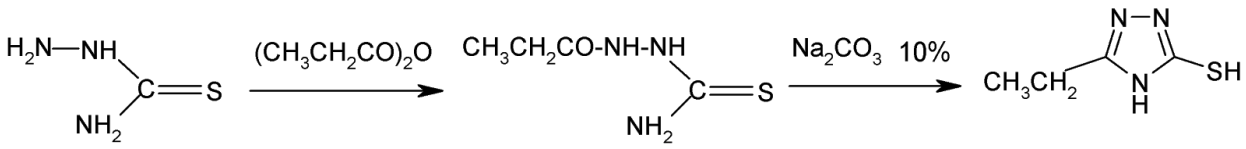


Figure 5.6

The cyclization reaction of 1-acetylthiosemicarbazide can be performed in sodium hydroxide.[3] The reaction yield is about 70%. However, with an excess of butyric anhydride diacylation occurs to give the 1,4-dibutyryl-thiosemicarbazide which cyclize with sodium carbonate solution (10%) at 100 °C, forming 3-propyl-1,2,4-triazoline-5-thione. The reaction yield is about 60% (**Figure 5.7**).[4]

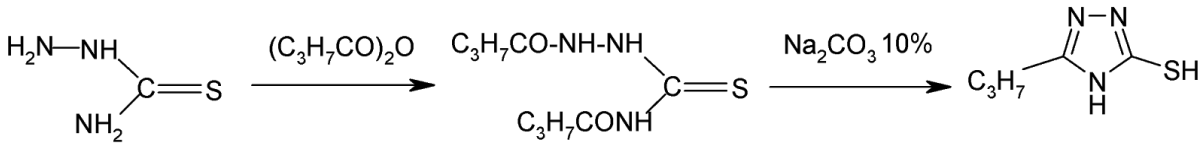


Figure 5.7

3-Ethyl-1,2,4-triazoline-5-thione is obtained in the reaction of thiosemicarbazide with appropriately substituted acid chlorides in the presence of pyridine. The reaction yield was about 71% (**Figure 5.8**).[5]

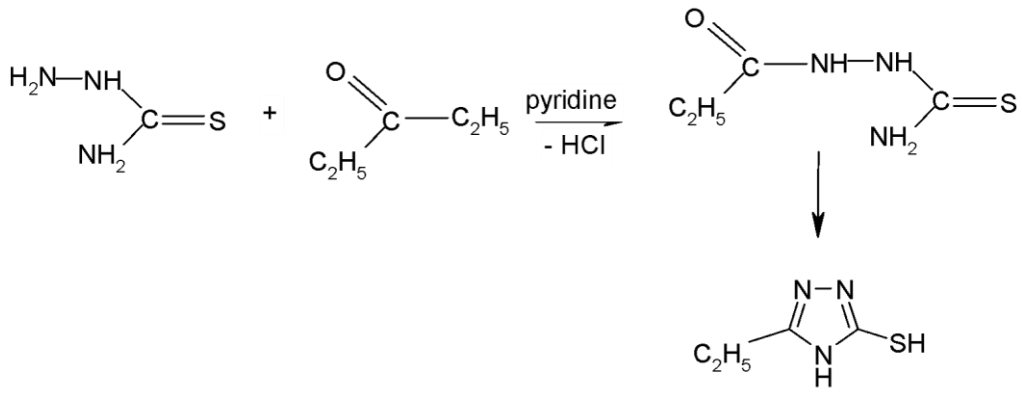


Figure 5.8

3-Substituted-1,2,4-triazoline-5-thione derivatives were obtained in the reaction of aroyl isothiocynate with an excess of hydrazine hydrate. The course of these reaction include formation of intermediate thiosemicarbazide derivatives which cyclize spontaneously to the 3-aryl-1,2,4-triazoline-5-thione and yields varying from 23 to 37% (**Figure 5.9**).[6]

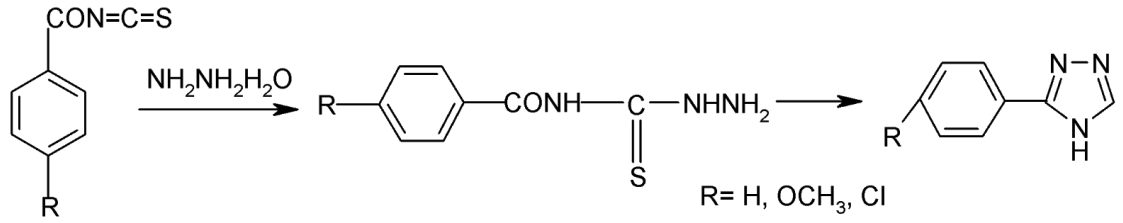


Figure 5.9

The cyclization of 1-benzoyl-3-thiosemicarabazide can be affected readily with aqueous sodium hydroxide and also with aqueous ammonia, trimethyl amine and hydrazine (**Figure 5.10**).[1]

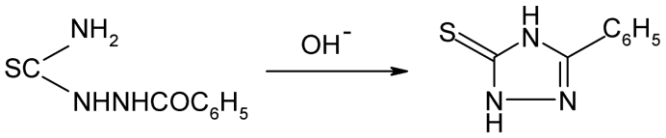


Figure 5.10

Also this type of cyclization is successful for the preparation of triazoline-5-thiones substituted with hetero-aromatic ring in the third position.[1]

In the fusion of hydrazides with thiourea at 130 °C the intermediate 1-aroyl-3-semicarbazide dehydrates to give the corresponding triazoline-5-thione. In the cyclization of 1-aroyl-3-semicarbazide a higher yield is obtained by heating 1-aroyl-3-semicarbazide in tetralin than by treatment with ethoxide which gave incomplete conversion (**Figure 5.11**).[1]

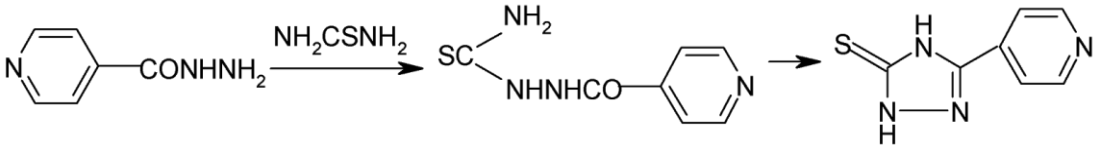


Figure 5.11

The condensation of aroyl isothiocyanates with excess hydrazine to give 3-aryltriazoline-5-thiones in fair yields (**Figure 5.12**).[1]

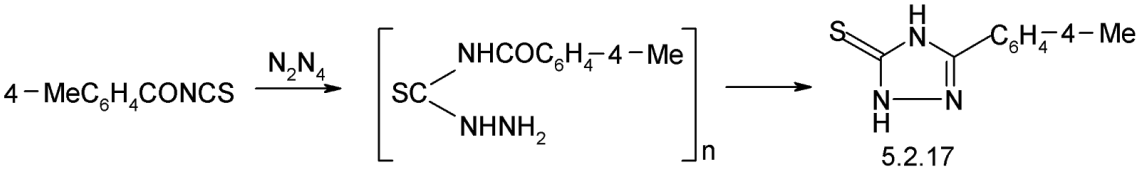


Figure 5.12

In the reaction of 1,4-dibenzoyl-3-thiosemicarbazide with aqueous sodium hydroxide the 4-benzoyl group is hydrolyzed and the resulting 1-benzoyl-3-thiosemicarbazide intermediate is converted to desired product (**Figure 5.13**).[1]

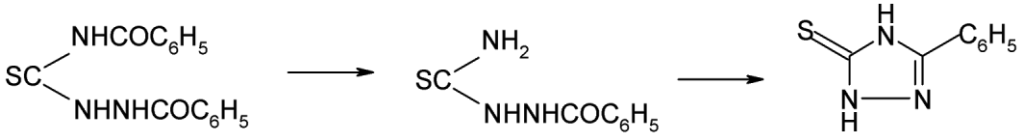


Figure 5.13

Several monosubstituted triazoline-5-thione have been reported from amidrazones, by the reaction with carbon disulfide in ethanolic potassium hydroxide as illustrated (**Figure 5.14**).[1]

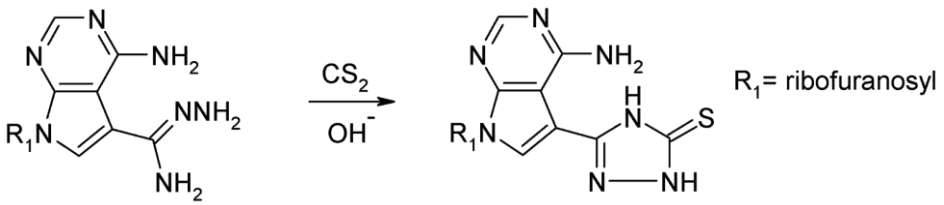


Figure 5.14

c. 3,4-Disubstituted-1,2,4-triazoline-5-thione

Treatment of 4-phenyl-3-thiosemicarbazide either with ethyl acetate in the presence of ethoxide or with ethylorthoacetate in refluxing xylene gave good yields of 3-methyl-4-phenyl-triazoline-5-thione (**Figure 5.15**).[1]

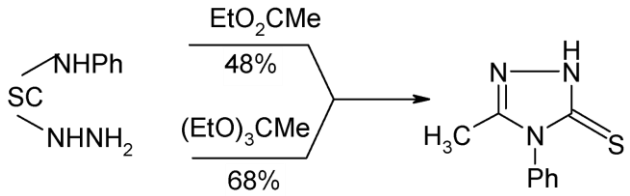


Figure 5.15

In the reactions of 4-phenyl-3-thiosemicarbazide with the iminoether, the product obtained depends upon the nature of the solvent. In refluxing ethanol, a good yield of 1,3,4-thiadiazole was isolated, whereas in refluxing pyridine a good yield of 3,4-diphenyl triazoline-5-thione was isolated (**Figure 5.16**).[1]

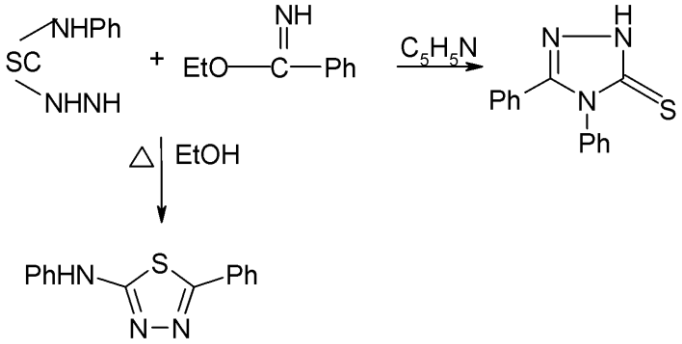


Figure 5.16

The conversion of acyl or aroyl-3-thiosemicarbazides to triazoline-5-thiones with (**Figure 5.17**) aqueous hydroxide includes the cyclization of 1-acetyl-4-methyl-3-thiosemicarbazide to 3,4-dimethyl-triazoline-5-thione and 1-(3,4,5-trimehoxybenzoyl)-4-propyl-3-thiosemicarbazide to 3-(3,4,5-trimethoxyphenyl)-4-propyltriazoline-5-thione.[1]

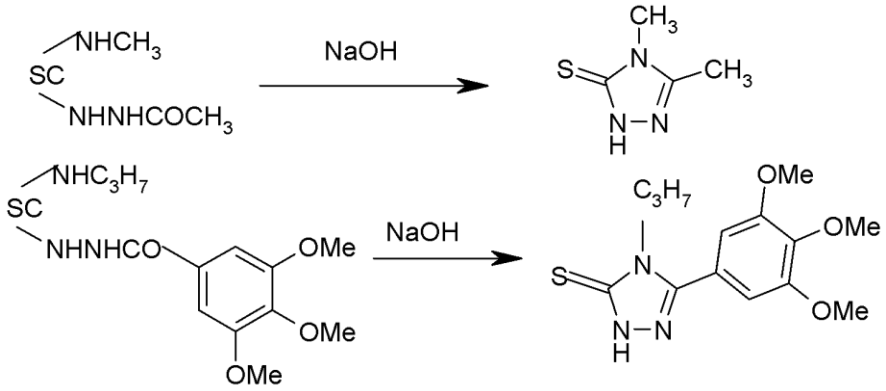


Figure 5.17

Oxidation of 4-aryl-1-benzylidene-3-thiosemicarbazones with bromine in chloroform give 2-(benzylidenehydrazino)-benzothiazoles when the ortho positions of the aryl group were unsubstituted and a

mixture of the benzothiazole and a 3,4-diaryl-triazoline-5-thiones when one of the ortho positions of the aryl group was blocked (**Figure 5.18**).[1]

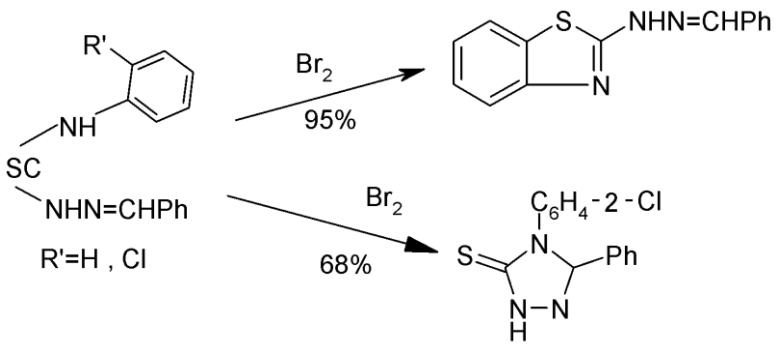


Figure 5.18

In contrast oxidation of 4-benzyl-3-thiosemicarbazones with bromine in chloroform gave mixtures of 3-aryl-4-benzyl-1,2,4-triazoline-5-thiones and 5-aryl-2-benzylamine-1,3,4-thiadiazoles. However, the major product was the triazoline-5-thiones when the oxidation was affected with bromine in acetic acid (**Figure 5.19**).[1]

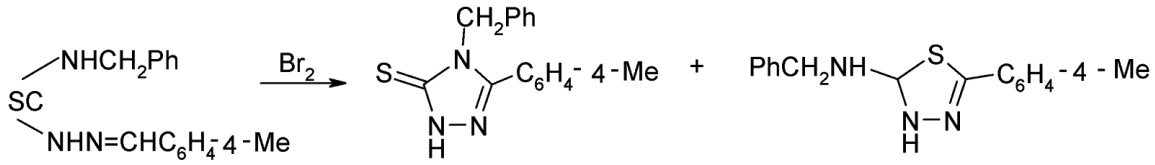


Figure 5.19

Several reports have been appeared on the conversion of amidrazones to triazoline-5-thiones. For example, the hydrochloride of amidrazone was heated with ethoxycarbonylmethyl isothiocyanate to give a good yield of 3,4-disubstituted-triazoline-5-thione. In this reaction the 4-N of the triazole ring was provided by the isothiocyanate indicating that the amino group of the amidrazone was displaced (**Figure 5.20**).[1]

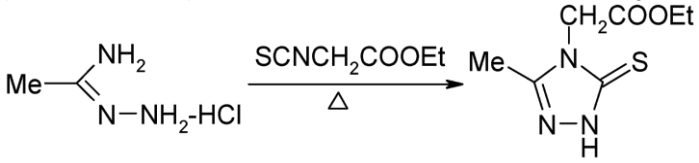


Figure 5.20

Acylhydrazides reacted with isothiocynates in a one-pot procedure using microwave irradiation of the starting materials in the presence of either silica or montmorillonite K10 to give the 3-mercapto-1,2,4-triazoles in high yield (**Figure 5.21**).[7]

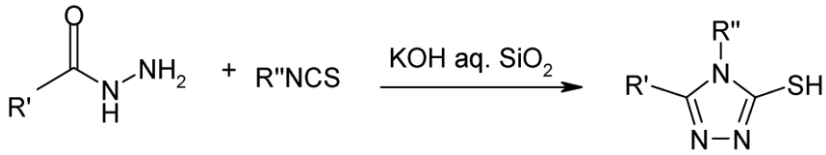


Figure 5.21

Reaction of carbohydrazonamides (**Figure 5.22**) with 1,1'-thiocarbonyldiimidazole as the donor of the remaining carbon atom required in tetrahydrofuran gave the corresponding 1,2,4-triazole-5-thiones.[8]

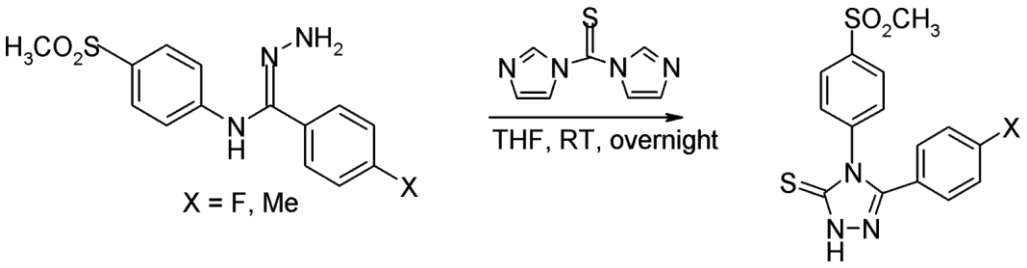


Figure 5.22

Cyclization of semicarbazide derivatives was achieved using microwave irradiation in the presence of sodium hydroxide for 2-4 minutes to give the corresponding 3-mercapto-1,2,4-triazoles in high yields (**Figure 5.23**).[9]

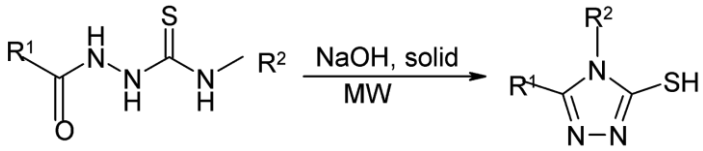


Figure 5.23

d. Ring synthesis by transformation of another ring

1,3,4-oxadiazole bearing a ferrocenyl substituent reacted with ammonium ethanoate and hydrazine yields the corresponding 1,2,4-triazoles in reasonable yield (**Figure 5.24**).[10]

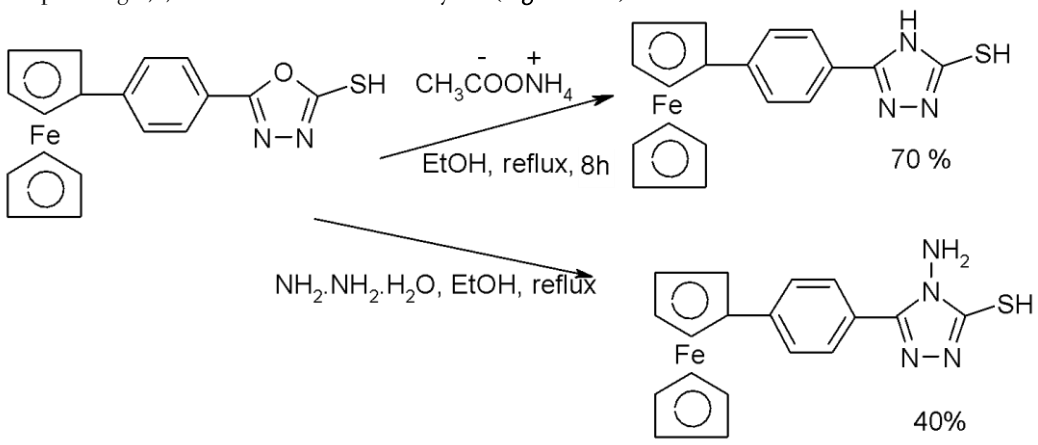


Figure 5.24

The formation of monosubstituted triazoline-5-thiones from a variety of other ring systems has been observed. Treatment of the thiazolidine with hydrazine hydrate at room temperature gave intermediate, which when heated with hydrazine gave desired product (**Figure 5.25**). Similarly it is formed directly by refluxing in aqueous hydrazine.[1]

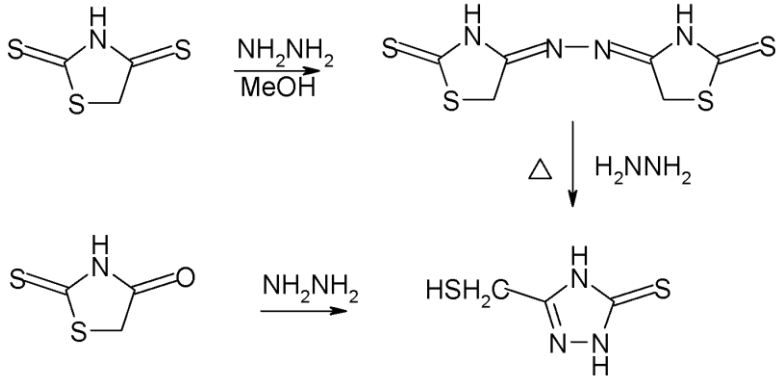


Figure 5.25

In the reaction of the benzoxazine with 80% hydrazine hydrate a 72% yield of the 3-(2-hyroxyphenyl)triazoline-5-thione was obtained (**Figure 5.26**).[1]

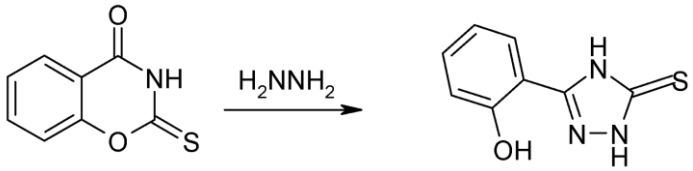


Figure 5.26

Synthesis of 3-substituted triazoles by diazotiation:-

Organic chemists have uses diazotization reactions of aromatic amines to synthesize a strong electrophile that can subsequently undergo nucleophilic attack to transform aromatic systems[11-12]. Our interest is in synthesis of the azido substituted triazole from the idea that azide functionalities could be exploited efficiently to react with substituted alkynes in a 1,3 dipolar cyclo-addition reaction to form a novel class of molecules encompassing both 1,2,4-triazole and 1,2,3- triazoles connected together.. We observed that if the diazo intermediate was react with another equivalent of amino triazole it leads to the formation of the self-coupling product. It is important to note that while halogenation and azide formation reactions through the application of diazotization chemistry are widely reported[13-14], very few examples of use of other nucleophiles exist[15-16]. On the other hand, virtually no reports exist of C-N bond formation through use of primary amines as nucleophiles. **Figure1.27** depicts the application of the diazotization strategy towards carrying out modifications at 3-position..

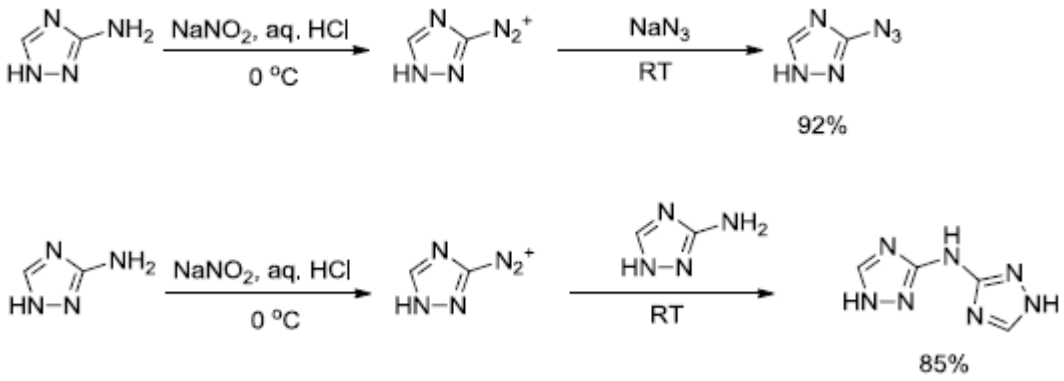
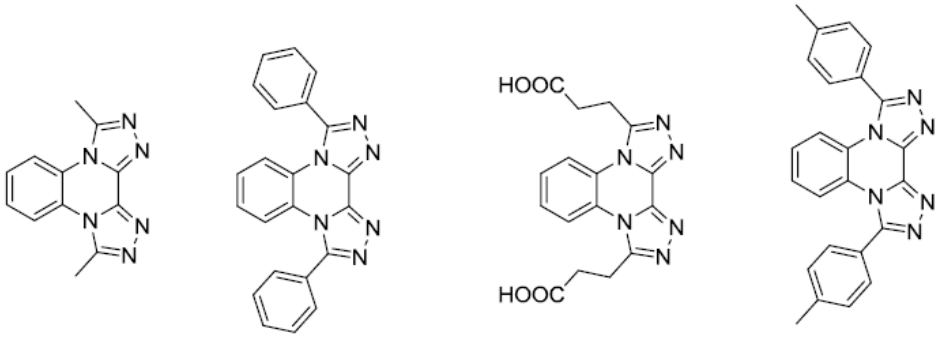


Figure 1.27

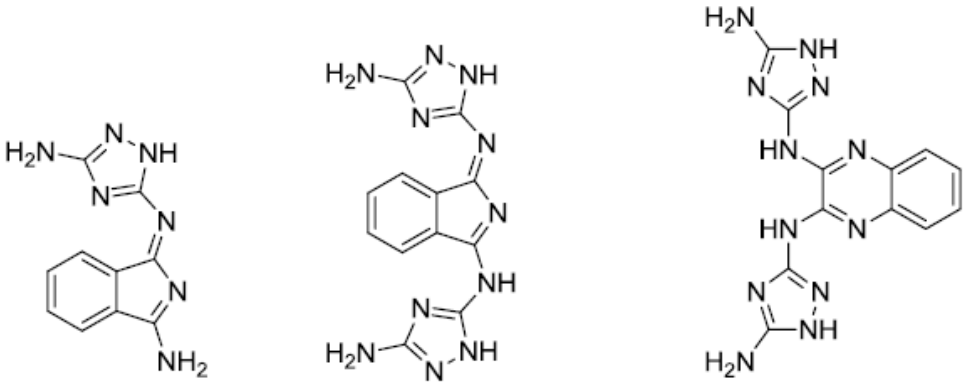
Synthesis of fused-1,2,4-triazoles

Figure 1.28 lists all of these molecules Compounds **a** to **g** were prepared [17]. This involved thermal fusion of hydrazides with dichloroquinoxalines, which led to the formation of tetracyclic molecules containing two triazoles fused with the quinoxaline ring system. The required dichloroquinoxaline precursors can be prepared over two steps starting from 1,2-diamines, as depicted in the **Figure 1.29**. 1,2-diamines were subjected to cyclization reaction with oxalic acid in acidic medium leading to diones. The diones upon treatment with thionyl chloride under reflux were converted to the dichloroquinoxalines.

The fusion reaction with hydrazide takes place only if hexamethyl phospharamide is used as a solvent. Due to high toxicity of this solvent we attempted to use various other solvents as substitutes for this reaction. However, none of the other solvents tested were successful in delivering the desired results. Use of microwave synthesizer did not result in any improvements.



A b c d



E f g .

Figure 1.28

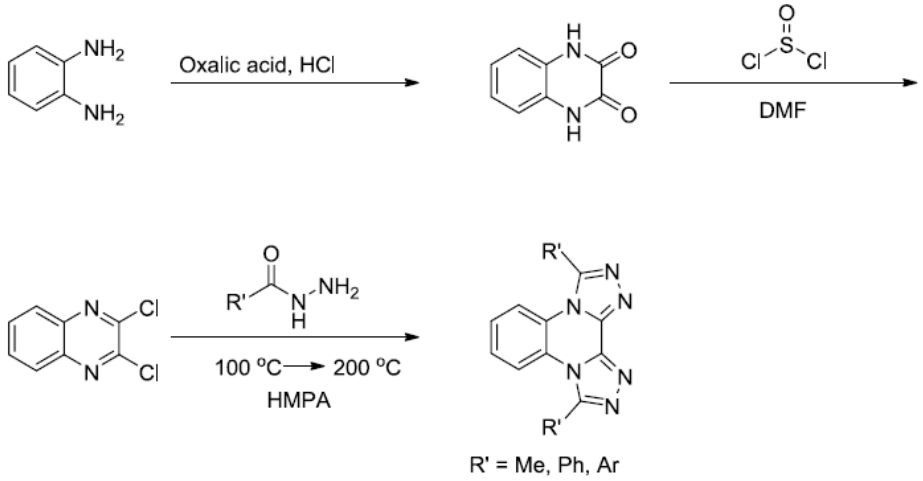


Figure 1.29

REFERENCES

1. Carroll Temple, John A. Montago Meri Chemistry of Heterocyclic Compounds: Triazoles 1,2,4, vol 37, editor, (1981), John Wiley and son's, 251-287.
2. Dobosz M., Pitucha M., Wujec M., Actapolon pharm., 53, 1, (1996), 31-38.
3. Mekuskiene G., Gaidelis P., Vainilavicius P., Pharmazie, 53 (2), (1998) 94-96.
4. Grand M., Compt. Rend, 225, (1947) 458.
5. Albrecht W.L., Jones W.D., U.S. Patent 4, 230, 715 (1979), Chem. Abstr. 94, 121552f (1981).
6. Hoggarth E., J. Chem. Soc.(1949) 1160-1163.
7. Rostamizadeh S., Mollahoseini K., Moghadusi S., Phosphorus, Sulfur, silicon, Relat. Elem. 181, (2006) 1839-1846.
8. Navidpour L., Shafaroodi H., Abdi K. Amini M., Ghahremani M.H., Dehpour A.R., & Shafiee A., Bioorg. Med. Chem.14, (2006) 2507-2517.
9. Zamani K. and Bagheri S., Phosphorous, Sulfur, Silicon, Relat. Elem. 181, (2006), 1913-1918.
10. . Sarhan A.A.O., Izumi T., J. Organomet. Chem. 675, (2003) 1-12.
11. Krasnokutskaya, E. A.; Semenischeva, N. I.; Filimonov, V. D.; Knochel, P., A new,one-step, effective protocol for the iodination of aromatic and heterocyclic compounds via aprotic diazotization of amines. Synthesis-Stuttgart 2007, (1), 81-84.
12. Moumne, R.; Lavielle, S.; Karoyan, P., Efficient synthesis of beta(2)-amino acid by homologation of alpha-amino acids involving the Reformatsky reaction and Mannichtype imminium electrophile. J Org Chem 2006, 71 (8), 3332-3334.
13. Barral, K.; Moorhouse, A. D.; Moses, J. E., Efficient conversion of aromatic amines into azides: A one-pot synthesis of triazole linkages. Org Lett 2007, 9 (9), 1809-1811.
14. Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M., Radical azidonation of aldehydes. J Org Chem 2003, 68 (24), 9453-9455.
15. Cadogan, J. I. G., A Convenient New Method of Aromatic Arylation. J Chem Soc
16. 1962, (10), 4257
17. Friedman, L.; Bayless, J. H., Aprotic Diazotization of Aliphatic Amines .Hydrocarbon Products and Reaction Parameters. Journal of the American ChemicalSociety 1969, 91 (7), 1790
18. Sastry, C. V. R.; Krishnan, V. S. H.; Narayan, G. K. A. S. S.; Vemana, K.; Vairamani, M., Reaction of 2,3-Dichloroquinoxaline with Acid Hydrazides - a Convenient Synthesis of 1,6-Disubstituted[1,2,4]Ditriazolo[4,3-a-3',4'-C]-Quinoxalines and 2-Aryl Heteroaryl[1,3,4]Oxadiazino[5,6-B]Quinoxalines. Indian J Chem B 1991, 30 (10), 936-940.