Hydrazinecarbothioamide group in the synthesis of heterocycles

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Abstract
The review summarizes recent literatures dealing with hydrazinecarbothioamide group in thiocarbohydrazides and other derivatives including their physical and chemical properties along with their applications in the synthesis of heterocycles.

Keywords: Hydrazinecarbothioamides, heterocycles

Contents

Introduction

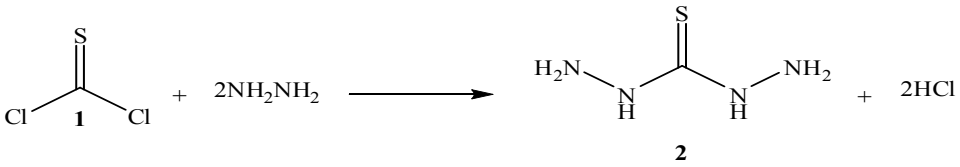
Carbohydrazide and thiocarbohydrazide are hydrazine derivatives of carbonic and thiocarbonic acids. Although in general thiocarbohydrazides are more widely used in heterocyclic synthesis than thioureas, both types contain the functional group RNHCSNHR. Substituted thiobiureas (RNHCONHNHCSNHR) are key to the synthesis of many organic heterocyclic ring systems. Several authors have investigated under various conditions the heterocyclization of 1-acylthiobiurea,[1] 1,6-disubstituted 2,5-dithiobiureas,[2] and 1-aryl/alkyl-2-thiobiureas.[3] Also, the heterocyclization of compounds having an extended urea-like chain such as 1,4- and 2,4-disubstituted thiosemicarbazides have been reported.[4,5] Thiocarbohydrazide derivatives have attracted much attention in recent years due to their applications in the synthesis of heterocyclic compounds,[6] synthesis of transition metal complexes,[7,8] and pharmacological studies.[3] Moreover, carbohydrazide derivatives were widely used as an oxygen scavenger (metal passivator) for water treatment systems, particularly for boiler-feed systems.[9] The chemistry of carbohydrazides has grown fast, and has not been reviewed in more than three decades. Accordingly, it is important to shed more light on the recent literature dealing with that chemistry, especially in the field of heterocycles.

1. Synthesis of Thiocarbohydrazides

Syntheses of carbohydrazide and thiocarbohydrazide of preparative value are exclusively variations of one basic reaction, *viz.* the hydrazinolysis of carbonic and thiocarbonic acid derivatives. The individual variants of this general synthesis differ from one another in their applicability and relative merit and are discussed separately below.

1.1. Hydrazinolysis of thiophosgene

Reaction of thiophosgene (**1**) with hydrazine afforded directly thiocarbohydrazide (**2**) as shown in Scheme 1.[10]



Scheme 1

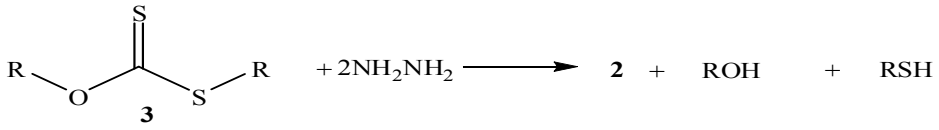
1.2. Hydrazinolysis of carbon disulfide

The reaction of hydrazine with carbon disulfide is no doubt the cheapest and most useful method for the preparation of thiocarbohydrazide (**2**) in quantity.[11]

$$CS_2 + 2NH_2NH_2 \rightarrow NH_2NHCSNHNH_2 \ (\mathbf{2}) + H_2S$$

1.3. Hydrazinolysis of dialkyl xanthates

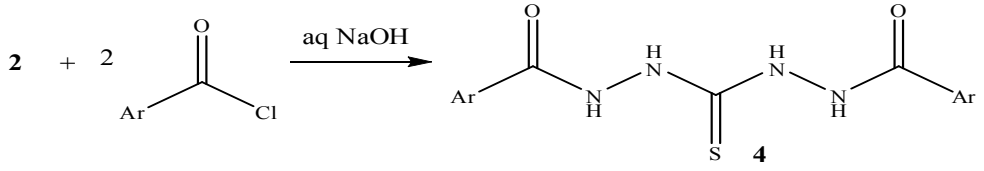
The hydrazinolysis of dialkyl xanthates **3** is a possible route to thiocarbohydrazide (**2**). By warming the two reactants, high yields of thiocarbohydrazide are claimed to be obtainable; the effluent gases, ethanol and ethanethiol, are ignited as they leave the reaction vessel (Scheme 2).[12,13]



Scheme 2

1.4. General procedure for the preparation of 1,5-diacyl thiocarbohydrazides

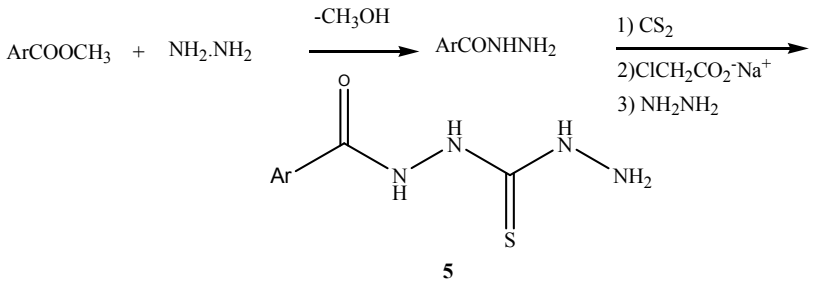
Thiocarbohydrazide (**2**) was dissolved in aqueous NaOH solution, which was added dropwise to a solution of acid chloride in tetrahydrofuran at 0-5 ^{o}C. The reaction mixture was then stirred at room temperature for 2 h to give products **4** in 71-80% yield (Scheme 3).[14]



Scheme 3

1.5. From acid hydrazides

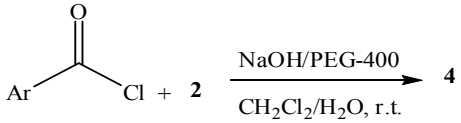
Varma[15] reported the synthesis of benzamidothiosemicarbazides (*N*-aroyl thiocarbohydrazides) **5** by treating successively the acid hydrazides prepared by the hydrazinolysis of the acid methyl ester with carbon disulphide, sodium monochloroacetate and hydrazine hydrate (Scheme 4).[15]



Scheme 4

1.6. By phase-transfer catalysis

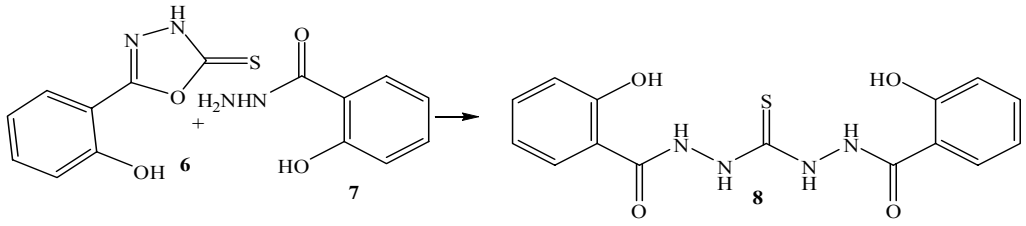
1,5-Diacyl thiocarbohydrazides **4** were efficiently synthesized in high yield (89-95%) by the reactions of thiocarbohydrazide **2** with a variety of aroyl chlorides at room temperature using PEG-400 as a phase-transfer catalyst (Scheme 5).[16]



Scheme 5

1.7. From 1,3,4-oxadiazole-2-thione

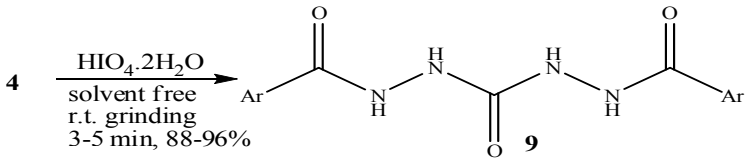
The reaction of 5-(2-hydroxyphenyl)-1,3,4-oxadiazole-2(3*H*)-thione (**6**) and salicyloyl hydrazide (**7**) led to the formation of disalicyloyl thiocarbohydrazide (**8**) (Scheme 6).[17]



Scheme 6

1.8. Action of periodic acid

1,5-Diacyl thiocarbohydrazides **4** were expeditiously transformed into the corresponding 1,5-diacyl carbohydrazides **9** with periodic acid by room temperature grinding under solvent free conditions. This protocol has the advantages of mild conditions, fast reaction rate, high yield, and simple work-up procedure (Scheme 7).[18]



Scheme 7

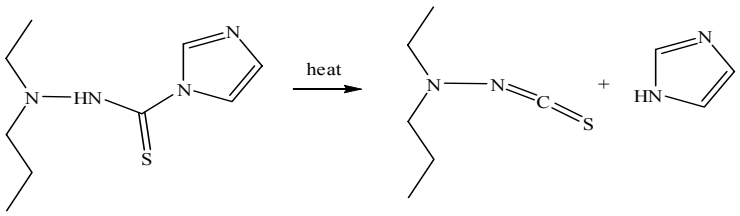
2. Biological activities of thiocarbohydrazide derivatives

Thiocarbohydrazide is the closest structural analog of thiosemicarbazide, derivatives of which are recommended as effective antitubercular[18,19] and antiviral preparations.[20] Thiocarbazides of the aromatic series also exhibit high antiviral[21] and antimicrobial activity.[22] Macrocycles synthesized in the reactions of thiocarbohydrazide (**2**) with polycarbonyl compounds and their complexes with the salts of divalent metals are effective fungistatic agents,[23] while the cytotoxicity of the carbohydrazones and thiocarbohydrazones of some ketones is commensurable with or even exceeds the cytotoxicity of the well-known product melphalan.[24]

3. Reactions of thiocarbohydrazides

3.1. Thermolysis of thiocarbohydrazides

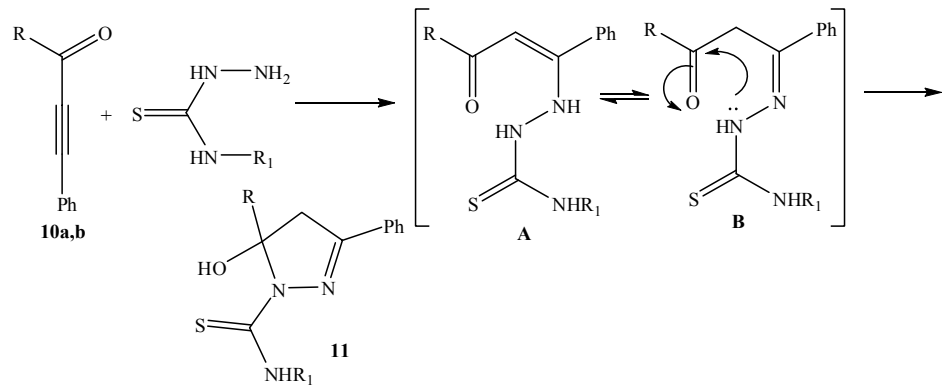
Thermolysis of dithiocarbohydrazides offers monomeric and dimeric aliphatic and aromatic *N*-isothiocyanatoamines. An example is shown in Scheme 8.[25]



Scheme 8

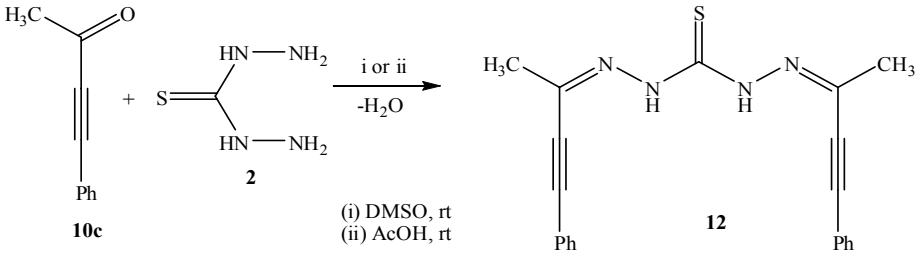
3.2. Reactions of thiocarbohydrazides with acetylenic compounds

1-Benzoyl-2-phenylacetylene (**10a**) and 1-(2-thienoyl)-2-phenylacetylene (**10b**) with thiocarbohydrazides in acetic acid/water or ethanol/water, with the reagents in an equimolar ratio, led to the formation of the corresponding 1-carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-*R*-2-pyrazolines **11** with yields of 60-88% (Scheme 9).[26]



Scheme 9

The structure of the compounds **11** so obtained demonstrated that the process takes place selectively through the intermediate formation of the enamine **A**, which is in tautomeric equilibrium with the hydrazone form **B**; at the second stage of the reaction attack by the amide nitrogen atom on the electron-deficient carbonyl carbon atom is accompanied by closure of the pyrazoline ring (Scheme 9).[26] By contrast, 1-acetyl-2-phenylacetylene **10c** reacted with thiocarbohydrazide (**2**) in (i) DMSO or (ii) AcOH at room temperature only through the carbonyl moiety to furnish N^2-(*Z*-*s*-*trans*)- and N^3-(*Z*-*s*-*cis*)-bis(1-methyl-3-phenyl-2-propynylidene)-carbonothioic dihydrazides **12** in 76 or 92% yield, respectively (Scheme 10).[27]



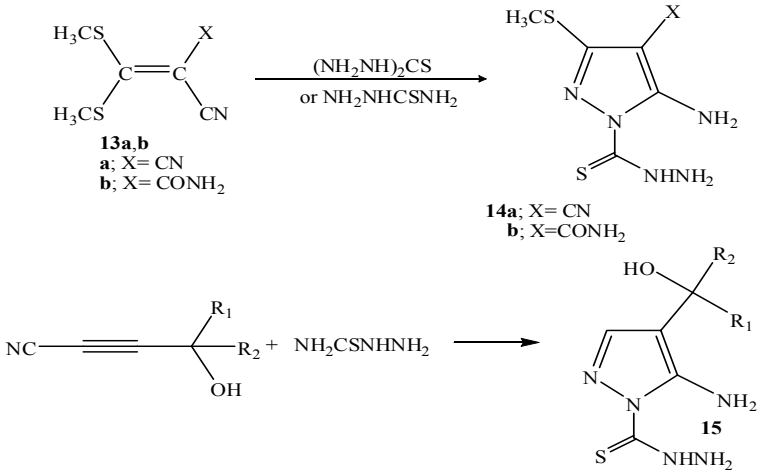
Scheme 10

4. Thiocarbohydrazides in the synthesis of heterocycles

4.1. Synthesis of pyrazoles

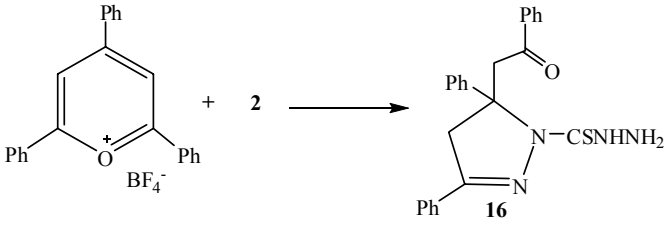
As previously mentioned, 1-benzoyl-2-phenylacetylene (**10a**) and 1-(2-thenoyl)-2-phenylacetylene (**10b**) reacted with thiocarbohydrazides to give 1-carbothiohydrazinoyl-5-hydroxy-3-phenyl-5-*R*-2-pyrazolines **11** with yields of 60-88% (Scheme 9).[26] The reaction of ketene dithioacetals **13a**,**b** with thiocarbohydrazide (**2**) in hot ethanol afforded the corresponding pyrazole derivatives **14a**,**b**, respectively (Scheme 11).[28a] The reaction of α,β-acetylenic γ-

hydroxy nitriles with thiosemicarbazide, under mild conditions (rt, no catalyst, in 1:1 aqueous ethanol, 4–14 h), proceeds chemo-, regio- and stereoselectively to give hitherto inaccessible tri-functionalized (amino, hydroxylalkyl and thioamide groups) pyrazoles **15** in 53–91% yields. The hydroxyl function is easily protected by using the corresponding acetals of the starting acetylenic hydroxynitriles (Scheme 11).[28b]



Scheme 11

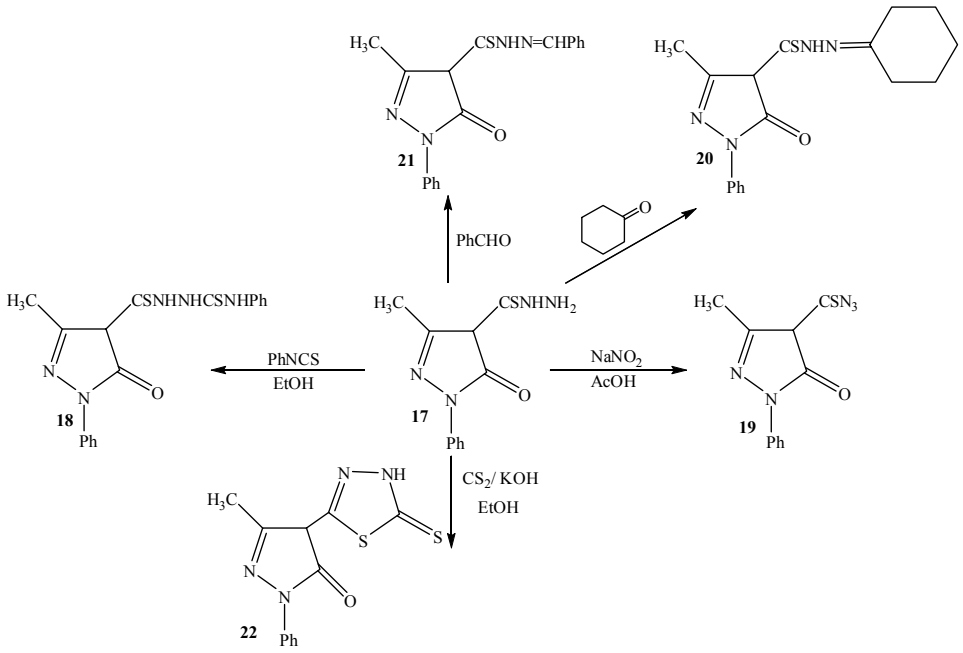
Reaction of 2,4,6-triphenylpyrylium tetrafluoroborate with **2** at room temperature in ethanol in the presence of triethylamine gave 5-(2-oxo-2-phenylethyl)-3,5-diphenylethyl)-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothiohydrazide (**16**, Scheme 12).[29]



Scheme 12

Heating of 3-methyl-5-oxo-1-phenyl-Δ^2-pyrazoline-4-thiocarbohydrazide (**17**) with phenyl isothiocyanate in absolute ethanol afforded N^1-(4,5-dihydro-3-methyl-5-oxo-1-phenylpyrazol-4-yl)thiocarbonyl-N^4-phenylthiosemicarbazide (**18**, Scheme 13).[30] Treatment of **17** with sodium nitrite in acetic acid yielded 4-azidothiocarbonyl-3-methyl-1-phenyl-Δ^2-pyrazolin-5-one (**19**). Compound **17** underwent facile condensation with cyclohexanone and benzaldehyde in absolute ethanol giving N^1-cyclohexylidine-3,4-dihydro-3-methyl-5-oxo-1-phenylpyrazole-4-thiocarbohydrazide (**20**) and N^1-benzylidine-3,4-dihydro-3-methyl-1-phenylpyrazole-4-

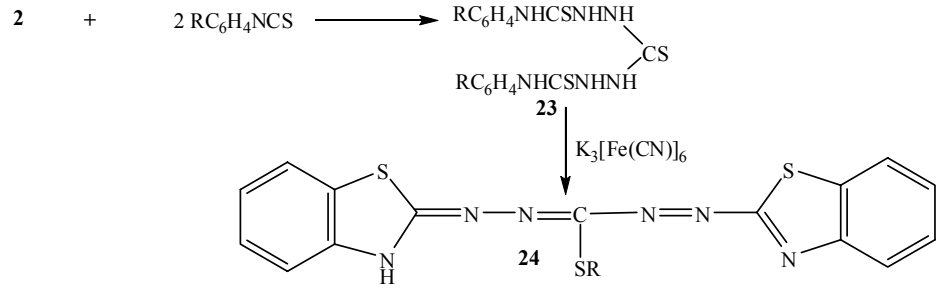
thiocarbohydrazide (**21**), respectively (Scheme 13). Compound **17** reacted with CS_2 in KOH to give 4-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)-3-methyl-1-phenyl-Δ^2-pyrazolin-5-one (**22**, Scheme 13).[31]



Scheme 13

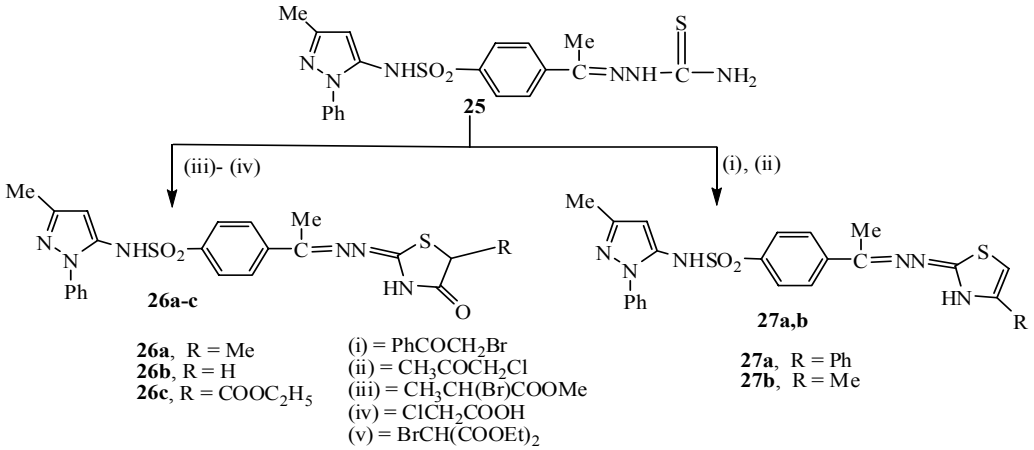
4.2. Synthesis of thiazoles and thiazolidines

Reaction of **2** with aryl isothiocyanates gave 1,5-di(arylamidothiocarbo)-thiocarbohydrazides **23** (Scheme 14). Oxidation of **23** with potassium ferrocyanide afforded symmetrical bis-benzothiazoles (**24**, Scheme 14).[31] Surprisingly, reaction proceeds *via* migration of alkyl substitutent to form the thionylated product **24** (Scheme 14).[13]



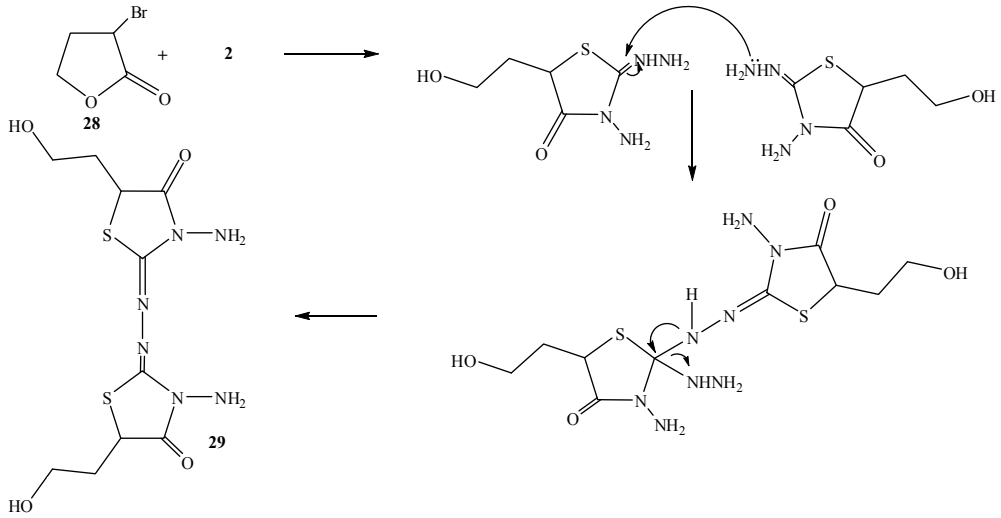
Scheme 14

Allowing compound **25** to react with α-halocarbonyl compounds such as phenacyl bromide, chloroacetone, 2-bromomethyl propionate, chloroacetic acid, and bromo- diethylmalonate afforded the thiazolines **26a-c** and thiazolidinones **27a**,**b**, respectively (Scheme 15).[32]



Scheme 15

When thiocarbohydrazide (**2**) was treated with an equivalent of α-bromo-γ-butyrolactone (**28**) in boiling ethanol, a 1,3-thiazolidine dimer (**29**) was provided in low yield (Scheme 16).[33]

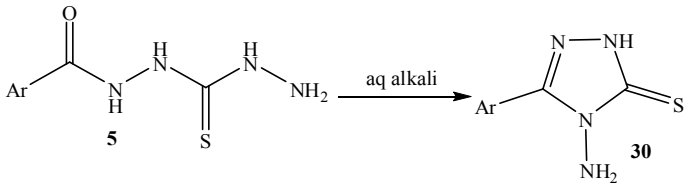


Scheme 16

4.3. Synthesis of 1,2,4-triazolethiones

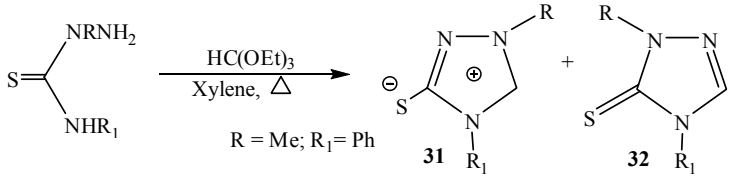
4-Amino-3-substituted-l,2,4-triazol-5-thiones have proven to possess high cytotoxicity in vitro against thymocytes.[34a] 1-Acyl thiocarbohydrazides **5** were cyclized with aqueous NaOH to 4-amino-3-aryl(*H*)-l,2,4-triazol-5-thione (**30**, Scheme 17).[34b] Several derivatives of compound **5**

have been similarly cyclized by aqueous NaOH.[34c] Additional syntheses of bis-[4-*N*-amino-5-mercapto-1,2,4-triazol-3-yl]alkanes were reported.[34d] Moreover, 4-amino-5-mercapto-5-[(1*H*-indol-3-yl)methyl]-1,2,4-triazole has been synthesized by heating thiocarbohydrazide with 1*H*-indol-3-acetic acid.[34e]



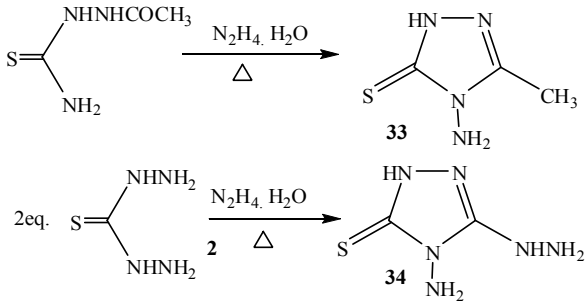
Scheme 17

Reactions of 2-methyl-4-phenylthiosemicarbazide with ethyl orthoformate in boiling xylene led to the formation of 2-methyl-4-phenyl-1,2,4-triazolium-5-thiolate (**31**) and 1-methyl-4-phenyl-1,2,4-triazoline-5-thione (**32**, Scheme 18).[35] The formation of these mesoionic compounds resulted from the rearrangements of 2,4-disubstituted thiosemicarbazides to 1,4-derivatives, which helped to depict the structure quite convincingly.[35]



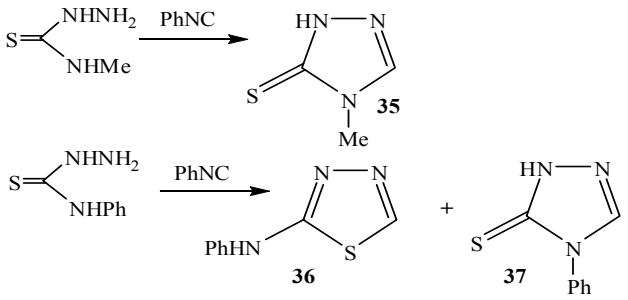
Scheme 18

Hydrazine reacted with acetylhydrazine-carbothioamide to afford 4-amino-3-methyl-Δ^2-1,2,4-triazoline-5-thione (**33**), whereas two molecules of **2** reacted together in presence of hydrazine to form 4-amino-3-hydrazino-Δ^2-1,2,4-triazoline-5-thione (**34**, Scheme 19).[36]



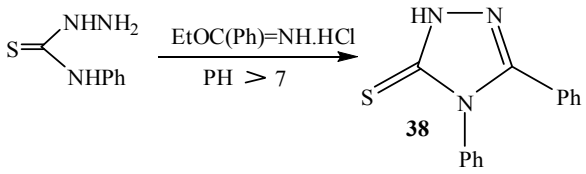
Scheme 19

N-Methyl hydrazinecarbothioamide reacted with phenyl isocyanide to yield only 4-methyl-Δ^2-1,2,4-triazoline-5-thione (**35**), whereas *N*-phenyl-hydrazine-carbothioamide afforded 2-phenylamino-1,3,4-thiadiazole (**36**) in addition to 4-phenyl-Δ^2-1,2,4-triazoline-5-thione (**37**, Scheme 20).[37]



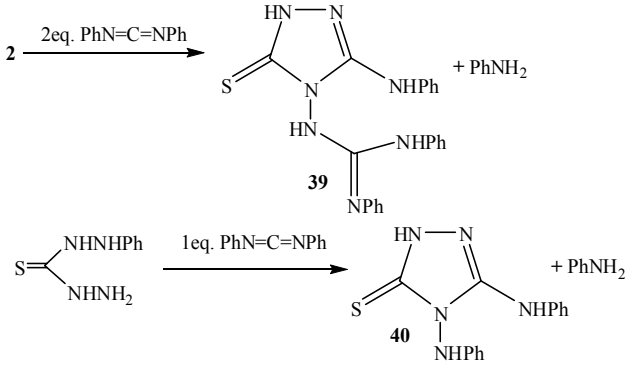
Scheme 20

Reactions of *N*-phenyl-hydrazine-carbothioamide with ethylphenylimidate hydrochloride at pH > 7 illustrated the formation of 3,4-diphenyl-Δ^2-1,2,4-triazoline-5-thione (**38**, Scheme 21).[38]



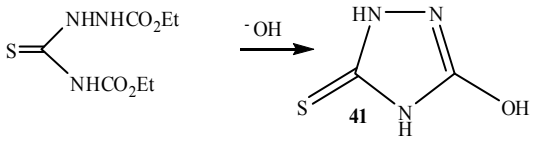
Scheme 21

Compound **2** reacted with two equivalents of diphenylcarbodiimide in DMF to yield 3-anilino-4-(*N*,*N*'-diphenylguanidino)-Δ^2-1,2,4-triazoline-5-thione (**39**, Scheme 22).[39] On the contrary, 1-phenylthiocarbohydrazide reacted with one equivalent of diphenylcarbodiimide in DMF to yield 3,4-bis(phenylamino)-Δ^2-1,2,4-triazoline-5-thione (**40**, Scheme 22).[40]



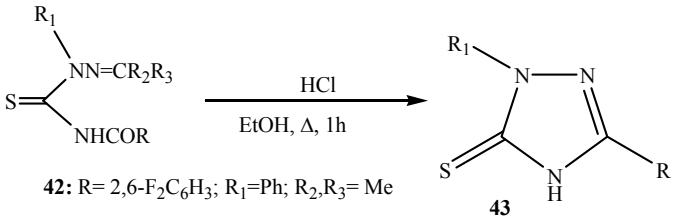
Scheme 22

Similarly, Kurzer and Secker reported the formation of 3-hydroxy-Δ^2-1,2,4-triazoline-5-thione (**41**) from 1,4-bis(ethoxycarbonyl) thiosemicarbazide under alkaline conditions (Scheme 23).[41]



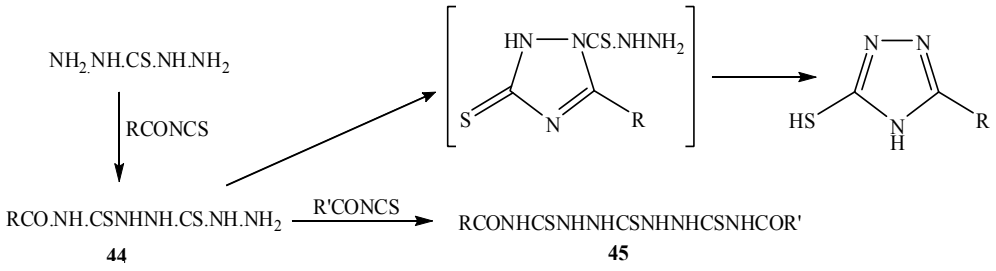
Scheme 23

Compounds like 3-(2,6-difluorophenyl)-1-phenyl-Δ^2-1,2,4-triazoline-5-thiones **43** having insecticidal properties were prepared by heating thiosemicarbazones **42** in ethanolic hydrochloric acid (Scheme 24).[42]



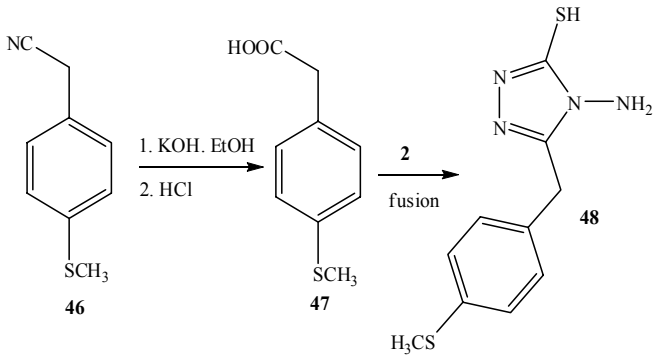
Scheme 24

Equimolar quantities of thiocarbohydrazide (**2**) and aroyl isothiocyanates reacted in DMF at room temperature, affording excellent yields of the monoadducts, *i.e.* l-amino-thiocarbamoyl-4-aroyl-3-thiosemicarbazides (**44**, R = C_6H_5, *p*-ClC_6H_4, or *p*-$MeOC_6H_4$, Scheme 25).[43] The action of two moles of benzoyl isothiocyanate readily gave the linear di-adduct, *e.g.* (**45**; R = R' = Ph). Boiling of compound **44** in alkali gave rise to cyclization, forming 3-mercapto-5-phenyl-1,2-4-triazole (R = C_6H_5) as shown in Scheme 25.[43]



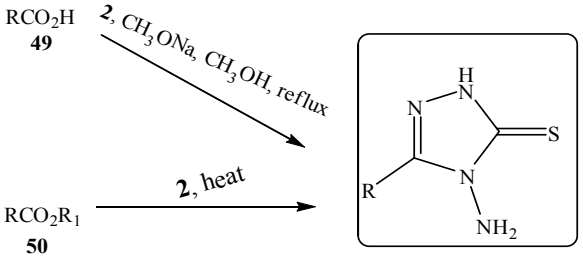
Scheme 25

4-Methylthiophenyl acetonitrile (**46**) was converted into 4-methylthiophenyl acetic acid (**47**) by alkaline hydrolysis (Scheme 26).[43] The acid **47** was fused with thiocarbohydrazide (**2**) to get 4-amino-5-(4-methylthio)benzyl)-4*H*-1,2,4-triazole-3-thiol (**48**) as illustrated in Scheme 26.[44] In this procedure, an equimolar mixture of **47** and **2** was heated in an oil bath till the contents melted. The reaction mixture was maintained at this temperature for 3 h. Then it was allowed to cool and treated with dilute sodium bicarbonate solution in order to remove any unreacted acid. The solid was filtered, washed with water, dried and recrystallized from ethanol to obtain the pure triazole.[44]



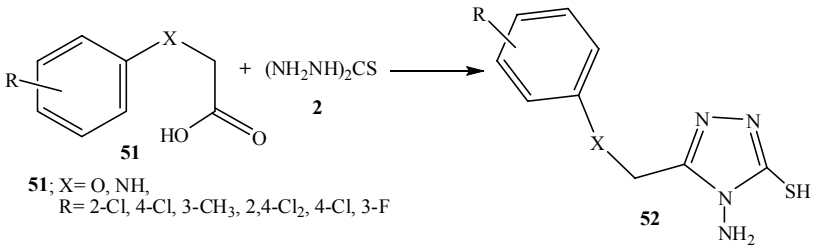
Scheme 26

Various 4-amino-2,3-dihydro-4*H*-triazoles with aromatic, aliphatic and heterocyclic substituents at the C(5) positions were synthesized from corresponding acids **49** and/or acid esters **50** and thiocarbohydrazide (**2**, Scheme 27).[44] This method allows the synthesis of these heterocycles in a short time and at reduced expense.[45]



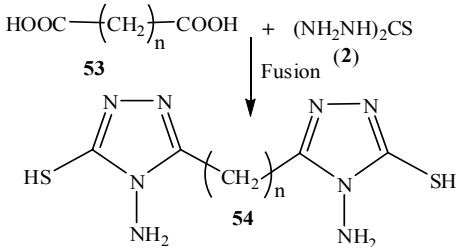
Scheme 27

Reaction of carboxylic acids **51** with thiocarbohydrazide (**2**) at melting temperature afforded 4-amino-5-mercapto-3-aryloxymethyl/anilinomethyl-1,2,4-triazoles **52** (Scheme 28).[46]



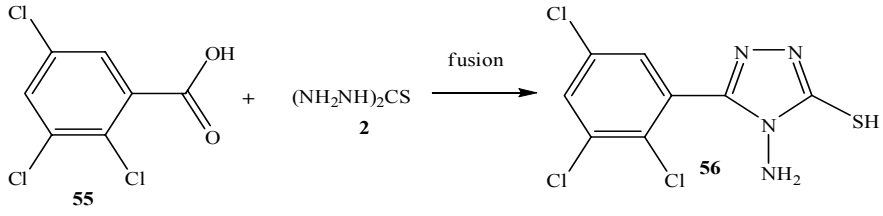
Scheme 28

Different dicarboxylic acids **53** were fused with **2** to obtain bis-[4-amino-5-mercapto-1,2,4-triazol-3-yl]alkanes (**54**, Scheme 29).[47]



Scheme 29

As an extension to the former work, fusing 2,3,5-trichlorobenzoic acid (**55**) with **2** afforded the corresponding 3-(2,3,5-trichlorophenyl)-4-amino-1,2,4-triazole-5-thione (**56**, Scheme 30).[48] Synthesized triazolethiols were screened for their antimicrobial and anti-inflammatory activities such as against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae*. Some of the compounds exhibited promising antimicrobial and anti-inflammatory activities.[48]

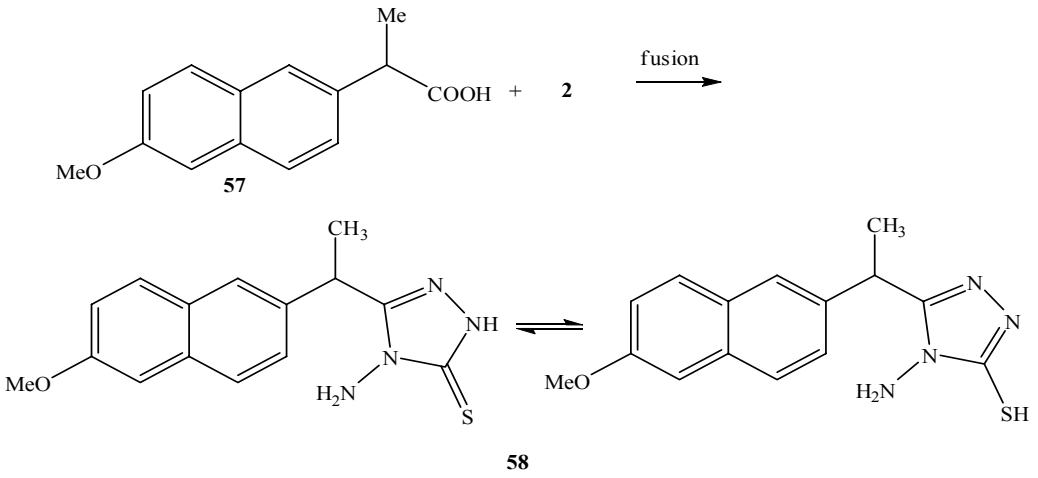


Scheme 30

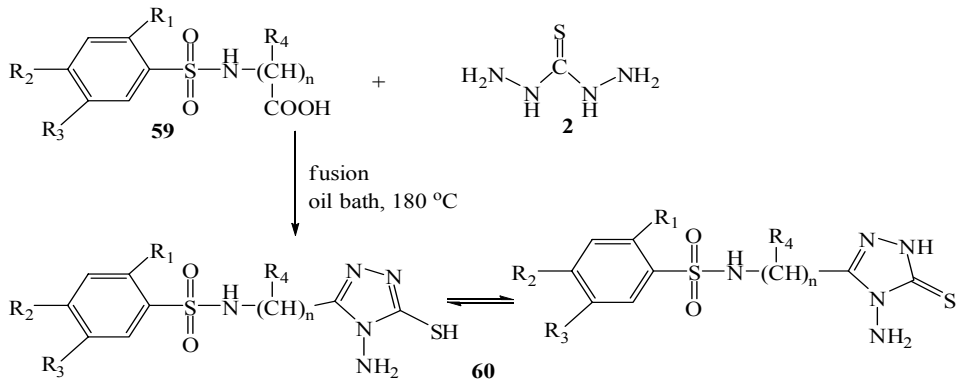
The biologically active 1-(6-methoxy-2-naphthyl)-1-(5-amino-4-mercapto-*s*-triazol-3-yl)ethane (**58**) was synthesized by the fusion of 2-(6-methoxy-2-naphthyl)-propanoic acid (**57**, Naproxen) and thiocarbohydrazide (**2**) as shown in Scheme 31.[49] Heterocyclic compound **58** exhibited a remarkable antifungal activity compared with the standard fungicide Mycostatine.

Radiosterilization of **58** in the dry state proves to be applicable (retaining their structures unchanged up to 40 kGy).[49]

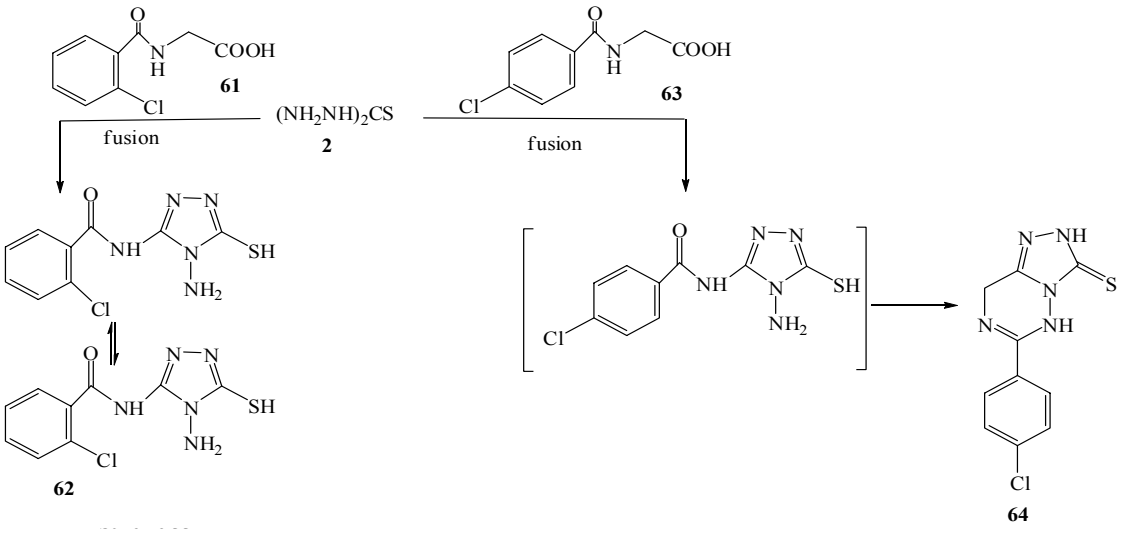
The *s*-triazolosulfonamide derivatives **60** were obtained in good yields by fusion of the tosyl amino acid derivatives **59** with **2** in an oil bath at 180 °C (Scheme 32).[50]



Scheme 31

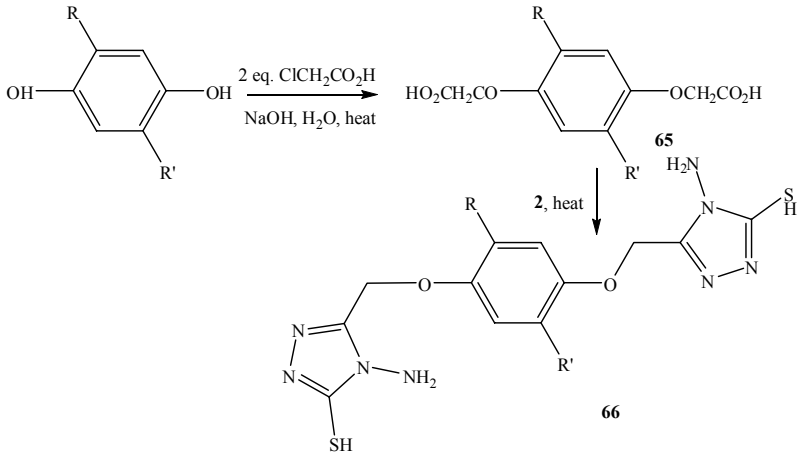


Scheme 32



Scheme 33

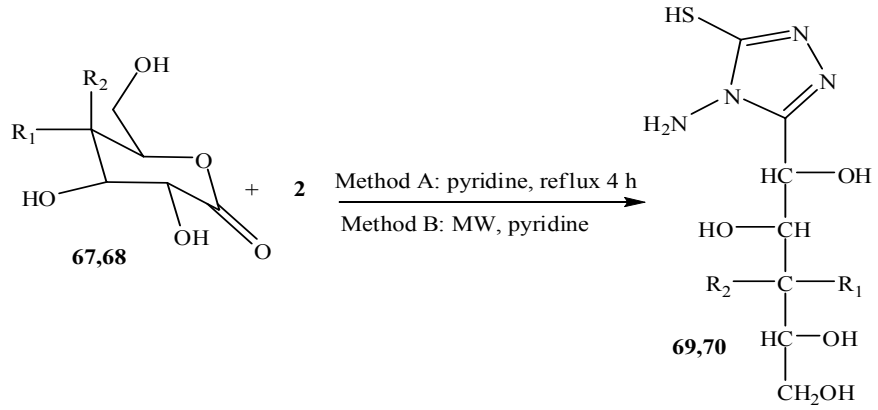
Fusion of **2** with 2-chlorohippuric acid (**61**) afforded the corresponding triazole derivative **62**. In the reaction of **2** with 4-chlorohippuric acid (**63**), double cyclization occurred to give the triazolotriazine (**64**) *via* the expected triazole derivative (Scheme 33),[50] while fusion of bis-phenoxyacetic acids **65** with thiocarbohydrazide (**2**) afforded 1,4-bis-[4-amino-5-mercapto-1,2,4-triazol-3-ylmethoxy]-phenylenes **66** in good yields (Scheme 34).[51]



Scheme 34

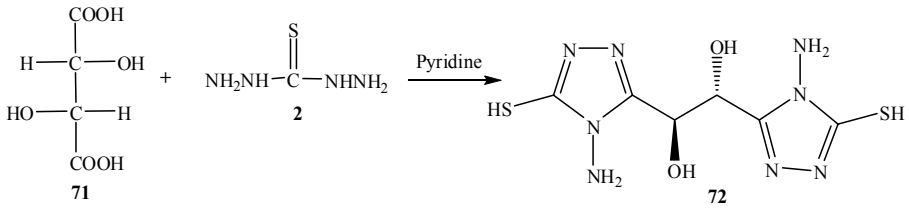
4.3.1. Glycosides of triazolethiols. Refluxing of equimolar amounts of *D*-glucono- and *D*-galactono-1,5-lactones (**67** and **68**) with thiocarbohydrazide (**2**) in pyridine for 4 h gave the respective 4-amino-3-mercapto-1,2,4-triazoles **69** and **70** in good yields. However, under

microwave irradiation (MW) compounds **69** and **70** were obtained with improved yields (88%) and shorter reaction times (5-6 min; Scheme 35).[52]



Scheme 35

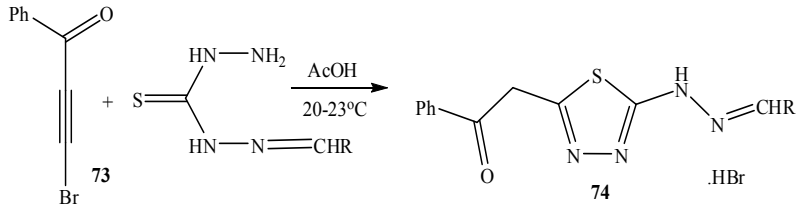
The synthesis of (1*R*,2*S*)-1,2-bis(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)ethane-1,2-diol (**72**) has been achieved by the dehydrative cyclization of *L*-tartaric acid (**71**) with thiocarbohydrazide (**2**) (Scheme 36).[53]



Scheme 36

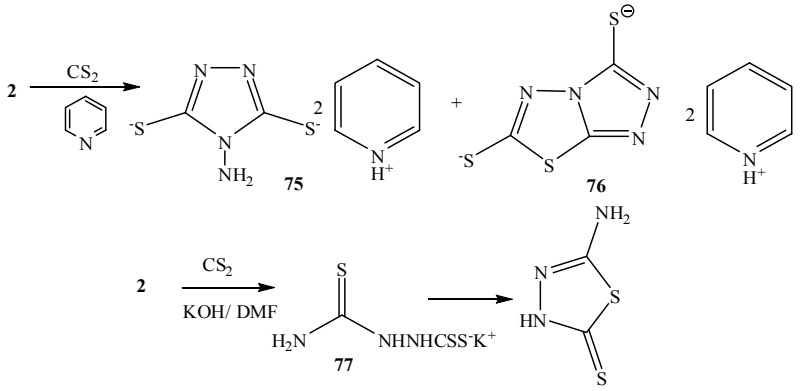
4.4. Synthesis of thiadiazoles, thiadiazolines and thiadiazolidines

Glotova *et al* synthesized 1,3,4-thiadiazole derivatives **74** from 1-benzylidene-thiocarbohydrazides and 3-bromo-1-phenylprop-2-yn-1-one (**73**) in acetic acid (Scheme 37).[54,55]



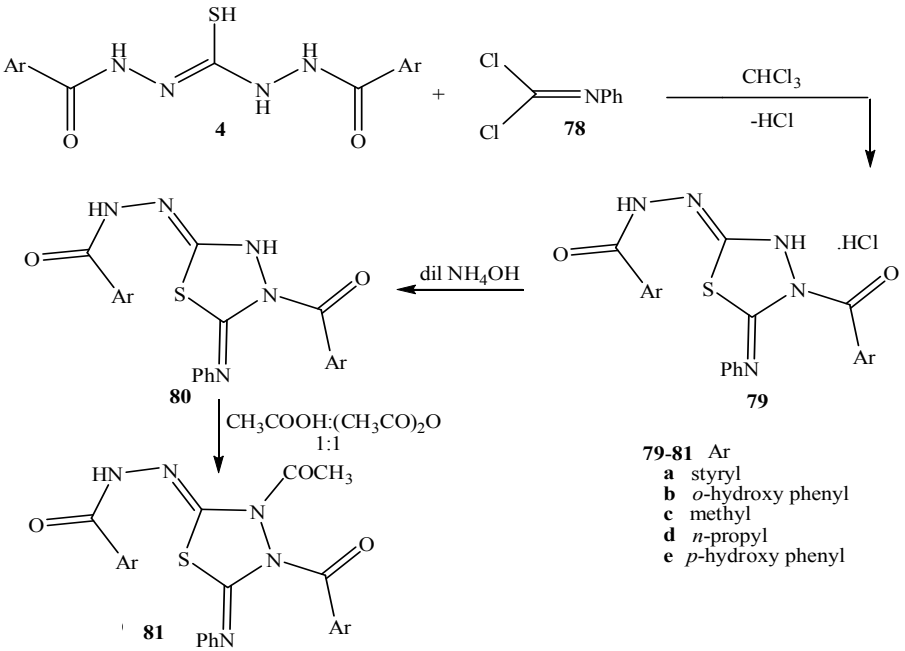
Scheme 37

Solvents affect the cyclized products resulting from the reaction of thiocarbohydrazide (**2**) with carbon disulfide. In pyridine, reaction of **2** with carbon disulfide afforded the salts **75** and **76**.[56] In DMF, compound **2** reacted with carbon disulfide and KOH to afford the salt **77** which can be cyclized on warming to give the corresponding 1,3,4-thiadiazoline-2-thione (Scheme 38).[56]



Scheme 38

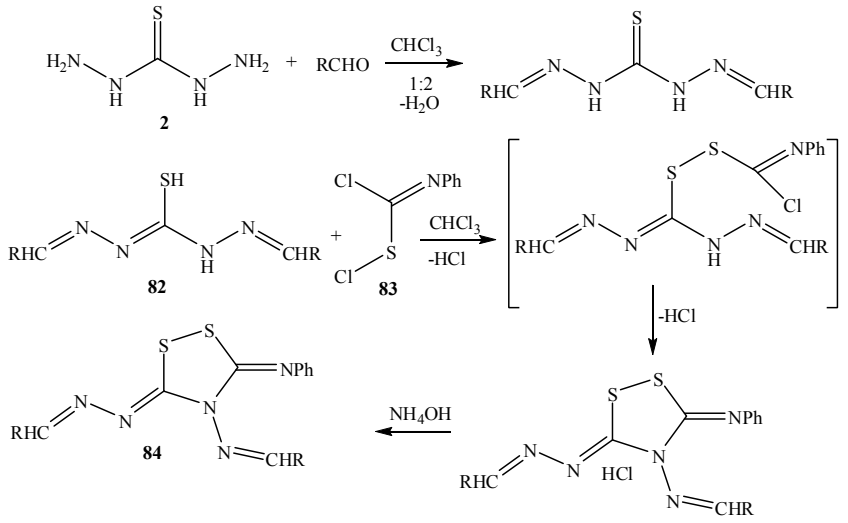
Several 2-phenylimino-1,5-diacyl- and/or-1,5-diaroyl-hydrazine-1,3,4-thiadiazolidines **80** were synthesized by the reaction of 1,5-diaroyl- and/or 1,5-diacyl-3-thiocarbohydrazides **4** with *N*-phenyl isocyanodichloride (**78**). The products **79** obtained on basification with dilute ammonium hydroxide afforded the free bases **80**, which were acetylated using a mixture of acetic acid and acetic anhydride in 1:1 ratio to afford monoacetyl derivatives **81** (Scheme 39).[57]



Scheme 39

4.5. Synthesis of dithiazolidines

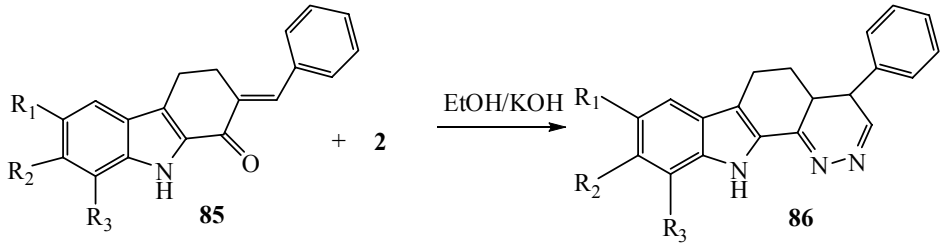
Choudhari and Berad reported the synthesis of several 3-phenylimino-4-arylidineamino-5-arylidinehydrazino-1,2,4-dithiazolidines **84** by one step condensation of bis-1,5-arylidine-3-thiocarbohydrazides **82** and *N*-phenyl-*S*-chloro-isothiocarbamoyl chloride (**83**), followed by basification of the first-formed hydrochloride salts (Scheme 40).[58]



Scheme 40

4.6. Synthesis of pyridazines

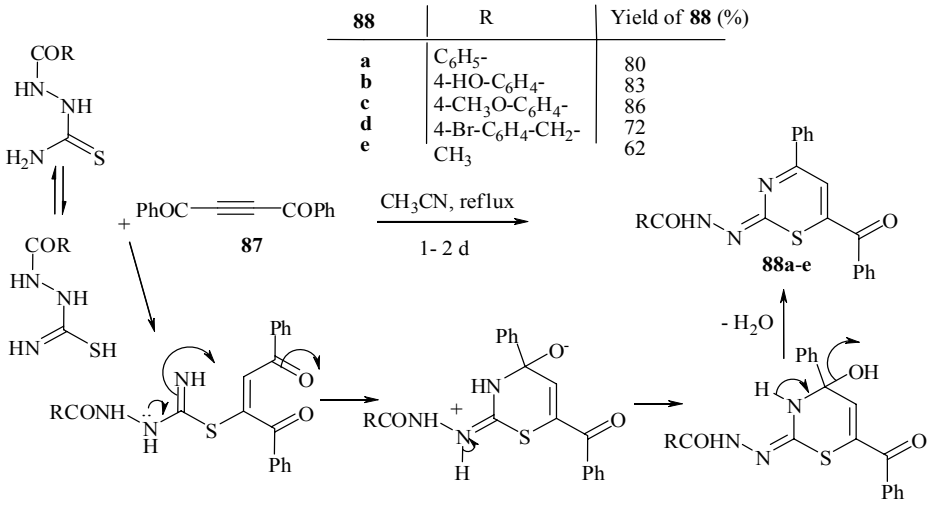
The reaction of 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones **85** with thiocarbohydrazide (**2**) yielded pyridazinocarbazoles **86** and *not* the thiol-substituted pyrazinocarbazoles as expected (Scheme 41).[59,60]



Scheme 41

4.7. Synthesis of thiazines

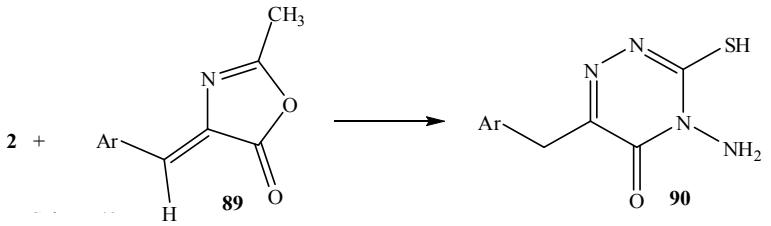
Aly *et al* recently demonstrated that 1,4-diphenylbut-2-yne-1,4-dione (**87**) reacted with *N*-substituted hydrazinocarbothioamides to form the corresponding *N*'-[(2*E*)-6-benzoyl-4-phenyl-2*H*-1,3-thiazin-2-ylidene]-substituted hydrazides **88a-e** (Scheme 42).[61]



Scheme 42

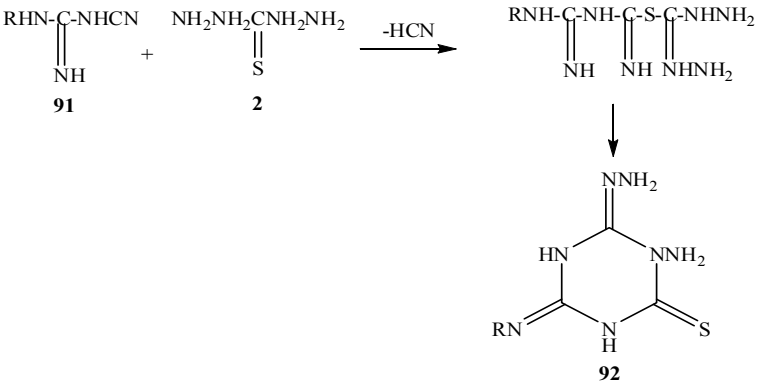
4.8. Synthesis of triazines

A facile synthetic route to triazinones **90** is outlined in Scheme 43.[62] The reaction mixture of **2** and oxazolones **89** was refluxed for nearly 2 h and the products separated upon cooling were collected by filtration.[62]



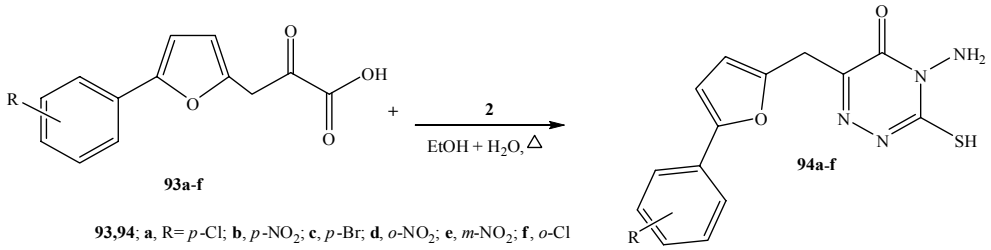
Scheme 43

Reaction of thiocarbohydrazide (**2**) with dicyandiamides **91** yielded 1-amino-6-hydrazono-4-imino(or ary1imino)hexahydro-1,3,5-triazine-2-thiones **92** (Scheme 44).[63]



Scheme 44

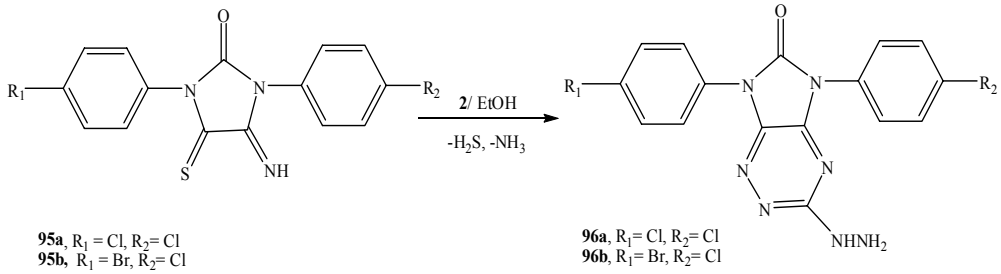
4-Amino-6-(aryl-furanylmethyl)-3-mercapto-1,2,4-triazin-5(4*H*)-ones **94a-f** were synthesized by refluxing the corresponding substituted aryl-furanylpyruvic acids **93a-f** with **2** in ethanolic solution on a steam-bath (Scheme 45).[64]



93,94; **a**, R= *p*-Cl; **b**, *p*-NO_2; **c**, *p*-Br; **d**, *o*-NO_2; **e**, *m*-NO_2; **f**, *o*-Cl

Scheme 45

Another class of fused triazines, identified as imidazo[4,5-*e*]triazine-2-ones **96a**,**b**, were obtained from the interaction of imidazolidineimino-thiones **95a**,**b** with **2** *via* elimination of both H_2S and NH_3 (Scheme 46).[30] The isolated products were investigated as antitumor agents.[30]



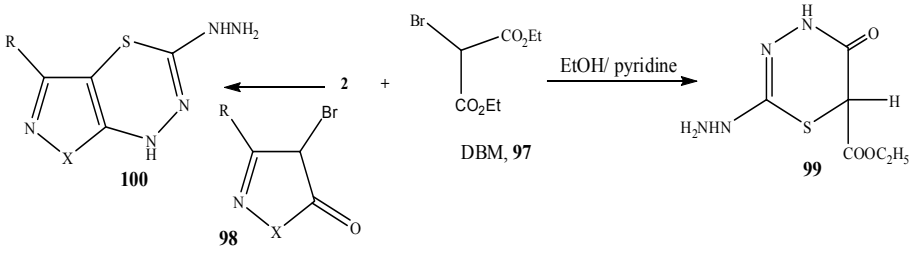
95a, R_1 = Cl, R_2= Cl
95b, R_1 = Br, R_2= Cl

96a, R_1= Cl, R_2= Cl
96b, R_1= Br, R_2= Cl

Scheme 46

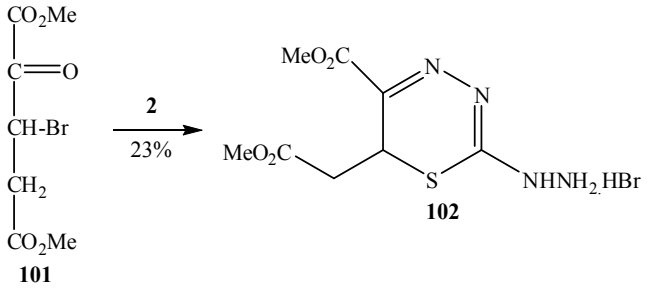
4.9. Synthesis of thiadiazines

Thiocarbohydrazide (**2**) reacted with diethyl bromomalonate (**97**, DBM) and with 4-bromo-4*H*-3-substituted-1,3-disubstituted-pyrzol-5-ones **98** in ethanolic pyridine solution affording 2-hydrazino-6-carbethoxy-4*H*,6*H*-1,3,4-thiadiazin-5-one (**99**) and 2-hydrazino-5-substituted-4*H*-pyrazolo[5,4-*e*]1,3,4-thiadiazines **100**, respectively (Scheme 47).[6] Reaction of **2** with 3-bromo-2-oxoglutaric acid dimethyl ester (**101**) in methanol gave (2-hydrazino-5-methoxycarbonyl-6*H*-1,3,4-thiadiazin-6-yl)acetic acid methyl ester hydrobromide (**102**, Scheme 48).[65]



98, **100**: X= NH, N-Ph, R= CH_3, Ph

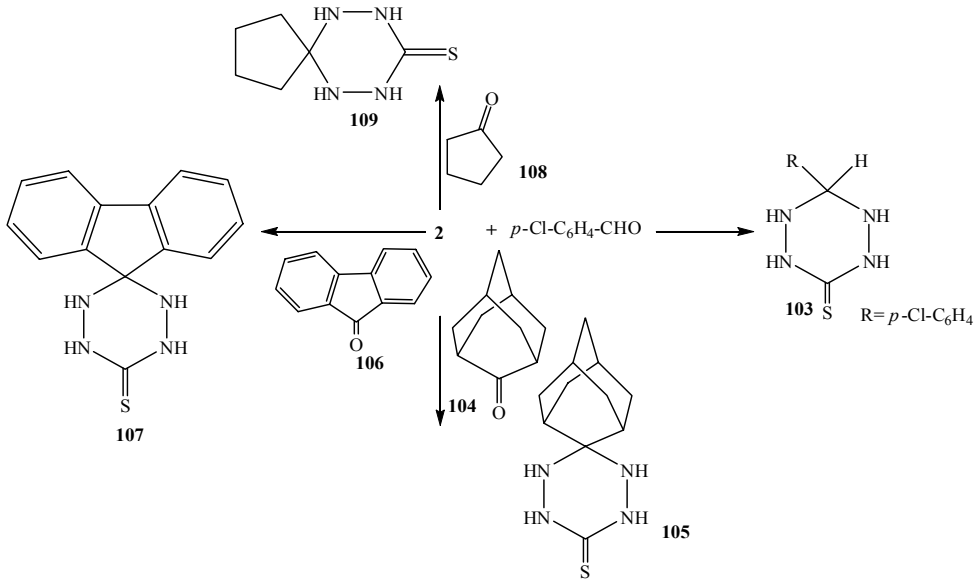
Scheme 47



Scheme 48

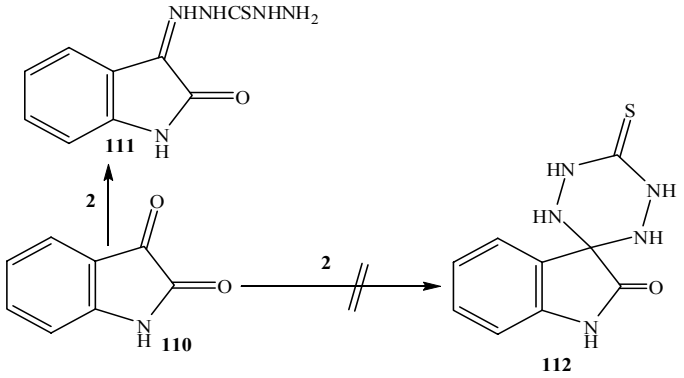
4.10. Synthesis of tetrazinethiones

Interestingly, Mohan and his group demonstrated the synthesis of a series of tetrazinethiones. For example, reaction of **2** with *p*-chloro-benzaldehyde proceeded to give successfully the tetrazine-3(2*H*)-thione **103** (Scheme 49).[66]

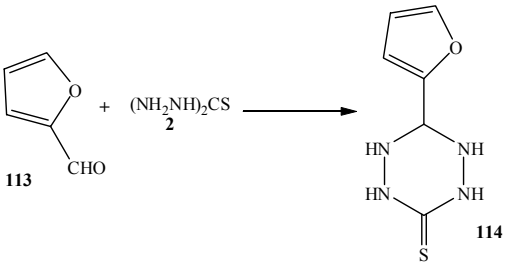


Scheme 49

The reaction of **2** with 2-adamantanone (**104**) in ethanol gave the spiro-[adamantine-2,3'-*s*-tetrazine]-6'-thione (**105**).[67] In the same manner, 1',2',4',5'-tetrahydrospiro[fluorene -9,3')-*s*-tetrazine]-6'(*H*)-thione (**107**) was obtained by the reaction of 9-fluorenone (**106**) with thiocarbohydrazide (**2**).[68] Cyclic alkanones such as cyclopentanone (**108**) reacted with **2** to form the corresponding tetrazinethione **109** (Scheme 49).[69] Isatin (**110**) reacted with **2** in similar fashion to give 1',2',4',5'-tetrahydro-3*H*-2-oxospiro[indole-3,3'-*s*-tetrazine]-6'-thione (**112**).[70] Reinvestigation of the reaction of **110** with **2** under the same reaction condition (the aqueous solution of thiocarbohydrazide was stirred without further heating and treated dropwise over 15 min with **110** in ethanol) proved that the obtained compound was isatin-*β*-thiocarbohydrazide (**111**, Scheme 50).[71]

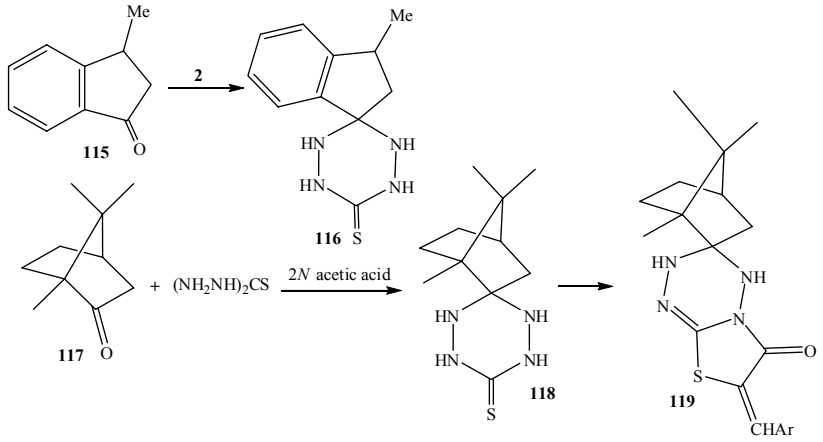


Scheme 50

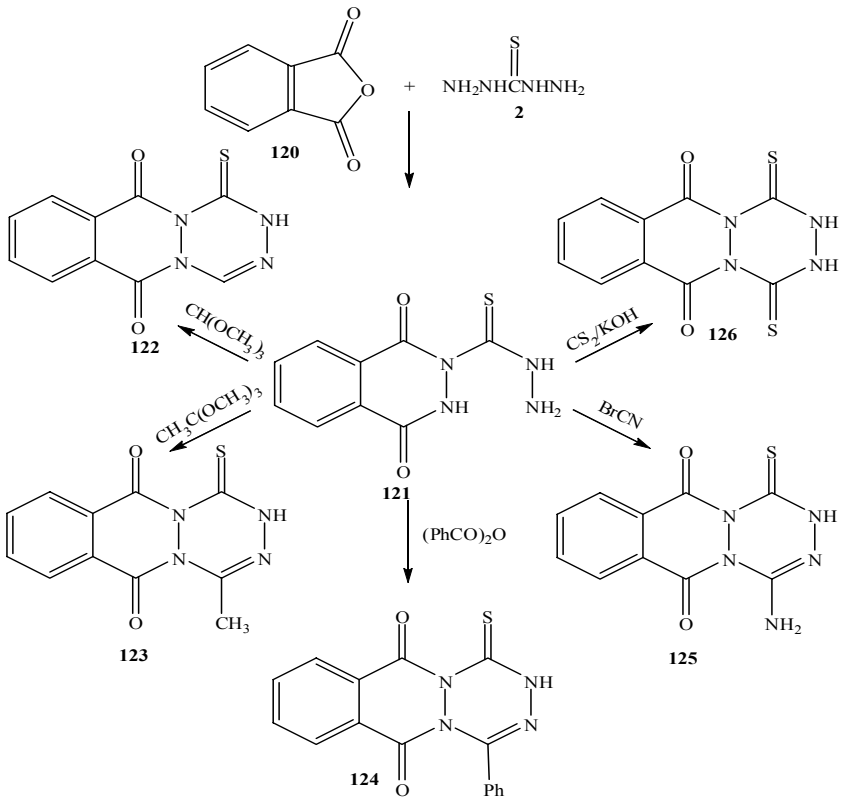


Scheme 51

Mohan reported on another tetrazinethione **114** from the reaction of furfural (**113**) with **2**, which was identified as 6-(2-furyl)-1,4,5,6-tetrahydro-*s*-tetrazine-3(2*H*)-thione (Scheme 51).[72] 3-Methylspiro[indane-1,3'-hexahydro-*s*-tetrazine]-6'-thione (**116**) was obtained from the reaction of 3-methylindan-1-one (**115**) with **2**.[73] 1,7,7-Trimethyl-bicyclo[2.2.1]-heptan-2-one (**117**) reacted with **2** in 2*N* acetic acid to give 1,7,7-trimethyl-spiro[bicycle-[2.2.1]heptane-2,3'-[1,2,4,5]tetrazinane]-6'-thione (**118**).[74] Treatment of **118** with ethyl chloroacetate and aldehydes in the presence of pyridine afforded 7-arylidenespiro-[bicycle-heptane-2'-3(4*H*)-[2*H*]-thiazolo[3,2-*b*]-*s*-tetrazin]-6-(7*H*)-ones **119** (Scheme 52).[74] 1,4-Dioxo-3,4-dihydro-2(1*H*)phthalazinecarbothiohydrazide (**121**) was initially synthesized by reaction of phthalic anhydride (**120**) with thiocarbohydrazide (**2**). Heterocycles **122-126**, *i.e.* 4-substituted-1-thioxo-1,2-dihydro[1,2,4,5]tetrazino[1,2-*b*]-phthalazine-6,11-diones, were subsequently synthesized by cyclocondensation of **121** with trimethyl orthoformate, trimethyl orthoacetate, benzoic anhydride, cyanogen bromide and carbon disulfide, respectively (Scheme 53).[75]



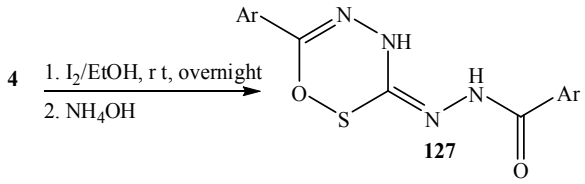
Scheme 52



Scheme 53

4.11. Synthesis of thiaoxadiazines

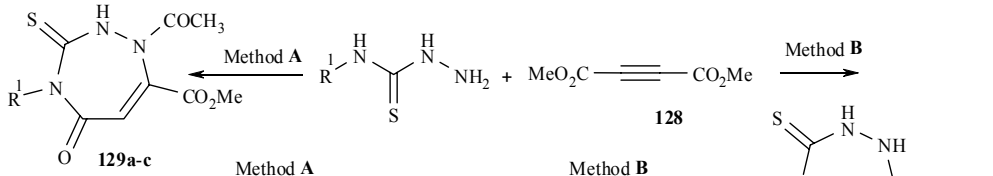
1,5-Diacyl thiocarbohydrazides **4** were cyclized with iodine to give 1,2,4,5-thiaoxadiazines **127** in 61-80% yields (Scheme 54).[17] Iodine solution in ethanol was added with continuous stirring; the color of iodine gradually disappeared. The addition of iodine was continued till it was in slight excess indicated by the persistence of its violet color. After keeping the reaction mixture overnight granular solids were obtained; these were identified as dihydroiodo-1,2,4,5-thiaoxadiazines, which on basification with dilute ammonium hydroxide gave the free base (Scheme 54).[17]



Scheme 54

4.12. Synthesis of triazepinothiones

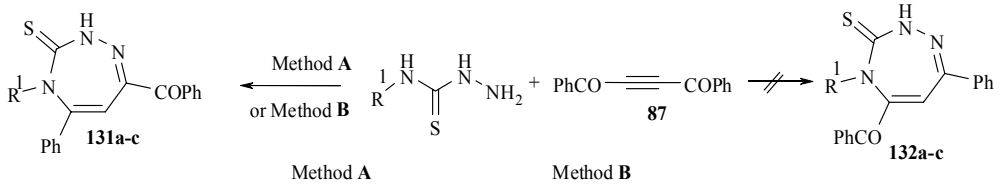
Aly *et al* reported the synthesis of 1,2,4-triazepine-3-thiones **129-131**.[76] These products were obtained in respective reactions of N^1-substituted thiosemicarbazides with dimethyl acetylenedicarboxylate (**128**, DMAD) and 1,4-diphenylbut-2-yne-1,4-dione (**87**) under prolonged reflux in DMF (Schemes 55 and 56).[76]



		Method **A** AcOH, reflux 10-18 h		Method **B** DMF, MW 5-10 min	
129,**130**	R^1	Time (h)	Yield of **129** (%)	Time (min)	Yield of **130** (%)
a	C_6H_5-	14	56	5	75
b	C_6H_5-CH_2-	10	60	7	87
c	CH_2=CH-CH_2-	18	54	10	70

Scheme 55

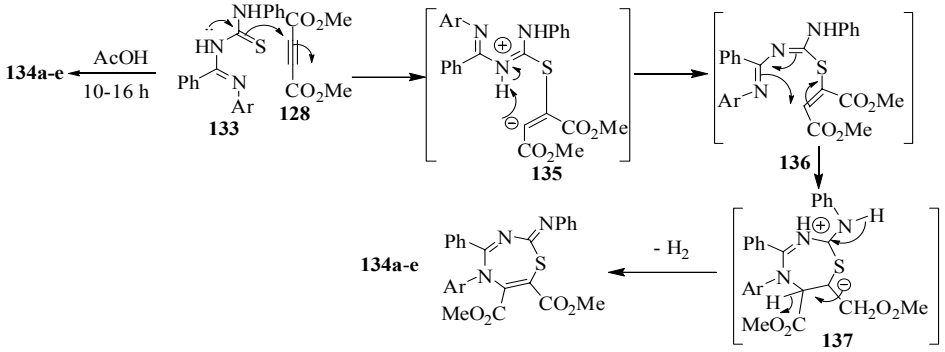
However, the reaction of the starting materials under microwave irradiation afforded the same products in higher yields within a few minutes.[76] Spectroscopic data excluded the formation of the regio-isomeric heterocycle **132** (Scheme 56).



		Method **A** DMF, reflux 24-48 h		Method **B** DMF, MW 10-20 min	
131, **132**	R^1	Time (h)	Yield of **131** (%)	Time (min)	Yield of **132** (%)
a	C_6H_5-	36	82	10	98
b	C_6H_5-CH_2-	24	72	12	82
c	CH_2=CH-CH_2-	48	76	20	92

Scheme 56

4.13. Synthesis of thiadiazepines

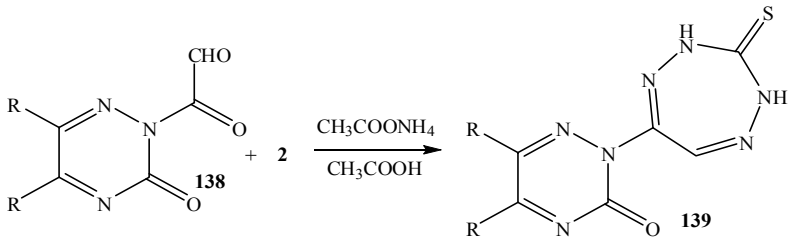


Scheme 57. Synthesis of 1,3,5-thiadiazepines **134a-e**. **a**: Ar=4-$CH_3OC_6H_4$ (84%); **b**: Ar=4-$CH_3C_6H_4$ (80%); **c**: Ar=4-ClC_6H_4 (75%); **d**: 4-$O_2NC_6H_4$ (65%); **e**: Ar=Ph (82%).

N-Imidoylthioureas (**133**, analogous to thiocarbohydrazides) reacted with DMAD (**128**) to form 1,3,5-thiadiazepines **134a-e** (Scheme 57).[77] The reaction mechanism can be simply described as due to sulfur atoms attacking the triple bond of DMAD in conjugate fashion, followed by proton transfer and nucleophilic attack of the amidine group on the double bond in **128** to form the intermediates **135**.[77] Thereafter a nucleophilic attack of the amidine-like nitrogen on the ethylenic-ester would form the salt **136**. Aromatization of **136** is accompanied by the extrusion of a hydrogen molecule to produce the stable compounds **134a-e** (Scheme 57).[77] A similar observation was reported by Alajarín and his group.[78]

4.14. Synthesis of tetrazepinethiones

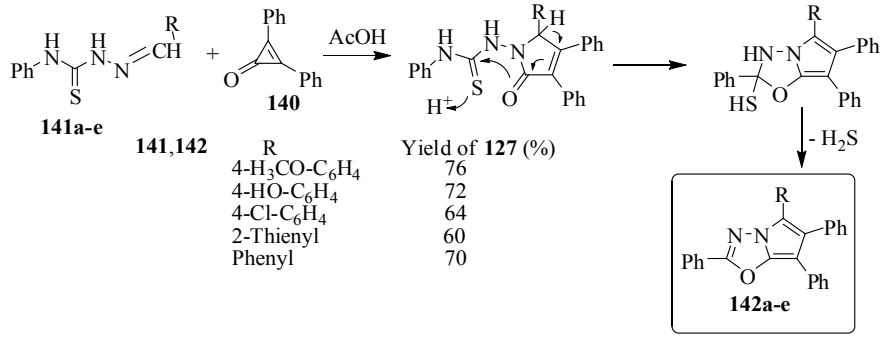
Reaction of 2-oxo-2-(3-oxo-5,6-disubstituted-1,2,4-triazin-2(3*H*)-yl)acetaldehydes **138** with thiocarbohydrazide (**2**) in a mixture of acetic acid and sodium acetate produced the corresponding 1,2,4,5-tetrazepine-3-thiones (**139**, Scheme 58).[79]



Scheme 58

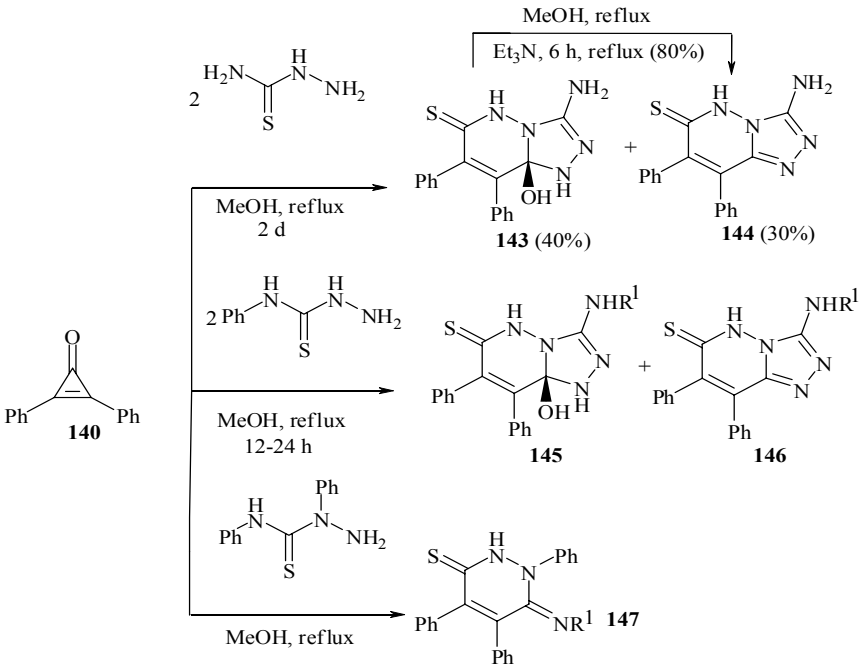
4.15. Synthesis of fused heterocycles

4.15.1. Synthesis of pyrrolo[2,1-*b*]-1,3,4-oxadiazoles. The Aly group[80] described the reaction of 2,3-diphenylcyclopropenone (**140**) with arylidene-*N*-phenylhydrazine-carbothioamides **141a-e**. The formed pyrrolo[2,1-*b*]-1,3,4-oxadiazoles **142a-e** can be described as due to initial [3+2]cycloaddition, followed by further cyclization with loss of H_2S (Scheme 59).[80]



Scheme 59

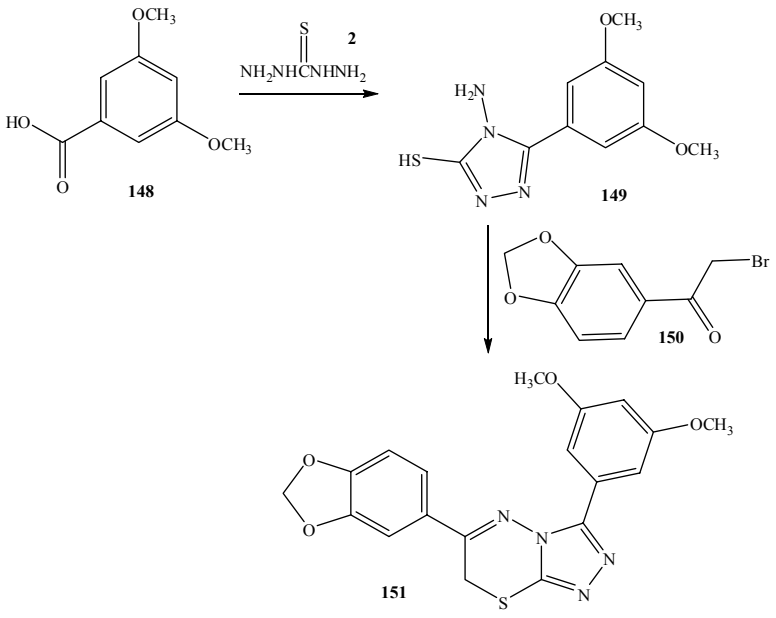
4.15.2. Synthesis of pyrrolo[2,1-*b*]-1,3,4-oxadiazoles, 1,2,4-triazolo[4,3-*b*]pyridazine-thiones and pyridazinethines. Aly *et al*[81] have also recently reported that cyclopropenone **140** reacted with two equivalents of either thiosemicarbazide or 1-phenylthiosemicarbazide to afford the corresponding 1,2,4-triazolo[4,3-*b*]-pyridazinethiones **143-146**.[81] However, the reaction of disubstituted hydrazine-carbothioamides with **140** occurs with stoichiometric amounts of the starting materials to produce pyridazinethiones **147** (Scheme 60). The reaction mechanism, in both cases, was described as a formal [3+3]-cycloaddition.[81]



Scheme 60

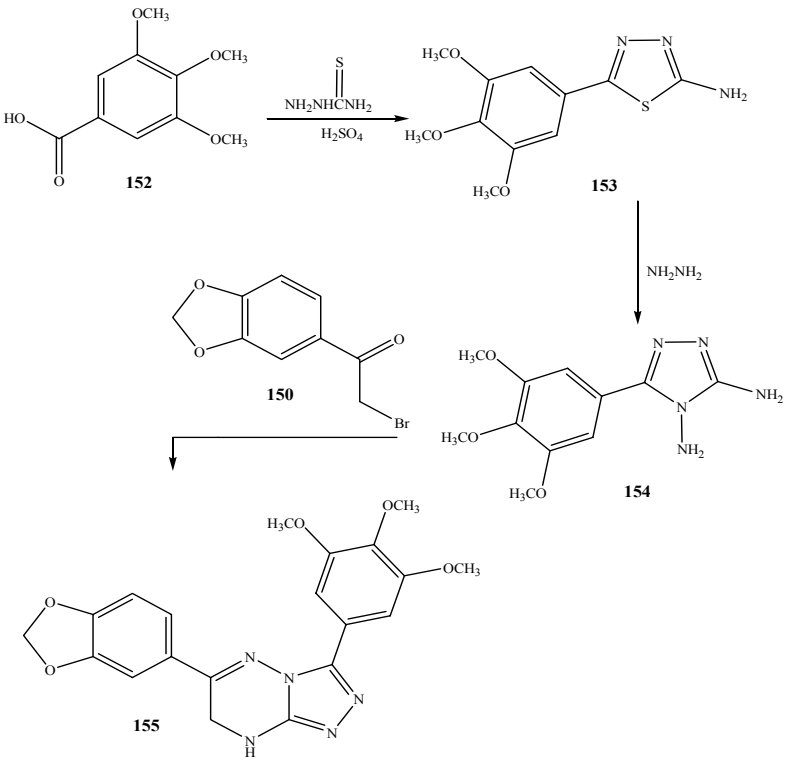
4.15.3. Synthesis of fused triazolo-heterocycles. 3-(3,5-Dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]-thiadiazines **151** and 6-(3,4-methylenedioxyphenyl)-7,8-dihydro-3-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo-[4,3-*b*]-[1,3,4]triazines **155** were discovered as activators of caspases and inducers of apoptosis so they may be used to induce cell death in a variety of clinical conditions in which uncontrolled growth and spread of abnormal cells occurs; accordingly, they may be used as therapeutic anti-cancer agents.[82]

Reaction of 3,5-dimethoxybenzoic acid (**148**) with thiocarbohydrazide (**2**) produced 4-amino-5-(3,5-dimethoxyphenyl)-3-mercapto-(4*H*)-1,2,4-triazole (**149**), which reacted with 2-bromo-1-(3,4-methylenedioxyphenyl)ethanone (**150**) to afford 3-(3,5-dimethoxyphenyl)-6-(3,4-methylene-dioxyphenyl)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazine (**151**, Scheme 61).[82]



Scheme 61

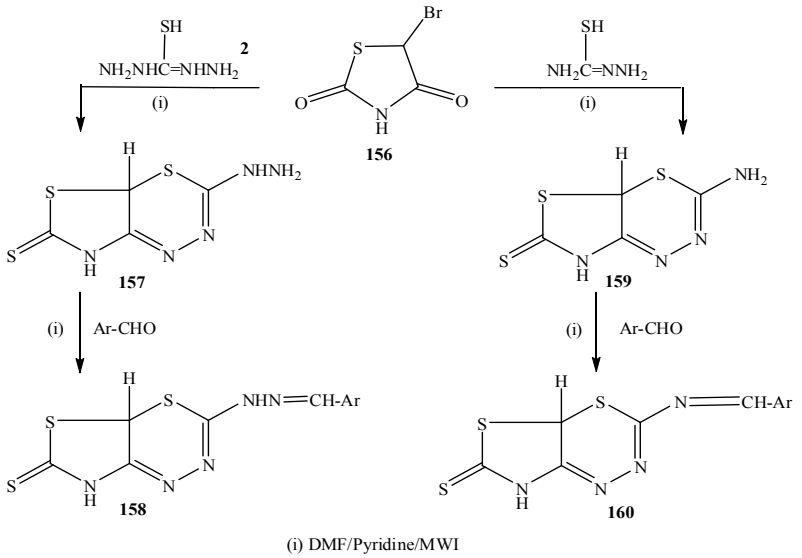
3-(3,5-Dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]-thiadiazines **151** and 6-(3,4-methylenedioxyphenyl)-7,8-dihydro-3-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo-[4,3-*b*]-[1,3,4]triazines **155** were discovered as activators of caspases and inducers of apoptosis so they may be used to induce cell death in a variety of clinical conditions in which uncontrolled growth and spread of abnormal cells occurs; accordingly, they may be used as therapeutic anti-cancer agents.[82]



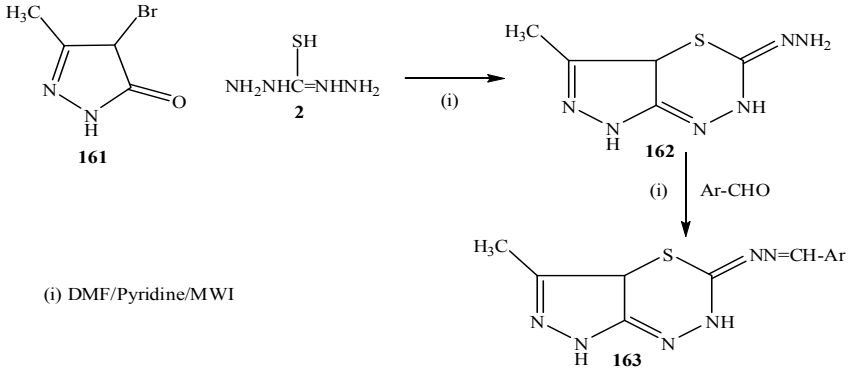
Scheme 62

On the other hand, reaction of 3,4,5-trimethoxybenzoic acid (**152**) and thiosemicarbazide produced 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-amine (**153**) which reacted with hydrazine hydrate to afford compound **154**, which reacted with 2-bromo-1-(3,4-methylenedioxyphenyl)-ethanone (**150**) to afford 6-(3,4-methylenedioxyphenyl)-7,8-dihydro-3-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo-[4,3-*b*][1,3,4]triazine (**155**, Scheme 62).[82]

4.15.4. Synthesis of fused 1,3,4-thiadiazines. Bromo rhodanine (**156**) when treated with thiocarbohydrazide (**2**) yielded 5*H*-2-hydrazino-6-thioxo-(1,3)-thiazolo[4,5-*e*]-1,3,4-thiadiazine (**157**) which was then condensed with aromatic aldehydes to obtain the Schiff bases **158**. Similarly, **156** was reacted with thiosemicarbazide to yield 5*H*-2-amino-6-thioxo-1,3-thiazolo[4,5-*e*]-1,3,4-thiadiazine (**159**). Schiff bases of **159** were also obtained by treating it with aromatic aldehydes (Scheme 63).[83]



Scheme 63



Scheme 64

Likewise, 3*H*,5*H*-2-iminoamino-7-methyl-(1,2)-pyrazolo[4,5-*e*]-1,3,4-thiadiazine (**162**) was formed when 4-bromopyrazole (**161**) was treated with thiocarbohydrazide (**2**). This was further allowed to react with aromatic aldehydes to obtain the corresponding Schiff bases **163** (Scheme 64).[83]

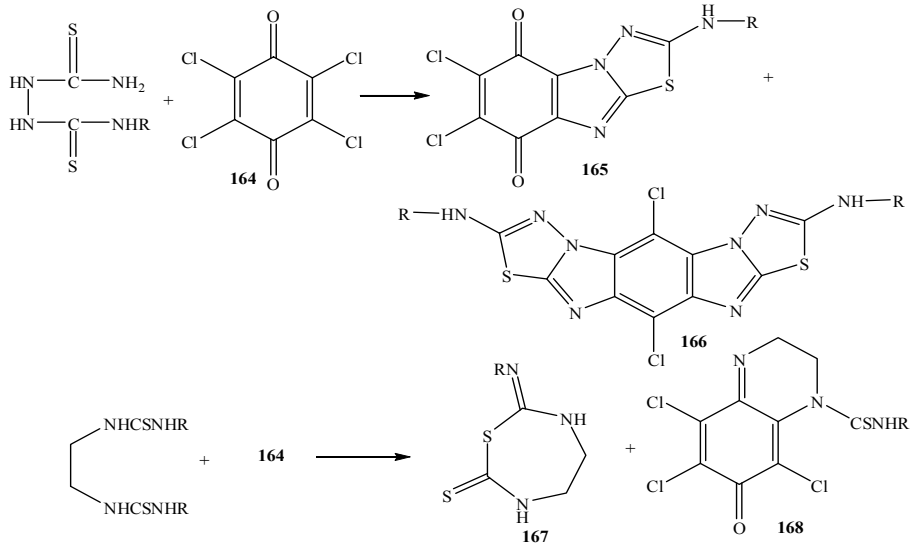
5. Reactions of thiocarbohydrazides with π-acceptors *p*-CHL, DCHNQ, CNIND, TCNE, DDQ, DCNQ, DECF and DEM

5.1. Reaction of thiocarbohydrazides with 2,3,5,6-tetrachloro-1,4-benzoquinone

Hassan *et al* reported[84] that addition of tetrahydrofuran (THF) solutions of substituted thiocarbohydrazides to a solution of 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-CHL, **164**) in a

ratio of 1:2 in the same solvent formed, after standing for 48 hours at room temperature, substituted imidazothiadiazolediones **165** as minor products (21-24%) and substituted benzo-bisimidazothiadiazoles **166** as major products (48-54%) (Scheme 65).[84]

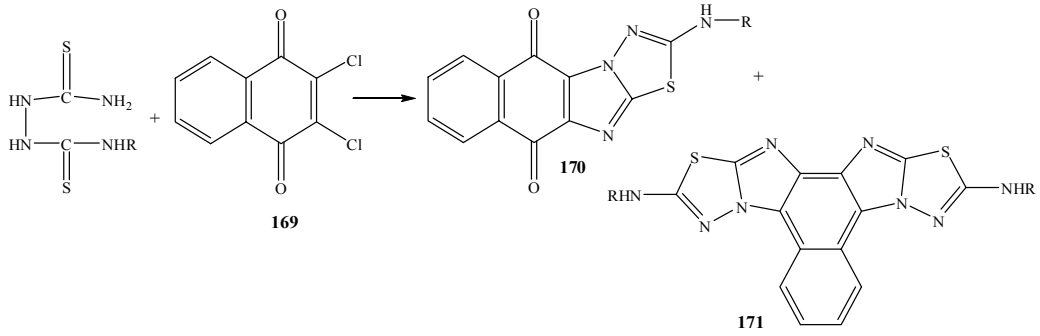
Other work was also undertaken to examine the reactions of thiocarbohydrazides derived from ethylene diamine *p*-CHL. Thus, two equivalents of thioureidoethylthiourea derivatives reacted with **164** in THF at room temperature to afford substituted imino-[1,3,6]-thiadiazepane-2-thiones **167** as minor products (14-19%) and trichloro-7-oxo-quinoxaline-1- carbothioamides **168** as major products (41-49%), in addition to the corresponding dihydrobenzoquinone (Scheme 65).[85]



Scheme 65

5.2. Reaction of thiocarbohydrazides with 2,3-dichloro-1,4-naphthoquinone

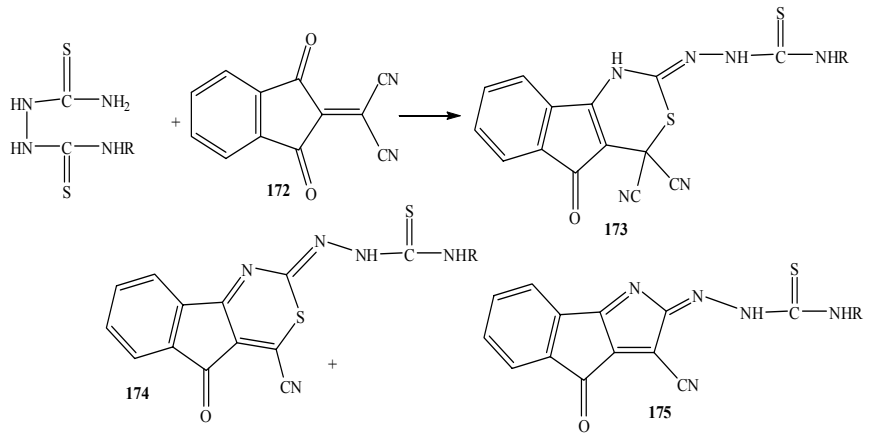
Hassan has also reported that substituted naphthimidazothiadiazolediones **170** and disubstituted naphthobisimidazo-thiadiazoles **171** were obtained from the reaction of substituted thiocarbohydrazides with 2,3-dichloro-1,4-naphthoquinone (DCHNQ, **169**, Scheme 66).[84]



Scheme 66

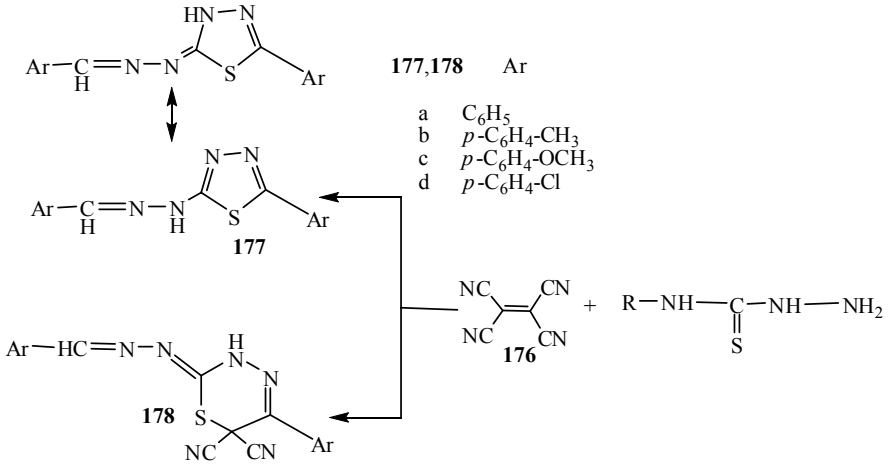
5.3. Reaction of thiocarbohydrazides with [1,3-dioxo-2,3-dihydro-1(*H*)-inden-2-ylidene]-propanedinitrile

The reaction of substituted thiocarbohydrazides with (1,3-dioxo-2,3-dihydro-1(*H*)-inden-2-ylidene)propanedinitrile (CNIND, **172**) was carried out in ethyl acetate under reflux, followed by chromatographic separation. The reaction mixture afforded the products **173-175** (Scheme 67), and numerous colored byproducts in very small quantities.[84]



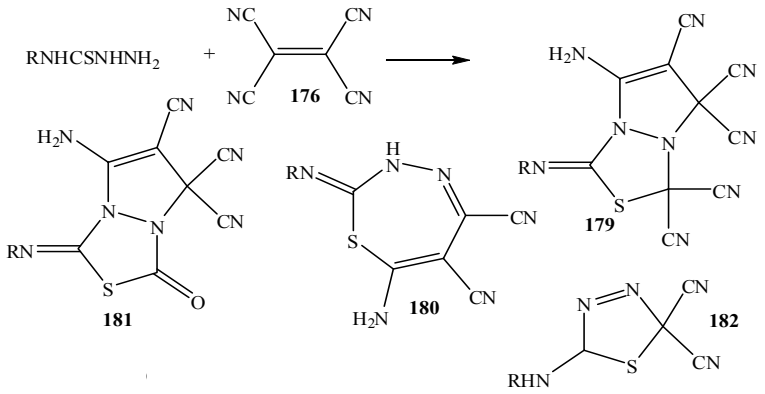
Scheme 67

5.4. Reaction of thiosemicarbohydrazides with 1,1,2,2-tetracyanoethylene The reaction of equimolar quantities of thiocarbohydrazides with 1,1,2,2-tetracyanoethylene (TCNE, **176**) afforded the thiadiazoles **177** and thiadiazine derivatives (**178**, Scheme 68).[84]



Scheme 66

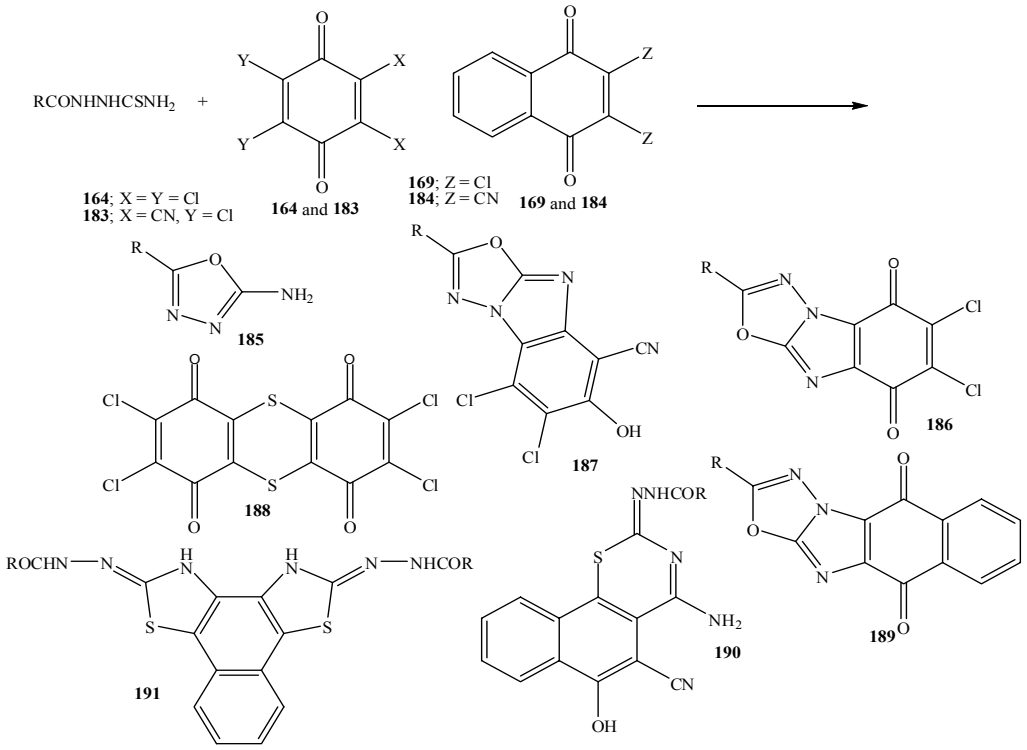
Upon addition of doubled molar amounts of **176** to a solution of 4-substituted thiosemicarbazides in ethyl acetate, with the admission of air, the green color of a transient charge-transfer complex is observed, which quickly gives way to a brown and finally to a characteristic reddish orange color. Chromatographic separation of the sublimation residue gave products **179–182** (see Scheme 69).[86]



Scheme 69

5.5. Reaction of acyl thiosemicarbohydrazides with π-acceptors

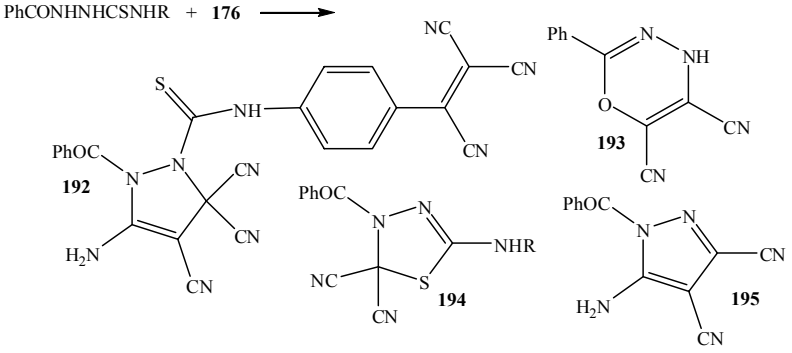
Mixing of two-fold molar amounts of acceptor **164** and/or 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ, **183**) with one mole of acyl thiosemicarbohydrazides in ethyl acetate, with admission of air, gave a blue color (λmax = 573-591 nm).



Scheme 70

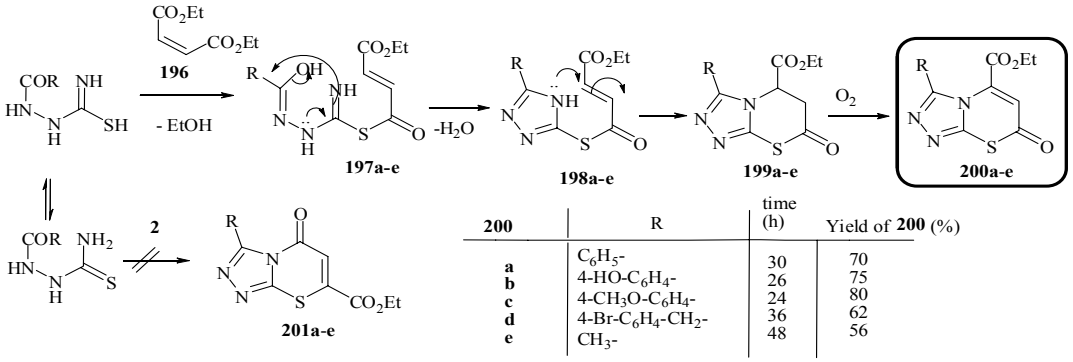
This behavior is explained as being due to initial formation of an unstable charge-transfer complex (CTC) followed by a chemical reaction which yields substituted oxadiazoles **185** and heterocycles **186-188**. Upon reaction of the same acyl thiosemicarbohydrazides with two equivalents of acceptors **169** and/or 2,3-dicyano-1,4-naphthoquinone (DCNQ, **184**) in ethyl acetate, the transient CT-complexes underwent conversion into heterocycles **189-191** (Scheme 70).[87]

Reactions of acyl thiosemicarbohydrazides with **176** in DMF were found to run smoothly, the conversions of starting materials, in case of phenyl substitutent, in chlorobenzene to **192**, whereas the other derivatives of the target donors gave with **176**, heterocycles **193-195** (Scheme 71).[88]



Scheme 71

Reaction of *N*-substituted-hydrazino-carbothioamides with diethyl maleate (DEM, **196**) gave mainly the corresponding ethyl 7-oxo-3-substituted-7*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-carboxylates **200a-e**.[89] This reaction can be ascribed to nucleophilic attack of the thiol group on the ester carbon accompanied by elimination of one molecule of ethanol to form the intermediate **197**. Thereafter amidine-like nucleophilic attack on the amide is accompanied by water elimination to give **198**. Nucleophilic attack of the terminal NH on the π-deficient double-bond produces the corresponding triazolo-dihydrothiazines **199**.



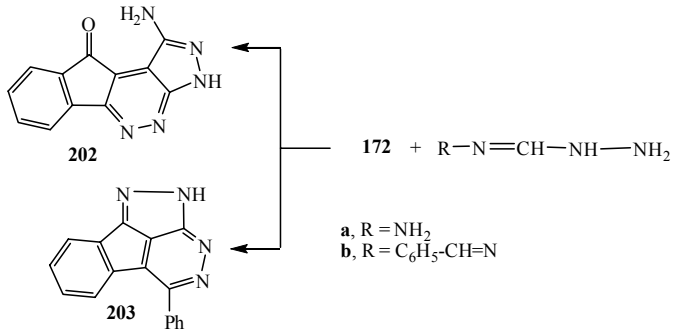
200	R	time (h)	Yield of **200** (%)
a	C_6H_5-	30	70
b	4-HO-C_6H_4-	26	75
c	4-CH_3O-C_6H_4-	24	80
d	4-Br-C_6H_4-CH_2-	36	62
e	CH_3-	48	56

Scheme 72. Reaction of *N*-substituted-hydrazino-carbothioamides with diethyl maleate (**196**). Condition: AcOH, reflux, 1-3d.

Ultimately, it was proposed that aerial oxidation of **199** gives the stable heterocyclic compounds **200** (Scheme 72).[89]

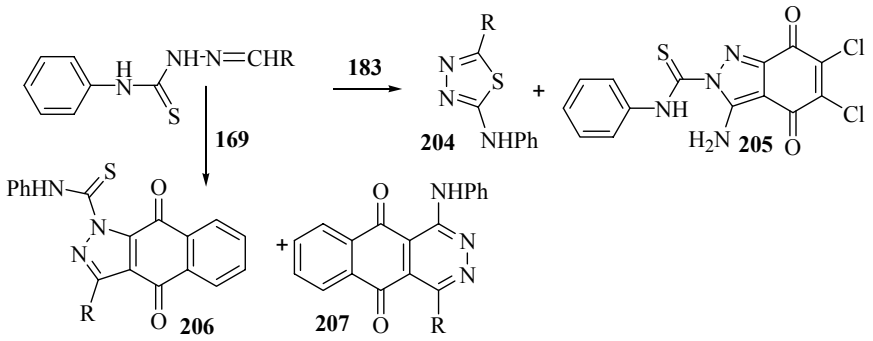
5.6. Reaction of thiosemicarbazones with selected π-acceptors

Acceptor **172** reacted with formohydrazonohydrazide and *N*-benzylideneformo-hydrazonohydrazide to respectively form aminoindenopyrazolo-pyridazinone **202** and phenyl-l,2,3,4-tetraazacyclopenta-fluorene **203** (Scheme 73).[84]



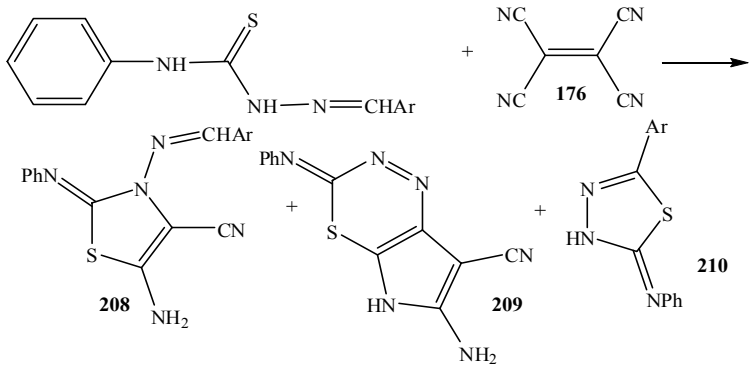
Scheme 73

Addition of methylene chloride solutions of 2-phenylidene-*N*-substituted-hydrazine-carbothioamides to solutions of **183** in the same solvent resulted in the appearance of a green color, which gradually changed into brown. 5-Substituted *N*-phenyl-1,3,4-thiadiazole-2-amines **204** (6-11%), together with 3-amino-5,6-dichloro-4,7-dioxo-*N*-phenyl-4*H*-indazole-2(7*H*)-carbothioamide **205** (71%), were isolated by preparative thin layer chromatography (Scheme 74).[88]



Scheme 74

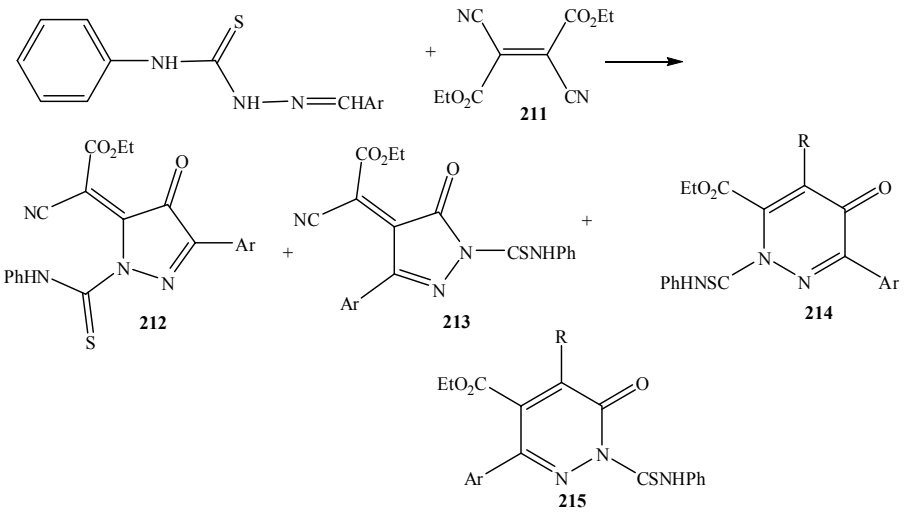
Mixing equimolar amounts of 2-phenylidene-*N*-substituted-hydrazine-carbothioamides and **169** in ethyl acetate for 72 h led to the formation of substituted benzindazole-4,9-diones **206** as major products and substituted benzophthalazinediones **207** as minor products (Scheme 74).[90] Addition of ethyl acetate solutions of 2-phenylidene-*N*-substituted-hydrazine-carbothioamides to solutions of **176** in the same solvent resulted in the formation of heterocycles **208**-**210** (Scheme 75).[91]



Scheme 75

5.6.1. Reaction of thiosemicarbazones with diethyl 2,3-dicyanofumarate. Equimolar solutions of aldehyde 4-phenylthiosemicarbazones and diethyl 2,3-dicyanofumarate (DECF, **211**)

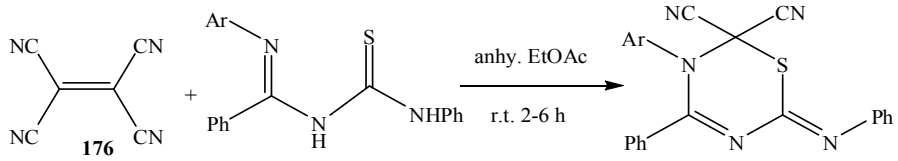
in ethyl acetate formed, on warming to reflux temperature for 14–18 h, major (**212**, **213** in 54–61%) and minor (**214**, **215** in 22–26%) products in each case (Scheme 76).[92]



Scheme 76

5.7. Reaction of *N*-imidoylthioureas with 1,1,2,2-tetracyanoethylene

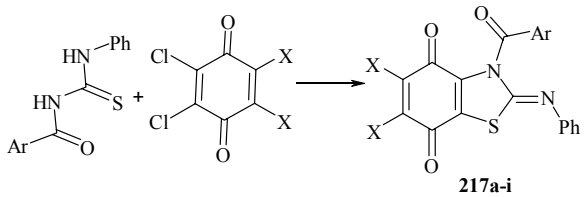
Aly *et al* also reported the reaction of *N*-imidoylthioureas (analogous to thiocarbohydrazides) with **176** in dry ethyl acetate at room temperature under a stream of N_2. Addition of electron donors to electron acceptor **176** in dichloromethane at room temperature led to complex formation characterized by CT-bands in the visible region. These CT-complexes gradually disappeared to give the precipitated thiadiazines **216** (Scheme 77).[93]



216	Ar	Yield (%)
a	4-OCH_3-C_6H_4-	85
b	4-CH_3-C_6H_4-	80
c	4-Cl-C_6H_4-	75
d	4-NO_2-C_6H_4-	68

Scheme 77

Aly has also demonstrated a very convenient synthesis of the fused thiazoles **217** (Scheme 78) from the reaction of aroylphenylthioureas (as analogues of thiocarbohydrazides) with π-acceptor quinones (CHL-*p*, DDQ and DCHNQ).[94]

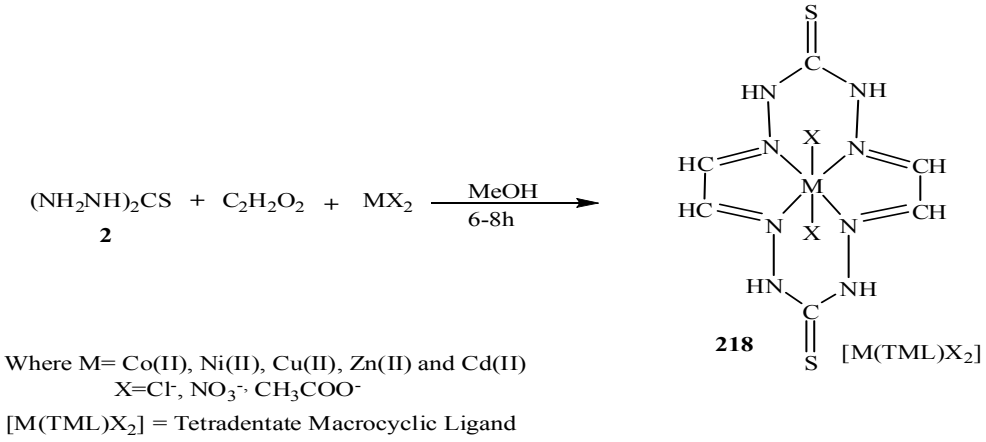


217	X	Yield (%)
a	Cl	70
b	Cl	65
c	Cl	60
d	CN	68
e	CN	65
f	CN	63
g	-CH=CH-CH=CH-	78
h	-CH=CH-CH=CH-	74
i	-CH=CH-CH=CH-	70

Scheme 78. Synthesis of fused 1,3-thiazoles.

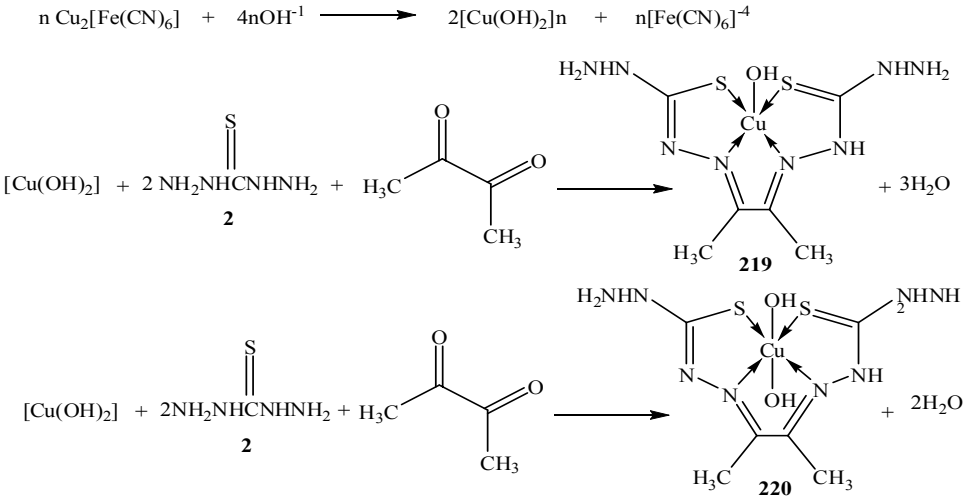
6. Heterocycles *via* Metal Complexation

A series of complexes **218** of the type $[M(TML)X_2]$; where TML is Tetradentate Macrocyclic Ligand; M = Co(II), Ni(II), Cu(II), Zn(II)or Cd(II); X = Cl, CH_3COO or NO_2 have been synthesized by template condensation of glyoxal and compound **2** in the presence of divalent metal salts in methanolic medium (Scheme 79).[95] The procedure can be summarized as follows: to a stirring methanolic solution (50 mL) of **2** (10 mmol) was added a divalent cobalt, nickel, copper, zinc or cadmium salt (5 mmol) dissolved in a minimum quantity of methanol (20 mL). The resulting solution was refluxed for 0.5 h. After that glyoxal (10 mmol) dissolved in 20 mL methanol was added to the refluxing mixture and refluxing continued for 6–10 h, depending upon the metal salt. The mixture was concentrated to half of its volume and kept in desiccators for 2 d. The complexes **218** were filtered, washed with methanol, acetone and ether and dried in *vacuo*: yield 40%. The complexes are soluble in DMF and DMSO, but are insoluble in common organic solvents and water.[95]



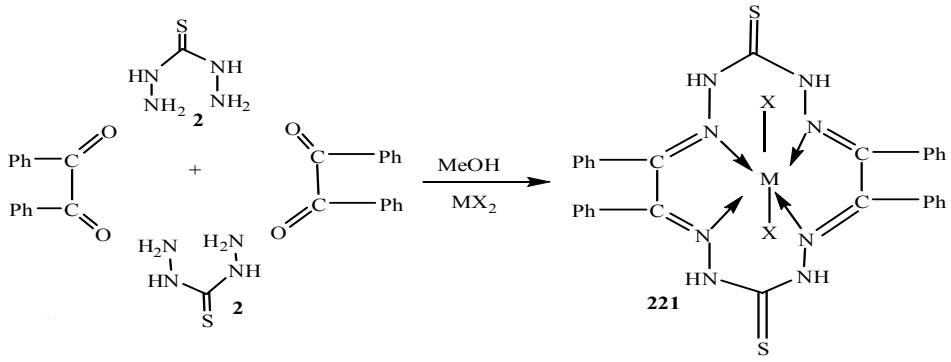
Scheme 79

The triple Cu(II) thiocarbohydrazide-2,3-butanedione system in the Cu(II) hexacyanoferrate gelatin immobilized matrix (**219** and **220**) has been prepared. The similar process in the nickel(II)hexacyanoferrate(II) matrices does not occur under such conditions (Scheme 80).[96]



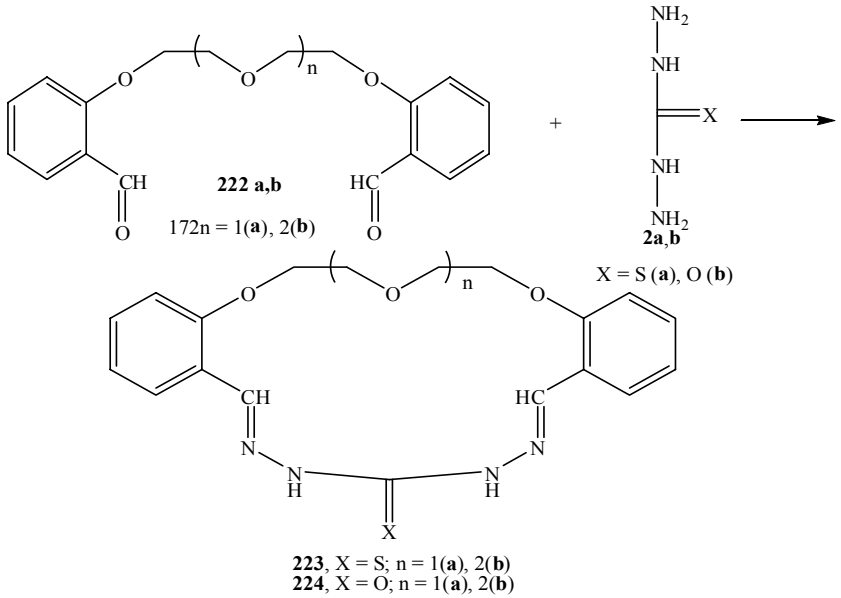
Scheme 80

Moreover, a series of complexes of the type [M(TML)X_2]; **221** where TML is a tetradenate macrocyclic ligand, M= Co(II), Ni (II), Cu (II); X= Cl^-, X= CH_3COO^- or NO_3^- have been synthesized by template condensation of benzil and thiocarbohydraide in the presence of divalent metal salts in methanolic medium (Scheme 81).[96]



Scheme 81

Reactions of formylpodands **222** with carbohydrazide (**2b**) or thiocarbohydrazide (**2a**) afforded macroheterocycles **223** and **224** with a carbo- or thiocarbohydrazone moiety respectively (Scheme 82).[97]



Scheme 82

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