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Utility of thiocarbohydrazide in heterocyclic synthesis

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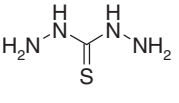
This review describes the synthesis and properties of thiocarbohydrazide and its utility as a building block for the synthesis of heterocyclic systems with pharmacological interest.

Keywords: thiocarbohydrazide; synthesis; properties; biological activity; heterocycles

1. Introduction

1.1. *General and historical*

Thiocarbohydrazide is surprisingly late in its arrival on the chemical scene; considering its close relationship with thiourea, the compound is most directly associated with the foundation of organic chemistry. Curtius (*1*) described, in 1894 and more fully in 1895 (*2*), the results of the hydrazinolysis of derivatives of thiocarbonic acid. The same paper (*2*) also described the condensation of carbon disulfide with hydrazine to form the hydrazine salt of dithiocarbazic acid, but stopped short of the final hydrazinolysis stage. It was not until 1908 that Stolle (*3*) completed this series of reactions and so discovered thiocarbohydrazide.



Many interesting articles have lately appeared that report on the functionalization of thiocarbohydrazide and its use in organic synthesis. In particular, thiocarbohydrazide has numerous reactive centers in the molecule and therefore, may serve as a convenient building block. The present review attempts to provide, a comprehensive and critical account of the utility of thiocarbohydrazide and all relevant derivatives in heterocyclic synthesis.

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1.2. *Nomenclature and structure*

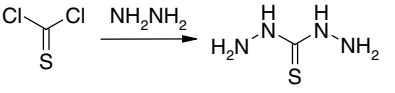
The nomenclature of these types of compounds presents no difficulty. The term thiocarbohydrazide (*3*) has served satisfactorily as the generic name for all relevant compounds and is adopted in chemical abstracts. Thiocarbohydrazide is occasionally indexed as thiocarbazide or thiocarbonohydrazide as it is a hydrazine derivative of thiocarbonic acid.

2. Synthesis of thiocarbohydrazide

Several effective methods of synthesizing thiocarbohydrazide are now available including the following:

2.1. *Hydrazinolysis of thiophosgene*

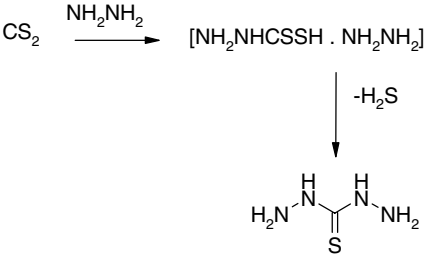
Thiophosgene readily undergoes hydrazinolysis. Thiocarbohydrazide is formed either in ether (*3*) or in aqueous media (*4*) in satisfactory yield (Scheme 1).



Scheme 1.

2.2. *Hydrazinolysis of carbon disulfide*

The reaction of hydrazine with carbon disulfide in water is no doubt the cheapest and most useful method for the preparation of thiocarbohydrazide in 60–70% yield (*3*, *5–10*). A modification of this method, in which 2-mercaptoethanol (*11*) and 2-chloroethanol are added as catalyst (*12*), increase the yield to 90–95% (Scheme 2).

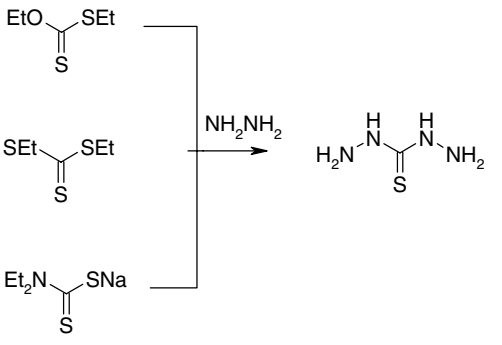


Scheme 2.

2.3. *Hydrazinolysis of diethyl xanthate, dialkyl trithiocarbonates and sodium diethyl dithiocarbamate*

Hydrazinolysis of diethyl xanthate (*13*), dialkyl trithiocarbonates (*14*) and sodium diethyl dithiocarbamate (*15*) are possible routes to thiocarbohydrazide. Aqueous media at room temperature promote the production of thiocarbohydrazide in high yields (Scheme 3). By merely warming the

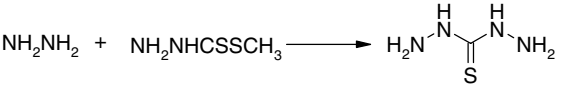
two reactants (*16*), high yields of thiocarbohydrazide are claimed to be obtainable; the effluent gases (ethanol and ethanethiol) are ignited as they leave the reaction vessel.



Scheme 3.

2.4. *Hydrazinolysis of methyl dithiocarbazinate*

Hydrazinolysis of methyl dithiocarbazinate in boiling ethanol produces thiocarbohydrazide in 65% yield (*5*) (Scheme 4).



Scheme 4.

3. Physical properties of thiocarbohydrazide

Thiocarbohydrazide is a white, crystalline solid, melting with decomposition at 169–171 °C (*17–19*). It may be recrystallized from water and is insoluble in most solvents at room temperature. The IR spectrum of thiocarbohydrazide (*20*) shows the following major peaks (with suggested assignments in parentheses): 3250, 3160 (NH_2, NH); and 1330 (C=S) cm^{-1}. Its ^1H NMR spectrum showed broad peaks at δ 3.0–5.0 ppm while its mass spectral (*20*) data was recorded at m/z 106 (M^+, 100%), 91 ($NH_2NHCSNH_2$), 75 ($CSNHNH_2$), 60 ($CSNH_2$).

4. Chemical properties of thiocarbohydrazide

The chemical behavior of thiocarbohydrazide was as expected based on its structure.

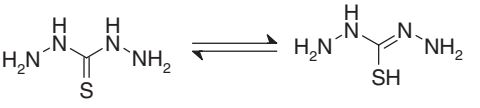
4.1. *Thermolysis*

Thiocarbohydrazide decomposes at its melting point of 169–171 °C, with the loss of ammonia and hydrogen sulfide (*3*, *18*, *19*). The decomposition of thiocarbohydrazide sets in at temperatures

considerably below its melting point (*e.g.* 110 °C), with speeds that increase to a constant rate after 6 days, resulting in a 24% loss in weight after 14 days (*5*).

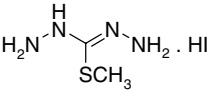
4.2. *Acidic and basic properties*

Thiocarbohydrazide, incorporating both acidic and basic functions in its structure is amphoteric, being soluble both in dilute bases and acids. The pH of a saturated solution of thiocarbohydrazide in carbon dioxide-free water is 6.95. This slight acidic character may be ascribed as in analogous examples, to the mobile hydrogen atom adjacent to the thiocarbonyl group permitting the formation of the acidic mercapto function in the *iso* form. Thiocarbohydrazide also behaves as a diacid base forming dihydrochloride and monosulfate, the composition of which was established by titration in aqueous solution (*5*).



4.3. *S-alkylation of thiocarbohydrazide*

Like analogous thioamido compounds such as thiourea or thiosemicarbazide, thiocarbohydrazide is *S*-alkylated readily by the usual methods. Thus, *S*-methylisothiocarbohydrazide is rapidly formed from thiocarbohydrazide and methyl iodide in ethanol in 80% yield and advantageously isolated as the highly crystalline hydroiodide (*21*).



4.4. *Condensation with carbonyl compounds*

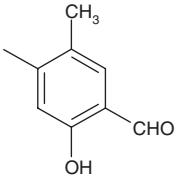
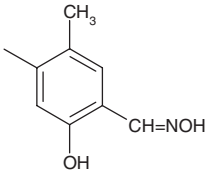
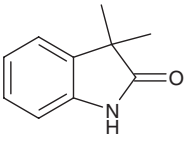
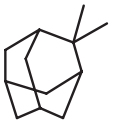
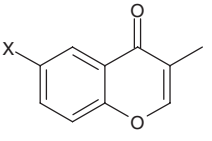
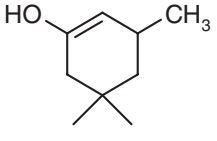
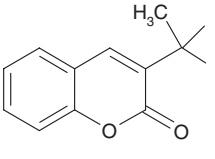
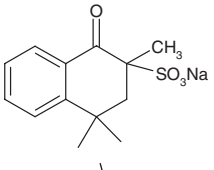
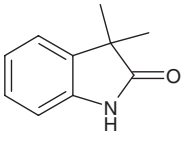
4.4.1. *Formation of mono- and dithiocarbohydrazones*

Both hydrazine groups of thiocarbohydrazide display normal reactivity towards carbonyl compounds and give rise to a large variety of crystalline mono- and dithiocarbohydrazones (Table 1). In general, the condensation products are formed so rapidly that the mono adducts **2** are only obtainable under specially controlled conditions (*18*, *20*, *22–45*). An effective method for the preparation of monothio-carbohydrazones **2** is based on the reaction of an aldehyde or ketone in ethanol being added to a warm solution of thiocarbohydrazide in water. The product separates on cooling. The dithiocarbohydrazones **3** formed only after prolonged boiling, using an excess of aldehyde or ketone (Scheme 5) (*39*).

4.4.2. *Formation of macrocycles of thiocarbohydrazones*

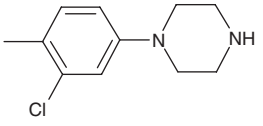
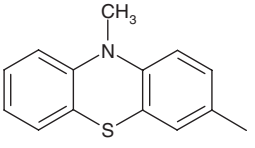
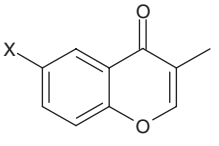
4.4.2.1. *Formation of* [1 + 1]*macrocycles.* Reaction of 1,1′-diacetylferrocene with thiocarbohydrazide gave [1 + 1] macrocyclic azomethines **4** (*46*). Macrocycles **5** ($n = 1, 2$) were prepared in 72% and 75% yields by cyclocondensation of di(phenoxy) ether derivative with thiocarbohydrazide in aqueous ethanol at 45–50 °C (Scheme 6) (*47*).

Table 1. Monothiocarbohydrazones **2** and dithiocarbohydrazones **3**.

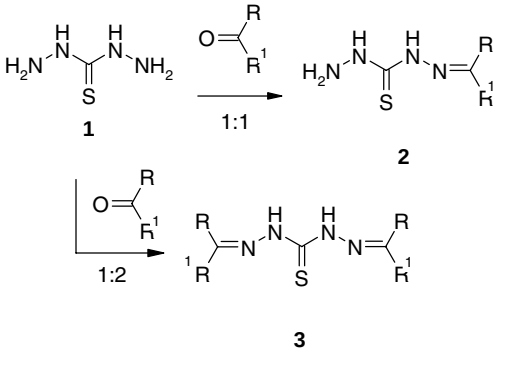
Monothiocarbohydrazones **2**			Dithiocarbohydrazones **3**		
R	R^1	Ref.	R	R^1	Ref.
CH_3	CH_3	(*29*)	CH_3	CH_3	(*29*)
$(CH_3)_2CH$	H	(*29*)	CH_3	CH_3CH_2	(*29*)
Ph	H	(*28*)	$HON=C(CH_3)$	CH_3	(*45*)
Ph	CH_3	(*29*)	CH_3	Ph	(*24*)
Ph	Ph	(*29*)	Ph	Ph	(*3*, *16*, *20*)
Cyclohexylidene		(*29*)	(*2*)-HOC_6H_4	H	(*43*, *44*)
4-$MeOC_6H_4$	H	(*34*)		H	(*35*)
4-$(Me)_2NC_6H_4$	H	(*34*)		H	(*35*)
Cinnamyl	H	(*30*)	2-Pyridyl	H	(*40*)
2-Thienyl	H	(*31*)	2-Naphthol-1-yl	H	(*42*)
		(*20*)			(*20*)
		(*20*)		H	(*39*)
		(*20*)			(*41*)
		(*33*)			
		(*20*)			

(*Continued*)

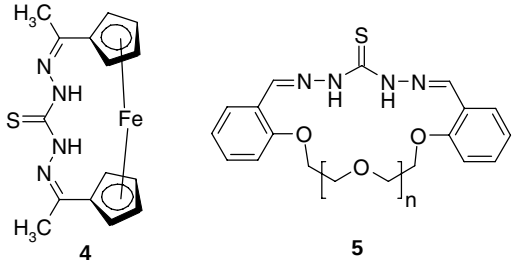
Table 1. Continued.

	H	(*38*)
	H	(*32*)
	H	(*39*)

$X = Cl, CH_3$

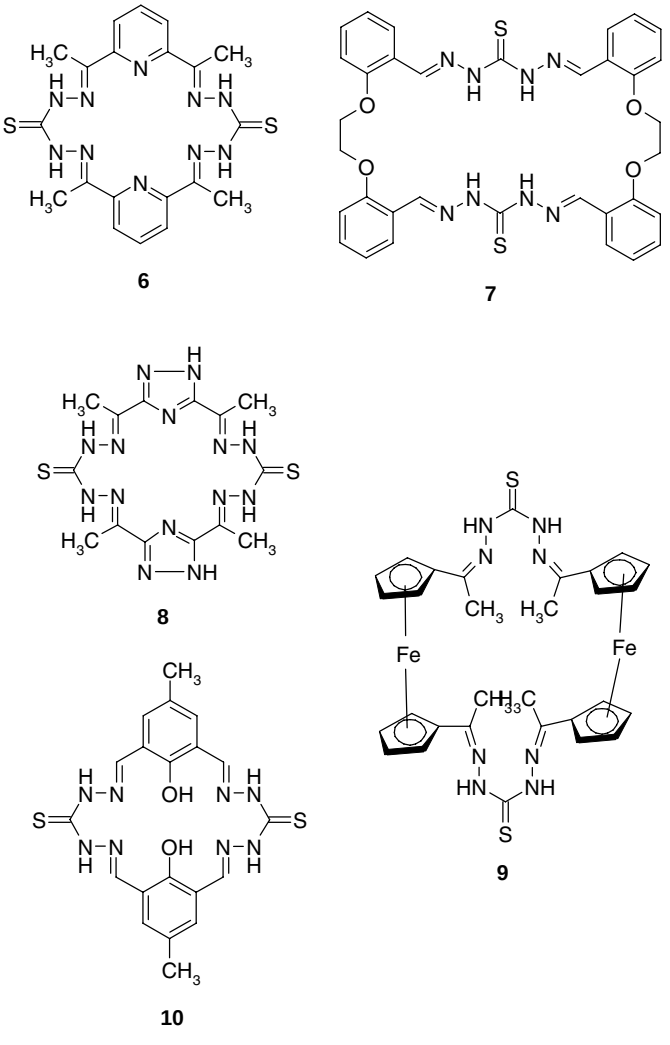


Scheme 5.



Scheme 6.

4.4.2.2. *Formation of* [2 + 2]*macrocycles.* Dinuclear macrocycles **6**–**10** were synthesized by using thiocarbohydrazide with 2,6-diacetylpyridine (*48*), di(2-formylphenoxy)ethylene (*49*), 3,5-diacetyl-1,2,4-triazole (*50*), 1,1′-diacetylferrocene (*51*) and 2,6-diformyl-*p*-cresol (*35*), respectively (Scheme 7).



Scheme 7.

5. Biological properties

Thiocarbohydrazides are carbonyl-trapping agents, diamine oxidase inhibitors and inhibitors of enzyme systems, and produce convulsions after a latent period of 1 h (*52–54*). Repeated maximal seizures occur for 4–5 h when topically applied to the cerebral cortex; it produces fast, high-voltage spiking activity as recorded by the electron cephalogram. Thiocarbohydrazide is active *in vitro* against *turbercle bacilli, Micrococcus pyogenes var. cureus* and *Escherichia coli* as antibacterial agent (*55*). Thiocarbohydrazides have fungicidal properties against *Helminthosporium salioum* and species of *Pythium* in agar cultures (*56*).

According to toxicological parameters, thiocarbohydrazide is a pesticide butrazin intermediate belonging to class I type material. Clinical symptoms show that, when taken by oral and inhalation routes, the central nervous system is most affected. The recommended safe exposure level in the working zone via its acute toxicological characteristics was 0.03 mg/m^3. Contact with

thiocarbohydrazide may lead to delayed type hypersensitivity (*57*). Thiocarbohydrazide at a dose of 29 mg/kg proved to be active against L 1210 leukemia in mice (*58*).

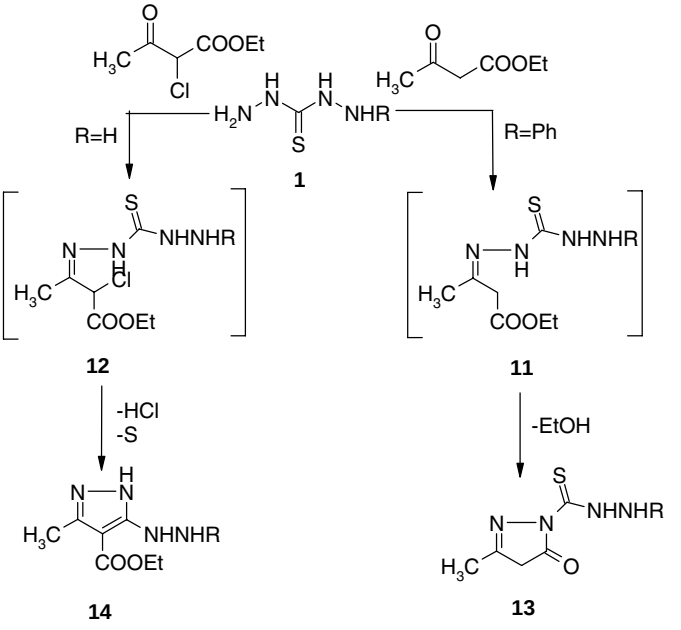
6. Utility of thiocarbohydrazide in heterocyclic synthesis

6.1. *Synthesis of five-membered rings with two heteroatoms*

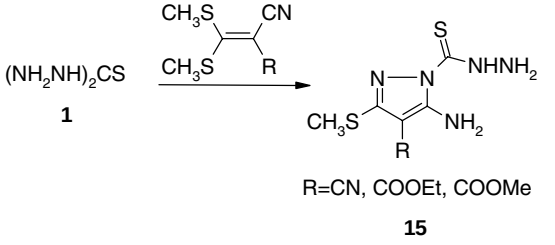
6.1.1. *Pyrazole*

The interaction of equimolar amounts of thiocarbohydrazide **1** with ethyl acetoacetate or ethyl α-chloroacetoacetate appears to form the corresponding thiocarbohydrazone intermediate **11** and **12** followed by cyclization to pyrazoles **13** and **14**, respectively (Scheme 8) (*59–61*).

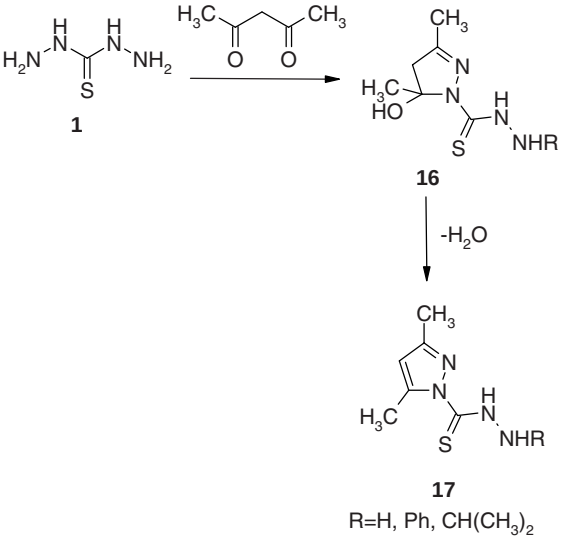
Refluxing of **1** with 2-[bis(methylsulfanyl)methylene]malononitrile and 2-cyano-3,3-bis (methyl-sulfanyl)acrylic acid ester in ethanol gave 70–75% yield of 1-(5-amino-4-substituted-3-methylthio-pyrazol-1-yl)carbothiohydrazides **15** (Scheme 9) (*62*, *63*).



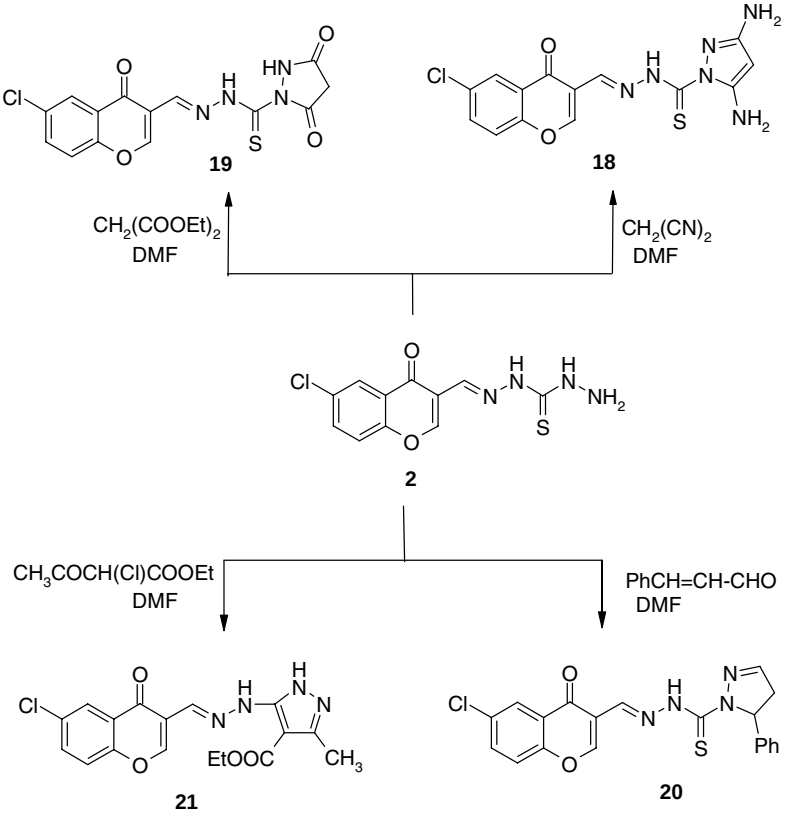
Scheme 8.



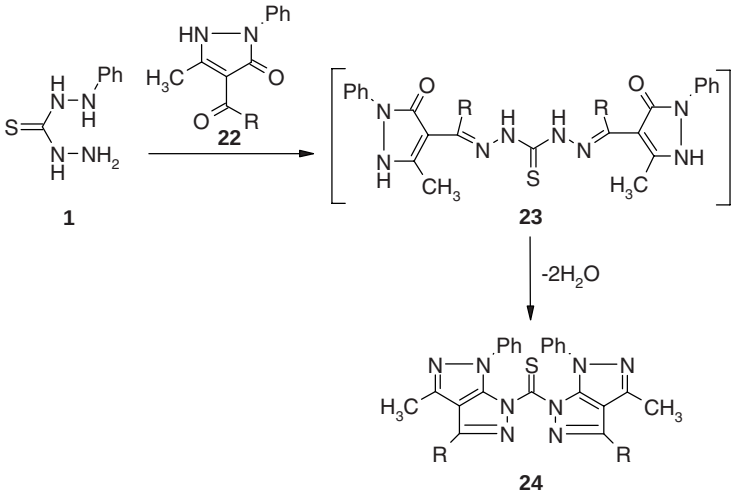
Scheme 9.



Scheme 10.



Scheme 11.



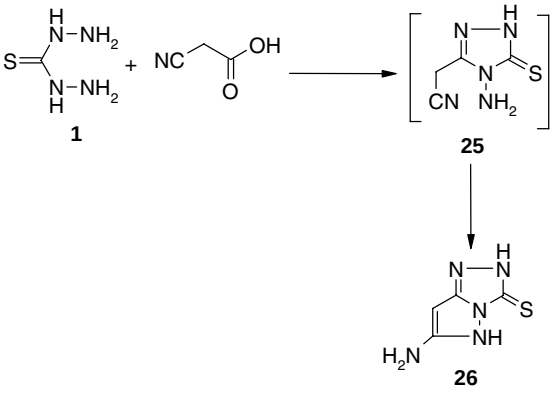
Scheme 12.

The cyclocondensation reaction of **1** with 2,4-pentandione gave the pyrazolinone derivative **16** (*64*), with the loss of a molecule of water to give **17** (Scheme 10) (*65*).

Treatment of monothiocarbohydrazone **2** with malononitrile, diethyl malonate or cinnamaldehyde in dimethyl formamide (DMF) and few drops of piperidine afforded the corresponding pyrazoles derivatives **18–20**, respectively, in yields of 37–60%. Also, treatment of **2** with ethyl 2-chloroacetoacetate in DMF yielded the unexpected product ethyl 5-[2-(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)hydrazino]-3-methyl-1*H*-pyrazole-4-carboxylate (**21**) in yield 78% (Scheme 11) (*39*).

Bis-(6-phenyl-4-methyl-3-substituted-pyrazolo[4,5-d]pyrazolo-1-yl)thioketones **24** have been obtained in good yield by allowing **1** to react with 1-phenyl-3-methyl-4-acetyl/benzoyl-pyrazol-5-one **22** followed by cyclization of the intermediate **23** (Scheme 12) (*66*).

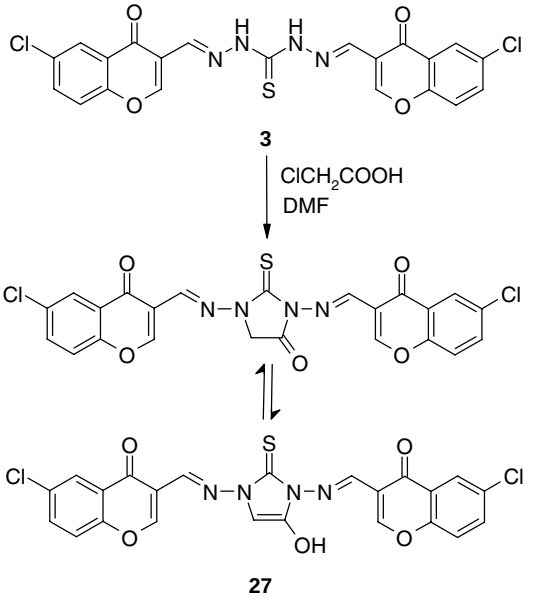
When cyanoacetic acid was treated with **1**, the pyrazolotriazole derivative **26** was obtained through the intermediate **25** (Scheme 13) (*67*).



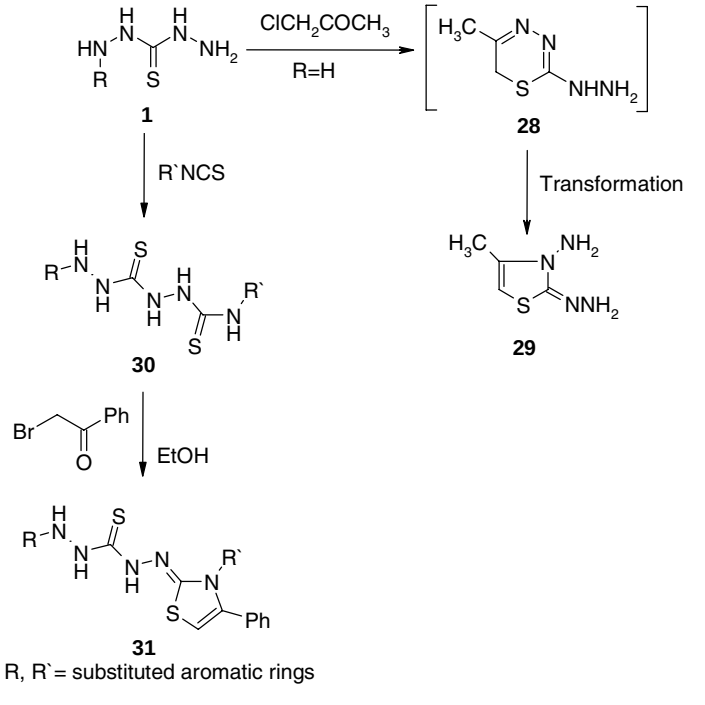
Scheme 13.

6.1.2. *Imidazole*

1,3-Bis[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]-2-thioxoimidazolidin-4-one (**27**) was obtained from treatment dithiocarbohydrazone **3** with chloroacetic acid in DMF containing a few drops of piperidine (Scheme 14) (*39*).



Scheme 14.



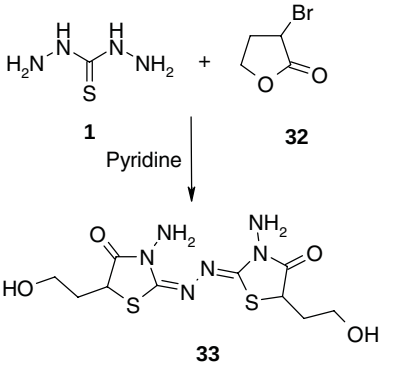
Scheme 15.

6.1.3. *1,3-Thiazole*

The condensation of thiocarbohydrazides **1** with α-haloketones in acidic media gave 1,3, 4-thiadiazine intermediate **28**, which can be easily converted into 1,3-thiazoline derivative **29** (*16*). Also, addition of isothiocyanates to **1** gave 1-aryl-5-arylthiocarbamoylthiocarbohydrazide **30** which condensed with α-bromoacetophenone in ethanol to yield the 1,3-thiazolium salt of type **31** (Scheme 15) (*68*, *69*).

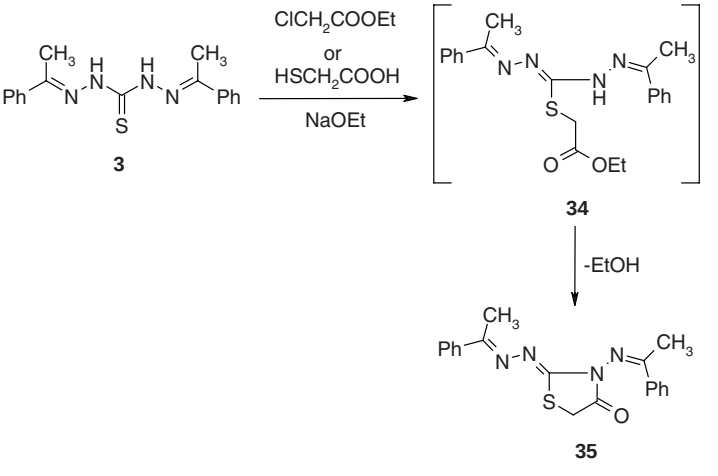
Cyclization of **1** with α-bromo-γ-butyrolactone **32** in pyridine gave 1,3-thiazolidinone derivative **33** (Scheme 16) (*30*).

Dithiocarbohydazone **3**, having both hydrazino groups blocked, is reported to react at its free 3-thio position with ethyl chloroacetate (*24*) or thioglycolic acid (*70*) to form 1,3-thiazolidinone **35** (Scheme 17).



1 **32** **33**

Scheme 16.



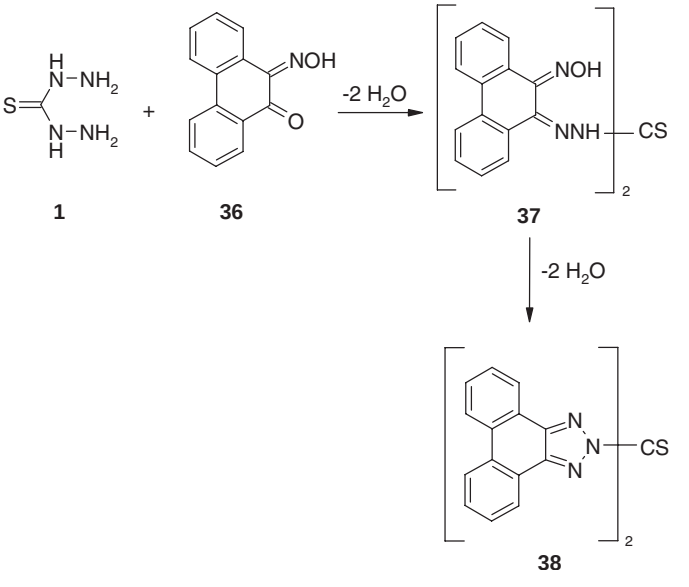
3 **34** **35**

Scheme 17.

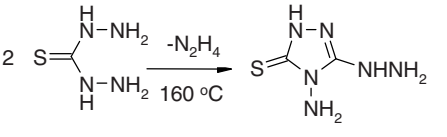
6.2. *Synthesis of five-membered rings with three heteroatoms*

6.2.1. *1,2,3-Triazole*

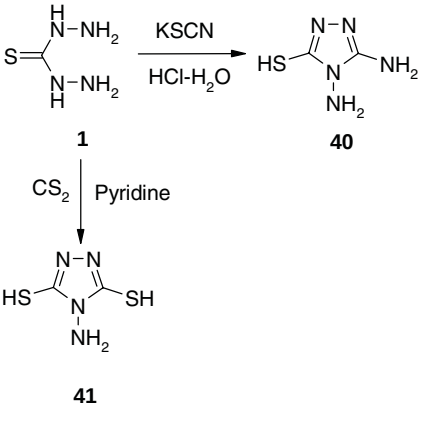
Condensation of thiocarbohydrazide **1** with phenanthraquione monoxime **36** is reported to yield bis-(1,2,3-triazolyl)thioketones **38** (Scheme 18) (*29*).



Scheme 18.



Scheme 19.



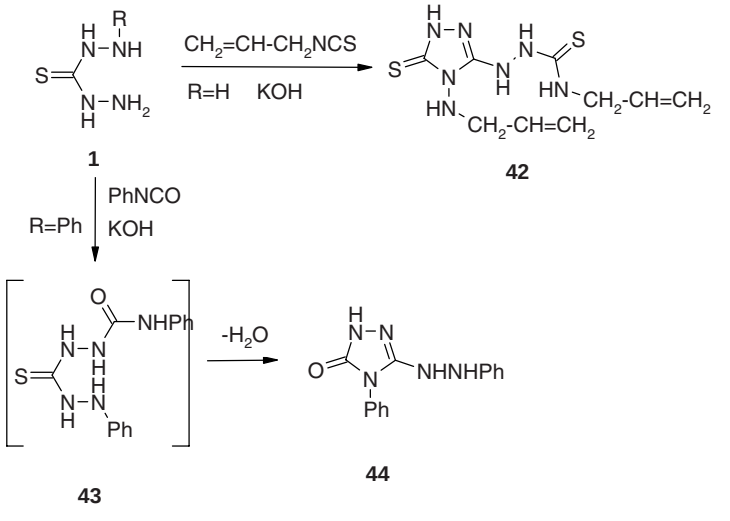
Scheme 20.

6.2.2. *1,2,4-Triazole*

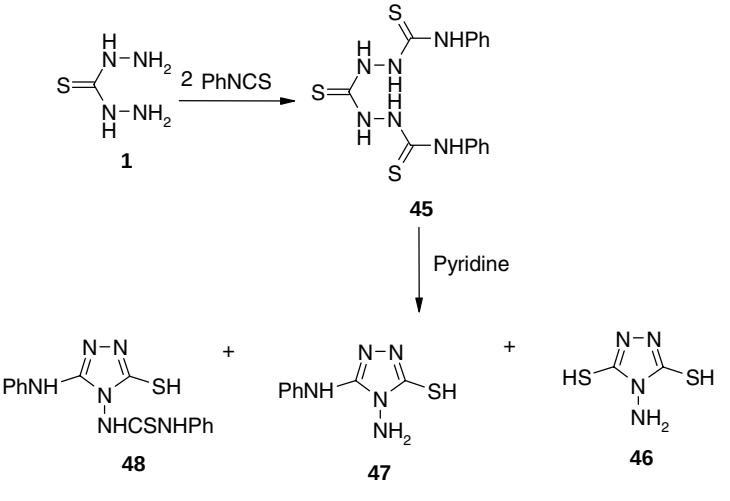
Two molecules of thiocarbohydrazide **1** were fused at 160 °C together to form 4-amino-3-hydrazino-Δ^2-1,2,4-triazoline-5-thione (**39**) (Scheme 19) (*71*).

Equimolar quantities of potassium isothiocyanate and **1** in boiling water containing hydrochloric acid gave a moderate yield of 4,5-diamino-2,4-dihydro-1,2,4-triazole-3-thione (**40**) (*72*). Also, reaction of **1** with carbon disulfide in boiling pyridine afforded 4-amino-3,5-dimercapto-1,2,4-triazole (**41**) (Scheme 20) (*73*, *74*).

When thiocarbohydrazides **1** are reacted with allyl isothiocyanate (*75*) or phenyl isocyanate (*76*) in the presence of aqueous KOH, 1,2,4-triazoline derivatives **42** and **44** can be obtained, respectively (Scheme 21).



Scheme 21.



Scheme 22.

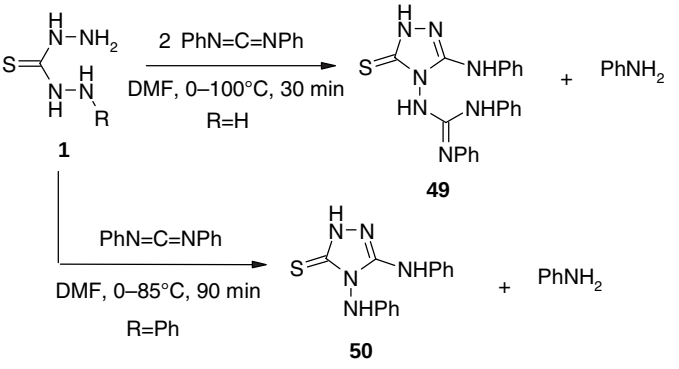
Similarly, 1,5-bis(phenylthiocarbamoyl)thiocarbohydrazide **45** is cyclized rapidly in boiling pyridine, giving the three different 1,2,4-triazoles **46–48** (Scheme 22) (*77*).

The reaction of thiocarbohydrazides **1** with diphenylcarboiimide depends on the reaction conditions. Using two equivalents of diphenylcarboiimide in DMF yield 3-anilino-4-(*N*,*N*′-diphenylguanidino)-Δ^2-1,2,4-triazoline-5-thione (**49**) (*78*). On the contrary, 1-phenylthiocarbohydrazide reacted with on equivalent of diphenylcarboiimide in DMF and yield 3,4-bis(phenylamino)-Δ^2-1,2,4-triazoline-5-thione (**50**) (Scheme 23) (*79*).

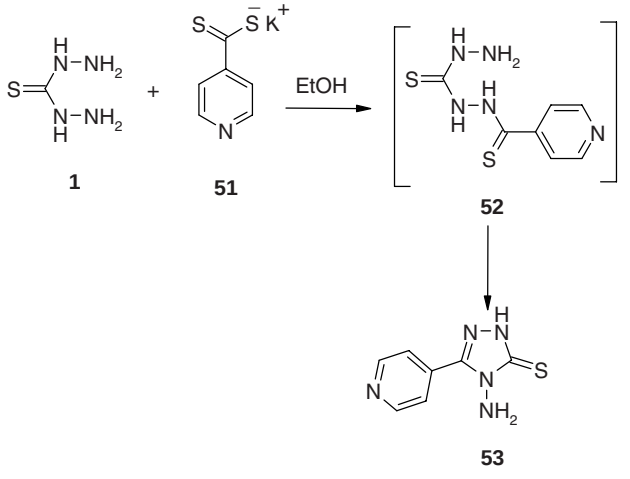
The interaction of **1** with the potassium salt of dithioisonicotinic acid **51** in boiling ethanol afforded a product that has been identified as 4-amino-3-mercapto-5-substituted-1,2,4-triazole (**53**) (Scheme 24) (*80*, *81*).

Cyclocondensation of compound **54** with **1** in pyridine gave 65% yield of 4-amino-3-mercapto-1,2,4-triazole derivative **55** (Scheme 25) (*82*).

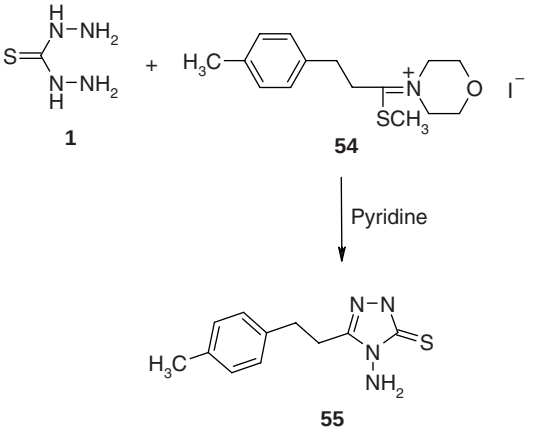
Equimolar amounts of thiocarbohydrazide **1** reacted with various carboxylic acid (Table 2) at their melting points, followed by simultaneous cyclization to give 4-amino-5-substituted-1,2,4-triazole-3-thione **57** (Scheme 26) (*67*, *83–108*).



Scheme 23.



Scheme 24.



1 **54** **55**

Scheme 25.

Condensation of γ-lactones **58** and **59** with **1** in boiling pyridine gave the corresponding 4-amino-3-mercapto-1,2,4-triazine derivatives **60** and **61**, respectively, in good yields (Scheme 27) (*110–113*).

Heating benzothiazine-4-thione **62** with **1** gave the mesoionic compound **63**, which upon treating with methyl iodide afforded methylthiotriazaoloquinazolinium **64** (Scheme 28) (*114*).

Oxidation of monothiocarbohydrone **2** with hydrogen peroxide gave 4-amino-5,5-(adamant-2-yl)-4,5-dihydro-1,2,4-triazole-3-thione (**65**) (Scheme 29) (*20*).

A facile route to synthesize 6-substituted-3-[3-thioxo-1,5-dihydro-1,2,4-triazol-4-ylimino-methyl]-4*H*-chromen-4-one derivatives **66–68** has been achieved by refluxing monothiocarbohydrazone **2** with triethylorthoformate, acetyl chloride or carbon disulfide in pyridine, respectively (Scheme 30) (*39*).

The fusion of dicarboxylic acids with thiocarbohydrazide **1** gave the corresponding bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkane/arylene **69** in a one-pot reaction (Scheme 31) (*115–120*).

6.2.3. *1,3,4-Thiadiazole*

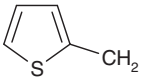
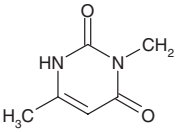
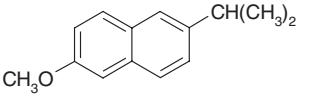
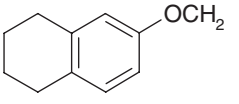
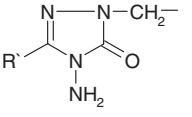
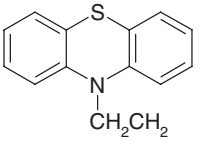
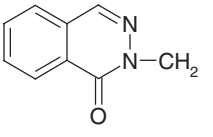
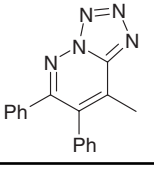
Thiocarbohydrazide **1** is rapidly ring closed with [(phenylcarbonothioyl)sulfanyl] acetic acid **70** in ethanolic hydrochloride acid to give a mixture of 2-hydrazino/2-mercapto-5-phenyl-1,3,4-thiadiazole **72** and **73** (Scheme 32) (*121*).

The action of hot aqueous ferric chloride on the adduct 1-arylthiocarbamoyl-5-phenylthiocarbohydrazide **30** yielded the deep orange phenylazo-1,3,4-thiadiazole **74** (*13*), while action of aqueous NaOH afforded 2-arylamino-5-phenylhydrazino-1,3,4-thiadiazole (**75**) (Scheme 33) (*13, 75, 122, 123*).

Refluxing bis-istain **76** with **1** in glacial acetic acid affords the corresponding bis-Schiff base **77**, which, when boiled in acetic anhydride, gives N-acetylated bis-1,3,4-thiadiazoline **78** (Scheme 34) (*124*).

When 4-carbethoxy-1-piperazine thiocarbohydrazone **81** (from **79** with **80**) is treated with formic acid, pyrazolyl-1,3,4-thiadiazoline derivative **82** is generated (Scheme 35) (*125*).

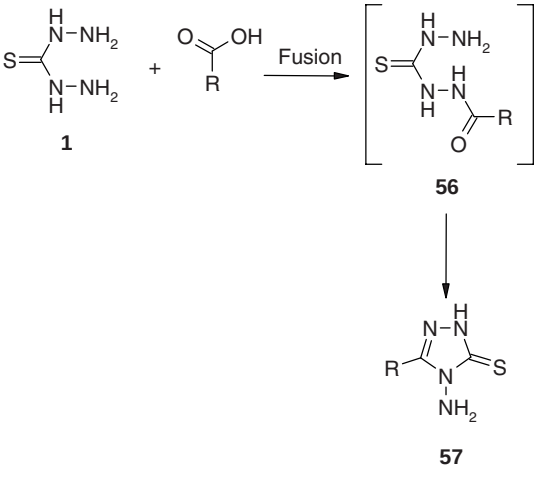
Table 2. 4-Amino-5-substituted-1,2,4-triazole-3-thione **57**.

R	Ref.	R	Ref.
H	(*108*)		(*106*)
CH_3	(*100*, *92*)		
CH_3CH_2	(*100*, *92*)		
$CH_3CH_2CH_2$	(*100*, *92*)		
$(CH_3)_2CHCH_2$	(*94*)		(*107*)
$HS(CH_2)_3$	(*109*)		
$CH_3CH_2OCH_2CH_2$	(*75*)		
$(CH_3(CH_2)_{11}SO_2(CH_2)_3$	(*99*)		
n-Heptayl	(*86*)		
n-Hexyl	(*86*)		
n-Octayl	(*87*)		(*85*)
Alditolyl	(*88*)		
Ph	(*94*, *100*)		
$Ph(CH_2)_2$	(*94*)		
$Ph(CH_2)_3$	(*94*)		
$PhOCH_2$	(*96*)		(*90*)
D-gluco	(*89*)		
D-galactopentitol-1-yl	(*94*)		
2-HOC_6H_4	(*100*)		
2-$H_2NC_6H_4$	(*100*)		
4-$H_2NC_6H_4$	(*100*)		(*107*)
4-$CH_3C_6H_4$	(*91*)		
2-$CH_3C_6H_4$	(*93*)		
3-$CH_3C_6H_4$	(*98*)		
4-$CH_3C_6H_4$	(*97*)		
4-ClC_6H_4	(*105*)	R`= CH_3, CH_3CH_2, $CH_3(CH_2)_2$, Ph, $PhCH_2$,	
2,4-$(Cl)_2C_6H_3OCH_2$	(*104*)		
			(*83*)
			(*95*)
			(*84*)

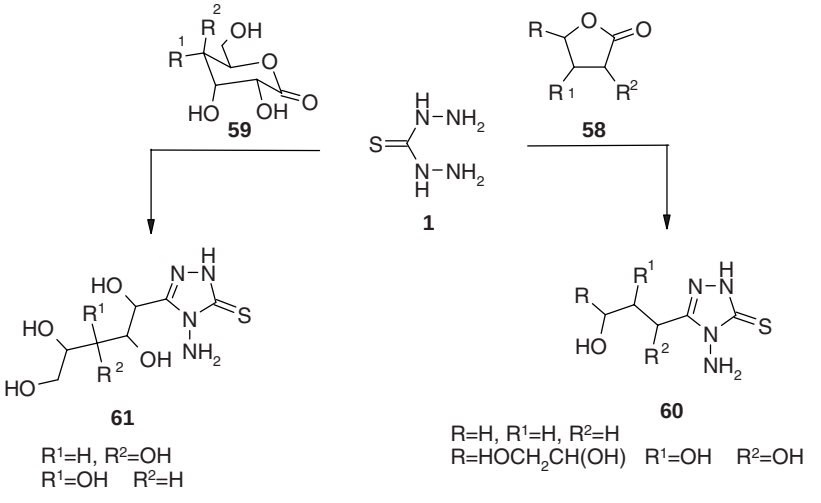
Reaction of **1** with 2,4,6-triphenylpyranium tetrafluoroborate **83** in ethanol gave the pyrazole-1-carbothiohydrazide **84**, which was cyclocondensed *in situ* with benzaldehyde affording 1,3,4-thiadiazoline derivative **85** (Scheme 36) (*126*).

Heterocyclization of monothiocarbohydrazones **2** with triethylorthoformate (*29*), formic acid (*39*), carbon disulfide (*73*), cyanic bromide (*30*) or acetic anhydride (*39*) gave the corresponding 1,3,4-thiadiazole derivatives **86**, **87**, **88** and **89**, respectively (Scheme 37).

Dithiocarbohydrazones **3** were cyclized with lead acetate (*22*, *31*) or acetyl chloride (*30*) or acetic anhydride (*36*, *39*) to give the corresponding 1,3,4-thiadiazole derivatives **90** and **91**, respectively (Scheme 38).



Scheme 26.



Scheme 27.

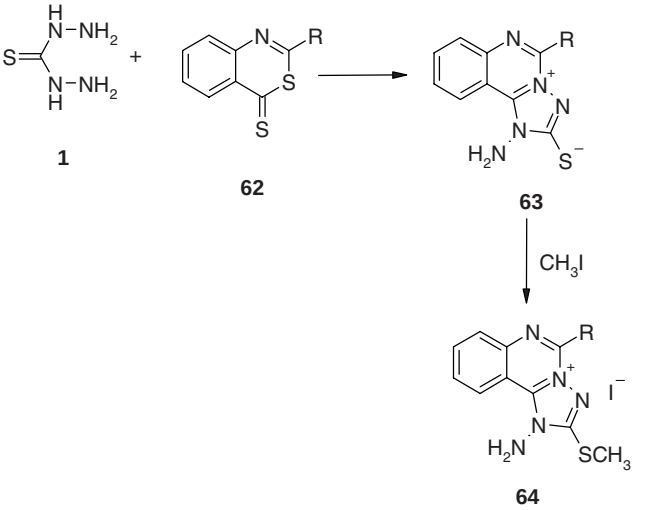
6.3. *Synthesis of five-membered rings with four heteroatoms*

6.3.1. *1,2,3,4-Thiatriazole*

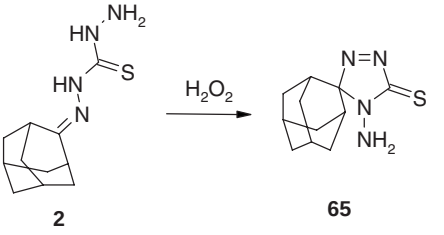
Thiocarbohydrazide **1** was treated with potassium nitrite and hydrochloride acid to afford the explosive 5-hydrazino-1,2,3,4-thiatriazole **92** (not isolated), which was condensed *in situ* with various ketones to give the corresponding stable hydrazones **93** (Scheme 39) (*127*).

6.3.2. *1,2,3,4-Dithiadiazole*

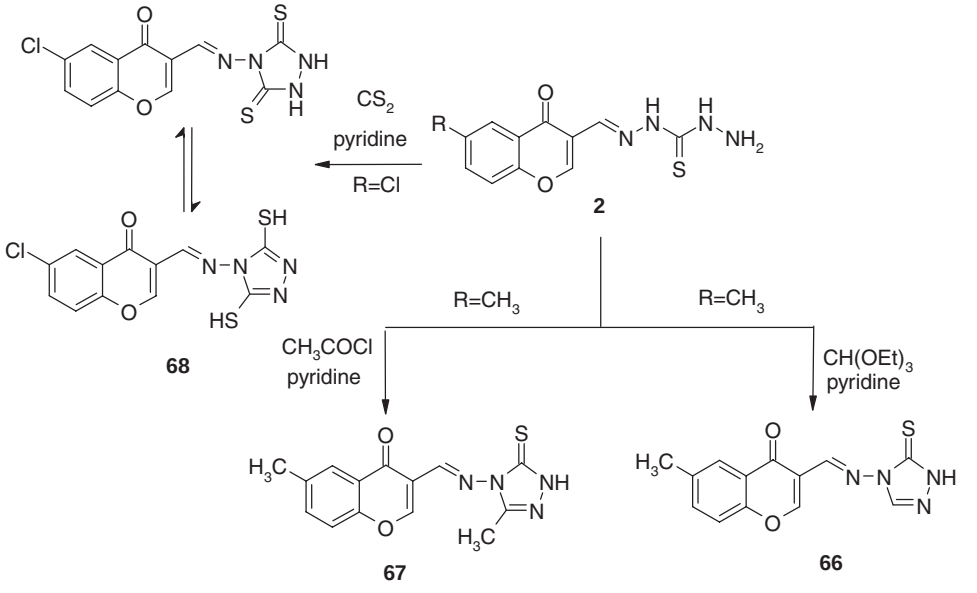
Thionyl chloride cyclized thiocarbohydrazide **1** to 5-(2-phenylhydrazinyl)-3*H*-1,2,3,4-dithiadiazole 2-oxide **94** (Scheme 40) (*75*).



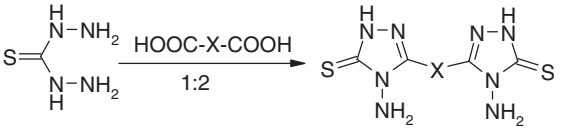
Scheme 28.



Scheme 29.



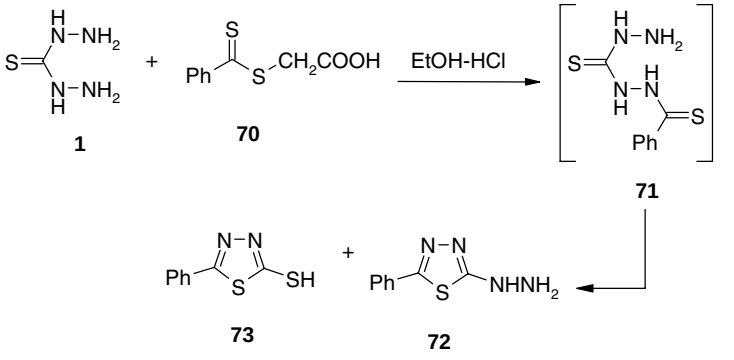
Scheme 30.



1 **69**

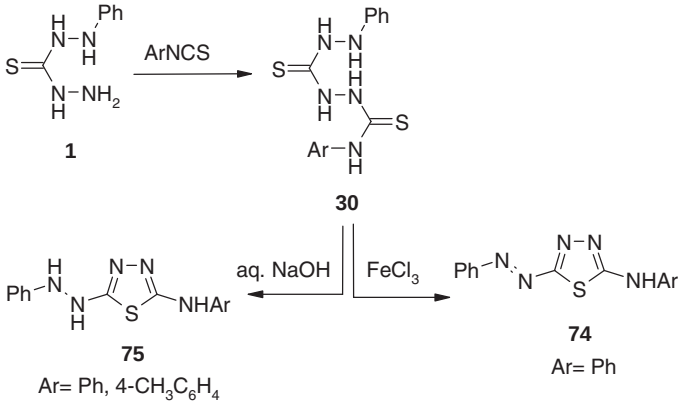
X= $-(CH_2)_n$, n=1-4, $-(CH_2)_8-$,
-CH2-CH(OH)-
-CH(OH)-CH(OH)-
$-CH_2-O-C_6H_4-O-CH_2-$

Scheme 31.



1 **70** **71** **73** **72**

Scheme 32.



1 **30** **75** **74**

Ar= Ph, 4-$CH_3C_6H_4$

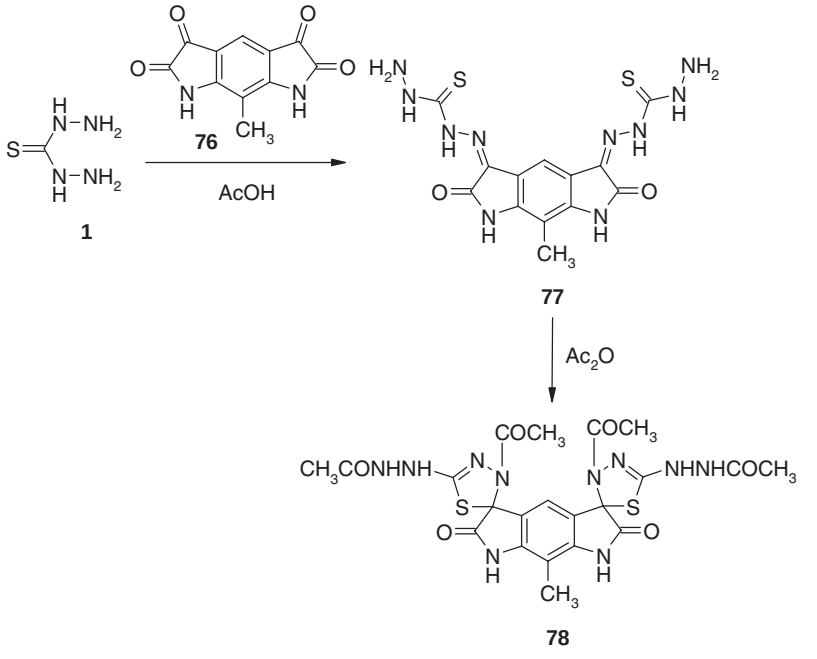
Ar= Ph

Scheme 33.

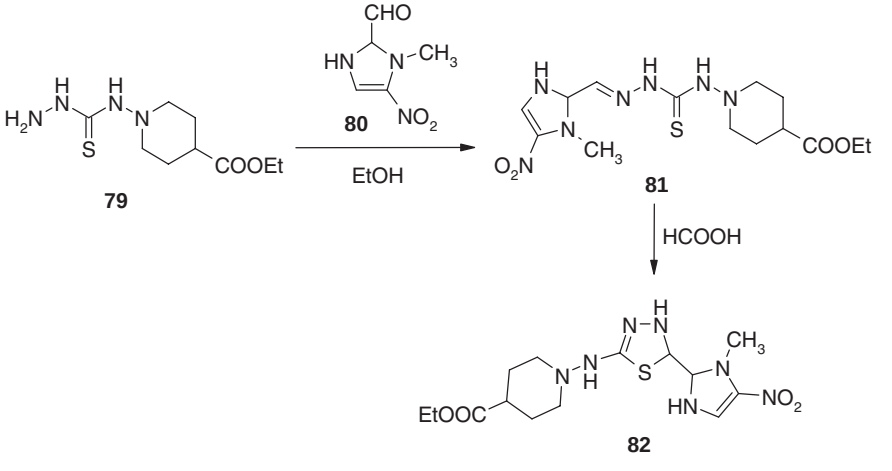
6.4. *Synthesis of six-membered rings with two heteroatoms*

6.4.1. *Pyridazine*

3,6-Dimethyl-*N*′-phenylpyridazine-1(4*H*)-carbothiohydrazide (**96**) was obtained as the major product from the cyclocondensation of **1** with 2,5-hexandione (**95**) (Scheme 41) (*59*).



Scheme 34.

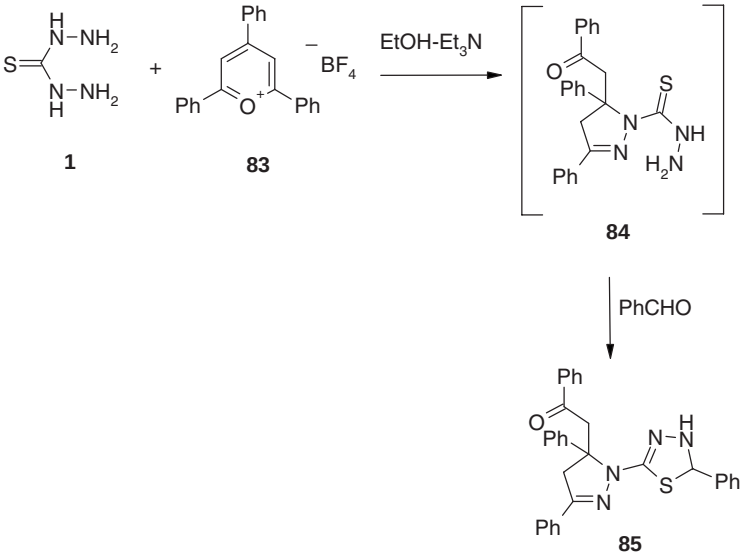


Scheme 35.

6.4.2. *Pyrimidine*

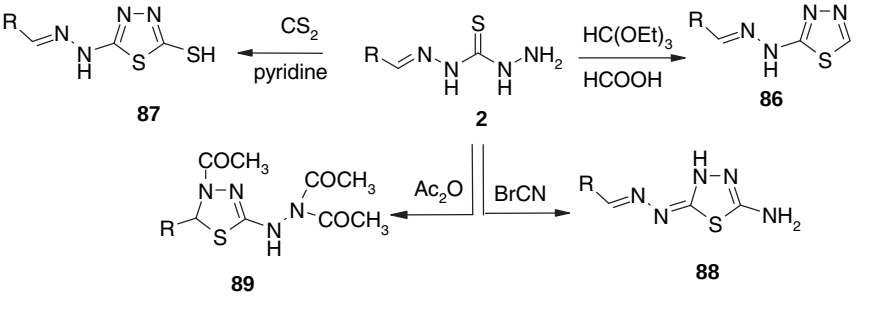
2,4,6-Triphenylpyrylim tetrafluoroborate **83** reacted with **1** in ethanol to give the pyrazole-1-carbothiohydrazide **84**, which underwent cyclization with benzoyl chloride *in situ* affording 6-phenylamido-2,3a,5-triphenylpyrazolo[1,5-c]pyrimidine-7-thione hydrochloride **97** (Scheme 42) (*126*).

1,3-Bis[(6-chloro-4-oxo-4*H*-chromen-3-ylmethylene)amino]-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (**98**) was obtained from treating dithiocarbohydrazone **3** with diethyl malonate in DMF containing a small amount of piperidine (Scheme 43) (*39*).



1 **83** **84** **85**

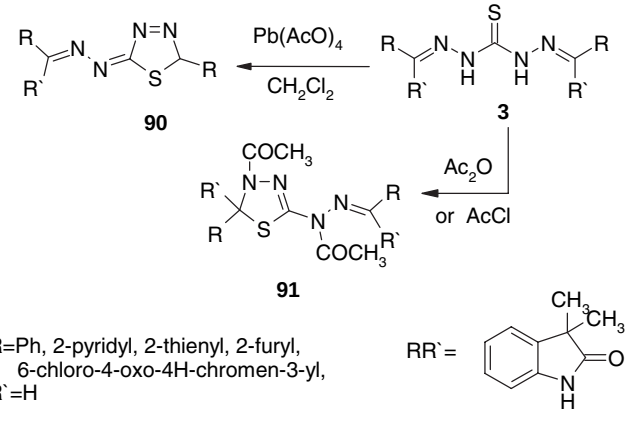
Scheme 36.



87 **2** **86** **89** **88**

R=Ph, $(CH_3)_2CH$, 2-thienyl, 2-furyl, cinnamyl,
6-methyl/6-chloro-4-oxo-4*H*-chromen-3-yl,

Scheme 37.

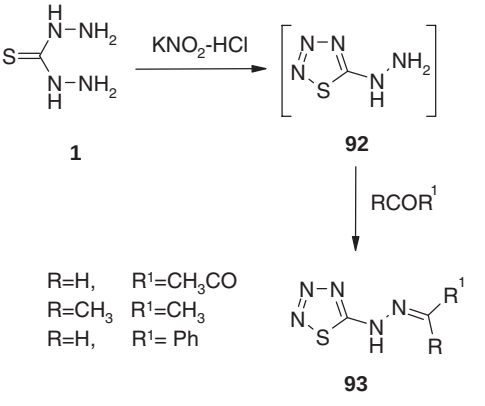


90 **3** **91**

R=Ph, 2-pyridyl, 2-thienyl, 2-furyl,
6-chloro-4-oxo-4H-chromen-3-yl,
R`=H

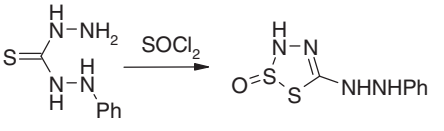
RR`=

Scheme 38.



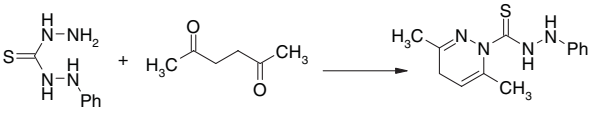
1 **92** **93**

Scheme 39.



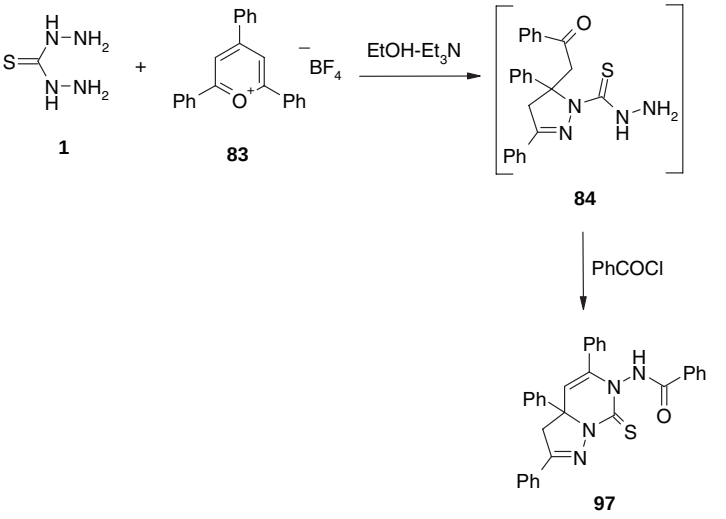
1 **94**

Scheme 40.



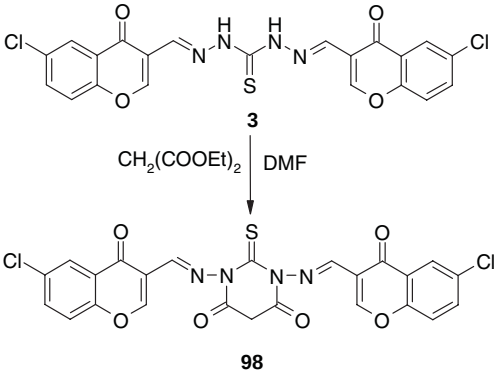
1 **95** **96**

Scheme 41.

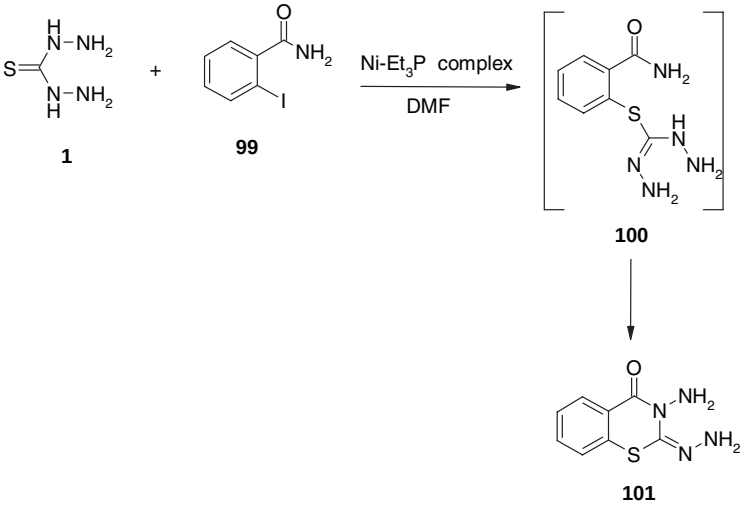


1 **83** **84** **97**

Scheme 42.



Scheme 43.



Scheme 44.

6.4.3. *1,3-Thiazine*

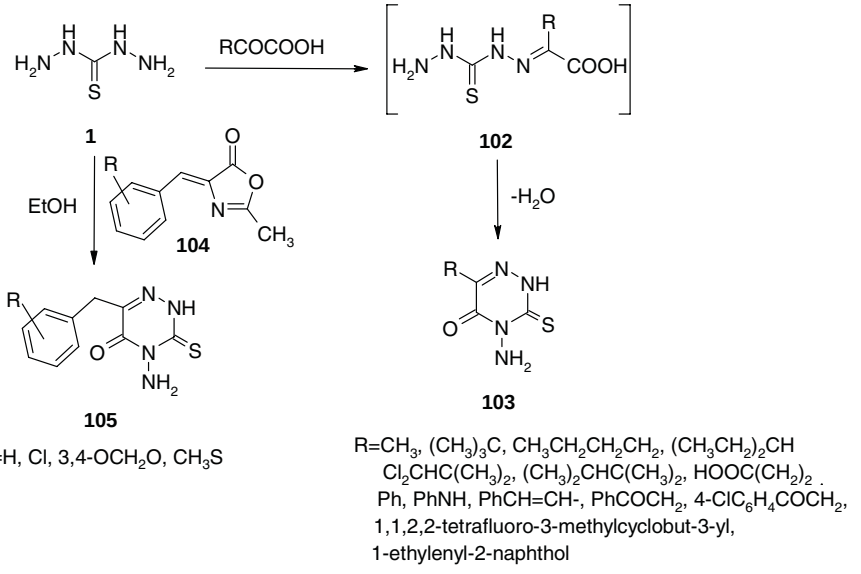
3-Amino-2-hydrazino-1,3-benzothiazin-4-one (**101**) was obtained by treating 2-iodobenzamide 99 with **1** in DMF at 60 °C in the presence of a Ni-Et_3P complex (Scheme 44) (*128*).

6.5. *Synthesis of six-membered rings with three heteroatoms*

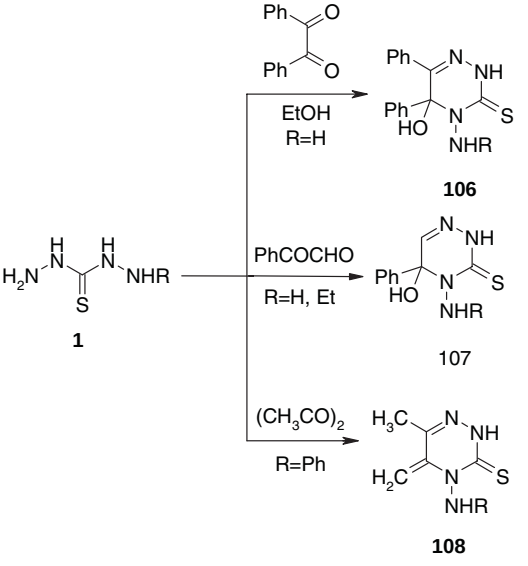
6.5.1. *1,2,4-Triazine*

Condensation of thiocarbohydrazide **1** with α-ketocarboxylic acid yielded 4-amino-3-mercapto-1,2,4-triazines **103** (*129–139*). Also, direct condensation of azalactone **104** with **1** gave 1,2,4-triazine **105** (Scheme 45) (*132*).

4-Amino-11,5-dihydro-5-hydroxy-5,6-diphenyl-1,2,4-triazine-3(2*H*)-thione (**106**) was obtained from **1** with benzil in ethanol (Scheme 46) (*140, 141*). Similarly, cyclocondensation of thiocarbohydrazides **1** with phenylglyoxal and diacetyl gave aminotriazinethiones **107** and anilinomethylenetriazinethione **108**, respectively (Scheme 46) (*64*).



Scheme 45.

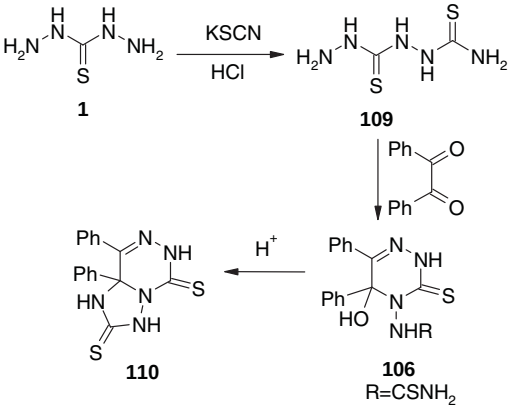


Scheme 46.

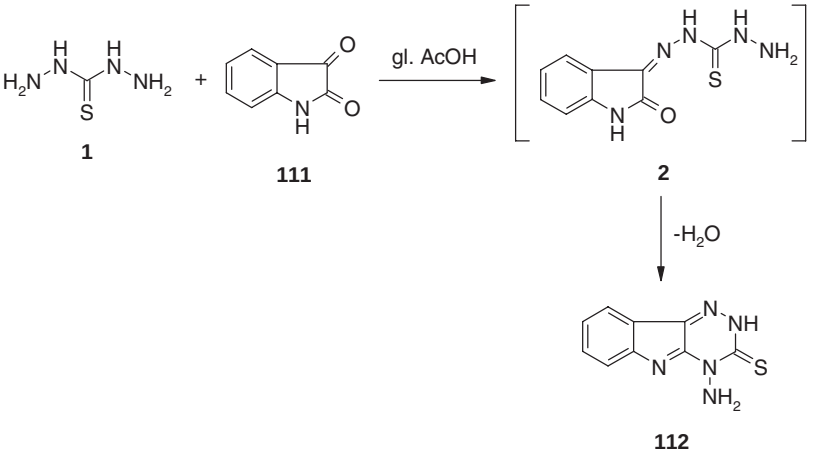
1,9-Dihydro-8,9-diphenyl-1,2,4-triazolo[2,3-d]1,2,4-triazine-3,6-dithione (**110**) was prepared by reacting benzil with 1-(carbothioamide)thiocarbohydrazide **109** followed by acid hydrolysis (Scheme 47) (*142*).

Thiocarbohydrazide **1** reacted with isatin **111** in glacial acetic acid to give 4-amino-2,4-dihydro-3*H*-[1,2,4]triazino[5,6-b]indole-3-thione (**112**) *via* the intermediate isatin α-thiocarbohydrazone (**2**) (Scheme 48) (*143*).

Cyclocondensation of monothiocarbohydrazone **2** with chloroacetyl chloride, dichloroacetic acid or oxalyl chloride in DMF and the addition of few drops of piperidine as a catalyst led



Scheme 47.



Scheme 48.

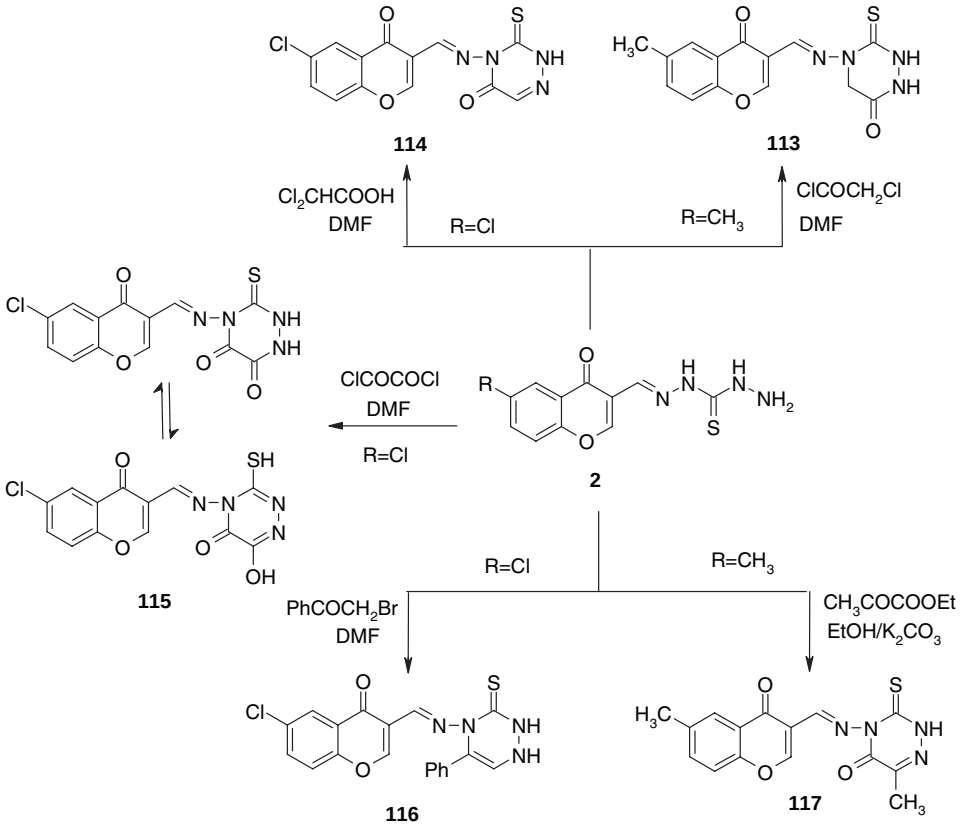
directly to the formation of 1,2,4-triazine-3-thione derivatives **113–115**, respectively. Treatment of **2** with phenacyl bromide and ethyl pyruvate in basic media gave 4-[(6-methyl-4-oxo-4*H*-chromen-3-ylmethylene) amino]-3-thioxo-1,2,4-triazine derivatives **116** and **117**, respectively (Scheme 49) (*39*).

6.5.2. *1,3,5-Triazine*

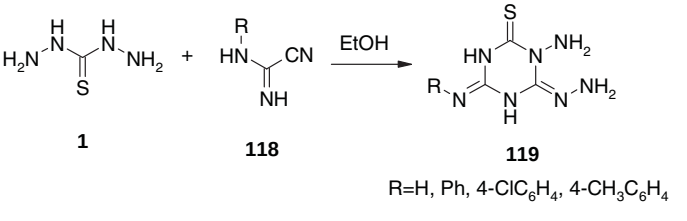
Reaction of R-NHC(NH)CN **118** with thiocarbohydrazide **1** in ethanol gave 1-amino-4-imino (arylamino)-6-hydrazonohexahydro-1,3,5-triazine-2-thiones **119** (Scheme 50) (*144*).

6.5.3. *1,3,4-Oxadiazine*

1-Phenylthiocarbohydrazide **1** reacts with orthodiketones such as phenanthraquinone and acenaphthaquinone followed by cyclization to yield 1,3,4-oxadiazine derivative **121** (Scheme 51) (*59*).



Scheme 49.



Scheme 50.

6.5.4. *1,3,4-Thiadiazine*

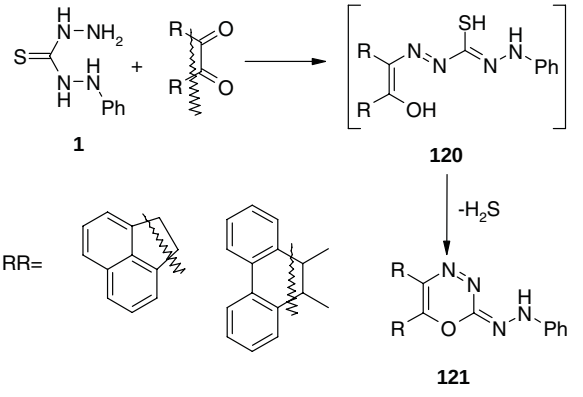
The interaction of thiocarbohydrazide **1** and ethyl chloroacetate in alkaline medium gives 2-hydrazino-1,3,4-thiadiazin-4-one (**123**) (Scheme 52) (*145*).

Thiocarbohydrazides **1** condensed with α-haloketones in ethanol (*146–148*) or acetic acid (*59*) to form 1,3,4-thiadiazine derivatives **124** (Scheme 53).

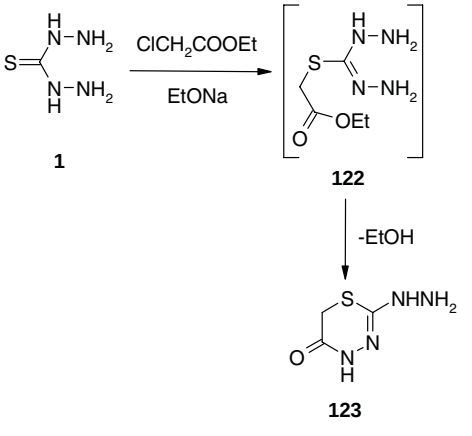
1,3,4-Thiadiazino[5,6-b]quinoxaline **126** was prepared in a one-pot reaction (*149*) on condensation of 6-benzoyl-2,3-dichloroquinoxaline **125** with **1** (Scheme 54).

Heating monothiocarbohydrazones **2** in acetic acid afforded 3-(2-phenyl-hydrazino)[1,3,4] thiadiazino[6,5-b]indole (**127**) (Scheme 55) (*59*).

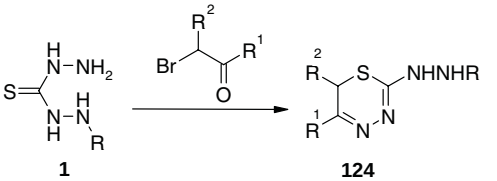
Condensation of chloroacetone with dibenzylidene thiocarbohydrazone **3** yielded 2-[2-benzylidenehydrazino]-5-methyl-6*H*-1,3,4-thiadiazine **128** in a neutral solution (Scheme 56) (*3, 16*).



Scheme 51.



Scheme 52.



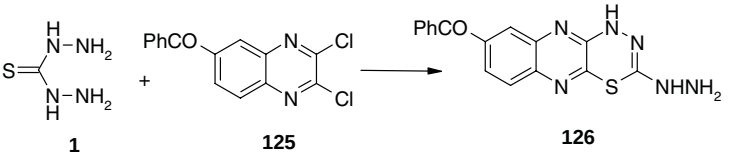
R=H R¹= t-Bu, 2,3,4-$(HO)_3C_6H_2$, 2,5-$(HO)_2C_6H_3$, 3,4-$(HO)_2C_6H_3$ R²=H
R=Ph R¹=Ph R²=H
R=H R¹=$COOCH_3$ R²=CH_2COOCH_3

Scheme 53.

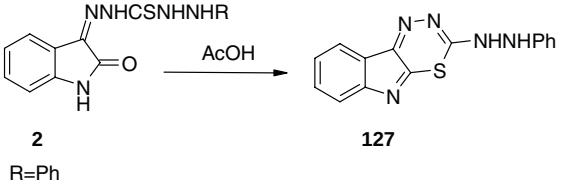
6.6. *Synthesis of six-membered rings with four heteroatoms*

6.6.1. *1,2,4,5-Tetrazine*

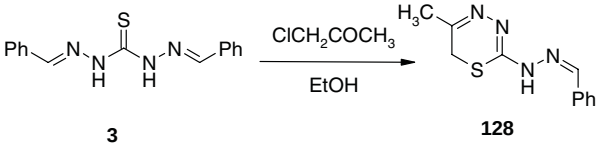
The interaction of thiocarbohydrazide **1** with urea or dimethyl carbonodithioimidoate hydrochloride results in products such as 6-thioxo-1,2,4,5-tetrahydro-1,2,4,5-tetrazin-3-one (**129**) (*18*) and 6-imino-1,2,4,5-tetrahydro-1,2,4,5-tetrazine-3-thione (**130**) (Scheme 57) (*150*).



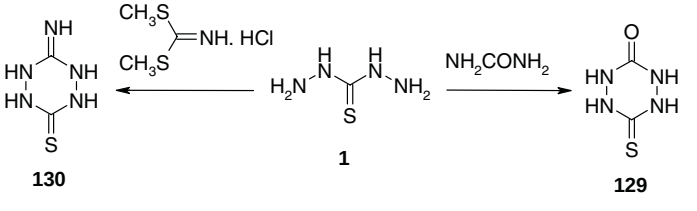
Scheme 54.



Scheme 55.



Scheme 56.



Scheme 57.

Cyclocondensation of **1** with various ketones gave 3-4-disubstituted-1,2,4,5-tetrahydro-1,2,4,5-tetrazine-6-thione derivatives **131** (Table 3) (Scheme 58) (*65, 151–163*).

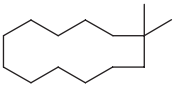
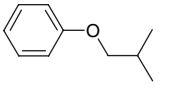
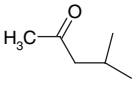
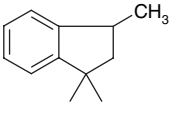
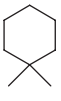
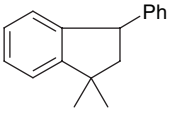
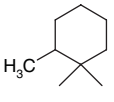
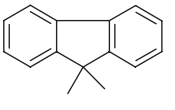
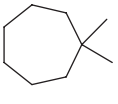
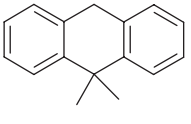
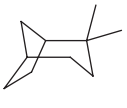
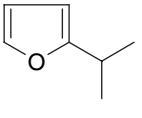
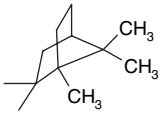
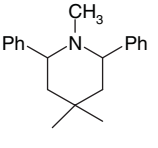
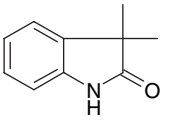
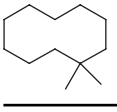
Treatment of 2-phenyl-4*H*-benoxazin-4-one (**132**) with **1** at 160 °C gave the thioxotetraaza-quinazoline derivative **133** (Scheme 59) (*164*).

6.7. *Synthesis of seven-membered rings with three heteroatoms*

6.7.1. *1,2,4-Triazepine*

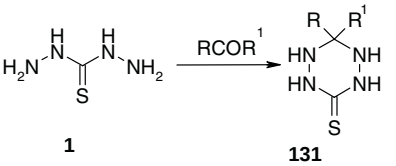
2,4,6-Triphenylpyrylim tetrafluoroborate **83** reacted with thiocarbohydrazide **1** in acetic acid to give pyrazole intermediate **84**, which underwent cyclization by prolonged heating to give 3, 3a-tetrahydro-2,3a,5-triphenylpyrazolo[2,3-d][1,2,4]triazepine-8-thione (**134**) (Scheme 60) (*126*).

Table 3. 3,4-Disubstituted-1,2,4,5-tetrahydro-1,2,4,5-tetrazine-6-thione derivatives **131**.

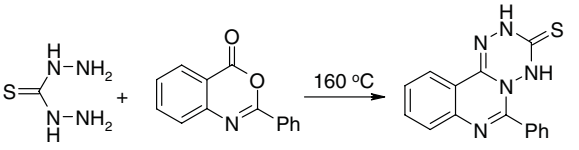
RR^1	Ref.	RR^1	Ref.
R=Et, R^1=Et	(*151*, *156*)		(*161*, *162*)
$R=CH_3(CH_2)_n$ $R^1=CH_3O_2C(CH_2)_m$ n = 0, 5, 8 *m* = 7, 8, 10	(*65*, *160*)		(*153*)
	(*157*)		(*159*)
	(*151*, *155*)		(*159*)
	(*153*)		(*151*, *158*)
	(*161*)		(*159*)
	(*154*)		(*151*)
	(*153*)		(*152*)
	(*153*)		(*159*)
	(*163*)		

6.7.2. *1,3,4-Thiadiazepine*

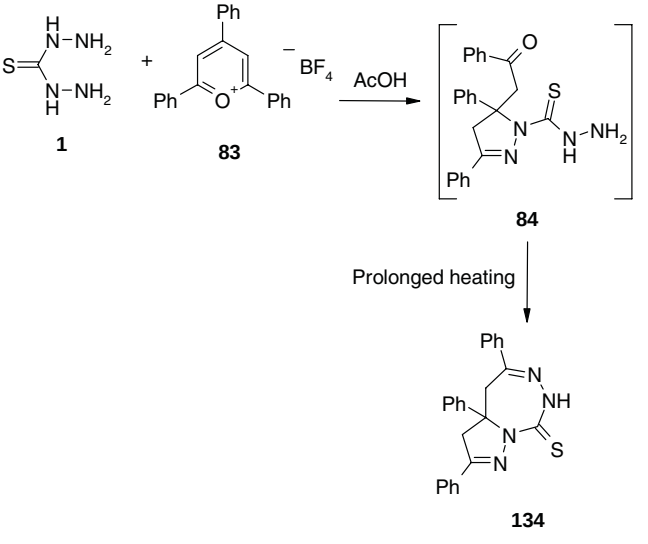
Cyclocondensation of thiocarbohydrazide **1** with malonyl chloride gave 2-(2-phenylhydrazinyl)-1,3,4-thiadiazepine-5,7(4*H*,6*H*)-dione (**135**) in high yield (*75*) while its reaction with 2-chlorobenzaldehyde did not yield the expected the corresponding 1-phenylthiocarbohydrazone



Scheme 58.



Scheme 59.



Scheme 60.

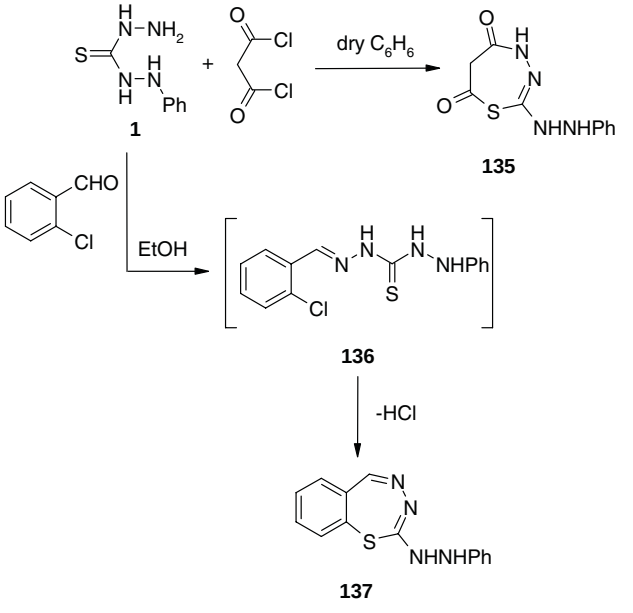
(**136**), but proceeded with cyclization to 2-(2-phenylhydrazino)-1,3,4-benzothiadiazepine (**137**) (*59*) (Scheme 61).

6.8. *Synthesis of seven-membered rings with four heteroatoms*

6.8.1. *1,2,4,5-Tetrazepine*

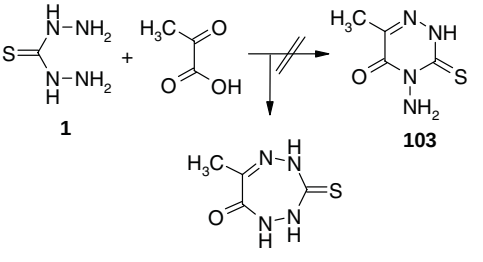
Zhang *et al.* (*33*) reported that reaction of thiocarbohydrazide **1** with pyruvic acid did not give 4-amino-3-mercapto-1,2,4-triazin-5-one (**103**), but gave 7-methyl-3-thioxo-2,3,4,5-tetrahydro-6*H*-1,2,4,5-tetrazepin-6-one (**138**) (Scheme 62).

Cyclocondensation of thiocarbohydrazide **1** with some orthoketones such as benzil, acenaphthaquinone and camphorquinone furnished 1,2,4,5-tetrazepines derivatives **140** (Scheme 63) (*23*).



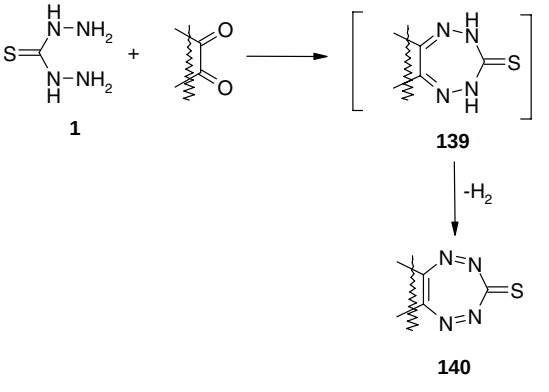
1 **135** **136** **137**

Scheme 61.



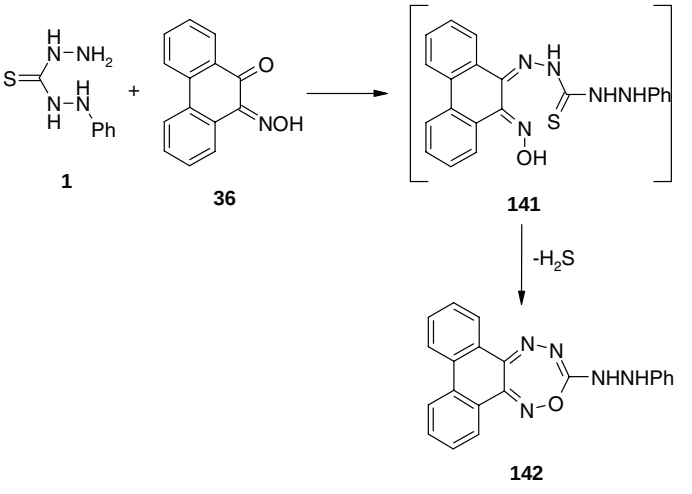
1 **103** **138**

Scheme 62.



1 **139** **140**

Scheme 63.



Scheme 64.

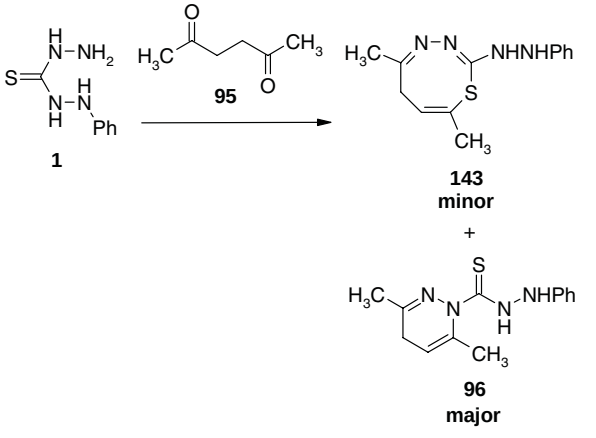
6.8.2. *1,2,5,6-Oxatriazepine*

Phenanthraquinone monoxime **36** condensed with 1-phenylthiocarbohydrazide **1** to give 1,2,5,6-oxatriazepine derivative **142** (Scheme 64) (*59*).

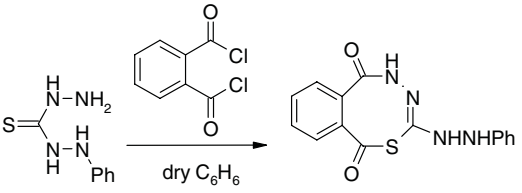
6.9. *Synthesis of eight-membered rings with three heteroatoms*

6.9.1. *1,3,4-Thiadiazoctine*

1-Phenylthiocarbohydrazide **1** condensed with 2,5-hexandione **95** to give 5,8-dimethyl-2-(2-phenylhydrazinyl)-6*H*-1,3,4-thiadiazocine (**143**) as minor product (Scheme 65) (*59*). Its reaction with phthaloyl chloride in dry benzene yielded 4-(2-phenyl-hydrazinyl)-2*H*-5,2,3-benzothiadiazocine-1,6-dione (**144**) (Scheme 66) (*75*).



Scheme 65.



1 **144**

Scheme 66.

7. Conclusion

This review clearly summarizes the high synthetic potential of thiocarbohydrazide. Biologically active heterocyclic compounds have been prepared based on thiocarbohydrazide. This suggests that thiocarbohydrazide can be a particularly promising starting material in synthesizing more functionalized heterocyclic compounds used in the design of new effective biological and pharmaceutical agents with a broad spectrum of applications.

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